

**SYNTHESIS AND CHARACTERIZATION OF MXENES-
BASED CONDUCTIVE SURFACES FOR ELECTRO-
SPECTRO APPLICATIONS**

BY

NASURULLAH MAHAR

A Dissertation Presented to the
FACULTY OF THE COLLEGE OF GRADUATE STUDIES
KING FAHD UNIVERSITY OF PETROLEUM & MINERALS
DHAHRAN, SAUDI ARABIA

In Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

May-2024

KING FAHD UNIVERSITY OF PETROLEUM & MINERALS
DHAHRAN- 31261, SAUDI ARABIA
DEANSHIP OF GRADUATE STUDIES

This thesis, written by **NASURULLAH MAHAR** under the direction of his thesis advisor and approved by his thesis committee, has been presented and accepted by the Dean of Graduate Studies, in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY IN CHEMISTRY**.

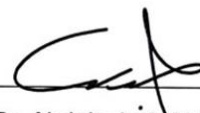


Dr. Jameel R. Al-Thagfi
Department Chairman

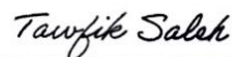


Dr. Suliman Saleh Al-Homidan
Dean of Graduate Studies

Date _____



Dr. Abdulaziz A Al-Saadi
(Advisor)



Dr. Tawfek Abdo Saleh
(Co-advisor)



Dr. Amir Al-Ahmed
(Member)



Dr. Tarek Kandiel
(Member)



Dr. Abdul Malik Puthan
(Member)

© NASURULLAH ABDUL WAHID

2024

**Dedicated to my Parents,
Wife, Kids and Siblings**

ACKNOWLEDGMENT

All praise belongs to Allah, lord of all that exists in the world, who blessed me with the courage to complete my Ph.D. All the praises for Him, the Merciful, Kind, Beneficent. After that, All the prodigious esteem for the greatest leader of the world, the messenger of Almighty Allah, our Holy Prophet Hazrat Muhammad (PBUH), the benefactor of humanity empowered mankind to know the creator and to comprehend the way of life.

I would like to express my sincere gratitude to my supervisor Dr. Abdulaziz A Al-Saadi, for the continuous support of my course work and research, for his enthusiasm, patience, insightful comments, helpful information, practical advice, and unceasing ideas that have always helped me tremendously in my research and writing of this thesis. His immense knowledge, profound experience and professional expertise in Optical Spectroscopy has enabled me to complete this research successfully. Without his support and guidance, this work would not have been possible. I could not have imagined having a better supervisor in my Ph.D.

I would also like to thank my committee members Dr. Tawfek Abdo Saleh, Dr. Amir Al-Ahmed, Dr. Abdul Malik Puthan, and Dr. Tarek Kandiel for their valuable comments, suggestions, and feedback to improve my thesis work.

I am greatly thankful to the King Fahd University of Petroleum and Minerals (KFUPM) for supporting my Ph.D. by providing a fully funded scholarship. I also wish to express my sincere thanks to Dr. Jameel R. Al-Thagfi (Chairman of Chemistry) for providing me research environment at KFUPM. I would like to acknowledge all the faculty members

who improved my Chemistry knowledge. Besides, I would also acknowledge the director Dr. M.A Kazi Institute of Chemistry for their support and coordination during my Ph.D. Studies. I would like to thank my lab fellows Dr. Muhammad Haroon, Mr. Muhammad Shehu, Abdul Raheem, Miss Atheer, Mr. Tahir Naveed Jahangir, Muhammad Chaudri and other lab members for the stimulating discussions, and cooperative support during lab work. My special thanks to Mr. Arif Baba for being very helpful and cooperative during my work in the department. I am grateful to staff of the Department of Chemistry KFUPM, their help and services. I would like to thank Pakistani community in KFUPM for their help and support during this journey.

TABLE OF CONTENTS

ACKNOWLEDGMENT	VI
TABLE OF CONTENTS.....	VIII
LIST OF TABLES.....	XIII
LIST OF FIGURES.....	XIV
LIST OF ABBREVIATIONS.....	XXI
ABSTRACT	XXIII
ملخص الرسالة	XXVIII
1 CHAPTER.....	1
INTRODUCTION.....	1
1.1 MXenes.....	1
1.2 Literature Review.....	4
1.3 Surface Modification.....	8
1.4 Intercalation	9
1.5 Surface Enhanced Raman Scattering	10
1.6 Energy Storage.....	12
1.7 Objectives	17
2 CHAPTER.....	19

SYNTHESIS OF VANADIUM CARBIDE MXENE WITH IMPROVED INTER-LAYER SPACING FOR SERS-BASED QUANTIFICATION OF ANTI-CANCER DRUGS 19

2.1	Introduction	19
2.2	Experimental	22
2.2.1	Reagents	22
2.2.2	Characterization methods	23
2.2.3	Synthesis of silver nanoparticles (AgNPs)	23
2.2.4	MAX Phase and nanolayered MXenes Sheets	24
2.2.5	Synthesis of V ₂ CT _x MXene	24
2.2.6	SERS active substrate	26
2.3	Results & Discussion	27
2.3.1	Properties of the synthesized MAX phase, V ₂ CT _x , and AgNPs-loaded V ₂ CT _x MXene:.....	27
2.3.2	MAX phase transformation into V ₂ CT _x MXene:.....	36
2.3.3	Detection of GMC using MXene-based SERS active substrate:	38
2.4	Reproducibility and stability of the prepared silver-loaded MXene:.....	45
3	CHAPTER	48

SILVER-LOADED BIMETALLIC MXENE SUBSTRATES FOR ULTRA-SENSITIVE SERS DETECTION OF ANTIBIOTIC DRUGS: THE SYNERGETIC IMPACT OF ELECTROMAGNETIC AND CHEMICAL CONTRIBUTIONS..... 48

3.1	Introduction	48
3.2	Experimental	51
3.2.1	Materials and Reagents	51
3.2.2	Characterization	52
3.2.3	Materials Preparation and Synthesis	52
3.3	Results and Discussion	56
3.3.1	Morphological and surface characterizations of AgNSs@ V _{0.25} (Zr _{1.75})AlC	56
3.3.2	SERS Analysis	59
3.3.3	Limit of detection, selectivity and interference effect	63
4	CHAPTER	66

FAST AND SENSITIVE DETECTION OF PROCAINAMIDE: COMBINED SERS AND DFT MODELING STUDIES 66

4.1	Introduction	66
4.2	Experimental.....	68
4.2.1	Chemicals and Synthesis	68
4.2.2	Preparation of Silver Nanoparticles.....	68
4.2.3	SERS Study	70
4.2.4	DFT Calculations	70
4.3	Results and Discussions.....	71
4.3.1	Silver nanoparticles Characterization	71
4.3.2	SERS Detection	75
4.3.3	DFT Modeling of Procainamide Interaction with Nano-substrate.....	79
4.3.4	Vibrational Assignments of SERS Spectra	83

5 CHAPTER87

SPECTROANALYTICAL SERS-BASED DETECTION OF TRACE-LEVEL PROCAINAMIDE USING GREEN-SYNTHEZIZED GOLD NANOPARTICLES.....87

5.1	Introduction	87
5.2	Experimental.....	91
5.2.1	Materials.	91
5.2.2	Green Synthesis.	91
5.2.3	Sample preparation.	92
5.2.4	SERS Study.	94
5.2.5	Theoretical Calculations.	94
5.3	Results & Discussions	95
5.3.1	Characterization.	95
5.3.2	Detection of Procainamide using SERS approach.....	99
5.3.3	Detection of PA in spiked urine sample.....	104
5.3.4	DFT modeling of procainamide interaction.	106
5.3.5	Vibrational Assignments.	109
5.3.6	Interference effect and reproducibility.	112

6 CHAPTER 114

SERS-BASED ULTRALOW CONCENTRATION DETECTION OF ANTICANCER GEMCITABINE USING SIZE-CONTROLLED SILVER NANOPARTICLES..... 114

6.1	Introduction	114
6.2	Experimental.....	115

6.2.1	Chemicals and Reagents.....	115
6.2.2	Silver nanoparticles (AgNPs) preparation	116
6.2.3	SERS Measurement	116
6.2.4	Computation	117
6.3	Results and discussions	118
6.3.1	Characterization of prepared AgNPs.....	118
6.3.2	SERS Detection of GMC	121
6.3.3	SERS Measurements.....	124
6.4	Theoretical calculations.....	125
6.5	Vibrational Assignments.....	127
7	CHAPTER	131
 LIGHT-INDUCED SYNTHESIS OF SILVER NANOPRISMS AS A SURFACE- ENHANCED RAMAN SCATTERING SUBSTRATE FOR N-ACETYL PROCAINAMIDE DRUG QUANTIFICATION.		
7.1	Introduction	131
7.2	Experimental	134
7.2.1	Materials.....	134
7.2.2	Synthesis of silver nanosphere and silver nanoprisms:.....	134
7.2.3	Raman and SERS measurements	136
7.3	Results & Discussion.....	137
8	CHAPTER.....	148
 HIGH PERFORMANCE, LOW-COST RECHARGEABLE ALUMINUM ION BATTERY USING NB₂CTX- MOS₂ COMPOSITE CATHODE.....		
8.1	Introduction	148
8.2	Chemical and materials	153
8.2.1	Instrumentation	153
8.2.2	Synthesis of MXenes and composite.....	154
8.2.3	Synthesis of MXenes and composite cathode	155
8.2.4	Pouch Cell fabrication.....	156
8.3	Results & Discussion.....	156
8.3.1	Electrochemical Study	164

8.3.2	Capacity Calculation	170
8.3.3	Intercalation Study	171
9.	CONCLUSION AND FUTURE ROSPECTIVES.....	174
	REFERENCES:	178
	VITAE	221

LIST OF TABLES

Table 1: Comparison between reported analytical methods to detect trace GMC concentrations compared to the present work. LOD: Limit of detection; LDR: Linear dynamic range; R2: Regression coefficient	39
Table 2: Tentative assignments of the vibrational modes of GMC in the normal Raman and SERS (before and after loading AgNPs on V2CTx) spectra.	42
Table 3: Reported analytical methods used in CP detection, their limits of detection, linear dynamic ranges, and linear regressions constants, as compared with the present work.	51
Table 4: Comparison of reported analytical methods for the trace detection of PA in aqueous solution. LDR: Linear dynamic range, LOD: Limit of detection.	79
Table 5: Interaction energies, binding distances and changes in the sum of Mulliken charges for possible interaction modes as computed at the B3LYP/6-311G(d,p) level.	82
Table 6: Vibrational assignments of the main peaks in the experimental a and calculated b Raman and SERS spectra of PA in the range below 2000 cm ⁻¹	83
Table 7: Assessment of developed approaches for trace detection of PA in water.	106
Table 8: Binding energies, distances, and sum of Mulliken charges for potential modes of interactions calculated with B3LYP/6-311G(d,p) level.	108
Table 9: The vibrational assignment of prominent bands in experimental Raman a, calculated Raman b and SERS spectrum of procainamide below 2000 cm ⁻¹	110
Table 10: Comparison of the outcome achieved in this work with previously reported analytical methods for the detection of trace GMC concentrations.	122
Table 11: Tentative assignments of the experimental a and B3LYP/6-311G(d,p) calculated b Raman and SERS spectra below 1800 cm ⁻¹ of free GMC and GMC with silver nanoparticles.	128
Table 12: The calculated energies of interaction between the drug and nanoclusters'	129
Table 13: Limit of detection (LODs) and linear dynamic ranges (LDRs) of some established techniques for the quantification of NAPA compared to this work.	142
Table 14: Comparison of the limit of detection (LOD), linear dynamic range (LDR), and Raman intensity enhancement factor (EF) parameters using AgNSs and AgNPMs materials as active substrates for sensing of NAPA drug	144
Table 15: Comparison of various materials and the energy capacity at 500 cycles range	152

LIST OF FIGURES

Figure 1. 1: Synthesis of MAX Phase and MXenes	3
Figure 1. 2 (a) XRD Patterns for the MAX Phase and MXenes (b) TEM images of the synthesized MXenes (c) atomic arrangement in a lattice at HR-TEM	6
Figure 1. 3: (a) Surface Modification of as synthesized V2CTx MXenes (b) Intercalation of MXenes (c) Modification of surface by nanotubes (d) Intercalation of MXenes	7
Figure 2. 1: (a) The UV-Vis. Spectra of TEA intercalated V2CTx MXenes showing stability for 4 weeks, (b) The UV-Vis. Spectra of SERS spectra of V2CTx MXenes after ion exchange depicting stability for 7 weeks	25
Figure 2. 2: Schematic representation of the synthesis of AgNPs@V2CTx hybrid SERS substrate MAX phase, followed by loading of GMC drug for SERS study	27
Figure 2. 3: (a) XRD pattern of the AgNPs loaded V2CTx (b) XRD patterns for the V2CTx. The XRD spectra of the as-prepared MXenes and after being loaded with AgNPs as depicted in (Fig. 2.2 a, b) posture the variation in the XRD patterns along with new intense peaks corresponding to (111), (200), (220), and (311) phases of AgNPs, further confirming the successful mobilization of the silver nanoparticles.	28
Figure 2. 4: UV/Vis Spectra of Free GMC drug	29
Figure 2. 5: (a) XRD spectra of V2CTx MXenes (black) and V2AlC MAX phase (red). (b) UV-Visible absorption spectra of V2CTx (black), pure AgNPs (red), and GMC-AgNPs@V2CTx (green). (c) AFM image of the synthesized V2CTx flakes. (d) Height profile of the dashed lines for the MXenes flakes.	30
Figure 2. 6: (a) EDS and elemental mapping of synthesized V2CTx (b) EDS and elemental mapping of V2AlC MAX phase	31
Figure 2. 7: (a) SEM Images of MXene loaded Ag-NPs on the paper. (b) SEM images of AgNPs loaded on V2CTx.	32
Figure 2. 8: FE-SEM images of (a) V2CTx flakes (inset: the TEA-V2CTx loaded in paper), and (b) the V2CTx delaminated flakes with high resolution. (c) TEM image of TEA-V2CTx flakes, and (d) High- resolution TEM image of lattice fringes for the TEA-V2CTx (Inset: the SAED image).	33
Figure 2. 9: The 3d core level spectrum of AgNPs@V2CTx shows the binding energy difference between two doublets 3d _{3/2} and 3d _{5/2} of Ag core	34
Figure 2. 10: XPS spectra of the synthesized V2CTx MXenes. States characterized are (a) V 2p, (b) C 1s, (c) F 1s, and (d) O 1s.....	35

Figure 2. 11: (a) FTIR of Free V2CTx and after loading the GMC at AgNPs@V2CTx hybrid SERS substrate. (b) FT-IR of pure GMC drug molecules and pure AgNPs.	36
Figure 2. 12: Raman spectra of (a) V2AlC MAX phase, (b) delaminated V2CTx, and (c) AgNPs loaded V2CTx MXenes.	38
Figure 2. 13: Raman spectra of free GMC, GMC with AgNPs, and GMC with AgNPs@V2CTx. The SERS spectrum was recorded by the drop-casting of 50 μ L of 10 ⁻⁴ M GMC solution on a 20x20 mm area of hybrid AgNPs@V2CTx substrate. Prominent SERS peaks associated with GMC are labeled for the sake of clarity.....	41
Figure 2. 14: (a) Raman spectra of free GMC, with AgNPs, and GMC with bare V2CTx MXenes, (b) Raman Spectra of free Ag-NPs.	43
Figure 2. 15: (a) SERS spectra of GMC at the concentration range 10 ⁻⁴ -10 ⁻¹² M using AgNPs@V2CTx substrate. (b) Logarithmic relationship between prominent SERS peak intensities and concentrations of GMC molecules.	45
Figure 2. 16: The SERS spectra of AgNPs@V2CTx hybrid materials of different peak positions	46
Figure 2. 17: (a) SERS spectra of GMC using AgNPs@MXene substrate taken over a four-week period (inset shows the Raman intensity distribution of the line at 779 cm ⁻¹). (b) Interference effect of different bioactive drugs (inset depicts the effect of interferent on the intensity of the Raman bands of the GMC).	47
Figure 3. 1: Synthesis of bimetallic V _{0.25} (Zr _{1.75})CTx MXene from its precursor MAX phase V _{0.25} (Zr _{1.75})AlC, intercalation of the etched MXenes and preparation of SERS substrate to laser exposure.	55
Figure 3. 2: SEM images of the prepared (a) V _{0.25} (Zr _{1.75})AlC bimetallic MAX phase, (b) V _{0.25} (Zr _{1.75})AlC MXenes, and (c) the hybrid SERS AgNS@ V _{0.25} (Zr _{1.75})AlC substrate, (d) a high resolution TEM image of the hybrid SERS AgNS@ V _{0.25} (Zr _{1.75})AlC substrate, (e) the EDS spectrum of the prepared V _{0.25} (Zr _{1.75})AlC MXenes, and (f) the elemental mapping of Zr, V, C and O in V _{0.25} (Zr _{1.75})AlC MXenes.	57
Figure 3. 3: X-ray diffraction (XRD) spectra of (a) V _{0.25} (Zr _{1.75})AlC MAX phase, and (b) the bimetallic V _{0.25} (Zr _{1.75})CTx MXene. The indexed peaks correspond to the respective crystallographic planes.	58
Figure 3. 4: Raman spectra of (a) V _{0.25} (Zr _{1.75})AlC bimetallic MAX phase, and (b) the prepared V _{0.25} (Zr _{1.75})CTx MXene. (c) UV-Vis spectra of the hybrid AgNS@ V _{0.25} (Zr _{1.75})CTx substrate (blue) compared to those of silver nanosphere (red) and prepared bimetallic V _{0.25} (Zr _{1.75})CTx MXene (black).	61

Figure 3. 5: Raman and SERS spectra of the ciprofloxacin, CP, drug (green), silver nanosphere-loaded CP drug (blue), and the hybrid substrate-loaded CP drug, V0.25(Zr1.75)CTx-CP, substrate (red).	62
Figure 3. 6: (a) SERS spectra collected for the CP concentrations in the 10 ⁻⁴ -10 ⁻¹⁴ M region in aqueous media using the hybrid AgNS@V0.25(Zr1.75)CTx substrate, and (b) the detected linear dynamic range and corresponding calculated correlation coefficients of SERS intensity vs. the logarithm of CP concentrations for the two characteristic peaks observed at 1394 and 1603 cm ⁻¹	64
Figure 3. 7: (a) Characteristic SERS spectra of the CP (10 ⁻⁵ M) after being mixed with selected interferents (10 ⁻⁴ M each), namely valeric acid (VA), citric acid (CA), and amphetamine (AN), and (b) the selectivity outcome of CP in terms of SERS intensity of the probe compared to the selected interferents.	65
Figure 4. 1: Scheme for the synthesis of silver nanoparticles and the associated SERS mechanism.....	69
Figure 4. 2: Theoretically Optimized Structure of Procainamide	71
Figure 4. 3: UV/Vis Spectra of the drug at different concentrations	72
Figure 4. 4: (a) UV-Vis and (b) FT-IR spectra of the prepared Ag-NPs before (black) and after (red) being mixed with PA.	73
Figure 4. 5: FE-SEM images showing the morphology of the prepared Ag-NPs.....	74
Figure 4. 6: Raman spectra of the as prepared silver nanoparticles	74
Figure 4. 7: The Raman spectra of the Procainamide drug	75
Figure 4. 8: SERS spectrum of PA at a concentration of 0.5 M (black) compared with normal Raman spectrum (red) of PA solution without Ag-NPs.	76
Figure 4. 9: (a) SERS spectra of PA solutions at different concentrations ranging from 1M to 10 ⁻⁹ M. (b) Logarithmic relationships between the Raman intensities in arbitrary units (y-axis) and concentrations of PA for the bands positioned at (i) 1246 cm ⁻¹ , (ii) 1370 cm ⁻¹ , (iii) 1613 cm ⁻¹ and (iv) 1661 cm ⁻¹	78
Figure 4. 10: Theoretically computed Raman and SERS spectra of the Procainamide drug	78
Figure 4. 11: Theoretically optimized structure of the drugs showing the possible sites of interaction with SERS substrates.	81
Figure 4. 12: Calculated molecular electrostatic potential (MESP) map of PA. Electron-rich and electron-deficient regions are displayed with the red and blue colors, respectively.Error! Bookmark not defined.	
Figure 4. 13: Calculated SERS spectra modeling silver cluster interactions with (a) the primary amine group and (b) the carbonyl group, as compared with (c) the experimental SERS of procainamide.	86
Figure 5. 1: The interaction of gold nanoparticles (Au-NPs) with various concentrations of PA (2-6 mM).	93

Figure 5. 2: (a) Raman spectrum of Au-NPs at 350-2000 cm ⁻¹ (b) Comparison UV-Vis Spectra of Au-NPs (Black line) and Au-NPs containing urine (Red Line), It suggest that there is almost no change at band 512 nm.	95
Figure 5. 3: (a) Raman spectrum of PA and Au-NPs at 350-2000 cm ⁻¹ (b) Raman spectrum of PA spiked urine and Au-NPs at 350-2000 cm ⁻¹ (Laser λ =633 nm, laser power; 25%, acquisition time; 20s, accumulations 4 and objective; 50x.	96
Figure 5. 4: (a) Raman Spectra of Procainamide at 350-2000 cm ⁻¹ (Laser λ =633 nm, laser power; 25%, acquisition time; 20s, accumulations 4 and objective; 50x. (b) calculated SERS spectra of Procainamide with Au-NPs.....	97
Figure 5. 5: (a) The UV-Vis spectrum of PA, Au-NPs, and Mixture (a) FT-IR spectrum of Au-NPs and PA drug combined with Au-NPs.	98
Figure 5. 6: (a) The FE-SEM images demonstrate the surface morphology of synthesized Au-NPs. The inset is the HR-TEM image of Au-NPs well scattered (b) The histogram showing the average size of the Au-NPs.	99
Figure 5. 7: Optimized structure of interactions of Au ₄ -cluster with (a) -C=O (b) HN- (c) H ₂ N- groups of procainamide molecule.....	100
Figure 5. 8: The SERS spectrum of the PA drug at 1M (green) matched through ordinary Raman spectrum (brown) of the drug solution exclusive of Au-NPs.....	101
Figure 5. 9: Calculated SERS spectra and model of gold nanoclusters interactions with (C=O) group as compared with the experimental SERS of procainamide.....	103
Figure 5. 10: The SERS spectra of drug at various concentrations (1.0 M to 10 ⁻¹¹ M) (a); and (b) Logarithmic connections among intensities Vs concentrations of drug in peaks situated at (i) 942, (ii) 1401, (iii) 1653 and (iv) 1690 cm ⁻¹	104
Figure 5. 11: The comparison spectra of (a) spiked (6 ppm) PA SERS (b) Raman of PA, and (c) Raman spectra of a real Urine sample.	105
Figure 5. 12: The calculated molecular electrostatic potential (MESP) map of the drug depicting the electron densities as red (high) and blue (low) accordingly.	108
Figure 5. 13: Computed SERS spectra for gold cluster interaction with (a) primary amine (b) amide, matched with (c) experimental SERS of PA.	112
Figure 5. 14: Plots of SERS response at 1690 cm ⁻¹ in presence of interferents; Interference study of SERS approach for the quantification of procainamide in presence of interferents	113
Figure 6. 1: An optimized structure of anticancer drug gemcitabine	118
Figure 6. 2: Raman spectra of the drug (Red) and silver nanoparticles (black).....	119

Figure 6. 3: FTIR spectra of the drug before (red) and after interaction with silver nanoparticles (black)	120
Figure 6. 4: (a) UV-visible and (b) FT-IR spectra of free AgNPs and AgNPs+GMC mixture.	120
Figure 6. 5: Size distribution of AgNPs with an average size of 23.3 nm (the inset shows the UV-vis spectra of AgNPs), and (b) the FE-SEM image showing the morphology of the prepared AgNPs.	121
Figure 6. 6: Raman signal enhancement at different ratio of drug to nanoparticles	123
Figure 6. 7: The Raman spectrum of GMC solution at 10 ⁻³ M concentration (blue) compared with the SERS spectrum of AgNPs+GMC solution mixture at 10 ⁻³ M concentration (red). Prominent peaks are highlighted, and wavenumber shifts due to the SERS effect can be noted.	123
Figure 6. 8: Theoretically calculated SERS (Red) and Raman Spectra (black) of GMC.	124
Figure 6. 9: SERS spectra of GMC solutions at different concentrations from 10 ⁻⁴ to 10 ⁻¹⁰ M (left), and the logarithmic relationship of Raman peak intensities and concentrations of GMC for the prominent bands located at 799 cm ⁻¹ (upper right) and 1252 cm ⁻¹ (lower right) in the dynamic range 10 ⁻⁴ - 10 ⁻⁹ M.	125
Figure 6. 10: Theoretically calculated sites of interaction between silver nanoparticles and GMC drug.	126
Figure 6. 11: Computed molecular electrostatic potential (MEP) map of GMC. The blue-colored region depicts the low electron density, and the red-colored regions are the high electron density regions.	127
Figure 6. 12: Interaction energies, Binding distances, and energies for computationally predicted different interaction modes at B3LYP/6-311G(d,p) level.	127
Figure 6. 13: Calculated SERS spectra mimicking the possible silver nanoparticle interaction modes with of GMC compared with the experimental SERS spectrum of GMC.	130
Figure 7. 1: UV-Vis spectra of the Nanoprisms for the time period of 6 weeks, inset shows the consistency and uniform patterns	135
Figure 7. 2: Photo-induced synthesis of Ag-NPM from Ag-NS materials and their respective roles as efficient SERS substrates.	136
Figure 7. 3: (a) UV-Vis spectra of the free NAPA drug (b) Excitation UV-vis-NIR spectra of the photo-induced silver nanoprisms (brown) after interacting with the NAPA drug (green).	138
Figure 7. 4: Excitation UV-vis-NIR spectra of the prepared silver nanospheres (red) and the photo-induced silver nanoprisms (black).	139
Figure 7. 5: The Raman spectra of AgNSs (Red) and of AgNPMs (black), acquired at 633 nm excitation source, using 50x lens, 1800 grating, 20 sec. acquisition time and 4-sec. accumulation. The Blu line spectra belong to AgNPMs taken at 532 nm.	140

Figure 7. 6: a) FE-SEM image of the Ag-nanospheres seeds b) the FE-SEM image of Ag- nanoprisms showing mixed morphologies c) histogram comparing the average particle sizes of the prepared silver nanospheres; d) Average particle sizes of the photo-induced silver nanoprisms inset is the real image of AgNSs (yellow) and NPMs (green).	141
Figure 7. 7: a) The SERS spectra of NAPA a) with AgNSs, and b) with AgNPMs, compared with c) the Raman spectra of pure NAPA, all acquired at 633 nm excitation source, using 50x lens, 20 sec. acquisition time and 4-sec. accumulation.	143
Figure 7. 8: SERS spectra showing the peak intensity-concentration dependence of the NAPA molecules in contact with (a) AgNPMs substrate (Raman line centered at 1652 cm ⁻¹), and (b) AgNSs substrate (Raman line centered at 1432 cm ⁻¹). (c) Comparison of the linear dynamic ranges and correlation coefficients of the intensity-concentration relationship in the case of Ag-nanoprisms and Ag-nanospheres.	146
Figure 7. 9: The SERS spectral stability for the period of 30 days of the two prominent peaks 1652 cm ⁻¹ and 1407 cm ⁻¹	147
Figure 7. 10: (a) Interference effect of different interferents, namely sulindac (SD), ciprofloxacin (CPS), citric acid (CA), and valeric acid (VA), 10-2 M each, mixed with NAPA at 10-6 M concentration, (b) Selectivity outcome in terms of SERS intensity (1652 cm ⁻¹) of the probe molecules (10-6 M) in presence of the same four interferents (10-2 M each), and (c) The stability of the NPMs-NAPA solution spectra taken over a time period of 30 days	147
Figure 8.1: The pouch cell components (a) Al foil anode (b) carbon paper coated with composite cathode (c) assembled single sheet pouch cell.	151
Figure 8.2: Schematic representation of fabrication of composite electrode material from MAX to MXenes and Synthesis of Nb ₂ CTx-MoS ₂ composites by hydrothermal method. Additionally, the preparation of slurry with 80:10:10 ratio of active material, conducting carbon and PVDF binder respectively followed by pasting slurry on carbon paper is depicted.	152
Figure 8.3: XRD spectra of the precursor MAX phase and multilayered Nb ₂ CTx MXenes.	157
Figure 8.4: Morphological and structural characterization of as-prepared Nb ₂ CTx and its composite (a) XRD patterns of few layered Nb ₂ CTx (b) XRD patterns for the Nb ₂ CTx-MoS ₂ composite (c) FE-SEM images of Nb ₂ CTx showing the layered structure (d) FE-SEM images of the composite after the loading of MoS ₂ with change in morphology (e) HR-TEM images of the Nb ₂ CTx flakes showing well scattered layers (f) SAED image of the spot where TEM was conducted.	159
Figure 8.5: EDS spectra of the Nb ₂ CTx-MoS ₂ composite cathode material before and after charging. ..	160
Figure 8.6: The structural analysis and morphology of cathode after the charge discharge process (a) Ex-situ XRD patterns for composite cathode after 10th and 500th cycles (b) Raman spectra of the	

cathode at the 10th and after 500th cycle showing the changes in electrolyte chemistry (c) FE-SEM images represent the cathode morphology after 500 cycles (d) shows the high-resolution FE-SEM images after 500th cycle.	161
Figure 8.7: Survey spectra of the Nb2CTx-MoS2 composite cathode.....	162
Figure 8.8: The XPS spectra depicting the change in position of binding energy of the major elements of the composite cathode before and after GCD process (a) XPS peaks for the Nb 3d core at fully charged state, (b) after discharging (c) original composite cathode before GCD (d) XPS peaks for Cl 2p at three stages (e) XPS peaks for the Al 2p at before charging, discharged, and fully charged stages (f) XPS peaks for carbon in all three stages of original to charged.	163
Figure 8.9: Cyclic voltammetry and GCD curves at different current densities for both electrodes(a) CV curve for the bare Nb2CTx at scan rate of 0.1 mV s ⁻¹ and carbon paper (b) charge/discharge curves of Nb2CTx at current densities ranging from 10-300 mA/g specific capacity (c) CV curves of Nb2CTx-MoS2 and carbon paper at 0.1 mV s ⁻¹ (d) charge/discharge curves of Nb2CTx-MoS2 at current densities ranging from 10-300 mA/g.	166
Figure 8.10: Specific capacity of both electrodes for 500 cycles and corresponding coulombic efficiency of the cathodes for 500 GCD cycles (a) Long-term GCD curves and specific capacity of Nb2CTx at 100 mA/g current density (b) long-term GCD curves and specific capacity of Nb2CTx-MoS2 at 100 mA/g current densities (c) coulombic efficiency and cyclic performance of Nb2CTx at 100 mA/g (d) Coulombic efficiency and cyclic performance for the Nb2CTx-MoS2 composite cathode at 100 mA/g.	168
Figure 8.11: (a) Nyquist plots of Nb2CTx at different cycles (b) Nyquist plots of Nb2CTx-MoS2 composite at 10, 50, 100, and 200th cycles (c) Open circuit potential and the equivalent circuit model of the pouch cell (d) rate capability and coulombic efficiency of Nb2CTx-MoS2 performed at varying current densities extending from 10 to 300 mA/g for 500 cycles.	170
Figure 8.12: The operation of the pouch cell for 40 hours.	172
Figure 8.13: Optimized structure of the respective ions, overall chemistry of electrolyte and complex ion formation, the model battery operation where the ions flow to respective electrodes during the charge and discharge process is observed and the ion intercalation/deintercalation during the charge discharge process at the cathode and anode.....	173

LIST OF ABBREVIATIONS

AIB	:	Aluminum Ion Batteries
[BMIM]Cl	:	3-Butyl-1-methyl imidazolium chloride
ILE	:	Ionic Liquid Electrolytes
LIBs	:	Lithium-Ion Batteries
EIS	:	Electron Impedance Spectroscopy
GCD	:	Galvanostatic Charge Discharge
NMP	:	N-Methyl Pyrrolidone
SERS	:	Surface Enhanced Raman Scattering
LSPR	:	Localized Surface Plasmon Resonance
EM	:	Electromagnetic Enhancement
CHEM	:	Chemical Enhancement
CT	:	Charge Transfer
AgNPs	:	Silver Nanoparticles
AuNPs	:	Gold Nanoparticles
CNS	:	Carbon Nano Sphere

CNPs	:	Circular Nano Plates
NPMs	:	Nanoprisms
DFT	:	Density Functional Theory
TEM	:	Transmission Electron Microscopy
FTIR	:	Fourier-transform Infrared Spectroscopy
EDS	:	Energy Dispersive X-ray Spectroscopy
XPS	:	X-ray Photoelectron Spectroscopy
CV	:	Cyclic Voltammetry
LOD	:	Limit of Detection
LDR	:	Linear Dynamic Range
VA	:	Valeric Acid
RSD	:	Relative Standard Deviation
EF	:	Enhancement Factor
SDD	:	Stuttgart/Dresden basis set

ABSTRACT

Full Name : [Nasurullah Mahar]

Thesis Title : [Synthesis and Characterization of MXenes-based Conductive Surfaces for Electro-Spectro Applications]

Major Field : [Chemistry]

Date of Degree : [May 2024]

This dissertation presents an extensive investigation into the synthesis and characterization of two-dimensional (2D) transition metal carbides and nitrides, commonly known as MXenes, along with the fabrication of noble metal nanoparticles, including gold and silver. The MXenes namely ($\text{Ti}_3\text{C}_2\text{Tx}$, Nb_2CTx , V_2CTx , Zr_2CTx , $\text{V}(\text{Zr})\text{CTx}$, Cr_2CTx) were synthesized using novel chemical methodologies, focusing on both conventional and HF-free etching processes. The traditional etching method involved mixed acid etchants ($\text{HCl}:\text{HF}$) with carefully optimized ratios, while the HF-free etching utilized FeCl_3 in the presence of strong complexing agents such as tartaric and citric acids. These approaches were designed to minimize structural damage while ensuring effective delamination of the MXene layers.

To further enhance the interlayer spacing and improve electrochemical properties, intercalation strategies were employed using organic molecules such as trimethylamine (TMA), triethylamine (TEA), tetrabutylammonium hydroxide (TBAOH), and dimethyl sulfoxide (DMSO). TEA and TMA, in particular, proved highly effective as intercalants, controlling the interlayer spacing in the range of 4–7 nm. This increase in interlayer distance improved ion diffusion, which is critical for applications in energy storage

systems. The study also explored the synthesis of bimetallic MXenes and their composites, including MXene-MoS₂, MXene-NiO₂, and MXene-Co₂O₃, which demonstrated synergistic effects for enhanced electrochemical performance.

In parallel, the research focused on the synthesis of silver and gold nanoparticles through both chemical reduction and green synthesis methods. In the case of silver nanoparticles, precise size control was achieved, while shape modification was carried out using a 450 nm LED light source, transforming spherical nanoparticles into nanoprisms. These modifications tailored the optical properties of the nanoparticles, particularly enhancing their surface plasmon resonance, which is vital for sensing applications.

Comprehensive characterization of both MXenes and nanoparticles was performed using a range of advanced techniques. X-ray diffraction (XRD) provided insight into the crystal structures and phase purity of the materials, while field emission scanning electron microscopy (FE-SEM) and transmission electron microscopy (TEM) revealed the morphological and structural details at the nanoscale. X-ray photoelectron spectroscopy (XPS) confirmed the surface chemistry and functional groups present on the MXenes, particularly the -OH, -F, and -O terminations. Raman spectroscopy was employed to study vibrational properties, while UV-Vis spectroscopy was used to monitor the optical properties of the nanoparticles. Brunauer-Emmett-Teller (BET) surface area analysis and Fourier-transform infrared spectroscopy (FT-IR) were additionally utilized for further structural and surface characterization.

In Addition, owing to the plasmonic and charge transfer characteristics of the MXenes, the V₂CTx-AgNPs composite was synthesized and studied for surface-enhanced Raman

spectroscopy (SERS) applications. This composite demonstrated enhanced Raman scattering compared to bare silver nanoparticles, primarily due to the superior plasmonic coupling between the MXene substrate and the silver nanoparticles. As a result, the composite was able to detect the anticancer drug gemcitabine at ultra-low concentrations, down to 10^{-12} M. This low detection limit was accompanied by a broad linear dynamic range (10^{-4} - 10^{-12} M) with great sensitivity and repeatability, making it a highly sensitive and selective SERS substrate. Likewise, The bimetallic MXene composite of $V_{0.25}(Zr_{1.75})CTx$ with silver nanoparticles (AgNPs) was utilized as a highly efficient SERS (Surface-Enhanced Raman Scattering) substrate for the detection of the antibiotic ciprofloxacin. The results demonstrated a significant enhancement in the Raman signal, which can be attributed to the unique synergy between the bimetallic MXene and the silver nanoparticles. This enhancement arises from two primary mechanisms, i.e., Charge Transfer Enhancement (CTE) from the bimetallic MXene, which enables more efficient electronic interactions between the MXene surface and the adsorbed ciprofloxacin molecules and Plasmonic Enhancement from the AgNPs, which provides intense localized electric fields (hot spots) necessary for strong Raman signal amplification. The combination of these two effects—simultaneous charge transfer and plasmonic activity—created a highly sensitive detection platform. The SERS substrate exhibited an exceptional limit of detection (LOD) of 10^{-14} M, enabling the detection of ciprofloxacin at trace concentrations. Moreover, the substrate offered a wide linear dynamic range, ensuring accurate and consistent detection of the drug across a broad range of concentrations. This performance was found to be significantly superior when compared to the use of bare silver

nanoparticles alone, which lack the charge transfer capabilities offered by the bimetallic MXene.

In addition, other SERS substrates, such as silver nanoprisms and gold/silver nanoparticles, were synthesized and tested for the detection of pharmaceuticals, including procainamide (PA), N-actylprocainamide (NAPA), and gemcitabine (GMC). These substrates exhibited excellent Raman signal enhancement, with enhancement factors (EF) of 10^7 , 10^6 , and 10^9 , respectively, and detection limits as low as 10^{-10} M to 10^{-14} M. The strong selectivity and linearity of the SERS substrates make them suitable for real-time detection of various analytes, offering great potential for biomedical and environmental applications.

Furthermore, the synthesized MXenes were also employed as electrodes for metal-ion batteries, with notable performances in aluminum-ion and lithium-ion battery systems. The Nb₂CTx-MoS₂ composite served as a cathode material for aluminum-ion batteries, achieving a specific capacity of 350 mAh/g after 500 cycles at a current density of 100 mA/g. This remarkable performance was attributed to the increased interlayer spacing provided by the MoS₂, which facilitated more efficient Al³⁺ ion intercalation. Comparatively, this composite outperformed traditional graphite and graphene cathodes, primarily due to its ability to undergo stage-1 intercalation, where all available interlayer sites are filled, resulting in higher capacity. In addition, for lithium-ion batteries, a Nb₂CTx-NiO₂-Co₂O₃ composite anode exhibited a specific capacity of 480 mAh/g at a current density of 1 A/g. The synergetic combination of Nb₂CTx and the metal oxides mitigated the typical dendrite formation associated with lithium metal, thus significantly improving the cycle life and safety of the batteries. The enhanced electrochemical performance was

further ascribed to the conductive nature of MXenes and the high theoretical capacity of the incorporated metal oxides.

ملخص الرسالة

الاسم الكامل: نصر الله ماهر

عنوان الرسالة: [توليف وتوصيف الأسطح الموصلة المعتمدة على MXenes للتطبيقات الطبية الكهربائية]

التخصص: الكيمياء

تاريخ الدرجة العلمية: مايو / 2024

تقدم هذه الأطروحة بحثاً مكثفًا في تخليق وتوصيف كربيدات ونيتريدات المعادن الانتقالية ثنائية الأبعاد، والمعروفة باسم MXenes، جنبًا إلى جنب مع تصنيع الجسيمات النانوية المعدنية النبيلة، بما في ذلك الذهب والفضة. تم تصنيع MXenes وهي (Zr_2CT_x ، V_2CT_x ، Nb_2CT_x ، Ti_3C_2Tx) باستخدام منهجيات كيميائية جديدة، مع التركيز على كل من عمليات النقش التقليدية والخالية من HF. تتضمن طريقة النقش التقليدية نقشًا حمضيًا مختلطًا ($HCl:HF$) بنسب محسنة بعناية، بينما استخدم النقش الخالي من HF $FeCl_3$ في وجود عوامل معقدة قوية مثل حمض الطرطريك وحمض الستريك. تم تصميم هذه الأساليب لتقليل الأضرار الهيكلية مع ضمان التصفية الفعال لطبقات MXene.

لزيادة تعزيز التباعد بين الطبقات وتحسين الخواص الكهروكيميائية، تم استخدام استراتيجيات الإقحام باستخدام الجزيئات العضوية مثل ثلاثي ميثيل أمين (TMA)، وثلاثي إيثيل أمين (TEA)، وهيدروكسيد رباعي بيوتيل الأمونيوم (TBAOH)، وثنائي ميثيل سلفوكسيد (DMSO). أثبتت TEA و TMA، على وجه الخصوص، فعاليتها العالية كمادة مقحمة، حيث تتحكم في تباعد الطبقات البينية في نطاق 4-7 نانومتر. أدت هذه الزيادة في المسافة البينية إلى تحسين انتشار الأيونات، وهو أمر بالغ الأهمية للتطبيقات في أنظمة تخزين الطاقة. استكشفت الدراسة أيضًا تخليق MXenes ثنائي المعدن ومركباتها، بما في ذلك

MXene-MoS₂، MXene-NiO₂، و MXene-Co₂O₃، والتي أظهرت تأثيرات تآزرية لتعزيز الأداء الكهروكيميائي.

وبالتوازي مع ذلك، ركز البحث على تصنيع جزيئات الفضة والذهب النانوية من خلال طريقتي الاختزال الكيميائي والتخليق الأخضر. في حالة الجسيمات النانوية الفضية، تم تحقيق التحكم الدقيق في الحجم، بينما تم إجراء تعديل الشكل باستخدام مصدر ضوء LED بطول 450 نانومتر، مما أدى إلى تحويل الجسيمات النانوية الكروية إلى منشورات نانوية. صممت هذه التعديلات الخصائص البصرية للجسيمات النانوية، وخاصة تعزيز رنين البلازمون السطحي، وهو أمر حيوي لتطبيقات الاستشعار.

تم إجراء توصيف شامل لكل من MXenes والجسيمات النانوية باستخدام مجموعة من التقنيات المتقدمة. قدم حيود الأشعة السينية (XRD) نظرة ثاقبة للهياكل البلورية ونقاء الطور للمواد، في حين كشف المجهر الإلكتروني لمسح الانبعاث الميداني (FE-SEM) والمجهر الإلكتروني النافذ (TEM) عن التفاصيل المورفولوجية والهيكلية على مقياس النانو. أكد التحليل الطيفي للأشعة السينية الضوئية (XPS) كيمياء السطح والمجموعات الوظيفية الموجودة في MXenes، وخاصة النهايات -OH، و-F، و-O. تم استخدام مطيافية رامان لدراسة الخواص الاهتزازية، بينما تم استخدام مطيافية الأشعة فوق البنفسجية لمراقبة الخواص البصرية للجسيمات النانوية. بالإضافة إلى ذلك، تم استخدام تحليل المساحة السطحية لـ Brunauer-Emmett-Teller (BET) والتحليل الطيفي للأشعة تحت الحمراء لتحويل فورييه (FT-IR) لمزيد من التوصيف الهيكلي والسطحي.

بالإضافة إلى ذلك، نظرًا لخصائص MXenes البلازمونية ونقل الشحنة، تم تصنيع مركب V₂CT_x-AgNPs ودرسته لتطبيقات مطياف رامان المحسّن على السطح (SERS). أظهر هذا المركب تشتت رامان محسّنًا مقارنةً بالجسيمات النانوية الفضية العارية، ويرجع ذلك أساسًا إلى الاقتران البلازموني الفائق بين ركيزة MXene والجسيمات النانوية الفضية. ونتيجة لذلك، كان المركب قادرًا على اكتشاف

عقار جيمسيتابين المضاد للسرطان بتركيزات منخفضة للغاية، تصل إلى 10⁻¹² م. وكان حد الاكتشاف المنخفض هذا مصحوبًا بنطاق ديناميكي خطي واسع (10⁻¹⁰-12 م) مع حساسية كبيرة وتكرار، مما يجعلها ركيزة SERS حساسة للغاية وانتقائية. وبالمثل، تم استخدام مركب MXene ثنائي المعدن المكون من V_{0.25}(Zr_{1.75})CT_x مع الجسيمات النانوية الفضية (AgNPs) كركيزة SERS (تشنت رامن المعزز السطحي) عالية الكفاءة للكشف عن المضاد الحيوي سيبروفلوكساسين. أظهرت النتائج تحسنًا كبيرًا في إشارة رامن، والذي يمكن أن يعزى إلى التآزر الفريد بين MXene ثنائي المعدن والجسيمات النانوية الفضية. ينشأ هذا التعزيز من آليتين أساسيتين، أي تحسين نقل الشحنة (CTE) من MXene ثنائي المعدن، والذي يتيح تفاعلات إلكترونية أكثر كفاءة بين سطح MXene وجزيئات السيبروفلوكساسين الممتصة وتعزيز Plasmonic من AgNPs، والذي يوفر مجالات كهربائية محلية مكثفة (النقاط الساخنة) اللازمة لتضخيم إشارة رامن قوية.

أدى الجمع بين هذين التأثيرين - نقل الشحنة المتزامنة والنشاط البلازموني - إلى إنشاء منصة كشف حساسة للغاية. أظهرت ركيزة SERS حدًا استثنائيًا للكشف (LOD) يبلغ 10⁻¹⁴ م، مما يتيح اكتشاف السيبروفلوكساسين بتركيزات ضئيلة. علاوة على ذلك، قدمت الركيزة نطاقًا ديناميكيًا خطيًا واسعًا، مما يضمن اكتشافًا دقيقًا ومتسقًا للدواء عبر نطاق واسع من التركيزات. وقد وجد أن هذا الأداء متفوق بشكل ملحوظ عند مقارنته باستخدام جسيمات الفضة النانوية العارية وحدها، والتي تفتقر إلى إمكانات نقل الشحنة التي يوفرها MXene ثنائي المعدن.

بالإضافة إلى ذلك، تم تصنيع واختبار ركائز SERS الأخرى، مثل المنشورات الفضية والجسيمات النانوية الذهبية/الفضية، واختبارها للكشف عن المستحضرات الصيدلانية، بما في ذلك البروكيناميد (PA)، و-N-actylprocainamide (NAPA)، وجيمسيتابين (GMC). أظهرت هذه الركائز تعزيزًا ممتازًا للإشارة رامن، مع عوامل تعزيز (EF) تبلغ 107 و106 و109 على التوالي، وحدود اكتشاف منخفضة تصل

إلى 10^{-10} م إلى 10^{-14} م. الانتقائية القوية والخطية لركائز SERS تجعل إنها مناسبة للكشف في الوقت الفعلي عن مختلف التحليلات، مما يوفر إمكانات كبيرة للتطبيقات الطبية الحيوية والبيئية.

علاوة على ذلك، تم استخدام MXenes المصنعة أيضًا كأقطاب كهربائية لبطاريات أيون المعدن، مع أداء ملحوظ في أنظمة بطاريات أيون الألومنيوم وأيونات الليثيوم. كان المركب $\text{Nb}_2\text{CT}_x\text{-MoS}_2$ بمثابة مادة كاثود لبطاريات أيون الألومنيوم، حيث حقق سعة محددة تبلغ 350 مللي أمبير/جرام بعد 500 دورة بكثافة حالية تبلغ 100 مللي أمبير/جرام. يُعزى هذا الأداء الرائع إلى زيادة التباعد بين الطبقات التي يوفرها MoS_2 ، مما سهّل إقحام Al^{3+} أيون بشكل أكثر كفاءة. نسبيًا، تفوق هذا المركب على كاثودات الجرافيت والجرافين التقليدية، ويرجع ذلك أساسًا إلى قدرته على الخضوع للإقحام في المرحلة الأولى، حيث يتم ملء جميع مواقع الطبقات البينية المتاحة، مما يؤدي إلى زيادة السعة. بالإضافة إلى ذلك، بالنسبة لبطاريات الليثيوم أيون، أظهر الأنود المركب $\text{Nb}_2\text{CT}_x\text{-NiO}_2\text{-Co}_2\text{O}_3$ قدرة محددة تبلغ 480 مللي أمبير/جرام عند كثافة تيار تبلغ 1 أمبير/جرام. أدى الجمع التآزري بين Nb_2CT_x وأكاسيد المعادن إلى تخفيف تكوين التشعبات النموذجية المرتبطة بمعدن الليثيوم، وبالتالي تحسين عمر دورة البطاريات وسلامتها بشكل كبير.

يُعزى الأداء الكهروكيميائي المعزز أيضًا إلى الطبيعة الموصلة للـ MXenes والقدرة النظرية العالية للأكاسيد المعدنية المدمجة.

1 CHAPTER

INTRODUCTION

1.1 MXenes

MXenes, a recently developed class of 2D transition metal carbides and nitrides, have gained significant attention across various scientific fields due to their unique structural, electronic, and surface properties. First synthesized in 2011 by Naguib et al., MXenes are derived from the parent MAX phase, a layered structure where "M" denotes an early transition metal, "A" represents a group 13 or 14 element, and "X" refers to carbon and/or nitrogen atoms [1]. By selectively etching the "A" element using an acid, usually hydrofluoric acid (HF), the layered MAX phase transforms into an MXene structure, where layers are separated by atomic-level spacing that provides MXenes with distinct surface functional groups such as $-OH$, $-O$, and $-F$ [2][3]. This unique composition leads to a wide range of tunable physical, chemical, and electrochemical properties, setting MXenes apart as a groundbreaking material for applications in energy storage and sensing. In recent years, MXenes have attracted considerable interest in the domains of lithium-ion batteries (LIBs) and aluminum-ion batteries (AIBs) due to their high electrical conductivity, tunable interlayer spacing, and stability. As electrodes in these batteries, MXenes can accommodate lithium and aluminum ions, which improves their energy density, stability, and cycle life [4],[5]. Lithium-ion batteries are a cornerstone of modern energy storage technology, widely used in portable electronics, electric vehicles, and renewable energy storage systems. Traditional LIB anodes rely on graphite, which has a limited theoretical

capacity of around 372 mAh/g due to its low lithium intercalation potential. Hence the major focus is to introduce efficient cost-effective methods for the synthesis of new electrode materials, such as metal oxide, conducting polymer as supercapacitor electrode [6], carbon derivatives [7], carbon nanotubes [8], carbon aerogels [9], ruthenium dioxide, polypropylene, activated carbon and graphene etc.[10],[11]. These materials were expected to be efficient devices as an electrode in batteries and super capacitors but the results showed limited efficiency and output [12] due to many reasons such as activated carbon posed large surface area (up to $3000 \text{ m}^2 \text{ g}^{-1}$) [12] and various pores size distribution and control on the establishment of macro, meso and micro pores is limited [12]. Similarly, the carbon nanotube and graphene posed serious limitation due to graphene layers agglomerate easily which result in limited access of ions at the electrode area [13],[14].

To find the exceptional resolution for energy storage new electrode materials were synthesized and tested by researchers. In this effort the key focus was turning to 2D materials which poses excellent chemical and physical properties as compared to bulk counter parts [15]. This led to the introduction of different types of 2D material such as metal organic frame works (MoF) [16], black phosphorus (BP) [17] and polyoxometallates (POM) [18]. These materials proved better electrodes but still had limitations and obstacles such as poor specific capacitance, low electrical conductivity, small interlayer spacing, structural degradation, limited ion/electrons transport, surface oxidation and surface defects limited their use in energy storage [19],[20]

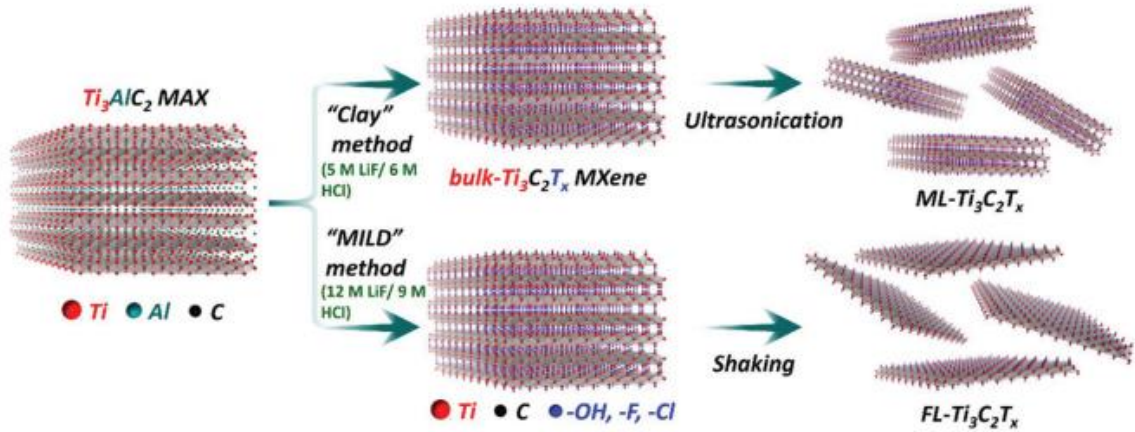


Figure 1. 1: Synthesis of MAX Phase and MXenes

The MXenes are assumed to be an important material in energy storage due to its 2D layered structure, high electrical conductivity, Lewis acidic properties, chemical durability, stress resistance and environmentally friendly features. Owing to wide chemical and structural varieties put the MXenes on top of all other 2D material in the field of energy storage [21]. However, bare MXenes did not show reasonable capacitance for Li ion intercalation as an anode in LIBs. Besides, the restacking of interlayers also pose serious problems when assembled as an electrode [22]. Furthermore, the MXenes solution has the ability to shape adhesive free electrodes with large capacity of up to 900 F m^{-3} at 2 mV s^{-1} [23][24]. Besides, the MXenes exhibited considerable capacitance (higher than 300 F cm^{-3}) in solutions containing large sized cation with significant capacitance. This suggests that the large ions can be inserted and removed between the layers of MXenes [25][26].

In addition, due to intriguing properties such as high conductivity and metallic nature, the MXenes possesses excellent surface plasmonic resonance (SPR) extending from infrared to ultraviolet region due to intra and inter band transition at the nanometer scale hence the MXenes can be the best material for the Surface Enhanced Raman Spectroscopy (SERS)

applications [27]. The SPR property also depends on its layered structure, transition metal atom, stacking order, large surface area and terminal functional groups [28]. Because of these factors the SPR can be altered by changing electronic structure, regulating film thickness, i.e. the thin film gives high surface plasmonic hence better SP intensity this was observed due to increase in the total cross section of the film [29]. Therefore, the film thickness is the key factor that provides the metallic character and reduces the fluorescence background [30]. The enhancement factor can also be tuned by surface functionalization and grouping with different substances [31]. For example, surface functionalization of 2D materials by gold nanorods for sensitive detection of organic pollutants, MXenes/metal composite materials, and selective ion doped MXenes materials were the common methods employed for the SERS applications [29].

1.2 Literature Review

To prepare the 2D layered ternary carbides and nitrides (MXenes) materials that evolved as promising material for various applications the researchers employed various techniques such as pressure less calcination of titanium, aluminum, and graphite-based carbides. But these techniques resulted in different stable intermediates and ternary phases such as Al_3Ti , TiC , AlTi , etc. [32]. Following this, to prepare the 2D MXenes materials researchers introduced gaseous halides in vacuum to etch the A atomic layer from MAX phase precursor but this technique showed serious limitations as it formed different structure (i.e. 3D instead of 2D) of these carbides and nitrides [33]. The first successful synthesis of 2D MXenes (Ti_3AlC_2) material was achieved by Naquib et al in 2011 by specific etching of an atomic layer using 48% hydro fluoric (HF) at room temperature for 2h from MAX phase precursors. The successful etching was verified from the XRD patterns before and after

etching of Ti_3AlC_2 as in Figure 1. 2. It is evident from the peak position after HF treatment the main peak shifted from 40 to around 10, indicating that Ti_3AlC_2 is replaced by $\text{Ti}_3\text{C}_2\text{Tx}$. Later on, a similar method was successfully applied to other MAX phases and yielded many new MXenes e.g., Ti_2CTx , Ti_3CNTx , $\text{V}_4\text{C}_3\text{Tx}$, $\text{Nb}_4\text{C}_3\text{Tx}$ etc. The overall chemical process starting from 3D MAX phase precursor to 2D MXenes (removal of Al) in aqueous F rich environment proposed in very first study is given below [34][35]



The reaction starts with removal of Al (1) and terminates (3) with different Tx terminals (OH and F or O sometimes). The resulting 2D materials (layers) were named MXenes with a structure similar to graphene. The surface of prepared layers is usually functionalized with anionic groups (Tx) such as oxygen (-O), hydroxyl (-OH) and fluorine (-F) etc. with different proportions [36] hence the overall chemical formula for MXenes is summarized as $(\text{M}_{n+1}\text{X}_n\text{Tx})$. Since the HF is highly carcinogenic and harmful to human and environment, Ghidui et al prepared the $\text{Ti}_3\text{C}_2\text{Tx}$ using safer mixture of HCl and LiF and soaked the MAX phases at 35 C for 24 h. following this alternative approach many protic

acids and salt combinations such as H_2SO_4 and LiF/NaF were employed and inferred similar results like previously obtained MXenes with fewer defects figure 1. 2b.

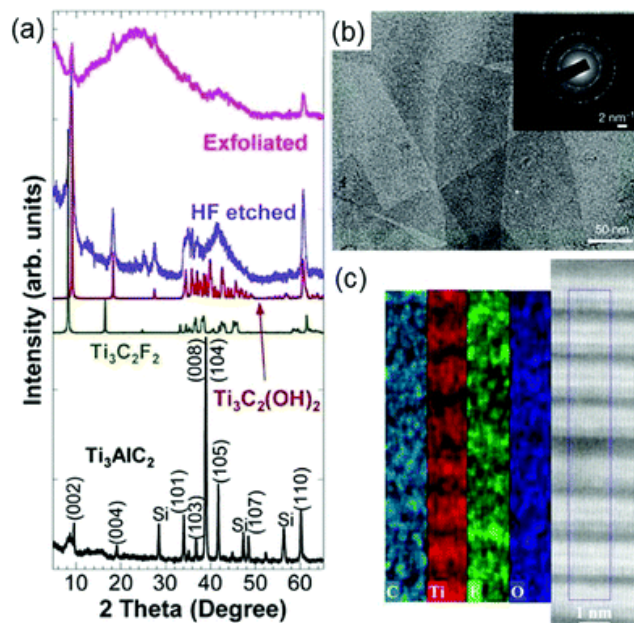


Figure 1. 2 (a) XRD Patterns for the MAX Phase and MXenes (b) TEM images of the synthesized MXenes (c) atomic arrangement in a lattice at HR-TEM

Likewise, Hilma et al. introduced the weakly acidic and environmentally friendly fluoride containing ammonium (NH_4HF_2) to synthesize the MXenes and observed no harmful gases as by-product [37]. As it is seen in STEM and EDX mapping shows the distribution of C, Ti, F and O and terminal $-\text{OH}$ groups. In addition, the c lattice parameter was also observed to have increased 25% than its precursor MAX phase Ti_3AlC_2 using HF etchant. Subsequently Feng et al studied the presence of surface functional groups make MXenes surface negative hence, cationic (NH_4^+) species are attracted and anchored on its surface consequently c lattice parameter is enhanced [37]. It is significant to observe the etching process based on several factors e.g., type of metal and number of atoms. For example, the higher atomic number transition metals and high “n” number (M_4AX_3) needs aggressive

etching, more etching time and higher concentration of acids than M_3AX_2 [38] it also affects in flake quality, crystallinity, defects, thickness and functionalization of terminating groups. The other factors affecting etching include the use of F based salts such as (LiF, NaF HCl and NH_4HF_2) used in different ratios and F ion concentrations which gives different flake quality, crystallinity and many other properties Furthermore less acidic etchants require higher temperature [39]. Besides MAX the other non-MAX phase such as Mo_2Ga_2C and $M_n[Al(Si)]_4$ precursors were used to synthesize the MXenes (Mo_2CT_x) Zr_3C_2Tx and Hf_3C_2Tx) this suggest that the scope of MXenes precursors could be further extended to other atom based carbides and nitrides [40].

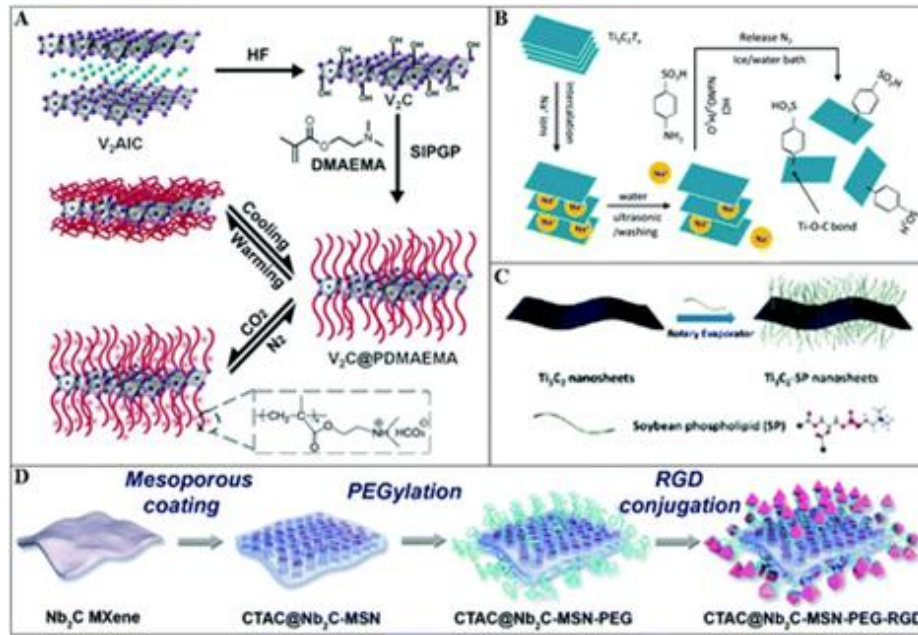


Figure 1. 3: (a) Surface Modification of as synthesized V2CTx MXenes (b) Intercalation of MXenes (c) Modification of surface by nanotubes (d) Intercalation of MXenes

1.3 Surface Modification

The Tx terminal atoms greatly affect physio-chemical properties of resulted MXenes [41] with greater thermodynamic stability compared to pristine counterparts[42],[43]. Nevertheless, the stable and uniform functionalization of these terminating groups is not yet achieved in both theoretical and practical research but from theoretical studies it has been proved that stability surges from $-OH$ to $-F$ to $-O$ respectively [44],[45]. Practically the stability order for termination group was found to be as $-F > -O > -OH$ [46]. Besides, stability also depends on type of MAX phase, method of preparation, particle size, intercalating agent, etching solution, temperature and time conditions are also contributing [47]. Therefore, surface modification and functionalization are necessary for endowing new applications. Xu and Gogotsi also modified the surface chemistry of HF-etched Ti_3C_2Tx with TiO_2 nanorods and SnO_2 nanowires utilizing tetrahydrofuran (THF). The hybrid MXenes showed excellent chemistry in batteries and supercapacitors with capacitance of 250 mAh g^{-1} than bare Ti_3C_2Tx [48]. In another attempt the surface modification was successfully achieved by robust strategy i.e., by grafting the poly(2-(dimethylamino) ethylmethacrylate) (PDMAEMA) brushed on MXenes by SINGP brushes at OH- group [48]. The surface modified MXenes such as $V_2C@PDMAEMA$ were investigated for CO_2 sensing. As in figure 1. 3 [49].

Owing to significant applications of Aryl diazonium ions e.g., making covalent bonds at surface of various substrates Zhang et al observed that Aryl diazonium salts can covalently bond to MXenes surface in the shape of Ti-O-C bonds this also caused the increase in inter layer spacing which resulted in enhanced supercapacitance performance [49]. In order to enhance the hydrophilicity, the MXenes were immobilized with Soybean phospholipids

for surface modification, this resulted in improved permeability, steady circulation, and retention ability.

1.4 Intercalation

Since the synthesized MXenes are multilayered, to make single layered MXenes the mechanical delamination (less efficient) and chemical intercalation (most efficient) methods are used to yield monolayers. The multilayer MXenes can house several ions and molecules in between the layers due to its large surface area. Besides, the interlayer distance in the MXenes influences many applications e.g., electrochemical performance, optical and mechanical properties [50]. Intercalation of MXenes represents a pivotal strategy in tailoring their properties for various applications, particularly in energy storage devices such as batteries.

Several intercalants have been reported in the literature for MXenes, each offering unique advantages and effects on material properties. The interlayer distance can be tuned by using various types of intercalating agents such as organic molecules, DMSO, isopropyl alcohol, isoprpopylamine, NH_4HF_2 , tertabutyl ammonium hydroxide (TBAOH), tetramethyl ammonium hydroxide (TMAOH), aryl diazonium salts and hydrazine monohydrate $\text{N}_2\text{H}_4\text{H}_2\text{O}$ (HM) dissolved in DMF are proved to be best organic molecules, polymers, and inorganic species. For instance, molecules such as dimethyl sulfoxide (DMSO), urea, and various alkali metal ions have been utilized to intercalate MXenes, enabling control over interlayer spacing and enhancing properties such as capacitance and conductivity. Polymers such as polyethylene glycol (PEG) and polyvinyl alcohol (PVA) have also been

employed as intercalants, imparting mechanical stability, and facilitating electrolyte infiltration in MXene-based electrodes.

In the context of battery applications, the choice of intercalant is crucial for optimizing electrochemical performance. The graphene and its derivatives emerge as promising candidates for enhancing MXene performance in batteries. Graphene possesses excellent electrical conductivity, mechanical strength, and chemical stability, making it an ideal intercalant for improving charge transport kinetics and structural integrity of MXene electrodes. Moreover, graphene-based intercalation preserves the inherent 2D structure of MXenes while providing additional pathways for ion diffusion, thereby enhancing battery efficiency and cyclability. (In batteries and supercapacitors as an electrode material) intercalating agent resulting in an interlayer space ranging from 4.2 to 14.4 Å [51],[52],[53].

