Dedicated to..... Late Uncle Mullugeta Fuchamo

Declaration of Academic Integrity

I declare that this written submission represents my ideas in my own words and where other's ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty, integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be caused for disciplinary action as per the rules and regulations of the Institute.

Due acknowledgement to all the related data used from different sources in order to support my research findings have been made wherever necessary. All funding agencies have been duly acknowledged for providing research grants to carry out my research work smoothly.

Date: 14-08-2023 Place: Tezpur University (**Mr. Tamrat Yimenu Zeleke**) TZ203943 of 2023



TEZPUR UNIVERSITY

(संसद के अधिनियम द्वारा स्थापित केंद्रीय विश्वविद्यालय) (A Central University established by an Act of Parliament)

Dr. Bipul Chandra Sarma Department of Chemical Sciences Tezpur University Tezpur 784 028, Assam, INDIA डॉ विपुल चंद्र शर्मा रसायन विज्ञान विभाग तेजपुर विश्वविद्यालय तेजपुर 784 028, असम, भारत

CERTIFICATE FROM SUPERVISOR

This is to certify that the thesis entitled "*Multicomponent Crystals of Famotidine and Trimethoprim as Improved Pharmaceutical Materials: Design, Characterization, and Properties*" submitted to the School of Sciences, Tezpur University in partial fulfilment for the award of the degree of Doctor of Philosophy in Chemical Sciences is a record of research work carried out by **Mr. Tamrat Yimenu Zeleke** under my supervision and guidance. He has been duly registered (Registration No. TZ203943 of 2023), and the thesis presented is worthy of being considered for the Degree of Doctor of Philosophy.

All help received by him from various sources have been duly acknowledged. No part of this thesis has been submitted elsewhere for award of any other degree.

Date: 14-08-2023 Place: Tezpur University (Dr. Bipul Ch. Sarma) Supervisor

E-mail: <u>bcsarma@tezu.ernet.in</u>, <u>sarmabipul@gmail.com</u>; Web: www.tezu.ernet.in Ph: +91 (3712) 275066 (O), +91 9435758147 (Mob); Fax: +91 (3712) 267005/6



TEZPUR UNIVERSITY (संसद के अधिनियम द्वारा स्थापित केंद्रीय विश्वविद्यालय) (A Central University established by an Act of Parliament) Napaam – 784 028, Tezpur, District– Sonitpur, Assam, India

CERTIFICATE OF THE EXTERNAL EXAMINER AND ODEC

This is to certify that the thesis entitled **"Multicomponent Crystals of Famotidine and Trimethoprim as Improved Pharmaceutical Materials: Design, Characterization, and Properties"** submitted by **Tamrat Yimenu Zeleke** to **Tezpur University** in the **Department of Chemical Sciences** under the **School of Sciences** in partial fulfilment for the award of the degree of Doctor of Philosophy in **Chemical Sciences** has been examined by us and found to be satisfactory.

The committee recommends for the award of the Degree of Doctor of Philosophy.

Signature of:

(Dr. Bipul Sarma) Thesis Supervisor Date: **External Examiner**

Date:

ACKNOWLEDGMENTS

In this happiest moment, it gives me immense pleasure in expressing my deep sense of gratitude to all those who contributed and supported me in various ways to the successful completion of my research work and made this thesis possible.

First of all, I would like to thank and praise my God for giving me good health, strength, courage, wisdom, and patience during my PhD study.

I am greatly indebted to my supervisor Dr. Bipul Sarma for giving me the opportunity to work under him, his valuable guidance, scholarly input, constructive criticism, and constant encouragement throughout my research career. I am deeply impressed by his patience, understanding, and ways of communicating with students. This achievement was possible only because of the unconditional support provided by Sir. I could not imagine having a better advisor and mentor for my PhD study. I pray to God for a healthy life for him and his family.