1.5 Surface Enhanced Raman Scattering

Exploring new types of two-dimensional (2D) nanomaterials and their role as effective substrates for surface-enhanced Raman scattering (SERS) based monitoring of organic traces have recently attracted great attention. A SERS-based sensing approach has been proven to be a state-of-the-art, non-destructive, and optically driven tool that exhibits a fast response time, high sensitivity, reproducibility, and convenient sample handling procedure [54], [55]. One of the most studied 2D materials is graphene, and that is due to its surface plasmonic resonance (SPR), along with its excellent mechanical and electrical properties [56]. However, SPR response by graphene was found limited to the infrared and terahertz (THz) regions [57], thus restricting the electromagnetically modified enhancement within

the visible region [58]. Such a challenge is often overcome through chemical treatments by *in-situ* and *ex-situ* hybridization processes [59]. Recently, MXene has been introduced as a promising 2D nanomaterial for SERS applications. These are the ceramics comprising one of the large families of 2D materials prepared from bulk crystals known as MAX, generally represented as $M_{n+1}AX_n$, where M is an early transition metal, A is aluminum or gallium, and X is C, N, or B atoms [60]. The MXenes are prepared by removing the “A” from the MAX through various techniques leading to $M_{n+1}X_nT_x$, where the “T” is the heterogeneous terminal (OH, F, O) with x number [61]. MXenes potential edge over graphene could be explained on basis of its fluorescence quenching ability, biocompatibility, and long-range spectral stability [62]. Due to their flatness and large surface area, they exhibit better photo-induced charge transfer (CT) resonance, excellent plasmonic resonance effect, and strong interaction of surface atoms with adsorbate molecules. The tunability of the chemical and physical properties of MXene renders it a promising candidate for hybridization using nanoparticles, thus enabling MXene to further enhance the electronic and optical competitive edge [63]. A few reports have been published on the hybridization of nanoparticles with MXenes and used in various applications, i.e., for energy storage in supercapacitors and lithium-ion batteries [64], [65], perovskite solar cells for improved PCE [66], photochemical water splitting [67], catalyzing oxygen reduction reactions [68], electrochemical detection of organic pollutants [69] and, which is the aim interest in this work, highly sensitive SERS sensing [70]. The hybridization of nanoparticles has exhibited a notable SERS effect due to increased surface-to-volume ratio, excellent plasmonic properties, and surface control [71], [72], [73]. In addition, the delocalized *d*-electrons and surface roughness would selectively

enhance electromagnetic radiation at selective excitation[70]. Considering the aforementioned aspects, MXene-based materials could be effectively employed to fabricate SERS substrates. In recent reports, a few MXenes, such as Ti_3C_2 , Ti_2N , Nb_2C , and Ta_2C , have been reported for possible SERS detection, yet the stability of metals into their respective oxides somehow lowered their progressive advances [74], [75], [76]. The remarkable SERS response in the few MXenes reported is attributed to several reasons, such as metal doping, tunable morphology, multi-coordination cationic sites, and the high oxidation state. These factors enable a rapid CT across the MXene surface, facilitating the interaction between surface atoms and analyte molecules and hence providing an enhanced SPR effect [77], [78], [79].

1.6 Energy Storage

Energy storage is the backbone of the energy sector after renewable energy technology. The fast growth of electric vehicles, electronic devices, and electrical infrastructure has hastened the development of safe and cost-effective energy storage/conversion devices. The growing demand for safe and cost-effective energy storage devices is the driving force for efforts on different battery technologies. Conventional Li-ion batteries have revolutionized energy storage technology and have been used as a major power source in portable electronics and even in electric vehicles. It has been proven to be a key energy storage device in the preceding decade with several shortcomings, such as, safety, higher price, and limited reserves [80], [81]. In recent time Aluminum-ion batteries (AIBs) are getting significant attention due to their lower cost (as Aluminum, as the 7th most abundant element), and environmental safety. Additionally, AIB has extraordinary theoretical volumetric capacity of 8046 mAh/cm^3 , which is even higher than that of Li, driven by its

three-electron redox process [82], [83], [84]. Over the past two decades, significant efforts have been directed towards the fabrication of AIBs using various cathode materials with the aim of enhancing performance, enabling fast charging, and improving energy density. Nonetheless, the development of AIBs operating at room temperature remained elusive until the utilization of chloroaluminate-based ionic liquid electrolytes (ILE) [85]. Cells prepared with ILEs demonstrated superior efficiency, capacity, and cyclic and high voltage stability [86]. Moreover, working with ILEs provides the benefit of wide electrochemical windows, good electrical conductivity, and thermal stability, rendering them ideal candidates for AIBs [86], [87], [88]. These attributes make ILEs well-suited to address the challenges associated with traditional electrolytes to move forward with the advancement of AIB technology. Recent research has demonstrated that molten ILE, such as, 1-butyl 3-methylimidazolium chloride ([BMIm]Cl), offer significant improvements in AIB [89]. The presence of chloroaluminate anions $[Al_xCl_y]_n^-$ (including $AlCl_4^-$, $Al_2Cl_7^-$, and $Al_3Cl_{10}^-$) plays a crucial role in the charge transfer process [86]. During the intercalation and de-intercalation of these complex anions cause structural deformities and lattice distortions within the cathode material due to the large effective radius of these anions [90], [91]. Consequently, these structural distortions lead to irreversibility and rapid capacity decay. This emphasizes a significant challenge that must be addressed in the development of AIBs to achieve long-term stability and improved performance. Thus, a cathode material with a larger interlayer space to accommodate these complex ions is required which would subsequently overcome the storage and lattice distortion challenges [92], [93]. To address these challenges multi-layered structures, such as, iron chalcogenides hybrid cathodes ($FeS_2@C$ [94], CuS [95], $NiCo_2S_4$ [96], and MoS_2/C [97]) were fabricated, because the

metal sulfur polar bond facilitated formation of the Al-Cl bond, and the less electronegative sulfur reduces the electrostatic interactions during the charge/discharge process [94], [95], [96], [97], [98], [99], [100], [101]. Likewise, Jiao *et al.* reported the Ni_3S_2 /graphene composite cathode, the initial capacity of the composite cathode was 300 mAh/g at 100 mA/g current density. Regardless of these efforts, the capacity decayed to 60 mAh/g after 100 cycles [102]. The abrupt drop in capacity observed due to cathodic degradation, lattice distortion, and strong coulombic ion-lattice contact inhibiting ion diffusion through the lattice [103]. Subsequently, it is essential to build an appropriate cathode with weak coulombic contact and a sturdy framework capable of housing the intercalated complex ions without considerable structural change following the GCD process. The research on batteries is going along to miniaturization of electronics, increasing energy density, reducing footprint, and reducing the charging time. Surprisingly, the MXenes were found as wonder material in the field of energy storage especially as a leading material in this field other than Li-ion batteries [104]. MXenes, which is known for its inspiring electrochemical properties, wide interlayer space, high conductivity, high surface area, and tunable surface chemistry, shows potential as an efficient cathode material in AIBs [105]. Among the various MXenes tried Niobium MXene (Nb_2CT_x) has better thermodynamic, and kinetic and oxidative stability due to better discharge voltage plateau compared to that of Ti and V-based MXenes, additionally, it also has a healthier theoretical capacity [106]. Furthermore, the highly conductive nature of the Nb_2CT_x and the pseudo-capacitive behavior of the MoS_2 are exploited to improve electrochemical kinetics, enabling rapid charge-discharge rates and high-power density [97]

The emergence of MXenes as a rising alternative in addressing the challenges faced in Surface-Enhanced Raman Spectroscopy (SERS) and energy storage technologies stems from their unique combination of properties and superiority over other 2D materials. MXenes, with their high electrical conductivity, large surface area, tunable surface chemistry, and mechanical stability, offer distinct advantages that make them well-suited for overcoming the limitations observed in traditional materials.

In the realm of SERS, MXenes exhibit exceptional potential due to their ability to enhance Raman signals with high sensitivity and reproducibility. By addressing the challenges of background interference, signal instability, and limited sensitivity faced in conventional SERS substrates, MXenes paves the way for more reliable and precise molecular detection and analysis. Their large surface area and tunable surface chemistry enable efficient adsorption of analyte molecules, while their mechanical stability ensures long-term performance in harsh chemical or biological environments.

Similarly, in energy storage technologies, MXenes have shown promise as efficient materials for various applications, including batteries, supercapacitors, and electrocatalysts. With their high capacity, excellent rate capability, and long-term cyclability, MXenes offers significant improvements over conventional electrode materials. Their ability to accommodate reversible ion intercalation/deintercalation processes, combined with their high electrical conductivity and mechanical stability, enhances charge storage and transport efficiency in energy storage devices.

The present dissertation work focuses on modifying the surface of MXenes and employing them as efficient materials for both SERS and energy storage applications. The execution of this work is supported by the following key steps:

1. **Surface Modification:** The surface chemistry of MXenes is modified to enhance their interaction with analyte molecules in SERS applications and to optimize their electrochemical performance in energy storage devices. Various surface functionalization and doping strategies are explored to tailor the properties of MXenes for specific applications.
2. **SERS Characterization:** The modified MXene materials are characterized using SERS techniques to evaluate their performance as substrates for molecular detection and analysis. The sensitivity, reproducibility, and stability of the MXene-based SERS substrates are assessed, and comparisons are made with conventional substrates.
3. **Energy Storage Evaluation:** The electrochemical performance of the modified MXenes is evaluated in energy storage devices, including batteries and supercapacitors. Key parameters such as capacity, cycling stability, and rate capability are measured to assess the suitability of MXenes for various energy storage applications.
4. **Optimization and Application:** The insights gained from the characterization and evaluation of modified MXenes are used to optimize their properties and performance for specific SERS and energy storage applications. The potential

applications of MXenes in fields such as environmental monitoring, biomedical diagnostics, and renewable energy are explored.

Overall, the present dissertation work aims to demonstrate the effectiveness of MXenes as versatile and efficient materials for addressing the challenges in SERS and energy storage technologies. Through systematic surface modification and characterization, MXenes offers promising solutions for advancing molecular detection, energy storage, and other related fields, paving the way towards more sustainable and technologically advanced solutions.

1.7 Objectives

The main objective of our work is to synthesize 2D MXenes based conductive surfaces and explore their application for spectroscopic trace detection and as an electrode for Aluminum ion/capacitors in coin cell assembly. Based on this, the detailed objectives of our proposed work are given below.

1. To develop a cost-effective approach to synthesize 2D metal carbides and nitrides (MXenes).
2. To carry out morphological and optoelectronic characterization of the prepared 2D MXenes by relevant techniques.
3. To fabricate MXenes based electrodes and evaluate their applications for energy storage devices.

4. To assess the optical properties of the MXenes-based surfaces by evaluating their use as efficient SERS substrates.

2 CHAPTER

Synthesis of vanadium carbide MXene with improved inter-layer spacing for SERS-based quantification of anti-cancer drugs

Taken from Mahar, Nasurullah, Amir Al-Ahmed, and Abdulaziz A. Al-Saadi. "Synthesis of vanadium carbide MXene with improved inter-layer spacing for SERS-based quantification of anti-cancer drugs." *Applied Surface Science* 607 (2023): 155034.

2.1 Introduction

Exploring new types of two-dimensional (2D) nanomaterials and their role as effective substrates for surface-enhanced Raman scattering (SERS) based monitoring of organic traces have recently attracted great attention. A SERS-based sensing approach has been proven to be a state-of-the-art, non-destructive, and optically driven tool that exhibits a fast response time, high sensitivity, reproducibility, and convenient sample handling procedure [54], [55]. One of the most studied 2D materials is graphene, and that is due to its surface plasmonic resonance (SPR), along with its excellent mechanical and electrical properties [56]. However, SPR response by graphene was found limited to the infrared and terahertz (THz) regions [57], thus restricting the electromagnetically modified enhancement within the visible region [58]. Such a challenge is often overcome through chemical treatments by *in-situ* and *ex-situ* hybridization processes [59]. Recently, MXenes have been introduced as promising 2D nanomaterials for SERS applications. These are the ceramics comprising one of the large families of 2D materials prepared from bulk crystals known as MAX,

generally represented as $M_{n+1}AX_n$, where M is an early transition metal, A is aluminum or gallium, and X is C, N, or B atoms [60]. The MXenes are prepared by removing the “A” from the MAX through various techniques leading to $M_{n+1}X_nT_x$, where the “T” is the heterogeneous terminal (OH, F, O) with x number [61]. MXene’s potential edge over graphene could be explained on basis of its fluorescence quenching ability, biocompatibility, and long-range spectral stability [62]. Due to their flatness and large surface area, they exhibit better photo-induced charge transfer (CT) resonance, excellent plasmonic resonance effect, and strong interaction of surface atoms with adsorbate molecules. The tunability of the chemical and physical properties of MXene renders it a promising candidate for hybridization using nanoparticles, thus enabling MXene to further enhance the electronic and optical competitive edge [63]. A few reports have been published on the hybridization of nanoparticles with MXenes and used in various applications, i.e., for energy storage in supercapacitors and lithium-ion batteries [64], [65], perovskite solar cells for improved PCE [66], photochemical water splitting [67], catalyzing oxygen reduction reactions [68], electrochemical detection of organic pollutants [69] and, which is the aim interest in this work, highly sensitive SERS sensing [70]. The hybridization of nanoparticles has exhibited a notable SERS effect due to increased surface-to-volume ratio, excellent plasmonic properties, and surface control [71], [72], [73]. In addition, the delocalized *d*-electrons and surface roughness would selectively enhance electromagnetic radiation at selective excitation [70]. Considering the aforementioned aspects, MXene-based materials could be effectively employed to fabricate SERS substrates. In recent reports, a few MXenes, such as Ti_3C_2 , Ti_2N , Nb_2C , and Ta_2C , have been reported for possible SERS detection, yet the stability of metals into

their respective oxides somehow lowered their progressive advances [74], [75], [76]. The remarkable SERS response in the few MXenes reported is attributed to several reasons, such as metal doping, tunable morphology, multi-coordination cationic sites, and the high oxidation state. These factors enable a rapid CT across the MXene surface, facilitating the interaction between surface atoms and analyte molecules and hence providing an enhanced SPR effect [77], [78], [79].

In this work, a vanadium-based MXene of the formula V_2CT_x was prepared, exfoliated, and modified with AgNPs. The synthesized hybrid AgNPs@ V_2CT_x was loaded on filter paper and successfully used as a SERS substrate for the trace detection of Gemcitabine (GMC). GMC is an important medication that is commonly used for the diagnosis of different types of cancer [107]. As an anti-cancer prodrug, it is activated by intracellular phosphorylation generating di- and tri-phosphate-based derivatives that inhibit the DNA synthesis and ribonucleotide reductase activity, resulting in the death of tumor cells [108], [109][110]. Exploring the potential of vanadium-based Ag-NP-loaded MXene materials in the SERS modality to detect low GMC concentrations can bring feasible alternatives toward quick monitoring of the drug in the human body.

It is important to point out that the intercalation procedure also influences the properties of MXenes [60]. The intercalants cleave the multilayered MXenes and convert them into few-layered 2D flakes with increased interlayer spacing [111]. Several reagents can be used as effective intercalants, including tetrabutylammonium, tetrabutylammonium hydroxide, hydrazine hydrate, urea, DMSO, and water [112]. Depending on the type of intercalants, flakes of different sizes and properties are obtained. For instance, Y. Gogotsi and co-workers recently explored the effect of tetrabutylammonium and tetramethylammonium

hydroxide-based, TBAOH and TMAOH respectively, intercalation on the V_2CT_x -based MXenes [113]. Such large-size intercalants resulted in some defect formation in flakes, early oxidation, low zeta potential, and increased band gap [114]. Likewise, the small-sized intercalants, such as metal ions, lead to the flocculation, crumpling, and restacking of MXenes flakes [115]. Therefore, to achieve the best performance and average-sized flakes with improved d-spacing, we have introduced the medium-sized triethylamine (TEA) as an intercalant with hydrated radius of 3.67 Å. The produced flakes were characterized by a larger size of $d_{(002)}$ -spacing of 8.13 Å and better zeta potential of -49.4 mV compared to counterpart reagents reported previously [113].

2.2 Experimental

2.2.1 Reagents

Vanadium pentoxide (V_2O_5 , 99.9%), silver nitrate ($AgNO_3$, 99.8%) hydrofluoric acid (HF, 48-54%), dimethyl sulfoxide (DMSO, A.R), and n-hexane (C_6H_{14} , A.R) were purchased from Sigma Aldrich. Graphite (99.8%), sodium citrate ($C_6H_5Na_3O_7 \cdot 2H_2O$, >99%), citric acid (99 %), and sodium borohydride ($NaBH_4$, 98.9 %) were obtained from Alfa Aesar. Aluminum powder (260 μm >90%) and Cytiva WhatmanTM Nylon membrane (47 mm with pore size 0.45 μm) were purchased from Fisher Scientific. Gemcitabine hydrochloride (99.8%) was purchased from Ambeed Pharmaceuticals USA. All the chemicals were used without further modification. De-ionized water was used for all required solution preparation.

2.2.2 Characterization methods

The X-ray diffraction (XRD) pattern was recorded using an Ultima IV multipurpose X-ray diffraction instrument. UV-visible absorption spectra were measured in a dispersed state in water on Agilent Cary 60. Surface morphology was studied by FE-SEM and EDS using JEM-2100 F Field Emission Microscope (Model: JEOL-USA) at 200 KV speeding up voltage. Transmission and high-resolution TEM (HR-TEM) were recorded on Tecnai G2 20 S-TWIN, D 2012. The Raman spectra was collected on a HORIBA Scientific LabRAM HR microscope equipped with an internal He-Ne 17 mW red laser at 633 nm excitation wavelength. Raman parameters of 25% laser power, 20 sec. acquisition time, 4 times accumulation and 50x objective lens were used.

2.2.3 Synthesis of silver nanoparticles (AgNPs)

The silver nanoparticles (AgNPs) were prepared by the reduction method following our previously reported work [116], [117]. The 0.1 ml of (0.10M) AgNO_3 solution was added into a round bottom flask along with 3.4 mL of (0.17M) sodium citrate, followed by the addition of 0.6 mL of (0.17 M) citric acid as a capping agent. The mixture was kept at room temperature for 3 min., and then 0.2 mL (0.5 mM) of freshly prepared NaBH_4 was added dropwise under constant stirring and allowed to stand for 5 min. The mixture was then boiled to 100 °C for 20 minutes and cooled on an ice bath to control the uniform size distribution of the formed AgNPs.

2.2.4 MAX Phase and nanolayered MXenes Sheets

The V_2AlC ternary carbide MAX phase was synthesized following the reported literature [113] with some modifications. The process was initiated by mixing commercially available powders of aluminum (Al, 200 mesh), vanadium (V, 300 mesh), and graphite (C, 200 mesh) in a 2:1:1 molar ratio. The powder was finely ground to 100 mesh size using a dual mixer/mill (SPEX Sample Prep. 8000 D). The finely ground mixture was transferred into an alumina heating boat and annealed at 1450 °C under Argon flow in the tubular furnace (Carbolyte STF 15/450) for 4 hours with a heating ramp of 10 °C min⁻¹ and then cooled down to room temperature. The aluminum contents were kept a little higher to avoid loss due to its low melting point (660 °C). The mixture was then washed to remove impurities with 10 M H_3PO_4 for 8 hours at 90 °C followed by redistribution in distilled water and sonicated for 5 min. The resultant solution was to settle down overnight at room temperature and collected for further study.

2.2.5 Synthesis of V_2CT_x MXene

MXenes are hexagonally shaped ($P6_3/mmc$ symmetry) 2D-layered materials with general representation $M_{n+1}X_nT_x$, where M is the transition metal, X is C and/or N, and T_x is the terminal groups (-OH, -O, and F), while $n = 1, 2$ or 3 [61]. The V_2CT_x MXenes were obtained using a reported method [113] after slight modification. A mixture of hydrofluoric acid (48%) and hydrochloric acid (12 M) was used as an etchant, and triethylamine (TEA) was used as an intercalant to intercalate the MXene flakes. V_2AlC MAX phase was gradually mixed with 20 mL of mixture (12 mL HF and 8 mL HCl) solution in an ice bath for 10 min (to avoid exothermic reaction) with constant stirring at 200 rpm, subsequently,

the bottle was transferred to an oil bath to initiate the itching at 50 °C temperature at 400 rpm for 48 hours in a Teflon jar covered with a loosely bound lid in the fume hood. The product was washed and centrifuged multiple times (3500 rpm, 5 min/cycle) with distilled water and ethanol alternatively, the first supernatant was decanted as waste to remove the salts, dissolved residual metals, and the nanosized MAX phase. The sedimented multilayer MXenes were repeatedly washed until the pH of the solution became neutral. The obtained product was filtered using Cytiva Whatman™ Nylon membrane (47 mm with pore size 0.45 μm) with nearly 50-55% yield. The filtrate was dispersed into 10% TEA solution (1 g/20 mL) at room temperature and kept under stirring for 6 hours.

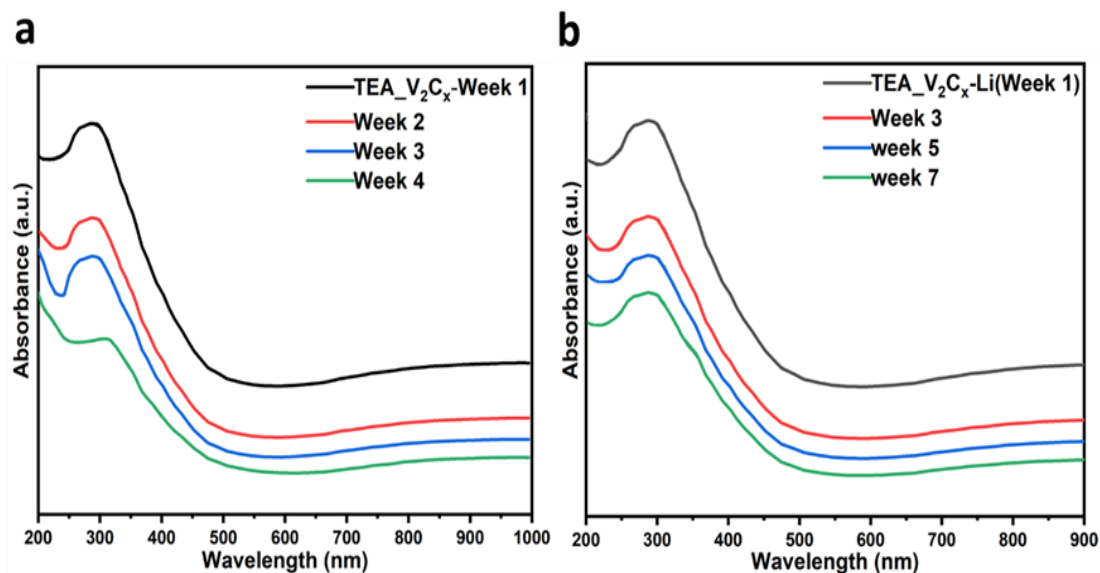


Figure 2. 1: (a) The UV-Vis. Spectra of TEA intercalated V₂CT_x MXenes showing stability for 4 weeks, (b) The UV-Vis. Spectra of SERS spectra of V₂CT_x MXenes after ion exchange depicting stability for 7 weeks

The intercalated V₂CT_x MXenes powder was centrifuged at 2500 rpm for 5 min., followed by sonication in water: ethanol (1:1) washing solution, the supernatant was collected each time until the supernatant turned transparent. The stability of the MXenes was checked at

different time intervals using a UV-Visible spectrophotometer (Fig 2.1 a) shows the 4-week stability without ion exchange while (Fig. 2.1 b) shows the 7-week long stability after processing the ion exchange process with cold 0.01M LiCl solution.

2.2.6 SERS active substrate

The SERS substrate was fabricated following previously reported methods (Figure 2.2) [118], [119]. The film was prepared by spin-casting the diluted aqueous solution ($50 \mu\text{g mL}^{-1}$) of V_2CT_x colloidal delaminated flakes on filter paper (WhatmanTM 20). The film thickness was adjusted to $\sim 15 \mu\text{m}$ by multiple spin-cast runs and vacuum dried at 60°C . The paper-supported V_2CT_x has demonstrated good metallic characteristics as reported previously [113]. AgNPs were self-assembled in a petri dish [120], [121] by using an n-hexane/water interface. It was followed by the slow addition of ethanol to extract the NPs from the solution and redistribute them at the n-hexane/water interface. Then the MXene-coated filter paper was immersed in the petri dish to disperse the AgNPs on the MXene surface. Finally, the filter paper was dried under a vacuum at room temperature.

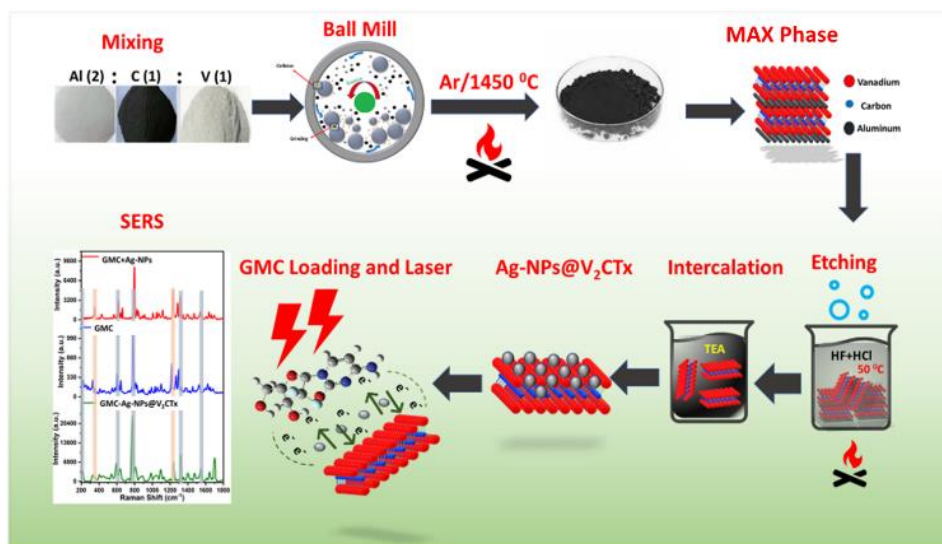


Figure 2. 2: Schematic representation of the synthesis of AgNPs@V₂CT_x hybrid SERS substrate MAX phase, followed by loading of GMC drug for SERS study

2.3 Results & Discussion

2.3.1 Properties of the synthesized MAX phase, V₂CT_x, and AgNPs-loaded V₂CT_x MXene:

To assess the morphology, lattice parameters, and optical properties of the precursor, TEA-intercalated V₂CT_x MXenes and AgNPs-loaded V₂CT_x hybrid materials, the delaminated products were investigated by XRD, UV-Vis, AFM, FE-SEM, TEM, Raman, and FT-IR techniques. The diffraction analysis (Fig. 2.5 a) shows XRD patterns for the precursor V₂AlC MAX phase and the as-prepared delaminated V₂CT_x MXene. The two prominent peaks that exist at 17.75° and 41.91° are associated with the precursor MAX phase as per JCPDS No. 29-101. In the case of V₂CT_x (black line), a new intense peak appeared at 8.87° corresponding to the (002) plane with a d-spacing of 8.13 Å. The decrease in the intensity of the peaks around 17.75° and 41.92° along with the waning of remaining residual peaks (non-basal peak 65.4°) suggests the successful removal of Al layers and the

full delamination of V_2AlC to a few-layered V_2CT_x sheet. These observations are in good agreement with the previously reported in the literature [33,42–44].

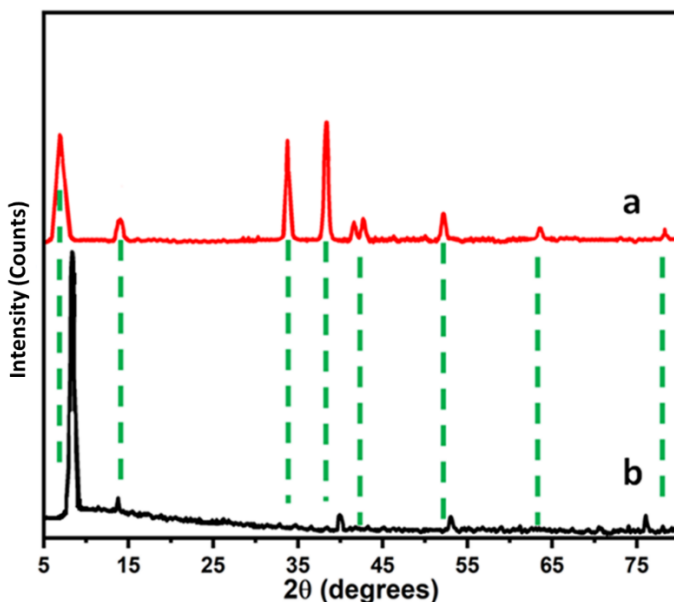


Figure 2. 3: (a) XRD pattern of the AgNPs loaded V_2CT_x (b) XRD patterns for the V_2CT_x .

The XRD spectra of the as-prepared MXenes and after being loaded with AgNPs as depicted in (Fig. 2.3 a, b) posture the variation in the XRD patterns along with new intense peaks corresponding to (111), (200), (220), and (311) phases of AgNPs, further confirming the successful mobilization of the silver nanoparticles.

The optical properties of the synthesized colloidal V_2CT_x MXenes, AgNPs, and GMC-loaded AgNPs@ V_2CT_x MXenes were compared using UV-Visible spectroscopy (Fig. 2.5 b). The UV-Vis absorption band at 280 nm pertaining to V_2CT_x may have resulted due to the localized surface plasmon, interband transition (IBT), or transversal mode [33,45] with a small plateau below 280 nm, indicating the formation of a stable V_2CT_x MXene phase with no sign of early oxidation [33]. The V_2CT_x spectra (green line) after loading with AgNPs and having the GMC drug molecules physisorbed on the surface show changes in

the two main bands at 270 nm and at 410 nm along with some band broadening. Both bands showed a decrease in intensity accompanied by a blue shift to 452 nm describing the surface plasmonic resonance, as compared to pure V₂CTx.

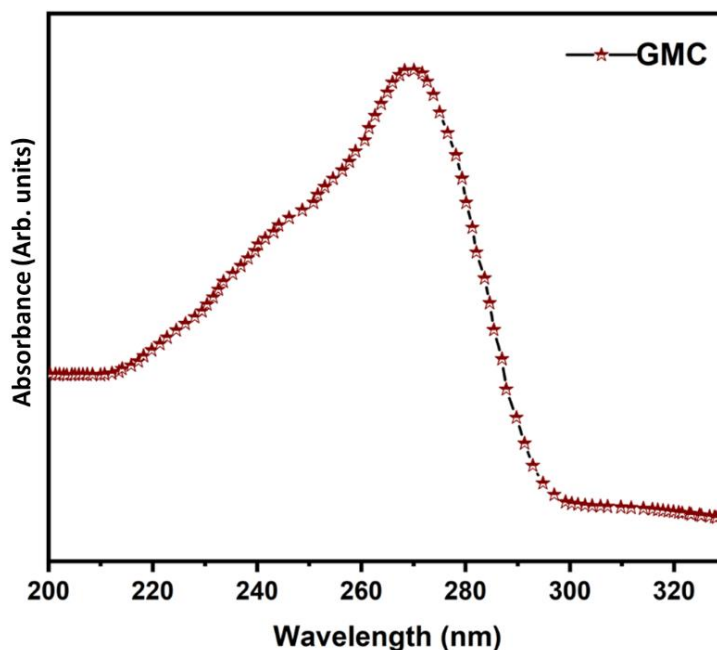


Figure 2. 4: UV/Vis Spectra of Free GMC drug

Likewise, the free GMC molecules exhibited a characteristic UV-Vis band at 268 nm (Fig. 2.4), however after being associated with AgNPs@V₂CTx a minor change, such as a band broadening with a slight shift to 270 nm (Fig. 2.5 b), could be observed. This could be due to the strong interaction between the drug adsorbate molecules and the surface of the AgNPs@V₂CTx hybrid SERS substrate.

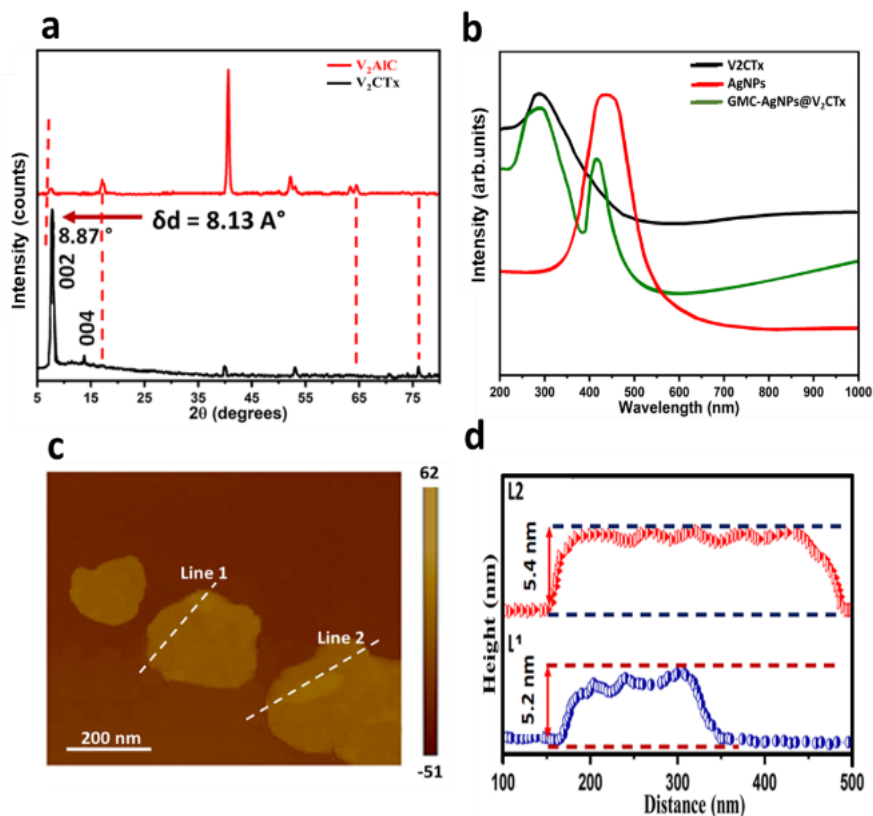


Figure 2. 5: (a) XRD spectra of V₂CTx MXenes (black) and V₂AlC MAX phase (red). (b) UV-Visible absorption spectra of V₂CTx (black), pure AgNPs (red), and GMC-AgNPs@V₂CTx (green). (c) AFM image of the synthesized V₂CTx flakes. (d) Height profile of the dashed lines for the MXenes flakes.

Nevertheless, it seems that the drug molecules did not affect the chemistry of the V₂CTx as a result of the physisorption interaction. The blue shift and decreased intensity of the band at 410 nm could be attributed to the interaction of the silver nanoparticles with GMC molecules. This phenomenon is the prime motivation for using AgNPs-loaded hybrid material as SERS active substrates [46]. The band broadened along with a plateau observed below 270 nm and the blue shift associated with a drop in intensity at 410 nm gesture the successful charges-transfer and electromagnetically facilitated interaction between as developed hybrid material and drug molecules. The AFM image of the as-prepared V₂CTx

MXenes (Fig. 2.5 c) was taken by drop-casting on Si substrate. Moreover, (Fig. 2.5 d) depicts the few-layered flakes with a thickness of ~ 5 -5.5 nm.

To illustrate the morphology and chemical structure of the prepared V_2CT_x further, the FE-SEM and TEM analyses were also carried out, and the results are presented in (Fig. 2.8). The SEM images of the delaminated V_2CT_x were collected at different resolutions and positions. While they depict stacked and delaminated V_2CT_x flakes, the recorded morphogram showed a typical accordion-like and few-layered structure of V_2CT_x thus validating the successful etching performed.

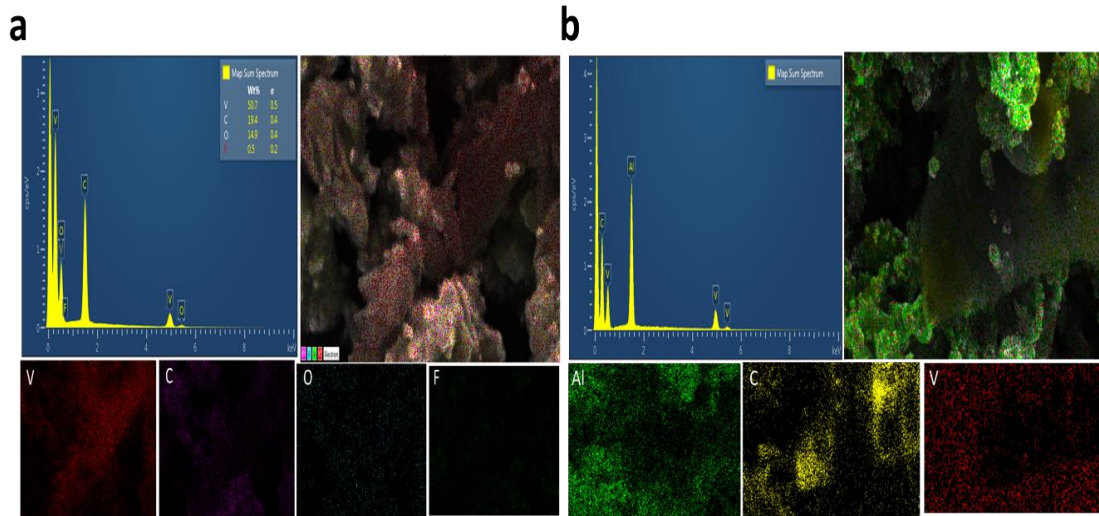


Figure 2. 6: (a) EDS and elemental mapping of synthesized V_2CT_x (b) EDS and elemental mapping of V_2AlC MAX phase

The chemical contents of the as-synthesized MXenes before and after etching were analyzed with energy dispersive spectroscopy (EDS) as shown in (Fig. 2.6 a,b). The spectra revealed the presence of vanadium and carbon along with traces of fluorine and oxygen as terminal groups, as compared to the precursor where the Al along with V and C elements are predominant, hinting to the successful etching of the MAX phase into MXenes.

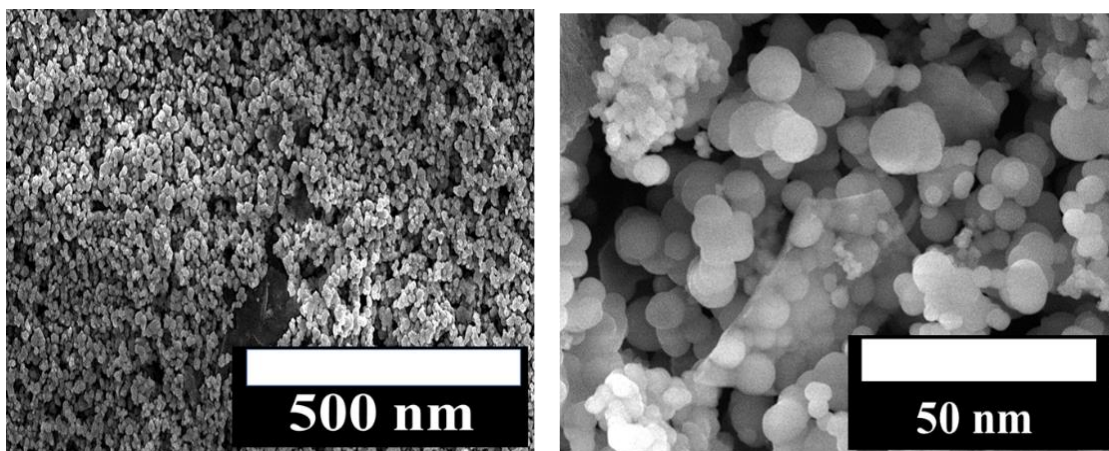


Figure 2. 7: (a) SEM Images of MXene loaded Ag-NPs on the paper. (b) SEM images of AgNPs loaded on V₂CTx.

Additionally, the SEM image in (Fig. 2.7 a) shows the self-assembled silver nanoparticle loaded on V₂CTx. The round-shaped AgNPs were evenly distributed on the surface of the MXene with a particle size distribution of 10-50 nm, as presented in (Fig. 2.7 b). The size variation could be due to polydispersity and/or anisotropy [47–49]. The microstructure and composition of the V₂CTx were further studied using the TEM technique (Fig. 2.8c). The 2D transparent stacked flakes could be observed with some V-C-V layers, while the high-resolution TEM image (Fig. 2.8d) shows the lattice fringes with d-spacing of 1.13 nm and 1.07 nm, in very good agreement with the XRD findings [35].

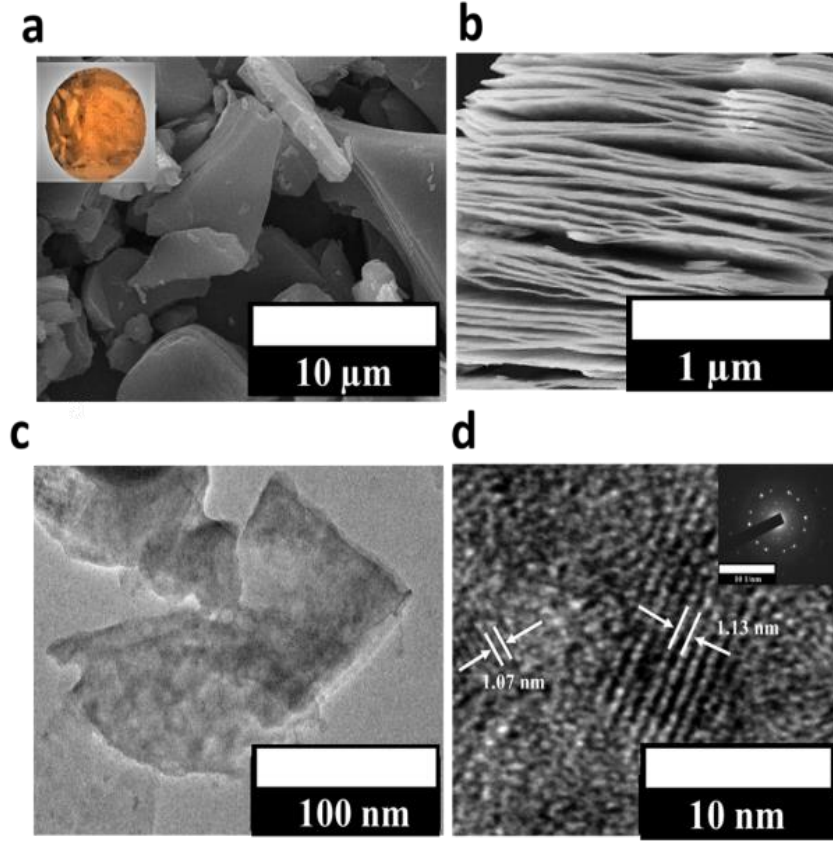


Figure 2. 8: FE-SEM images of (a) V₂CTx flakes (inset: the TEA-V₂CTx loaded in paper), and (b) the V₂CTx delaminated flakes with high resolution. (c) TEM image of TEA-V₂CTx flakes, and (d) High-resolution TEM image of lattice fringes for the TEA-V₂CTx (Inset: the SAED image).

The elemental states, terminal group amounts, and chemical structure at the V₂CTx MXene surface were further explored using the XPS method. (Fig. 2.10a) depicts the high-resolution V 2p spectrum fitted with two doublets. The peak at 513.29 eV is associated with the V-C bond, while the peak at 516.81 eV is assigned to the V-O bond. Mostly the vanadium is in the V⁺⁴ state due to the O-containing terminals, similar to that of previous reports in the literature [50–52]. Likewise, the XPS spectrum depicted in Fig. 2.10b corresponds to the C 1s state. The presence of C-C and C-O is mainly due to the impurities, while the V-C component corresponding to the V₂C lattice is located at 283.36 eV

accordingly. The F 1s spectrum (Fig. 2.10c) shows the V-F peak at 684.91 eV terminal components and residual C-F bonds at 687.02 eV. The analysis of the O 1s state depicts the peaks of V-C-O, V-C-(OH)_x, and V-O along with H₂O components (Fig. 2.10d), in good agreement with the previously reported work [53].

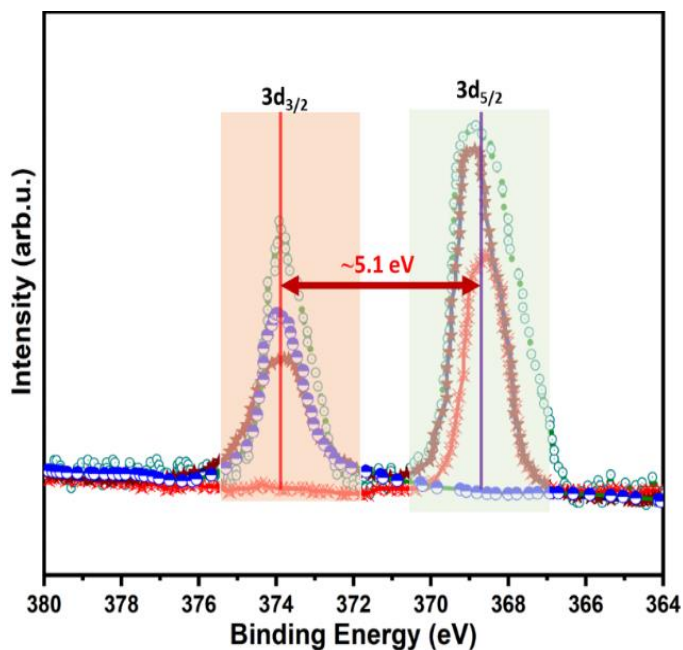


Figure 2. 9: The 3d core level spectrum of AgNPs@V₂CTx shows the binding energy difference between two doublets 3d_{3/2} and 3d_{5/2} of Ag core

Fig. 2.9 shows the shift in binding energies interaction between AgNPs and V₂CTx hybrid SERS substrate. The two doublets peaks of 3d_{3/2} (373.94 eV) and 3d_{5/2} (368.81 eV) are associated with two spin-orbit pairs, the lower binding energy component (368.81 eV) is a characteristic peak of electron emission from the silver nanocore respectively. The difference in binding energies of the two doublets confirms the presence of self-assembled AgNPs on V₂CTx film [17].

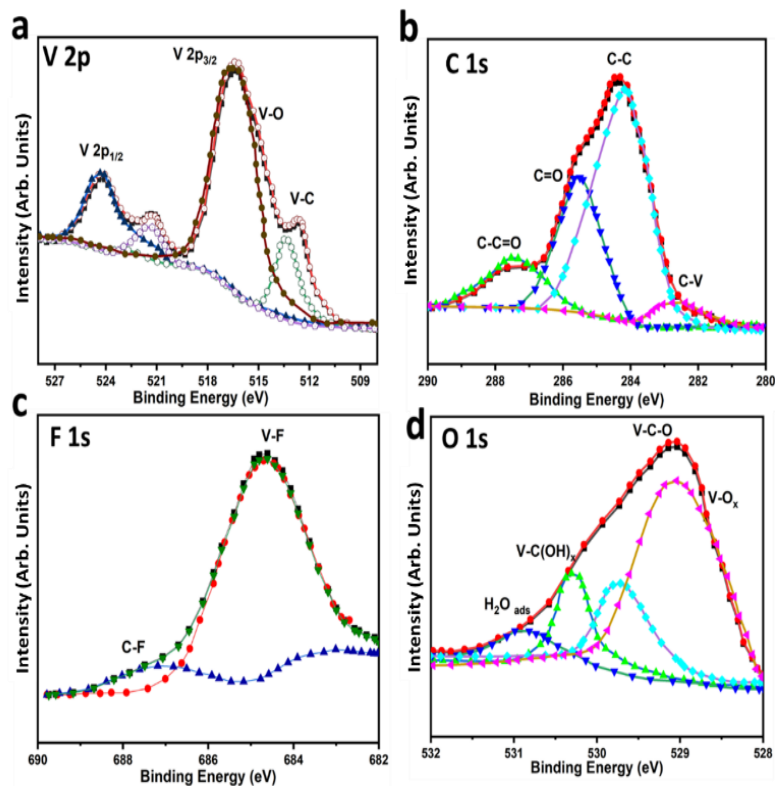


Figure 2. 10: XPS spectra of the synthesized V₂CT_x MXenes. States characterized are (a) V 2p, (b) C 1s, (c) F 1s, and (d) O 1s.

Moreover, the surface state of the V₂CT_x MXenes and the interaction with AgNPs and GMC were investigated by FT-IR spectroscopy (Fig. 2.11 a). The characteristic vibrational bands for the pure V₂CT_x located at 3427, 1614, 1145, and 834 cm⁻¹ correspond to the O-H, C=O, C-OH, and in-plane motion of carbon atoms. The observed FT-IR bands are in good agreement with the reported literature [43]. Shifts in band position and drop in intensity were observed after the loading of silver nanoparticles and interaction with GMC.

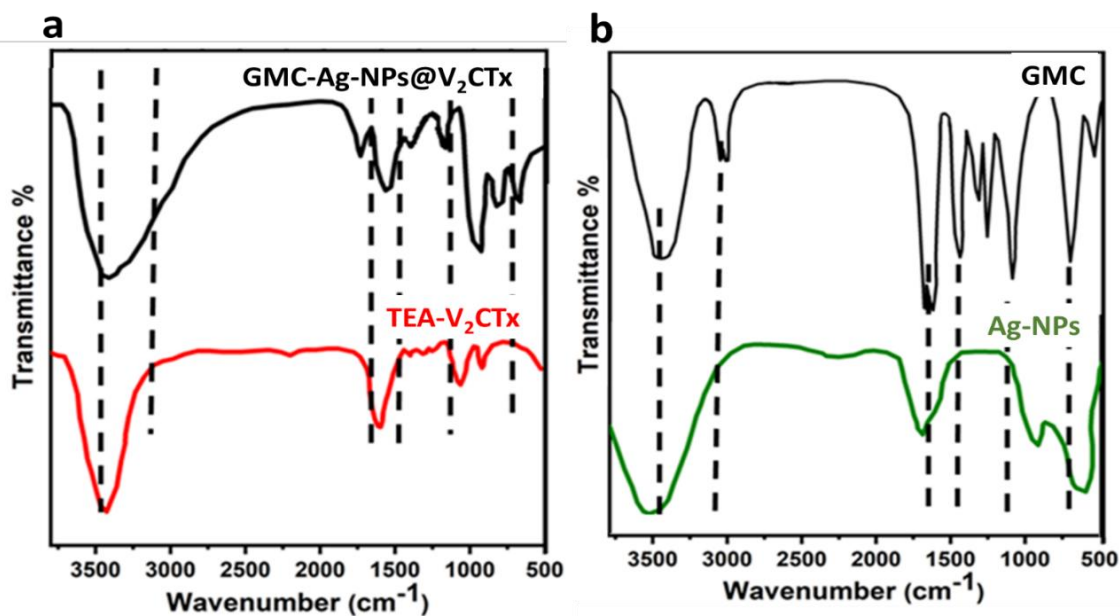


Figure 2. 11: (a) FTIR of Free V₂CT_x and after loading the GMC at AgNPs@V₂CT_x hybrid SERS substrate. (b) FT-IR of pure GMC drug molecules and pure AgNPs.

For instance, the vibrational wavenumbers got shifted to 3409, 1562, 1184, and 820 cm⁻¹, besides a few new vibrational bands at 1729, 1164, and 636 cm⁻¹ that were observed in the case of GMC-AgNPs@V₂CT_x as compared to non-interacted AgNPs, and GMC as shown in (Fig. 2.11 b). The observed variations in the infrared spectral intensities and band positions indicate that the V₂CT_x is successfully loaded by silver nanoparticles and GMC.

2.3.2 MAX phase transformation into V₂CT_x MXene:

The transformation of the precursor V₂AlC into a 2D V₂CT_x phase and the mobilization after-effects of the AgNPs with GMC adsorbates were assessed using Raman spectroscopy (Fig. 2.12). Raman shifts of the V₂AlC MAX phase showed four prominent peaks at 188, 251, 270, and 388 cm⁻¹ corresponding to E_{2g}, E_{2g}, E_{1g}, and A_{1g} symmetry modes, respectively (Fig. 2.12a). The former two modes are associated with the in-plane vibration

of Al and V atoms, while the latter two are ascribed to in-plane and out-of-plane vibrations of the vanadium atom. These modes of vibration are in agreement with reported values [54,55]. After treatment with a mixed acid etchant, the formed V_2CTx MXenes showed a reduction in peak intensities associated with the rising of a wide band above 400 cm^{-1} (Fig. 2.12b). Such a spectral change could be explained based on the increased interlayer spacing in the delaminated MXene flakes compared to the 3D precursor [56]. Since the etching involves replacing aluminum with other terminal groups, such as F, O, and -OH, it resulted in a broad Raman signature at 291, 415, and 477 cm^{-1} , and a hump at 650 cm^{-1} . These additional bands confirm the successful and homogenous removal of Al. The hump appearing at 650 cm^{-1} seems to have originated from heterogeneous terminals as predicted theoretically and observed experimentally in other reports [54,57].

The Raman spectrum of V_2CTx MXenes after loading with self-assembled nanoparticles is shown in Fig. 2.12c. Since AgNPs showed almost a blank Raman background in the $200\text{--}2000\text{ cm}^{-1}$ region (Fig. 2.14 b), they posed minimum interference with the Raman spectrum of V_2CTx . Therefore, any Raman peak observed within this range can be exclusively attributed to the as-prepared V_2CTx sheets. However, the Raman spectrum Fig. 2.12c showed a shift and a rise of new lines at 253, 342, and 393 cm^{-1} along with a wide band at 550 cm^{-1} associated with a shoulder at 639 cm^{-1} that may have resulted due to the in vitro interaction or photoinduced charge transfer of the AgNPs with the MXene hetero terminal groups [33] This further explains the self-assembled NPs observed to agglomerate on the MXene surface (Fig. 2.7 b).

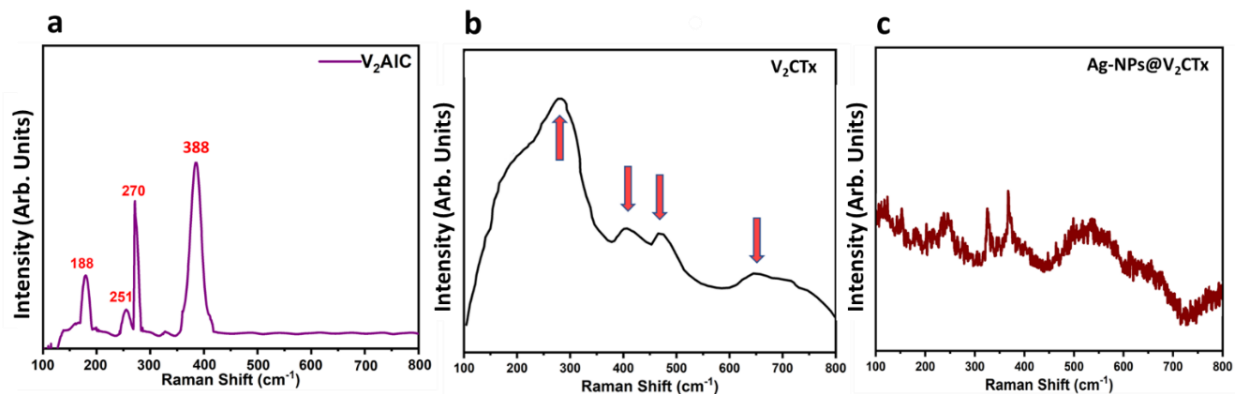


Figure 2. 12: Raman spectra of (a) V₂AlC MAX phase, (b) delaminated V₂CTx, and (c) AgNPs loaded V₂CTx

MXenes.

2.3.3 Detection of GMC using MXene-based SERS active substrate:

MXenes are known for their tunable electronic structure, excellent conductivity, high transmission of light, and negatively charged surface [58,59]. These interesting characteristics make MXenes attractive to potentially explored as SERS active substrates for the trace detection of biomolecules. In particular, the V₂CTx family can be an excellent candidate owing to their unique plasmonic, fluorescence quenching, interband charge transition, and magnetic coupling characteristics [60,61]. Given the extended use of GMC drugs in chemotherapy, a critical challenge is to monitor its level in the human body in order to constrict its adverse effect as a secondary metabolite. A number of analytical techniques are employed to detect GMC traces in human fluids. Examples of these techniques include spectrophotometry [62–64], electrochemistry [64,65], chromatography [66–68], fluorescent microscopy [69], HPLC-TM, LC-MS [70,71] and confocal microscopy [72]. However, most of these are time-consuming and destructive methods. When used to detect organic molecules in several cases they encounter photo-bleaching, bio-auto-fluorescence interference, and spectral overlapping. Nonetheless, these

techniques (Table 2.1) were able to detect and quantify the GMC drug in an aqueous solution and achieved a good outcome. Achieving a competitive low detection limit in the range of 10 nM of GMC, however, still presents a challenge. In our previous reports using the SERS technique [73,74] we succeeded in quantifying as low as 10⁻¹⁰ M of GMC with an excellent recovery of 98% using locally green synthesized AgNPs and Au-NPs as SERS substrates. This has prompted us to develop a sophisticated approach for GMC detection. In this work, AgNPs-loaded V₂CTx-based hybrid material was employed as a novel SERS substrate to develop a more sensitive protocol for GMC traces. The AgNPs function as a charge transport bridge and a plasmonic compact between GMC molecules and V₂CTx nanosheet, resulting in outstanding Raman signal enhancement.

Table 1. Comparison between reported analytical methods to detect trace GMC concentrations compared to the present work. LOD: Limit of detection; LDR: Linear dynamic range; R²: Regression coefficient

Ref.	Method	LOD	LDR	R ²
[122]	EC	1.5 µg mL ⁻¹	0.5-65 µg mL ⁻¹	0.998
[123]	Chromatography	20 ng	20-50 ng/ml	0.999
[124]	LC-MS	20 ng mL ⁻¹	20-5000 ng/mL	-
[125]	RP-HPLC	0.1 ng mL ⁻¹	0.1-42 ng mL ⁻¹	0.997
[126]	ECL	6.25 µM	6.25–100 µM	0.998
[127]	DPV Gold	0.260 ng mL ⁻¹	0.026-3.94 ng/L	-
[128]	SERS (AuNPs)	1×10 ⁻¹¹ M	10 ⁻⁴ - 10 ⁻⁹ M	0.998
Present work	SERS (AgNPs@V ₂ CTx)	1x10 ⁻¹² M	10 ⁻⁴ -10 ⁻¹² M	0.998

The SERS spectra (Fig. 2.13) of free GMC, loaded on AgNPs and loaded on AgNPs@GMC hybrid substrate indicate shifts in band position, i.e., the blue shift was observed in Raman lines at; i. 781 (ring def. and OH bending) to 779 cm^{-1} , ii. 1098 (CH bend., C-F str.) to 1093 cm^{-1} , iii. 605 (C-F bend.) to 599 cm^{-1} , iv. 335 (Ring breathing.) to 322 cm^{-1} v. 1651 (NH_2 bend.) to 1643 cm^{-1} . Likewise, red shifts were also noted for the Raman peaks; i. 1683 (C=O str.) to 702 cm^{-1} , ii. 1503 (C=C str.) to 1526 cm^{-1} , iii, 1285 (C-N bend.) to 1309 cm^{-1} , iv. 1216 (CH_2 def.) to 1239 cm^{-1} respectively. These shifts were observed along with a noticeable but variable increase in Raman intensities. The detailed assignments of the SERS peaks are provided in Table 2.2. Similarly, (Fig. 2.14 a), depicts the comparison between the Raman spectrum of free GMC, SERS spectrum when loaded with AgNPs, and the Raman spectrum of bare V_2CT_x MXenes, for the sake of comparison. The spectra showed noteworthy shifts in peak position that is assumed to be due to the interaction of GMC molecules with MXenes, however, it could not show the significant enhancement in the Raman peaks compared to AgNPs@ V_2CT_x hybrid materials. The enhancement factor (EF) was calculated by using the formula: $EF = (I_{\text{SERS}}/N_{\text{ads}})/(I_{\text{bulk}}/N_{\text{bulk}})$, where I_{SERS} and N_{ads} are the probe molecules under laser illumination area in both SERS and Raman experiments, and the I_{bulk} and N_{bulk} are intensities of characteristic Raman modes of the SERS and analyte accordingly. The SERS line centered at 779 cm^{-1} in the spectrum of GMC adsorbed on the AgNPs@ V_2CT_x substrate (Fig. 2.13) was used to compute the enhancement factor which turned out to be in the order of 10^9 .

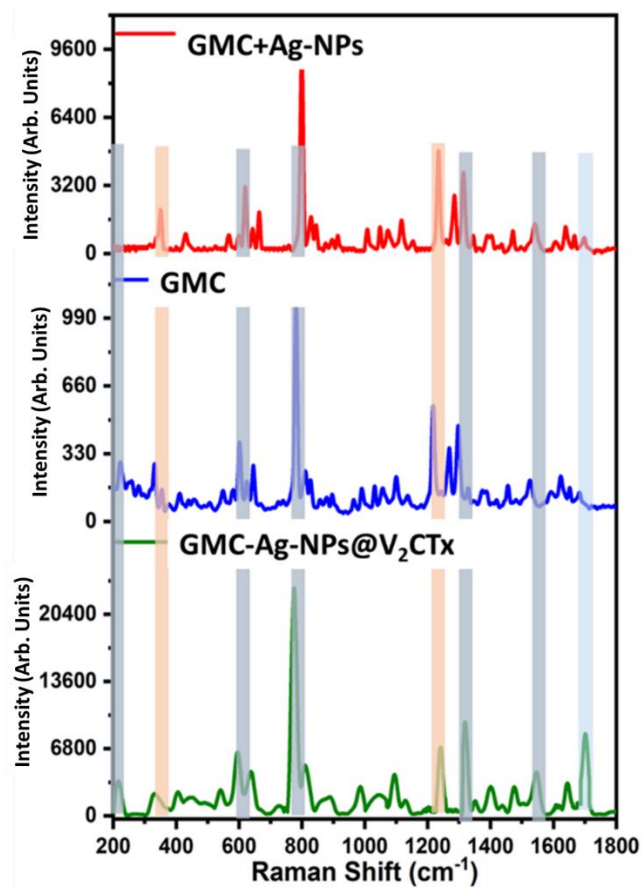


Figure 2. 13: Raman spectra of free GMC, GMC with AgNPs, and GMC with AgNPs@V₂CTx. The SERS spectrum was recorded by the drop-casting of 50 μ L of 10⁻⁴ M GMC solution on a 20x20 mm area of hybrid AgNPs@V₂CTx substrate. Prominent SERS peaks associated with GMC are labeled for the sake of clarity.

Table 2: Tentative assignments of the vibrational modes of GMC in the normal Raman and SERS (before and after loading AgNPs on V₂CT_x) spectra.

Description	SERS		
	Raman	AgNPs	AgNPs@V ₂ CT _x
C=O str.	1683 vw	1689 vw	1702 s
NH ₂ bend	1651 vw	1655 w	1643 w
C=C str.	1503 w	1516 w	1526 w
CN bend.	1279 m	1292 m	1309 s
CH ₂ def.	1216 s	1234 s	1239 w
CH bend, C-F str.	1098 w	1105 w	1093 m
CH bend, CCN str.	990 vw	917 vw	--
Ring def., -OH bend	781 vs	806 vs	779 vs
C-F bend	605 m	618 m	599 w
Ring def.,	335 w	325 w	322 vw
Ring def.	222 w	--	219 vw

Abbreviations: vs: very strong; s: strong; m: medium; w: weak; vw: very weak

The shifts in peak positions accompanied with remarkable enhancement observed in Raman intensities witness distinct types of interactions between GMC and AgNPs@V₂CT_x hybrid material. Some reports in the literature refer to the chemical interaction (mostly facilitating redshifts in wavenumbers) and the electromagnetic coupling interaction (mainly giving rise to blue shifts) [129], [130]. Such an enhancement is triggered by the large specific surface area of the hybrid substrate and the strong plasmonic light field

resonance-shaped surface turbulence by the mutual contribution of AgNPs and V₂CT_x MXenes [131], [132]. From the stacked plots (Fig. 2.13), the Raman peaks centered at 1702, 1309, 1239, and 779 cm⁻¹ have exercised maximum enhancements, confirming that the interaction between AgNPs-V₂CT_x and GMC is based on the CT and interband transition [133]. It is worth mentioning here that the parental Raman bands of V₂CT_x (Fig. 2.14 a) have not been observed in the SERS spectra of GMC-AgNPs@V₂CT_x film due to the AgNPs being effectively loaded across the hybrid substrate surface [119].

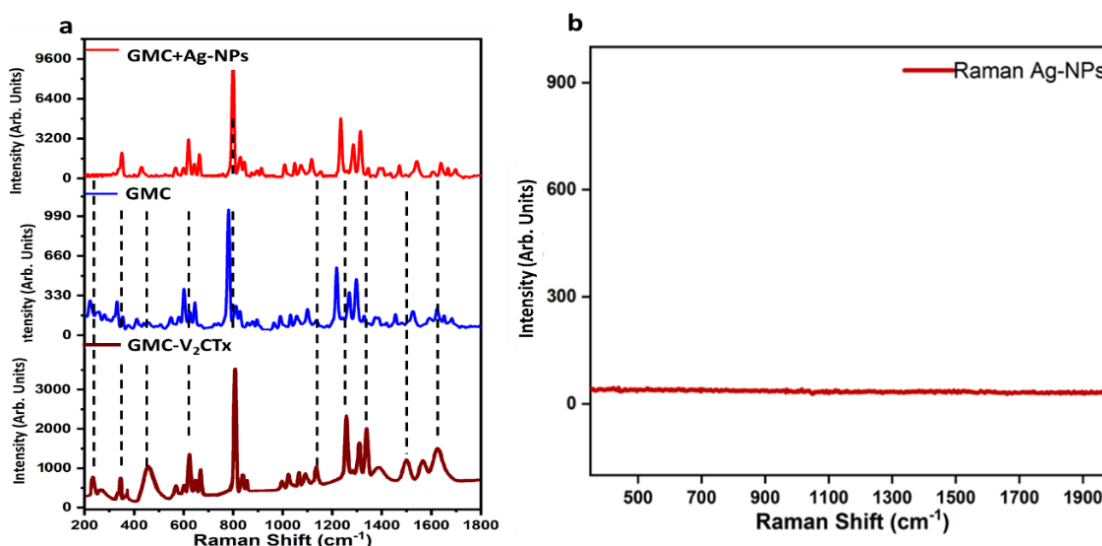


Figure 2. 14: (a) Raman spectra of free GMC, with AgNPs, and GMC with bare V₂CT_x MXenes, (b) Raman Spectra of free Ag-NPs.

The limit of detection (LOD) of GMC was determined by measuring the SERS spectra at various drug concentrations in the range of 10⁻⁴-10⁻¹²M (Fig. 2.15a). A uniform spectral pattern can be observed with a decrease in peak intensity associated with a change in concentration of the GMC. It can be concluded that the intensities are linearly proportional to the logarithm of the concentration of the drug analyte, thus, spectral intensity enhancement is indicative of the simultaneous interaction of GMC molecules with

AgNPs@V₂CT_x hybrid substrate at multiple spots (Fig. 2.15a). The LOD for the present approach reached an order of 10⁻¹² M concentration. Further, it corresponded to a wide linear dynamic range (LDR) of 10⁻⁴ to 10⁻¹² M (Fig. 2.14b) for a peak at 779 cm⁻¹ postured maximum LDR due to strong interaction leading to a very intense signal, while the other bands (1239 cm⁻¹, 1309 cm⁻¹, and 1702 cm⁻¹) posed narrow LDR compared to the first band, due to different molecular orientation, type, and extent of interaction which resulted in weak signals. The intensity is in logarithmic relation to the concentration of the analyte, this leads to a decrease in signal intensity linearly as concentration decreases [134], [135]. The observed enhancement is a two-logarithmic-step more sensitive quantification than our previous report that utilized only AgNPs [128]. The linear regression coefficient (R^2) of the prominent Raman peaks at: (i) 779 cm⁻¹, (ii) 1239 cm⁻¹, (iii) 1309 cm⁻¹, and (iv) 1702 cm⁻¹ were calculated to be 0.9965, 0.99734, 0.9984 and 0.9982, respectively.

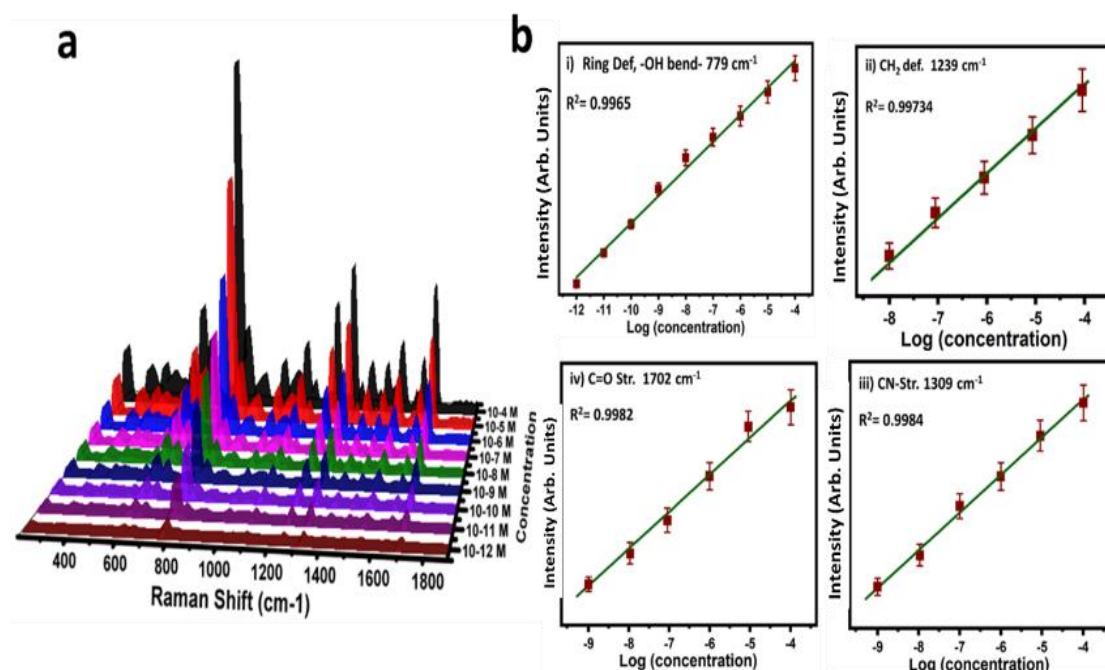


Figure 2. 15: (a) SERS spectra of GMC at the concentration range 10-4-10-12M using AgNPs@V2CTx substrate. (b)

Logarithmic relationship between prominent SERS peak intensities and concentrations of GMC molecules.

2.4 Reproducibility and stability of the prepared silver-loaded MXene:

The reproducibility of the as-prepared silver-loaded V₂CT_x MXene film was investigated with the 1x10⁻⁵ M concentration of the GMC by selecting ten random spots in the film with an area of 25x25 μm at a gap of 2 μm, as depicted in (Fig. 2.16). The characteristic peak intensities for the representative peaks, i.e., 779 cm⁻¹, 1241 cm⁻¹, 1309 cm⁻¹, and 1702 cm⁻¹, were shown to be consistent and uniform. Moreover, the stability and liability of the as-prepared Ag-NPs-loaded MXene film were further verified by comparing the SERS spectra of the film with and without the loading of the drug molecules at different time intervals for an extended period of four weeks. The results depicted in (Fig. 2.17 a) showed a minimum change in peak intensities across the time interval of 4 weeks. For example, the

Raman intensity distribution of the peak 779 cm^{-1} over the examined period of time posed a consistency with an RSD of 1.89%, proving the repeatability of the developed approach.

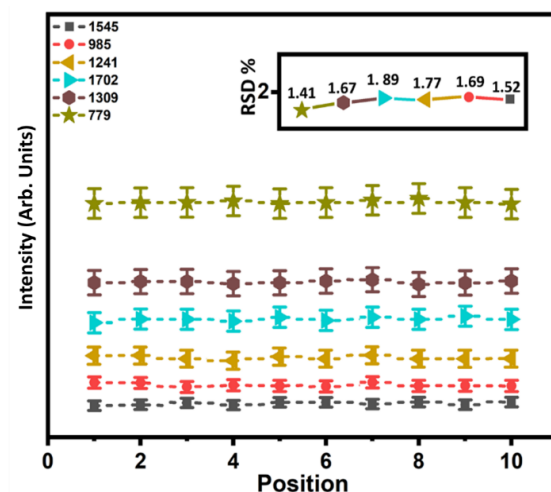


Figure 2. 16: The SERS spectra of AgNPs@V2CTx hybrid materials of different peak positions

Likewise, to evaluate the selectivity of the developed approach, an interference study was carried out by mixing different interferents, namely procainamide (PA), ciprofloxacin (CPN), amphetamine (AA), and valeric acid (VA), of $1 \times 10^{-3}\text{M}$ concentration each with GMC that is kept at a concentration of $1 \times 10^{-5}\text{M}$. The SERS spectra of the interferents and analyte (Fig. 2.17b) show a negligible impact of interference by the other bioactive species, and the Raman intensities are 96% consistent with the originally observed ones. The RSD of the SERS peaks for the concentration ($1 \times 10^{-5}\text{M}$) was noted to be 1.45 %, while the average recovery was calculated to be 98%. These results confirmed that the prepared AgNPs@V₂CT_x films could be reliably used for the long term with excellent selectivity, linearity, efficiency, and reproducibility in GMC drug analysis.

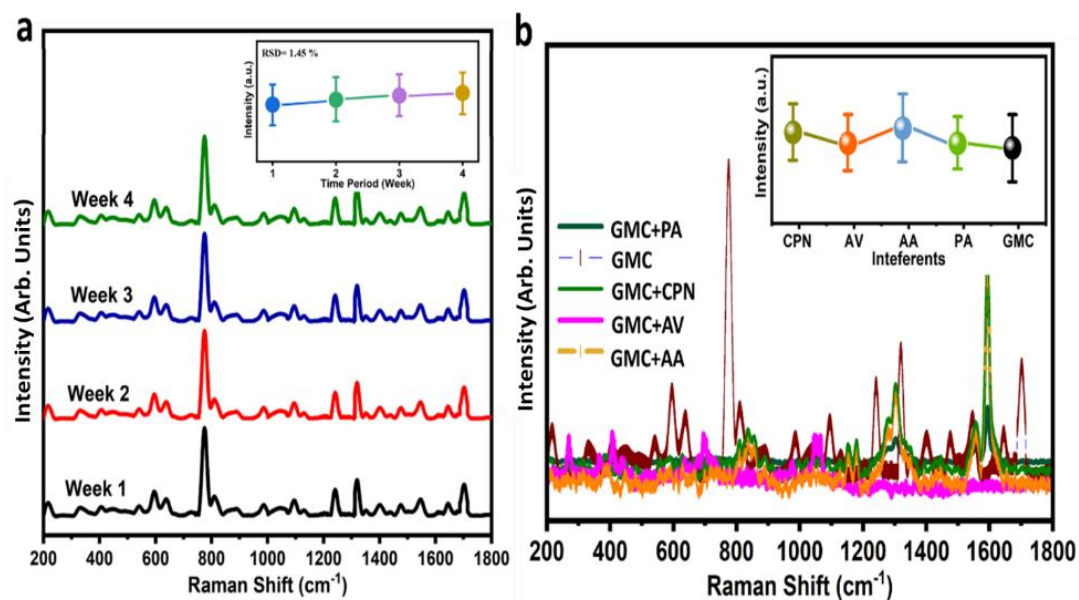


Figure 2. 17: (a) SERS spectra of GMC using AgNPs@MXene substrate taken over a four-week period (inset shows the Raman intensity distribution of the line at 779 cm^{-1}). (b) Interference effect of different bioactive drugs (inset depicts the effect of interferent on the intensity of the Raman bands of the GMC).

3 CHAPTER

Silver-loaded bimetallic MXene substrates for ultra-sensitive SERS detection of antibiotic drugs: The synergetic impact of electromagnetic and chemical contributions

Taken from: Nasurullah Mahar¹, Areej H. Al-Mebti¹, Abdulaziz A. Al-Saadi^{1,2,*}

¹*Department of Chemistry, King Fahd University of Petroleum & Minerals, Dhahran 31261 Saudi Arabia.*

²*Interdisciplinary Research Center for Refining and Advanced Chemicals, King Fahd University of Petroleum & Minerals, Dhahran 31261, Saudi Arabia.*

3.1 Introduction

Surface-enhanced Raman scattering (SERS) spectroscopy has emerged as a powerful, sensitive and non-destructive analytical technique for the quantification of trace organic compounds [136], [137]. It has been utilized in pesticide detection, environmental hazard monitoring, and biofluid clinical measurements [138], [139]. Noble metals, namely gold, silver and platinum, have been widely used as ad-atoms to fabricate nanostructured surface substrates, giving rise to local surface plasmon resonance (LSPR) characteristics [140], [141]. However, a few challenges are still being faced in terms of synthesis procedures, including high cost, aggregates formation, cluster instability, limiting to some extent their use and efficiency [142], [143]. Hence, the fabrication of novel and stable substrates has been a subject of study, aiming to enhance the detection limits and improve the selectivity of SERS-based assays. As a result of their remarkable structural and electronic properties, MXenes, which are described as two-dimensional transition metal carbide-based materials,

have exhibited a great potential to serve as a promising component in generating a new class of SERS substrates [144], [145], [146]. Several studies have been reported for the use of different MXenes and their nanocomposites with noble metals in this area [147], [148], [149]. However, a major disadvantage reported is the chemical instability, restacking, and oxidative degradation, hence limited their use as sustainable substrates for a reliable use [150], [151], [152]. Bimetallic MXenes have recently demonstrated several advantages over conventional single metal analogues [153], [154], [155]. They hold immense promises for applications in optical spectroscopy, owing to their notable charge transfer characteristics and excellent plasmonic aspects [156], [157]. The presence of heteroatoms not only impacts plasmonic coupling behavior but also alters the electronic features, thus affecting charge transfer capabilities, conductivity and optical properties [155], [158]. In addition, the diffuse Fermi levels expand the charge distribution along the layered structure, making the materials more electron sufficient with a wider inter-layer space and appreciable porosity [159], [160]. This phenomenon significantly enhances the interaction between analyte molecules and substrates, making such a new generation of MXenes as a potential candidate to promote both the chemical and electromagnetic mechanisms leading to the desirable Raman signal enhancements. It is also noteworthy that bimetallic MXenes demonstrate a promising fluorescence quenching ability. That arises from the smooth energy transfer processes between fluorophore molecules and the bimetallic MXene-fabricated substrates [161], as earlier reported in fluorescence sensing and imaging applications [162].

The present study demonstrates a new advancement in the field of ciprofloxacin (CP) antibiotic drug detection using silver-loaded vanadium-zirconium bimetallic MXene

hybrid SERS substrate. CP detection is of utmost importance in pharmaceutical and clinical monitoring due to the widespread use and potential health implication associated with its presence in various matrices [163], [164]. Several studies explored the use of different techniques, aiming to achieve lower CP detection limits, improved sensitivity, and an enhanced selectivity [165], [166], [167], [168], [169], [170]. However, most of these approaches encounter challenges, such as high background noise, poor reproducibility, or insufficient sensitivity. These techniques, summarized in Table 3.1, could quantify CP drug up to limits of detection (LOD) within the range between 10^{-6} to 10^{-9} M concentrations. Reaching a more competitive LOD represents a major target to achieve. In a prior SERS study using a vanadium-based MXene decorated with silver nanosphere, an LOD of 10^{-10} M of gemcitabine drug was successfully established with an excellent recovery of 98% [171]. This has prompted us to foster another advanced methodology to design novel bimetallic MXenes targeting an ultra-low concentration of CP in aqueous media. Herein, a systematic approach to investigate SERS performance of silver-loaded vanadium-zirconium MXene ($\text{AgNSs}@V_{0.25}(\text{Zr}_{1.75})\text{CT}_x$) was established for ciprofloxacin detection. The sensitivity and selectivity of that approach have been assessed.

Table 3: Reported analytical methods used in CP detection, their limits of detection, linear dynamic ranges, and linear regressions constants, as compared with the present work.

Method	LDR	LOD	R^2	Reference
MI-SERS	--	10^{-9} M	--	[165]
EC-Sensor	0.5- to 64.0 ng mL ⁻¹	0.5 ng mL ⁻¹	--	[166]
Chemical Sensing	0.01-120 μ M	2.7 nM	--	[167]
PEC	0.4-1000 nM	0.13 nM	--	[168]
SPR	--	7.1 ppb	0.993	[169]
EC-sensors	0.05-10 μ M	5 nM	--	[170]
SERS	$10^{-4} - 1.0 \times 10^{-14}$ M	1.0×10^{-14} M	0.998	Present Work

3.2 Experimental

3.2.1 Materials and Reagents

Here are the materials and reagents utilized in this study; ZrH₂ (6 μ m, 99.9% Chemetall, Germany), aluminum (5 μ m, 99% AFE, US), silver nitrate (AgNO₃, 99.9%), V₂O₅ (6 μ m, 99.8%), lithium fluoride (LiF, 99%), HCl (99%), dimethyl sulfoxide (DMSO, A.R), and n-hexane (C₆H₁₄, A.R) were all purchased from Sigma Aldrich. Moreover, graphitic carbon

(99.8%), sodium citrate ($\text{C}_6\text{H}_5\text{Na}_3\text{O}_7 \cdot 2\text{H}_2\text{O}$, >99%), tartaric acid (99 %), and sodium borohydride (NaBH_4 , 98.9 %) were obtained from Alfa Assar. Ciprofloxacin, CP (99.8%) was purchased from GlaxoSmithKline USA. All the solutions were prepared in deionized water.

3.2.2 Characterization

Comprehensive characterization protocols were carried out to develop a reliable understanding of the nature of the MAX and the corresponding bimetallic MXene materials developed during this study. A multifunctional X-ray diffraction device Ultima IV was exploited to study the X-ray diffraction (XRD) pattern. Agilent Cary 60 was used to analyze UV-visible absorption spectra. A JEM-2100 field emission microscope (Model: JEOL-USA) at 200 KV to study surface morphology. Utilizing a Tecnai G2 20 S-TWIN, D 2012, the transmission and high-resolution (HR-TEM) recordings were made. The Raman and SERS spectra were collected using a HORIBA Scientific LabRAM HR microscope at optimized conditions, particularly the 25% laser power, 633 nm excitation wavelength, 50x objective lens, 20s acquisition time, and 10 accumulations. The final collected spectra were the results of an average of 5 runs.

3.2.3 Materials Preparation and Synthesis

Silver nanospheres (AgNSs): In accordance with our previously published work [172], AgNSs were prepared by a chemical reduction method. With a standard procedure in a 200 mL round-bottom flask, 0.1 ml of the 0.10 M AgNO_3 solution, 3.4 mL of the 0.17M sodium citrate, and 0.6 mL of the 0.17 M tartaric acid were added simultaneously. After allowing the mixture to stabilize at room temperature for three minutes, 0.2 mL (0.5 mM) of newly

produced NaBH_4 was added dropwise. The mixture was then let stand for five minutes to maintain the uniform size distribution of AgNSs, followed by adding 95 mL deionized water. The final mixture was boiled for 20 minutes at 100 °C and then cooled down in an ice bath.

Vanadium-zirconium MAX phase: A bimetallic $\text{V}_{0.25}(\text{Zr}_{1.75})\text{AlC}$ MAX phase was synthesized with some modification to the reported literature procedure [159], [160]. Initially, commercially available precursors of Zr, Al, V, and C were mixed in a $(\text{V}_{0.25}+\text{Zr}_{1.75})$:1.8:1 molar ratio in 100 ml ZrC jar in presence of propyl alcohol. A dual mixer/mill (SPEX Sample Prep. 8000 D) was used to grind the powder to a fineness of 100 mesh. The fine ground mixture was placed in a heating boat and heated in an inert environment at 1450 °C for 180 minutes with a ramp of 10°/min in a tube furnace (Carbolyte STF 15/450). To compensate for the loss of Al above (660 °C), an additional amount of Al was added. The cooled mixture was then dispersed in deionized water and sonicated for five minutes after being cleaned from contaminants for two hours at 30 °C using 2M H_2SO_4 . The resulting mixture was collected for further investigation after dried in a vacuum drier at 60 °C.

Bimetallic $\text{Zr}_{0.25}(\text{V}_{1.75})\text{CT}_x$ MXenes and silver-loaded SERS substrate: The synthesis of bimetallic MXenes $\text{V}_{0.25}(\text{Zr}_{1.75})\text{CT}_x$ and loading them with AgNS involves a multi-step process that begins with a selective removal of the Al from the MAX phase precursor, followed by intercalation of etched product exfoliate the layers and obtain MXene nanosheets. Traditionally, hydrofluoric acid (HF) has been the preferred etchant due to its high efficiency in MAX phase etching [147], [171]. However, HF is highly corrosive, toxic, and poses significant environmental and safety concerns. In this study, we

implemented a green approach for the synthesis of bimetallic MXenes $V_{0.25}(Zr_{1.75})CT_x$ using environmentally friendly mixed acid etchants (Fig. 3.1). The method employs a soft etching solution (LiF+HCl) as an alternative which is non-toxic, less corrosive, and environmentally benign, making it a safer and more sustainable approach for MXene synthesis. In a typical procedure the precursor $V_{0.25}(Zr_{1.75})AlC$ is subjected to a mixture of 2:1 HCl+LiF etchant for selective etching of the Al in a Teflon bottle. The amount of $V_{0.25}(Zr_{1.75})AlC$ powder (typically 1g) was added slowly as 100 mg in an interval of 5 minutes to avoid the oxidative degradation of the mixture. Initially the temperature of the contents is kept very low (4 °C) to control the reaction kinetics and avoid any early oxidation. After 20 minutes of stirring on an ice bath, the mixture was transferred to an oil bath at 40 °C for (48 hours). Afterwards, the product was cleaned and centrifuged in a 1:1 water/ethanol mixture at 8000 rpm, and the sedimented product collected while the supernatant was discarded as impurities. The collected solid contents were further dispersed in a washing solution by mechanical mixing and sonication followed by a multiple time washing and centrifuging at 5000 rpm. The supernatant was collected as multilayered etched bimetallic MXenes while the sedimented product got further treated for washing. The procedure was repeated until the pH of the solution reached 6.5 and the supernatant turned transparent, reflecting no more suspended MXene flakes. After the selective etching, the intercalation of the MXene layers was achieved by immersing the etched product in 20% TEA intercalant and stirred at 400 rpm for 2 hours. The intercalated product was further centrifuged at 5000 rpm followed by 2500 rpm. The supernatant was discarded in a first run, while for the subsequent runs the supernatant was collected as delaminated flakes of the target bimetallic MXenes. The collected bimetallic MXenes were

freeze-dried and used for further preparation of the SERS substrates, where in a standard method 50 mg of the as-synthesized $V_{0.25}(Zr_{1.75})CT_x$ powder was dispersed in 50 mL of deionized water. The mixture was sonicated for 1 hour to ensure the exfoliation of stacked MXene layers. That was followed by a dropwise addition of 5ml of (30%) AgNS seed at a constant sonication to ensure the effective intercalation of the nanospheres. Different volumes (5, 10, 15, 20 ml) of AgNSs were added in 50 mL solution of dispersed bimetallic MXene, and the resultant $AgNS@V_{0.25}(Zr_{1.75})CT_x$ materials were investigated for the SERS response. It was observed that 5mL exhibited a remarkable enhancement, hence used for further study.

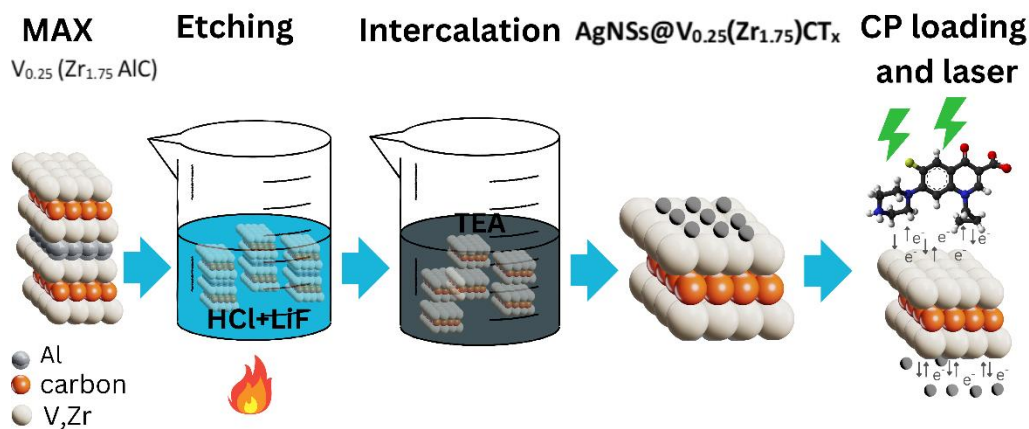


Figure 3. 1: Synthesis of bimetallic $V_{0.25}(Zr_{1.75})CT_x$ MXene from its precursor MAX phase $V_{0.25}(Zr_{1.75})AlC$, intercalation of the etched MXenes and preparation of SERS substrate to laser exposure.

3.3 Results and Discussion

3.3.1 Morphological and surface characterizations of AgNSs@ $V_{0.25}(Zr_{1.75})AlC$

Morphological features of the prepared $V_{0.25}(Zr_{1.75})CT_x$ are illustrated in Fig. 3.2. The MAX phase has a typical ternary-layered 3D structure, and the EDS mapping of the $V_{0.25}(Zr_{1.75})AlC$ shows a homogeneous solution of the phase. Likewise, Fig. 8.2b depicts the morphology of the etched bimetallic MXenes composed of loosely packed 2D evenly spaced multi-layered structure with an accordion-like shape as compared to the precursors. Furthermore, the SEM images indicate silver nanospheres distributed on the surface of the $V_{0.25}(Zr_{1.75})CT_x$ with a particle size distribution of nearly 20-80 nm. The assembly of nanospheres on the MXene surface is induced by their positive charge and the negatively charged T_x groups (either -O, -F, or -Cl). The presence of vanadium, zirconium, and carbon accompanied by remnants of fluorine and oxygen as terminal groups was also analyzed using EDS before and after the loading of AgNSs (Fig. 3.2 e and f). Compared to the precursor, the percentages of the Zr, V and C elements are predominant in the etched MXenes, suggesting the effective transformation from MAX phase to the desired MXene phase. The microstructure of $V_{0.25}(Zr_{1.75})CT_x$ was further investigated using a high-resolution TEM (Fig. 3.2d) which displays 2D transparent stacked flakes with circular fringes showing the distribution of AgNS along the Zr-V-C layers in a parallel lattice fashion (d -spacing of 1.27 - 1.45 nm). These findings are in good agreement with previous reports [115].

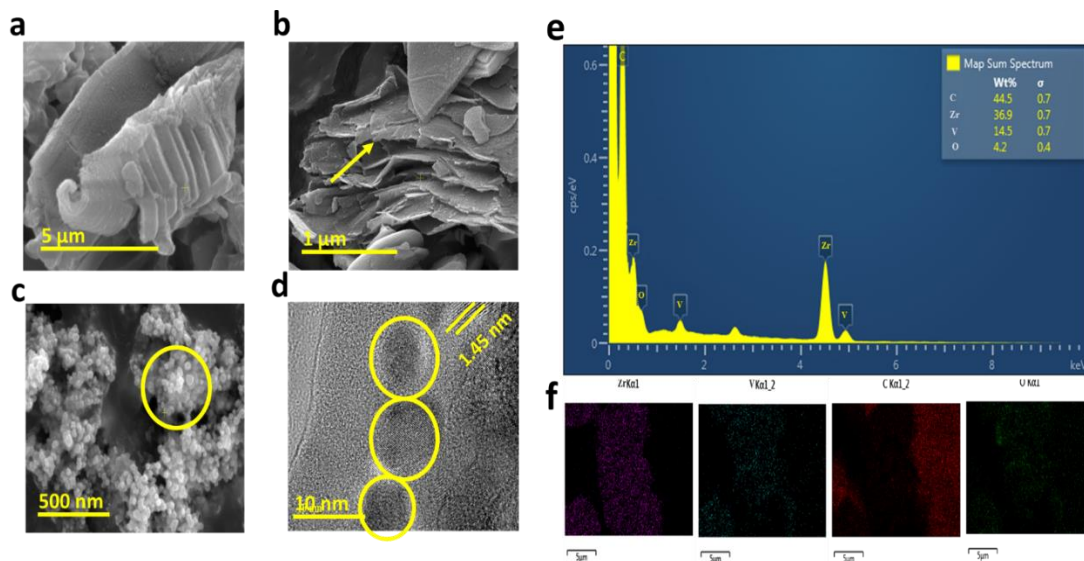


Figure 3. 2: SEM images of the prepared (a) V_{0.25}(Zr_{1.75})AlC bimetallic MAX phase, (b) V_{0.25}(Zr_{1.75})AlC MXenes, and (c) the hybrid SERS AgNS@ V_{0.25}(Zr_{1.75})AlC substrate, (d) a high resolution TEM image of the hybrid SERS AgNS@ V_{0.25}(Zr_{1.75})AlC substrate, (e) the EDS spectrum of the prepared V_{0.25}(Zr_{1.75})AlC MXenes, and (f) the elemental mapping of Zr, V, C and O in V_{0.25}(Zr_{1.75})AlC MXenes.

The XRD patterns for the V_{0.25}(Zr_{1.75})AlC phase are depicted in Fig. 3.3 as a primary constituent of V₂AlC (indexed by JCPD card No. 29-0095) where respective impurities were not detected. It can be observed that the main pattern of the V_{0.25}(Zr_{1.75})AlC has experienced shifting to less θ values due to the increased Zr contents and the expanded c-lattice parameter along the c-axis owing to the larger radii of zirconium [173]. The XRD for the V_{0.25}(Zr_{1.75})CTx MXene, on the other hand, displays a characteristic diffraction profile. While sharing some similarities with the MAX phase spectrum, it shows distinct peak positions and intensities, indicating a remarkably different crystal structure. While the presence of peaks like (002), (101), and (111) suggests a layered structure common in MAX phases, the specific positions of these peaks differ from the MAX phase, implying differences in lattice parameters. The peak emerged at 8.77°, linked to the (002) plane,

indicated a change in the crystallographic orientation into a 2D layered structure. Likewise, the substantial decrease in intensities for (210), (111), and (101) peaks and rise in the intensities for (106) and (004) peaks signify a modification in the unit cell dimension along a , b and c axes. The change in dimensionality from MAX to MXene as depicted by the x-ray spectra is well aligned with the previous reports [173], [174].

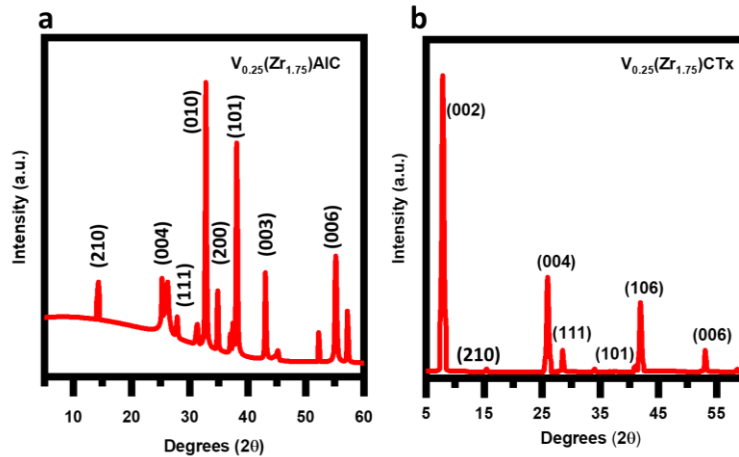


Figure 3. 3: X-ray diffraction (XRD) spectra of (a) V_{0.25}(Zr_{1.75})AlC MAX phase, and (b) the bimetallic V_{0.25}(Zr_{1.75})CTx MXene. The indexed peaks correspond to the respective crystallographic planes.

The Raman spectra (Fig. 3.4) offer further insights linked to the vibrational properties of V_{0.25}(Zr_{1.75})AlC and the prepared bimetallic MXenes. The spectra can be divided into three distinct regions: the Zr-V, Al/T_x, and carbon regions. The spectrum of the MAX phase exhibits prominent, sharp peaks in the Zr-V region at 198, 261, 280, and 390 cm⁻¹ corresponding to E_{2g}, E_{2g}, E_{1g}, and A_{1g} symmetry modes. The earlier two modes are related to in-plane vibrations of Zr-V bonding, while the latter are attributed, respectively, to in-plane and out-of-plane vibrations associated with V and Al atoms [171]. In the region around 600 cm⁻¹, a sharp peak can be observed, indicating the presence of vibrational modes relevant to aluminum. The carbon region (1400 cm⁻¹) shows an intense and well

resolved peak, suggesting a lower concentration of carbon-based bonds compared to the other components. Likewise after etching, the $V_{0.25}(Zr_{1.75})CT_x$ spectrum shows a similar set of peaks but with substantial wavenumber shifts or a variation in their intensities (Fig. 3.4b). This spectral variation is assumed to be due to the wide interlayer spacing in the delaminated MXene flakes compared to the precursor, while the peaks in Zr-V region between $100-300\text{ cm}^{-1}$ suggest the presence of Zr-V bonds. Conversely, the Al/ T_x region (around 600 cm^{-1}) exhibits a different peak profile, suggesting the presence of T_x -related (-O, -F or -Cl) modes instead of Al. The carbon region (around 1400 cm^{-1}) shows a diffused peak as compared to the MAX phase, indicating the successful removal of aluminum and a change in crystallinity of the material [175]. Moreover, the UV-Vis spectrum depicted in Figure 3.2c shows that the delaminated $V_{0.25}(Zr_{1.75})CT_x$ solution is characterized with maximum absorbance bands at 270, 310 and 795 nm. According to Satheeshkumar *et al.*, the first two bands correspond to the bimetallic MXene bandgap energies, whereas the latter one is assigned to the longitudinal oscillation in the near infrared region. The UV-Vis spectrum of AgNS is characterized with a maxima at 405 nm, confirming the plasmonic behavior of the nanospheres. Likewise, the AgNS@ $V_{0.25}(Zr_{1.75})CT_x$ composite exhibited a set of distinct absorption bands at ~ 270 and 314 nm (liable to the bimetallic MXene) and that at 405 nm confirming the successful loading of AgNSs.

3.3.2 SERS Analysis

All the Raman and SERS spectra for the free CP, AgNS-CP and AgNS@ $V_{0.25}(Zr_{1.75})CT_x$ -CP were collected at room temperature with an optimized ratio of 1:2 of the drug to the substrate of bimetallic MXenes. The Raman spectrum of free CP (**Fig. 3.5**) shows a number of prominent peaks located at 230, 303, 627, 789, 1378, 1404 and 1633 cm^{-1} which are

likely described as skeletal bending, C-H bending, N-H bending, C-N stretching, and C=O stretching vibrational modes. These modes are characteristic in the sense that the corresponding SERS spectrum acquired with the silver nanosphere shows a similar peak pattern yet with remarkably enhanced intensities, making them good candidates for further SERS investigations. This enhancement could be attributed to the interaction of CP molecules with the spherical surface of silver which amplifies the Raman signal by the localized surface plasmonic resonance (LSPR) features. The SERS spectrum after incorporating the drug with the hybrid SERS substrate (AgNS@ $V_{0.25}(Zr_{1.75})CT_x$ -CP) exhibits a comparable set of peaks but with a further improvement in intensity and associated with appreciable wavenumber shifts. For instance, a significant rise in the intensity of the peak associated with the carbonyl group stretching accompanied with a red shift (down to 1603 cm^{-1}) could be noticed, as compared to the AgNS-CP combination (1633 cm^{-1}). It suggests that a proper incorporation of the bimetallic MXene $V_{0.25}(Zr_{1.75})CT_x$ with the silver nanospheres results in a stronger photo-interaction with drug molecules compared with only AgNSs. The spread-out of the nanostructured silver particles on the MXene surface is likely to provide more hot spots and hamper the clustering of the nanospheres [176], [177]. In Addition, the negatively charged terminals shall provide a better adsorption of the substrate through complexation, thus maximizing the interaction between the probe molecules and the plasmonic substrates.

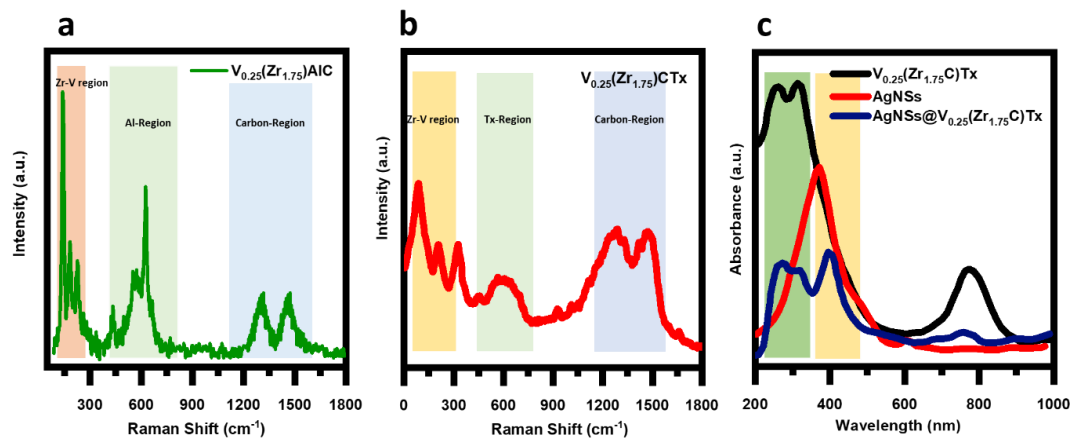


Figure 3. 4: Raman spectra of (a) $V_{0.25}(Zr_{1.75})AlC$ bimetallic MAX phase, and (b) the prepared $V_{0.25}(Zr_{1.75})CTx$ MXene. (c) UV-Vis spectra of the hybrid $AgNS@ V_{0.25}(Zr_{1.75})CTx$ substrate (blue) compared to those of silver nanosphere (red) and prepared bimetallic $V_{0.25}(Zr_{1.75})CTx$ MXene (black).

The observed alterations in the spectral features and the detected wavenumber shifts at various magnitudes in the characteristic Raman lines (e.g. 789 to 781, 1340 to 1345, 1405 to 1394, and 1634 to 1603 cm^{-1}) not only reflect the inherent SERS effect but also are credited to both the chemical and electromagnetic mechanisms (abbreviated as CM and EM, respectively) facilitated by the hybrid substrates used. The EM is normally prominent when there is an electron-rich substrate, thus it induces LSPR features on laser excitation. Since the bimetallic MXene has mixed types of atoms of different properties, the Fermi level is expected to be diffused generating a high density of electrons, thus becoming an ideal candidate for the EM effect. Such a conclusion is evident from the frequency shifts associated with the intense Raman signals. In addition, the different nature of vanadium and zirconium results in coupling of the plasmonic characteristics and hence can augment the inter-band charge transfer (IBCT), which contributes primarily to the CM aspects. It is worthwhile to comment on that the signal intensity is also sparked by the substantial surface area of the hybrid substrate and the strong plasmonic light field resonance-shaped

surface turbulence by the mutual impact of AgNS and $V_{0.25}(Zr_{1.75})CT_x$. Therefore, the hybrid substrate is a potential candidate that notably stimulates Raman signal enhancements due to the outstanding coupling between EM and CM, leading to an enhancement factor (EF) of 1.14×10^7 . The most intense SERS peak (1345 cm^{-1}) was chosen to determine the maximum EF using the following reported formula [178]:

$$EF = I_s / N_s \times I_r / N_r \quad (3.1)$$

where I_s and N_s are intensity and concentration of the probe molecules in SERS signal while I_r and N_r are the intensities of distinguishing Raman modes of the probe molecules, respectively.

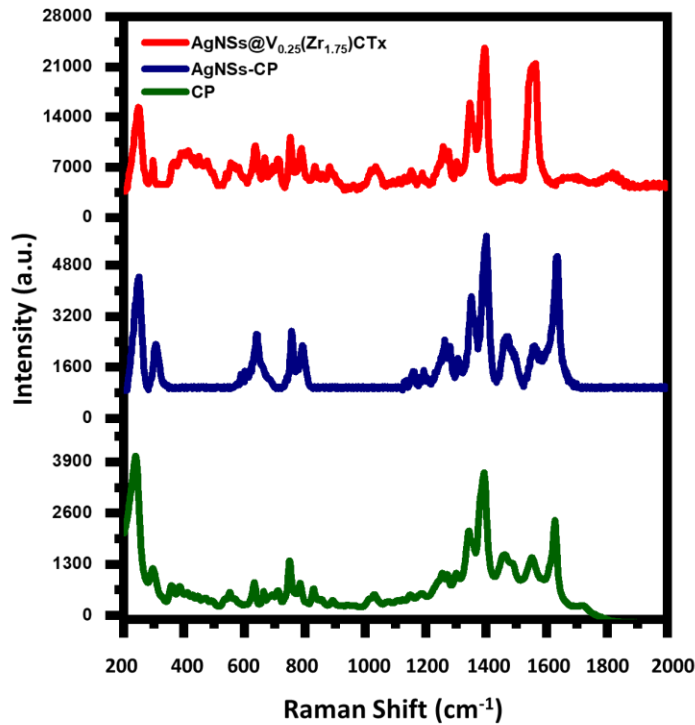


Figure 3. 5: Raman and SERS spectra of the ciprofloxacin, CP, drug (green), silver nanosphere-loaded CP drug (blue), and the hybrid substrate-loaded CP drug, $V_{0.25}(Zr_{1.75})CT_x$ -CP, substrate (red).

3.3.3 Limit of detection, selectivity and interference effect

A quantitative detection of CP within a wide concentration range was studied in aqueous solutions to establish the reliability of the developed spectro-analytical method. The hybrid substrate AgNS@V_{0.25}(Zr_{1.75})CT_x posed a notable detection ability towards CP traces. A uniform spectral pattern of SERS intensities decreasing with the decrease of CP concentrations in the range of 10⁻⁴ to 10⁻¹⁴ M was observed (Fig. 3.6a). Within this concentration range, the intensity-concentration relationship demonstrating a wide linear dynamic range for the two characteristic SERS 1394 and 1563 cm⁻¹ lines showed a decent correlation corresponding to an R^2 value of 0.981 and 0.979, respectively (Figs. 3.6b and 6c). The detection limit of the developed method was confirmed to be as low as 10⁻¹⁴ M CP concentration. The observed detection limit was the lowest concentration ever detected for CP when compared to other previously reported analytical approaches (Table 1). Moreover, to rectify the discerning ability of the hybrid AgNS@V_{0.25}(Zr_{1.75})CT_x substrate, an interference study was conducted, where the solutions of the probe molecule (10⁻⁵ M CP) and other interferent drug compounds, namely valeric acid (VA), citric acid (CA), and amphetamine (AN), of 10⁻⁴ M concentration each were mixed. Fig. 3.7a demonstrates the characteristic SERS spectra of CP after adding the interferents. The characteristic spectrum is still persistent with almost no recognizable peak displacement nor a change in the spectral pattern observed, signifying that such a SERS substrate can selectively interact and distinguish between the interferents and the probe CP molecules. The SERS method can detect analytes at concentrations as low as parts per trillion (ppt), making it an ideal tool for monitoring ultra-trace levels of bioactive compounds. Hence, the hybrid substrate designed using bimetallic MXenes has proven to be merely insensitive to matrix effects,

allowing the possibility for direct analysis of complex samples, such as water, soil, or biological fluids without extensive sample preparation. Besides, using this approach in a portable instrument can be deployed for in-situ analysis, enabling rapid response to contamination events. In addition, it can have a profound impact on assessing the impact of wastewater treatment plants, agricultural runoff, and livestock operations on antibiotic contamination in water bodies. Studying the absorption, distribution, metabolism, and excretion of CP in humans and animals is highly proposed to optimize drug therapy.

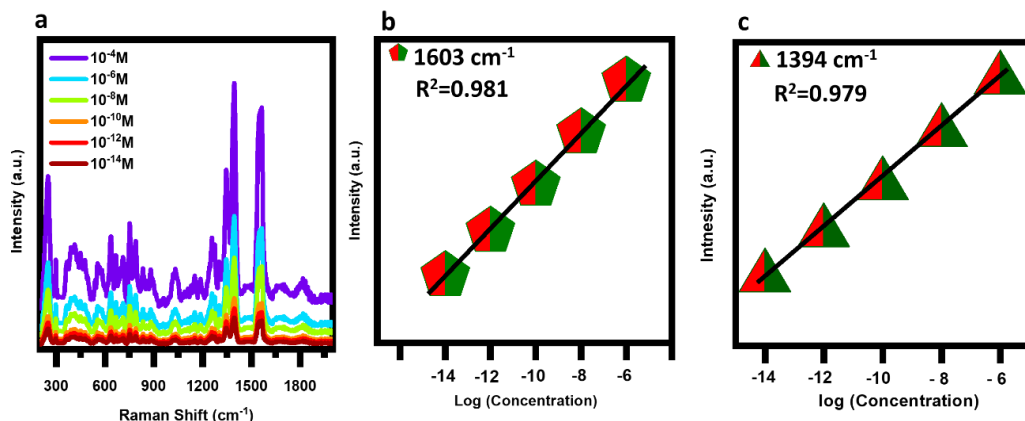


Figure 3. 6: (a) SERS spectra collected for the CP concentrations in the 10^{-4} - 10^{-14} M region in aqueous media using the hybrid $\text{AgNS@V0.25(Zr1.75)CTx}$ substrate, and (b) the detected linear dynamic range and corresponding calculated correlation coefficients of SERS intensity vs. the logarithm of CP concentrations for the two characteristic peaks observed at 1394 and 1603 cm^{-1} .

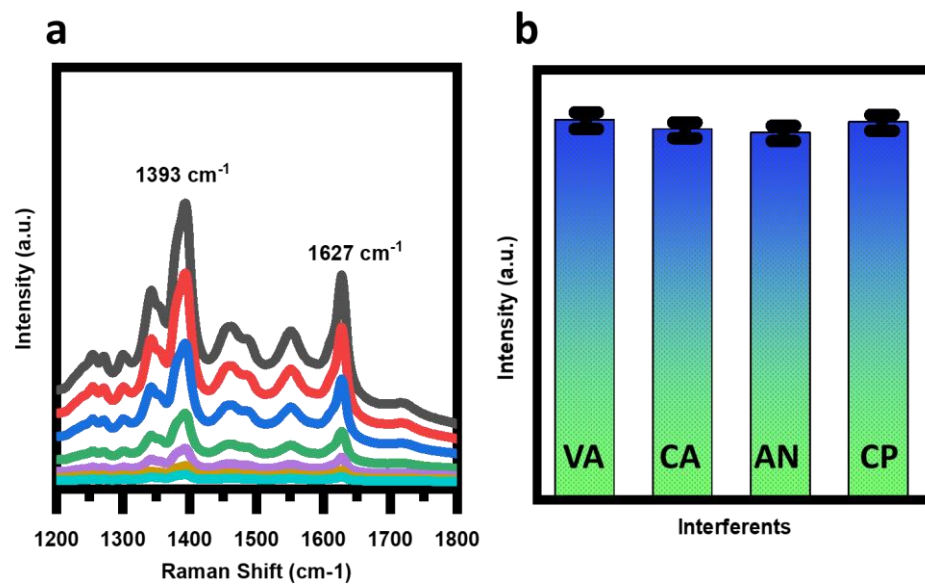


Figure 3. 7: (a) Characteristic SERS spectra of the CP (10-5 M) after being mixed with selected interferents (10-4 M each), namely valeric acid (VA), citric acid (CA), and amphetamine (AN), and (b) the selectivity outcome of CP in terms of SERS intensity of the probe compared to the selected interferents.

4 CHAPTER

Fast and Sensitive Detection of Procainamide: Combined SERS and DFT Modeling Studies

Taken from Mahar, Nasurullah, Muhammad Haroon, Tawfik A. Saleh, and Abdulaziz A. Al-Saadi. "Fast and sensitive detection of Procainamide: Combined SERS and DFT modeling studies." *Journal of Molecular Liquids* 343 (2021): 117633.

4.1 Introduction

Procainamide (PA) is an antiarrhythmic agent mainly for cardiac medication. It is also extensively used to cure ventricular arrhythmia or supraventricular arrhythmia for almost half a decade [179]. Other illnesses, such as ventricular tachycardia, atrial flutter and fibrillation, AV nodal re-entrant tachycardia, as well as Wolf Parkinson-White syndrome [179], [180], have been treated with PA-based formulations. Another historic use of PA was diagnostic testing for Brugada syndrome, although it is no longer used due to the low sensitivity of detection [181]. Besides its cardiac-related applications, it decreases the nephrotoxic and hepatotoxic influences of cisplatin [182], [183]. The continuous use of PA medication, however, posed potentially serious adverse effects, including lupus-like syndrome, bone marrow toxicity, polymorphous ventricular tachycardia, hypotension, and cardiac toxicity [184], [185]. It is metabolized to N-acetyl procainamide (NAPA) by N-acetyltransferase-II in the liver and is excreted through urine in greater proportions as NAPA and unmetabolized PA. NAPA presents a comparable pharmacologic activity and, hence, similar adverse effects [179], [186]. Therefore, the development of a reliable and

sensitive analytical approach for the detection of the concentrations of PA in aqueous solutions is necessary to investigate the pharmacodynamics and toxicodynamic properties.

Due to the importance of having fast and reliable determination tools of trace PA concentrations, several analytical protocols have been developed to quantify PA in plasma, urine, and blood. These protocols were established using a variety of techniques, namely thin-layer chromatography [187], high-pressure liquid chromatography (HPLC), ultra HPLC [179], PVC membrane-based potentiometric sensors [188], and molecular imprinted electrochemical sensors based on glassy carbon electrodes [189]. Moreover, spectrophotometric methods that employ chemical sensors, such as Bratton–Marshall reagent, which convert PA into [190] a Schiff base detectable at 542 nm were successfully established. Such methods are also useful for the detection of PA and NAPA in drugs through the colored naphthoquinone-4-sulfonic acid product with linearity ranging from 50 to 250.0 $\mu\text{g ml}^{-1}$ for PA [190]. Flow injection analysis was also explored for the possible detection of PA, and the absorption was measured at 480 nm [190]. The aforementioned methods reliably achieved a concentration detection of as low as 10^{-9}M , with multi-step sample preparation, extraction, evaporation, and reconstitution. The development of an analytical technique which can go to lower detection limits than ones reported with feasible sample handling and preparation has been highlighted in this work using the surface-enhanced Raman scattering (SERS) spectrophotometric approach. SERS has been more attractive compared to other analytical techniques due to its high-cost efficiency, short analysis time, sample non-destructiveness, most robust, rapid response, and ultra-sensitivity [191]. It is found particularly useful in the determination of trace amounts of

bio-organic molecules with significant Raman signal enhancements by a factor up to 10^6 [192].

Herein we report a sensitive and fast SERS-based analytical methodology for the quantification of PA in aqueous media using silver nanoparticles (Ag-NPs) as a SERS substrate. The Ag@PA demonstrated strong Raman signal enhancements compared to individual PA and NPs and possesses the features of low detection limits, high sensitivity, and good linearity. By utilizing the electromagnetic mechanism due to the interaction of Ag-NPs with PA drug, a low detection of 10^{-10} M towards PA was obtained.

4.2 Experimental

4.2.1 Chemicals and Synthesis

Procainamide hydrochloride (PA), named also *p*-amino-N-[2-(diethylamino)ethyl] benzamide monohydrochloride, silver nitrate (99.9995%), sodium citrate (>98%), and citric acid (99.899%) were obtained from Sigma-Aldrich (St. Louis, MO). The sodium borohydride (99.9%) was obtained from Alfa Aesar (Wardhill, MA). All the reagents were utilized without additional purification. The solutions were made in deionized water and the glassware used for experimentation was drenched in sulfuric acid overnight then washed carefully with distilled water followed by deionized water.

4.2.2 Preparation of Silver Nanoparticles

The silver nanoparticles (Ag-NPs) were prepared by the following method (Figure 4.1) with modification on that reported in the literature [193]. In a typical method, 0.1 mL of silver nitration (0.10 M), 3.40 mL of 0.17 M sodium citrate, and 0.60 mL of 0.17 M citric

acid were combined in a round bottom flask with 45.0 mL of deionized water and stirred for 5 minutes at room temperature. Later, 0.20 mL of newly made sodium borohydride (0.5 mM) was then added slowly into the mixture and allowed to stand for 5 min. After that, the system was heated at 100 °C under continuous stirring for 1 hour. The heating was then off and after cooling the obtained Ag-NPs were collected.

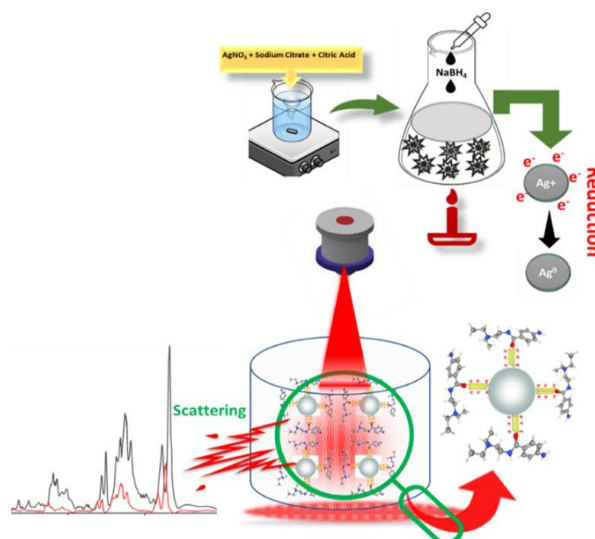


Figure 4. 1: Scheme for the synthesis of silver nanoparticles and the associated SERS mechanism

The characterization of the prepared Ag-NPs was performed by Fourier-transform infrared spectrometer (FT-IR), UV-Visible spectrometer, and field emission scanning electron microscope (FE-SEM). The FT-IR spectrum was collected in the wavelength range from 400 to 4000 cm^{-1} with 2 cm^{-1} resolution by Nicolet 6700 FT-IR spectrometer equipped with KBr beam splitter and DTGS KBr detector. The UV-Visible spectrum was collected with the use of a UV-Visible spectrophotometer (model: Agilent, with standard quartz cuvettes). FE-SEM images were documented with JEM-2100 F Field Emission Microscope (Model: JEOL-USA) at 200 KV speeding up voltage.

4.2.3 SERS Study

Solutions of PA with different concentrations extending from (0.1 M to 10^{-10} M) were prepared in deionized water for SERS experiments by the subsequent dilution method. The spectra of PA were measured using HORIBA Scientific LabRAM HR evolution spectroscopy equipped with an internal He-Ne 17 mW red laser at 633 nm excitation wavelength which attained a high signal-to-noise ratio with improved baselines and symmetric peaks [194], [195]. A 50x objective lens was utilized to focus the laser on the solutions. The microscope was equipped confocally with 600 mm focal length spectrograph and two switching gratings. A laser power of 5% with data acquisition time every 25 seconds and 4 accumulations of collection for SERS spectra were selected. The spectra were collected at an optimized ratio of 1:1 of PA and Ag-NPs which were mixed in a cuvette that is 1 cm height and 1 cm radius. No sign of degradation was observed during the Raman measurements.

4.2.4 DFT Calculations

The DFT calculations were carried out using the B3LYP density functional introduced by Becke [196] and Lee et al [197] with aid of Gaussian 09 package [198]. Two different basis sets were employed to demonstrate the orbitals of metal and non-metal atoms. Stuttgart/Dresden (SDD) basis set was used for silver atoms, while 6-311G(d,p) was employed for other non-metal atoms. The basis sets were chosen in order to produce results consistent with the experimental findings [199], [200]. The frequency calculation was conducted with the same basis sets, and complete relaxed geometries were obtained by confirming that no imaginary frequency was observed [22]. The calculated wavenumbers

were scaled with a scaling factor of 0.962 for better agreement with experimental spectra. The optimized geometry of the procainamide molecule is given in Fig. 4.2. The vibrational assignments of the PA fundamentals before and after the interaction with the silver cluster were concluded with the help of GaussView6 software visualization capability. The energy interaction was computed by taking the energy difference before and after the interaction between the drug molecule and Ag-cluster.

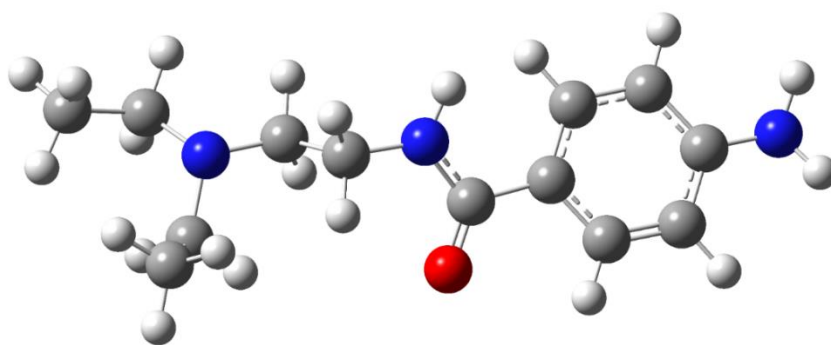


Figure 4. 2: Theoretically Optimized Structure of Procainamide

4.3 Results and Discussions

4.3.1 Silver nanoparticles Characterization

Ag-NPs prepared in this study were characterized by several techniques. The UV-Vis spectrum of Ag-NPs shows an excitation at 409 nm (black line) in 50 mM solution Fig. 4. 4(a) belonging to the synthesized Ag-NPs. The band position exhibited a small shift due to the small size of nanoparticles compared to the literature reported band position at 420 nm [203], [204]. The shoulder observed at 500 nm on Fig. 4. 4 (a) is ascribed to size heterogeneity of Ag-NPs, which could be due to surface defects in nanoparticles [205]. The peak excitation observed at 320 nm is due to the mixture of the drug and Ag-NPs. The red

shift associated with the drug molecules from 278 to 320 nm and the blue shift for Ag-NPs from 409 to 320 nm confirmed the adequate interaction between the drug and Ag-NPs. It is ascribed to the charge transfer between procainamide molecules and the Ag-NP substrate [206], [207].

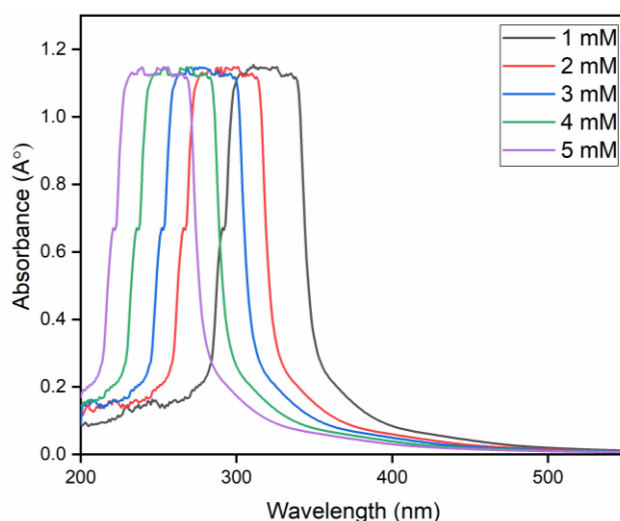


Figure 4. 3: UV/Vis Spectra of the drug at different concentrations

The stability of Ag-NPs was studied by mixing different concentrations of drug (1 mM to 5 mM). No decrease in the intensity was observed. The nanoparticles were thus found stable and consistently exhibited blue shifts due to the interaction with different drug concentrations, as depicted in Fig. 4.3. Fig. 4. 4(b) displays the FT-IR spectrum of Ag-NPs with a broad band recorded at 3446 cm^{-1} assigned to the -OH stretching pertains to the presence of moisture on Ag-NPs. The sharp peak recorded at 1574 cm^{-1} is attributed to the citrate stabilizer used for the preparation of NPs and could be ascribed to the C=O stretching vibrations. The band at 1376 cm^{-1} is mainly associated with the C-O stretching. Moreover, the band located at 590 cm^{-1} is attributed to CH_2 rocking and COO deformation modes. The recorded FT-IR spectrum agrees with the literature [208]. The Ag@PA

spectrum shown in Fig. 4. 4(b) depicts band shifts and changes in intensity confirming the interaction of the drug with the silver atoms. The 3446 cm^{-1} band has shifted to 3377 cm^{-1} , and its intensity got significantly enhanced. Similarly, the 1574 cm^{-1} infrared band has been shifted, while the 1376 cm^{-1} band has been quenched.

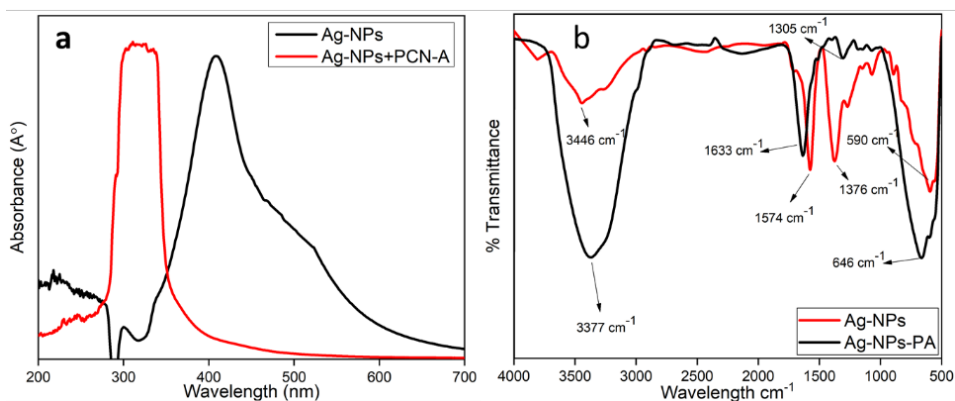


Figure 4. 4: (a) UV-Vis and (b) FT-IR spectra of the prepared Ag-NPs before (black) and after (red) being mixed with PA.

The morphology of Ag-NPs as shown from the FE-SEM images Fig. 4.5 revealed a spherical shape of the nanoparticle of about 20 nm average size. Such a small size with a larger surface area enabled sufficient accumulation, and thus a greater number of drug molecules are irradiated leading to an adequate interaction between PA molecules and Ag-NPs, which resulted in considerable peak intensity enhancements.

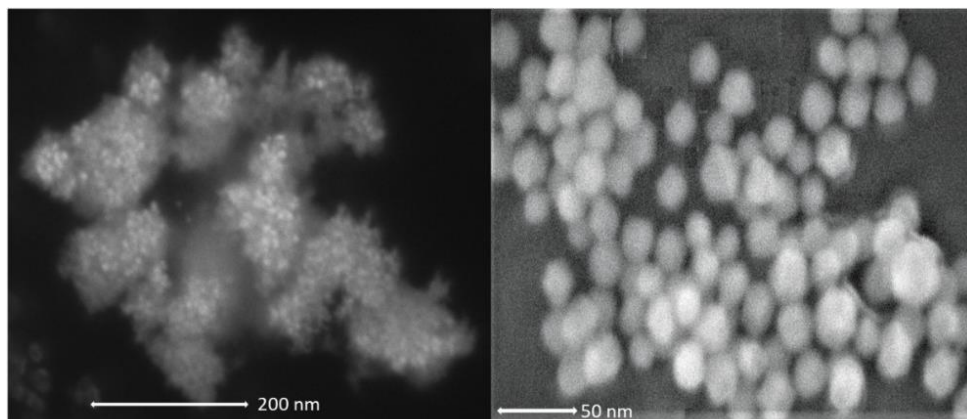


Figure 4. 5: FE-SEM images showing the morphology of the prepared Ag-NPs.

The Raman spectrum Fig. 4. 6 shows that there are no peaks associated with Ag-NPs in the range of 300 to 4000 cm^{-1} , allowing the use of the substrate in this range without significant interference with PA. Hence, SERS peaks observed below the 2000 cm^{-1} range Fig. 4.7 can be considered only for the PA molecules.

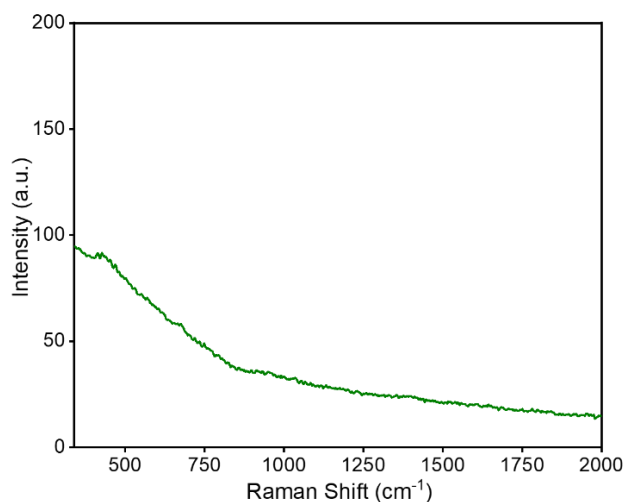


Figure 4. 6: Raman spectra of the as prepared silver nanoparticles

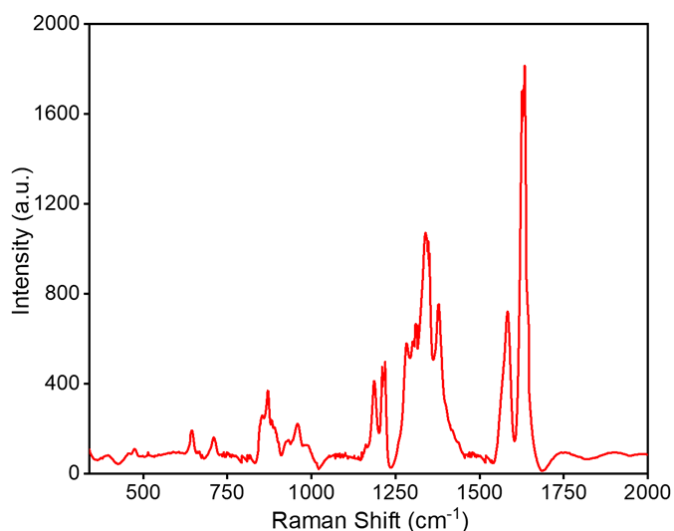


Figure 4. 7: The Raman spectra of the Procainamide drug

4.3.2 SERS Detection

Some chromatographic and spectrophotometric approaches have been designed for sensitive and accurate detections of PA. Despite the good and reasonable determinations demonstrated, the research to achieve even lower detection limits and more feasible protocols is still ongoing. The implementation of Raman spectroscopy to explore biomolecules and their trace presence in aqueous and nonaqueous systems [209], [210] presented a potential path to advance our analytical capabilities in the area of pharmaceuticals. The multiband structure of Raman spectra has enabled us to discriminate the false-positive results due to interfering compounds [211] and more importantly to provide molecular fingerprints capable of facilitating ultra-trace limits of detection and even in some cases on-site determination [192]. The coinage metal nanoparticles associated mainly with silver and gold are utilized to fabricate active substrate due to their stability, as well as the chemical and electromagnetic signal amplifications [192].

In previous reports [192], [200], [212], [213] we were able to successfully develop SERS and electrochemical SERS protocols for the detection of trace procaine concentrations. This has prompted us to explore the Raman signal amplification phenomenon in the corresponding procainamide (PA) drug. The SERS effect was efficiently utilized as presented in this work to determine a trace concentration of less than nanomolar PA in aqueous solutions. The SERS spectrum of PA mixed in a 1:1 portion with the NaBH_4 reduced Ag-NPs substrate is compared with the normal PA spectrum, as can be seen in Fig. 4. 8. Significant enhancements associated with NH_2 bending, $\text{C}=\text{O}$ stretching, and $\text{C}-\text{C}$ stretching, as well as $\text{C}-\text{N}$ stretching modes were noticed. The changes in these peak positions in the SERS as compared to the normal Raman spectrum confirmed the meaningful interaction of the drug with the substrate. The mechanism of enhancement using silver substrates could be referred to as the interplay of chemical and electromagnetic interactions [212], [214].

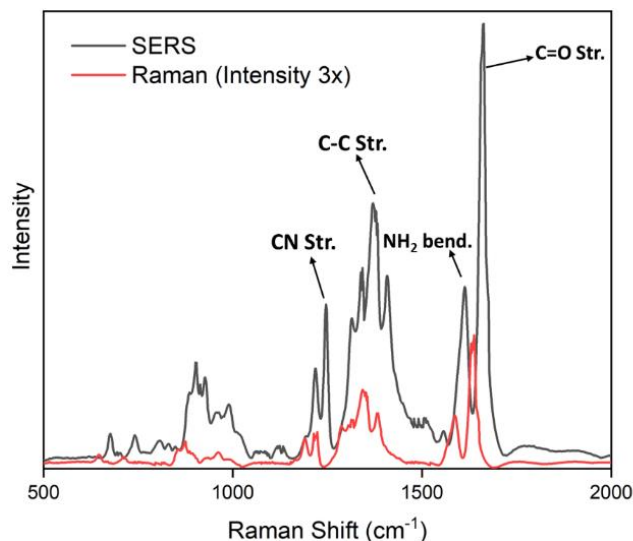


Figure 4. 8: SERS spectrum of PA at a concentration of 0.5 M (black) compared with normal Raman spectrum (red) of PA solution without Ag-NPs.

The SERS spectra recorded in the range of 325-2000 cm^{-1} at various concentrations are depicted in Fig. 4. 9(a). Varying the concentration of PA results in a systematic change in the Raman intensity. It has been inducted from Fig. 4. 9(b) that the SERS peak intensities increased logarithmically with the concentrations of PA in the solution. Hence, the intensity is linearly proportional with the logarithm of the drug concentrations, and thus the spectral enhancements can be in relation with the drug molecules' population and their interaction with nanoparticles. An interesting observation from the SERS spectra is that several of the PA peaks encountered significant enhancements in their intensities. Representative prominent peaks (labeled in Fig. 4.8) and their intensities were verified to have a systematic change with drug concentrations in the range of 1 M to 10^{-9} M, as presented in Fig. 4. 9(b) for 1661 cm^{-1} (iv), 1613 cm^{-1} (iii), 1370 cm^{-1} (ii) and 1246 cm^{-1} (i). The distinct intensity, shapes, and positions observed were due to different types of interactions between PA drug and Ag-NPs. The lowest detectable concentration of PA was attained at 0.5×10^{-10} M with a calculated enhancement factor of 10^8 [215], [216] that is comparable to reported literature values [217], [218]. The peaks enhanced observed for the C=O stretching at 1637 cm^{-1} and NH_2 bending at 1580 cm^{-1} have blue-shifted to 1661 and 1613 cm^{-1} , respectively, which can be due to the high plasmonic light field resonance fashioned by surface roughness of silver nanomaterials upon Raman laser excitations. That causes an increase in the light scattering of PA molecules residing within the plasmonic field. Such observations are in good agreement with the sliding change in wavenumbers and prove the possible interaction between the Ag-NPs based substrate and PA drug. The experimental and DFT calculated SERS spectra are given on Fig. 4.10.