I am indebted to the honourable Vice-Chancellor Prof. Shambhu Nath Singh and former Vice-Chancellor Prof. Vinod K. Jain of Tezpur University for allowing me to carry out my research in this beautiful University in a peaceful and scientific environment.

Besides, I am extremely grateful to Prof. Panchanan Puzari (current HoD) and Prof. Ruli Borah (former HoD), Department of Chemical Sciences, Tezpur University for their valuable support and help in various aspects. I also extend my deep sense of gratitude to my doctoral committee member Dr. Utpal Bora Associate Professor, and Dr. Pankaj Bharali Assistant Professor, Department of Chemical Sciences, Tezpur University for their valuable suggestions and insightful comments during the entire PhD period.

My whole-hearted thanks go to all teaching and non-teaching staff of the Department of Chemical Sciences, Tezpur University. I would also like to thank the Sophisticated Analytical Instrumentation Centre (SAIC), Tezpur University for providing the instrumental facilities during my research work.

I am hugely indebted to the people of India and gratefully acknowledge the Indian Council for Cultural Relations (ICCR), Government of India for providing me with financial support during my PhD tenure. My labmates- Debabrat, Himanshu, Bikash, Archita, Priya, and Dr. Nazima for their love and unlimited support and for making the laboratory an enjoyable and comfortable place to work, and for giving me fond memories of my time in Lab no. 13. I also gratefully acknowledge the family of Dr. Bipul Sarma. I would like to thank all my batchmates and research scholars in the Department of Chemical Sciences.

Last but not the least, a special thanks to my family. Words cannot express how grateful I am to my beloved parents, brothers, sisters and Mr. Ayeno Handeno, Mr. Arega Lombaso, and Lt. Uncle and brother-in-law, Mullugeta Fuchamo and Abate Erabo for their constant support to bring me up to this stage. Thank you very much.

(Tamrat Yimenu Zeleke)

List of Tables

	List of Tables	
Table No.	Table Title	Page No.
Chapter 1		
1.1	Strength of non-covalent interactions commonly found in organic crystals.	3
1.2	BCS Classification of drugs and representative examples of each class.	6
1.3	Analytical techniques used to characterize the multicomponent solid state.	15
1.4	Commercially available pharmaceutical cocrystals and salts.	28
Chapter 2		
2.1	Important hydrogen bond geometry observed in Form-I and II.	50
2.2	Estimated energy of various intermolecular interactions in Form-I and Form-II.	52
Chapter 3		
3.1	Reported cocrystals/salts of FAM with improved physicochemical property.	66
3.2	Cocrystallization of FAM with isomeric hydroxybenzoic acids and aminobenzoic acids resulted in hydrated molecular salts, C-1 to C-6.	68
3.3	The ΔpK_a values of FAM and coformers. The COOH hydrogen atom location was estimated from single crystal X-ray data analysis to understand the proton transfer phenomenon in the products.	69
3.4	DSC endotherms represent the melting onset and peak of the salt hydrates.	70
3.5	Important hydrogen bond parameters observed in the salts, C-1 to C-6	76
3.6	The solubility comparison of starting materials with their respective salts.	81
Chapter 4		
4.1	Crystallization of famotidine with isomeric dihydroxybenzoic acids leads to the formation of molecular salt hydrates and their respective stoichiometric ratio.	97
4.2	Commentioner of DCC multimentation of multimentation and the multi-	00