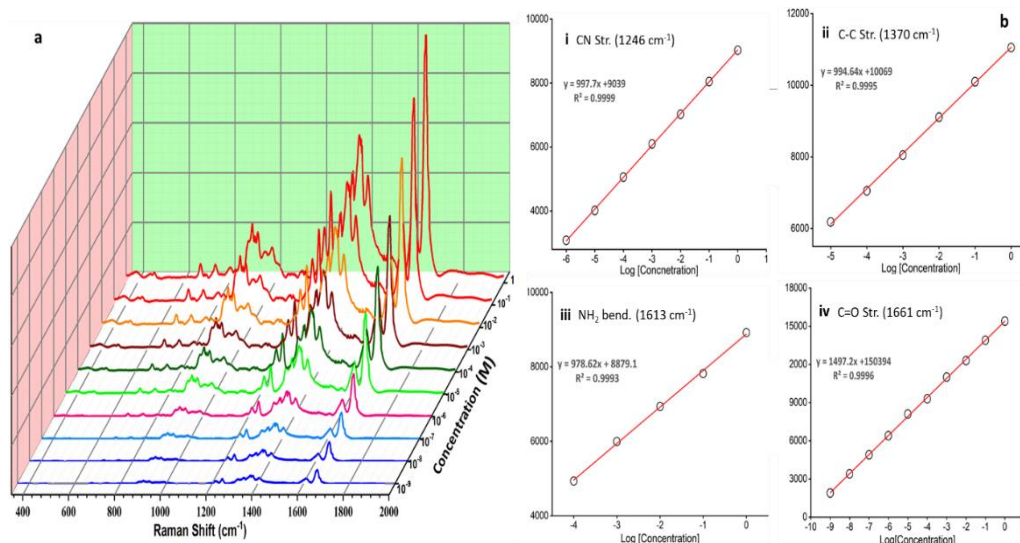


Figure 4. 9: (a) SERS spectra of PA solutions at different concentrations ranging from 1M to 10^{-9} M. (b) Logarithmic relationships between the Raman intensities in arbitrary units (y-axis) and concentrations of PA for the bands positioned at (i) 1246 cm^{-1} , (ii) 1370 cm^{-1} , (iii) 1613 cm^{-1} and (iv) 1661 cm^{-1} .

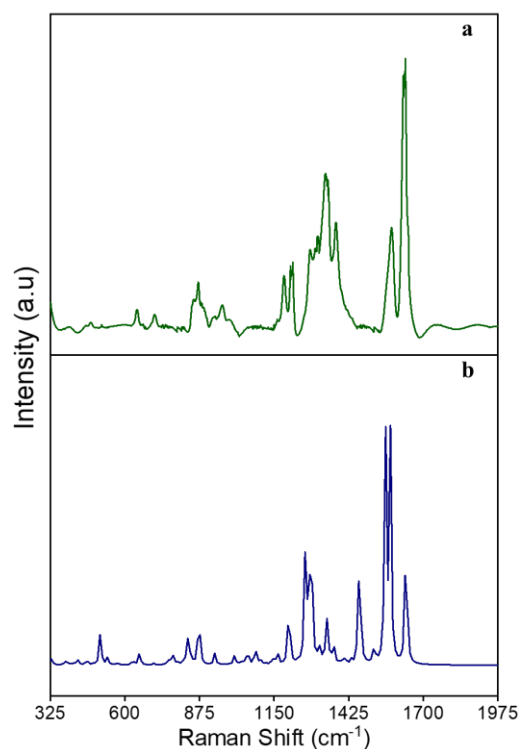


Figure 4. 10: Theoretically computed Raman and SERS spectra of the Procainamide drug

The outcome of SERS approach presented here is compared with previously reported methods (Table 2.1) in terms of linear dynamic ranges, regression coefficients, and limits of detection. The SERS approach is differentiated with its ultra-trace detection limit of PA and a wider dynamic range, with a better signal-to-noise ratio [219].

Table 4: Comparison of reported analytical methods for the trace detection of PA in aqueous solution. LDR: Linear dynamic range, LOD: Limit of detection.

Method	LDR	LOD	R^2	Reference
SFM	5×10^{-6} to 5×10^{-5} M	1.5×10^{-6} M	0.988	[220]
PVC Sensors	1×10^{-3} to 8×10^{-6} M	2.4×10^{-6}	0.998	[221]
Spectrometric	50-700 $\mu\text{g/ml}$	25 μg	0.999	[222]
Ultra HPLC	20-10000ng/ml	20 ng/ml	0.998	[223]
CE	1-200 $\mu\text{g/ml}$	1.235 $\mu\text{g/ml}$	0.995	[224]
EC-sensors	4.00×10^{-5} – 4.97×10^{-9} M	1.30×10^{-9} M	0.994	[225]
GC	4-10 $\mu\text{g/mL}$	0.5 $\mu\text{g/mL}$	0.993	[226]
SERS	1 M 0.5×10^{-10} M	0.5×10^{-10} M	0.999	our Work

4.3.3 DFT Modeling of Procainamide Interaction with Nano-substrate

First-principle calculations were undertaken to illustrate potential mechanisms of interaction between the substrate and analyte [227]. To achieve that, an Ag-cluster

containing four silver atoms with rhombus geometry was optimized and utilized to mimic the interaction at the atomistic level. The rhombus-shaped silver cluster has been reported and implemented in quantum chemical investigations due to its stable geometry owing to the higher binding energy per atom and to the electron sustainability it provides for ionization [208]. Recognizing possible interaction positions in PA from the molecular electrostatic potential (MESP) map was established and shown in Fig. 4.12. The primary amine and to a lesser extent the amide nitrogen regions both possess a high electrostatic potential of low electron density, while a high electron density was predicted in the vicinity of the carbonyl moiety. These sites have potential for the interaction with silver nanoparticles. The charge transfer process between the target molecule and substrate can be traced by analyzing Mulliken atomic charges. It was noticed that electrons tend to migrate from silver to PA in both $\text{C=O}\dots\text{Ag}_4$ and $\text{H}_2\text{N}\dots\text{Ag}_4$ modes of interaction (Table 4.2). Another helpful parameter to assess favorable interactions is the computed binding energy. In this study, the binding energy of $\text{C=O}\dots\text{Ag}$ -cluster interaction was calculated to be -3.03 kcal/mol with a binding distance of 2.43 Å, which was found more feasible as compared to the binding energy -0.544 kcal/mol and binding distance 2.35 Å in the case of $\text{H}_2\text{N}\dots\text{Ag}$ -cluster. Another observation from the DFT results (Table 4.2) is the unfavorable ring...Ag-cluster type of interaction that corresponds to positive binding energy. This scenario is interestingly unlike the ones reported for the counterpart procaine molecule, in which the silver nanoparticles tend to interact with the aromatic ring [212]. The replacement of the ester group in procaine with an amide group in procainamide seems to impact the electronic nature of the aromatic ring. A bonding distance of 3.75 Å and an interaction energy of 4.04 kcal/mol (suggesting a non-attractive interaction) for the

Ag₄...C-Ring type (Table 4.2) both indicate that the ring in PA was not showing a sustainable interaction. The atomic charge distributions of procainamide and procaine were analyzed (Fig. 4.11), and it can be noticed that in procaine the aromatic ring close to the carbonyl group possesses a higher negative charge, yet it carries a very slightly positive charge in the case of PA.

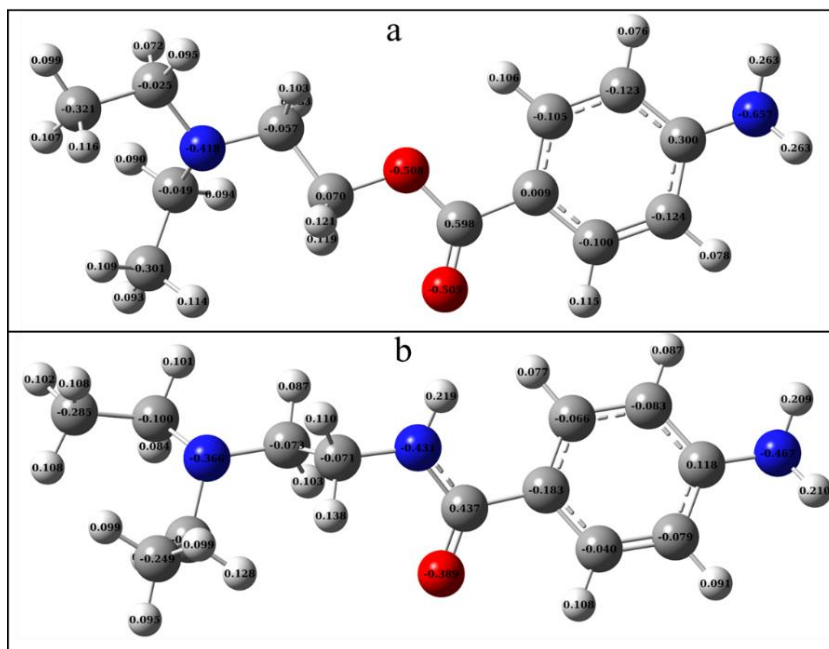


Figure 4. 11: Theoretically optimized structure of the drugs showing the possible sites of interaction with SERS substrates.

From the comparison of atomic charges, the amide linkage influences the charge density of the benzene ring and thus minimizes the chance of PA to interact with the Ag-NP substrate through the aromatic moiety of the molecule.

Table 5: Interaction energies, binding distances and changes in the sum of Mulliken charges for possible interaction modes as computed at the B3LYP/6-311G(d,p) level.

Interaction mode	Interaction Energy (kcal/mol)	Binding Distance (Å)	Mulliken Charge	
			Free	Complex
-C=O...Ag ₄	-3.030	2.43	Ag ₄ : 0.000	Ag ₄ : -0.113
				PA: +0.113
H ₂ N...Ag ₄	-0.544	2.35	PA: 0.000	Ag ₄ : -0.0645
				PA: +0.0645
C-Ring...Ag ₄	+4.042	3.75		Ag ₄ : -0.0623
				PA: 0.0623

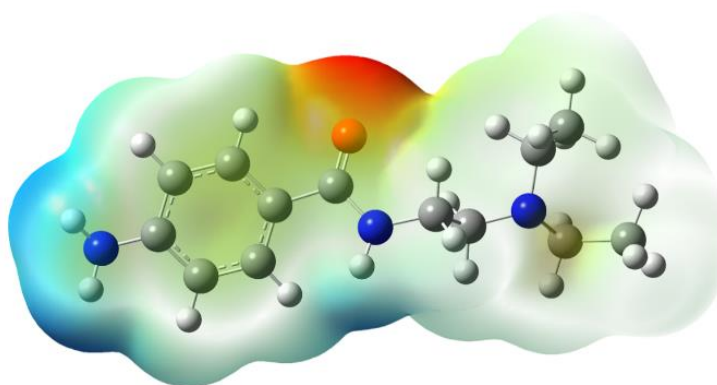


Figure 4.12: Calculated molecular electrostatic potential (MESP) map of PA. Electron-rich and electron-deficient regions are displayed with red and blue colors, respectively.

Table 6: Vibrational assignments of the main peaks in the experimental^a and calculated^b Raman and SERS spectra of

PA in the range below 2000 cm ⁻¹ .					
Approximate description	Experimental (cm ⁻¹)		Calculated (cm ⁻¹)		
	Raman	SERS	Raman	Interaction mode	
				C=O...Ag ⁴	H ₂ N...Ag ₄
ν (C=O str.)	1637 vs	1661 vs	1633 (100)	1635 (100)	1642 (18)
ν (NH ₂ bend)	1580 m	1613 s	1560 (40)	1597 (21)	1561 (100)
ν (CC str.)	1380 w	1370 s	1372 (42)	1345 (22)	1345 (21)
ν (Ring bend) , ν (CH ₂ def.)	1340 s	1342 s	1345 (55)	1300 (47)	2191 (50)
ν (CN str.)	1284 vw	1314 m	1282 (44)	1273 (17)	1260 (7)
ν (CH ₃ def.) , ν (CH bend)	1220 w	1246 w	1264 (38)	1210 (11)	1210 (9)
ν (CH bend)	1186 w	1217 m	1200 (28)	1180 (9)	1165 (3)
ν (Ring breath)	959 vw	989 m	932 (22)	985 (3)	972 (24)
ν (CH bend)	873 vw	925 w	877 (17)	931 (2)	941 (23)
ν (CH bend) , ν (CCN def.)	854 vw	885 m	832 (21)	877 (31)	868 (4)
ν (Ring bend)	709 vw	743 w	778 (4)	760 (2)	706 (2)
ν (CNC def.)	645 vw	674 w	652 (4)	652 (4)	652(1)

4.3.4 Vibrational Assignments of SERS Spectra

To have more insights on the type of drug/substrate interaction, the fundamental modes observed in the Raman spectra of the PA and PA@Ag-NPs aqueous solutions were analyzed. The spectra obtained by SERS experiments depict clear wavenumber shifts accompanied by an increase in peak intensities when compared with the normal Raman spectrum of PA. Vibrational assignments were performed in the range below 2000 cm^{-1} (Table 4.3). To elaborate the effect of the band shifts, it was further undertaken with the help of the visualization tools in GuassView 6.0 [228] for the theoretical spectra conducted at the B3LYP/6-311G(d,p) level. The computed spectra were in fair agreement with experimental results (Table 4.3). Further, Fig. 4.13 depicts the computational SERS spectra of PA corresponding to the $\text{H}_2\text{N}\dots\text{Ag}_4$ and $\text{C}=\text{O}\dots\text{Ag}_4$ interactions of the drug molecule with the silver nanocluster. The spectral features of the simulated SERS spectra of both interactions match well with the experimental one. Given that these interaction modes are energetically favorable (Table 4.3), they are both believed to contribute to the most prominent SERS peaks observed at 1661 cm^{-1} and 1613 cm^{-1} . The other vibrational frequencies are also listed in Table 4.3 and compared as possible with the experimental spectra.

The stretching vibrational modes in the SERS spectrum assigned to C=O group were observed at 1661 cm^{-1} (1635 cm^{-1} from DFT). These wavenumbers are in accord with reported C=O stretching modes [229]. Likewise, the wavenumber peak noticed at 1613 cm^{-1} (calculated as 1597 cm^{-1} and 1561 cm^{-1}) were assigned to the NH_2 bending coupled with C=C stretching modes, which were confirmed from reported NH_2 bending and C=C stretching modes [229], [230]. Since the calculated SERS intensity of this specific frequency is the highest in the $\text{H}_2\text{N}\dots\text{Ag}_4$ mode of interaction, was assigned exclusively to

the NH₂ bending mode (Table 4.3). Besides, the uncoupled C-C stretching was observed at 1370 cm⁻¹ while calculated at 1345 cm⁻¹ in the SERS spectra. The peak located at 1342 cm⁻¹ and (1300 cm⁻¹ from DFT) was coupled by the ring stretching and CH bending modes without evidence of wavenumber shift encountered. The very weak Raman peak observed at 1284 cm⁻¹ was significantly enhanced and blue-shifted to 1314 cm⁻¹ in the SERS spectrum. This was attributed to the CN stretching mode, and it is considered a reference SERS peak that demonstrated a consistent intensity/concentration linearity (Fig. 4.6). The assignments assent to SERS peaks at 925 cm⁻¹, 885 cm⁻¹ and 743 cm⁻¹ were made to the CH bending, CCN deformation and aromatic ring deformation modes, respectively, in fair agreement with the interaction associated with the carbonyl group (931 cm⁻¹, 877 cm⁻¹, and 760 cm⁻¹ from DFT, respectively). These bands have a resemblance to reported literature values [231]. The peak detected at 674 cm⁻¹ (and at 652 cm⁻¹ from the DFT calculations) is highly coupled with both the ring bending and CNC deformation modes [45].

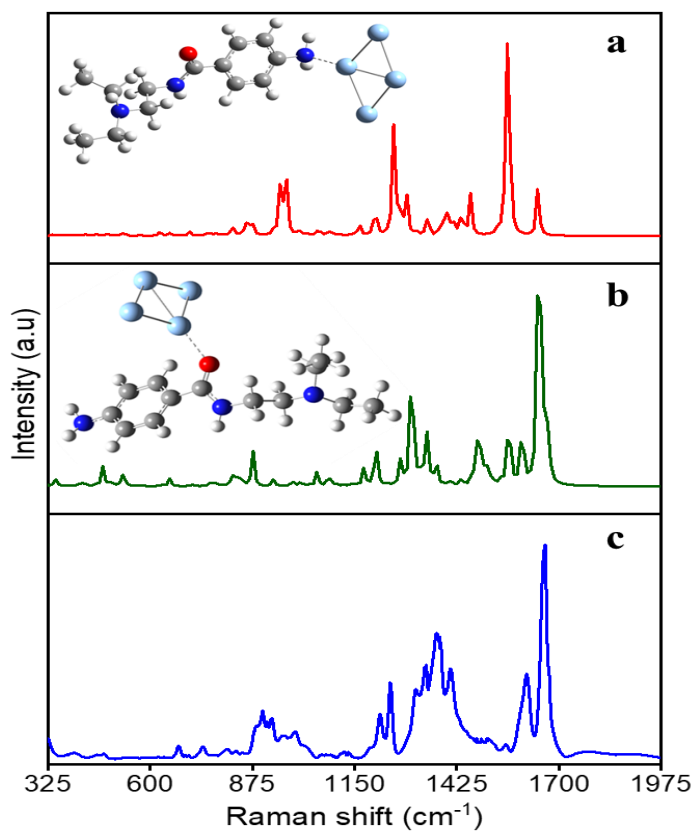


Figure 4. 12: Calculated SERS spectra modeling silver cluster interactions with (a) the primary amine group and (b) the carbonyl group, as compared with (c) the experimental SERS of procainamide.

5 CHAPTER

Spectroanalytical SERS-based detection of trace-level procainamide using green-synthesized gold nanoparticles.

Taken from Mahar, Nasurullah, Muhammad Haroon, Tawfik A. Saleh, and Abdulaziz A. Al-Saadi. "Spectroanalytical SERS-based detection of trace-level procainamide using green-synthesized gold nanoparticles." *Surfaces and Interfaces* 31 (2022): 102059.

5.1 Introduction

The drugs used for pre-and post-operative treatment have a key impact on patients' health if not consumed properly with appropriate dosing frequency. The long-term use of drugs can adversely affect the physiology of organs and may lead to organ failure if not monitored properly. Therapeutic drug monitoring was introduced in the 70s originally, to prevent overdosing, toxicity, as well as the increased residence time of drugs in the human body [232]. Subject to the risks associated with the medicinal therapy, clinical assessments were conducted to develop an understanding of the pharmacokinetics and pharmacodynamic (PK-PD) factors of the drug [233]. The procainamide (PA) is an efficient type I antiarrhythmic, which means it acts against a variety of atrial and ventricular dysrhythmias in both pre-and post-operative treatments [234][235], [236]. Another important usage of PA is for Brugada syndrome [182], and also for cancer prevention by inhibiting the hemimethylase activity of DNA methyltransferase 1 (DNMT1) [237], [238].

Generally, PA is well tolerated by patients, nevertheless, numerous statements have been published regarding its adverse effects e.g., it results in drug-induced lupus in about 25-30% of the users, decreases the number of cells in bone marrow, and may cause renal failure among the patients with chronic kidney disease by accumulating in kidneys [239], [240]. It also results in cardiotoxicity, myocardial depression, and polymorphic ventricular tachycardia [241], [242]. Other adverse effects include lethargy, confusion, seizures, antimuscarinic effects, agranulocytosis, and thrombocytopenia have been reported with the long-term use of PA [243]. In addition, as PA has a similar structure to amphetamine, the patients with PA overdose may show false-positive results for amphetamine [244]. The drug is promptly absorbed into the body raising its plasma levels between 15-60 min following the oral or intravenous intake [245], [246]. The liver as a major metabolic factory breaks down the PA into secondary metabolites e.g., N-acetyl procainamide with antiarrhythmic activity, a major metabolite along with many other sub metabolites. PA is metabolized to a limited extent in the human body, about one-half of the administered medicine is excreted in its original form through urine within 3-4 hours from its ingestion [247]. Consequently, its clearance rate needs to be examined by verifying its lowest concentration detected in urine. This facilitates the physicians by studying the overall PK and PD of drugs that could help in predicting the potential harmful effects. Various analytical methods have been developed to detect the PA levels in urine namely, high-pressure liquid chromatography coupled (HPLC-UV) [245], capillary zone electrophoresis (CE) [248], electrochemiluminescence (ECL) [249], thin-layer chromatography (TLC) [250], reverse-phase liquid chromatography (RP-LC) [251] and enzyme-based immune assay techniques[252].

The above-mentioned analytical methods attained a concentration detection limit to only 10^{-6} M. These methods have disadvantages of many steps in sample preparation, time-consuming, and are expensive. The solution to these shortcomings is to develop an analytical method that can detect much lower concentrations, and high sample throughput with cost-effective, reagent-free, quick sample preparation and fast analysis is the urgent need of the present day. Surface-enhanced Raman spectroscopy or surface-enhanced Raman scattering (SERS) spectrophotometric approach is the most modern, rapid, robust, ultra-sensitive, non-destructive, and a cost-efficient technique with tremendous multiplexing capabilities [253]. It is highly useful for the determination of illicit drugs at trace amounts, especially bio-organic molecules with high Raman signals.

Among the nanoparticles as an active SERS substrate, the nanoparticles with plasmonic characteristics have gained a special interest owing to their unique physical and chemical properties. In particular, green synthesized gold nanoparticles (Au-NPs) as a novel approach for SERS detection due to their being more efficient, simpler, economic, free of biohazards, high biocompatibility, and inertness, ease of preparation have drawn the attention of researchers [254], [255]. Besides, the more prominent characteristic e.g., when irradiated with high wavelength laser light, owing to a larger radius of the atom than the wavelength of light, leads to free electrons in Au-NPs resulting in collective coherent non-propagative oscillations of the surface plasmons (hot spots), hence the name localized surface plasmonic resonance (LSPR) [256]. This results in strong interaction between the analyte and Au-NPs resulting in signal amplification called Raman enhancement or simply the surface-enhanced Raman spectroscopy (SERS) [254], [257]. The LSPR depends on the size and shape of the nanoparticles, and mainly those ranging in size between 30-100 nm

have exhibited excellent plasmonic behavior owing to their highly ordered nanogaps and extended edge length, leading to specific regions called hotspots [256], [258].

In our previous analytical approach, we achieved a lower detection limit (10^{-10} M) with a wide linear dynamic range ($0.5\text{-}10^{-9}$ M) for the PA drug in aqueous media using silver nanoparticles [259]. Herein, we register the highly sensitive and rapid SERS-based analytical method to determine the PA in an actual urine sample and aqueous media using green synthesized Au-NPs in SERS as an active substrate. The Au-NPs owing to their biocompatibility and the average size of (~ 40 nm), their resonant character matches well with higher wavelength laser 633 nm, which results in better amplification in the Raman signal than silver nanoparticles [260]. To the best of our knowledge, the quantitative detection of PA in aqueous and spiked urine samples using green synthesized Au-NPs as SERS active substrate has never been reported in the literature. The results that the Au interactions with PA in spiked urine samples exhibited strong Raman signal enhancement in aqueous and spiked urine samples with an excellent enhancement factor (EF) of 10^9 compared to free urine and PA drug with a limit of detection (LOD) of 10^{-11} M than our previously reported work using Ag-NPs [259]. Besides the DFT calculations, binding energies and Mulliken charges were also testified for the interaction between drug molecules and Au-NPs. The present approach demonstrated high sensitivity, good linearity, and a lower detection limit considerably better than previously reported work.

5.2 Experimental

5.2.1 Materials.

Procainamide hydrochloride (purity 99%, $C_{13}H_{22}ClN_3O$, 271.78 g/mol), sodium citrate (purity >99%, $Na_3C_6H_5O_7$, 258.06 g/mol), citric acid (purity 99.89%, $C_6H_8O_7$, 192.124 g/mol), and Gold (III) chloride (purity 99%, $AuCl_3$, 303.33 g/mol), valeric acid (purity 99.5%, $C_5H_{10}O_2$, 102.133 g/mol), sulindac (purity 99.5%, $C_{20}H_{17}FO_3S$, 356.411 g/mol), ciprofloxacin (purity 99.5%, $C_{17}H_{18}FN_3O_3$, 331.347 g/mol), and ascorbic acid (purity 99.5%, $C_6H_8O_6$, 176.124 g/mol) were purchased from Sigma-Aldrich. The reagent solutions were prepared in D.I water.

5.2.2 Green Synthesis.

To prepare gold nanoparticles using plant leaf extract, the Sidr leaves (known also as Lote tree leaves, which are excellent sources of mucilage and saponins) were collected and washed with water. Then, the leaves were washed with chloroform to remove wax and were allowed to dry. After that, the leaves were powdered by a blender. 5 g powder was added into 100 mL distilled water and heated at 120 °C for 3h. After cooling, the mixture was filtered through Whatman filter paper No.1. The obtained extract is retained for further use. An aqueous solution of 0.1 M gold chloride (100 mL) was prepared. Around 30 mL of the obtained extract was mixed with the gold solution. The solution was stirred vigorously. The sidr leaves (*Zizyphus spina christi*) are rich in organic reducing agents e.g., phenols, alpha-tocopherol, carotene, flavonoids, sterols, tannins, saponin, etc. These constituents, especially flavonoids and phenols, have a strong reducing ability, therefore,

resulting in the reduction of gold metal ions [261]. The reduction of gold ions to gold nanoparticles was proceeded at ambient conditions under stirring for 6h. The gold nanoparticles obtained were washed several times to remove extra unreacted components and impurities. The gold nanoparticles were then dispersed in water under sonication. The structure and composition were well preserved by the use of a citrate capping agent [262]. The stability of Au-NPs was investigated by taking UV-Vis and Raman spectra at different time intervals of up to 15 hours as shown in Fig. 5.2 (a) and (b), respectively. A negligible decrease in absorbance and intensity is observed in both spectra with a time interval of 1 to 15 hours. This revealed that the synthesized nanoparticles are stable and well dispersed. The stability and SERS efficiency were also verified from the reproducibility and interference test of the approach.

The prepared Au-NPs were characterized by UV-Visible, FT-IR, and FE-SEM instruments. The spectrum gathered in FT-IR at wavelength range $4000\text{-}400\text{ cm}^{-1}$ with a resolution of 2.0 cm^{-1} , using Nicolet 6700 FT-IR spectrometer furnished with KBr beam splitter. The UV-Visible spectra were acquired using a UV-Visible spectrophotometer in the range of 200-800 nm. The surface morphology of gold nanoparticles was studied using JEM-2100 F Field Emission Microscope (JEOL-USA) at 200 KV.

5.2.3 Sample preparation.

The PA drug solutions were prepared in deionized water according to subsequent dilution protocols published by Haroon *et al.*, [263]. The final (11 different) concentrations of PA ranged from (1M to 10^{-11} M). The solutions were stable for 1 month at 4 °C, the stability

of the drug solution was verified by observing UV-VIs spectra at different time intervals as shown in Fig 5.1.

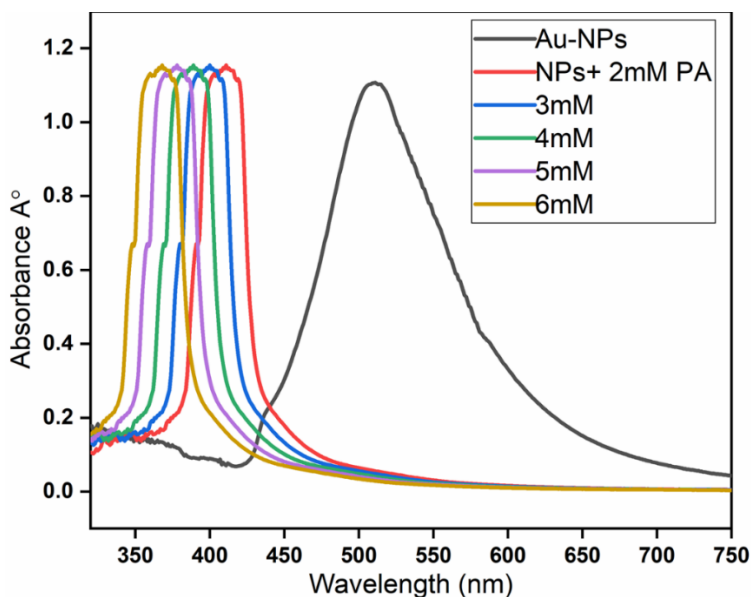


Figure 5. 1: The interaction of gold nanoparticles (Au-NPs) with various concentrations of PA (2-6 mM).

Anonymized human urine samples were collected. The approval form was abandoned as the samples were left over for regular analysis. Authorizing the study by the ethics committee was not achieved because PA treatment was performed only for artificial (in vitro) spiking of gathered urine samples and the participant did not ingest it orally. The sample was stored at 4°C until the filtration was carried out for sterilization, following the protocol previously reported [264]. The debris and cells were removed with a sterile syringe filter (Millex-GV Syringe Filter Unit, pore size 0.22 μm). Further purification was carried out after cooling to 25 °C to remove the possible salt precipitates before SERS analysis of PA. Stock aqueous solutions of PA (0.5-6 $\mu\text{g/mL}$) concentrations were used for artificial spiking of samples (20 μL of stock solution per 980 μL of a urine sample). The blank samples were utilized as reference samples.

5.2.4 SERS Study.

Raman spectra of the PA samples were measured using HORIBA Scientific Lab RAM HR evolution spectroscopy outfitted along with an internal He-Ne 17 mW red laser at a wavelength of 633 nm. The (50x) objective lens is used to focus the beam on the solutions. Besides, the microscope (with two switchable gratings) was equipped confocally with a 600 nm focal length spectrograph to achieve better spectral resolution and maximum optical throughput [265], 25% laser power, 20s acquisition time with 4 accumulation collections for the SERS study. The spectra were accumulated at 1:1 for the drug to Au-NPs in a glass cuvette with a volume capacity of 1 cm³. It was observed that strong signal enhancement could not be acquired using pure colloidal suspension because of the presence of Au-NPs [253]. Consequently, selecting lasers below 600 nm (such as 407 nm and 532 nm) did not offer the highest SERS enhancement. Instead, the 633 nm laser source exhibited the enhanced symmetric and intense signal due to coupled plasmonic resonance positioned at the “hot spots” sandwiched between Au-NPs (gold nanocluster Au₄) and free PA.

5.2.5 Theoretical Calculations.

Computational studies were conducted by employing B3LYP DFT presented by Becke and Lee *et al.*, [197], [253]. The Stuttgart/Dresden (SDD) basis set was applied to explore the orbital visualization of a gold, while 6-311G(d,p) were utilized in non-metal atoms. These sets were additionally selected to generate outcomes related to experimental outcomes [266]. The frequency calculations were performed using these as a base and the obtained

complete relaxed geometries proved that there was no imaginary frequency detected. The simulated geometry of the PA molecules is depicted in Fig. 5.2.

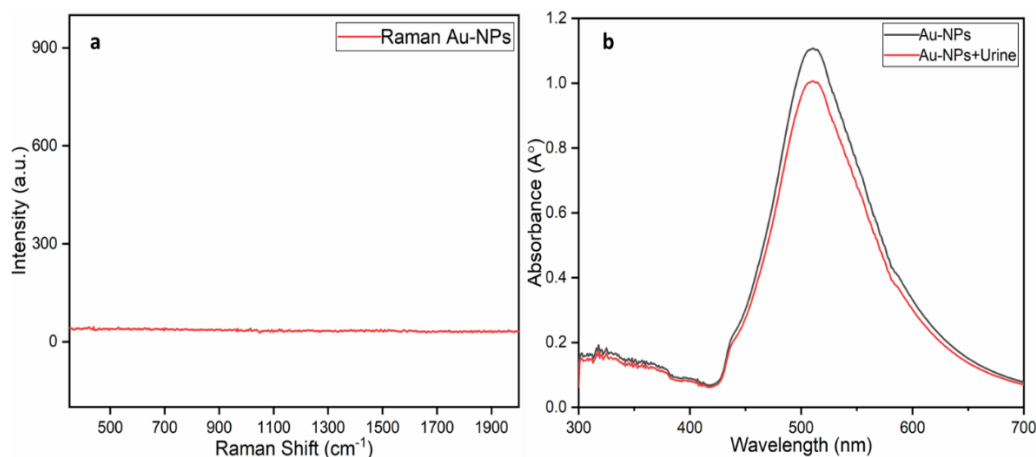


Figure 5. 2: (a) Raman spectrum of Au-NPs at 350-2000 cm^{-1} (b) Comparison UV-Vis Spectra of Au-NPs (Black line) and Au-NPs containing urine (Red Line), It suggests that there is almost no change at band 512 nm.

While the vibrational assignments concerning drugs with and without Au-NPs interface were achieved through the support of GaussView6 software visualization ability. The energy of interaction was calculated by comparing the energy differences before and after the interaction of PA with the Au_4 -cluster.

5.3 Results & Discussions

5.3.1 Characterization.

The synthesized Au-NPs were characterized using various techniques. Fig. 5.5 (a) shows the UV-Vis spectrum. The colloidal solution of gold nanoparticles exhibited well-defined sharp excitation owing to their plasmonic resonance at 510 nm corresponding to electronic oscillation [267], [268]. The sharp band observed for the gold nanoparticles may be due to an increased concentration of chloride ions, increased poly-dispersity, and /or anisotropic

shape of the Au-NPs [269]. Besides, the band at 293 nm Fig. 5.5 (a) corresponds to free PA drug, while the bands at 389 nm and 519 nm were ascribed to a mixture of PA and Au-NPs. It is inscribed from the sandwiched peak at 389 nm may be developed due to the strong electrostatic interactions (charge transfer) between Au-NPs and PA drug, likewise, the other band located at 519 nm with a small redshift and decreased intensity [270] [271], [272]. It is important to note that mixing urine with gold nanoparticles did not exhibit a significant impact on the optical properties of nanoparticles, furthermore, no additional broadening in the bands of the Au-NPs was observed, thus, ruling out the aggregation or reaction of particles upon mixing the urine sample as in Fig. 5.5 (a).

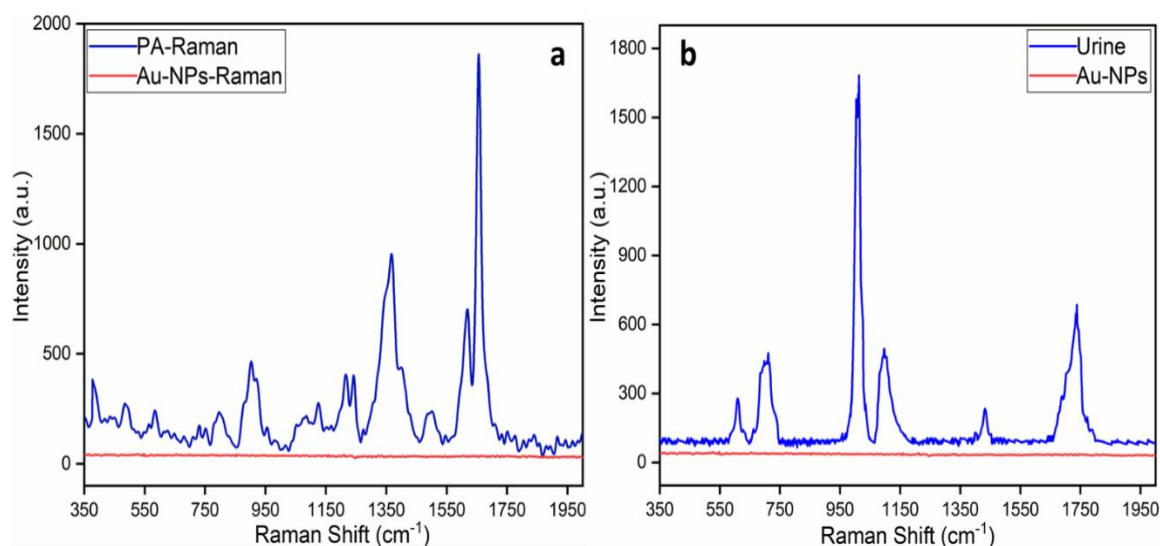


Figure 5. 3: (a) Raman spectrum of PA and Au-NPs at 350-2000 cm^{-1} (b) Raman spectrum of PA spiked urine and Au-NPs at 350-2000 cm^{-1} (Laser $\lambda=633$ nm, laser power; 25%, acquisition time; 20s, accumulations 4 and objective; 50x.

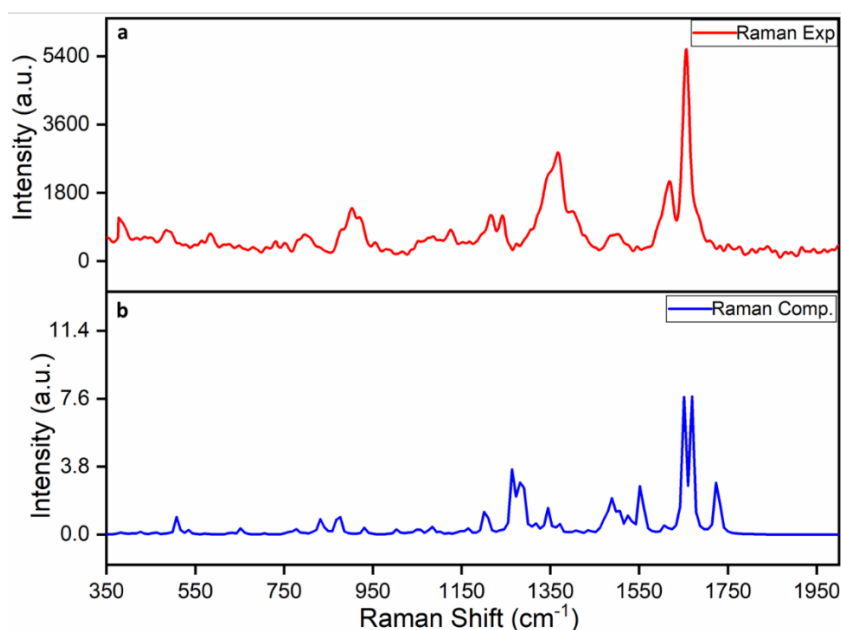


Figure 5. 4: (a) Raman Spectra of Procainamide at 350-2000 cm^{-1} (Laser $\lambda=633$ nm, laser power; 25%, acquisition time; 20s, accumulations 4 and objective; 50x. (b) calculated SERS spectra of Procainamide with Au-NPs

The effect of different concentrations (10, 25, and 50 %) of Au-NPs with PA was also investigated, and the results showed a change in intensity in the 2nd band along with a redshift with increasing the concentration as shown in Fig. 5.4. It is incurred from the figure that the interaction varies with concentration. The plasmonic effect and charge transfer interaction between Au-NPs and PA were further verified with peak shifts and increased intensity of some bands in the FT-IR spectrum as depicted in Fig. 5.5 (b). The broadband observed at 3423 cm^{-1} (after an interaction at 3440 cm^{-1}) is allocated to -OH stretching, which may be due to humidity on the gold nanoparticle surface. Likewise, the band observed at 1693 cm^{-1} (before interaction at 1681 cm^{-1}) ascribed to (C=O stretching) of citrate stabilizers. Similarly, the peak at 1465 cm^{-1} has disappeared, this may be attributed due to the possible interaction between PA and Au-NPs. Furthermore, the peak positioned at 584 cm^{-1} is ascribed to CH_2 rocking modes and is as per the literature [273].

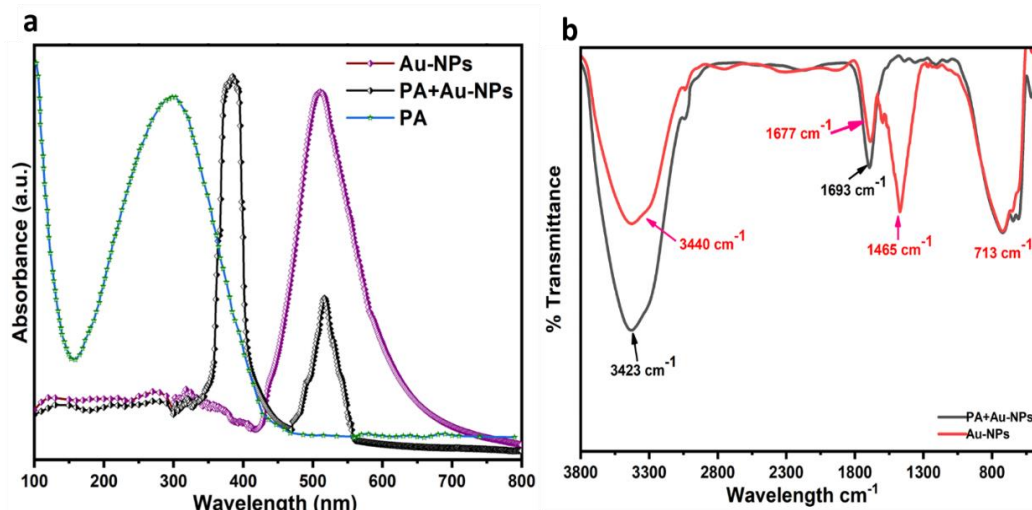


Figure 5. 5: (a) The UV-Vis spectrum of PA, Au-NPs, and Mixture (a) FT-IR spectrum of Au-NPs and PA drug combined with Au-NPs.

The surface texture and the size of gold nanoparticles were examined by FE-SEM Fig. 5.6. As shown in the figure, the Au-NPs are uniform and spherical in shape with an average size of ~ 42.6 nm Fig. 5.6(b). This resulted in an increased surface area and improved optical and plasmonic properties of gold nanoparticles due to the well-matched resonance frequency of Au-NPs and 633 nm laser light source used for excitation[260]. This results in accumulation and increased interaction of PA molecules that resulted in significant Raman signal enhancement.

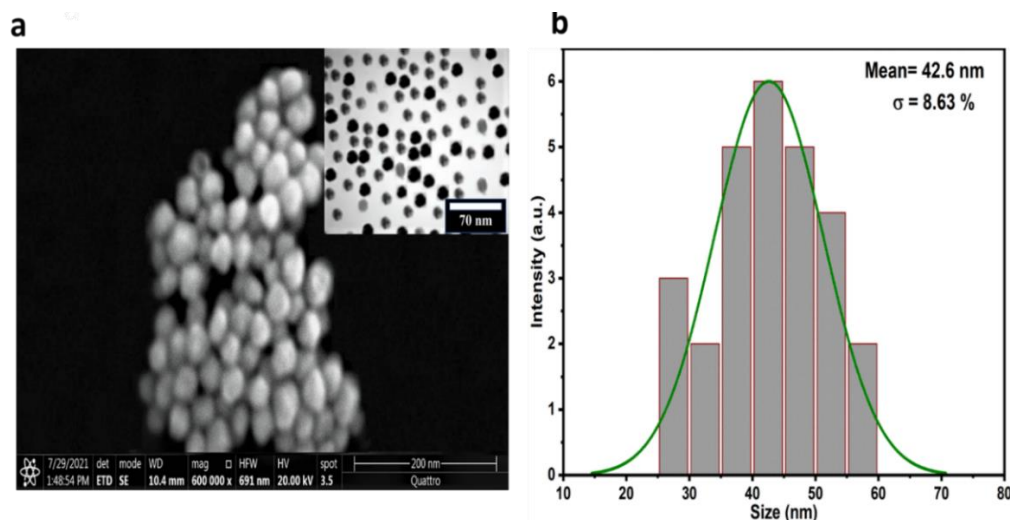


Figure 5. 6: (a) The FE-SEM images demonstrate the surface morphology of synthesized Au-NPs. The inset is the HR-TEM image of Au-NPs well scattered (b) The histogram showing the average size of the Au-NPs.

Raman measurement of Au-NPs in Fig. 5.3 (b) shows no peaks belonging to gold nanoparticles in the range of 200 to 3000 cm^{-1} . Thus, the synthesized Au-NPs can be utilized as SERS active substrate without substantial intervention with PA and the spiked urine samples. Any peak observed in this range would be considered for PA and urine components only.

5.3.2 Detection of Procainamide using SERS approach.

The previously designed spectrometric and chromatographic approaches to determine PA in both aqueous and urine posed promising outcomes but failed to attain the low detection limits and more viable protocols are yet enduring to achieve trace-level detection. Establishing Raman spectroscopy-based approach to detect trace-level biomolecules in aqueous and non-aqueous media has demonstrated a potential path to expand competencies in the pharmaceuticals field. The multiband uniform pattern and symmetric structural features of Raman spectra have aided to present molecular fingerprints, thus, enabling

ultra-trace limits of detection [253]. Besides it has ruled out the pseudo-positive results, a major challenge in trace analysis due to structural resemblance such as PA is interfered with by amphetamine drugs because of the similarities in structure [274]. In our previous study [263], [275], [276], [277], we successfully developed SERS and (EC-SERS) approaches to detect the procaine concentration at a trace level. The results and good linearity and reproducibility have encouraged us to delve into intensifying Raman signals for the detection of procainamide drug in aqueous and more importantly in spiked urine samples using gold nanoparticles as a promising substrate for SERS application, Fig. 5.4, and 5.7.

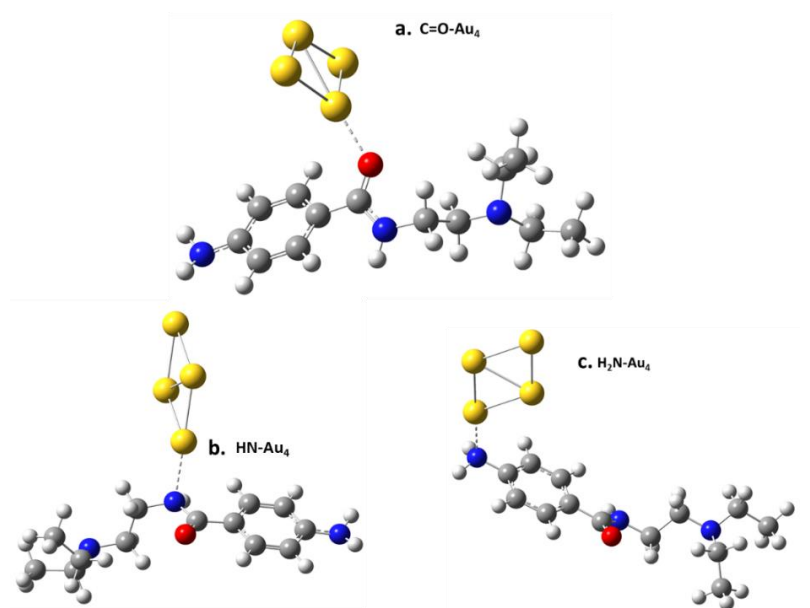


Figure 5. 7: Optimized structure of interactions of Au₄-cluster with (a) -C=O (b) HN- (c) H₂N- groups of procainamide molecule

To evaluate the sensitivity of SERS, the SERS phenomenon was effectively employed in this report to detect the PA at a lower concentration of less than 10^{-10} M in aqueous media and below 2 $\mu\text{g/mL}$ in the spiked urine sample. The SERS spectra were achieved in a

mixture of drug and Au-NPs in an optimized ratio of 1:1, keeping the volume of medium constant in both cases and kept for 5 minutes to ensure maximum interaction. Fig. 5.8 displays the comparison of Raman and SERS spectra of PA in aqueous media, as can be seen, significant enhancement along with redshift in Raman bands, especially at 942 cm^{-1} (i), 1401 cm^{-1} (ii), 1653 cm^{-1} (iii), and 1690 cm^{-1} (iv) showed the major differences associated with some prominent bands e.g., with C-C twisting, NH_2 bending $\text{C}=\text{O}$, and C-N stretching modes were spotted. Besides significant enhancement, and displacement of these bands in SERS in comparison to simple Raman spectra indicates a remarkable interaction of procainamide with Au-NPs. The enhancement is caused by concerted systematic chemistry of interaction (chemical and electromagnetic) involved between the drug and gold nanoparticles [278], [279].

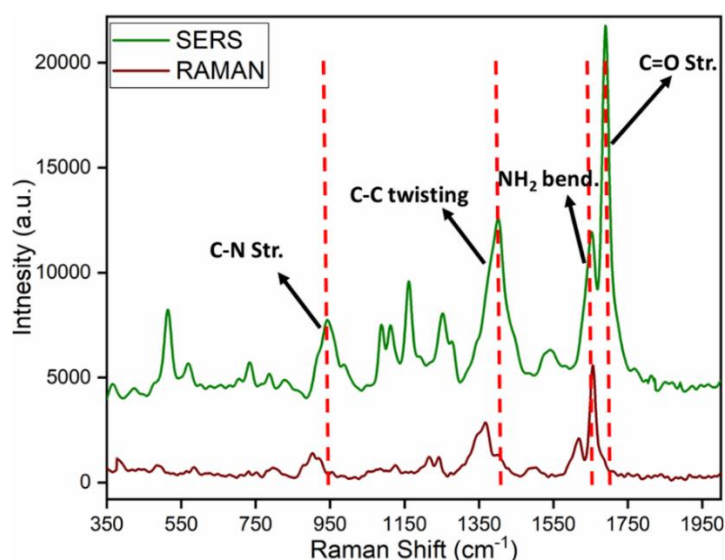


Figure 5. 8: The SERS spectrum of the PA drug at 1M (green) matched through ordinary Raman spectrum (brown) of the drug solution exclusive of Au-NPs.

The SERS spectra at numerous concentrations of PA were recorded. It was noticed that varying PA concentration resulted in a methodical variation in Raman intensity. It was

inducted that the SERS band intensities enhanced logarithmically with a concentration of procainamide in an aqueous solution, as shown in Fig. 5.10. This demonstrated that the SERS intensity is linearly proportionate to the logarithm of PA concentration, so it was implied that the spectral enhancement was associated with drug molecule population and meaningful interaction with Au-NPs. Many Raman bands exhibited significant enhancement in intensities, the leading peaks and respective intensities have witnessed the systematic variation with a change in PA concentration in the range from 1 to 10^{-10} M as in Fig. 5.10 (b) at 942 cm^{-1} (i), 1401 cm^{-1} (ii), 1653 cm^{-1} (iii), and 1690 cm^{-1} (iv). Diverse intensity, shapes, and locations examined are a consequence of distinct types of interactions among PA and Au-NPs substrates. The enhancement examined for C=O stretching at 1655 cm^{-1} and NH_2 bending at 1618 cm^{-1} has red-shifted to 1690 cm^{-1} and 1653 cm^{-1} accordingly, this is assumed for high plasmonic light field resonance-shaped surface turbulence of gold nanoparticles after laser excitation. This further triggered the light dispersion on procainamide dwelling inside the plasmonic field. It authenticates the possible interaction between drug molecules and gold nanoparticles. The experimental and simulated Raman spectra are displayed in Fig. 5.9.

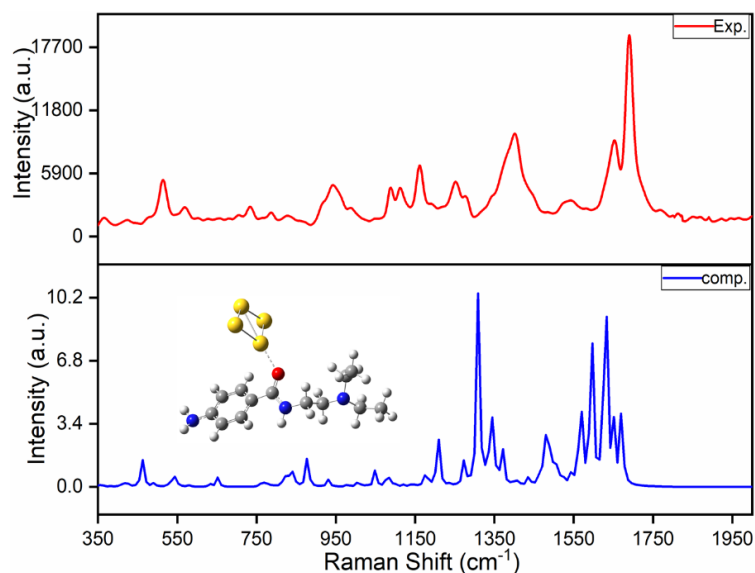


Figure 5. 9: Calculated SERS spectra and model of gold nanoclusters interactions with (C=O) group as compared with the experimental SERS of procainamide.

The smallest detectable limit of the drug achieved was at 5×10^{-11} M. In a typical procedure, the blank solutions were detected 5 times, the noise at 1690 cm^{-1} was recorded and the mean and standard deviation were calculated. The LOD was calculated by using the formula: $LOD = \text{Mean Blank value} \times 3 \text{ Standard Deviations}$. The enhancement factor (EF) was determined by following the reported method [280], [281] using the formula given below.

$$EF = \frac{I_{\text{SERS}}}{I_{\text{NRS}}} \times \frac{N_{\text{NRS}}}{N_{\text{SERS}}}$$

where I_{SERS} is the SERS mode intensity in presence of PA and Au-NPs and N_{SERS} is the sample concentration, while I_{NRS} is the Raman mode intensity in presence of PA without Au-NPs and N_{NRS} is sample concentration. The results show an enhancement factor of (10^8), which is considerably greater than previously reported literature values [263], [282].

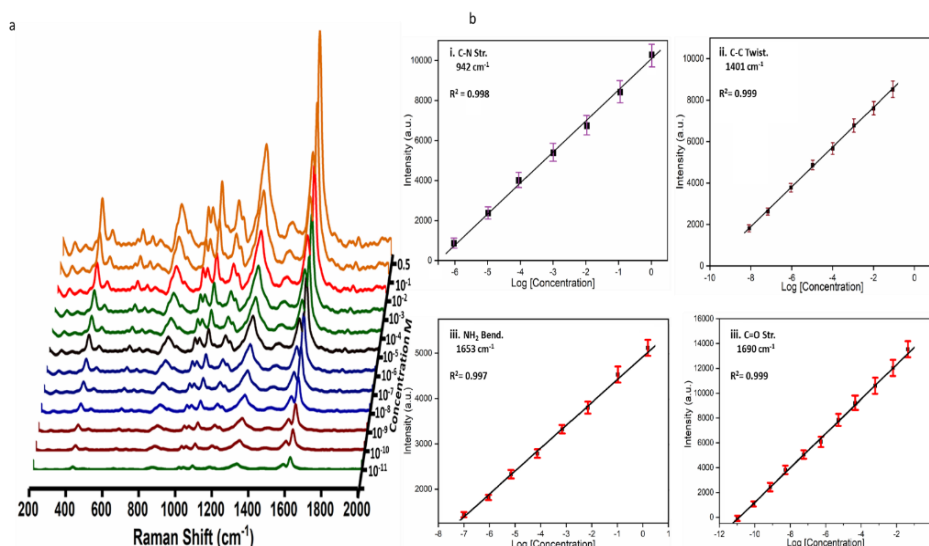


Figure 5. 10: The SERS spectra of drug at various concentrations (1.0 M to 10⁻¹¹M) (a); and (b) Logarithmic connections among intensities Vs concentrations of drug in peaks situated at (i) 942, (ii) 1401, (iii) 1653 and (iv) 1690 cm⁻¹

5.3.3 Detection of PA in spiked urine sample.

The developed approach was further investigated for the detection of PA in a real urine sample collected from a healthy volunteer. Fig. 5.11 displays the comparison of Raman and SERS spectra of a spiked urine sample and the pure PA drug. As reflected in Fig. 3.11 (c), the Raman spectrum depicts the typical features of urine. The corresponding Raman peaks at 620 cm⁻¹ (O=C-N deformation), 710 cm⁻¹ (structural transformation of creatinine), 1010 cm⁻¹ (C-N stretching), 1107 cm⁻¹ (C-N stretching) 1430 cm⁻¹ (Tryptophan vibration) and 1720 cm⁻¹ (water and ring stretching), can be identified as human urine sample [283], [284]. The prominent band at 1010 cm⁻¹ shows higher intensity than other peaks pertaining to the urea being the chief nitrogen-containing component in the urine sample. Besides the major component, the characteristic vibrational bands of creatinine were situated at 710

cm^{-1} and some proteins at 1430 cm^{-1} . Fig. 5.11a shows the SERS bands of spiked urine with (6 ppm) concentration of PA. It has been observed that most of the urine peaks (Fig. 5.11c) are retained, meanwhile, some new Raman bands appeared at 932 cm^{-1} , 1432 cm^{-1} , 1646 cm^{-1} and at 1684 cm^{-1} . These features could be ascribed to the vibrational bands of PA, which are in good agreement with the pure PA spectra. The different concentrations (8 to 1ppm) of PA were spiked in the urine samples and SERS spectra were recorded. It was observed that changing PA concentration logarithmically changes Raman intensity. This again exhibited the Raman intensity is proportional to the logarithm of PA concentration in the urine sample.

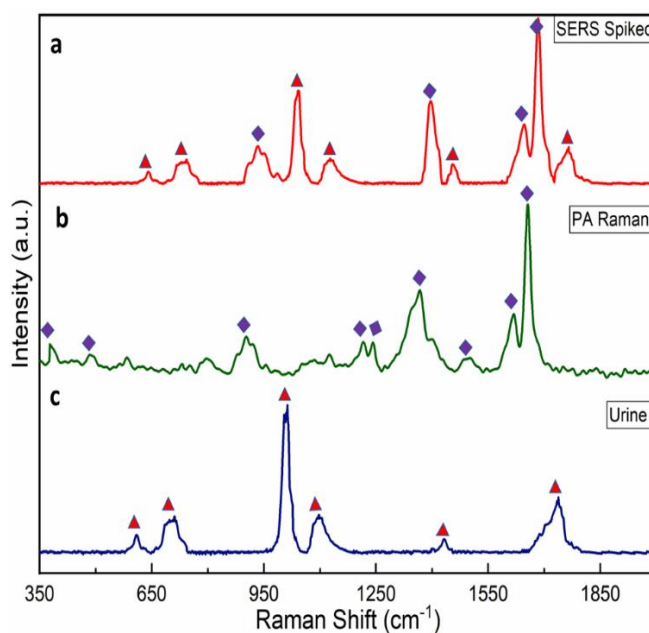


Figure 5. 11: The comparison spectra of (a) spiked (6 ppm) PA SERS (b) Raman of PA, and (c) Raman spectra of a real Urine sample.

The findings of the SERS approach stated above were contrasted with formerly stated techniques such as regression coefficients, limits of detection, and linear dynamic ranges,

Table 5.1. The present work has supremacy with an ultra-trace detection limit of drugs with a broader dynamic range and improved signal-to-noise ratio [285].

Table 7: Assessment of developed approaches for trace detection of PA in water.

Method	LDR	LOD	R^2	Reference
HPLC-UV	6×10^{-7} to 4×10^{-5} M	2×10^{-7} M	0.988	[245]
CE	1×10^{-3} to 8×10^{-6} M	1.235 $\mu\text{g}/\text{mL}$	0.998	[248]
ECL	50-700 $\mu\text{g}/\text{mL}$	25 $\mu\text{g}/\text{mL}$	0.999	[249]
TLC	-	7 $\mu\text{g}/\text{mL}$	0.998	[250]
RP-LC	16.3 -38.7 mg/mL	0.05 mg/mL	-	[251]
EC-sensors	4.00×10^{-5} – 4.97×10^{-9} M	1.30×10^{-9} M	0.994	[275]
Immune assay	4-10 $\mu\text{g}/\text{mL}$	2 $\mu\text{g}/\text{mL}$	-	[252]
SERS	1 M - 5×10^{-9} M	5×10^{-10} M	0.998	[277]
SERS	0.01- 10^{-10} M	5×10^{-11} M	0.999	Our work

LOD: Limit of detection, LDR: Linear dynamic range.

5.3.4 DFT modeling of procainamide interaction.

The use of density functional theory (DFT) calculations allows for interpreting the SERS data and collecting information on the structures of the complexes formed on the metal surface and the Raman enhancement mechanism. The DFT studies were commenced to explain the potential mechanism of interaction between a drug and its substrate. It was

explored thoroughly by optimizing the Au-cluster consisting of four gold atoms having rhombus geometry and exploited to imitate the interaction at the atomic scale. It is previously described in a quantum chemical investigation that a rhombus-shaped gold cluster is the most stable geometry with greater energies for binding per atom and sustainability for ionization [273]. The molecular electrostatic potential (MESP) map was created to locate the possible interaction sites between Au-NPs and PA as shown in Fig. 5.12. The map displays that primary amine and amide nitrogen have the extreme electrostatic potential of low electron density, whereas a high electron population detected in the vicinity of the C=O group, it is reflected that the earlier two are potential sites to interact with Au-NPs. The charge transfer among the substrate and its analyte was investigated by evaluating Mulliken atomic charges. It is inducted from calculated binding energies, electrons have a propensity to transfer from gold-cluster to procainamide for $\text{NH}\dots\text{Au}_4$, $\text{H}_2\text{N}\dots\text{Au}_4$ and $\text{C}=\text{O}\dots\text{Au}_4$. Modes of interaction. Interestingly mode of interaction between PA drug and Au_4 -cluster is different in comparison to our previously reported work on PA drug with Ag_4 -cluster [277]. One more important aspect that helped to predict the most favorable interaction was the computed binding energies. The binding energy calculated for $\text{NH}\dots\text{Au}_4$ interaction was -8.27 kcal/mol with a bonding distance of 2.47 Å, which is most feasible as compared to $\text{H}_2\text{N}\dots\text{Au}_4$ interaction with computed energy of binding as -3.20 kcal/mol at a binding distance of 2.35 Å. The third one was $\text{C}=\text{O}\dots\text{Au}_4$, which also appeared to be the most probable and stable interaction with binding energy -6.02 kcal/mol at a binding distance of 2.42 Å, Table 5.2. But the experimental observations did not favor this interaction and peak positions observed in experimental

SERS spectra were in good agreement with the first interaction (NH...Au₄), hence, this interaction was preferred for further studies.

Table 8: Binding energies, distances, and sum of Mulliken charges for potential modes of interactions calculated with B3LYP/6-311G(d,p) level.

Interaction	Energy (kcal/mol)	B. Distance (Å)	Mulliken Charges	
			Free	Complex
Au ₄ -NH	-8.27	2.47	Au ₄ : 0.000	Au ₄ : -0.0178
				PA: +0.0178
Au ₄ -NH ₂	-3.20	2.37	PA: 0.000	Au ₄ : -0.163
				PA: +0.163
Au ₄ -O=C	-6.02	2.42		Au ₄ : -0.223
				PA: +0.223

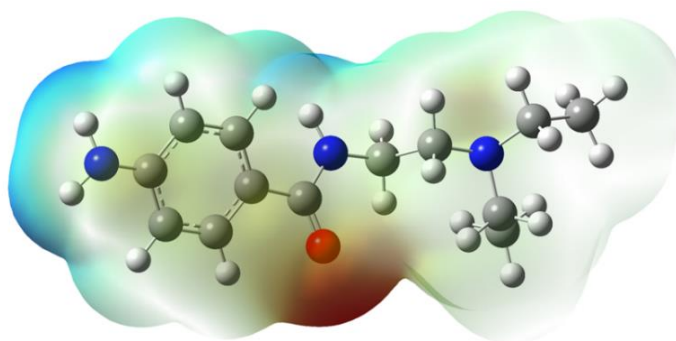


Figure 5. 12: The calculated molecular electrostatic potential (MESP) map of the drug depicting the electron densities as red (high) and blue (low) accordingly.

5.3.5 Vibrational Assignments.

To get a deep-rooted understanding of the type of interaction, the important modes of Au and PA interactions were examined in the SERS spectrum of drug@Au-NPs both in aqueous and urine media. In aqueous media, it was observed that experimental SERS spectra posed increased peak intensities accompanied by a shift in peak position compared to the Raman spectrum of PA. The vibrational assignments of the different modes were achieved between 350 cm^{-1} to 2000 cm^{-1} . The change in peak position was additionally delineated using the visualization tool in GuassView 6.0 [286]. The computed spectra were performed at the B3LYP/6-311(d,p) level and matched well with the practical findings. Fig. 5.13 shows simulated SERS spectra of procainamide relating to, $\text{NH}\dots\text{Au}_4$, $\text{H}_2\text{N}\dots\text{Au}_4$, and $\text{C=O}\dots\text{Au}_4$. Likewise, (Fig. 5.7) depicts the different computed interactions of PA molecules with the gold cluster. Besides, the spectral features of computed SERS spectra were found to be well-matched with the experimental ones. The three interaction modes are energetically most satisfactory and were anticipated to provide the most prominent SERS bands examined. The vibrational frequencies are detailed in Table 5.3 and are compared to experimentally obtained spectra.

In the case of spiked urine, the Raman spectral features of urine samples were examined in between the range of 300 cm^{-1} to 2000 cm^{-1} . It is inducted from SERS spectra that most Raman bands of urine were retained along with the rise of new bands (at 932 cm^{-1} , 1432 cm^{-1} , 1646 cm^{-1} , and 1684 cm^{-1} respectively), which were in good agreement with SERS spectra of procainamide with their respective modes. This confirms the presence of unmetabolized PA drug concentration.

Table 9: The vibrational assignment of prominent bands in experimental Raman a, calculated Raman b and SERS spectrum of procainamide below 2000 cm⁻¹

Approximate descriptions	Experimental (cm ⁻¹)		Calculated (cm ⁻¹)		
	Raman	SERS	Raman	Interaction mode	
				HN-Au4	H ₂ N-Au4
ν (C=O str)	1656 vs	1690 vs	1723 (40)	1705 (100)	1732 (19)
ν (NH ₂ bend)	1618 m	1653 s	1669 (100)	1669 (66)	1651 (100)
ν (CC twist.)	1489 w	1401 s	1489 (30)	1552 (22)	1489 (15)
ν (CH ₂ def.), ν (Ring bend)	1366 s	1344 s	1346 (15)	1489 (20)	1345 (10)
ν (CN str.)	1274 vw	1278 m	1281 (43)	1282 (16)	1291 (8)
ν (CH ₃ def.), ν (CH bend)	1241 w	1251 w	1263 (48)	1255 (40)	1255 (9)
ν (CH bend)	1215 w	1161 m	1201 (27)	1201 (19)	1201 (3)
ν (Ring breath)	901w	1113 m	931 (12)	1120 (3)	1165 (24)
ν (CH bend)	880 vw	1087 w	878 (16)	1102 (3)	967 (22)
ν (CH bend), ν (CCN def.)	797 vw	828 m	831 (22)	841 (11)	949 (5)
ν (Ring bend)	751 vw	787 w	779 (5)	762 (3)	778 (4)
ν (CNC def.)	584 w	567 w	652(1)	517(1)	535(1)

The vibrational modes (str.) in the SERS spectrum allocated to the C=O group noted at 1690 cm^{-1} (1705 and 1732 cm^{-1} calculated) were well matched with the stated C=O stretching modes [287]. The peaks observed at 1653 cm^{-1} (computed as 1669 And 1651 cm^{-1}) were designated as NH_2 bending along with C-C stretching modes, these modes are further verified by the literature [287], [288]. The calculated SERS intensity favors the NH_2 bending modes and hence was assigned accordingly. The peaks observed at 1401 cm^{-1} (calculated at 1552 and 1489 cm^{-1}) were assigned to uncoupled C-C stretching, likewise, the peak located at 1344 cm^{-1} (1449 and 1345 cm^{-1} in DFT) is ascribed to ring stretching. The weak Raman modes detected at 1284 cm^{-1} assigned to CN stretching mode have experienced a blue shift and a significant enhancement in the case of SERS spectra. The peak assignments spotted at 1087 , 828 , 787 , and 567 cm^{-1} were assumed to be for CH bending, CCN, as well as aromatic ring deformation, accordingly, are in good understanding to DFT calculated bands, these peaks exhibited high similarity with the reported literature value [289].

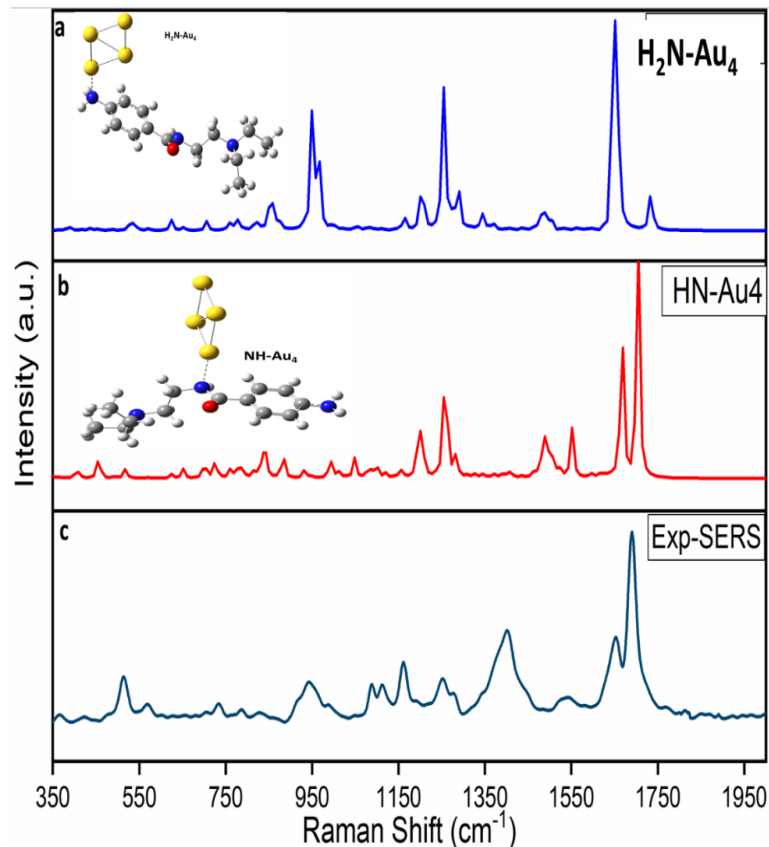


Figure 5. 13: Computed SERS spectra for gold cluster interaction with (a) primary amine (b) amide, matched with (c) experimental SERS of PA.

5.3.6 Interference effect and reproducibility.

As is known, some additional species exist in the drug samples together with PA molecules, and these species can interfere with PA molecules in their detection. Therefore, it is crucial to develop a SERS technique to detect the PA molecules selectively in the presence of these interferents. In this study, to verify the reliability, selectivity, and practicality of the developed approach, the responses of possible interferents, such as valeric acid, sulindac, ciprofloxacin, and ascorbic acid, were investigated. The concentration selected for interferant was 1000 times the concentration of procainamide solution (10^{-4} M). The results revealed that the tested interfering species displayed a negligible interference, and that the

Raman intensity of the procaine analyte was consistent above 95% of the original intensity as depicted in Fig. 5.14. This concludes that the developed analytical approach has high potential to serve as a quantitative detection method by virtue of its high sensitivity and selectivity. Likewise, the reproducibility and stability of the developed method were evaluated by performing five SERS experiments to quantify the procainamide. The relative standard deviation (RSD) of the SERS response towards 1.5×10^{-6} M was 1.6 %, besides the reproducibility of the developed SERS approach was also investigated in 1.5×10^{-6} M solution of PA and Au-NPs. The RSD calculated for the SERS response was observed to be 1.9%. Fig 5.14 all the spectra depict the characteristic peak of PA and peak intensities were consistent and almost homogeneous. This implies that the quantification of PA can be carried out with high precision and reproducibility. The average recovery was found to be 98%, which indicates that the present analytical approach exhibited excellent selectivity towards the target analyte.

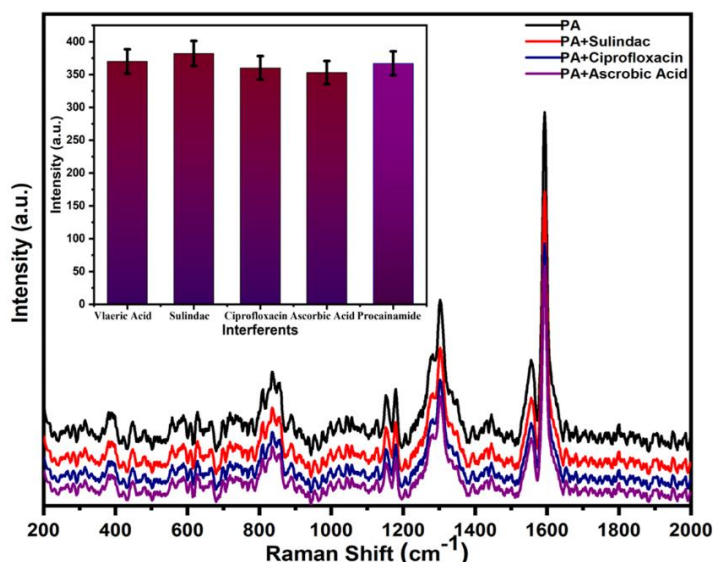


Figure 5. 14: Plots of SERS response at 1690 cm⁻¹ in presence of interferences; Interference study of SERS approach for the quantification of procainamide in presence of interferences

6 CHAPTER

SERS-based ultralow concentration detection of anticancer gemcitabine using size-controlled silver nanoparticles.

Taken from Mahar, Nasurullah, and Abdulaziz A. Al-Saadi. "SERS-Based Ultralow Concentration Detection of Anticancer Gemcitabine Using Size-Controlled Silver Nanoparticles." *Arabian Journal for Science and Engineering* 47, no. 6 (2022): 7197-7205.

6.1 Introduction

Gemcitabine (GMC) is considered amongst the most potent and widely used anticancer drugs used in chemotherapy treatment of several malignant diseases, such as ovarian cancer, breast cancer and metastatic pancreatic [290][291][292][293]. It transforms into its functioning metabolite (gemcitabine triphosphate) through nucleoside transport after being ingested as a parent drug [292][294]. Besides, GMC has been marketed as an antiviral, immunosuppressive and enzyme inhabitant agent [295][296]. The dosing frequency of GMC is carefully prescribed based on the specific weight volume ratio of the drug in solution [297]. Any alterations in the dosing frequency, amount, or concentration can cause drug toxicity which may lead eventually to death [298]. The quantitative detection of drug ingested and net metabolized products to target cells, and the monitoring of its clinicopathology characteristics represent a major challenge, especially when dosed at very small concentrations [299] [300]. Considering the widespread use of the GMC drug in chemotherapy, there is a pressing need to detect its traces in different sources, including

bio-samples and hospital waste. That shall be of interest as well for pharmaceutical formulation control in both hospitals and laboratories. Therefore, a number of analytical approaches have been researched for the efficient detection of GMC at very small concentrations. Spectrophotometric [301][302][303], electrochemical [299], chromatographic [304], LC-MS/MS [305], RP-HPLC [306], HP-TLC [307] and ultra-violet [308] techniques were previously reported as potential means to monitor the GMC level in various media. Although these approaches postured significant results, exploring other alternatives which are reliable and more cost-effective is still ongoing. The ultra-sensitivity of the surface-enhanced Raman scattering (SERS) approach made it an attractive and agile technique for routine quality assurance practices. Silver-based nanoparticles (AgNPs) pose a noticeable enhancement in Raman signals owing to their strong electromagnetic interaction and high plasmonic resonance properties [309]. In continuation of our previous efforts in trace characterization of common therapeutic drugs by employing SERS techniques [310][311][312], a spectroscopic detection approach of GMC using chemically reduced AgNPs with an apt particle size as a SERS substrate has been explored.

6.2 Experimental

6.2.1 Chemicals and Reagents

All chemicals and reagents reported in this work were used without additional purification. The silver nitrate (AgNO_3), trisodium citrate ($\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$), and citric acid ($\text{C}_6\text{H}_8\text{O}_7$) were purchased from Sigma Aldrich (St Louis, MO), while sodium borohydride (NaBH_4) (>99,9 %) was purchased from Alfa Aesar USA. The gemcitabine (>99,8 %) target analyte was

purchased from Ambeed Pharmaceutical, USA. Gemcitabine (GMC) belongs to a difluoro class of deoxycytidines and was first approved by FDA in 1996 [313][314]. All solutions were prepared in double-distilled water at room temperature.

6.2.2 Silver nanoparticles (AgNPs) preparation

There are several reports on the fabrication of SERS substrates with effective size-controlled procedures [315][316]. Herein we mainly focused on the development of non-colloidal silver-based substrates for SERS detection. The silver nanoparticles (AgNPs) were prepared by the reduction method following our previously reported work with a minimal modification in the concentration of the reagents to achieve an optimum particle size [317]. A stepwise procedure started with the mixing of solutions of AgNO₃ (0.2 mL of 0.15 M), citric acid (1.2 mL of 0.18 M), and sodium citrate (6.8 mL of 0.18 M) in a round bottom flask and making a total volume of 100 mL. The mixture was kept at room temperature for 5 minutes, and then 0.4 mL of 0.6 M sodium borohydride solution was added slowly under constant stirring. The final mixture was heated to boiling for 80 minutes. The final yellow-brownish product was stored at 4 °C for further study. The characteristics of the synthesized AgNPs were acquired with the help of UV, FT-IR, Raman, and SEM techniques.

6.2.3 SERS Measurement

The SERS study was conducted in aqueous solutions of gemcitabine (GMC) with a concentration range (10^{-4} to 10^{-11} M) using the subsequent dilution method in double-distilled water. The solutions were stable at 4°C for 48 h. The ratio of AgNPs to GMC drugs was optimized. The pH of the solution was maintained between 6-8 to enhance the

interaction with the silver nanoparticles [292]. The Raman and SERS spectra were collected on LabRAM HR Evolution Raman microscope with internal He-Ne 17 mW laser at 633 nm wavelength excitation. An objective lens with 50x power and switching grating of 600 mm focal length were utilized. These parameters were implemented with a low power laser of 5% and an acquisition time of 20 s to attain both Raman and SERS data throughout the analysis.

6.2.4 Computation

Theoretical calculations were carried out using Gaussian 09 [318] by implementing the correlation-exchange B3LYP density functional originally introduced by Becke and Lee *et al.*, [319][320]. The basis sets of Stuttgart/Dresden (SDD) and 6-311G(d,p) were selected to describe the orbitals of the metal and non-metal atoms, respectively. The fully optimized structure of the GMC molecule (Fig. 6.1) was verified by computing the vibrational frequencies which were all shown to be real with no imaginary values [320] [321]. The possible interaction modes between the target molecule and the silver-loaded substrate were depicted using a silver tetramer cluster. The assignments of the Raman and SERS spectra of GMC before and after the interaction were conducted by correlating the experimental modes with the corresponding computed ones visualized using GaussView6 software [310]. The binding energies were estimated by comparing the differences earlier and after the interaction between Ag₄ and GMC to achieve the possible ground state configurations.

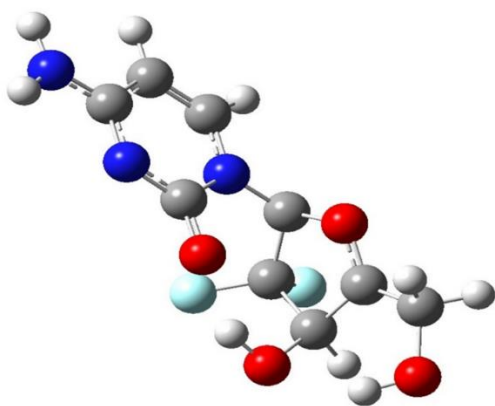


Figure 6. 1: An optimized structure of anticancer drug gemcitabine

6.3 Results and discussions

6.3.1 Characterization of prepared AgNPs

The desired sensitivity of SERS can be achieved by developing metal-loaded nano-fabricated substrates. The prepared AgNPs were characterized to get an idea regarding their size uniformity and morphology. The UV-vis spectrum exhibited a plasmonic excitation at 401 nm owing to the electronic oscillation as shown in Fig. 6.4 (a). The excitation band is at a lower wavelength position than the previously reported at 420 nm, which is due to the pronounced longitudinal LSPR behavior [322] [323]. The excitation observed at 296 nm corresponds to the mixture of the drug molecules with the nanoparticles. The blue shift could be ascribed to strong interaction and appreciable charge transfer. Such an excitation band is intermediately positioned between the absorptions by AgNPs at 401 nm and free GMC at 270 nm. The interaction between AgNPs and GMC was verified by the shift in band positions and the change in intensities as revealed by the FT-IR spectra Fig. 6.4 (b). For AgNPs, the three principal broad FT-IR bands observed at 3363 cm^{-1} , 1639 cm^{-1} and

667 cm^{-1} can be associated to the $-\text{OH}$ stretching, $-\text{C}=\text{O}$ stretching, and $-\text{OH}$ deformation modes, respectively, due to the presence of the citrate salt stabilizer in good agreement with the literature [324]. Moreover, it can be noticed from Fig. 6.4 (b) that the band at 3363 cm^{-1} has become less broad as a result of the interaction of GMC with AgNPs. The bands at 1305 cm^{-1} and at 765 cm^{-1} for free GMC (Fig. 6.2) vanished after being placed in contact with the nanostructured substrate. Moreover, the Raman spectrum of the synthesized AgNPs (Fig. 6.3) shows no significant background peaks within the range of 200-1800 cm^{-1} giving a minimum interference with the SERS peaks. The morphological texture of the SERS substrate was further examined (Fig. 6.5).

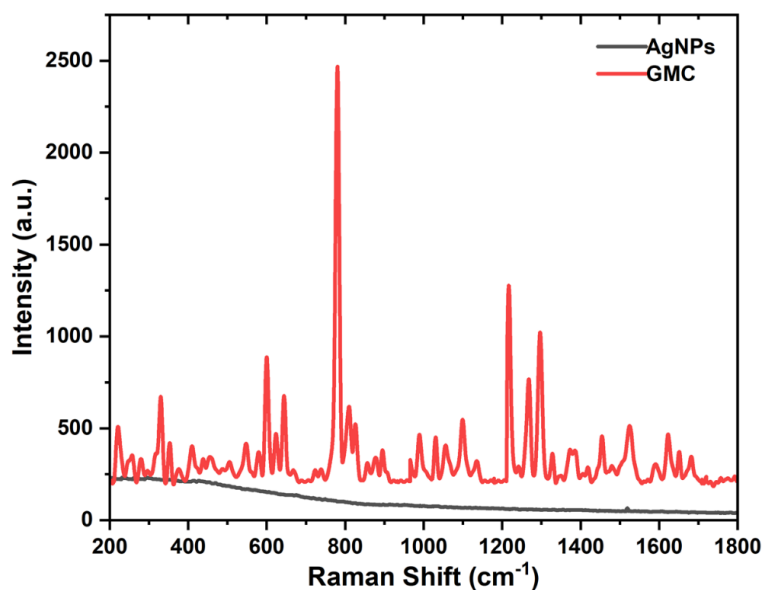


Figure 6. 2: Raman spectra of the drug (Red) and silver nanoparticles (black)

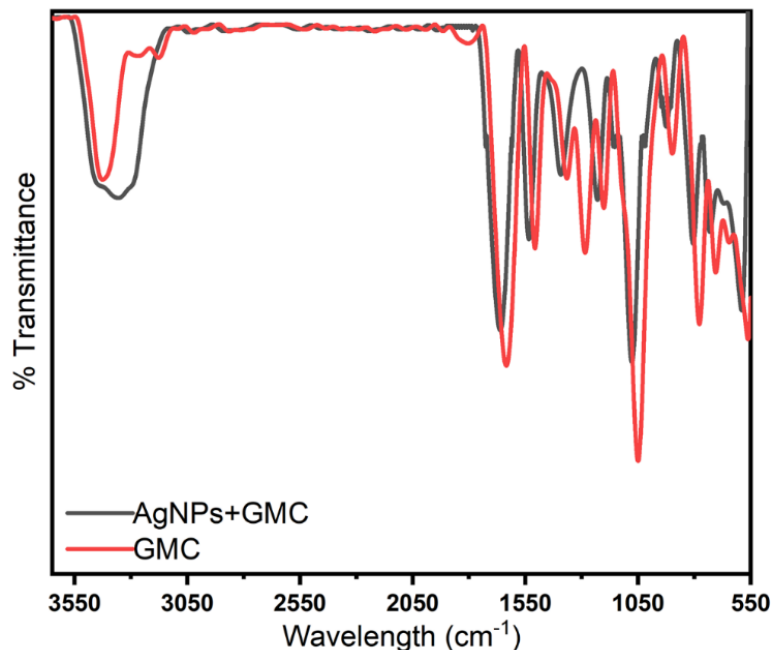


Figure 6. 3: FTIR spectra of the drug before (red) and after interaction with silver nanoparticles (black)

The size distribution shows that the AgNPs possess an average size of 23 nm. The FE-SEM image indicates that the particles result in surface roughness and uniform size distribution. The small average size favors an increased surface area, advocating the optical and plasmonic properties of the nanoparticles and hence delivering sufficient SERS signal amplification.

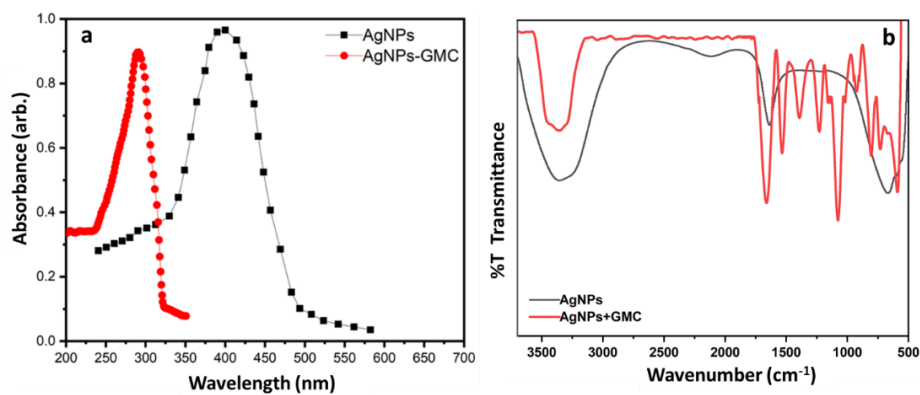


Figure 6. 4: (a) UV-visible and (b) FT-IR spectra of free AgNPs and AgNPs+GMC mixture.

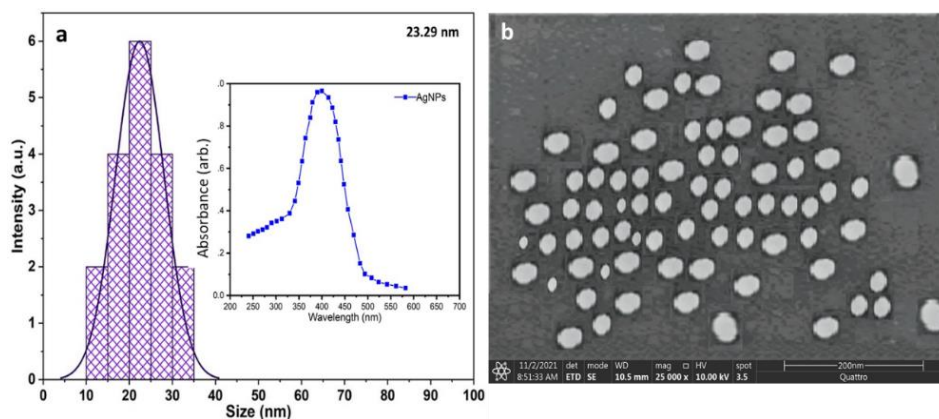


Figure 6. 5: Size distribution of AgNPs with an average size of 23.3 nm (the inset shows the UV-vis spectra of AgNPs), and (b) the FE-SEM image showing the morphology of the prepared AgNPs.

6.3.2 SERS Detection of GMC

The successful implementation of Raman spectroscopy as a potential source to detect biomolecules in trace quantities opened a door to extending our capabilities in innumerable analytical areas including pharmaceuticals. The unique multiband and spectral uniformity of the Raman technique enabled researchers to identify molecular fingerprints even at ultralow concentrations. The surface plasmonic activity is essential for Raman signal enhancements, and it can be utilized by employing coinage metals that are engineered within the SERS substrates. As explained earlier, numerous methods have been developed for the sensitive detections of GMC. However, searching for more competent quantitative means to achieve even lower detection limits (LODs) with practicable procedures is still a subject of large interest. A comparison of LODs and linear dynamic ranges (LDRs) for some reported analytical approaches with the present work is given in Table 6.1.

Table 10: Comparison of the outcome achieved in this work with previously reported analytical methods for the detection of trace GMC concentrations.

Method	LDR	LOD	R^2	Ref.
Spectroscopy	2.0-40 $\mu\text{g mL}^{-1}$	0.060 $\mu\text{g mL}^{-1}$	-	[303]
EC	0.5-65 $\mu\text{g mL}^{-1}$	1.5 $\mu\text{g mL}^{-1}$	0.998	[299]
Chromatography	20-50 ng/ml	20 ng	0.999	[325]
LC-MS	20-5000 ng/mL	20 ng mL^{-1}	-	[326]
RP-HPLC	0.1-42 ng mL^{-1}	0.1 8ng mL^{-1}	0.997	[327]
ECL	6.25–100 μM	6.25 μM	0.998	[328]
DPV Gold	0.026-3.94 ng/L	0.260 ng mL^{-1}	-	[304]
SERS	10^{-4} - 10^{-9} M	1.5×10^{-10} M	0.998	Our work

Therefore, the SERS effects were efficiently immobilized in the present study for the trace detection of GMC in aqueous solutions. The comparison of Raman spectra of free GMC solution (Fig. 6.2) and its mixture with AgNPs in a 1:2 optimized ratio (Fig. 6.6) exhibited a noteworthy intensity enhancement along with band shifts of several Raman lines. The two most prominent peaks taken into further analysis here are those appearing at 799 cm^{-1} and 1252 cm^{-1} .

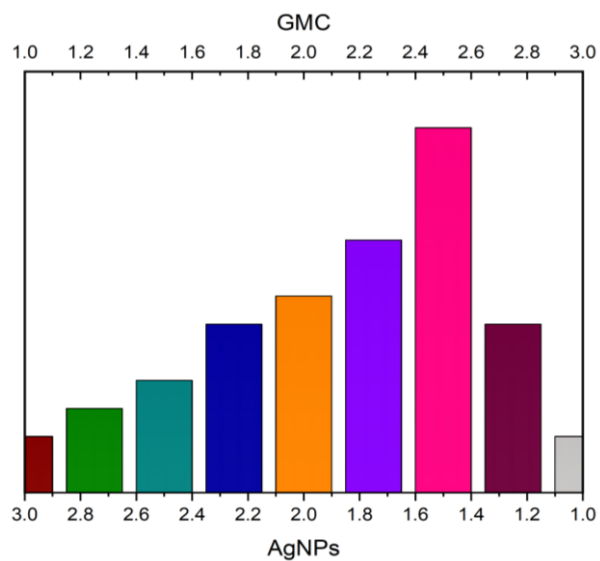


Figure 6. 6: Raman signal enhancement at different ratio of drug to nanoparticles

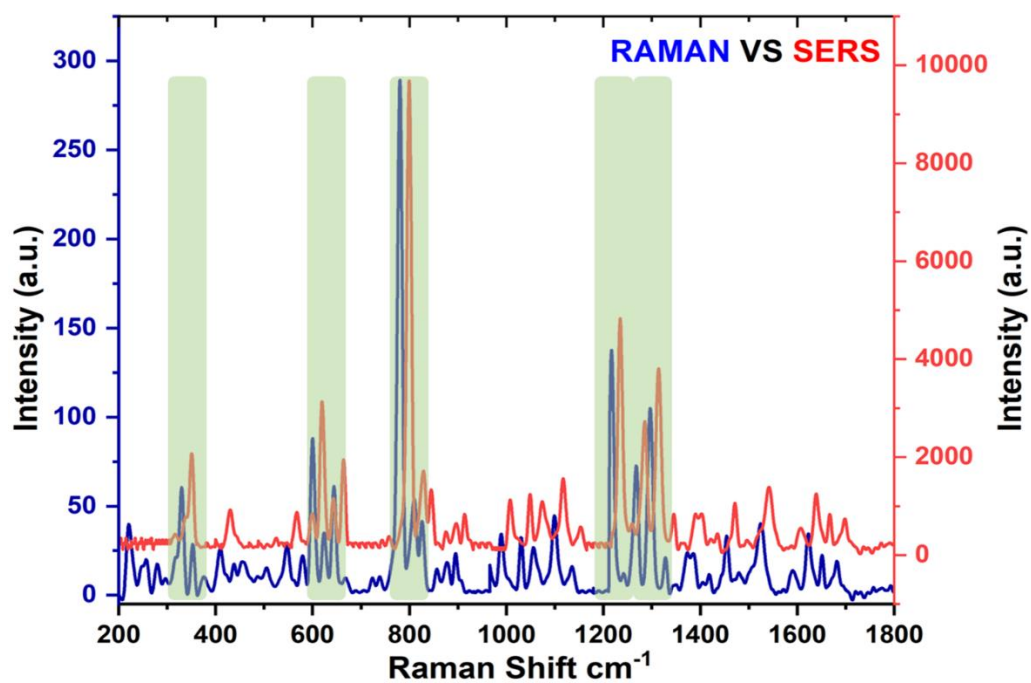


Figure 6. 7: The Raman spectrum of GMC solution at 10-3M concentration (blue) compared with the SERS spectrum of AgNPs+GMC solution mixture at 10-3M concentration (red). Prominent peaks are highlighted, and wavenumber shifts due to the SERS effect can be noted.

6.3.3 SERS Measurements

The SERS spectra of wide-range concentrations of GMC solutions are shown in Fig. 6.9. The peak intensities decrease logarithmically while reducing concentration. A wide linear dynamic range (10^{-4} to 10^{-9} M) was achieved with peaks at 799 cm^{-1} and 1252 cm^{-1} as shown in Fig. 6.9. The distinct intensities and position of the peaks observed in the SERS spectra are due to different possible interaction modes between AgNPs substrate and GMC molecules. The lowest observable limit for the GMC drug was achieved at 1.5×10^{-10} M with an enhancement factor of 5.6×10^7 .

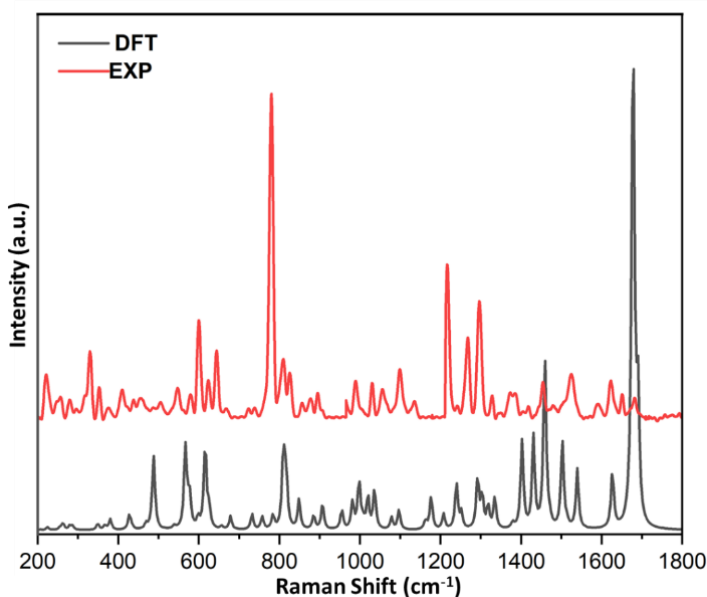


Figure 6. 8: Theoretically calculated SERS (Red) and Raman Spectra (black) of GMC

The resultant enhancement and subsequent redshift observed are likely due to the large specific surface area and pronounced plasmonic resonance of silver nanoparticles, accompanied by a charge transfer at multiple sites of the molecule. The latter accounts were verified using a theoretical calculation model as elaborated in the following section.

That was further assessed by the comparison of the experimental and simulated Raman spectra (Fig. 6.8).

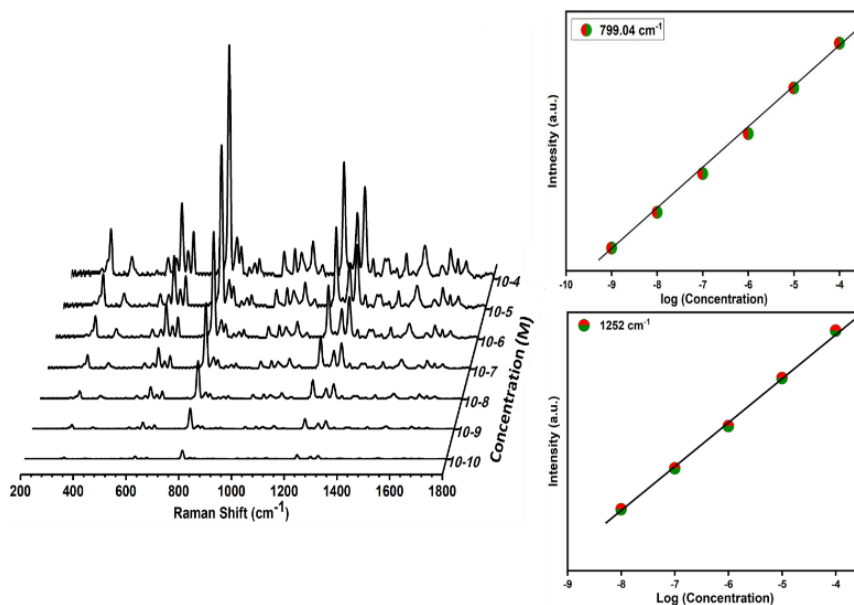


Figure 6. 9: SERS spectra of GMC solutions at different concentrations from 10⁻⁴ to 10⁻¹⁰ M (left), and the logarithmic relationship of Raman peak intensities and concentrations of GMC for the prominent bands located at 799 cm⁻¹ (upper right) and 1252 cm⁻¹ (lower right) in the dynamic range 10⁻⁴ - 10⁻⁹ M.

6.4 Theoretical calculations

A first-principle computational study was carried out to realize the impact of various interaction types. This was simulated by bringing an optimized rhombic geometry Ag₄ cluster in different vicinities of the GMC molecule, then identifying and optimizing the most stable interactions. From previously reported quantum chemical studies, the silver rhombus arrangement is stable, possesses a high binding energy per atom, and is resistant to ionization [329], [330], [331]. The molecular electrostatic potential (MEP) map computed for GMC (Fig. 6.10) implied that both primary amine and pyrimidine nitrogen retain a large electrostatic potential with a low electron population, whereas the C=O group

poses the least electrostatic corresponding to a high electron density. It is incurred from the predicted potential that the earlier two sites are more prone to associate with silver atoms. To gain more insights, the charge transfer was demonstrated on the basis of the calculated Mulliken atomic charges for the main modes of interaction Fig. 6.11. From the theoretically calculated charges Table 6.3, it is inducted that the electrons have more tendency to transfer from silver atoms to GMC molecule through the primary amine and hydroxyl moieties in addition to the pyrimidine nitrogen atom. Among these four most feasible interactions, the binding energies and bonding distances indicate the amine and pyrimidine nitrogen atoms that play a vital role in terms of interaction with silver nanoparticles Fig 6.10.

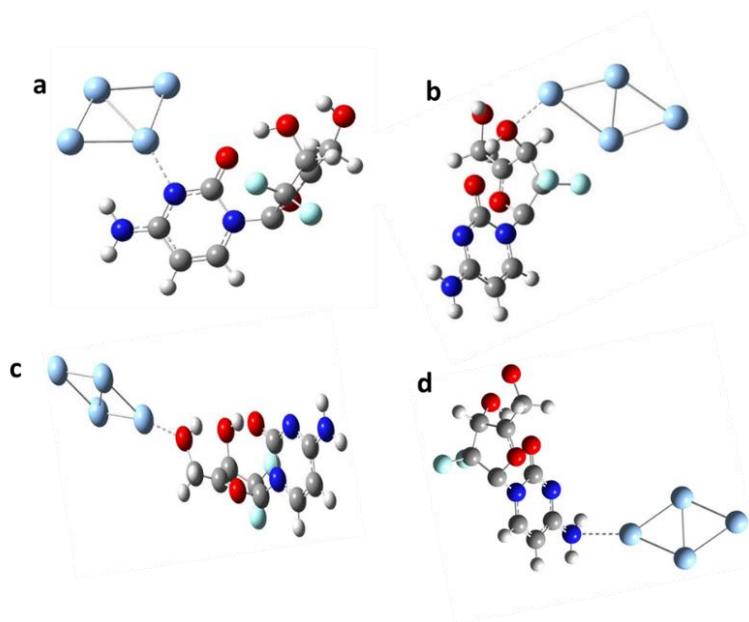


Figure 6. 10: Theoretically calculated sites of interaction between silver nanoparticles and GMC drug.

The modeled SERS spectra of these two interactions with the Ag₄ cluster are in good agreement with the experimental spectra (Fig. 6.9). Besides, there is also a close resemblance of the other two theoretical SERS spectra of the Ag...OH interactions with the experiment, suggesting that there are several possible interaction spots availed by the

drug molecules. The shifts noticed in peak positions and Raman signal enhancements led to a remarkable limit of detection.

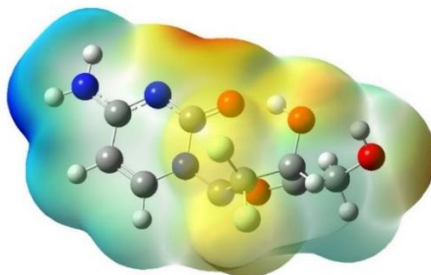


Figure 6. 11: Computed molecular electrostatic potential (MEP) map of GMC. The blue-colored region depicts the low electron density, and the red-colored regions are the high electron density regions.

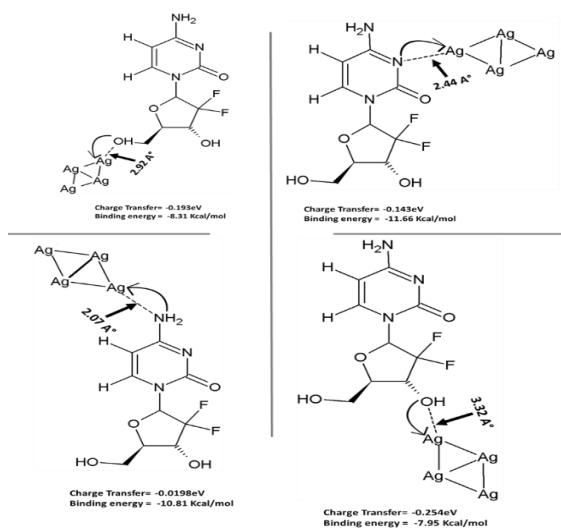


Figure 6. 12: Interaction energies, Binding distances, and energies for computationally predicted different interaction modes at B3LYP/6-311G(d,p) level.

6.5 Vibrational Assignments

The SERS spectrum of GMC showed an appreciable wavenumber redshift in several peaks accompanied with notable intensity enhancements. That prompted us to analyze the frequencies of the Raman and SERS spectra and assign them to appropriate vibrational

modes within the 200 cm⁻¹ to 1800 cm⁻¹ range (Table 6.2) [320], [332], [333]. The observed redshift in the SERS originated peaks indicated the dominance of the electrostatic interaction of the silver nanoparticles with GMC [40], [335], [336], [337].

Table 11: Tentative assignments of the experimental^a and B3LYP/6-311G(d,p) calculated^b Raman and SERS spectra below 1800 cm⁻¹ of free GMC and GMC with silver nanoparticles.

Vibration description	Experimental (cm ⁻¹)		Calculated (cm ⁻¹)		
	Raman	SERS	Raman	Interaction mode	
				CN-Ag ₄	H ₂ N-Ag ₄
C=O str.	1690 vw	1700 vw	1709	1685 (100)	1698 (19)
NH ₂ bend	1658 vw	1663 vw	1669 (20)	1647 (66)	1651
C=C str.	1515 w	1521 w	1532 (15)	1519 (22)	1553 (15)
CN str.	1306 s	1314 s	1474 (40)	1328 (20)	1340 (10)
CH ₂ def.	1245 s	1252 s	1251 (18)	1240 (40)	1254 (9)
CH bend, C-F str.	1115 w	1125 w	1151 (27)	1201 (19)	1202 (3)
Ring breath	1011w	1019 w	1022 (12)	1019 (3)	1037 (24)
Ring def., OH bend	661 m	672 w	678 (15)	683 (3)	688 (4)
Ring def., C-F bend	614 m	618 m	625(11)	609(1)	600(1)
Ring def.	340 w	348 m	366(5)	377(1)	355(1)

^a Observed Raman intensities, vs.: very strong, s.: strong, m.: medium, w.: weak, vw.: very weak

^b Relative computed intensities are provided in parenthesis.

The table lists the vibrational modes of the experimental Raman and SERS spectra compared with the theoretically calculated most probable interactions (i.e., Ring-N...Ag₄, H₂N...Ag₄, CP-OH...Ag₄, and Ter-OH...Ag₄) between nanoparticles and drug molecules. It is inscribed from the tabulated results that the simulated vibrational modes are in fair agreement with experimentally observed modes. The spectral patterns corresponding to Ring-N...Ag₄ and H₂N...Ag₄ poses more close resemblance to observed ones (Fig. 6.13). Among the vibrational modes depicted in Table 6.2, the most prominent bands are those at 799 cm⁻¹ ascribed to CCN and CH bending, at 1252 cm⁻¹ corresponding to CH₂ bending, and at 618 cm⁻¹ corresponding to ring deformation and C-F bending modes.

Table 12: The calculated energies of interaction between the drug and nanoclusters^a

Interaction	Energy (kcal/mol)	B. Distance (Å)	Mulliken Charges	
			Free	Complex
Ag ₄ -NH ₂	-10.81	2.67	Ag ₄ : 0.000	Ag ₄ : -0.0198
				GMC: +0.0198
Ag ₄ -N	-11.66	2.44	GMC: 0.000	Ag ₄ : -0.143
				GMC: +0.143
Ag ₄ -O-H	-7.95	3.32		Ag ₄ : -0.253
				GMC: +0.253
Ag ₄ -O-H	-8.31	2.92		Ag ₄ : -0.193
				GMC: +0.193

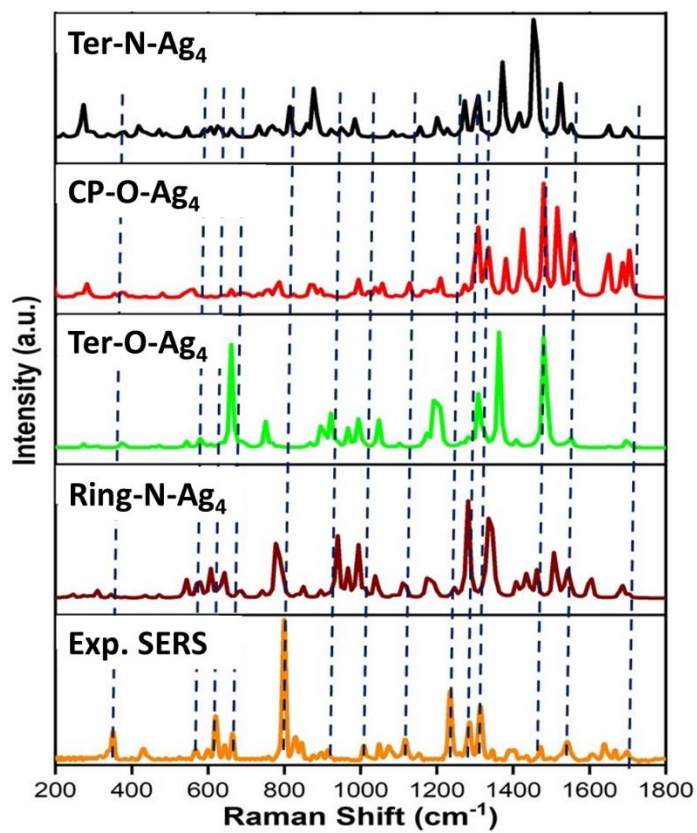


Figure 6. 13: Calculated SERS spectra mimicking the possible silver nanoparticle interaction modes with of GMC compared with the experimental SERS spectrum of GMC.

7 CHAPTER

Light-induced synthesis of silver nanoprisms as a surface-enhanced Raman scattering substrate for N-acetyl procainamide drug quantification.

Taken from Mahar, Nasurullah, and Abdulaziz A. Al-Saadi. "Light-induced synthesis of silver nanoprisms as a surface-enhanced Raman scattering substrate for N-acetyl procainamide drug quantification." *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* 302 (2023): 122996.

7.1 Introduction

Raman spectroscopy emerged as a powerful tool that can be employed as an optical sensing technique. It opened an alternative, yet convenient, window to characterize a variety of analytes as compared to traditional analytical methods [338], [339]. That is based on incident photon scattering whose inelastic light signals reveal spectral properties that define molecule-specific barcodes. However, conventional Raman methods suffered a low signal-to-noise ratio as only one out of 10⁸ incoming photons experiences Raman scattering [340]. This hampered the widespread use of Raman spectroscopy until Albrecht and Creighton introduced plasmon-supporting structures of the noble metals as a plasmonic source for signal intensity enhancements [341]. The intensity can be drastically enhanced by integrating the tested samples with nanostructured supports using their surface plasmon-

related phenomena evolving from nonclassical absorption behaviors and physicochemical interaction between analyte species and inert metal substrates [342]. Such an approach is known as surface-enhanced Raman scattering (SERS) spectroscopy. It is considered one of the key spectroanalytical tools that make advantage of surface roughness, photochemical activity, and second harmonic generation together with nonelastic scattering processes [343], [344], [345]. Although it is well known that a number of factors influence how light interacts with molecules nearby plasmonic substrates, it is now generally acknowledged that the large field amplification produced by plasmons affects both the externally incident light and the inelastically scattered signal [343], [346].

Noble metal-containing nanoparticles are vital materials for use as SERS substrates for trace-level quantification in the field of biosensing, therapeutics, and catalysis. Numerous methods have been employed to develop and control the size and shape of the gold, silver, and other many-metal-based SERS substrates between the range of 2-200 nm scale [347], [348]. The design of extremely effective SERS substrates with longitudinal localized surface plasmon resonance (LLSPR) properties is, therefore, considered an attractive area of spectroscopy research. The plasmonic metallic nanostructure composition, size, and morphology configure a wide variety of potential optimization factors such as the gaps between curved/sharp metallic surfaces where hotspots are produced most effectively, especially when the spacing is lowered to 1-4 nm [349], [350]. Earlier computational studies and experimental outcomes have also predicted and proved that the local electrical field enhancement in noble metal nanostructures strongly depends on the shape of metal protrusion by an effective lightning rod mechanism and shape-dependent plasmonic

resonance frequencies [348], [351], [352]. Therefore, it resulted in the highest electrical field along the sharp edges and corners, i.e., in the case of nanoprisms, nanostars, nanorods, nanotriangles, etc. [350]. Successful efforts were made to develop a wide variety of nanostructures including rods, wires, cubes, octahedra, triangles, and nanoprisms [15,16,20,21]. Most of these structures were carried out by conventional thermally driven methods, laser-induced transfer [353], [354], while light-driven photo-mediated reactions are more efficient in developing anisotropic nanostructures with controlled size and shape. Within the plasmonic materials context, silver produces significant Raman spectral enhancements and is more adaptable in practice due to its higher chemical stability and a wider range of available nanoparticle morphologies [355], [356]. Additionally, anisotropic morphologies, in particular those with well-defined points and edges, such as nanoprisms, could be more appropriate for achieving a greater signal amplification [356].

In this study, an efficient SERS-based analytical approach using shape-modified sharp-edged substrates has been developed. Silver nanoparticle spheres (AgNSs) were used as a seed for a photo-induced transformation into silver nanoprisms (AgNPMs). The developed nanoprisms were employed as a SERS substrate for a trace-level quantification of the N-acetyl procainamide (NAPA) drug as a probe molecule. NAPA is a major metabolite product of procainamide drug having an analogous pharmacological role. The metabolic role of NAPA poses a high inter-subject variant owing to its genetic polymorphism [357]. Since it is a highly active secondary metabolite, the adverse effect and other pharmacological complications are similar to that of its precursor procainamide. Therefore, the quantitative study of NAPA is essential to examine the toxicokinetic and toxicodynamic parameters.

7.2 Experimental

7.2.1 Materials

All materials and chemicals utilized in this work were used without further modifications. Trisodium citrate ($\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$), silver nitrate (NaNO_3), N-Acetyl procainamide (NAPA), and citric acid ($\text{C}_6\text{H}_8\text{O}_7$) were purchased from Sigma Aldrich. Bis(p-sulfonatophenyl) phenylphosphine dihydrate (BSPP), sodium tetrahydroborate (NaBH_4), and sodium hydroxide (NaOH) were purchased from Alfa Aesar, USA. Throughout all of the tests, Milli-Q grade (mQ) water ($>18\text{ M}$) was utilized for solution preparation.

7.2.2 Synthesis of silver nanosphere and silver nanoprisms:

Colloidal silver nanosphere was prepared and modified to prepare the nanoprisms following a reported method [358], [359]. Applying a typical synthesis procedure (Scheme 1), in a 250 mL 3-neck flask 95 mL of mQ water was added followed by N_2 purging for 40 minutes on an ice bath with constant stirring at 500 RPM. Then 2 mL of (0.10 M) AgNO_3 was injected along with 1 mL (0.17 M) sodium citrate, followed by 1 mL of cooled (50 mM) NaBH_4 was injected resulting in a chemical reduction and pale-yellow appearance of the mixture. After 20 minutes of stirring an ice bath in the mixture, 0.5 mL of additional NaBH_4 was injected (5 minutes interval) followed by the addition of 1 mL of BSPP to efficiently reduce and cap with negative charges on silver nanosphere to avoid early agglomeration. To adjust the pH (9.5-11), the 0.2 M NaOH was added dropwise as the higher pH (>10) and a $[\text{BSPP}]/[\text{Ag}^+]$ ratio close to 1 are optimal for the synthesis of a monodisperse triangular bipyramidal silver [350]. Then the mixture was kept in the dark

in a closed container for 15 hours for the aging of the solution. After, the solution was irradiated for a photoreaction to convert the nanospheres into nanoprisms in the dark with monochromatic LED light of 455 nm wavelength and 150 W of power for 24 hours. The selection of a specific LED wavelength depends on the desired size of the seed as well as the targeted morphology, as was reported by J.C. Scaiano and Kevin [344]. By increasing the wavelength, the dipolar absorption decreases with an increase in the longitudinal plasmon modes, and the 455-nm wavelength was noticed to favor the truncated geometry. For the nanoprisms morphology, the favorable size of the seed is between 20-120 nm, therefore, to attain the targeted morphology a wavelength-specified LED light source was employed [360]. The resulting product was green-colored nanoprisms with an average size of 95.2 nm. The prepared AgNPM solutions were used for the SERS study without further treatment. They showed stability for a one-month duration as depicted by the measured excitation spectrum (Fig. 5.1) in which the peak consistency proves stability.

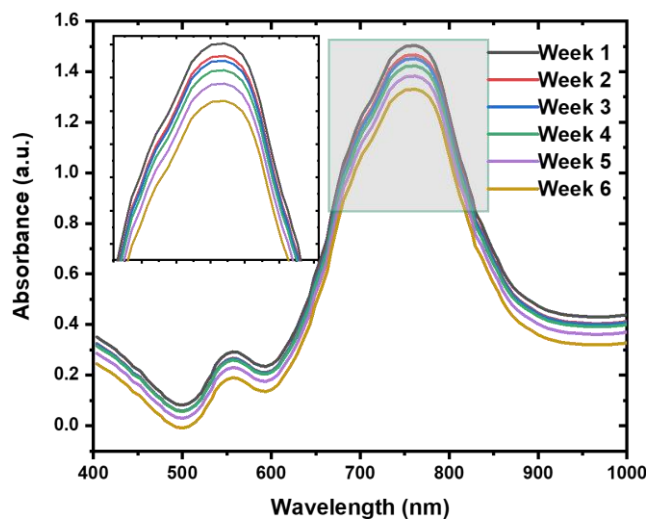


Figure 7. 1: UV-Vis spectra of the Nanoprisms for the time period of 6 weeks, inset shows consistency and uniform patterns

The shape transformation and morphology of prepared AgNSs and AgNPMs were compared using a variety of characterization techniques. A UV-visible spectrophotometer (model: Agilent, with standard quartz cuvettes) was used to collect the electronic spectra. A JEOL-USA JEM-2100F field emission microscope was used to capture the morphological characteristics at 200 kV accelerating voltage. Raman and SERS spectra were measured on the LabRam Horriba HR evolution spectrophotometer.

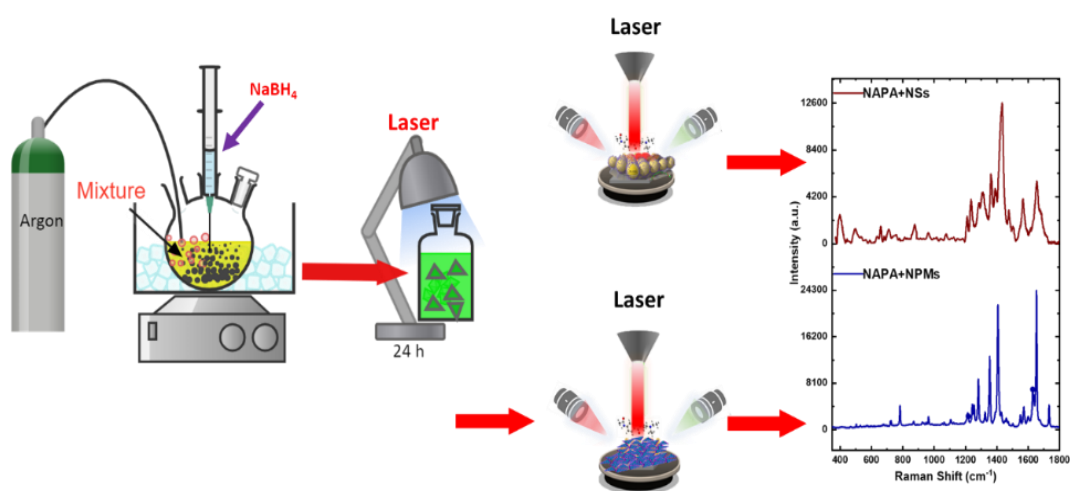


Figure 7. 2: Photo-induced synthesis of Ag-NPM from Ag-NS materials and their respective roles as efficient SERS substrates.

7.2.3 Raman and SERS measurements

Both Raman and SERS spectra were collected using a LabRAM HR evolution spectrometer with He-Ne 17 mW power laser source at 633 nm wavelength excitation. An objective lens of 50x power and 1800 mm switching grating at an acquisition time of the 20s was selected for both the Raman and SERS spectra. The SERS study to quantify NAPA was conducted in an aqueous solution at a concentration range from 10^{-3} to 10^{-14} M by a subsequent dilution method in mQ water. The prepared solutions were used without further

treatment. The v/v ratio of the NAPA probe to the substrate (AgNSs and AgNPMs) was optimized (2:1), and all the spectra were collected at room temperature. The results are an average of 3 runs of each spectrum. The enhancement factor (EF) was determined using the formula $EF = (ISERS/IRaman) \times (CRaman/NSERS)$, where ISERS and IRaman are the intensities of probe molecules in the laser-illuminated area in both SERS (23585 a.u.) and normal Raman (1505 a.u.) experiments, and CRaman (10^{-4} M) and CSERS (10^{-12} M) are the concentrations of the characteristic Raman and SERS peaks of the analyte, respectively.

7.3 Results & Discussion

The UV/vis-NIR spectra of prepared nanoparticles are shown in Fig. 7.3. It can be seen from Fig. 7.3 that a characteristic absorption band at 569 nm was observed with an average size of 38.7 nm (Fig. 7.5 c). The observed red shift in the band position as compared to the reported literature value of 400 nm could be attributed to size analogy and agglomeration [361]. After the photo-induced shape transformation of nanospheres seed into a nanoprisms morphology, a concomitant rise of a new band at 769 nm is the in-plane dipole peak (Fig. 7.3) associated with the large bimodal distributed prisms with 95.2 nm edged-length (Fig. 7.5). There is a small band observed at 569 nm attributed to the out of plane dipole peak of the nanoprisms, a characteristic feature of bimodal growth. Since the AgNPMs are coated by negatively charged BSPP and citrates ligands, their components should repel each other, but the irradiated light induces the optically attractive forces which resulted in a pronounced dipole plasmon resonance [362]. As a result, a redshift in the exciton wavelength was observed in the case of AgNPMs. Besides this photoexcitation process, the edges and the tips of the nanoprisms are extremely polarized resulting in overcoming

the electrostatic repulsion and leading to a fusion of a few types of nanoprisms, hence the average size of the nanoprisms was enhanced (Fig. 7.5b).

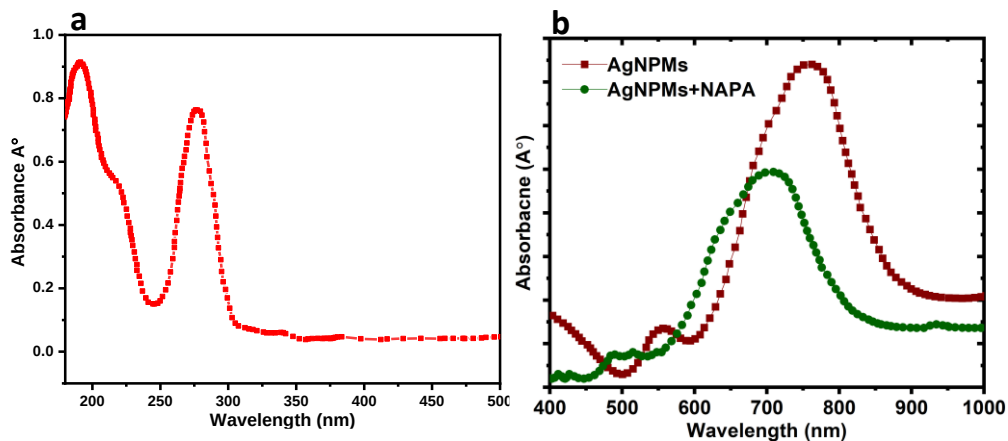


Figure 7. 3: (a) UV-Vis spectra of the free NAPA drug (b) Excitation UV-vis-NIR spectra of the photo-induced silver nanoprisms (brown) after interacting with the NAPA drug (green).

The interaction of the probe molecule (NAPA) could be observed in the excitation spectrum depicted in Fig. 7.2 (b). Where a blue shift in a band position from 769 to 713 nm accompanied by a change in its intensity and rise of small shoulders was observed indicating that a photo-induced charge transition took place between the substrate and the NAPA molecules at hot spots. Fig. 7.2 (a) shows the UV-Vis spectra of free NAPA molecules.

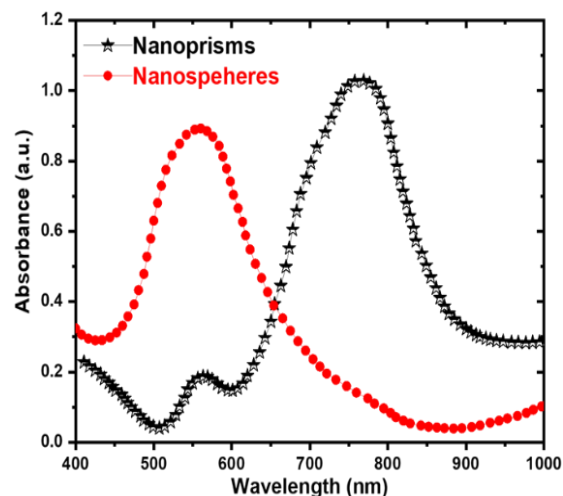


Figure 7. 4: Excitation UV-vis-NIR spectra of the prepared silver nanospheres (red) and the photo-induced silver nanoprisms (black).

The corresponding FE-SEM images shown in the inset in Fig. 7.5 confirm that the nanospheres have been successfully converted into nanoprisms with various sizes and shapes, possibly due to a photo-induced fusion. The majority of the thermally synthesized nanoparticles have a diameter ranging between 35 to 40 nm and are spherical in nature (Fig. 7.5a). After being exposed to light for 24 hours, AgNSs transformed into a nanoprism-based structure due to photoinduced plasmonic truncation associated with a change in color from yellow to green with an average size of 95 nm as depicted in Fig 7.5.

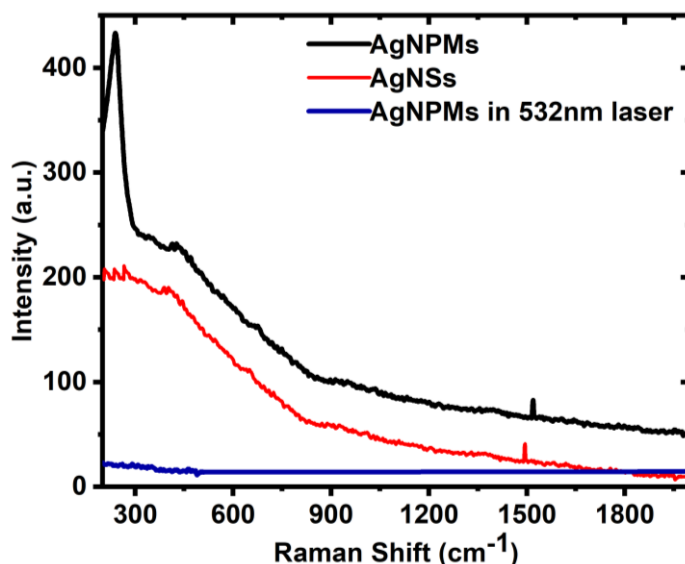


Figure 7. 5: The Raman spectra of AgNSs (Red) and of AgNPMs (black), acquired at 633 nm excitation source, using 50x lens, 1800 grating, 20 sec. acquisition time and 4-sec. accumulation. The Blu line spectra belong to AgNPMs taken at 532 nm.

Categorically, photoexcitation plays multiple roles in seed growth from sphere to nanoprisms, as it initiates the formation of enlarged length-edged nanoparticles and excites the dipole plasmon band of the formed nanoprisms. That resulted in the fusion of the AgNPMs and, hence, deformed the uniform sphere-shaped nanoparticles. The Raman spectra of the prepared nanoparticles (Fig 7.4) show no Raman peaks at 532 nm laser excitation though this wavelength is close to the SPR band (569 nm) of the silver nanospheres. However, there are a few less intense peaks and shoulders along with an intense band at 288 cm⁻¹. A shift in the band position was observed in the case of the 633 nm laser source. This could be attributed to the photoinduced aggregation to generate the local hot spots [363].

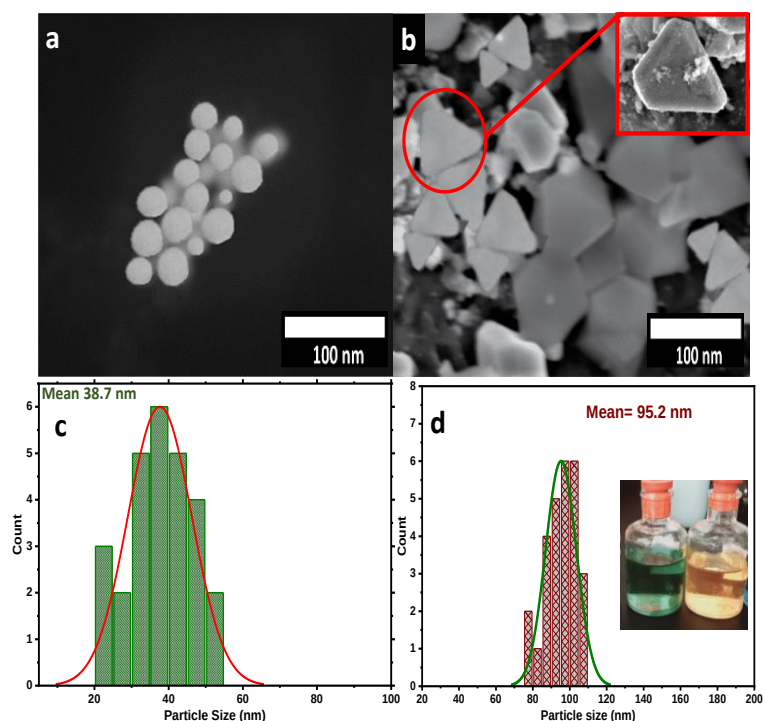


Figure 7. 6: a) FE-SEM image of the Ag-nanospheres seeds b) the FE-SEM image of Ag- nanoprisms showing mixed morphologies c) histogram comparing the average particle sizes of the prepared silver nanospheres; d) Average particle sizes of the photo-induced silver nanoprisms inset is the real image of AgNSs (yellow) and NPMs (green).

The uniform and unique patterns of the Raman spectra provide a reliable means to identify the fingerprints of biomolecules and active drug contents. SERS-based techniques are particularly useful to detect very low concentrations of bioactive components. There are two acceptable concepts promoting Raman signal enhancements: the electromagnetic (EM) and chemical (CM) mechanisms. The EM can lead to an enhancement factor of up to 10^8 [364] owing to the longitudinal localized surface plasmonic resonance (LLSPR) emanated when the probe molecules trapped within hot spots in the range of a few nanometers (4-10 nm) distances [365]. The analyte molecules position themselves within hotspots filling small gaps in the vicinity with noble metal nanoparticles. Several analytical protocols, a summary of which is shown in Table 7.1, were developed and reported for the detection of the drug NAPA.

Table 13: Limit of detection (LODs) and linear dynamic ranges (LDRs) of some established techniques for the quantification of NAPA compared to this work.

Method	LDR	LOD	R^2	Ref.
TLC	1-5 $\mu\text{g/ml}$	60 ng/ml	----	[366]
GLC	--	10 ng/ml	--	[367]
HPLC	---	2-10 mg	---	[368]
RP-LC	--	10 ng	--	[369]
UV-HPLC	0.1-8 $\mu\text{g/ml}$	0.1 $\mu\text{g/ml}$	0.99	[370]
SERS	0.5×10^{-4} to 0.5×10^{-12} M	0.5×10^{-13} M	0.945	Our Work

Achieving an even lower detection limit with a reproducible method is still an area of interest. A comparison of SERS and Raman spectra of NAPA with both the AgNSs and NPMs substrates is displayed in Fig 7.6. Eight distinct Raman signals of NAPA between 600-1800 cm^{-1} spectral range of wavelength shifts were identified in Fig. 7.6 c. Notably, the five prominent Raman bands at 680 cm^{-1} (assigned to C-N-C bending), 1431 cm^{-1} (C-C stretching), 1576 cm^{-1} (NH₂ bending), 1643 cm^{-1} (C-C stretching), and 1719 cm^{-1} (C=O stretching) encountered notable changes in terms of spectral intensities as well as wavenumber shifts after the SERS phenomenon (Fig. 7.6 a-b). Such changes occurred due to shape, and high symmetry which result in more hot spots hence strong EM and chemical interactions gesturing the role of the photo-induced charge transfer, LLSPR, and hotspot characteristics [371], [372]. For instance, shifts in peak positions were noted in the case of AgNPMs substrate for the Raman lines centered at 1719 cm^{-1} (shifted to 1733 cm^{-1}) and 1643 (shifted to 1652 cm^{-1}), while redshifts were encountered with the decrease in peak

intensity at 1576 cm^{-1} (shifted to 1568 cm^{-1}), and 1431 cm^{-1} (shifted to 1407 cm^{-1}). Likewise, for the case of AgNSs, NAPA peaks appearing in 1719, 1576, 1431, and 680 cm^{-1} were shifted to 1721, 1578, 1432, and 682 cm^{-1} , respectively, while the C=O stretching band at 1643 cm^{-1} demonstrated a red-shift to 1654 cm^{-1} .

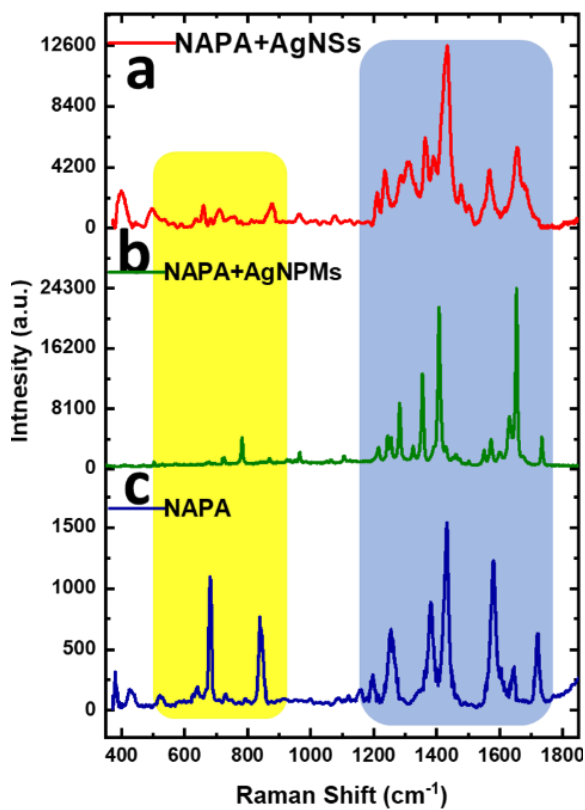


Figure 7. 7: a) The SERS spectra of NAPA a) with AgNSs, and b) with AgNPMs, compared with c) the Raman spectra of pure NAPA, all acquired at 633 nm excitation source, using 50x lens, 20 sec. acquisition time and 4-sec. accumulation.

By analyzing the SERS spectra at various drug concentrations in the range of 10^{-4} - 10^{-14} M, a limit of detection (LOD) of NAPA was successfully achieved to be in orders of 10^{-13} M in the case of AgNPMs and 10^{-9} M for AgNSs (Table 5.2 and Fig. 7.7).

Table 14: Comparison of the limit of detection (LOD), linear dynamic range (LDR), and Raman intensity enhancement factor (EF) parameters using AgNSs and AgNPMs materials as active substrates for sensing of NAPA drug.