4.2 Comparison of DSC melting points of molecular salts with 99 their respective starting materials.

4.3	The pKa values of API and coformers. The observed acid hydrogen distance parameters from donor (d) and acceptor (a) atoms are calculated from the single crystal structure of the products.	101
4.4	Important hydrogen bond parameters observed in the salts F-23 to F-35.	106
Chapter 5		
5.1	Reported cocrystals/salts of TRM with improved physicochemical property.	126
5.2	Molecular salts of TRM with isomeric DHBAs used as coformers.	126
5.3	The melting onset endotherms comparison of salt products TRM-23 to TRM-35 and with their respective starting materials.	128
5.4	The pK_a values for TRM and coformers. The estimated distance parameters of COOH hydrogen atom from donor (<i>d</i>) and acceptor (<i>a</i>) atoms and N-atom bond angle parameters in the crystal structures of TRM salts.	131
5.5	Hydrogen bond parameters of salts of the drug TRM with isomeric DHBA.	134
5.6	Solubility amount of the TRM and its molecular salts in unit mg/mL.	137
Chapter 6		
6.1	The multicomponent solids of drug TRM with isomeric HBA and ABA and their stoichiometric ratio.	151
6.2	The comparison of melting onset endotherms of products with their respective starting materials.	152
6.3	The acid proton distances from donor (<i>d</i>) and acceptor (a) atoms and bond angle and distance of basic N-atom of the pyrimidine ring and COOH group of the coformers in the salts.	155
6.4	Important hydrogen bond parameters observed in the molecular salts of TRM.	157

Appendix

A1	Crystal data parameter of form-I and Form-II.	А
A2	Crystal X-ray diffraction data of C-1 to C-6.	В
A3	Change in the torsion angles of FAM in C-1 to C-6.	D
A4	Comparison of hydrogen bond synthons observed in FAM molecular salts with the Crystal Structure Database (CSD).	D

A5	Crystallographic parameters of F-23 to F-35.	G
A6	Bond length and bond angle parameters of imine group of guanidine moiety of the FAM and carboxylic acid group in the DHBA of the salt products.	Ι
A7	Comparison of change in the torsion angles of FAM conformers in crystal structures of F-23 to F-35.	Ι
A8	Crystallographic parameters of the TRM-23 to TRM-35.	Ι
A9	Crystallographic parameters of the TRM-1 to TRM-6.	М

List of Figures

	List of Figures	
Figure No.	Figure Caption	Page No.
Chapter 1		
1.1	Various scope and important applications of crystal engineering.	1
1.2	Examples of hydrogen-bonded supramolecular heterosynthons and homosynthons.	4
1.3	Occurrence of neutral AB (gray-zone 1) and ionic A^-B^+ (orange-zone 3) vs the calculated $\Delta p K_a$ values obtained from a CSD survey of 6465 acid-base adducts.	9
1.4	The ionic cocrystal of fluoxetine hydrochloride with benzoic acid is sustained by ionic hydrogen bonds.	10
1.5	Crystal structure of ethyl acetate solvated 1,4- Di[bis(40-hydroxyphenyl)methyl]benzene	11
1.6	Crystal structures of dimorphic forms of the paracetamol. Form I doesn't have a slip plane in the crystal structure, whereas the layered structure of Form II has it and demonstrates better tablelability.	12
1.7	Crystal structures of trimorphic cocrystals of celecoxib with δ-valerolactam (1:1). (a) In the form I valerolactam dimmers are linked by sulfonamide dimer of celecoxib. (b) Celecoxib and valerolactam molecules in form II interact through N–H···O catemers. (c) Valerolactam dimers in form III are linked via an N–H···O catemer.	13
1.8	Solubility and (b) intrinsic dissolution rate comparison of pure nicorandil and its cocrystals/salts in phosphate buffer saline (pH 7) media at 37 ± 1 °C.	17
1.9	Solubility curves of nevirapine and its cocrystals vs pH of the media. Symbols refer to the measured solubility from saturated solutions at 25 °C. Curved lines represent the calculated solubility using the solubility-pH equations.	18
1.10	Dissolution rates comparison of compressed tablets of the two pure drugs and the ternary salt cocrystal in pH 1.2 buffer.	19
1.11	A plot of the cumulative amount of HCT and its cocrystals diffused vs time at pH 7.4.	20
1.12	The mean plasma concentration vs time profiles of Apixaban (Apx) after oral delivery of pure Apx (black circle) and its cocrystal (red circle) in male beagle dogs.	22
1.13	Plasma concentration-time profile for pure KET and KET-PABA.	22