SERS Substrate	LOD	LDR	R^2	EF
AgNSs	0.5×10^{-9} M	10^{-5} - 10^{-9} M	0.9172	1.21×10^5
AgNPMs	0.5×10^{-13} M	10^{-4} - 10^{-12} M	0.9456	1.57×10^8

The decline in peak intensity as a result of the change in NAPA concentrations follows a consistent SERS spectral pattern. Since the signal strength is directly proportional to the analyte concentration, it falls linearly as concentration decreases [373]. The results show that the intensities can be correlated with the drug analyte's logarithm of concentration with correlation coefficients of 0.9456 and 0.9173 for NPMs (Raman peak at 1652 cm^{-1}) and NSs (Raman peak at 1432 cm^{-1}), respectively. Furthermore, the peak at 1652 cm^{-1} had a wide linear dynamic range (LDR) of 10^{-4} to 10^{-13} M for NPMs (Fig 7.7. 4b), whereas the NSs (1432 cm^{-1}) had a relatively narrower one in comparison to the first band. While the wider spectral bandwidths reflect a stronger interaction in the case of NSs with NAPA (Figure 7.6), the Raman signal intensity enhancement when the NPMs substrate is employed was observed multiple folds stronger, which could be explained in terms of the anisotropic morphology of NPMs due to the photo-induced truncation and lightning rod effect. Having three double-edged sharp vertices/tips of $\sim 60 \text{ nm}$ is believed to significantly contribute to the nanoprisms superior optical and electronic properties [344]. That consequently led to a strong plasmonic influence to spectroscopically detect the low concentrations of probe molecules[374]. To quantify the enhancement efficiency, Raman enhancement factors were computed using the same aforementioned reference peaks.

While the enhancement factor in Raman signals reached up to 1.21×10^5 in the case of AgNSs-NAPA interaction, the AgNPMs-NAPA system exhibited a further better EF of the value of 1.57×10^8 . The variation in the nanostructures between the two nanoparticles is believed to be the main reason behind the difference in their SERS performance, although both contributed notably to the intensity enhancement process. Establishing a link between SERS characteristics and the role of shape and absorbance of nanomaterials has taken a lot of interest as demonstrated in the literature. Aggregated nanospheres are known to have excellent absorbances at 633 nm, according to Talley et al., and 785 nm, which results in a pronounced SERS efficiency. The location of the SPR between 600 and 900 nm is connected to SERS efficiency for aggregated nanospheres, shape, and the distance between the analyte and the substrate hotspots, according to Wustholz, K. L. et al. There are other possible explanations for why AgNPMs exhibit significantly more enhancement than AgNSs. The light-induced fusion of NPMs results in an aggregation of four orders of magnitude and a decreased distance between the analyte molecules and hotspots, which is not the case with NSs. It should be noted that the nanospheres aggregation led to a splitting of SPR bands into two components; longitudinal (low frequency) and transverse (high frequency), therefore, due to the spherical morphologic nature, these modes are not well resolved. On the contrary, in the case of NPMs, owing to their anisotropic form, the SPR splits into three distinct plasmon modes: the out-of-plane dipole, in-plane dipole, and quadruple [375]. These modes are generated due to the sharp edges and corners and to the degree and direction of polarization of electron clouds relative to the incident electric field [376].

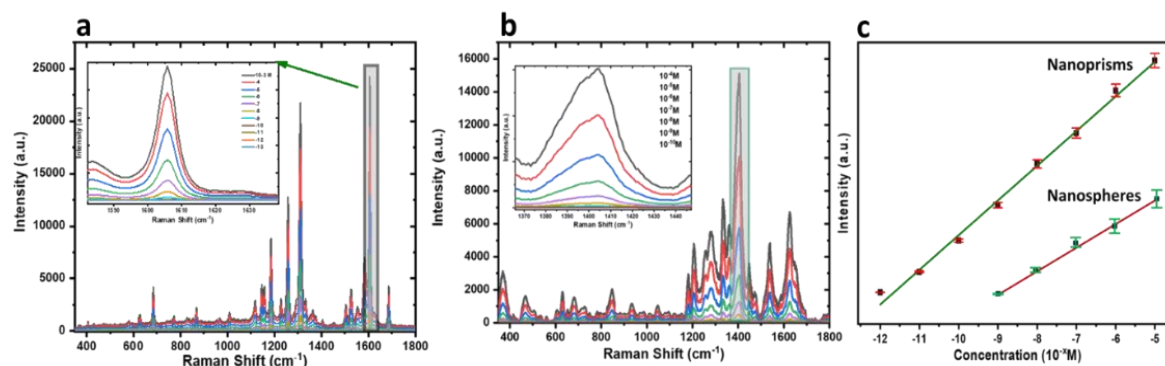


Figure 7. 8: SERS spectra showing the peak intensity-concentration dependence of the NAPA molecules in contact with (a) AgNPMs substrate (Raman line centered at 1652 cm⁻¹), and (b) AgNSs substrate (Raman line centered at 1432 cm⁻¹). (c) Comparison of the linear dynamic ranges and correlation coefficients of the intensity-concentration relationship in the case of Ag-nanoprisms and Ag-nanospheres.

The stability of the synthesized materials and the reproducibility of their SERS performance were also tested. The repeatability of the suggested method is demonstrated, for instance, by the Raman intensity distribution of the peak 1652 cm⁻¹ during the period of time studied, which demonstrated an adequate consistency with an RSD of 1.89 %. Likewise, the selectivity of the approach was tested by considering four distinct interferents in 1000 times higher concentration than the analyte and mixing them with a NAPA solution maintained at a concentration of 1x10⁻⁶ M. The other bioactive species' interference can be seen to have little effect on the SERS spectra of the NAPA solution (Fig. 7.9).

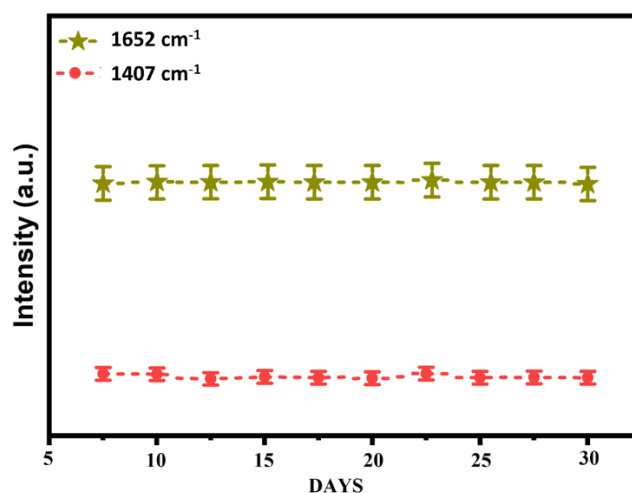


Figure 7. 9: The SERS spectral stability for period of 30 days of the two prominent peaks 1652 cm^{-1} and 1407 cm^{-1}

The average recovery was estimated to be 97 %, while the RSD of the SERS peaks for the concentration of 1×10^{-6} M was found to be 1.45%. The findings shown in Fig. 7.9c indicated that Raman peak intensity at 1652 and 1407 cm^{-1} barely changed throughout the course of a four-week period for the period of 30 days Fig. 7.8. It is obvious that the peak intensity is persistent with negligible shift and change in peak pattern.

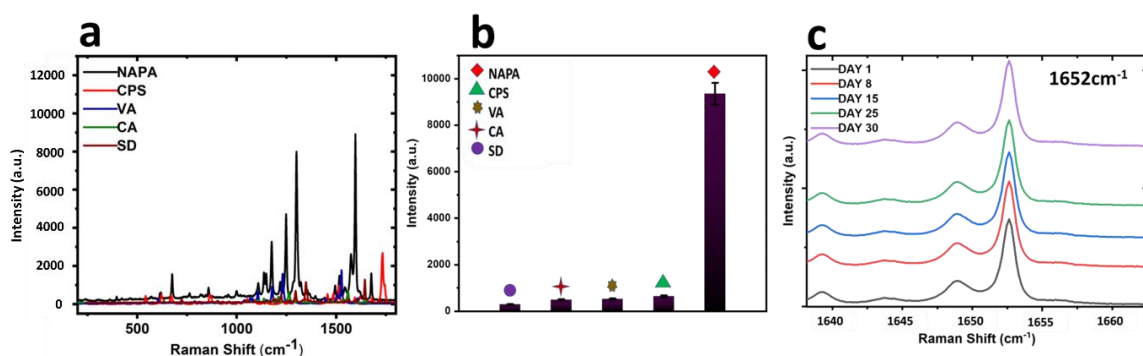


Figure 7. 10: (a) Interference effect of different interferents, namely sulindac (SD), ciprofloxacin (CPS), citric acid (CA), and valeric acid (VA), 10-2 M each, mixed with NAPA at 10-6 M concertation, (b) Selectivity outcome in terms of SERS intensity (1652 cm^{-1}) of the probe molecules (10-6 M) in presence of the same four interferents (10-2 M each), and (c) The stability of the NPMs-NAPA solution spectra taken over a time period of 30 days

8 CHAPTER

High Performance, low-cost Rechargeable Aluminum ion Battery using Nb₂CTx- MoS₂ Composite Cathode

Taken from Nasurullah Mahar¹, Tawfik Abdo Saleh¹, Amir Al-Ahmed*,^{2,1}, Abdulaziz A.

Al-Saadi**,^{1,3}

¹*Department of Chemistry, King Fahd University of Petroleum & Minerals, Dhahran
31261 Saudi Arabia.*

²*Interdisciplinary Research Center for Sustainable Energy Systems (SES), King Fahd
University of Petroleum & Minerals, Dhahran 31261, Saudi Arabia.*

³*Interdisciplinary Research Center for Refining and Advanced Chemicals, King Fahd
University of Petroleum & Minerals, Dhahran 31261, Saudi Arabia.*

Energy Materials. EM-2024-111

8.1 Introduction

The growing demand for safe and cost-effective energy storage devices is the driving force for efforts on different battery technologies. Conventional Li-ion batteries have revolutionized energy storage technology and have been used as a major power source in portable electronics and even in electric vehicles. It has been proven to be a key energy storage device in the preceding decade with several shortcomings, such as safety, higher price, and limited reserves [80], [81]. In recent time Aluminum-ion batteries (AIBs) are getting significant attention due to their lower cost (as Aluminum, as the 7th most abundant element), and environmental safety. Additionally, AIB has an extraordinary theoretical volumetric capacity of 8046 mAh/cm³, which is even higher than that of Li, driven by its

three-electron redox process [82], [83], [84]. Over the past two decades, significant efforts have been directed towards the fabrication of AIBs using various cathode materials with the aim of enhancing performance, enabling fast charging, and improving energy density [6]. Nonetheless, the development of AIBs operating at room temperature remained elusive until the utilization of chloroaluminate-based ionic liquid electrolytes (ILE) [85]. Cell prepared with ILEs demonstrated superior efficiency, capacity, and cyclic and high voltage stability [86]. Moreover, working with ILEs provides the benefit of wide electrochemical windows, good electrical conductivity, and thermal stability, rendering them ideal candidates for AIBs [86], [87], [88]. These attributes make ILEs well-suited to address the challenges associated with traditional electrolytes to move forward with the advancement of AIB technology. Recent research has demonstrated that molten ILE, such as, 1-butyl 3-methylimidazolium chloride ([BMIm]Cl), offer significant improvements in AIB [89]. The presence of chloroaluminate anions $[Al_xCl_y]^-$ (including $AlCl_4^-$, $Al_2Cl_7^-$, and $Al_3Cl_{10}^-$) plays a crucial role in the charge transfer process [86]. During the intercalation and de-intercalation of these complex anions cause structural deformities and lattice distortions within the cathode material due to the large effective radius of these anions [90], [91]. Consequently, these structural distortions lead to irreversibility and rapid capacity decay. This emphasizes a significant challenge that must be addressed in the development of AIBs to achieve long-term stability and improved performance. Thus, a cathode material with a larger interlayer space to accommodate these complex ions is required which would subsequently overcome the storage and lattice distortion challenges [92], [93]. To address these challenges multi-layered structures, such as, iron chalcogenides hybrid cathodes ($FeS_2@C$ [94], CuS [95], $NiCo_2S_4$ [96], and MoS_2/C [97]) were fabricated, because the

metal sulfur polar bond facilitated formation of the Al-Cl bond, and the less electronegative sulfur reduces the electrostatic interactions during the charge/discharge process [94], [95], [96], [97], [98], [99], [100], [101]. Likewise, Jiao *et al.* reported the Ni₃S₂/graphene composite cathode, the initial capacity of the composite cathode was 300 mAh/g at 100 mA/g current density. Regardless of these efforts, the capacity decayed to 60 mAh/g after 100 cycles [102]. The abrupt drop in capacity observed due to cathodic degradation, lattice distortion, and strong coulombic ion-lattice contact inhibiting ion diffusion through the lattice [103]. Subsequently, it is essential to build an appropriate cathode with weak coulombic contact and a sturdy framework capable of housing the intercalated complex ions without considerable structural change following the GCD process. MXenes, which is known for its inspiring electrochemical properties, wide interlayer space, high conductivity, high surface area, and tunable surface chemistry, shows potential as an efficient cathode material in AIBs [105]. Among the various MXenes tried Niobium MXene (Nb₂CT_x) has better thermodynamic, and kinetic and oxidative stability due to better discharge voltage plateau compared to that of Ti and V-based MXenes, additionally, it also has a healthier theoretical capacity [106]. Furthermore, the highly conductive nature of the Nb₂CT_x and the pseudo-capacitive behavior of the MoS₂ are exploited to improve the electrochemical kinetics, enabling rapid charge-discharge rates and high-power density. [97]. In this work, a green process was adopted to prepare Nb₂CT_x MXene, stabilizing its interlayer spacing and further modify with MoS₂ to obtain a modified composite cathode for AIBs. Combination of Nb₂CT_x and MoS₂ in a composite structure supposed to enhance the overall electrochemical performance of the cathode material due

to its characteristic superiority with added synergistic effect, this approach to enhance the cathodic capacity has not been reported yet [377], [378].

Nb₂CTx-MoS₂ composite cathode material was prepared using hydrothermal process, characterized, and used for pouch cell fabrication. For comparison cell with pure Nb₂CTx as cathode was also prepared and tested. Overall, the synthesis process is shown schematically in Fig.8.2. The pouch cell was fabricated comprising of a cathode (Nb₂CTx-MoS₂ or Nb₂CTx), Al metal anode, and [BMIm]Cl:AlCl₃ as electrolyte (Fig. 8.1). 1-butyl-3-methylimidazolium chloride ([BMIm]Cl, 99.9%, Sigma-Aldrich.) and anhydrous high-purity aluminum chloride (AlCl₃, 99.99%, Sigma-Aldrich) mixed in 1.5 ratio at room temperature inside an argon-filled glovebox with <0.1 oxygen and humidity levels. The yellow mixture was stirred at 60 °C for 1 hour at 300 rpm, which slowly turned into a brown-colored liquid. The electrochemical performances were evaluated using CV, EIS, and GCD (galvanostatic charge-discharge) tests. The proposed mechanism was supported through XRD, FE-SEM-EDX, XPS, and Raman studies.

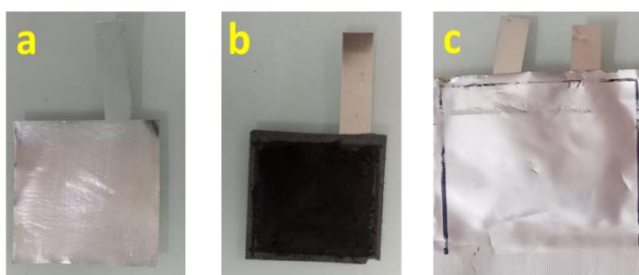


Figure 8.1: The pouch cell components (a) Al foil anode (b) carbon paper coated with composite cathode (c) assembled single sheet pouch cell.

The composite cathode-based AIBs exhibited a discharge capacity of 350 mAh/g over 500 cycles at a current density of 100 mA/g. This performance significantly surpassed that of bare Nb₂CTx cathode-based AIB and other reported cells (see Table 8.1).

Table 15: Comparison of various materials and the energy capacity at 500 cycles range

Cathode	Specific Capacity (mAh/g)	cycles	References
Nb ₂ CTx	108	100	[379] ¹
Ti ₃ C ₂ @CTAB	132	400	[380]
MoS ₂ -Ti ₃ C ₂ Tx	166	400	[377]
V ₂ C@Se	210	500	[381] ¹
V ₂ CTx	300	500	[382] ¹
MoS ₂ -Nb ₂ CTx	350	500	This work

These findings highlight the potential of the modified MXene synthesis process and composite cathode to improve the performance and stability of the AIBs.

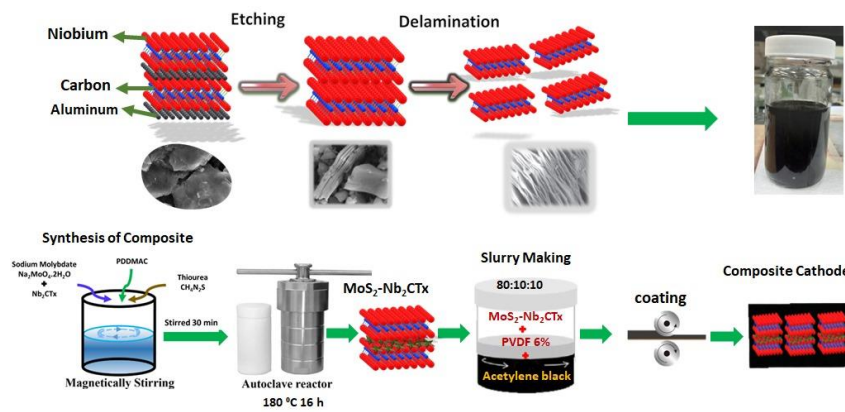


Figure 8.2: Schematic representation of fabrication of composite electrode material from MAX to MXenes and Synthesis of Nb₂CTx-MoS₂ composites by hydrothermal method. Additionally, the preparation of slurry with

80:10:10 ratio of active material, conducting carbon and PVDF binder respectively followed by pasting slurry on carbon paper is depicted.

8.2 Chemical and materials

Nb₂AlC MAX phase precursor, hydrofluoric acid (HF, 48-54%), and triethylamine (TEA) were purchased from Alfa Aesar. Anhydrous aluminum chloride (99.99%), 1-butyl-3-methylimidazolium chloride (98.0%), and aluminum foil of 0.010 mm thickness (99.99%) were purchased from Sigma-Aldrich. The carbon paper, Celgard 2500 monolayer PP membrane of 16 μ m thickness, and aluminum laminated film were purchased from the local supplier. All the chemicals and reagents were consumed without additional purification.

8.2.1 Instrumentation

Synthesized Nb₂CTx, and Nb₂CTx-MoS₂ composites were characterized by Field Emission scanning electron microscopy (FE-SEM: Zeiss Merlin), high-resolution TEM, X-ray diffraction (XRD: Bruker D8 Advance), Raman spectroscopy, and X-ray photoelectron spectroscopy (XPS: Amicus). Electrochemical studies such as cyclic voltammetry (CV), and impedance of the cell were recorded using a Gamry (Reference 3000) while the galvanostatic charge/discharge GCD was conducted using 8-channel battery analyzers BTS8-5V5A. XPS was used to analyze the interactions of Nb₂CTx MXene with intercalated ions. After 500 consecutive cycles, the Nb₂CTx-MoS₂ MXene cathode was removed from the cell, carefully cleaned with acetone, dried, and characterized by XRD, Raman spectroscopy, and XPS to study the structural changes that occurred during cycling.

8.2.2 Synthesis of MXenes and composite

Nb₂CT_x MXenes were synthesized from Nb₂AlC precursor using a modified method [383]. In a typical wet etching process, a solution of hydrofluoric acid (48%) and hydrochloric acid (12 M) (1:4 ratio) was prepared in a Teflon bottle over an ice bath. Then 2g of Nb₂CT_x was slowly mixed into this cold solution with constant stirring at 300 rpm for 10 minutes. The mixture was transferred over an oil bath at 35 °C for 24 hours. The product was washed several times with an ethanol-water (1:1) mixture until the pH becomes natural. Subsequently, Nb₂CT_x was intercalated with 20% TEA at room temperature for 3 hours. The dispersed Nb₂CT_x flakes were washed with an ethanol-water (1:1) mixture by centrifuging followed by sonication for 10 minutes. The supernatant was collected each time until the transparent supernatant was observed. Composite Nb₂CT_x-MoS₂ was prepared by hydrothermal method [384]. In a modified approach, 4.8 g of Na₂MoO₄·2H₂O and the required amount of thiourea in 50 mL of D.I water was added by continuous stirring, followed by the addition of 76 mg of Nb₂CT_x dispersed in 3 mL of PDDMAC 20%. To maintain the pH of the solution at 6.5, the required amount of HCl was added. The mixture was then transferred into a teflon-lined stainless-steel autoclave and heated at 180 °C for 24 hours. The black-colored powder was washed several times to eliminate the impurities. Finally, the composite dried in a vacuum oven and annealed at 400 °C under constant Argon flow. The various concentrations and ratio of the respective salts were tried, the above procedure posed better results hence selected for further study.

8.2.3 Synthesis of MXenes and composite cathode

Nb₂CT_x MXenes were synthesized from Nb₂AlC precursor using a modified method [383]. In a typical wet etching process, a solution of hydrofluoric acid (48%) and hydrochloric acid (12 M) (1:4 ratio) was prepared in a Teflon bottle over an ice bath. Then 2g of Nb₂CT_x was slowly mixed into this cold solution with constant stirring at 300 rpm for 10 minutes. The mixture was transferred over an oil bath at 35 °C for 24 hours. The product was washed several times with an ethanol-water (1:1) mixture until the pH becomes natural. Subsequently, Nb₂CT_x was intercalated with 20% TEA at room temperature for 3 hours. The dispersed Nb₂CT_x flakes were washed with an ethanol-water (1:1) mixture by centrifuging followed by sonication for 10 minutes. The supernatant was collected each time until the transparent supernatant was observed. Composite Nb₂CT_x-MoS₂ was prepared by hydrothermal method [384]. In a modified approach, 4.8 g of Na₂MoO₄·2H₂O and the required amount of thiourea in 50 mL of D.I water was added by continuous stirring, followed by the addition of 76 mg of Nb₂CT_x dispersed in 3 mL of PDDMAC 20%. To maintain the pH of the solution at 6.5, the required amount of HCl was added. The mixture was then transferred into a teflon-lined stainless-steel autoclave and heated at 180 °C for 24 hours. The black-colored powder was washed several times to eliminate the impurities. Finally, the composite dried in a vacuum oven and annealed at 400 °C under constant Argon flow. The various concentrations and ratio of the respective salts were tried, the above procedure posed better results hence selected for further study.

8.2.4 Pouch Cell fabrication

The anode was prepared by cutting the (0.2mm) Al foil into (1.8x2 cm²) pieces and washed with acetone to remove the moisture. Cleaned foil was scratched with the doctor's blade to remove the shine and soaked in electrolyte for 2 hours. Nb₂CTx-MoS₂ composite cathode material for the AIBs was fabricated by evenly mixing Nb₂CTx-MoS₂, with acetylene black powder and (6%) PVDF binder in the mass ratio of 80:10:10 in NMP. The resultant slurry was coated on carbon paper (1.7x2 cm²) by the doctor's blade and was dried at 110°C, the final effective mass of active material coated was found to be 10 mg. The prepared cathode was wrapped into a celgard polypropylene separator sheet (16 µm thick) and soaked into the electrolyte for 2 hours. Fig. 8.1 displays the corresponding assembly of the Al battery's components with the tantalum foil current collectors, which include the 2D Nb₂CTx-MoS₂ cathode, aluminum metal anode (99.999 percent pure aluminum foil (0.2 mm thick)), and AlCl₃/[BMIm]Cl electrolyte. The pouch cell was assembled inside a nitrogen-filled glove box with oxygen and moisture less than 0.1 ppm.

8.3 Results & Discussion

To investigate the structure and morphology, both MXenes and composite Nb₂CTx-MoS₂ were studied by using various techniques, including XRD, FE-SEM, HR-TEM, XPS, and Raman spectroscopy. XRD patterns of exfoliated few-layer Nb₂CTx can be seen in Fig. 8.3a. The (002) peak of Nb₂CTx has shifted to a smaller angle of 6.92°, compared to multilayered M-Nb₂CTx at 9.46° and the precursor MAX phase (13.92°) (Fig. 8.2).

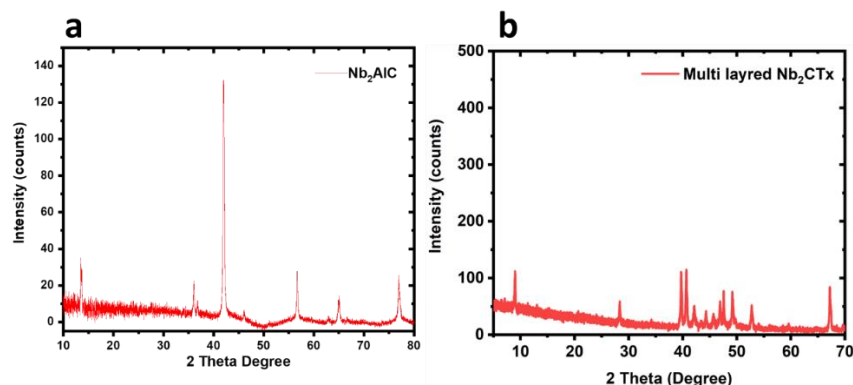


Figure 8.3: XRD spectra of the precursor MAX phase and multilayered Nb₂CTx MXenes.

This shift indicates an increase in the d-spacing to 1.27 nm after the etching of Al and TEA intercalation. Fig. 2b displays the diffraction patterns of the composite Nb₂CTx-MoS₂. Here, all characteristic peaks of Nb₂CTx and MoS₂ are visible, with slight shifts in peak position and changes in intensity for instance, the Nb₂CTx peak at 8.12° has shifted to higher degrees compared to pure Nb₂CTx [377]. Additionally, a new wide range of bands at 14.67° emerges, signifying the successful incorporation of MoS₂. The diffraction patterns observed at 28.74°, 35.23°, and 55.32° are in good agreement with the pure phase of the layered structure of MoS₂ (PDF #37-1492) [378]. However, it can be observed that there are a few patterns in Fig. 8.2b does not match well with the corresponding PDF. This observation which reflects the structural changes in the composite following the hydrothermal treatment of layered Nb₂CTx with MoS₂ [385]. Moreover, non-basal-plane peaks, such as, (004), (103), and (106) at 13.92°, 36.12°, and 42.21°, respectively, have either eroded or experienced a decrease in intensity. These observations suggest structural modifications induced by the incorporation of MoS₂ and ion intercalation processes. The layered morphology of the Nb₂CTx is clear in FE-SEM image (Fig.8.3 c). It is a few-layered accordion like structure of Nb₂CTx which reflects the successful etching of Al.

Likewise, Fig.8.3d shows the FE-SEM images of the Nb₂CTx-MoS₂ composite, the substantial change in morphology with small flower like crystallites of MoS₂ covering the Nb₂CTx flakes are observed, which confirms the formation of a well-defined composite and is assumed to enhance the conductivity and surface area of electrode [386]. Fig.8.3e shows the HR-TEM images of the Nb₂CTx transparent sheets and accordion-like shapes due to the chemical etching of the Al atomic layers showing the few-layered arrangements of the as-prepared Nb₂CTx. Fig.8.3f shows the selected area diffraction (SAED) image. The diffraction rings demonstrate the (100), (102), (421) and (002) planes of the Nb₂CTx crystals. These patterns are in line with the (PDF #15-0127) for the hexagonal phase Nb₂C of space group P63/mmc [378].

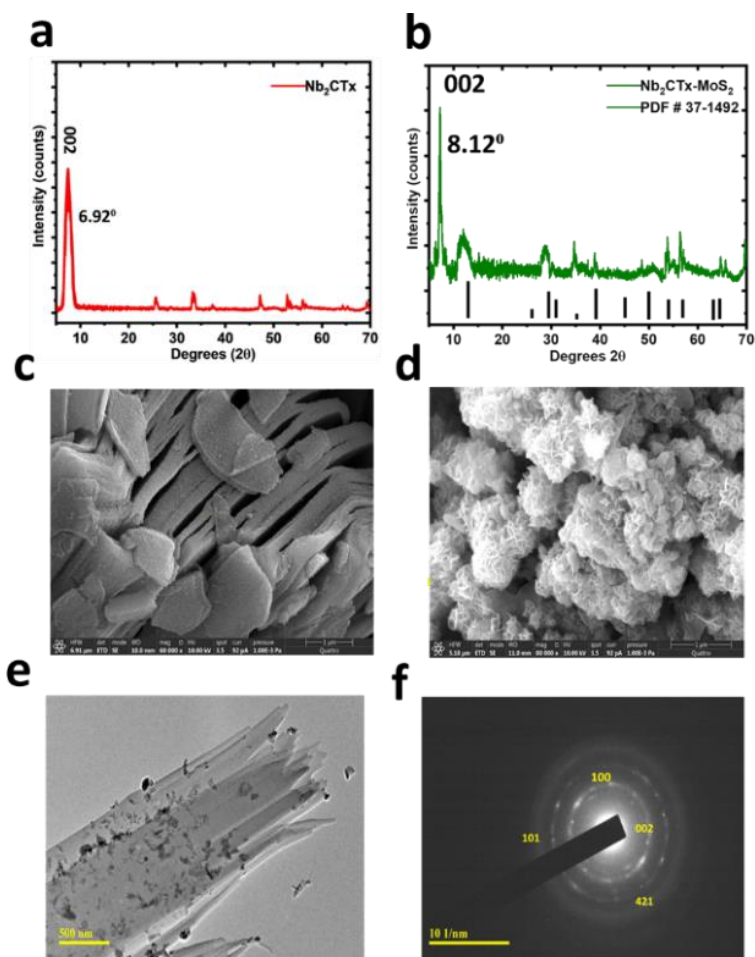


Figure 8.4: Morphological and structural characterization of as-prepared Nb₂CTx and its composite (a) XRD patterns of few layered Nb₂CTx (b) XRD patterns for the Nb₂CTx-MoS₂ composite (c) FE-SEM images of Nb₂CTx showing the layered structure (d) FE-SEM images of the composite after the loading of MoS₂ with change in morphology (e) HR-TEM images of the Nb₂CTx flakes showing well scattered layers (f) SAED image of the spot where TEM was conducted.

Fig. 8.5a shows ex-situ XRD patterns for free and composite electrodes after successive 10 and 500 charge/discharge cycles. The change in the pattern is observed after the GCD process with the appearance of the three new peaks at 26.01°, 25.19° and 24.39°. The change observed in the XRD patterns indicates the successful intercalation of [AlCl₄]⁻ ions on the cathode, these outcomes are in good agreement with the reported literature [387], [388], [389].

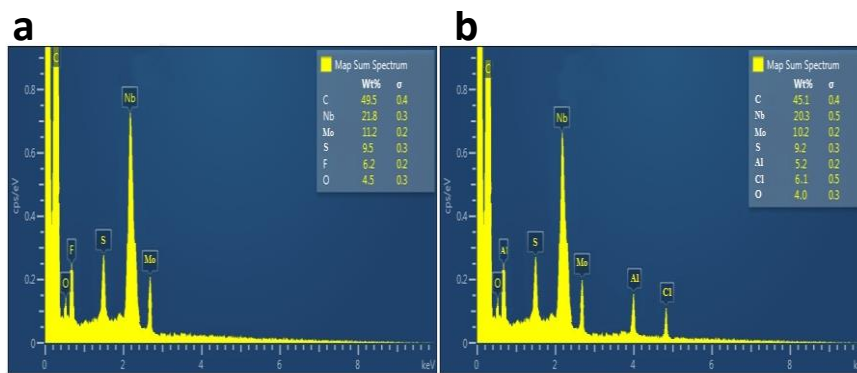


Figure 8.5: EDS spectra of the Nb₂CT_x-MoS₂ composite cathode material before and after charging.

This was further confirmed by the Raman spectroscopy (Fig.8.5b) and EDS characterization Fig. 8.6. Likewise, Fig.8.5b. shows the Raman peaks located at 147, 168, 297, and 405 cm⁻¹ ascribed to Al₂Cl₇⁻ and AlCl₄⁻ ions accordingly, a shift in band position and change in intensities (i.e., 147, 168, 297, and 405 cm⁻¹ to 139, 174, 290 and 398 cm⁻¹) after the 500 cycles have been observed as well. This again confirms the successful intercalation of complex ions and well matches with the previously reported Raman spectra [390]. Fig.8.5c shows the ex-situ SEM images for the Nb₂CT_x-MoS₂ after the first 10 GCD cycles. The pores and cracks on the electrode surface gesture the impact of ion intercalation and deintercalation on the cathode. Similarly, Fig.8.3d shows SEM images after the 500 charging-discharging cycles, where the appearance of the buds-like growth on the surface of the cathode pits suggests the long intercalation and deintercalation during the cycling study, however the basic layered structure is still intact with no significant structural degradation.

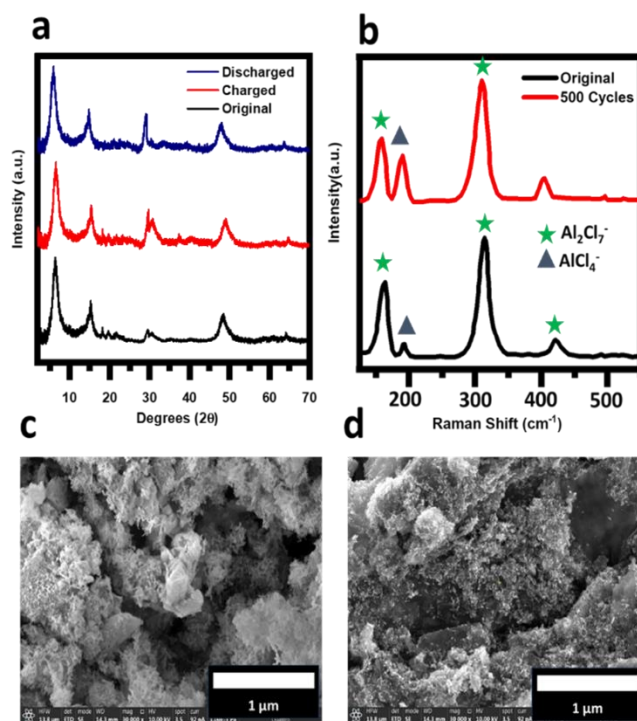


Figure 8.6: The structural analysis and morphology of cathode after the charge discharge process (a) Ex-situ XRD patterns for composite cathode after 10th and 500th cycles (b) Raman spectra of the cathode at the 10th and after 500th cycle showing the changes in electrolyte chemistry (c) FE-SEM images represent the cathode morphology after 500 cycles (d) shows the high-resolution FE-SEM images after 500th cycle.

Figure 8.6 presents the survey XPS analysis of $\text{Nb}_2\text{CTx-MoS}_2$, revealing the presence of Mo, S, Nb, C, and terminations resulting from the mild etching technique. To delve deeper into the anticipated operating mechanism, surface electronic states, and chemical composition, XPS tests were conducted on the electrode pre- and post-charging/discharge cycles. Figure 8.7a-c showcases the XPS spectra of the Nb 3d core levels of $\text{Nb}_2\text{CTx-MoS}_2$ before and after charging.

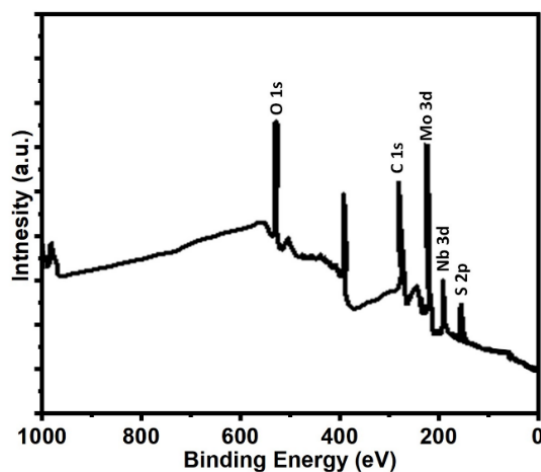


Figure 8.7: Survey spectra of the Nb₂CT_x-MoS₂ composite cathode.

Notably, during full charge, the binding energy of the Nb 3d core increased from 207.17 from original to 207.59 eV after fully charged, indicative of a chemisorption interface between the cathode surface and the intercalated ions [385]. This shift suggests that chemisorption-induced electron release has elevated the effective positive charge within the cathode. Figures 8.7d-f elucidate changes in the XPS core levels of Al 2p, Cl 2p, and C 1s respectively. These changes likely reflect modifications in surface chemistry and elemental composition induced by the charging/discharging processes, offering valuable insights into the electrochemical behavior and performance of the electrode material [391].

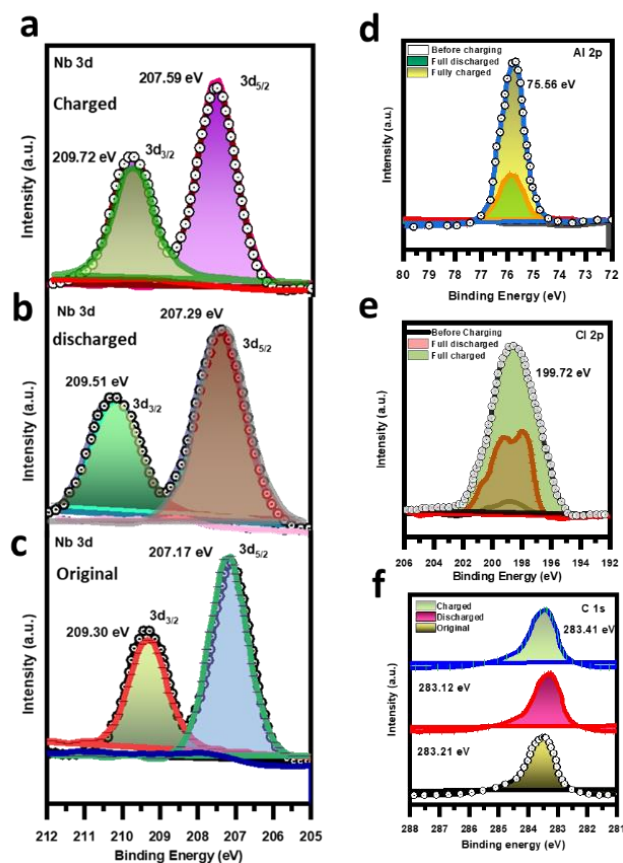


Figure 8.8: The XPS spectra depicting the change in position of binding energy of the major elements of the composite cathode before and after GCD process (a) XPS peaks for the Nb 3d core at fully charged state, (b) after discharging (c) original composite cathode before GCD (d) XPS peaks for Cl 2p at three stages (e) XPS peaks for the Al 2p at before charging, discharged, and fully charged stages (f) XPS peaks for carbon in all three stages of original to charged.

Prior to GCD, minimal peaks are visible for Al 2p and Cl 2p, suggesting a sparse presence of these elements. However, post-charging, a notable augmentation in Al 2p and Cl 2p XPS peaks (at 75.56, and 199.56 eV respectively) underscores the pronounced intercalation of $[\text{AlCl}_4]^-$ ions within the cathode (Fig. 8.7e). This heightened intensity provides compelling evidence of successful ion intercalation. Similarly, upon full discharge, a noticeable reduction in both Al 2p and Cl 2p signals signifies the substantial de-intercalation of $[\text{AlCl}_4]^-$ ions from the cathode. Additionally, a noticeable increase in binding energies

(from 283.21 to 283.41 eV) in the C 1s spectra following charging/discharging sequences (Fig. 8.7e) confirms the observed chemisorption phenomena between the cathode and embedded ions [377]. These observations collectively illustrate the interaction between electrode components and embedded ions during charge-discharge cycles, offering valuable insights into the electrochemical behavior of the system.

8.3.1 Electrochemical Study

The performance of bare and composite cathodes was evaluated by taking CV and EIS using Biologic VMP3 multichannel Potentiostat, while the GCD was conducted using 8-channel battery analyzers BTS8-5V5A, the cut-off voltage (upper/lower) was set as 2.8/0.5 V accordingly and all the electrochemical measurements were taken at room temperature. (Fig.8.8) displays the CV and GCD curve of the bare Nb₂CTx and Nb₂CTx-MoS₂ composite cathode in an optimized 1.5 ratio of AlCl₃/[BMIm]Cl electrolyte. Fig.8.8a depicts the CV responses of Nb₂CTx cathode recorded between the potential window of 0.5 to 2.7 V versus Al³⁺/Al at a sweep rate of 0.1 mVs⁻¹. It shows two anodic peaks around 1.7-1.8 V (I) and 2.4-2.5 V (II), whereas the two cathodic peaks at 2.2-2.1 V (III) and 1.6-1.5 V (IV) were observed. Likewise, Fig.8.8b displays CV curves for the composite cathode Nb₂CTx-MoS₂ and carbon paper at similar conditions. These complimentary anodic/cathodic peaks show the two-step electrochemical reaction between composite cathode and Al which could be linked to Al ion intercalation and deintercalation at two different positions on the cathode. Significant changes have been observed at anodic peaks such as a shift in position and increase in current has been observed at 1.9-2.1 V (I) and 2.3-2.4 V (II) likewise, a change in the cathodic curve has also been witnessed with a wide

band at 1.9-1.7 V (III) and 2.4-2.2 V (IV). This indicates the increased reversible ions intercalation on respective electrodes. The increase in the anodic peak current reflects that the electrode intercalates more electroactive species in the double layer (the layer in close proximity to the working electrode) and therefore, more charge transfer at that potential which indicated that the current intensity has been maximized [378].

The charge/discharge cycles of the bare Nb₂CTx cathode (Fig.8.8c) were evaluated at various current densities extending from 10-300 mA/g. It has been observed that by varying the current densities as 10, 50, 100, and 300 mA/g, the charge/discharge capacity drops quickly with an increase in the current densities. In addition, it can be observed from Fig. 8.8c that the charge/discharge plateaus split progressively and grow with the rise in the current density, which is due to the increased polarization, sluggish diffusion of complex ions through the Nb₂CTx structure. It resulted not only in slow charge/discharge rates but also with poor cycle stability. In Fig.8.8d the charge/discharge curves of the cell with Nb₂CTx-MoS₂ as the cathode. are shown for the current densities of 10, 50, 100, and 300 mA/g. The specific capacities observed to be 510, 400, 350, and 290 mAh/g, respectively for the current densities of 10, 50, 100, and 300 mA/g. It shows a comparatively slow decay, and close specific capacities compared to bare Nb₂CTx. Likewise, in figure 8.5d the two charge plateaus are observed between 2.16-2.43 V and 2.65-2.70 V, while the discharge plateaus are located around 2.6-2.43 V and 2.10-1.89 V accordingly at a current density of 100 mA/g. It is evident that the composite cathode can maintain 350 mAh/g capacity after 50 to 500 cycles (Fig 8.9), which is much greater than the bare Nb₂CTx cathode with better cycle stability.

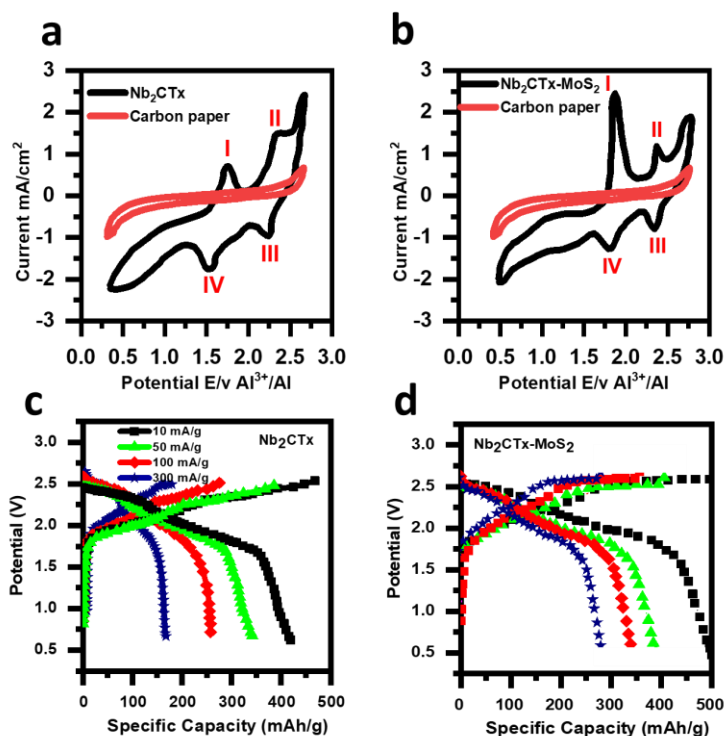


Figure 8.9: Cyclic voltammetry and GCD curves at different current densities for both electrodes (a) CV curve for the bare Nb₂CTx at scan rate of 0.1 mV s⁻¹ and carbon paper (b) charge/discharge curves of Nb₂CTx at current densities ranging from 10-300 mA/g specific capacity (c) CV curves of Nb₂CTx-MoS₂ and carbon paper at 0.1 mV s⁻¹ (d) charge/discharge curves of Nb₂CTx-MoS₂ at current densities ranging from 10-300 mA/g.

The cycle stability and corresponding CE of AIBs were examined at a current density of 100 mA/g. Fig. 8.9a vividly portrays the cyclic stability and coulombic efficiency of the Nb₂CTx cathode over 500 cycles. Initially, the Nb₂CTx cathode boasted an impressive capacity of 400 mAh/g. However, after just 50 cycles, a precipitous decline ensued, with the capacity plateauing at 250 mAh/g over the subsequent 500 cycles at a steady current density of 100 mA/g. The accompanying coulombic efficiency, documented in Fig. 8.9c, remained suboptimal at 83%. This trend may be attributed to robust coulombic interactions between the chloroaluminate ions and the strong electronegative terminals inherent in the

Nb₂CTx electrode materials. Conversely, Fig. 8.9b offers insight into the cycle stability of the modified Nb₂CTx-MoS₂ cathode over the same 500-cycle period at a 100 mA/g current density. Notably, the GCD curves remained remarkably consistent and stable throughout the duration of the test. Although exhibiting a similar trend during the initial 50 cycles, the modified cathode displayed a notably higher initial capacity of approximately 550 mAh/g, which gradually decayed at a slower pace compared to its Nb₂CTx counterpart. The observed enhancement in cyclic stability and capacity retention of the composite cathode can be attributed to the incorporation of MoS₂, which likely suppressed undesirable coulombic interactions. The pseudocapacitive behavior of the MoS₂, facilitates rapid and reversible redox reactions with aluminum ions [377]. Besides, the combination of high surface area, pseudocapacitive behavior, electrical conductivity, synergistic effects, and structural stability of Nb₂CTx-MoS₂ composite cathode contributes to the excellent enhancement of specific capacity. This indicates that the Nb₂CTx-MoS₂ is more stable than the pure Nb₂CTx cathode, overcoming the structural deformity and columbic forces. Which can be attributed to the presence and synergic effect of MoS₂ and eventually improved the reversibility of the composite electrode [377], [392]. The composite electrode-based cell was able to maintain the charge-discharge plateaus at 500 cycles indicating stable reversibility. The composite cathode has shown an outstanding cycling stability with the retention of nearly 98% of its initial capacity of 350 mAh/g at a current density of 100 mA/g even after 500 cycles. (Fig.8.9d).

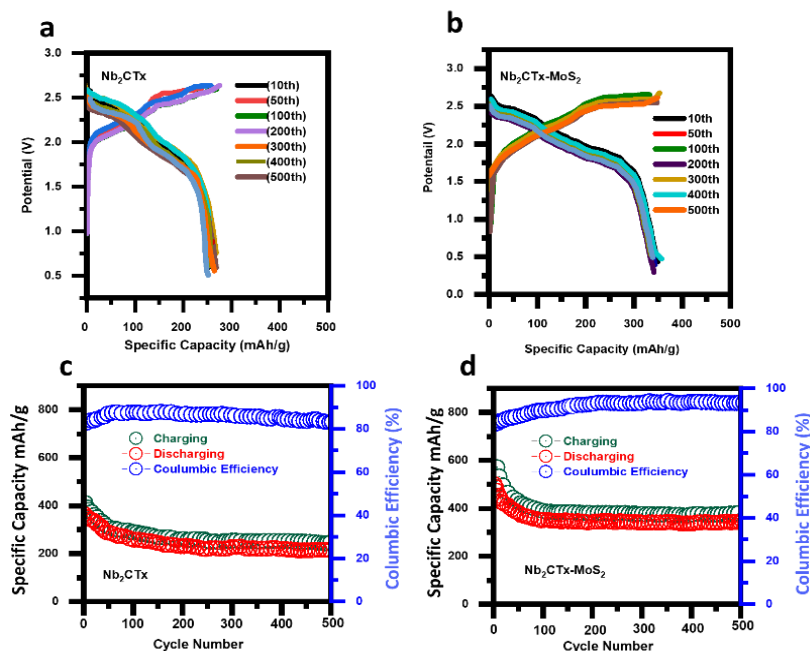


Figure 8.10: Specific capacity of both electrodes for 500 cycles and corresponding coulombic efficiency of the cathodes for 500 GCD cycles (a) Long-term GCD curves and specific capacity of Nb₂CTx at 100 mA/g current density (b) long-term GCD curves and specific capacity of Nb₂CTx-MoS₂ at 100 mA/g current densities (c) coulombic efficiency and cyclic performance of Nb₂CTx at 100 mA/g (d) Coulombic efficiency and cyclic performance for the Nb₂CTx-MoS₂ composite cathode at 100 mA/g.

To further evaluate the electrochemical performance of the Nb₂CTx-MoS₂ cathode, EIS study was conducted on both bare and composite Nb₂CTx-MoS₂ cathodes across the frequency range of 10⁵ Hz to 10 Hz. Nyquist plots of the Nb₂CTx-MoS₂ composite and Nb₂CTx bare electrodes at 10, 50, 100, and 200 cycles are shown in Fig. 8.10a, b. The open circuit potential of the Nb₂CTx-MoS₂ cathode-based cell was measured at approximately 2.68 V (Fig. 8.10c). Notably, the inset showcases the successful powering of a 1.8V red LED lamp for 40 hours, underscoring the practical utility of the battery. The fitting results for the equivalent circuit model of the modified cathode material revealed R_s and R_{ct} values of 1.12 Ω and 2.13 Ω for the composite and bare electrodes, respectively.

Remarkably, the charge transfer resistance of the modified cathode material was determined to be $6.45\ \Omega$, substantially lower than that of the bare Nb_2CTx cathode material ($21.4\ \Omega$) after 200 cycles this trend is well matching with the previously reported work [393]. This improvement is attributed to the integration of MoS_2 , which enhances the conductivity and structural integrity of the composite. Figures 8.11a, b, and c depict the LED lamp's operation over 0, 20, and 40 hours, respectively, following full charging. The rate capabilities of the fabricated AIB based on the $\text{Nb}_2\text{CTx-MoS}_2$ cathode battery were assessed across different current densities ranging from $10\ \text{mA/g}$ to $300\ \text{mA/g}$ over 100 cycles (Fig. 8.10d). Although the discharge capacity exhibited a decline with increasing current density, it notably rebounded to $350\ \text{mAh/g}$ with a columbic efficiency of 98% upon reducing the current density back to $100\ \text{mA/g}$. This behavior emphasizes the stability and reversibility of the composite cathode, suggesting promising prospects for its practical application.

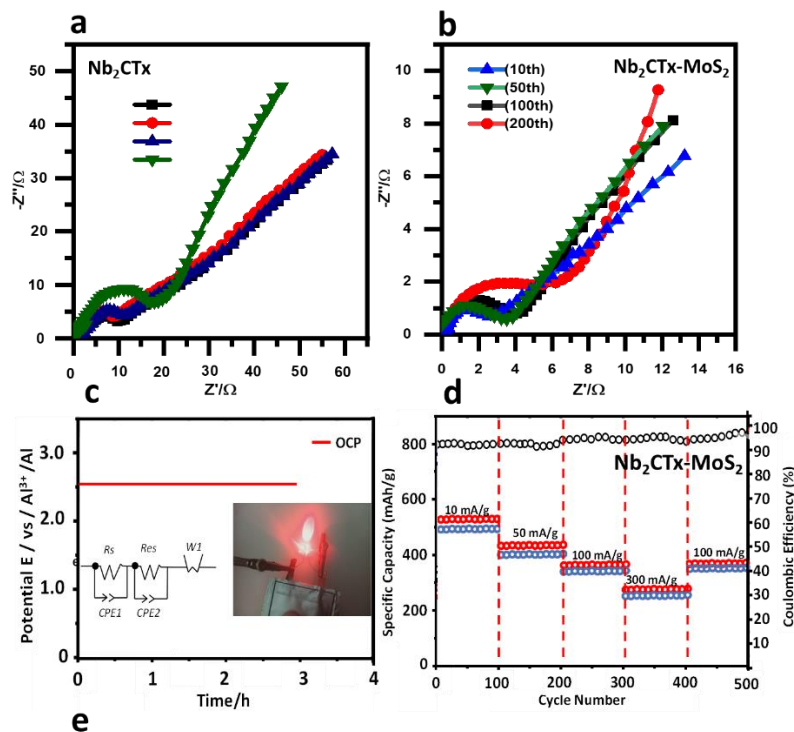


Figure 8.11: (a) Nyquist plots of Nb₂CTx at different cycles (b) Nyquist plots of Nb₂CTx-MoS₂ composite at 10, 50, 100, and 200th cycles (c) Open circuit potential and the equivalent circuit model of the pouch cell (d) rate capability and coulombic efficiency of Nb₂CTx-MoS₂ performed at varying current densities extending from 10 to 300 mA/g for 500 cycles.

8.3.2 Capacity Calculation

The theoretical specific capacity (C) was calculated by using Faradays' law.

$$C = 1000 \cdot nF / 3600 \cdot M \text{ (mAh/g)} \quad (I)$$

Where “n” is the number of moles of electrons transferred “F” is the Faraday constant and M is the molar mass of aluminum. The calculated specific capacity of Al is 2977 mAh/g. In practical terms, it is difficult to accurately estimate the number of electrons exchanged,

therefore, we used the total mass of the pouch cell to calculate the specific capacity of the device. The following formulas were used to calculate the discharge capacity (Cd) of AIB.

$$Cd = i \cdot M \cdot \Delta t / 3600 \quad (II)$$

Where i = Discharge Current (mA/g), M is the total mass (g) and Δt is the discharge time (s). Therefore, the current discharge employed was 100 mA g^{-1} , the total mass of the cell was 9g and the discharge time was found to be 3.5 hours (12600 s), by plugging in these values in equation II we obtained $Cd = 3150 \text{ mAh/g}$. Likewise, the specific capacity Cs was calculated by plugging in the value of Cd and Mass of the cell in equation III.

$$Cs = Cd / M \quad (III)$$

Plugging in the value we obtained the specific capacity of $\approx 350 \text{ mAh/g}$.

8.3.3 Intercalation Study

Fig.8.12 shows the schematic intercalating/de-intercalating process of AlCl_4^- , Cl^- and Al^{3+} ions at the cathode during the charge/discharge process. The AlCl_4^- was observed to be the key ion for the electrochemistry of battery. The $\text{AlCl}_3/[\text{BMIm}]\text{Cl}$ ILE comprised two key anionic species at room temperature (AlCl_4^- and Al_2Cl_7^-) [388], [394]. The molar ratio of ILE was established as 1.5 to assure high concentration of $[\text{Al}_2\text{Cl}_7]^-$ and low pH, which favors the reversible accumulation and dissolution of aluminum metal on the electrodes. During charging process, the AlCl_4^- and Cl^- ions are intercalated into cathode $\text{Nb}_2\text{CTx-MoS}_2$ interlayers and an electron is released (I). While, at the anode, free electron is accepted by Al_2Cl_7^- , which results in AlCl_4^- and Al which deposit on anode (II). During the discharge process, the AlCl_4^- are deintercalated from the cathode (III), while at anode the

Al reacts with AlCl_4^- anions thus produces Al_2Cl_7^- and three electrons are liberated (V), thus disturbing the concentration balance of anions in the electrolyte. The proposed charge/discharge mechanism is well aligned with the CV response, where the anodic peak at 1.9-2.1 V (I) and 2.3-2.4 V (II) with increased current, similarly, a change in the cathodic curve has also been witnessed with a wide band at 1.9-1.7 V (III) and 2.4-2.2 V (IV) (Fig.8.8).

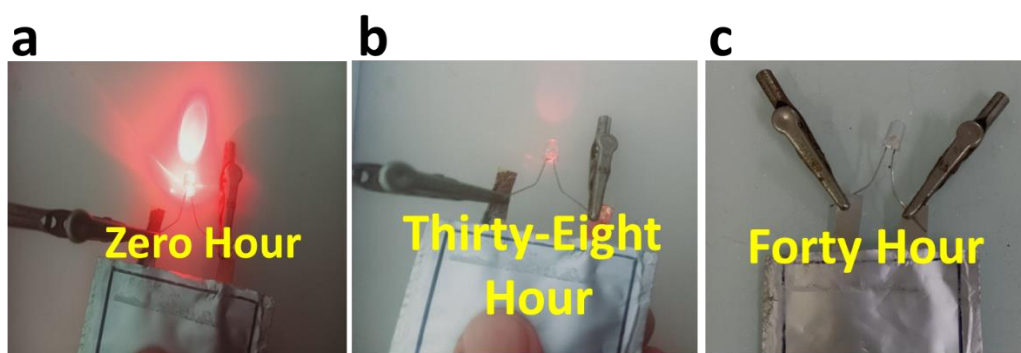


Figure 8.12: The operation of the pouch cell for 40 hours.

This indicates the increased reversible intercalation of ions during the charge/discharge process on respective electrodes [395], [396], [397]. Consequently, the $\text{Nb}_2\text{CTx-MoS}_2$ composite cathode offers a significant improvement of performance of the AIB, addressing some key challenges (specific capacity, kinetics, and structural stability). The unique synergy of the Nb_2CTx MXene and MoS_2 into the composite structure holds great promise for advancing the development of high-performance and cost-effective AIB.

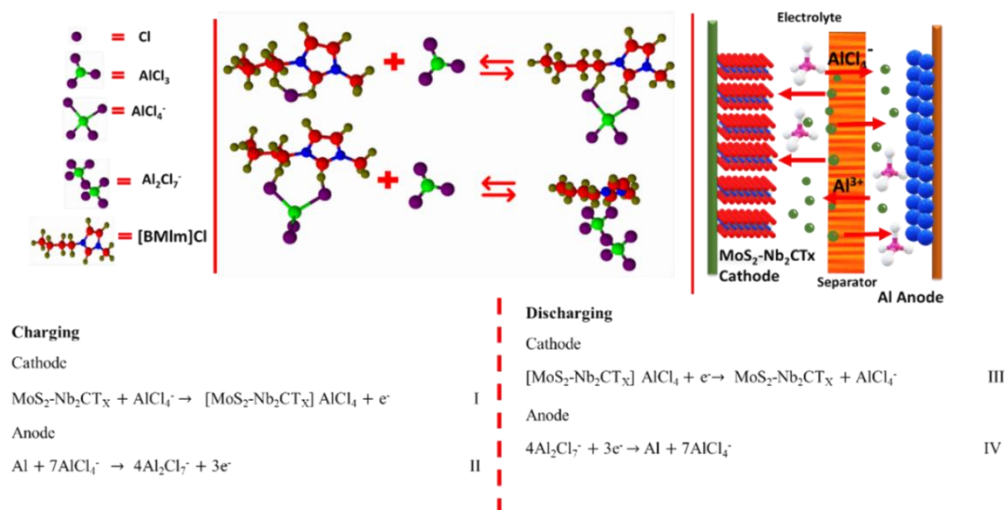


Figure 8.13: Optimized structure of the respective ions, overall chemistry of electrolyte and complex ion formation, the model battery operation where the ions flow to respective electrodes during the charge and discharge process is observed and the ion intercalation/deintercalation during the charge discharge process at the cathode and anode.

9. CONCLUSION AND FUTURE ROSPECTIVES

This thesis has explored the multifaceted potential of MXenes, a unique class of two-dimensional (2D) transition metal carbides, nitrides, and carbonitrides, in advancing the fields of Surface-Enhanced Raman Scattering (SERS) and energy storage, specifically in the development of aluminum-ion and lithium-ion batteries. Through a detailed investigation of their synthesis, characterization, and application, this work has highlighted the versatility and promise of MXenes in these cutting-edge technological domains.

The synthesis of MXenes from their parent MAX phases is a critical process that defines their structure and properties. In this work, MXenes were synthesized through a selective etching process, where the "A" element (typically aluminum) was removed from the MAX phase particularly the (Nb_2AlC , Cr_2AlC , Ti_3AlC_2 , $\text{V}(\text{Zr})\text{AlC}$ and Mo_2AlC) using various etchants namely concentrated HF, mixed acid etchants HF+HCl, green etchants FeCl_3 , and soft etchants LiF+HCl. The result was the exfoliation of the layered MAX phase into individual or few-layered MXene nanosheets with varying interlayer spaces based on the etching conditions. The methods yielded MXenes with high purity, controlled thickness, and a high degree of surface terminations such as -OH, -O, and -F, which are crucial for their chemical reactivity and stability.

Characterization techniques such as X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and Raman spectroscopy were employed to confirm the successful transformation of MAX to MXenes and to study their structural, morphological, and chemical properties. XRD provided insights into the

crystalline structure and phase purity of the MXenes, while SEM and TEM were used to examine their morphology and nanoscale features, confirming the formation of 2D layered structures. Likewise, the XPS provided electronic structure changes in the surface modification and composite structures. Raman spectroscopy was particularly useful in identifying the surface terminations and their impact on the electronic properties of MXenes, which are critical for their performance in various applications. One of the significant contributions of this thesis is the application of MXenes in Surface-Enhanced Raman Scattering (SERS) for the trace detection of drugs and biomolecules. MXenes, with their high electrical conductivity, large surface area, and tunable surface chemistry, were demonstrated to be excellent SERS substrates. The presence of surface terminations, such as hydroxyl and oxygen groups, enhanced the adsorption of target molecules, while the high conductivity facilitated the transfer of electrons, leading to significant enhancement of the Raman signals.

The thesis successfully demonstrated the use of coinage metal-based nanoparticles and MXenes for the detection of low-concentration analytes, including drug molecules and biomarkers namely the Procainamide, Gemcitabine, N-Acetyl procainamide and Glucose in real and spiked samples environments. By the shape modification, controlled size and functionalizing the surface of MXenes with specific molecules, the selectivity of the SERS substrates was improved, enabling the detection of specific targets with high sensitivity. This work not only underscores the potential of shape modified nanoparticles and MXenes in SERS-based sensing applications (LOD 10^{-9} to 10^{-14} M) but also opens up new avenues for the development of portable and reliable sensors for environmental monitoring, medical diagnostics, and forensic analysis.

In addition to their application in SERS, this thesis explored the use of MXenes in the development of electrodes for aluminum-ion and lithium-ion batteries. The unique combination of high electrical conductivity, mechanical flexibility, and chemical stability of MXenes makes them ideal candidates for energy storage applications.

For aluminum-ion batteries, MXenes based composites with metal chalcogenides particularly the Nb₂CTx with MoS₂ were employed as electrode materials, due to their ability to intercalate aluminum ions. The layered structure of the composite facilitates the intercalation and deintercalation of aluminum ions, while their high synergy and conductivity ensures efficient charge transport, leading to improved rate performance and cycle life. The results obtained in this thesis show that the composite can deliver high capacity (350 mAh g⁻¹) and excellent cycling stability 98% for 500 cycles, making them promising materials for the next generation of aluminum-ion batteries.

In lithium-ion batteries, MXenes were used as anode materials, leveraging their ability to intercalate lithium ions and their high surface area for charge storage. The surface terminations on MXenes were found to play a crucial role in enhancing the interaction with lithium ions, thereby improving the capacity and rate performance of the batteries. Furthermore, the formation of MXene-based composites with other materials, such as graphene or transition metal oxides (NiO₂ and Co₂O₃) as composites were explored to enhance electrochemical performance. These composites exhibited synergistic effects, combining the strengths of both materials, and resulting in electrodes with higher capacity, better cycle stability, and improved rate performance.

The findings of this thesis open up several exciting possibilities for future research. The tunability of MXenes through surface functionalization and the exploration of new MXene compositions could lead to the development of even more efficient SERS substrates and battery electrodes. Additionally, the integration of MXenes with other nanomaterials offers a promising route to further enhance their properties and extend their applications in areas such as catalysis, water purification, and electromagnetic shielding.

In conclusion, this thesis has demonstrated that MXenes, with their unique structure and properties, are powerful materials for advancing the fields of SERS-based sensing and energy storage. The successful synthesis, characterization, and application of MXenes in these domains underscore their potential to revolutionize technologies that are critical for the future. As research on MXenes continues to evolve, their role in next-generation materials and devices is expected to expand, driving innovations across a wide range of industries.

References:

- [1] B. Dunn, H. Kamath, and J. M. Tarascon, “Electrical energy storage for the grid: A battery of choices,” Nov. 18, 2011, *American Association for the Advancement of Science*. doi: 10.1126/science.1212741.
- [2] A. Pandolfo, A. H.-J. of power sources, and undefined 2006, “Carbon properties and their role in supercapacitors,” *Elsevier*.
- [3] N. Danilovic *et al.*, “Angewandte Chemie Surface Analysis Hot Paper Using Surface Segregation To Design Stable Ru-Ir Oxides for the Oxygen Evolution Reaction in Acidic Environments**,” *Wiley Online Library*, vol. 126, no. 51, pp. 14240–14245, Dec. 2014, doi: 10.1002/ange.201406455.
- [4] H. Gasteiger, S. Kocha, ... B. S.-A. C. B., and undefined 2005, “Activity benchmarks and requirements for Pt, Pt-alloy, and non-Pt oxygen reduction catalysts for PEMFCs,” *Elsevier*.
- [5] M. D.- Nature and undefined 2012, “Electrocatalyst approaches and challenges for automotive fuel cells,” *nature.com*.
- [6] A. Pandolfo, A. H.-J. of power sources, and undefined 2006, “Carbon properties and their role in supercapacitors,” *Elsevier*.
- [7] J. Gamby, P. Taberna, P. Simon, ... J. F.-J. of power, and undefined 2001, “Studies and characterisations of various activated carbons used for carbon/carbon supercapacitors,” *Elsevier*.
- [8] K. H. An *et al.*, “Supercapacitors using single-walled carbon nanotube electrodes,” *Advanced Materials*, vol. 13, no. 7, pp. 497–500, Apr. 2001, doi: 10.1002/1521-4095(200104)13:7<497::AID-ADMA497>3.0.CO;2-H.
- [9] L. Zhang, X. Z.-C. S. Reviews, and undefined 2009, “Carbon-based materials as supercapacitor electrodes,” *pubs.rsc.org*.
- [10] C. Liu, Z. Yu, D. Neff, A. Zhamu, and B. Z. Jang, “Graphene-Based Supercapacitor with an Ultrahigh Energy Density,” *ACS Publications*, vol. 10, no. 12, pp. 4863–4868, Dec. 2010, doi: 10.1021/nl102661q.
- [11] Y. S. Meng, “A Symmetric RuO₂/RuO₂ Supercapacitor Operating at 1.6 V by Using a Neutral Aqueous Electrolyte Article in Electrochemical and Solid-State Letters · Multifunctional Battery Systems for Electric Vehicles View project,” *iopscience.iop.org*, vol. 15, no. 4, 2012, doi: 10.1149/2.023204esl.