- **1.14** Mean plasma concentration vs time profiles of cocrystal 23 (test formulation) and marketed form of pirfenidone (reference formulation).
- 1.15 In pure theophylline structure, its molecules are 24 connected by N–H···N hydrogen bonds. (b) Theophylline dimers are formed by N–H···O hydrogen bonding in the cocrystal structures. The diclofenac molecules are linked to the theophylline dimers through O–H···N hydrogen bonds.
- **1.16** (a) Molecular structures of vitamin K₃ (MD), its 25 photoproducts, and coformers. (b) Changes in the MD assay quantity in pure MD and its cocrystal with 1-HNA during the illumination of 4500 lx for 5 days.
- **1.17** Tabletability of vanillin derivatives cocrystals with 27 CDA.
- **1.18** The compression properties study of nicorandil and its 27 binary solids, where A–C are the process parameters with different dwell and blending times.

Chapter 2

2.1	The comparison of IR spectra of the dimorphic forms and the starting materials.	46
2.2	DSC endothermic profiles for dimorphic salts and their starting materials.	47
2.3	The observed TGA weight loss matches well with a 1:1:1 ratio of FAM, 2-ABA, and water estimated by single crystal X-ray structure analysis.	47
2.4	The comparison of PXRD patterns of dimorphic forms	48
2.5	(a) The water molecule serves as a linker between three dimers in the crystal structure of Form-I through auxiliary O–H…N and N–H…O hydrogen bonds. (b) 2D packing of Form-I.	49
2.6	(a) The water molecule connects four dimers in the crystal structure of Form-II via auxiliary O–H…N and N–H…O hydrogen bonds and (b) the 2D structure of Form-II patterns along the crystallographic line.	49
2.7	The overlay of molecular conformers (a) drug FAM and (b) 2-ABA extracted from the crystal structures of Form-I and II.	50
2.8	2D fingerprint plots and percentage contribution of various intermolecular interactions of Form-I and Form-II comparison with pure FAM-A.	51

2.9	Crystal voids of (a) Form-I and (b) Form-II view along the <i>a</i> -axis.	52
2.10	Energy frameworks for Form-I with an energy cutoff at -10 kJ mol^{-1} along the crystallographic <i>a</i> -axis. (a) Electrostatic energy (red framework), (b) Dispersion energy (green framework), and (c) Total energy (purple framework).	53
2.11	Energy frameworks for Form-II with an energy cutoff at -10 kJ mol ⁻¹ along the crystallographic <i>a</i> -axis. (a) Electrostatic energy (red framework), (b) Dispersion energy (green framework), (c) Total energy (purple framework).	53
2.12	Comparison of PXRD profiles of (a) Form-I and (b) Form-II extracted from the slurry experiments in 1.2 and 7.4 pH buffer solutions with the PXRD patterns of respective initial product materials.	54
2.13	The solubility comparison of FAM and its dimorphic salts in a buffer solution of pH 1.2 and 7.4.	55
2.14	(a) The main structural $R_2^2(8)$ motif is common in both crystalline forms. (b) and (c)The water molecules of crystallization in Form-II forms a higher number of hydrogen bonds with the drug and coformer, but those bonds are found to be weaker than that of Form-I.	56
2.15	(a) Permeability rate and (b) drug flux of FAM and its dimorphic salts with respect to time.	57
Chapter 3		
3.1	Vibrational absorption frequencies of various functional groups in molecular salts C-1 to C-6, compared with that of the pure drug FAM.	69
3.2	Guanidiniumcarboxylate hydrogen bond heterosynthon in FAM salts.	69
3.3	DSC endotherms represent the melting onset of the six molecular salts of FAM.	70
3.4	Weight loss measured by TGA agrees well with a 1(Drug):1(Coformer):1(Water) ratio molecular salt confirmed by single crystal X-ray structure elucidation.	71
3.5	PXRD patterns of the six FAM molecular salts, <i>viz</i> C-1 to C-6.	72
3.6	Ionic guanidinium…COO ⁻ heterodimers in the C-1 crystal structure. Water molecule connects such drug…conformer units via O–H…O hydrogen bonds supported by auxiliary N–H…O hydrogen bonds. (b)	73

Water molecules further connect the aggregates of dimers via O–H…O hydrogen bonds.

- 3.7 (a) Dimeric water unit connects the R₂²(8) heterodimer 73 that further extends to a tapelike structure via O–H···O and N–H···O hydrogen bonds. Such molecular tapes are linked through the OH group of the *m*-HBA coformer.
 (b) The R₂²(8) heterodimer between FAM and *m*-HBA is present in the C-2 crystal structure.
- **3.8** (a) As observed in the crystal structures of C-1 and C-2, the $R_2^2(8)$ ring motif via N⁺-H···O⁻ and N-H···O strong interactions are also formed in the C-3. Water molecule acts as a linker between these supramolecular dimers. (b) The layered crystal structure of C-3 is linked by the $R_2^2(8)$ ring motif along the crystallographic axis [100].
- 3.9 (a) R₂²(8) heterosynthon between FAM and *o*-ABA 75 formed via N⁺-H···O⁻ and N-H···O strong interactions. Auxiliary N-H···O and O-H···O hydrogen bonds from water and the NH₂ group extend the molecular packing in the crystal lattice of C-4. (b) 3D molecular packing of C-4.
- 3.10 (a) Prime synthons in the crystal structure of C-5. (b) 75 The sheetlike structure of C-5 is connected by N–H…O hydrogen bonds along the [10] plane. (c) *p*-ABA molecule is connected with FAM dimer by R₂²(8) ring motif in the crystal structure of C-6. (d) Crystal structure of C-6 is sustained by N–H…O hydrogen bonding to form a layer structure along the [001] axis.
- **3.11** Overlay of FAM conformations extracted from the 77 crystal structures of C-1 to C-6.
- **3.12** Conformational variation in FAM molecule was 77 observed in the crystal structures of C-1 to C-6 through four different torsion angles referred to in Table A3.
- **3.13** Observed hydrogen bond synthons in the crystal 78 structures of C-1 to C-6 of the API and coformers.
- **3.14** Phase stability study of C-3 (a) and C-6 (b) by a slurry 79 experiment in an aqueous medium and buffer solution of pH 1.2 and 7.4.
- **3.15** Solubility of pure FAM and its salts in pure water and 81 at pH 1.2 and 7.4.
- **3.16** Relative packing energy comparison of molecular salts 82 C-1 to C-6. The C-5 structure is obtained after removing highly disordered water molecules of crystallization using the PLATON SQUEEZE program.

3.17	(a) Main hydrogen-bonded synthon observed in all crystal structures from C-1 to C-6. (b) Relative energy values of the prime hydrogen-bonded synthon in the crystal structures of C-1 to C-6.	83
3.18	(a) Permeability rate percentage and (b) drug flux of FAM and its salts with time at pH 1.2.	84
3.19	(a) Permeability rate percentage and (b) flux of FAM and its salts with time at pH 7.4.	85
3.20	Percentage contribution of noncovalent interactions obtained using Hirshfeld surface area analysis of FAM and its salts C-1 to C-6.	87
Chapter 4		
4.1	Vibrational spectroscopy of FAM and its molecular salts with isomeric DHBA.	98
4.2	DSC thermograms of molecular salts of FAM with isomeric DHBAs.	99
4.3	The observed weight loss measured by TGA is consistent with the 1:1:2 for dihydrates (F-23, F-25, and F-34), 1:1:2.25 for F-35, and 1:1:1 for monohydrate (F-24) ratios obtained from X-ray crystal structural analysis.	100
4.4	PXRD patterns of molecular salts F-23 to F-35 along with the parent API.	101
4.5	The prime guanidinium…carboxylate supramolecular heterosynthon in the molecular salts F-23 to F-34.	101
4.6	(a) In F-23, symmetrical independent FAM molecules which are connected with 23-DHBA by N^+ -H···O ⁻ hydrogen bonds form guanidinium···COO ⁻ supramolecular heterodimers. Such dimers are linked by water molecules via O-H···O interactions. (b) Water tetramer in the voids of F-23 interacts with 23-DHBA by O-H···O hydrogen bonds.	103
4.7	(a) FAM homodimer is connected with 24-DHBA molecular tape via $R_2^2(8)$ ring motif to form (b) a 2D molecular packing in the crystal structure of F-24.	103
4.8	MeOH molecules serve as a linker between the drug–coformer dimers to form a 2D structure in the F-25.	104
4.9	The 2D sheets in the F-26 are connected by N–H…O hydrogen bonds.	105
4.10	(a) Dimers in the crystal structure of F-34 are connected by water molecules. (b) 34-DHBA molecules are connected by water molecules to form a 1D molecular	106