- [12] B. E. Conway, “Transition from ‘supercapacitor’ to ‘battery’ behavior in electrochemical energy storage,” in *Proceedings of the International Power Sources Symposium*, Publ by IEEE, Nov. 1991, pp. 319–327. doi: 10.1149/1.2085829.
- [13] F. Yang, M. Xu, S. Bao, H. Wei, H. C.-E. Acta, and undefined 2014, “Self-assembled hierarchical graphene/polyaniline hybrid aerogels for electrochemical capacitive energy storage,” *Elsevier*.
- [14] G. Yu *et al.*, “Enhancing the Supercapacitor Performance of Graphene/MnO₂ Nanostructured Electrodes by Conductive Wrapping,” *Nano Lett*, vol. 11, no. 10, pp. 4438–4442, Oct. 2011, doi: 10.1021/nl2026635.
- [15] R. Mas-Ballesté *et al.*, “Tunable Nanocatalysts for the Production of Solar Fuels View project SPANC (Scanning-Probe-Assisted Nanowire Circuitry) View project,” *pubs.rsc.org*, 2015, doi: 10.1039/c0nr00323a.
- [16] D. Sheberla, J. Bachman, J. Elias, C. S.-N. materials, and undefined 2017, “Conductive MOF electrodes for stable supercapacitors with high areal capacitance,” *nature.com*.
- [17] C. Hao *et al.*, “Flexible All-Solid-State Supercapacitors based on Liquid-Exfoliated Black-Phosphorus Nanoflakes,” *Wiley Online Library*, vol. 28, no. 16, pp. 3194–3201, Apr. 2016, doi: 10.1002/adma.201505730.
- [18] V. Ruiz, J. Suárez-Guevara, P. G.-R.- Electrochemistry, and undefined 2012, “Hybrid electrodes based on polyoxometalate–carbon materials for electrochemical supercapacitors,” *Elsevier*.
- [19] J. Come *et al.*, “A Non-Aqueous Asymmetric Cell with a Ti₂C-Based Two-Dimensional Negative Electrode,” *J Electrochem Soc*, vol. 159, no. 8, pp. A1368–A1373, 2012, doi: 10.1149/2.003208jes.
- [20] B. Anasori and Y. Gogotsi, “Introduction to 2D transition metal carbides and nitrides (MXenes),” in *2D Metal Carbides and Nitrides (MXenes): Structure, Properties and Applications*, Springer International Publishing, 2019, pp. 3–12. doi: 10.1007/978-3-030-19026-2_1.
- [21] X. Hui, X. Ge, R. Zhao, Z. Li, and L. Yin, “Interface Chemistry on MXene-Based Materials for Enhanced Energy Storage and Conversion Performance,” *Adv Funct Mater*, vol. 30, no. 50, p. 2005190, Dec. 2020, doi: 10.1002/adfm.202005190.
- [22] Z. Xiao, Z. Li, X. Meng, and R. Wang, “MXene-engineered lithium-sulfur batteries,” 2019, *Royal Society of Chemistry*. doi: 10.1039/c9ta08600e.

- [23] F. Li, C. R. Cabrera, J. Wang, and Z. Chen, “A Cr₂CO₂ monolayer as a promising cathode for lithium and non-lithium ion batteries: A computational exploration,” *RSC Adv*, vol. 6, no. 85, pp. 81591–81596, Aug. 2016, doi: 10.1039/c6ra13491b.
- [24] M. Greaves, S. Barg, and M. A. Bissett, “MXene-Based Anodes for Metal-Ion Batteries,” *Batter Supercaps*, vol. 2020, no. 3, pp. 214–235, Mar. 2019, doi: 10.1002/batt.201900165.
- [25] H. Avireddy, B. Byles, D. Pinto, J. G.-N. Energy, and undefined 2019, “Stable high-voltage aqueous pseudocapacitive energy storage device with slow self-discharge,” *Elsevier*.
- [26] S. Zheng *et al.*, “All-Solid-State Planar Sodium-Ion Microcapacitors with Multidirectional Fast Ion Diffusion Pathways,” *Wiley Online Library*, vol. 6, no. 23, Dec. 2019, doi: 10.1002/advs.201902147.
- [27] E. Satheeshkumar, T. Makaryan, A. M.-S. reports, and undefined 2016, “One-step solution processing of Ag, Au and Pd@ MXene hybrids for SERS,” *nature.com*.
- [28] R. Cheng *et al.*, “MXenes induce epitaxial growth of size-controlled noble nanometals: A case study for surface enhanced Raman scattering (SERS),” *Elsevier*.
- [29] R. Liu *et al.*, “Large-scale two-dimensional titanium carbide MXene as SERS-active substrate for reliable and sensitive detection of organic pollutants,” *Elsevier*.
- [30] A. Sarycheva, T. Makaryan, ... K. M.-T. J. of, and undefined 2017, “Two-dimensional titanium carbide (MXene) as surface-enhanced Raman scattering substrate,” *ACS Publications*.
- [31] J. D. Orlando, S. Kumari, and F. Yan, “Green Synthesis of Reduced Ti₃C₂T_x MXene Nanosheets with Enhanced Conductivity, Oxidation Stability, and SERS Activity Understanding Magnetic LaSrMnO₃ Thin Films View project Simulation and synthesis of silver dendritic nanostructures for surface-enhanced Raman scattering View project SEE PROFILE,” *pubs.rsc.org*, 2020, doi: 10.1039/C9TC06984D.
- [32] M. Yoshida, Y. Hoshiyama, J. Ommyoji, and A. Yamaguchi, “Reaction mechanism for the synthesis of Ti₃AlC₂ through an intermediate carbide of Ti₃AlC from elemental Ti, Al, and C powder mixture,” 2010.
- [33] Z. W. Seh *et al.*, “Two-Dimensional Molybdenum Carbide (MXene) as an Efficient Electrocatalyst for Hydrogen Evolution,” *ACS Energy Lett*, vol. 1, no. 3, pp. 589–594, Sep. 2016, doi: 10.1021/acsenenergylett.6b00247.

- [34] M. Naguib *et al.*, “Two-Dimensional Nanocrystals Produced by Exfoliation of Ti_3AlC_2 ,” *Advanced Materials*, vol. 23, no. 37, pp. 4248–4253, Oct. 2011, doi: 10.1002/adma.201102306.
- [35] M. Naguib, M. Kurtoglu, V. Presser, J. Lu, ... J. N.-A., and undefined 2011, “Two-Dimensional Nanocrystals Produced by Exfoliation of Ti_3AlC_2 ,” *Wiley Online Library*, vol. 23, no. 37, pp. 4248–4253, Oct. 2011, doi: 10.1002/adma.201102306.
- [36] N. Chaudhari, H. Jin, B. Kim, and D. San Baek, “MXene: An Emerging Two-Dimensional Material for Future Energy Conversion and Storage Applications Materials Chemistry A Materials for energy and sustainability,” *Article in Journal of Materials Chemistry A*, 2017, doi: 10.1039/C7TA09094C.
- [37] A. Feng *et al.*, “Synthesis and characterization of hierarchical Y zeolites using NH_4HF_2 as dealumination agent,” *Elsevier*.
- [38] F. Liu *et al.*, “Preparation of Ti_3C_2 and Ti_2C MXenes by fluoride salts etching and methane adsorptive properties,” *Appl Surf Sci*, vol. 416, pp. 781–789, Sep. 2017, doi: 10.1016/j.apsusc.2017.04.239.
- [39] A. Pandolfo, A. H.-J. of power sources, and undefined 2006, “Carbon properties and their role in supercapacitors,” *Elsevier*.
- [40] J. Halim *et al.*, “Synthesis and Characterization of 2D Molybdenum Carbide (MXene),” *Wiley Online Library*, vol. 26, no. 18, pp. 3118–3127, May 2016, doi: 10.1002/adfm.201505328.
- [41] N. Chaudhari, H. Jin, B. Kim, and D. San Baek, “MXene: An Emerging Two-Dimensional Material for Future Energy Conversion and Storage Applications Materials Chemistry A Materials for energy and sustainability,” *Article in Journal of Materials Chemistry A*, 2017, doi: 10.1039/C7TA09094C.
- [42] X. Guo, X. Zhang, S. Zhao, ... Q. H.-... C. C., and undefined 2016, “High adsorption capacity of heavy metals on two-dimensional MXenes: an ab initio study with molecular dynamics simulation,” *pubs.rsc.org*.
- [43] L. Karlsson, J. Birch, J. Halim, and M. W. Barsoum, “Atomically Resolved Structural and Chemical Investigation of Single MXene Sheets,” *Nano letters (Print)*, vol. 8, no. 15, pp. 4955–4960, Aug. 2015, doi: 10.1021/acs.nanolett.5b00737.
- [44] M. Pandey and K. S. Thygesen, “Two-Dimensional MXenes as Catalysts for Electrochemical Hydrogen Evolution: A Computational Screening Study,” *The*

- Journal of Physical Chemistry C*, vol. 121, no. 25, pp. 13593–13598, Jun. 2017, doi: 10.1021/acs.jpcc.7b05270.
- [45] H. Zhang, G. Yang, X. Zuo, H. Tang, ... Q. Y.-J. of M., and undefined 2016, “Computational studies on the structural, electronic and optical properties of graphene-like MXenes (M_2CT_2 , $M = Ti, Zr, Hf$; $T = O, F, OH$) and their potential,” *pubs.rsc.org*.
- [46] I. Persson, L. Näslund, J. Halim, ... M. B.-2D, and undefined 2017, “On the organization and thermal behavior of functional groups on Ti_3C_2 MXene surfaces in vacuum,” *iopscience.iop.org*, 2017, doi: 10.1088/2053-1583/aa89cd.
- [47] M. Naguib *et al.*, “MXene: A promising transition metal carbide anode for lithium-ion batteries,” *Electrochem commun*, vol. 16, no. 1, pp. 61–64, Mar. 2012, doi: 10.1016/j.elecom.2012.01.002.
- [48] Y.-T. Liu *et al.*, “Communication Self-Assembly of Transition Metal Oxide Nanostructures on MXene Nanosheets for Fast and Stable Lithium Storage,” *Adv. Mater*, vol. 30, no. 23, p. 1707334, Jun. 2018, doi: 10.1002/adma.201707334.
- [49] J. Chen, K. Chen, D. Tong, Y. Huang, J. Z.-... Communications, and undefined 2015, “CO₂ and temperature dual responsive ‘Smart’ MXene phases,” *pubs.rsc.org*.
- [50] D. Xiong, X. Li, Z. Bai, and S. Lu, “Recent Advances in Layered $Ti_3C_2T_x$ MXene for Electrochemical Energy Storage,” *Small*, vol. 14, no. 17, p. 1703419, Apr. 2018, doi: 10.1002/sml.201703419.
- [51] A. Feng *et al.*, “Fabrication and thermal stability of NH_4HF_2 -etched Ti_3C_2 MXene,” *Ceram Int*, vol. 43, no. 8, pp. 6322–6328, Jun. 2017, doi: 10.1016/j.ceramint.2017.02.039.
- [52] S. H. Overbury *et al.*, “Complexity of Intercalation in MXenes: Destabilization of Urea by Two-Dimensional Titanium Carbide,” *J Am Chem Soc*, vol. 140, no. 32, pp. 10305–10314, Aug. 2018, doi: 10.1021/jacs.8b05913.
- [53] O. Mashtalir *et al.*, “Amine-Assisted Delamination of Nb_2C MXene for Li-Ion Energy Storage Devices,” *Wiley Online Library*, vol. 27, no. 23, pp. 3501–3506, Jun. 2015, doi: 10.1002/adma.201500604.
- [54] M. Eryilmaz, E. Acar Soykut, D. Çetin, I. H. Boyaci, Z. Suludere, and U. Tamer, “SERS-based rapid assay for sensitive detection of Group A Streptococcus by evaluation of the swab sampling technique,” *Analyst*, vol. 144, no. 11, pp. 3573–3580, May 2019, doi: 10.1039/C9AN00173E.

- [55] A. Olshtrem *et al.*, “Plasmon-assisted grafting of anisotropic nanoparticles – spatially selective surface modification and the creation of amphiphilic SERS nanoprobes,” *Nanoscale*, vol. 12, no. 27, pp. 14581–14588, Jul. 2020, doi: 10.1039/D0NR02934C.
- [56] M. Liu, R. Zhang, and W. Chen, “Graphene-supported nanoelectrocatalysts for fuel cells: Synthesis, properties, and applications,” *Chem Rev*, vol. 114, no. 10, pp. 5117–5160, May 2014, doi: 10.1021/CR400523Y/ASSET/IMAGES/CR400523Y.SOCIAL.JPEG_V03.
- [57] S. Huang *et al.*, “Molecular selectivity of graphene-enhanced raman scattering,” *Nano Lett*, vol. 15, no. 5, pp. 2892–2901, May 2015, doi: 10.1021/NL5045988.
- [58] S. Huang *et al.*, “Molecular selectivity of graphene-enhanced raman scattering,” *Nano Lett*, vol. 15, no. 5, pp. 2892–2901, May 2015, doi: 10.1021/NL5045988.
- [59] D. Chen, H. Feng, and J. Li, “Graphene oxide: Preparation, functionalization, and electrochemical applications,” *Chem Rev*, vol. 112, no. 11, pp. 6027–6053, Nov. 2012, doi: 10.1021/CR300115G.
- [60] Z. Wu *et al.*, “The Assembly of MXenes from 2D to 3D,” *Advanced Science*, vol. 7, no. 7, p. 1903077, Apr. 2020, doi: 10.1002/ADVS.201903077.
- [61] M. Naguib, M. W. Barsoum, and Y. Gogotsi, “Ten Years of Progress in the Synthesis and Development of MXenes,” *Advanced Materials*, vol. 33, no. 39, p. 2103393, Oct. 2021, doi: 10.1002/ADMA.202103393.
- [62] L. Lu *et al.*, “Ultrasensitive fluorometric biosensor based on Ti₃C₂ MXenes with Hg²⁺-triggered exonuclease III-assisted recycling amplification,” *Analyst*, vol. 146, no. 8, pp. 2664–2669, Apr. 2021, doi: 10.1039/D1AN00178G.
- [63] D. Zhang, D. Shah, A. Boltasseva, and Y. Gogotsi, “MXenes for Photonics,” *ACS Photonics*, p. acsphotonics.2c00040, Mar. 2022, doi: 10.1021/ACSPHOTONICS.2C00040.
- [64] L. Li, N. Zhang, M. Zhang, L. Wu, X. Zhang, and Z. Zhang, “Ag-Nanoparticle-Decorated 2D Titanium Carbide (MXene) with Superior Electrochemical Performance for Supercapacitors,” *ACS Sustain Chem Eng*, vol. 6, no. 6, pp. 7442–7450, Jun. 2018, doi: 10.1021/ACSSUSCHEMENG.8B00047.
- [65] X. Zhang *et al.*, “Ag nanoparticles grafted vanadium carbide MXene as a superior anode material for lithium-ion battery: High capacity and long-term cycle capability,” *J Alloys Compd*, vol. 909, p. 164730, Jul. 2022, doi: 10.1016/J.JALLCOM.2022.164730.

- [66] L. Qin *et al.*, “Formation and operating mechanisms of single-crystalline perovskite NaNbO₃ nanocubes/few-layered Nb₂CT_x MXene hybrids towards Li-ion capacitors,” *J Mater Chem A Mater*, vol. 9, no. 36, pp. 20405–20416, Sep. 2021, doi: 10.1039/D1TA03684J.
- [67] B. Sun *et al.*, “Ti₃C₂ MXene-bridged Ag/Ag₃PO₄ hybrids toward enhanced visible-light-driven photocatalytic activity,” *Appl Surf Sci*, vol. 535, p. 147354, Jan. 2021, doi: 10.1016/J.APSUSC.2020.147354.
- [68] Y. Lin, J. Xie, L. Chen, J. Fu, R. Chen, and H. Zhang, “Hybridization of Binary Non-Precious-Metal Nanoparticles with d-Ti₃C₂ MXene for Catalyzing the Oxygen Reduction Reaction,” *Wiley Online Library*, vol. 5, no. 21, pp. 3307–3314, Nov. 2018, doi: 10.1002/celc.201800693.
- [69] W. Chen, X. Jiang, S. Lai, ... D. P.-N., and undefined 2020, “Nanohybrids of a MXene and transition metal dichalcogenide for selective detection of volatile organic compounds,” *nature.com*, Accessed: Jun. 08, 2022. [Online]. Available: <https://www.nature.com/articles/s41467-020-15092-4>
- [70] E. Satheeshkumar, T. Makaryan, A. M.-S. reports, and undefined 2016, “One-step solution processing of Ag, Au and Pd@ MXene hybrids for SERS,” *nature.com*, Accessed: Mar. 26, 2022. [Online]. Available: <https://www.nature.com/articles/srep32049>
- [71] H. Zhang *et al.*, “Spherical Nanoparticle Arrays with Tunable Nanogaps and Their Hydrophobicity Enhanced Rapid SERS Detection by Localized Concentration of Droplet Evaporation,” *Adv Mater Interfaces*, vol. 2, no. 9, Jun. 2015, doi: 10.1002/ADMI.201500031.
- [72] H. Zhang *et al.*, “Physical deposition improved SERS stability of morphology controlled periodic micro/nanostructured arrays based on colloidal templates,” *Small*, vol. 11, no. 7, pp. 844–853, Feb. 2015, doi: 10.1002/SMLL.201402630.
- [73] D. Liu *et al.*, “Rapid synthesis of monodisperse Au nanospheres through a laser irradiation-induced shape conversion, self-assembly and their electromagnetic coupling,” *nature.com*, Accessed: Mar. 26, 2022. [Online]. Available: <https://www.nature.com/articles/srep07686>
- [74] K. Shevchuk, A. Sarycheva, and Y. Gogotsi, “Evaluation of two-dimensional transition-metal carbides and carbonitrides (MXenes) for SERS substrates,” *MRS Bulletin* 2022, pp. 1–10, Mar. 2022, doi: 10.1557/S43577-022-00276-8.
- [75] J. Zhang *et al.*, “Novel synthesis method and microstructure evolution of Ti₃C₂(OH)₂/K₂Ti₈O₁₇ nanocomposites as an effective surface enhanced Raman

- scattering substrate,” *Ceram Int*, vol. 47, no. 14, pp. 19864–19872, Jul. 2021, doi: 10.1016/J.CERAMINT.2021.03.325.
- [76] A. Iqbal, J. Hong, T. Y. Ko, and C. M. Koo, “Improving oxidation stability of 2D MXenes: synthesis, storage media, and conditions,” *Nano Converg*, vol. 8, no. 1, pp. 1–22, Dec. 2021, doi: 10.1186/S40580-021-00259-6/FIGURES/14.
- [77] C. Ma *et al.*, “MXene saturable absorber enabled hybrid mode-locking technology: A new routine of advancing femtosecond fiber lasers performance,” *Nanophotonics*, vol. 9, no. 8, pp. 2451–2458, Aug. 2020, doi: 10.1515/NANOPH-2019-0527/DOWNLOADASSET/SUPPL/NANOPH-2019-0527_SUPPL.DOCX.
- [78] Q. He, H. Hu, Y. Shao, and Z. Z. Zhao, “Switchable optical nonlinear properties of monolayer V2CTX MXene,” *Optik (Stuttg)*, vol. 247, p. 167629, Dec. 2021, doi: 10.1016/J.IJLEO.2021.167629.
- [79] W. Huang *et al.*, “Highly stable MXene (V2CTx)-based harmonic pulse generation,” *Nanophotonics*, vol. 9, no. 8, pp. 2577–2585, Aug. 2020, doi: 10.1515/NANOPH-2020-0134/ASSET/GRAPHIC/J_NANOPH-2020-0134_FIG_006.JPG.
- [80] K. Chayambuka *et al.*, “From Li-Ion Batteries toward Na-Ion Chemistries: Challenges and Opportunities,” *Adv Energy Mater*, vol. 10, no. 38, p. 2001310, Oct. 2020, doi: 10.1002/AENM.202001310.
- [81] E. Fan *et al.*, “Sustainable Recycling Technology for Li-Ion Batteries and Beyond: Challenges and Future Prospects,” *Chem Rev*, vol. 120, no. 14, pp. 7020–7063, Jul. 2020, doi: 10.1021/ACS.CHEMREV.9B00535/ASSET/IMAGES/MEDIUM/CR9B00535_0022.GIF.
- [82] S. Ponnada, M. S. Kiai, R. Krishnapriya, R. Singhal, and R. K. Sharma, “Lithium-Free Batteries: Needs and Challenges,” *Energy and Fuels*, vol. 36, no. 12, pp. 6013–6026, Jun. 2022, doi: 10.1021/ACS.ENERGYFUELS.2C00569/ASSET/IMAGES/MEDIUM/EF2C00569_0008.GIF.
- [83] S. M. Abu Nayem, A. Ahmad, S. Shaheen Shah, A. Saeed Alzahrani, A. J. Saleh Ahammad, and M. A. Aziz, “High Performance and Long-cycle Life Rechargeable Aluminum Ion Battery: Recent Progress, Perspectives and Challenges,” *The Chemical Record*, vol. 22, no. 12, p. e202200181, Dec. 2022, doi: 10.1002/TCR.202200181.

- [84] Z. Liu *et al.*, “Low-Cost Gel Polymer Electrolyte for High-Performance Aluminum-Ion Batteries,” *ACS Appl Mater Interfaces*, vol. 13, no. 24, pp. 28164–28170, Jun. 2021, doi: 10.1021/ACSAMI.1C05476/SUPPL_FILE/AM1C05476_SI_001.PDF.
- [85] H. Wang *et al.*, “Anion-effects on electrochemical properties of ionic liquid electrolytes for rechargeable aluminum batteries,” *J Mater Chem A Mater*, vol. 3, no. 45, pp. 22677–22686, Nov. 2015, doi: 10.1039/C5TA06187C.
- [86] D. MacFarlane, M. Forsyth, P. Howlett, M. K.-... R. Materials, and undefined 2016, “Ionic liquids and their solid-state analogues as materials for energy generation and storage,” *nature.com*, Accessed: Mar. 24, 2023. [Online]. Available: <https://www.nature.com/articles/natrevmats20155>
- [87] T. Liu, J. P. Vivek, E. W. Zhao, J. Lei, N. Garcia-Araez, and C. P. Grey, “Current Challenges and Routes Forward for Nonaqueous Lithium-Air Batteries,” *Chem Rev*, vol. 120, no. 14, pp. 6558–6625, Jul. 2020, doi: 10.1021/ACS.CHEMREV.9B00545/ASSET/IMAGES/MEDIUM/CR9B00545_0026.GIF.
- [88] Y. Hu *et al.*, “Cyclic-anion salt for high-voltage stable potassium-metal batteries”, doi: 10.1093/nsr/nwac134.
- [89] K. L. Ng, Z. Lu, Y. Wang, C. V. Singh, and G. Azimi, “Fundamental Insights into Electrical and Transport Properties of Chloroaluminate Ionic Liquids for Aluminum-Ion Batteries,” *Journal of Physical Chemistry C*, vol. 125, no. 28, pp. 15145–15154, Jul. 2021, doi: 10.1021/ACS.JPCC.1C02415/SUPPL_FILE/JP1C02415_SI_001.PDF.
- [90] N. Jayaprakash, S. K. Das, and L. A. Archer, “The rechargeable aluminum-ion battery,” *Chemical Communications*, vol. 47, no. 47, pp. 12610–12612, Nov. 2011, doi: 10.1039/C1CC15779E.
- [91] J. Li *et al.*, “A chloric polycation binder enables rapid ionic transport in thick electrodes of high-energy aluminum-ion batteries,” *J Mater Chem A Mater*, 2023, doi: 10.1039/D2TA09259J.
- [92] M. Ates, A. Chebil, O. Yoruk, C. Dridi, and M. Turkyilmaz, “Reliability of electrode materials for supercapacitors and batteries in energy storage applications: a review,” *Ionics 2021 28:1*, vol. 28, no. 1, pp. 27–52, Oct. 2021, doi: 10.1007/S11581-021-04296-3.

- [93] S. Wang *et al.*, “Anatase TiO₂ Nanorods as Cathode Materials for Aluminum-Ion Batteries,” *ACS Appl Nano Mater*, vol. 2, no. 10, pp. 6428–6435, Oct. 2019, doi: 10.1021/ACSANM.9B01391/SUPPL_FILE/AN9B01391_SI_001.PDF.
- [94] L. Geng, J. P. Scheifers, C. Fu, J. Zhang, B. P. T. Fokwa, and J. Guo, “Titanium Sulfides as Intercalation-Type Cathode Materials for Rechargeable Aluminum Batteries,” *ACS Appl Mater Interfaces*, vol. 9, no. 25, pp. 21251–21257, Jun. 2017, doi: 10.1021/ACSAMI.7B04161/SUPPL_FILE/AM7B04161_SI_001.PDF.
- [95] S. Wang *et al.*, “High-Performance Aluminum-Ion Battery with CuS@C Microsphere Composite Cathode,” *ACS Nano*, vol. 11, no. 1, pp. 469–477, Jan. 2017, doi: 10.1021/ACSNANO.6B06446.
- [96] S. Li, J. Tu, G.-H. Zhang, M. Wang, and S. Jiao, “NiCo₂S₄ Nanosheet with Hexagonal Architectures as an Advanced Cathode for Al-Ion Batteries,” *J Electrochem Soc*, vol. 165, no. 14, pp. A3504–A3509, 2018, doi: 10.1149/2.1201814JES/META.
- [97] W. Yang, H. Lu, Y. Cao, B. Xu, ... Y. D.-... S. C. &, and undefined 2019, “Flexible Free-Standing MoS₂/Carbon Nanofibers Composite Cathode for Rechargeable Aluminum-Ion Batteries,” *ACS Publications*, Accessed: Jul. 01, 2023. [Online]. Available: <https://pubs.acs.org/doi/abs/10.1021/acssuschemeng.8b05292>
- [98] W. Xing *et al.*, “Layered double hydroxides derived NiCo-sulfide as a cathode material for aluminum ion batteries,” *Electrochim Acta*, vol. 344, p. 136174, Jun. 2020, doi: 10.1016/J.ELECTACTA.2020.136174.
- [99] Y. Hu *et al.*, “A Binder-Free and Free-Standing Cobalt Sulfide@Carbon Nanotube Cathode Material for Aluminum-Ion Batteries,” *Advanced Materials*, vol. 30, no. 2, p. 1703824, Jan. 2018, doi: 10.1002/ADMA.201703824.
- [100] W. D. Pan *et al.*, “Non-aqueous Al-ion batteries: cathode materials and corresponding underlying ion storage mechanisms,” *Rare Metals*, vol. 41, no. 3, pp. 762–774, Mar. 2022, doi: 10.1007/S12598-021-01860-8/METRICS.
- [101] Z. Zhao *et al.*, “Tailoring multi-layer architected FeS₂@C hybrids for superior sodium-, potassium- and aluminum-ion storage,” *Energy Storage Mater*, vol. 22, pp. 228–234, Nov. 2019, doi: 10.1016/J.ENSMS.2019.01.022.
- [102] S. Wang *et al.*, “A Novel Aluminum-Ion Battery: Al/AlCl₃-[EMIm]Cl/Ni₃S₂@Graphene,” *Adv Energy Mater*, vol. 6, no. 13, Jul. 2016, doi: 10.1002/AENM.201600137.

- [103] D. Wang *et al.*, “A manganese hexacyanoferrate framework with enlarged ion tunnels and two-species redox reaction for aqueous Al-ion batteries,” *Nano Energy*, vol. 84, p. 105945, Jun. 2021, doi: 10.1016/J.NANOEN.2021.105945.
- [104] M. Okubo, A. Sugahara, S. Kajiyama, and A. Yamada, “MXene as a Charge Storage Host,” *Acc Chem Res*, vol. 51, no. 3, pp. 591–599, Mar. 2018, doi: 10.1021/acs.accounts.7b00481.
- [105] D. Yuan *et al.*, “Atomically Thin Materials for Next-Generation Rechargeable Batteries,” *Chem Rev*, vol. 122, no. 1, pp. 957–999, Jan. 2022, doi: 10.1021/ACS.CHEMREV.1C00636/ASSET/IMAGES/MEDIUM/CR1C00636_0022.GIF.
- [106] J. Zhao *et al.*, “One-step synthesis of few-layer niobium carbide MXene as a promising anode material for high-rate lithium ion batteries,” *Dalton Transactions*, vol. 48, no. 38, pp. 14433–14439, Oct. 2019, doi: 10.1039/C9DT03260F.
- [107] M. Slusarczyk *et al.*, “Application of ProTide technology to gemcitabine: A successful approach to overcome the key cancer resistance mechanisms leads to a new agent (NUC-1031) in clinical development,” *J Med Chem*, vol. 57, no. 4, pp. 1531–1542, Feb. 2014, doi: 10.1021/JM401853A/SUPPL_FILE/JM401853A_SI_001.PDF.
- [108] W. Wu, J. Sigmond, G. J. Peters, and R. F. Borch, “Synthesis and biological activity of a gemcitabine phosphoramidate prodrug,” *J Med Chem*, vol. 50, no. 15, pp. 3743–3746, Jul. 2007, doi: 10.1021/JM070269U/SUPPL_FILE/JM070269USI20070509_041757.PDF.
- [109] S. Yang, D. Luo, N. Li, C. Li, S. Tang, and Z. Huang, “New Mechanism of Gemcitabine and Its Phosphates: DNA Polymerization Disruption via 3'-5' Exonuclease Inhibition,” *Biochemistry*, vol. 59, no. 45, pp. 4344–4352, Nov. 2020, doi: 10.1021/ACS.BIOCHEM.0C00543/SUPPL_FILE/BI0C00543_SI_001.PDF.
- [110] L. De Sousa Cavalcante and G. Monteiro, “Gemcitabine: Metabolism and molecular mechanisms of action, sensitivity and chemoresistance in pancreatic cancer,” *Eur J Pharmacol*, vol. 741, pp. 8–16, Oct. 2014, doi: 10.1016/J.EJPHAR.2014.07.041.
- [111] H. Chen, H. Ma, and C. Li, “Host-Guest Intercalation Chemistry in MXenes and Its Implications for Practical Applications,” *ACS Nano*, vol. 15, no. 10, pp. 15502–15537, Oct. 2021, doi: 10.1021/ACSNANO.1C04423/ASSET/IMAGES/ACSNANO.1C04423.SOCIAL.JPEG_V03.

- [112] V. M. Hong Ng *et al.*, “Recent progress in layered transition metal carbides and/or nitrides (MXenes) and their composites: synthesis and applications,” *J Mater Chem A Mater*, vol. 5, no. 7, pp. 3039–3068, Feb. 2017, doi: 10.1039/C6TA06772G.
- [113] K. Matthews, T. Zhang, C. E. Shuck, A. Vahidmohammadi, and Y. Gogotsi, “Guidelines for Synthesis and Processing of Chemically Stable Two-Dimensional V₂CT_xMXene,” *Chemistry of Materials*, vol. 34, no. 2, pp. 499–509, Jan. 2022, doi: 10.1021/ACS.CHEMMATER.1C03508.
- [114] K. Maleski, C. E. Shuck, A. T. Fafarman, and Y. Gogotsi, “The Broad Chromatic Range of Two-Dimensional Transition Metal Carbides,” *Adv Opt Mater*, vol. 9, no. 4, Feb. 2021, doi: 10.1002/ADOM.202001563.
- [115] K. Matthews, T. Zhang, C. E. Shuck, A. Vahidmohammadi, and Y. Gogotsi, “Guidelines for Synthesis and Processing of Chemically Stable Two-Dimensional V₂CT_xMXene,” *Chemistry of Materials*, vol. 34, no. 2, pp. 499–509, Jan. 2022, doi: 10.1021/ACS.CHEMMATER.1C03508.
- [116] B. H. C. Greene, D. S. Alhatab, C. C. Pye, and C. L. Brosseau, “Electrochemical-Surface Enhanced Raman Spectroscopic (EC-SERS) Study of 6-Thiouric Acid: A Metabolite of the Chemotherapy Drug Azathioprine,” *Journal of Physical Chemistry C*, vol. 121, no. 14, pp. 8084–8090, Apr. 2017, doi: 10.1021/ACS.JPCC.7B01179/SUPPL_FILE/JP7B01179_SI_001.PDF.
- [117] N. Mahar, M. Haroon, T. A. Saleh, and A. A. Al-Saadi, “Fast and sensitive detection of Procainamide: Combined SERS and DFT modeling studies,” *J Mol Liq*, vol. 343, p. 117633, Dec. 2021, doi: 10.1016/J.MOLLIQ.2021.117633.
- [118] K. Chen *et al.*, “Preparation of Self-Assembled Composite Films Constructed by Chemically-Modified MXene and Dyes with Surface-Enhanced Raman Scattering Characterization,” *Nanomaterials 2019, Vol. 9, Page 284*, vol. 9, no. 2, p. 284, Feb. 2019, doi: 10.3390/NANO9020284.
- [119] X. Cui *et al.*, “Detection of glucose in diabetic tears by using gold nanoparticles and MXene composite surface-enhanced Raman scattering substrates,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 266, p. 120432, Feb. 2022, doi: 10.1016/J.SAA.2021.120432.
- [120] H. Liu, Y. He, and K. Cao, “Flexible Surface-Enhanced Raman Scattering Substrates: A Review on Constructions, Applications, and Challenges,” *Adv Mater Interfaces*, vol. 8, no. 21, p. 2100982, Nov. 2021, doi: 10.1002/ADMI.202100982.

- [121] W. Zhao *et al.*, “Binary ‘island’ shaped arrays with high-density hot spots for surface-enhanced Raman scattering substrates,” *pubs.rsc.org*, Accessed: Mar. 25, 2022. [Online]. Available: <https://pubs.rsc.org/en/content/articlehtml/2018/nr/c8nr02669f>
- [122] I. Rus *et al.*, “Gemcitabine Direct Electrochemical Detection from Pharmaceutical Formulations Using a Boron-Doped Diamond Electrode,” *Pharmaceuticals* 2021, Vol. 14, Page 912, vol. 14, no. 9, p. 912, Sep. 2021, doi: 10.3390/PH14090912.
- [123] K. Freeman, S. Anliker, M. Hamilton, ... D. O.-... B. B. S., and undefined 1995, “Validated assays for the determination of gemcitabine in human plasma and urine using high-performance liquid chromatography with ultraviolet detection,” *Elsevier*, Accessed: May 08, 2022. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0378434794005216>
- [124] C. Bowen, S. Wang, H. L.-P.-J. of C. B, and undefined 2009, “Development of a sensitive and selective LC–MS/MS method for simultaneous determination of gemcitabine and 2, 2-difluoro-2-deoxyuridine in human plasma,” *Elsevier*, Accessed: May 08, 2022. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S1570023209004103>
- [125] “Simultaneous determination of procainamide and N-acetylprocainamide in serum by gas chromatography with nitrogen-selective detection,” *Elsevier*, Accessed: May 08, 2022. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0378434700832028>
- [126] K. Brown, L. D.-S. and A. Reports, and undefined 2021, “2+ for the electrochemiluminescence detection of gemcitabine and leucovorin toward diagnostic point-of-care sensors within precision medicine,” *Elsevier*, Accessed: May 08, 2022. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S2666053921000400>
- [127] S. Shahzad, L. Karadurmus, B. Dogan-Topal, T. Taskin-Tok, A. Shah, and S. A. Ozkan, “Sensitive Nucleic Acid Detection at NH₂-MWCNTs Modified Glassy Carbon Electrode and its Application for Monitoring of Gemcitabine-DNA Interaction,” *Electroanalysis*, vol. 32, no. 5, pp. 912–922, May 2020, doi: 10.1002/ELAN.201900597.
- [128] N. Mahar and A. A. Al-Saadi, “SERS-Based Ultralow Concentration Detection of Anticancer Gemcitabine Using Size-Controlled Silver Nanoparticles,” *Arabian Journal for Science and Engineering* 2022, pp. 1–9, May 2022, doi: 10.1007/S13369-022-06799-1.

- [129] S. Moreton, K. Faulds, N. C. Shand, M. A. Bedics, M. R. Detty, and D. Graham, “Functionalisation of hollow gold nanospheres for use as stable, red-shifted SERS nanotags,” *Nanoscale*, vol. 7, no. 14, pp. 6075–6082, Mar. 2015, doi: 10.1039/C5NR00091B.
- [130] F. J. Colas *et al.*, “Red-Shift Effects in Surface Enhanced Raman Spectroscopy: Spectral or Intensity Dependence of the Near-Field?,” *Journal of Physical Chemistry C*, vol. 120, no. 25, pp. 13675–13683, Jun. 2016, doi: 10.1021/ACS.JPCC.6B01492/SUPPL_FILE/JP6B01492_SI_001.PDF.
- [131] M. Haroon, I. Abdulazeez, T. A. Saleh, and A. A. Al-Saadi, “SERS-based trace-level quantification of sulindac: Spectroscopic and molecular modeling evaluation,” *J Mol Liq*, vol. 312, p. 113402, Aug. 2020, doi: 10.1016/J.MOLLIQ.2020.113402.
- [132] H. Yilmaz and M. Culha, “A Drug Stability Study Using Surface-Enhanced Raman Scattering on Silver Nanoparticles,” *Applied Sciences 2022, Vol. 12, Page 1807*, vol. 12, no. 4, p. 1807, Feb. 2022, doi: 10.3390/APP12041807.
- [133] A. Sarycheva *et al.*, “Two-Dimensional Titanium Carbide (MXene) as Surface-Enhanced Raman Scattering Substrate,” *Journal of Physical Chemistry C*, vol. 121, no. 36, pp. 19983–19988, Sep. 2017, doi: 10.1021/ACS.JPCC.7B08180/SUPPL_FILE/JP7B08180_SI_001.PDF.
- [134] Z. M. Zhou *et al.*, “Improving SERS Sensitivity toward Trace Sulfonamides: The Key Role of Trade-Off Interfacial Interactions among the Target Molecules, Anions, and Cations on the SERS Active Surface,” *Anal Chem*, vol. 93, no. 24, pp. 8603–8612, Jun. 2021, doi: 10.1021/ACS.ANALCHEM.1C01530/SUPPL_FILE/AC1C01530_SI_001.PDF.
- [135] M. Adier, A.-M. Jurdyc, B. Dussardier, C. Hurel, and F. Goutaland, “Towards Surface-Enhanced Raman Scattering using electroless substrate for trace arsenic detection and speciation”, Accessed: Aug. 31, 2022. [Online]. Available: <https://hal.archives-ouvertes.fr/hal-03577648>
- [136] W. Peng *et al.*, “Advances in surface-enhanced Raman scattering detection of foodborne pathogens: From recognition-based fingerprint to molecular diagnosis,” *Coord Chem Rev*, vol. 518, p. 216083, Nov. 2024, doi: 10.1016/J.CCR.2024.216083.
- [137] S. R. Balasubramani *et al.*, “Recent developments in surface-enhanced Raman spectroscopy in the field of chemical, biochemical and clinical application– a

- critical review,” *Int J Environ Anal Chem*, May 2024, doi: 10.1080/03067319.2024.2339453.
- [138] P. Hu *et al.*, “A SERS-based point-of-care testing approach for efficient determination of diquat and paraquat residues using a flexible silver flower-coated melamine sponge,” *Food Chem*, vol. 454, p. 139831, Oct. 2024, doi: 10.1016/J.FOODCHEM.2024.139831.
- [139] Y. Han, P. Matteini, and B. Hwang, “Fabrication method of colloidal dispersions and substrates for detection of pesticide, veterinary drug, and biomolecule using surfaced-enhanced Raman spectroscopy: a review,” *Appl Spectrosc Rev*, 2024, doi: 10.1080/05704928.2024.2367450.
- [140] J. Lv *et al.*, “Status and applications of femtosecond laser preparation of SERS substrates containing noble metals nanoparticles,” *Surfaces and Interfaces*, vol. 51, p. 104719, Aug. 2024, doi: 10.1016/J.SURFIN.2024.104719.
- [141] G. Awiaz, J. Lin, and A. Wu, “Recent advances of Au@Ag core-shell SERS-based biosensors,” *Exploration*, vol. 3, no. 1, p. 20220072, Feb. 2023, doi: 10.1002/EXP.20220072.
- [142] D. Y. Lin, C. Y. Yu, C. A. Ku, and C. K. Chung, “Design, Fabrication, and Applications of SERS Substrates for Food Safety Detection: Review,” *Micromachines* 2023, Vol. 14, Page 1343, vol. 14, no. 7, p. 1343, Jun. 2023, doi: 10.3390/MI14071343.
- [143] R. Borah, A. G. Karthick Raj, A. C. Minja, and S. W. Verbruggen, “A Review on Self-Assembly of Colloidal Nanoparticles into Clusters, Patterns, and Films: Emerging Synthesis Techniques and Applications,” *Small Methods*, vol. 7, no. 6, p. 2201536, Jun. 2023, doi: 10.1002/SMTD.202201536.
- [144] S. Adomaviči *et al.*, “Selective Enhancement of SERS Spectral Bands of Salicylic Acid Adsorbate on 2D Ti₃C₂T_x-Based MXene Film,” 2021, doi: 10.3390/chemosensors9080223.
- [145] X. Liu *et al.*, “Plasmonic Coupling of Au Nanoclusters on a Flexible MXene/Graphene Oxide Fiber for Ultrasensitive SERS Sensing,” *ACS Sens*, vol. 8, no. 3, pp. 1287–1298, Mar. 2023, doi: 10.1021/ACSSENSORS.2C02808/SUPPL_FILE/SE2C02808_SI_001.PDF.
- [146] B. Zhang *et al.*, “Surface plasmon resonance effects of Ti₃C₂ MXene for degradation of antibiotics under full spectrum,” *Appl Catal B*, vol. 339, p. 123132, Dec. 2023, doi: 10.1016/J.APCATB.2023.123132.

- [147] M. Yang *et al.*, “Three-Dimensional MXene-AgNP Hollow Spheres for In Situ Surface-Enhanced Raman Scattering Detection of Catalysis Reactions,” *Journal of Physical Chemistry Letters*, vol. 14, no. 40, pp. 9019–9026, Oct. 2023, doi: 10.1021/ACS.JPCLETT.3C02379/SUPPL_FILE/JZ3C02379_SI_001.PDF.
- [148] X. Xue *et al.*, “Controllable preparation of Ti₃C₂Tx/Ag composite as SERS substrate for ultrasensitive detection of 4-nitrobenzenethiol,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 302, p. 123019, Dec. 2023, doi: 10.1016/J.SAA.2023.123019.
- [149] elumalai satheeshkumar *et al.*, “one-step solution processing of Ag, Au and pd@MXene Hybrids for seRs”, doi: 10.1038/srep32049.
- [150] X. Xue *et al.*, “Controllable preparation of Ti₃C₂Tx/Ag composite as SERS substrate for ultrasensitive detection of 4-nitrobenzenethiol,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 302, p. 123019, Dec. 2023, doi: 10.1016/J.SAA.2023.123019.
- [151] S. K. Bhardwaj, H. Singh, M. Khatri, K. H. Kim, and N. Bhardwaj, “Advances in MXenes-based optical biosensors: A review,” *Biosens Bioelectron*, vol. 202, p. 113995, Apr. 2022, doi: 10.1016/J.BIOS.2022.113995.
- [152] S. Mathew *et al.*, “Synthesis, mechanisms, challenges, and future prospects of Ti₃C₂ MXene and its heterojunctions for photocatalytic dye degradation efficiency: a comprehensive review,” *Materials Today Sustainability*, vol. 24, p. 100568, Dec. 2023, doi: 10.1016/J.MTSUST.2023.100568.
- [153] W. Zhao *et al.*, “Toward an Understanding of Bimetallic MXene Solid-Solution in Binder-Free Electrocatalyst Cathode for Advanced Li–CO₂ Batteries,” *Adv Funct Mater*, vol. 33, no. 5, p. 2210037, Jan. 2023, doi: 10.1002/ADFM.202210037.
- [154] K. Gong, L. Yin, H. Pan, S. Mao, L. Liu, and K. Zhou, “Novel exploration of the flame retardant potential of bimetallic MXene in epoxy composites,” *Compos B Eng*, vol. 237, p. 109862, May 2022, doi: 10.1016/J.COMPOSITESB.2022.109862.
- [155] A. C. Foucher, M. Han, C. E. Shuck, K. Maleski, Y. Gogotsi, and E. A. Stach, “Shifts in valence states in bimetallic MXenes revealed by electron energy-loss spectroscopy (EELS),” *2d Mater*, vol. 9, no. 2, p. 025004, Jan. 2022, doi: 10.1088/2053-1583/AC4BA2.
- [156] N. Hussain *et al.*, “Oxidation of Molybdenum-Based Single-Metallic/bimetallic Carbide MXenes in Aqueous Suspensions: Mechanistic Insights,” *Langmuir*, vol.

- 40, no. 17, pp. 9170–9179, Apr. 2024, doi: 10.1021/ACS.LANGMUIR.4C00568/SUPPL_FILE/LA4C00568_SI_001.PDF.
- [157] M. Li, Z. Li, P. Wang, and Q. Ma, “A novel bimetallic MXene derivative QD-based ECL sensor for miRNA-27a-3p detection,” *Biosens Bioelectron*, vol. 228, p. 115225, May 2023, doi: 10.1016/J.BIOS.2023.115225.
- [158] P. Liu *et al.*, “Bimetallic MXene with tailored vanadium d-band as highly efficient electrocatalyst for reversible lithium-oxygen battery,” *J Colloid Interface Sci*, vol. 655, pp. 364–370, Feb. 2024, doi: 10.1016/J.JCIS.2023.11.027.
- [159] R. Syamsai *et al.*, “Double transition metal MXene ($\text{Ti}_x\text{Ta}_{4-x}\text{C}_3$) 2D materials as anodes for Li-ion batteries,” *Scientific Reports* 2021 11:1, vol. 11, no. 1, pp. 1–13, Jan. 2021, doi: 10.1038/s41598-020-79991-8.
- [160] Y. Wang, W. Zheng, P. Zhang, W. Tian, J. Chen, and Z. M. Sun, “Preparation of ($\text{V}_x, \text{Ti}_{1-x}$) 2C MXenes and their performance as anode materials for LIBs,” *J Mater Sci*, vol. 54, no. 18, pp. 11991–11999, Sep. 2019, doi: 10.1007/S10853-019-03756-6/METRICS.
- [161] T. Zhu *et al.*, “Sensitive determination of prostate-specific antigen with graphene quantum dot-based fluorescence aptasensor using few-layer V_2CT_x MXene as quencher,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 293, p. 122474, May 2023, doi: 10.1016/J.SAA.2023.122474.
- [162] G. Yang, J. Zhao, S. Yi, X. Wan, and J. Tang, “Biodegradable and photostable Nb_2C MXene quantum dots as promising nanofluorophores for metal ions sensing and fluorescence imaging,” *Sens Actuators B Chem*, vol. 309, p. 127735, Apr. 2020, doi: 10.1016/J.SNB.2020.127735.
- [163] N. Salimiaghdam *et al.*, “Potential adverse effects of ciprofloxacin and tetracycline on ARPE-19 cell lines,” *BMJ Open Ophthalmol*, vol. 5, no. 1, p. e000458, Jul. 2020, doi: 10.1136/BMJOPHTH-2020-000458.
- [164] A. I. A. Ahmed, F. M. M. A. van der Heijden, H. van den Berkmortel, and K. Kramers, “A man who wanted to commit suicide by hanging himself: an adverse effect of ciprofloxacin,” *Gen Hosp Psychiatry*, vol. 33, no. 1, pp. 82.e5–82.e7, Jan. 2011, doi: 10.1016/J.GENHOSPPSYCH.2010.07.002.
- [165] Z. Guo, L. Chen, H. Lv, Z. Yu, and B. Zhao, “Magnetic imprinted surface enhanced Raman scattering (MI-SERS) based ultrasensitive detection of ciprofloxacin from a mixed sample,” *Analytical Methods*, vol. 6, no. 6, pp. 1627–1632, Feb. 2014, doi: 10.1039/C3AY40866C.

- [166] X. Hu *et al.*, “Disposable electrochemical aptasensor based on carbon nanotubes-V2O5-chitosan nanocomposite for detection of ciprofloxacin,” *Sens Actuators B Chem*, vol. 268, pp. 278–286, Sep. 2018, doi: 10.1016/J.SNB.2018.03.155.
- [167] T. S. H. Pham, P. J. Mahon, G. Lai, and A. Yu, “Reduced Graphene Oxide Nanocomposite Modified Electrodes for Sensitive Detection of Ciprofloxacin,” *Electroanalysis*, vol. 30, no. 9, pp. 2185–2194, Sep. 2018, doi: 10.1002/ELAN.201700738.
- [168] C. Yuan, Z. He, Q. Chen, X. Wang, C. Zhai, and M. Zhu, “Selective and efficacious photoelectrochemical detection of ciprofloxacin based on the self-assembly of 2D/2D g-C3N4/Ti3C2 composites,” *Appl Surf Sci*, vol. 539, p. 148241, Feb. 2021, doi: 10.1016/J.APSUSC.2020.148241.
- [169] E. Sari, R. Üzek, M. Duman, and A. Denizli, “Detection of ciprofloxacin through surface plasmon resonance nanosensor with specific recognition sites,” *J Biomater Sci Polym Ed*, vol. 29, no. 11, pp. 1302–1318, Jul. 2018, doi: 10.1080/09205063.2018.1457417.
- [170] P. Gayen and B. P. Chaplin, “Selective Electrochemical Detection of Ciprofloxacin with a Porous Nafion/Multiwalled Carbon Nanotube Composite Film Electrode,” *ACS Appl Mater Interfaces*, vol. 8, no. 3, pp. 1615–1626, Jan. 2016, doi: 10.1021/ACSAMI.5B07337/SUPPL_FILE/AM5B07337_SI_001.PDF.
- [171] N. Mahar, A. Al-Ahmed, and A. A. Al-Saadi, “Synthesis of vanadium carbide MXene with improved inter-layer spacing for SERS-based quantification of anti-cancer drugs,” *Appl Surf Sci*, vol. 607, p. 155034, Jan. 2023, doi: 10.1016/J.APSUSC.2022.155034.
- [172] N. Mahar and A. A. Al-Saadi, “SERS-Based Ultralow Concentration Detection of Anticancer Gemcitabine Using Size-Controlled Silver Nanoparticles,” *Arab J Sci Eng*, vol. 47, no. 6, pp. 7197–7205, Jun. 2022, doi: 10.1007/S13369-022-06799-1/METRICS.
- [173] T. Lapauw *et al.*, “Synthesis of the new MAX phase Zr2AlC,” *J Eur Ceram Soc*, vol. 36, no. 8, pp. 1847–1853, Jul. 2016, doi: 10.1016/J.JEURCERAMSOC.2016.02.044.
- [174] Y. Wang, W. Zheng, P. Zhang, W. Tian, J. Chen, and Z. M. Sun, “Preparation of (V_x, Ti_{1-x})₂C MXenes and their performance as anode materials for LIBs,” *J Mater Sci*, vol. 54, no. 18, pp. 11991–11999, Sep. 2019, doi: 10.1007/S10853-019-03756-6/METRICS.

- [175] S. Saboori, W. Wang, Z. Li, and J. She, “Raman spectra of MXenes $Zr_2X(X=C \text{ and } N)$,” *Nanotechnology*, vol. 31, no. 40, p. 405708, Jul. 2020, doi: 10.1088/1361-6528/AB9A74.
- [176] X. Liu *et al.*, “Triple-enhanced Raman scattering sensors from flexible MXene/Au nanocubes platform via attenuating the coffee ring effect,” *Biosens Bioelectron*, vol. 237, p. 115531, Oct. 2023, doi: 10.1016/J.BIOS.2023.115531.
- [177] N. N. Yusoff, F. S. Nor Azmi, N. Abu Bakar, T. H. Tengku Abdul Aziz, and J. G. Shapter, “Titanium carbide MXene/silver nanostars composite as SERS substrate for thiram pesticide detection,” *Chemical Papers*, vol. 78, no. 5, pp. 2855–2865, Apr. 2024, doi: 10.1007/S11696-023-03276-3/FIGURES/7.
- [178] N. Mahar and A. A. Al-Saadi, “Light-induced synthesis of silver nanoprisms as a surface-enhanced Raman scattering substrate for N-acetyl procainamide drug quantification,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 302, p. 122996, Dec. 2023, doi: 10.1016/J.SAA.2023.122996.
- [179] A. Balla, K. H. Cho, Y. C. Kim, and H. J. Maeng, “Simultaneous determination of procainamide and N-acetylprocainamide in Rat plasma by ultra-high-pressure liquid chromatography coupled with a diode array detector and its application to a pharmacokinetic study in Rats,” *Pharmaceutics*, vol. 10, no. 2, p. 41, Jun. 2018, doi: 10.3390/pharmaceutics10020041.
- [180] C. C. Shih *et al.*, “Procainamide inhibits DNA methylation and alleviates multiple organ dysfunction in rats with endotoxic shock,” *PLoS One*, vol. 11, no. 9, Sep. 2016, doi: 10.1371/journal.pone.0163690.
- [181] M. N. Obeyesekere and G. J. Klein, “Preventing Sudden Death in Asymptomatic Wolf-Parkinson-White Patients *,” Apr. 01, 2018, *Elsevier Inc.* doi: 10.1016/j.jacep.2017.11.014.
- [182] “Morphological and histochemical evidence of the protective effect of procainamide hydrochloride on tissue damage induced by repeated administration of low doses of cisplatin - PubMed.” Accessed: Jun. 23, 2021. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/16309206/>
- [183] C. C. Shih *et al.*, “Procainamide inhibits DNA methylation and alleviates multiple organ dysfunction in rats with endotoxic shock,” *PLoS One*, vol. 11, no. 9, Sep. 2016, doi: 10.1371/journal.pone.0163690.
- [184] D. Lawson and H. Jick, “Adverse reactions to procainamide.,” *Br J Clin Pharmacol*, vol. 4, no. 5, pp. 507–511, 1977, doi: 10.1111/j.1365-2125.1977.tb00777.x.

- [185] J. Danielly, R. DeJong, L. C. Radke-Mitchell, and A. C. G. Uprichard, "Procainamide-associated blood dyscrasias," *Am J Cardiol*, vol. 74, no. 11, pp. 1179–1180, Dec. 1994, doi: 10.1016/0002-9149(94)90478-2.
- [186] B. Strasberg *et al.*, "Procainamide-Induced polymorphous ventricular tachycardia," *Am J Cardiol*, vol. 47, no. 6, pp. 1309–1314, 1981, doi: 10.1016/0002-9149(81)90264-2.
- [187] A. Yamaji, K. Kataoka, M. Oishi, N. Kanamori, E. Hiraoka, and M. Mishima, "Simultaneous determination of procainamide and N-acetylprocainamide in serum by gas chromatography with nitrogen-selective detection," *J Chromatogr B Biomed Sci Appl*, vol. 415, no. C, pp. 143–147, 1987, doi: 10.1016/S0378-4347(00)83202-8.
- [188] H. Alrabiah, A. Homoda, A. Bakheit, and G. Ae Mostafa, "Cyclodextrin potentiometric sensors based on selective recognition sites for procainamide: Comparative and theoretical study," *Open Chem*, vol. 17, no. 1, pp. 1222–1234, Jan. 2019, doi: 10.1515/chem-2019-0131.
- [189] K. Wang, X. Guan, S. Chai, Q. Zou, X. Zhang, and J. Zhang, "A novel, molecularly imprinted polymer sensor made using an oligomeric methyl silsesquioxane-TiO₂ composite sol on a glassy carbon electrode for the detection of procainamide hydrochloride," *Biosens Bioelectron*, vol. 64, pp. 94–101, Feb. 2015, doi: 10.1016/j.bios.2014.08.053.
- [190] S. Al-Tamrah and S. Al-Abbad, "Spectrophotometric determination of procainamide hydrochloride using sodium periodate," Sep. 01, 2015, *Elsevier*. doi: 10.1016/j.arabjc.2012.02.004.
- [191] Y. Nie, C. Jin, and J. X. J. Zhang, "Microfluidic *In Situ* Patterning of Silver Nanoparticles for Surface-Enhanced Raman Spectroscopic Sensing of Biomolecules," *ACS Sens*, p. acssensors.1c00117, Jun. 2021, doi: 10.1021/acssensors.1c00117.
- [192] M. Haroon, I. Abdulazeez, T. A. Saleh, and A. A. Al-Saadi, "Electrochemically modulated SERS detection of procaine using FTO electrodes modified with silver-decorated carbon nanosphere," *Electrochim Acta*, vol. 387, p. 138463, Aug. 2021, doi: 10.1016/j.electacta.2021.138463.
- [193] B. H. C. Greene, D. S. Alhatab, C. C. Pye, and C. L. Brosseau, "Electrochemical-Surface Enhanced Raman Spectroscopic (EC-SERS) Study of 6-Thiouric Acid: A Metabolite of the Chemotherapy Drug Azathioprine," *Journal of Physical*

- Chemistry C*, vol. 121, no. 14, pp. 8084–8090, Apr. 2017, doi: 10.1021/acs.jpcc.7b01179.
- [194] “Selecting an Excitation Wavelength for Raman Spectroscopy.” Accessed: Sep. 02, 2021. [Online]. Available: <https://www.spectroscopyonline.com/view/selecting-excitation-wavelength-raman-spectroscopy>
- [195] “How to Choose Your Lasers for Raman Spectroscopy | Quick Guide.” Accessed: Sep. 02, 2021. [Online]. Available: <https://www.edinst.com/blog/lasers-for-raman-spectroscopy/>
- [196] A. D. Becke, “Density-functional exchange-energy approximation with correct asymptotic behavior,” *Phys Rev A (Coll Park)*, vol. 38, no. 6, pp. 3098–3100, Sep. 1988, doi: 10.1103/PhysRevA.38.3098.
- [197] C. Lee, W. Yang, and R. G. Parr, “Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density,” *Phys Rev B*, vol. 37, no. 2, pp. 785–789, Jan. 1988, doi: 10.1103/PhysRevB.37.785.
- [198] A. D. Becke, “A new mixing of Hartree–Fock and local density-functional theories,” *J Chem Phys*, vol. 98, no. 2, pp. 1372–1377, Jan. 1993, doi: 10.1063/1.464304.
- [199] S. A. Popoola, N. Ullah, and A. A. Al-Saadi, “Spectroscopic and DFT assessment of bridging ligand effect on the structural and electronic properties of dinuclear iridium- and rhodium-based complexes,” *Inorganica Chim Acta*, vol. 482, pp. 299–306, Oct. 2018, doi: 10.1016/J.ICA.2018.06.026.
- [200] A. T. Onawole, S. A. Popoola, T. A. Saleh, and A. A. Al-Saadi, “Silver-loaded graphene as an effective SERS substrate for clotrimazole detection: DFT and spectroscopic studies,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 201, pp. 354–361, Aug. 2018, doi: 10.1016/J.SAA.2018.05.018.
- [201] A. A. Al-Saadi, “Further insights on the molecular structure, vibrational spectra and ring-puckering potentials of silacyclopent-3-ene and its 1,1-dihalo derivatives: Ab initio and DFT study,” *Vib Spectrosc*, vol. 62, pp. 188–199, Sep. 2012, doi: 10.1016/J.VIBSPEC.2012.04.012.
- [202] S. A. Popoola and A. A. Al-Saadi, “Spectroscopic and theoretical evaluation of the metal-olefin interaction in di- μ -chlorobis (1,5-cyclooctadiene) complexes of Ir and Rh,” *Vib Spectrosc*, vol. 86, pp. 109–123, Sep. 2016, doi: 10.1016/J.VIBSPEC.2016.06.013.

- [203] K. G. Stamplecoskie, J. C. Scaiano, V. S. Tiwari, and H. Anis, "Optimal size of silver nanoparticles for surface-enhanced raman spectroscopy," *Journal of Physical Chemistry C*, vol. 115, no. 5, pp. 1403–1409, Feb. 2011, doi: 10.1021/jp106666t.
- [204] M. Çulha, M. Kahraman, N. Tokman, and G. Türkoğlu, "Surface-enhanced Raman scattering on aggregates of silver nanoparticles with definite size," *Journal of Physical Chemistry C*, vol. 112, no. 28, pp. 10338–10343, Jul. 2008, doi: 10.1021/jp711177z.
- [205] J. Helmlinger *et al.*, "Silver nanoparticles with different size and shape: equal cytotoxicity, but different antibacterial effects," *RSC Adv*, vol. 6, no. 22, pp. 18490–18501, Feb. 2016, doi: 10.1039/C5RA27836H.
- [206] "Procainamide | C13H21N3O - PubChem." Accessed: Sep. 01, 2021. [Online]. Available: <https://pubchem.ncbi.nlm.nih.gov/compound/Procainamide#section=UV-Spectra>
- [207] M. D. Meti, S. D. Gunagi, S. T. Nandibewoor, and S. A. Chimatadar, "Investigation of the interaction of the new antiarrhythmic drug procainamide hydrochloride with bovine serum albumin and the effect of some metal ions on the binding: A fluorescence quenching study," *Monatsh Chem*, vol. 144, no. 8, pp. 1253–1259, Aug. 2013, doi: 10.1007/s00706-013-0933-7.
- [208] M. Kamran, M. Haroon, S. A. Popoola, A. R. Almohammed, A. A. Al-Saadi, and T. A. Saleh, "Characterization of valeric acid using substrate of silver nanoparticles with SERS," *J Mol Liq*, vol. 273, pp. 536–542, Jan. 2019, doi: 10.1016/j.molliq.2018.10.037.
- [209] S. Chen, X. Li, Y. Zhao, L. Chang, and J. Qi, "Graphene oxide shell-isolated Ag nanoparticles for surface-enhanced Raman scattering," *Carbon N Y*, vol. 81, no. 1, pp. 767–772, 2015, doi: 10.1016/j.carbon.2014.10.021.
- [210] N. Karthikeyan, J. Joseph Prince, S. Ramalingam, and S. Periandy, "Spectroscopic [FT-IR and FT-Raman] and theoretical [UV-Visible and NMR] analysis on α -Methylstyrene by DFT calculations," *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 143, pp. 107–119, May 2015, doi: 10.1016/j.saa.2015.02.015.
- [211] N. E. Markina, A. M. Zakharevich, and A. V. Markin, "Determination of methotrexate in spiked human urine using SERS-active sorbent," *Anal Bioanal Chem*, vol. 412, no. 28, pp. 7757–7766, Nov. 2020, doi: 10.1007/s00216-020-02932-x.

- [212] A. A. Al-Saadi, M. Haroon, S. A. Popoola, and T. A. Saleh, "Sensitive SERS detection and characterization of procaine in aqueous media by reduced gold nanoparticles," *Sens Actuators B Chem*, vol. 304, p. 127057, Feb. 2020, doi: 10.1016/j.snb.2019.127057.
- [213] M. Haroon, I. Abdulazeez, T. A. Saleh, and A. A. Al-Saadi, "SERS-based trace-level quantification of sulindac: Spectroscopic and molecular modeling evaluation," *J Mol Liq*, vol. 312, Aug. 2020, doi: 10.1016/j.molliq.2020.113402.
- [214] C. S. Seney, B. M. Gutzman, and R. H. Goddard, "Correlation of size and surface-enhanced raman scattering activity of optical and spectroscopic properties for silver nanoparticles," *Journal of Physical Chemistry C*, vol. 113, no. 1, pp. 74–80, Jan. 2009, doi: 10.1021/jp805698e.
- [215] E. C. Le Ru, E. Blackie, M. Meyer, and P. G. Etchegoint, "Surface enhanced raman scattering enhancement factors: A comprehensive study," *Journal of Physical Chemistry C*, vol. 111, no. 37, pp. 13794–13803, Sep. 2007, doi: 10.1021/jp0687908.
- [216] K. M. Kosuda, J. M. Bingham, K. L. Wustholz, R. P. Van Duyne, and R. J. Groarke, "Nanostructures and surface-enhanced raman spectroscopy," in *Comprehensive Nanoscience and Nanotechnology*, vol. 1–5, Elsevier, 2019, pp. 117–152. doi: 10.1016/B978-0-12-803581-8.00611-1.
- [217] C. Chen, W. Liu, S. Tian, and T. Hong, "Novel surface-enhanced raman spectroscopy techniques for DNA, protein and drug detection," Apr. 01, 2019, *MDPI AG*. doi: 10.3390/s19071712.
- [218] T. A. Saleh, "Pharmaceutical Characterization and Detection Using Surface-Enhanced Raman Scattering," *International Archives of Clinical Pharmacology*, vol. 3, no. 1, Dec. 2017, doi: 10.23937/2572-3987.1510010.
- [219] "Methods for the determination of limit of detection and limit of quantitation of the analytical methods - Drug Development and Therapeutics." Accessed: Jul. 13, 2021. [Online]. Available: <https://ddtjournal.net/methods-for-the-determination-of-limit-of-detection-and-limit-of-quantitation-of-the-analytical-methods/>
- [220] L. Nugbienyo, A. Shishov, S. Garmonov, L. Moskvina, V. Andruch, and A. Bulatov, "Flow method based on liquid-liquid extraction using deep eutectic solvent for the spectrofluorimetric determination of procainamide in human saliva," *Talanta*, vol. 168, pp. 307–312, Jun. 2017, doi: 10.1016/j.talanta.2017.03.057.

- [221] H. Alrabiah, A. Homoda, A. Bakheit, and G. Ae Mostafa, "Cyclodextrin potentiometric sensors based on selective recognition sites for procainamide: Comparative and theoretical study," *Open Chem*, vol. 17, no. 1, pp. 1222–1234, Jan. 2019, doi: 10.1515/chem-2019-0131.
- [222] S. Al-Tamrah and S. Al-Abbad, "Spectrophotometric determination of procainamide hydrochloride using sodium periodate," Sep. 01, 2015, *Elsevier*. doi: 10.1016/j.arabjc.2012.02.004.
- [223] A. Balla, K. Cho, Y. Kim, and H.-J. Maeng, "Simultaneous Determination of Procainamide and N-acetylprocainamide in Rat Plasma by Ultra-High-Pressure Liquid Chromatography Coupled with a Diode Array Detector and Its Application to a Pharmacokinetic Study in Rats," *Pharmaceutics*, vol. 10, no. 2, p. 41, Mar. 2018, doi: 10.3390/pharmaceutics10020041.
- [224] G. Vargas, J. Havel, and E. Hadašová, "Direct determination of procainamide and N-acetylprocainamide by capillary zone electrophoresis in pharmaceutical formulations and urine," *J Chromatogr A*, vol. 772, no. 1–2, pp. 271–276, Jun. 1997, doi: 10.1016/S0021-9673(97)00106-4.
- [225] K. Wang, X. Guan, S. Chai, Q. Zou, X. Zhang, and J. Zhang, "A novel, molecularly imprinted polymer sensor made using an oligomeric methyl silsesquioxane-TiO₂ composite sol on a glassy carbon electrode for the detection of procainamide hydrochloride," *Biosens Bioelectron*, vol. 64, pp. 94–101, Feb. 2015, doi: 10.1016/j.bios.2014.08.053.
- [226] A. Yamaji, K. Kataoka, M. Oishi, N. Kanamori, E. Hiraoka, and M. Mishima, "Simultaneous determination of procainamide and N-acetylprocainamide in serum by gas chromatography with nitrogen-selective detection," *J Chromatogr B Biomed Sci Appl*, vol. 415, no. C, pp. 143–147, Jan. 1987, doi: 10.1016/S0378-4347(00)83202-8.
- [227] K. A. Willets, "Probing nanoscale interfaces with electrochemical surface-enhanced Raman scattering," Feb. 01, 2019, *Elsevier B.V.* doi: 10.1016/j.coelec.2018.10.005.
- [228] A. Golan, N. Mayorkas, S. Rosenwaks, and I. Bar, "Raman spectral signatures as conformational probes of gas phase flexible molecules," *Article in The Journal of Chemical Physics*, vol. 131, no. 2, 2009, doi: 10.1063/1.3168402.
- [229] L. C. Lee, C. Y. Liong, and A. A. Jemain, "A contemporary review on Data Preprocessing (DP) practice strategy in ATR-FTIR spectrum," Apr. 15, 2017, *Elsevier B.V.* doi: 10.1016/j.chemolab.2017.02.008.