	chain. (c) F-35 structure with N–H···O [–] , N–H···O, and O–H···O [–] interactions. (d) Water dimers in the voids held by O–H···O hydrogen bonds connect the drug dimers via N–H···O [–] and N–H···O interactions.	
4.11	Various hydrogen bonding interactions observed in the crystal structures of F-23 to F-35.	107
4.12	An overlay of molecular conformers of FAM extracted from the single crystal structures of products F-23 to F-35.	108
4.13	The observed conformational deviation in drug molecules in the crystal structures of F-23 to F-35 via two different torsion angles of the flexible moiety of the FAM structure referred to in Scheme 4.	108
4.14	The phase stability test of molecular salts of FAM in pure water and at pH 1.2 and 7.4 conditions.	110
4.15	The crystal packing energy of the FAM and its molecular salts, F-23 to F-35.	111
4.16	Comparison of solubility behavior of molecular salts F-23 to F-35 with its parent drug FAM in aqueous medium and buffer solutions of pH 1.2 and 7.4.	111
4.17	Prime hydrogen-bonded synthon observed in the crystal structure of (a) F-23 and (b) F-24 to F-34. (c) The relative energy of synthon I and II.	112
4.18	(a) Permeability rate and (b) drug flux of molecular salts and the parent drug at a buffer solution of pH 1.2.	114
4.19	(a) Permeability rate and (b) drug flux of molecular salts and the parent drug at a buffer solution of pH 7.4.	115
4.20	Comparison of various intermolecular interactions contribution in the product materials of FAM and DHBA.	116
Chapter 5		
51	The comparison of IP spectra of TPM and its molecular	127

The comparison of IR spectra of TRM and its molecular 5.1 127 salts with isomeric DHBA. 5.2 DSC endotherms represent the melting onset of the drug 128 TRM salts. The weight loss estimated by TGA for hydrated 5.3 129 products agrees well with the calculated values from the crystal structures. Powder X-ray diffraction patterns for salts of drug TRM 5.4 129 with isomeric DHBA. 5.5 130 Pyrimidinium---carboxylate heterosynthon in the crystal structure of TRM salts.