- [230] S. A. Popoola, "Spectroscopic study of 2-methylindole and 3-methylindole: Solvents interactions and DFT studies," *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 189, pp. 578–585, Jan. 2018, doi: 10.1016/j.saa.2017.08.062.
- [231] "Scopus - Document details - Infrared and Raman characteristic group frequencies: Tables and charts | Signed in." Accessed: Jul. 12, 2021. [Online]. Available: <https://www.scopus.com/record/display.uri?eid=2-s2.0-84930667665&origin=inward>
- [232] I. J. Hidi, M. Jahn, M. W. Pletz, K. Weber, D. Cialla-May, and J. Popp, "Toward Levofloxacin Monitoring in Human Urine Samples by Employing the LoC-SERS Technique," *Journal of Physical Chemistry C*, vol. 120, no. 37, pp. 20613–20623, 2016, doi: 10.1021/acs.jpcc.6b01005.
- [233] S. N, M. K, and K. ADM, "Clinical Pharmacokinetics and Pharmacodynamics of Drugs in the Central Nervous System," *Clin Pharmacokinet*, vol. 57, no. 9, pp. 1059–1074, Sep. 2018, doi: 10.1007/S40262-018-0632-Y.
- [234] B. A, C. KH, K. YC, and M. HJ, "Simultaneous Determination of Procainamide and N-acetylprocainamide in Rat Plasma by Ultra-High-Pressure Liquid Chromatography Coupled with a Diode Array Detector and Its Application to a Pharmacokinetic Study in Rats," *Pharmaceutics*, vol. 10, no. 2, Jun. 2018, doi: 10.3390/PHARMACEUTICS10020041.
- [235] M. N. Obeyesekere and G. J. Klein, "Preventing Sudden Death in Asymptomatic Wolf-Parkinson-White Patients *," *JACC Clin Electrophysiol*, vol. 4, no. 4, pp. 445–447, Apr. 2018, doi: 10.1016/J.JACEP.2017.11.014.
- [236] C. C. Shih *et al.*, "Procainamide inhibits DNA methylation and alleviates multiple organ dysfunction in rats with endotoxic shock," *PLoS One*, vol. 11, no. 9, Sep. 2016, doi: 10.1371/JOURNAL.PONE.0163690.
- [237] Z. Gao *et al.*, "Procaine and procainamide inhibit the Wnt canonical pathway by promoter demethylation of WIF-1 in lung cancer cells," *Oncol Rep*, vol. 22, no. 6, pp. 1479–1484, Dec. 2009, doi: 10.3892/OR_00000590.
- [238] V. Singh, P. Sharma, and N. Capalash, "DNA Methyltransferase-1 Inhibitors as Epigenetic Therapy for Cancer".
- [239] P. Jacobs, L. Wood, and D. M. Dent, "Splenectomy and the thrombocytopenia of systemic lupus erythematosus.," *Ann Intern Med*, vol. 105, no. 6, pp. 971–972, 1986, doi: 10.7326/0003-4819-105-6-971_3.

- [240] T. P. Gibson, A. J. Atkinson, E. Matusik, L. D. Nelson, and W. A. Briggs, "Kinetics of procainamide and N-acetylprocainamide in renal failure," *Kidney Int*, vol. 12, no. 6, pp. 422–429, Dec. 1977, doi: 10.1038/KI.1977.133.
- [241] M. R. Bibler, T. C. Chou, R. J. Toltzis, and P. A. Wade, "Recurrent Ventricular Tachycardia Due to Pentamidine-Induced Cardiotoxicity," *Chest*, vol. 94, no. 6, pp. 1303–1306, Dec. 1988, doi: 10.1378/CHEST.94.6.1303.
- [242] D. Lawson and H. Jick, "Adverse reactions to procainamide.," *Br J Clin Pharmacol*, vol. 4, no. 5, pp. 507–511, 1977, doi: 10.1111/J.1365-2125.1977.TB00777.X.
- [243] J. Danielly, R. DeJong, L. R.-M.-... journal of cardiology, and undefined 1994, "Procainamide-associated blood dyscrasias," *Elsevier*.
- [244] J. M. Boyd and S. M. H. Sadrzadeh, "Limitations of immunoassays for screening of drugs of abuse in urine: issues of false positive and false negative results," *Accurate Results in the Clinical Laboratory*, pp. 233–242, Jan. 2019, doi: 10.1016/B978-0-12-813776-5.00014-5.
- [245] L. Nugbienyo *et al.*, "Automated sugaring-out liquid-liquid extraction based on flow system coupled with HPLC-UV for the determination of procainamide in urine," *Talanta*, vol. 167, pp. 709–713, May 2017, doi: 10.1016/J.TALANTA.2017.02.051.
- [246] J. Koch-Weser and S. W. Klein, "Procainamide Dosage Schedules, Plasma Concentrations, and Clinical Effects," *JAMA*, vol. 215, no. 9, pp. 1454–1460, Mar. 1971, doi: 10.1001/JAMA.1971.03180220036006.
- [247] T. Niwa, T. Shiraga, Y. Ohno, and A. Kagayama, "Interindividual Variability in 5-Fluorouracil Metabolism and Procainamide N-Acetylation in Human Liver Cytosol," *Biol Pharm Bull*, vol. 28, no. 6, pp. 1071–1074, Jun. 2005, doi: 10.1248/BPB.28.1071.
- [248] G. Vargas, J. Havel, and E. Hadašová, "Direct determination of procainamide and N-acetylprocainamide by capillary zone electrophoresis in pharmaceutical formulations and urine," *J Chromatogr A*, vol. 772, no. 1–2, pp. 271–276, Jun. 1997, doi: 10.1016/S0021-9673(97)00106-4.
- [249] H. B. Duan, J. T. Cao, J. J. Yang, H. Wang, and Y. M. Liu, "Simultaneous determination of four local anesthetics by CE with ECL and study on interaction between procainamide and human serum albumin," *Talanta*, vol. 154, pp. 341–345, Jul. 2016, doi: 10.1016/j.talanta.2016.03.093.

- [250] B. Kark, N. Sistovaris, and A. Keller, “Thin-layer chromatographic determination of procainamide and N-acetylprocainamide in human serum and urine at single-dose levels,” *J Chromatogr B Biomed Sci Appl*, vol. 277, no. C, pp. 261–272, Jan. 1983, doi: 10.1016/S0378-4347(00)84843-4.
- [251] J. D. Coyle, J. J. Macichan, H. Boudoulas, and J. J. Lima, “Reversed-phase liquid chromatography method for measurement of procainamide and three metabolites in serum and urine: Percent of dose excreted as deethyl metabolites,” *J Pharm Sci*, vol. 76, no. 5, pp. 402–405, May 1987, doi: 10.1002/jps.2600760513.
- [252] P. R. Henry and R. A. Dhruv, “More-sensitive enzyme-multiplied immunoassay technique for procainamide and N-acetylprocainamide in plasma, serum, and urine,” *Clin Chem*, vol. 34, no. 5, pp. 957–960, May 1988, doi: 10.1093/clinchem/34.5.957.
- [253] R. Dong, S. Weng, L. Yang, and J. Liu, “Detection and Direct Readout of Drugs in Human Urine Using Dynamic Surface-Enhanced Raman Spectroscopy and Support Vector Machines,” *Anal Chem*, vol. 87, no. 5, pp. 2937–2944, Mar. 2015, doi: 10.1021/ACS.ANALCHEM.5B00137.
- [254] S. Y. Ding *et al.*, “Nanostructure-based plasmon-enhanced Raman spectroscopy for surface analysis of materials,” *Nat Rev Mater*, vol. 1, no. 6, Apr. 2016, doi: 10.1038/NATREVMATS.2016.21.
- [255] S. A. Maier, “Plasmonics: Fundamentals and applications,” *Plasmonics: Fundamentals and Applications*, pp. 1–223, 2007, doi: 10.1007/0-387-37825-1.
- [256] M. Ashley, M. Bourgeois, ... R. M.-T. J. of, and undefined 2018, “Shape and size control of substrate-grown gold nanoparticles for surface-enhanced raman spectroscopy detection of chemical analytes,” *ACS Publications*, vol. 122, no. 4, pp. 2307–2314, Feb. 2018, doi: 10.1021/acs.jpcc.7b11440.
- [257] G. Yang, J. Nanda, B. Wang, G. Chen, and D. T. Hallinan, “Self-Assembly of Large Gold Nanoparticles for Surface-Enhanced Raman Spectroscopy,” *ACS Appl Mater Interfaces*, vol. 9, no. 15, pp. 13457–13470, Apr. 2017, doi: 10.1021/ACSAMI.7B01121.
- [258] M. Tahghighi, D. Janner, J. I.-M.- Nanomaterials, and undefined 2020, “Optimizing Gold Nanoparticle Size and Shape for the Fabrication of SERS Substrates by Means of the Langmuir–Blodgett Technique,” *mdpi.com*, Accessed: Jan. 07, 2022. [Online]. Available: <https://www.mdpi.com/891150>

- [259] N. Mahar, M. Haroon, T. A. Saleh, and A. A. Al-Saadi, “Fast and sensitive detection of Procainamide: Combined SERS and DFT modeling studies,” *J Mol Liq*, vol. 343, p. 117633, Dec. 2021, doi: 10.1016/J.MOLLIQ.2021.117633.
- [260] S. Hong and X. Li, “Optimal Size of Gold Nanoparticles for Surface-Enhanced Raman Spectroscopy under Different Conditions,” *J Nanomater*, vol. 2013, pp. 1–9, 2013, doi: 10.1155/2013/790323.
- [261] A. El-Ansary *et al.*, “Characterization, antibacterial, and neurotoxic effect of Green synthesized nanosilver using Ziziphus spina Christi aqueous leaf extract collected from Riyadh, Saudi Arabia,” *Mater Res Express*, vol. 5, no. 2, Feb. 2018, doi: 10.1088/2053-1591/AAAF5F.
- [262] M. M. Khalaf, H. M. Abd El-Lateef, I. M. A. Mohamed, M. E. A. Zaki, and A. Toghan, “Facile synthesis of gold-nanoparticles by different capping agents and their anticancer performance against liver cancer cells,” *Colloid Interface Sci Commun*, vol. 44, p. 100482, Sep. 2021, doi: 10.1016/J.COLCOM.2021.100482.
- [263] A. Al-Saadi, M. Haroon, ... S. P.-S. and A. B., and undefined 2020, “Sensitive SERS detection and characterization of procaine in aqueous media by reduced gold nanoparticles,” *Elsevier*, vol. 304, Feb. 2019, doi: 10.1016/j.snb.2019.127057.
- [264] Z. Han, H. Liu, J. Meng, L. Yang, J. Liu, and J. Liu, “Portable Kit for Identification and Detection of Drugs in Human Urine Using Surface-Enhanced Raman Spectroscopy,” *Anal Chem*, vol. 87, no. 18, pp. 9500–9506, Sep. 2015, doi: 10.1021/acs.analchem.5b02899.
- [265] “Spectral Resolution in Raman Spectroscopy | Edinburgh Instruments.” Accessed: May 06, 2022. [Online]. Available: <https://www.edinst.com/blog/spectral-resolution-in-raman-spectroscopy/>
- [266] S. Popoola, N. Ullah, A. A.-S.-I. C. Acta, and undefined 2018, “Spectroscopic and DFT assessment of bridging ligand effect on the structural and electronic properties of dinuclear iridium-and rhodium-based complexes,” *Elsevier*.
- [267] K. G. Stamplecoskie, J. C. Scaiano, V. S. Tiwari, and H. Anis, “Optimal size of silver nanoparticles for surface-enhanced raman spectroscopy,” *Journal of Physical Chemistry C*, vol. 115, no. 5, pp. 1403–1409, Feb. 2011, doi: 10.1021/JP106666T.
- [268] M. Culha, M. Kahraman, ... N. T.-T. J. of, and undefined 2008, “Surface-enhanced Raman scattering on aggregates of silver nanoparticles with definite

- size,” *ACS Publications*, vol. 112, no. 28, pp. 10338–10343, Jul. 2008, doi: 10.1021/jp711177z.
- [269] L. Zhao *et al.*, “Tuning the size of gold nanoparticles in the citrate reduction by chloride ions,” *pubs.rsc.org*, Accessed: Feb. 23, 2022. [Online]. Available: <https://pubs.rsc.org/en/content/articlehtml/2012/nr/c2nr30957b>
- [270] L. Guerrini and R. A. Alvarez-Puebla, “Surface-Enhanced Raman Scattering Sensing of Transition Metal Ions in Waters,” *ACS Omega*, vol. 6, no. 2, pp. 1054–1063, Jan. 2021, doi: 10.1021/acsomega.0c05261.
- [271] M. Meti, S. Gunagi, ... S. N.-M. für C., and undefined 2013, “Investigation of the interaction of the new antiarrhythmic drug procainamide hydrochloride with bovine serum albumin and the effect of some metal ions on the binding,” *Springer*.
- [272] Q. Zhou, X. Li, Q. Fan, X. Zhang, and J. Zheng, “Charge Transfer between Metal Nanoparticles Interconnected with a Functionalized Molecule Probed by Surface-Enhanced Raman Spectroscopy,” *Angewandte Chemie*, vol. 118, no. 24, pp. 4074–4077, Jun. 2006, doi: 10.1002/ANGE.200504419.
- [273] M. Kamran, M. Haroon, S. A. Popoola, A. R. Almohammed, A. A. Al-Saadi, and T. A. Saleh, “Characterization of valeric acid using substrate of silver nanoparticles with SERS,” *J Mol Liq*, vol. 273, pp. 536–542, Jan. 2019, doi: 10.1016/J.MOLLIQ.2018.10.037.
- [274] A. S. Maharjan and K. L. Johnson-Davis, “Issues of Interferences With Immunoassays Used for Screening of Drugs of Abuse in Urine,” *Critical Issues in Alcohol and Drugs of Abuse Testing*, pp. 129–139, Jan. 2019, doi: 10.1016/B978-0-12-815607-0.00010-1.
- [275] M. Haroon, I. Abdulazeez, T. Saleh, A. A.-S.-E. Acta, and undefined 2021, “Electrochemically modulated SERS detection of procaine using FTO electrodes modified with silver-decorated carbon nanosphere,” *Elsevier*, vol. 387, p. 138463, 2021, doi: 10.1016/j.electacta.2021.138463.
- [276] A. Onawole, S. Popoola, ... T. S.-S. A. P., and undefined 2018, “Silver-loaded graphene as an effective SERS substrate for clotrimazole detection: DFT and spectroscopic studies,” *Elsevier*.
- [277] N. Mahar, M. Haroon, T. A. Saleh, and A. A. Al-Saadi, “Fast and sensitive detection of Procainamide: Combined SERS and DFT modeling studies,” *J Mol Liq*, vol. 343, p. 117633, Dec. 2021, doi: 10.1016/J.MOLLIQ.2021.117633.

- [278] D. J. Trivedi, B. Barrow, and G. C. Schatz, “Understanding the chemical contribution to the enhancement mechanism in SERS: Connection with Hammett parameters,” *J Chem Phys*, vol. 153, no. 12, p. 124706, Sep. 2020, doi: 10.1063/5.0023359.
- [279] G. C. Schatz, M. A. Young, and R. P. Van Duyne, “Electromagnetic Mechanism of SERS,” *Surface-Enhanced Raman Scattering*, pp. 19–45, Sep. 2006, doi: 10.1007/3-540-33567-6_2.
- [280] E. C. le Ru, E. Blackie, M. Meyer, and P. G. Etchegoint, “Surface enhanced raman scattering enhancement factors: A comprehensive study,” *Journal of Physical Chemistry C*, vol. 111, no. 37, pp. 13794–13803, Sep. 2007, doi: 10.1021/JP0687908/SUPPL_FILE/JP0687908SI20070717_104641.PDF.
- [281] L. Zhang, C. Guan, Y. Wang, and J. Liao, “Highly effective and uniform SERS substrates fabricated by etching multi-layered gold nanoparticle arrays,” *Nanoscale*, vol. 8, no. 11, pp. 5928–5937, Mar. 2016, doi: 10.1039/C6NR00502K.
- [282] B. de Nijs *et al.*, “Inhibiting Analyte Theft in Surface-Enhanced Raman Spectroscopy Substrates: Subnanomolar Quantitative Drug Detection,” *ACS Sens*, vol. 4, no. 11, pp. 2988–2996, Nov. 2019, doi: 10.1021/ACSSENSORS.9B01484.
- [283] W. R. Premasiri, R. H. Clarke, and M. E. Womble, “Urine analysis by laser Raman spectroscopy,” *Lasers Surg Med*, vol. 28, no. 4, pp. 330–334, Apr. 2001, doi: 10.1002/LSM.1058.
- [284] T. Yang *et al.*, “Facile and label-free detection of lung cancer biomarker in urine by magnetically assisted surface-enhanced Raman scattering,” *ACS Appl Mater Interfaces*, vol. 6, no. 23, pp. 20985–20993, Dec. 2014, doi: 10.1021/AM5057536.
- [285] A. Shrivastava, V. G.-C. of young scientists, and undefined 2011, “Methods for the determination of limit of detection and limit of quantitation of the analytical methods,” *researchgate.net*, 2011, doi: 10.4103/2229-5186.79345.
- [286] A. Golan, N. Mayorkas, ... S. R.-T. J. of chemical, and undefined 2009, “Raman spectral signatures as conformational probes of gas phase flexible molecules,” *aip.scitation.org*, vol. 131, no. 2, 2009, doi: 10.1063/1.3168402.
- [287] L. C. Lee, C. Y. Liong, and A. A. Jemain, “A contemporary review on Data Preprocessing (DP) practice strategy in ATR-FTIR spectrum,” *Chemometrics and Intelligent Laboratory Systems*, vol. 163, pp. 64–75, Apr. 2017, doi: 10.1016/J.CHEMOLAB.2017.02.008.

- [288] S. A. Popoola, "Spectroscopic study of 2-methylindole and 3-methylindole: Solvents interactions and DFT studies," *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 189, pp. 578–585, Jan. 2018, doi: 10.1016/J.SAA.2017.08.062.
- [289] G. Karakus, Z. A. Polat, A. S. Yaghioglu, M. Karahan, and A. F. Yenidunya, "Synthesis, characterization, and assessment of cytotoxic, antiproliferative, and antiangiogenic effects of a novel procainamide hydrochloride-poly(maleic anhydride-co-styrene) conjugate," <http://dx.doi.org/10.1080/09205063.2012.750209>, vol. 24, no. 10, pp. 1260–1276, Jul. 2013, doi: 10.1080/09205063.2012.750209.
- [290] Y. Wang *et al.*, "Disulfide bond bridge insertion turns hydrophobic anticancer prodrugs into self-assembled nanomedicines," *Nano Lett*, vol. 14, no. 10, pp. 5577–5583, Oct. 2014, doi: 10.1021/NL502044X.
- [291] B. Palecz, A. Buczkowski, H. Piekarski, and Ö. Kılınçarslan, "Thermodynamic Interaction between PAMAM G4-NH₂, G4-OH, G3.5-COONa Dendrimers and Gemcitabine in Water Solutions," *International Journal of Secondary Metabolite*, vol. 3, no. 1, pp. 21–26, Jul. 2016, doi: 10.21448/IJSM.240699.
- [292] A. Buczkowski, A. Stepniak, P. Urbaniak, and B. Palecz, "Calorimetric and spectroscopic investigations of interactions between cucurbituril Q7 and gemcitabine in aqueous solutions," *J Therm Anal Calorim*, vol. 134, no. 1, pp. 595–607, Oct. 2018, doi: 10.1007/S10973-018-7295-7/FIGURES/14.
- [293] D. Mauri, N. P. Polyzos, G. Salanti, N. Pavlidis, and J. P. A. Ioannidis, "Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer," *J Natl Cancer Inst*, vol. 100, no. 24, pp. 1780–1791, Dec. 2008, doi: 10.1093/JNCI/DJN414.
- [294] B. Pili *et al.*, "Interaction of an anticancer drug, gemcitabine, with phospholipid bilayers," *akjournals.com*, doi: 10.1007/s10973-009-0229-7.
- [295] L. Toschi, G. Finocchiaro, S. Bartolini, V. Gioia, and F. Cappuzzo, "Role of gemcitabine in cancer therapy," *Future Oncology*, vol. 1, no. 1, pp. 7–17, 2005, doi: 10.1517/14796694.1.1.7.
- [296] R. Singh, A. K. Shakya, R. Naik, and N. Shalan, "Stability-indicating HPLC determination of gemcitabine in pharmaceutical formulations," *Int J Anal Chem*, vol. 2015, 2015, doi: 10.1155/2015/862592.
- [297] J. W. G. van Putten, A. Price, A. H. D. van der Leest, A. Gregor, F. A. Little, and H. J. M. Groen, "A Phase I Study of Gemcitabine with Concurrent Radiotherapy in

Stage III, Locally Advanced Non-Small Cell Lung Cancer,” *Clinical Cancer Research*, vol. 9, no. 7, 2003.

- [298] S. Paroha *et al.*, “Recent advances and prospects in gemcitabine drug delivery systems,” *Int J Pharm*, vol. 592, p. 120043, Jan. 2021, doi: 10.1016/J.IJP.2020.120043.
- [299] I. Rus *et al.*, “Gemcitabine Direct Electrochemical Detection from Pharmaceutical Formulations Using a Boron-Doped Diamond Electrode,” *Pharmaceuticals* 2021, Vol. 14, Page 912, vol. 14, no. 9, p. 912, Sep. 2021, doi: 10.3390/PH14090912.
- [300] B. Başeskioglu, B. B. Duman, I. O. Kara, C. Can, M. Yildirim, and M. Açikalin, “Early Detection and Gemcitabine/Cisplatin Combination Positively Effect Survival in Sarcomatoid Carcinoma of the Urinary Bladder,” *Asian Pacific Journal of Cancer Prevention*, vol. 13, no. 11, pp. 5729–5733, 2012, doi: 10.7314/APJCP.2012.13.11.5729.
- [301] Y. Lee, J. Kim, J. Han, H. Jeong, Y. A. Woo, and H. Chung, “Axially slanted laser illumination scheme for direct and accurate Raman spectroscopic determination of gemcitabine concentration in freeze-dried gemcitabine injection powder housed in a glass container,” *Anal Chim Acta*, vol. 1175, p. 338746, Aug. 2021, doi: 10.1016/J.ACA.2021.338746.
- [302] “Sankar: UV spectrophotometric determination of temozolami... - Google Scholar.” Accessed: Dec. 07, 2021. [Online]. Available: https://scholar.google.com/scholar_lookup?title=UV%20spectrophotometric%20determination%20of%20temozolamide%20and%20gemcitabine&author=D.%20G.%20Sankar&author=P.%20V.%20M.%20Latha&author=B.%20A.%20Kumar&author=P.%20J.%20Babu&publication_year=2007
- [303] S. K. Menon, B. R. Mistry, K. v. Joshi, P. G. Sutariya, and R. v. Patel, “Analytical detection and method development of anticancer drug Gemcitabine HCl using gold nanoparticles,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 94, pp. 235–242, Aug. 2012, doi: 10.1016/J.SAA.2012.02.061.
- [304] S. Shahzad, L. Karadurmus, B. Dogan-Topal, T. Taskin-Tok, A. Shah, and S. A. Ozkan, “Sensitive Nucleic Acid Detection at NH₂-MWCNTs Modified Glassy Carbon Electrode and its Application for Monitoring of Gemcitabine-DNA Interaction,” *Electroanalysis*, vol. 32, no. 5, pp. 912–922, May 2020, doi: 10.1002/ELAN.201900597.
- [305] T. E. Bapiro *et al.*, “A novel method for quantification of gemcitabine and its metabolites 2',2'-difluorodeoxyuridine and gemcitabine triphosphate in tumour

- tissue by LC-MS/MS: Comparison with ^{19}F NMR spectroscopy,” *Cancer Chemother Pharmacol*, vol. 68, no. 5, pp. 1243–1253, Nov. 2011, doi: 10.1007/S00280-011-1613-0/TABLES/6.
- [306] R. Losa, M. I. Sierra, M. O. Gi3n, E. Esteban, and J. M. Buesa, “Simultaneous determination of gemcitabine di- and triphosphate in human blood mononuclear and cancer cells by RP-HPLC and UV detection,” *Journal of Chromatography B*, vol. 840, no. 1, pp. 44–49, Aug. 2006, doi: 10.1016/J.JCHROMB.2006.04.036.
- [307] S. Borisagar, H. Patel, C. P.-J.-J. of Planar, and undefined 2012, “A validated stability-indicating HPTLC method for the estimation of gemcitabine HCl in its dosage form,” *akjournals.com*, 2012, doi: 10.1556/JPC.25.2012.1.13.
- [308] K. M. Naik and S. T. Nandibewoor, “Electro-oxidation and determination of gemcitabine hydrochloride, an anticancer drug at gold electrode,” *Journal of Industrial and Engineering Chemistry*, vol. 19, no. 6, pp. 1933–1938, Nov. 2013, doi: 10.1016/J.IJEC.2013.02.040.
- [309] M. Culha, M. Kahraman, ... N. T.-T. J. of, and undefined 2008, “Surface-enhanced Raman scattering on aggregates of silver nanoparticles with definite size,” *ACS Publications*, vol. 112, no. 28, pp. 10338–10343, Jul. 2008, doi: 10.1021/jp711177z.
- [310] N. Mahar, M. Haroon, T. A. Saleh, and A. A. Al-Saadi, “Fast and sensitive detection of Procainamide: Combined SERS and DFT modeling studies,” *J Mol Liq*, vol. 343, 2021, doi: 10.1016/j.molliq.2021.117633.
- [311] A. Al-Saadi, M. Haroon, ... S. P.-S. and A. B., and undefined 2020, “Sensitive SERS detection and characterization of procaine in aqueous media by reduced gold nanoparticles,” *Elsevier*, vol. 304, Feb. 2019, doi: 10.1016/j.snb.2019.127057.
- [312] M. Haroon, I. Abdulazeez, T. Saleh, A. A.-S.-E. Acta, and undefined 2021, “Electrochemically modulated SERS detection of procaine using FTO electrodes modified with silver-decorated carbon nanosphere,” *Elsevier*, vol. 387, p. 138463, 2021, doi: 10.1016/j.electacta.2021.138463.
- [313] I. Ghosh, W. N.-A. drug delivery reviews, and undefined 2012, “The strategic use of supramolecular pKa shifts to enhance the bioavailability of drugs,” *Elsevier*, Accessed: Dec. 07, 2021. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0169409X1200018X?casa_token=e9sOZnWE1HMAAAAA:O9eTOUYACKB5Ean-IJv_oBNrO59SZKBmH0QFIafmU6qxC86n0o_WuOhEpHzLPiKFaaajkAKJpZ0

- [314] L. Reddy, P. C.-C. pharmaceutical design, and undefined 2008, “Novel approaches to deliver gemcitabine to cancers,” *ingentaconnect.com*, Accessed: Dec. 07, 2021. [Online]. Available: <https://www.ingentaconnect.com/content/ben/cpd/2008/00000014/00000011/art00007>
- [315] J. Helmlinger *et al.*, “Silver nanoparticles with different size and shape: equal cytotoxicity, but different antibacterial effects,” *RSC Adv*, vol. 6, no. 22, pp. 18490–18501, Feb. 2016, doi: 10.1039/C5RA27836H.
- [316] V. Devaraj, J. M. Lee, and J. W. Oh, “Distinguishable Plasmonic Nanoparticle and Gap Mode Properties in a Silver Nanoparticle on a Gold Film System Using Three-Dimensional FDTD Simulations,” *Nanomaterials 2018, Vol. 8, Page 582*, vol. 8, no. 8, p. 582, Jul. 2018, doi: 10.3390/NANO8080582.
- [317] N. Mahar, M. Haroon, T. A. Saleh, and A. A. Al-Saadi, “Fast and sensitive detection of Procainamide: Combined SERS and DFT modeling studies,” *J Mol Liq*, vol. 343, p. 117633, Dec. 2021, doi: 10.1016/J.MOLLIQ.2021.117633.
- [318] M. Guidon, J. Hutter, and J. VandeVondele, “Robust Periodic Hartree–Fock Exchange for Large-Scale Simulations Using Gaussian Basis Sets,” *J Chem Theory Comput*, vol. 5, no. 11, pp. 3010–3021, Nov. 2009, doi: 10.1021/CT900494G.
- [319] “Lee, C., Yang, W. and Parr, R.G. (1988) Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. Physical Review B, 37, 785-789. - References - Scientific Research Publishing.” Accessed: Sep. 19, 2021. [Online]. Available: [https://www.scirp.org/\(S\(351jmbntvnsjt1aadkposzje\)\)/reference/ReferencesPapers.aspx?ReferenceID=1974378](https://www.scirp.org/(S(351jmbntvnsjt1aadkposzje))/reference/ReferencesPapers.aspx?ReferenceID=1974378)
- [320] P. M. W. Gill, B. G. Johnson, J. A. Pople, and M. J. Frisch, “The performance of the Becke—Lee—Yang—Parr (B—LYP) density functional theory with various basis sets,” *Chem Phys Lett*, vol. 197, no. 4–5, pp. 499–505, Sep. 1992, doi: 10.1016/0009-2614(92)85807-M.
- [321] O. Lukin and J. Leszczynski, “Rationalizing the strength of hydrogen-bonded complexes. Ab initio HF and DFT studies,” *Journal of Physical Chemistry A*, vol. 106, no. 29, pp. 6775–6782, Jul. 2002, doi: 10.1021/JP0145154/SUPPL_FILE/JP0145154_S.PDF.
- [322] K. S. Lee and M. A. El-Sayed, “Gold and Silver Nanoparticles in Sensing and Imaging: Sensitivity of Plasmon Response to Size, Shape, and Metal

- Composition,” *Journal of Physical Chemistry B*, vol. 110, no. 39, pp. 19220–19225, Oct. 2006, doi: 10.1021/JP062536Y.
- [323] S. Kaushal, S. S. Nanda, D. K. Yi, and H. Ju, “Effects of Aspect Ratio Heterogeneity of an Assembly of Gold Nanorod on Localized Surface Plasmon Resonance,” *Journal of Physical Chemistry Letters*, vol. 11, no. 15, pp. 5972–5979, Aug. 2020, doi: 10.1021/ACS.JPCLETT.0C01507/SUPPL_FILE/JZ0C01507_SI_001.PDF.
- [324] A. F. Chrimes *et al.*, “Active control of silver nanoparticles spacing using dielectrophoresis for surface-enhanced Raman scattering,” *Anal Chem*, vol. 84, no. 9, pp. 4029–4035, May 2012, doi: 10.1021/AC203381N/SUPPL_FILE/AC203381N_SI_001.PDF.
- [325] K. B. Freeman *et al.*, “Validated assays for the determination of gemcitabine in human plasma and urine using high-performance liquid chromatography with ultraviolet detection,” *J Chromatogr B Biomed Sci Appl*, vol. 665, no. 1, pp. 171–181, Mar. 1995, doi: 10.1016/0378-4347(94)00521-6.
- [326] C. Bowen, S. Wang, and H. Licea-Perez, “Development of a sensitive and selective LC–MS/MS method for simultaneous determination of gemcitabine and 2,2-difluoro-2-deoxyuridine in human plasma,” *Journal of Chromatography B*, vol. 877, no. 22, pp. 2123–2129, Jul. 2009, doi: 10.1016/J.JCHROMB.2009.06.002.
- [327] A. Yamaji, K. Kataoka, M. Oishi, N. Kanamori, E. Hiraoka, and M. Mishima, “Simultaneous determination of procainamide and N-acetylprocainamide in serum by gas chromatography with nitrogen-selective detection,” *J Chromatogr B Biomed Sci Appl*, vol. 415, no. C, pp. 143–147, Jan. 1987, doi: 10.1016/S0378-4347(00)83202-8.
- [328] K. Brown and L. Dennany, “Assessment of [Ru(bpy)₂]³⁺ and [Os(diars)₂(bthp)]²⁺ for the Electrochemiluminescence Detection of Gemcitabine and Leucovorin toward Diagnostic Point-of-Care Sensors within Precision Medicine,” *Sensors and Actuators Reports*, p. 100065, Dec. 2021, doi: 10.1016/J.SNR.2021.100065.
- [329] M. Haroon, I. Abdulazeez, T. A. Saleh, and A. A. Al-Saadi, “Electrochemically modulated SERS detection of procaine using FTO electrodes modified with silver-decorated carbon nanosphere,” *Electrochim Acta*, vol. 387, p. 138463, Aug. 2021, doi: 10.1016/j.electacta.2021.138463.

- [330] A. Onawole, S. Popoola, ... T. S.-S. A. P., and undefined 2018, "Silver-loaded graphene as an effective SERS substrate for clotrimazole detection: DFT and spectroscopic studies," *Elsevier*, Accessed: Sep. 19, 2021. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S1386142518304086?casa_token=3OsOrKIYFEgAAAAA:nW8ibkOxDF96ciiQI_7p3hTv1cGKdNwMLKq-YlpQRfipROX3V-w6CznBAL7aRqgBfO3qdXFHlk
- [331] K. G. Stamplecoskie, J. C. Scaiano, V. S. Tiwari, and H. Anis, "Optimal size of silver nanoparticles for surface-enhanced raman spectroscopy," *Journal of Physical Chemistry C*, vol. 115, no. 5, pp. 1403–1409, Feb. 2011, doi: 10.1021/JP106666T.
- [332] A. D. Becke, "Density-functional exchange-energy approximation with correct asymptotic behavior," *Phys Rev A (Coll Park)*, vol. 38, no. 6, pp. 3098–3100, Sep. 1988, doi: 10.1103/PhysRevA.38.3098.
- [333] A. D. Becke, "A new mixing of Hartree–Fock and local density-functional theories," *J Chem Phys*, vol. 98, no. 2, pp. 1372–1377, Jan. 1993, doi: 10.1063/1.464304.
- [334] M. Futamata, Y. Yu, and T. Yajima, "Elucidation of electrostatic interaction between cationic dyes and ag nanoparticles generating enormous SERS enhancement in aqueous solution," *Journal of Physical Chemistry C*, vol. 115, no. 13, pp. 5271–5279, Apr. 2011, doi: 10.1021/JP110146Y/SUPPL_FILE/JP110146Y_SI_001.PDF.
- [335] D. J. Trivedi, B. Barrow, and G. C. Schatz, "Understanding the chemical contribution to the enhancement mechanism in SERS: Connection with Hammett parameters," *J Chem Phys*, vol. 153, no. 12, p. 124706, Sep. 2020, doi: 10.1063/5.0023359.
- [336] G. C. Schatz, M. A. Young, and R. P. van Duyne, "Electromagnetic Mechanism of SERS," *Surface-Enhanced Raman Scattering*, pp. 19–45, Sep. 2006, doi: 10.1007/3-540-33567-6_2.
- [337] I. J. Hidi, M. Jahn, M. W. Pletz, K. Weber, D. Cialla-May, and J. Popp, "Toward Levofloxacin Monitoring in Human Urine Samples by Employing the LoC-SERS Technique," *Journal of Physical Chemistry C*, vol. 120, no. 37, pp. 20613–20623, 2016, doi: 10.1021/acs.jpcc.6b01005.
- [338] I. J. Hidi, M. Jahn, M. W. Pletz, K. Weber, D. Cialla-May, and J. Popp, "Toward Levofloxacin Monitoring in Human Urine Samples by Employing the LoC-SERS

- Technique,” *Journal of Physical Chemistry C*, vol. 120, no. 37, pp. 20613–20623, Sep. 2016, doi: 10.1021/ACS.JPCC.6B01005.
- [339] N. Srinivas, K. Maffuid, and A. D. M. Kashuba, “Clinical Pharmacokinetics and Pharmacodynamics of Drugs in the Central Nervous System,” *Clin Pharmacokinet*, vol. 57, no. 9, pp. 1059–1074, Sep. 2018, doi: 10.1007/S40262-018-0632-Y.
- [340] C. C. Shih *et al.*, “Procainamide inhibits DNA methylation and alleviates multiple organ dysfunction in rats with endotoxic shock,” *PLoS One*, vol. 11, no. 9, Sep. 2016, doi: 10.1371/JOURNAL.PONE.0163690.
- [341] C. Fenoglio, E. Boncompagni, ... B. C.-A., and undefined 2005, “Morphological and histochemical evidence of the protective effect of procainamide hydrochloride on tissue damage induced by repeated administration of low doses,” *ar.iijournals.org* C Fenoglio, E Boncompagni, B Chiavarina, S Cafaggi, M Cilli, M Viale *Anticancer research*, 2005 • *ar.iijournals.org*, Accessed: May 04, 2024. [Online]. Available: <https://ar.iijournals.org/content/25/6B/4123.short>
- [342] Z. Ur Rehman, F. Yang, M. Wang, and T. Zhu, “Fundamentals and Advances in Laser-Induced Transfer,” *Opt Laser Technol*, vol. 160, p. 109065, May 2023, doi: 10.1016/J.OPTLASTEC.2022.109065.
- [343] V. Scardaci, M. Pulvirenti, M. Condorelli, and G. Compagnini, “Monochromatic light driven synthesis and growth of flat silver nanoparticles and their plasmon sensitivity,” *J Mater Chem C Mater*, vol. 8, no. 28, pp. 9734–9741, Jul. 2020, doi: 10.1039/D0TC00367K.
- [344] K. G. Stamplecoskie and J. C. Scaiano, “Light emitting diode irradiation can control the morphology and optical properties of silver nanoparticles,” *J Am Chem Soc*, vol. 132, no. 6, pp. 1825–1827, 2010, doi: 10.1021/JA910010B/SUPPL_FILE/JA910010B_SI_001.PDF.
- [345] L. Yang, D. Zhang, M. Wang, and Y. Yang, “Effects of solvent polarity on the novel excited-state intramolecular thiol proton transfer and photophysical property compared with the oxygen proton transfer,” *Spectrochim Acta A Mol Biomol Spectrosc*, vol. 293, p. 122475, May 2023, doi: 10.1016/J.SAA.2023.122475.
- [346] H. Wei *et al.*, “Improved Quantitative SERS Enabled by Surface Plasmon Enhanced Elastic Light Scattering,” *Anal Chem*, vol. 90, no. 5, pp. 3227–3237, Mar. 2018, doi: 10.1021/ACS.ANALCHEM.7B04667/ASSET/IMAGES/LARGE/AC-2017-04667V_0005.JPEG.

- [347] J. E. Ortiz-Castillo, R. C. Gallo-Villanueva, M. J. Madou, and V. H. Perez-Gonzalez, “Anisotropic gold nanoparticles: A survey of recent synthetic methodologies,” *Coord Chem Rev*, vol. 425, p. 213489, Dec. 2020, doi: 10.1016/J.CCR.2020.213489.
- [348] F. Tian, F. Bonnier, A. Casey, ... A. S.-A., and undefined 2014, “Surface enhanced Raman scattering with gold nanoparticles: effect of particle shape,” *pubs.rsc.org*, 2013, doi: 10.1039/x0xx00000x.
- [349] I. Pastoriza-Santos, X. Yan, H. Shi, P. Jia, and X. Sun, “LSPR Tunable Ag@PDMS SERS Substrate for High Sensitivity and Uniformity Detection of Dye Molecules,” *Nanomaterials 2022, Vol. 12, Page 3894*, vol. 12, no. 21, p. 3894, Nov. 2022, doi: 10.3390/NANO12213894.
- [350] M. G. Blaber, A. I. Henry, J. M. Bingham, G. C. Schatz, and R. P. Van Duyne, “LSPR imaging of silver triangular nanoprisms: Correlating scattering with structure using electrodynamics for plasmon lifetime analysis,” *Journal of Physical Chemistry C*, vol. 116, no. 1, pp. 393–403, Jan. 2012, doi: 10.1021/JP209466K/SUPPL_FILE/JP209466K_SI_002.PDF.
- [351] J. Hu, Z. Wang, J. L.- Sensors, and undefined 2007, “Gold nanoparticles with special shapes: controlled synthesis, surface-enhanced Raman scattering, and the application in biodetection,” *mdpi.com*, Accessed: Nov. 27, 2022. [Online]. Available: <https://www.mdpi.com/1424-8220/7/12/3299>
- [352] H. Yockell-Lelièvre, F. Lussier, and J. F. Masson, “Influence of the Particle Shape and Density of Self-Assembled Gold Nanoparticle Sensors on LSPR and SERS,” *Journal of Physical Chemistry C*, vol. 119, no. 51, pp. 28577–28585, Dec. 2015, doi: 10.1021/ACS.JPCC.5B09570/SUPPL_FILE/JP5B09570_SI_001.PDF.
- [353] K. Chaudhari *et al.*, “Appearance of SERS activity in single silver nanoparticles by laser-induced reshaping,” *Nanoscale*, vol. 11, no. 1, pp. 321–330, Dec. 2018, doi: 10.1039/C8NR06497K.
- [354] Y. Li, Z. Hao, H. Cao, S. Wei, T. Jiao, and M. Wang, “Study on annealed graphene oxide nano-sheets for improving the surface enhanced fluorescence of silver nanoparticles,” *Opt Laser Technol*, vol. 160, p. 109054, May 2023, doi: 10.1016/J.OPTLASTEC.2022.109054.
- [355] M. Knaapila, U. Vainio, S. E. Canton, and G. Karlsson, “Structural Study of the Photo-Mediated Growth of Silver Nanoprisms,” *Molecules*, vol. 25, no. 22, Nov. 2020, doi: 10.3390/MOLECULES25225413.

- [356] X. Xu *et al.*, “Synthesis of triangular silver nanoprisms and studies on the interactions with human serum albumin,” *J Mol Liq*, vol. 220, pp. 14–20, Aug. 2016, doi: 10.1016/J.MOLLIQ.2016.02.103.
- [357] K. M. Kessler *et al.*, “Simultaneous quantitation of quinidine, procainamide, and N-acetylprocainamide in serum by gas-liquid chromatography with a nitrogen-phosphorus selective detector.,” *Clin Chem*, vol. 28, no. 5, pp. 1187–1190, May 1982, doi: 10.1093/CLINCHEM/28.5.1187.
- [358] L. Mikac, M. Ivanda, M. Gotić, T. Mihelj, and L. Horvat, “Synthesis and characterization of silver colloidal nanoparticles with different coatings for SERS application,” *Journal of Nanoparticle Research* 2014 16:12, vol. 16, no. 12, pp. 1–13, Dec. 2014, doi: 10.1007/S11051-014-2748-9.
- [359] A. Balla, K. H. Cho, Y. C. Kim, and H. J. Maeng, “Simultaneous Determination of Procainamide and N-acetylprocainamide in Rat Plasma by Ultra-High-Pressure Liquid Chromatography Coupled with a Diode Array Detector and Its Application to a Pharmacokinetic Study in Rats,” *Pharmaceutics* 2018, Vol. 10, Page 41, vol. 10, no. 2, p. 41, Mar. 2018, doi: 10.3390/PHARMACEUTICS10020041.
- [360] A. J. Frank, N. Cathcart, K. E. Maly, and V. Kitaev, “Synthesis of Silver Nanoprisms with Variable Size and Investigation of Their Optical Properties: A First-Year Undergraduate Experiment Exploring Plasmonic Nanoparticles,” *J Chem Educ*, vol. 87, no. 10, pp. 1098–1101, Oct. 2010, doi: 10.1021/ED100166G.
- [361] K. Wang, D. W. Sun, H. Pu, and Q. Wei, “Shell thickness-dependent Au@Ag nanoparticles aggregates for high-performance SERS applications,” *Talanta*, vol. 195, pp. 506–515, Apr. 2019, doi: 10.1016/J.TALANTA.2018.11.057.
- [362] B. N. Khlebtsov, D. N. Bratashov, and N. G. Khlebtsov, “Tip-Functionalized Au@Ag Nanorods as Ultrabright Surface-Enhanced Raman Scattering Probes for Bioimaging in Off-Resonance Mode,” *Journal of Physical Chemistry C*, vol. 122, no. 31, pp. 17983–17993, Aug. 2018, doi: 10.1021/ACS.JPCC.8B04772/SUPPL_FILE/JP8B04772_SI_001.PDF.
- [363] P. Dey, V. Baumann, and J. Rodríguez-Fernández, “Gold Nanorod Assemblies: The Roles of Hot-Spot Positioning and Anisotropy in Plasmon Coupling and SERS,” *Nanomaterials* 2020, Vol. 10, Page 942, vol. 10, no. 5, p. 942, May 2020, doi: 10.3390/NANO10050942.
- [364] S. Y. Ding, E. M. You, Z. Q. Tian, and M. Moskovits, “Electromagnetic theories of surface-enhanced Raman spectroscopy,” *Chem Soc Rev*, vol. 46, no. 13, pp. 4042–4076, Jul. 2017, doi: 10.1039/C7CS00238F.

- [365] S. Y. Ding, E. M. You, Z. Q. Tian, and M. Moskovits, "Electromagnetic theories of surface-enhanced Raman spectroscopy," *Chem Soc Rev*, vol. 46, no. 13, pp. 4042–4076, Jul. 2017, doi: 10.1039/C7CS00238F.
- [366] B. Wesley-Hadzija and A. M. Mattocks, "Quantitative thin-layer chromatographic method for the determination of procainamide and its major metabolite in plasma," *J Chromatogr B Biomed Sci Appl*, vol. 143, no. 3, pp. 307–313, May 1977, doi: 10.1016/S0378-4347(00)81811-3.
- [367] B. Kark, N. Sistovaris, and A. Keller, "Thin-layer chromatographic determination of procainamide and N-acetylprocainamide in human serum and urine at single-dose levels," *J Chromatogr B Biomed Sci Appl*, vol. 277, no. C, pp. 261–272, Jan. 1983, doi: 10.1016/S0378-4347(00)84843-4.
- [368] F. Stearns *et al.*, "Determination of procainamide and N-acetylprocainamide by 'high-performance' liquid chromatography Ix1 Determination of Procainamide and N-Acetylprocainamide by 'High-Performance' Liquid Chromatography," *CLIN. CHEM.* 27, vol. 27, no. 12, pp. 2064–2067, 1981, doi: 10.1093/clinchem/27.12.2064.
- [369] J. D. Coyle, J. J. Macichan, H. Boudoulas, and J. J. Lima, "Reversed-Phase Liquid Chromatography Method for Measurement of Procainamide and Three Metabolites in Serum and Urine: Percent of Dose Excreted as Deethyl Metabolites," *J Pharm Sci*, vol. 76, no. 5, pp. 402–405, May 1987, doi: 10.1002/JPS.2600760513.
- [370] K. M. Kessler *et al.*, "Simultaneous quantitation of quinidine, procainamide, and N-acetylprocainamide in serum by gas-liquid chromatography with a nitrogen-phosphorus selective detector.," *Clin Chem*, vol. 28, no. 5, pp. 1187–1190, May 1982, doi: 10.1093/CLINCHEM/28.5.1187.
- [371] M. Stavytska-Barba, M. Salvador, A. Kulkarni, D. S. Ginger, and A. M. Kelley, "Plasmonic enhancement of Raman scattering from the organic solar cell material P3HT/PCBM by triangular silver nanoprisms," *Journal of Physical Chemistry C*, vol. 115, no. 42, pp. 20788–20794, Oct. 2011, doi: 10.1021/JP206853U/SUPPL_FILE/JP206853U_SI_002.TXT.
- [372] A. G. Butterfield, J. K. Cooper, and K. K. Midha, "Simultaneous determination of procainamide and N-acetylprocainamide in plasma by high-performance liquid chromatography," *J Pharm Sci*, vol. 67, no. 6, pp. 839–842, Jun. 1978, doi: 10.1002/JPS.2600670630.
- [373] N. Mahar and A. A. Al-Saadi, "SERS-Based Ultralow Concentration Detection of Anticancer Gemcitabine Using Size-Controlled Silver Nanoparticles," *Arabian*

- Journal for Science and Engineering* 2022 47:6, vol. 47, no. 6, pp. 7197–7205, May 2022, doi: 10.1007/S13369-022-06799-1.
- [374] S. M. Novikov *et al.*, “Highly stable silver nanoparticles for SERS applications,” *J Phys Conf Ser*, vol. 1092, no. 1, p. 012098, Sep. 2018, doi: 10.1088/1742-6596/1092/1/012098.
- [375] A. Shiohara, Y. Wang, and L. M. Liz-Marzán, “Recent Approaches toward Creation of Hot Spots for SERS Detection*,” *Colloidal Synthesis of Plasmonic Nanometals*, pp. 563–622, Apr. 2020, doi: 10.1201/9780429295188-18.
- [376] J. Reguera, J. Langer, D. J. de Aberasturi, and L. M. Liz-Marzán, “Anisotropic Metal Nanoparticles for Surface-Enhanced Raman Scattering*,” *Colloidal Synthesis of Plasmonic Nanometals*, pp. 713–754, Apr. 2020, doi: 10.1201/9780429295188-24.
- [377] B. Tan, T. Lu, W. Luo, Z. Chao, R. Dong, and J. Fan, “A Novel MoS₂-MXene Composite Cathode for Aluminum-Ion Batteries,” *Energy and Fuels*, vol. 35, no. 15, pp. 12666–12670, Aug. 2021, doi: 10.1021/ACS.ENERGYFUELS.1C01461/ASSET/IMAGES/MEDIUM/EF1C01461_0010.GIF.
- [378] J. Li *et al.*, “Nb₂CT_xMXene Cathode for High-Capacity Rechargeable Aluminum Batteries with Prolonged Cycle Lifetime,” *ACS Appl Mater Interfaces*, vol. 14, no. 40, pp. 45254–45262, Oct. 2022, doi: 10.1021/ACSAMI.2C09765/SUPPL_FILE/AM2C09765_SI_001.PDF.
- [379] J. Li *et al.*, “Nb₂CT_xMXene Cathode for High-Capacity Rechargeable Aluminum Batteries with Prolonged Cycle Lifetime,” *ACS Appl Mater Interfaces*, vol. 14, no. 40, pp. 45254–45262, Oct. 2022, doi: 10.1021/ACSAMI.2C09765/SUPPL_FILE/AM2C09765_SI_001.PDF.
- [380] Z. Li, X. X. Wang, W. Zhang, and S. Yang, “Two-dimensional Ti₃C₂@CTAB-Se (MXene) composite cathode material for high-performance rechargeable aluminum batteries,” *Chemical Engineering Journal*, vol. 398, p. 125679, Oct. 2020, doi: 10.1016/J.CEJ.2020.125679.
- [381] W. Lv, G. Wu, X. Li, J. Li, and Z. Li, “Two-dimensional V₂C@Se (MXene) composite cathode material for high-performance rechargeable aluminum batteries,” *Energy Storage Mater*, vol. 46, pp. 138–146, Apr. 2022, doi: 10.1016/J.ENSMS.2022.01.019.
- [382] A. Vahidmohammadi, A. Hadjikhani, S. Shahbazmohamadi, and M. Beidaghi, “Two-Dimensional Vanadium Carbide (MXene) as a High-Capacity Cathode

- Material for Rechargeable Aluminum Batteries,” *ACS Nano*, vol. 11, no. 11, pp. 11135–11144, Nov. 2017, doi: 10.1021/ACSNANO.7B05350/SUPPL_FILE/NN7B05350_SI_002.MPG.
- [383] N. Mahar, A. Al-Ahmed, and A. A. Al-Saadi, “Synthesis of vanadium carbide MXene with improved inter-layer spacing for SERS-based quantification of anti-cancer drugs,” *Appl Surf Sci*, vol. 607, p. 155034, Jan. 2023, doi: 10.1016/J.APSUSC.2022.155034.
- [384] B. Miao *et al.*, “Scalable synthesis of 2D Ti₂CT_x MXene and molybdenum disulfide composites with excellent microwave absorbing performance,” 2023, doi: 10.21203/rs.3.rs-2523981/v1.
- [385] B. Tan, T. Lu, W. Luo, Z. Chao, R. Dong, and J. Fan, “A Novel MoS₂-MXene Composite Cathode for Aluminum-Ion Batteries,” *Energy and Fuels*, vol. 35, no. 15, pp. 12666–12670, Aug. 2021, doi: 10.1021/ACS.ENERGYFUELS.1C01461/ASSET/IMAGES/MEDIUM/EF1C01461_0010.GIF.
- [386] M. Ikram, A. Raza, and S. Ali, “2D-Materials for Energy Harvesting and Storage Applications,” 2022, doi: 10.1007/978-3-030-96021-6.
- [387] Z. Yu, J. Tu, C. Wang, and S. Jiao, “A Rechargeable Al/Graphite Battery Based on AlCl₃/1-butyl-3-methylimidazolium Chloride Ionic Liquid Electrolyte,” *ChemistrySelect*, vol. 4, no. 11, pp. 3018–3024, Mar. 2019, doi: 10.1002/SLCT.201900374.
- [388] H. Wang *et al.*, “Anion-effects on electrochemical properties of ionic liquid electrolytes for rechargeable aluminum batteries,” *J Mater Chem A Mater*, vol. 3, no. 45, pp. 22677–22686, Nov. 2015, doi: 10.1039/C5TA06187C.
- [389] M. K. Nahian and R. G. Reddy, “Electrical conductivity and species distribution of aluminum chloride and 1-butyl-3-methylimidazolium chloride ionic liquid electrolytes,” *J Phys Org Chem*, p. e4549, Jun. 2023, doi: 10.1002/POC.4549.
- [390] Y. Zheng, K. Dong, Q. Wang, J. Zhang, and X. Lu, “Density, viscosity, and conductivity of lewis acidic 1-butyl- and 1-hydrogen-3-methylimidazolium chloroaluminate ionic liquids,” *J Chem Eng Data*, vol. 58, no. 1, pp. 32–42, Jan. 2013, doi: 10.1021/JE3004904.
- [391] C. Chen, M. Shi, Y. Zhao, C. Yang, L. Zhao, and C. Yan, “Al-Intercalated MnO₂ cathode with reversible phase transition for aqueous Zn-Ion batteries,” *Chemical Engineering Journal*, vol. 422, p. 130375, Oct. 2021, doi: 10.1016/J.CEJ.2021.130375.

- [392] C. Chen *et al.*, “MoS₂-on-MXene Heterostructures as Highly Reversible Anode Materials for Lithium-Ion Batteries,” *Angewandte Chemie - International Edition*, vol. 57, no. 7, pp. 1846–1850, Feb. 2018, doi: 10.1002/ANIE.201710616.
- [393] Z. Li, B. Niu, J. Liu, J. Li, and F. Kang, “Rechargeable Aluminum-Ion Battery Based on MoS₂ Microsphere Cathode,” *ACS Appl Mater Interfaces*, vol. 10, no. 11, pp. 9451–9459, Mar. 2018, doi: 10.1021/ACSAMI.8B00100/SUPPL_FILE/AM8B00100_SI_001.PDF.
- [394] X. Shen *et al.*, “Ultra-fast charging in aluminum-ion batteries: electric double layers on active anode,” *Nature Communications* 2021 12:1, vol. 12, no. 1, pp. 1–12, Feb. 2021, doi: 10.1038/s41467-021-21108-4.
- [395] D. Pradhan and R. G. Reddy, “Mechanistic study of Al electrodeposition from EMIC–AlCl₃ and BMIC–AlCl₃ electrolytes at low temperature,” *Mater Chem Phys*, vol. 143, no. 2, pp. 564–569, Jan. 2014, doi: 10.1016/J.MATCHEMPHYS.2013.09.033.
- [396] V. A. Elterman, P. Y. Shevelin, L. A. Yolshina, and A. V. Borozdin, “Features of aluminum electrodeposition from 1,3-dialkylimidazolium chloride chloroaluminate ionic liquids,” *J Mol Liq*, vol. 351, p. 118693, Apr. 2022, doi: 10.1016/J.MOLLIQ.2022.118693.
- [397] X. Shen, T. Sun, Z. Wu, L. T.-J. of M. C. A, and undefined 2022, “Ultrafast charging and ultralong cycle life in solid-state Al-ion batteries,” *pubs.rsc.org*, 2022, doi: 10.1039/D2TA00630H.

Vitae

Name :NASURULLAH MAHAR

Nationality :PAKISTANI

Date of Birth :10/28/1986

Email :nasrullah.mahar@usindh.edu.pk/nasar.chem@gmail.com

Address :University of Sindh, Jamshoro 76080 Pakistan

Academic Background :M. Phil. (Chemistry) University of Sindh, Pakistan

Conferences:

- RamanFest 9th International conference in Paris (France), September 2022
- Recent Appointees in Material Science (RAMS-2022 by RSC) Bradford University (United Kingdom), August 2022.
- Daltons 2023 (RSC) Warwick University, United Kingdom
- “Deep Technology.” And “Deep Tech Startup”. Workshop at KFUPM. 2020
- Chemical Engineering Seminar "Predicting fuel properties; A functional group approach" By Dr. Abdul Gani Abdul Jameel 01 Nov 2021
- Materials Science and Engineering Department Forum 16 Feb 2022 KFUPM.
- "Research Skills" Workshop by Dr. Abdulrahman Al-Betar 8th Feb 2021 College of Chemicals and Materials (KFUPM) Virtual Symposium 23 Feb 2022.

- Advanced Materials and Technology Mehran University of Engineering and Technology 2018.
- Attended Virtual Conference on Chemistry and its Applications (VCCA-2022).
- Attended technical meetings at Saudi Arabian International Chemical Sciences Chapter- American Chemical Society ((SAICSC-ACS)

Patent:

- ❖ **N Mahar**, A Al-Ahmed, AA Al-saadi - US Patent App. 18/164,163, 2024:
Surface-enhanced raman spectroscopic method of detecting an anti-cancer drug in a solution:
- ❖ **Nasurullah Mahar**, Abdulaziz A. Al-Saadi*. Nanoplates of gold-decorated copper oxide with enhanced plasmon sers performance for the detection of anti-cancer drug hydroxycarbamide. (Submitted, KFUPM Ref # 2022-153)

Memberships:

- Community Associate of the American Chemical Society (ACS),
- International Younger Chemists Network- International Union of Pure and Applied Chemistry (IYCN-IUPAC)
- Saudi Arabian International Chemical Sciences Chapter- American Chemical Society ((SAICSC-ACS)
- Royal Society of Chemicals (RSC)

Current Position: Assistant Professor (University of Sindh, Pakistan)

Publications

1. **Nasurullah Mahar**, Amir Al-Ahmed, Abdulaziz A. Al-Saadi, Synthesis of vanadium carbide MXene with improved inter-layer spacing for SERS-based quantification of anti-cancer drugs, *Applied Surface Science*, Volume 607, 2023, 155034, ISSN 0169-4332, <https://doi.org/10.1016/j.apsusc.2022.155034>
2. **Nasurullah Mahar**, Abdulaziz A. Al-Saadi, Light-induced synthesis of silver nanoprisms as a surface-enhanced Raman scattering substrate for N-acetyl procainamide drug quantification, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, Volume 302, 2023, 122996, ISSN 1386-1425, <https://doi.org/10.1016/j.saa.2023.122996>.
3. **Nasurullah Mahar**, Amir Al-Ahmed, Abdulaziz A. Al-Saadi, Synthesis of vanadium carbide MXene with improved inter-layer spacing for SERS-based quantification of anti-cancer drugs, *Applied Surface Science*, Volume 607, 2023, 155034, ISSN 0169-4332, <https://doi.org/10.1016/j.apsusc.2022.155034>.
4. **Nasurullah Mahar**, Muhammad Haroon, Tawfik A. Saleh, Abdulaziz A. Al-Saadi, Spectroanalytical SERS-based detection of trace-level procainamide using green-synthesized gold nanoparticles, *Surfaces and Interfaces*, Volume 31, 2022, 102059, ISSN 2468-0230, <https://doi.org/10.1016/j.surfin.2022.102059>.
5. **Mahar, N.**, Al-Saadi, A.A. SERS-Based Ultralow Concentration Detection of Anticancer Gemcitabine Using Size-Controlled Silver Nanoparticles. *Arab J Sci Eng* **47**, 7197–7205 (2022). <https://doi.org/10.1007/s13369-022-06799-1>

6. **Nasurullah Mahar**, Muhammad Haroon, Tawfik A. Saleh, Abdulaziz A. Al-Saadi, Fast and sensitive detection of Procainamide: Combined SERS and DFT modeling studies, Journal of Molecular Liquids, Volume 343, 2021, 117633, ISSN 0167-7322, <https://doi.org/10.1016/j.molliq.2021.117633>.
7. **Nasurullah Mahar**, Tawfik Abdo Saleh Awadh, Amir Al Ahmed, Abdulaziz Al Saadi: High-Capacity, low cost, Aluminum ion Battery using Nb₂CTx-MoS₂ as cathode (Dissertation Work) Energy Material EM-2024-111.

Other Publication

1. **Nasurullah Mahar**, V. Vetrivelan, S. Muthu, Saleem Javed, Abdulaziz A. Al-Saadi, Surface enhanced Raman spectra (SERS) and computational study of gemcitabine drug adsorption on to Au/Ag clusters with different complexes: Adsorption behavior and solvent effect (IEFPCM) – Anticancer agent, Computational and Theoretical Chemistry, Volume 1217, 2022, 113914, ISSN 2210-271X, <https://doi.org/10.1016/j.comptc.2022.113914>.
2. Tahir Naveed Jahangir, Tarek A. Kandiel, **Nasurullah Mahar**, Abdul Zeeshan Khan, Abdulaziz A. Al-Saadi, Exploring the role of Ti₃C₂TxMXene in photoelectrochemical water splitting over solution-processed BiVO₄ photoanode, Materials Today Energy, Volume 40, 2024, 101469, ISSN 2468-6069, <https://doi.org/10.1016/j.mtener.2023.101469>.
3. Abdul Ghaffar Chandio, Abdul Wahab Memon, Noor Ahmed Nahyoon, Sanam Irum Memon, Ayaz Ali Memon, **Nasurullah Mahar**, Mehrunnisa Khilji, Ali Hyder,

- Mohsin Kazi, Khalid Hussain Thebo. Synthesis of visible-light-driven heterojunction graphitic carbon nitride (g-C₃N₄/Feo/TiP) material: An efficient photocatalytic agent for degradation of rhodamine 6G from wastewater, *Diamond and Related Materials*, Volume 148, 2024, 111398,, <https://doi.org/10.1016/j.diamond.2024.111398>.
4. Jamil A. Buledi, **Nasrullah Mahar**, Arfana Mallah, Amber R. Solangi, Ismail M. Palabiyik, Nadeem Qambrani, Fatemeh Karimi, Yasser Vasseghian, Hassan Karimi-Maleh, Electrochemical quantification of mancozeb through tungsten oxide/reduced graphene oxide nanocomposite: A potential method for environmental remediation, *Food and Chemical Toxicology*, Volume 161, 2022, 112843, ISSN 0278-6915, <https://doi.org/10.1016/j.fct.2022.112843>.
 5. Muhammad Ali Ehsan, Abuzar Khan, Amir Al-Ahmed, Abbas Saeed Hakeem, Mohammad Afzaal, Sadanand Pandey, **Nasurullah Mahar**, Aerosol-assisted chemical vapour deposited vanadium oxide thin films on nickel foam with auspicious electrochemical water oxidation properties, *International Journal of Hydrogen Energy*, Volume 52, Part C, 2024, Pages 718-727, ISSN 0360-3199, <https://doi.org/10.1016/j.ijhydene.2023.05.364>.
 6. Olalekan, O.N., Hassan, S.F., Al-Ahmed, A. **N.Mahar** *et al.* Nb₂CT_x MXene reinforcement stimulated microstructure and mechanical properties of magnesium. *Sci Rep* **13**, 14289 (2023). <https://doi.org/10.1038/s41598-023-41067-8>

7. Jamil A. Buledi, Amber R. Solangi, Ali Hyder, Nadir H. Khand, Saba A. Memon, Arfana Mallah, **Nasrullah Mahar**, Elena Niculina Dragoi, Pau Show, Marzyeh Behzadpour, Hassan Karimi-Maleh, Selective oxidation of amaranth dye in soft drinks through tin oxide decorated reduced graphene oxide nanocomposite based electrochemical sensor, Food and Chemical Toxicology, Volume 165, 2022, 113177, ISSN 0278-6915, <https://doi.org/10.1016/j.fct.2022.113177>.

8. J. Jamil A. Buledi, Amber R. Solangi, Ali Hyder, Madeeha Batool, **Nasrullah Mahar**, Arfana Mallah, Hassan Karimi-Maleh, Onur Karaman, Ceren Karaman, Masoumeh Ghalkhani, Fabrication of sensor based on polyvinyl alcohol functionalized tungsten oxide/reduced graphene oxide nanocomposite for electrochemical monitoring of 4-aminophenol, Environmental Research, Volume 212, Part C, 2022, 113372, ISSN 0013-9351, <https://doi.org/10.1016/j.envres.2022.113372>.

9. Inamullah Mahar, Faraz Khan Mahar, **Nasrullah Mahar**, Ayaz Ali Memon, Azhar Ali Ayaz Pirzado, Zeeshan Khatri, Khalid Hussain Thebo, Ayaz Ali, Fabrication and characterization of MXene/carbon composite-based nanofibers (MXene/CNFs) membrane: An efficient adsorbent material for removal of Pb⁺² and As⁺³ ions from water, Chemical Engineering Research and Design, Volume 191, 2023, Pages 462-471, ISSN 0263-8762, <https://doi.org/10.1016/j.cherd.2023.02.005>.

10. Buledi, J.A., Solangi, A.R., Malah, A., **N. Mahar** et al. Electrochemical characterization of SnO₂/rGO nanostructure for selective quantification of

captopril in real matrix. Journal of Materials Research 38, 2764–2774 (2023).

<https://doi.org/10.1557/s43578-023-01000-1>

11. V₂CTx MXene Suppresses V⁵⁺ Dissolution and Boosts the Stability and Performance of BiVO₄ for Solar Water Splitting, TA-ART-11-2024-007992 |