5.6	 (a) The water dimer extends the structure of the TRM-24 in 2D and 3D by linking the drug…coformer dimers. (b) Dimers are connected by O-H…O interaction to form a 1D layer in the crystal structure of TRM-24. 	131
5.7	(a) Drug…coformer dimers in TRM-25 salt are connected with another $R_2^2(8)$ motif to form molecular tape. (b) 2D structure of the TRM-25 salt. (c) The molecular tapes are stacked via N–H…O interactions to complete the 1D crystal structure of TRM-26.	132
5.8	(a) The netlike 2D structure of TRM-34 is connected by $N-H\cdots O$ and $O-H\cdots O$ interactions. (b) 2D molecular packing in the crystal structure of TRM-35.	134
5.9	Phase stability study of TRM-25 salt of drug TRM which shows stable phase up to 24 h.	1.36
5.10	Solubility determination of the drug TRM and its molecular salts.	137
5.11	Various intermolecular interaction contributions in the molecular salts of TRM with DHBA as coformers.	138
5.12	Plots of (a) membrane permeability rate and (b) drug flux of TRM and its salts with respect to time at pH 1.2.	139
5.13	Plots of membrane permeability rate (a) and drug flux (b) of TRM and its salts with respect to time at pH 7.4.	140
Chapter 6		
6.1	Comparison of vibrational spectroscopy of TRM and its molecular salts with isomeric HABA and ABA.	152
6.2	DSC endotherms represent the melting onset of TRM salts.	153
6.3	The weight loss estimated by TGA for hydrated products agrees well with the calculated values from the single crystal structures.	153
6.4	Overlaid PXRD patterns of TRM and its molecular salts.	154
6.5	Pyrimidinium…carboxylate supramolecular interaction in the crystal structure of TRM salts.	155
6.6	(a) Sheetlike structure of TRM-1 connected by water molecules via N–H···O and O–H···O interactions. (b) The layered structure of TRM-2 is connected by water molecules through O–H···O hydrogen bonds. (c) The drug-coformer dimers are linked by water molecules to form a 1D molecular chain in the crystal structure of TRM-3.	156

6.7	(a) Pyrimidiumcarboxylate dimers in the crystal structure of TRM-4 are connected by N–H…O interactions. (b) The water molecules in the crystal structure of TRM-6 connect the drug and coformer molecules via N–H…O and O–H…O hydrogen bonds.	157
6.8	An overlay of molecular conformers of TRM extracted from its molecular salt crystal structures.	158
6.9	Torsion angle of flexible methylene group in pure TRM and its molecular salts.	159
6.10	Solubility of trimethoprim comparison with its molecular salts in three different pH conditions.	160
6.11	The prime hydrogen bonding interactions of TRM with isomeric HBA and ABA in the crystal structures of (a) TRM-1 to TRM-4 and (b) TRM-6.	161
6.12	Relative energy values of the prime hydrogen-bonded synthon in the crystal structures of salts of TRM.	161
6.13	(a) Permeation rate and (b) drug flux of molecular salts of TRM with isomeric HBA and ABA at pH 1.2.	162
6.14	(a) Permeation rate and (b) drug flux of molecular salts of TRM with isomeric HBA and ABA at pH 7.4.	163
6.15	Various noncovalent interactions percentage present in the TRM and its molecular salts.	164

Appendix

A1	The Rietveld refinement of (a) Form-I and (b) Form-II.	А
A2	Rietveld refinement of PXRD pattern of C-1 to C-6.	С
A3	Phase stability study of C-1, C-2, C-4, and C-5.	F
A4	The amount of drug flux for FAM and its products at (5 min) and 180 min at pH of (a) 1.2 and (b) 7.4.	G
A5	Rietveld refinement of experimental PXRD pattern of F-23 to F-35.	Н
A6	Rietveld refinement of experimental PXRD pattern of TRM-23 to TRM-35.	K
A7	The overlaid PXRD patterns of phase stability tests of TRM-23 to TRM-35.	Ι
A8	The comparison of PXRD patterns of undissolved materials of TRM-34 and TRM-35 from 1.2 pH medium after 24 h with the simulated PXRD profile of trimethoprim hydrochloride salt.	М
A9	Rietveld refinement of experimental PXRD pattern of TRM-1 to TRM-6.	N

A10 The phase stability tests of molecular salts of TRM at pH 1.2 and 7.4 at 12 h.

Ν

List of Schemes

Scheme No.	Scheme Caption	Page No.
Chapter 1		
1.1	Schematic representation of various single and multi- component solids.	5
1.2	Schematic representation of the difference between (a) cocrystal, (b) salt-cocrystal continuum, and (c) salt.	8
1.3	Schematic representation that demonstrates the interactions between neutral molecules and metal complex or salts in the ionic cocrystals.	9
Chapter 2		
2.1	Synthesis of dimorphic salts from API famotidine and 2-aminobenzoic acid.	45
Chapter 3		
3.1	Molecular structures of the drug famotidine and isomeric aminobenzoic acid and isomeric hydroxybenzoic acids as coformers.	67
Chapter 4		
4.1	Molecular structures of drug famotidine and isomeric dihydroxybenzoic acids.	96
Chapter 5		
5.1	Molecular structure of drug trimethoprim (TRM).	125
Chapter 6		
6.1	Molecular structures of the drug trimethoprim and coformers.	150
Chapter 7		
7.1	Dimorphic salts of FAM isolated from methanol and ethanol crystallization.	172
7.2	The variation of the drug conformation in the crystal structures of molecular salts results in the difference in the permeability rate.	172
7.3	The molecular salts of famotidine demonstrated better phase stability in different pH media when compared with the parent API.	173

7.4	The hydrated salts of TRM demonstrated a significant improvement in solubility as compared to the anhydrous salts.	174
7.5	The impact of hydrogen-bonded synthon strength on the solubility of salts of TRM.	174
7.6	A pictorial illustration of applications of pharmaceutical cocrystals and future aspects.	175

Abbreviations and Symbols

А	Acceptor
Å	angstrom Acetonitrile
a.u.	Arbitrary unit
API	Pharmaceutical Ingredients
ABA	Aminobenzoic acid
ACN	Acetonitrile
Au	Absorbance of the unknown solution
BCS	Biopharmaceutics Classification System
cm^{-1}	Per centimeter
°C	Degree Celsius
°min ⁻¹	Degree Celsius per minute
Calc.	Calculated
cm	Centimeter
CSD	Cambridge Structural Database
Cu	Concentration of an unknown solution
D	Donor
1D	One dimensional
2D	Two dimensional
3D	Three dimensional
DFT	Density Functional Theory
DHBA	Dihydroxybenzoic acid
23-DHBA	2,3-dihydroxybenzoic acid
24-DHBA	2,4-dihydroxybenzoic acid
25-DHBA	2,5-dihydroxybenzoic acid
26-DHBA	2,6-dihydroxybenzoic acid
34-DHBA	3,4-dihydroxybenzoic acid
35-DHBA	3,5-dihydroxybenzoic acid
DSC	Differential scanning calorimetry
EtOH	Ethanol
FAM	Famotidine
FDA	Food and Drug Administration
FT-IR	Fourier-transform infrared spectroscopy
GRAS	Generally regarded as safe list
HBA	Hydroxybenzoic acid
h	Hours
HCl	Hydrochloric acid
kJ mol ⁻¹	Kilojoules per mole

kcal mol ⁻¹	kilocalorie per mole
KBr	Potassium bromide
<i>m</i> -ABA	<i>m</i> -Aminobenzoic acid
<i>m</i> -HBA	<i>m</i> -Hydroxybenzoic acid
μm	Micrometer
mg	Milligram
min	Minutes
mL	Milliliter
mm	Millimetre
g cm ⁻³	gram per centimeter cube
mmol	Millimolar
MeOH	Methanol
M.Pt.	Melting point
Obs.	Observed
o-ABA	o-Aminobenzoic acid
o-HBA	o-Hydroxybenzoic acid
<i>p</i> -ABA	p-Aminobenzoic acid
<i>p</i> -HBA	p-Hydroxybenzoic acid
PXRD	Powder X-ray diffraction
rpm	revolutions per minute
ss-NMR	solid-state nuclear magnetic resonance
TGA	Thermogravimetric analysis
UV	Ultraviolet
UV-vis	Ultraviolet-visible
TRM	Trimethoprim
X-RD	X-ray diffraction
XPS	X-ray photoelectron spectroscopy