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Research Article

Modulating The Solubility of Mesalamine by Means of Cocrystals

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ABSTRACT

The aim of the present research was to increase the solubility and dissolution rate of poorly water-soluble drugs through pharmaceutical cocrystal. The liquid assisted grinding method were used for the preparation of cocrystals by screening various coformers. The cocrystals were prepared in 1:1 molar ratio of drug and coformers. Initially, the resulting product was evaluated for the solubility. The selected potential cocrystal was further characterized and confirmed by FTIR, DSC, PXRD, etc. Further, dissolution rate and flowability of the selected cocrystals were also investigated. Finally, the performance of selected cocrystals was examined in the tablet dosage form. The changes in solubility provided the preliminary evidence of formation of new solid phase. In addition, the alteration in FTIR absorption, thermal behavior and PXRD pattern signaled the formation of cocrystal. Mesalamine formed cocrystal with ascorbic, sodium acetate, Urea, Saccharin Sodium and saccharin sodium showed highest solubility. The flowability of cocrystals was found superior to pure drugs. The dissolution rate of cocrystals was improved significantly as compared to original drugs. Pharmaceutical cocrystals of mesalamine having enhanced solubility, dissolution, flowability were designed, prepared and evaluated. The prepared cocrystals showed good performance in the tablet dosage form as well.

INTRODUCTION

One of the major problems in drug discovery and development is the poor solubility of new chemical entities (NCEs). Compounds with low solubility not only complicate the drug development process but also hinder the effectiveness of in vitro and in vivo assays during drug discovery. Successful absorption of drug requires the drug to be dissolved in gastrointestinal fluids, and dissolution depends on the drug's solubility in the surrounding medium. Advancements in pharmaceutical sciences have led to the development of various strategies to address the problem of low aqueous solubility. Methods such as micronization, salt formation,

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cosolvency, micellar solubilization, and cyclodextrin complexation have been employed to enhance solubility and dissolution. However, the effectiveness of these techniques largely depends on the specific physicochemical properties of the molecules involved. Solubility is defined as the quantity of solute that can be dissolved in a saturated solution at a specific temperature. Crystal engineering designs drug delivery systems by improving dissolution properties without compromising stability. It focuses on understanding and applying non-covalent interactions, like hydrogen bonding and π-π interactions, to form solid structures with desired characteristics, helping to address challenges such as poor aqueous solubility and enhance bioavailability. Desiraju expanded this concept to define "supramolecular synthons," which are structural units within supermolecules formed by intermolecular interactions, also referred to as "cocrystals". These supramolecular synthons can be formed by various groups, including acids (e.g., carboxylic, sulfonic, phosphonic, and boronic), primary and secondary amides, alcohols, amino-pyridines, ketones, aldehydes, ethers, esters, and amines. Supramolecular synthons are categorized into two types:

(a) Supramolecular homosynthons: Composed of identical self-complementary functional groups.

(b) Supramolecular heterosynthons: Composed of different but complementary functional groups.

Crystal engineering, in general, involves designing molecular solids to customize their physical and chemical properties, which can be used to control the solubility and dissolution rates of crystalline substances. Cocrystallization, provides a more flexible approach for engineering drug molecules. A cocrystallization can be applied to any active pharmaceutical ingredient (API), regardless of whether it contains ionizable groups. Pharmaceutical cocrystals offer advantages such as enhanced solubility, dissolution rate, physical and chemical stability, and improved bioavailability of the API. Additionally, the availability of many coformers listed in the GRAS (Generally Recognized as Safe) and EAFUS (Everything Added to Food in the US) databases provides opportunities for patenting and extending the life cycle of existing APIs. "Cocrystals are typically defined as crystalline substances consisting of at least two components: an API (neutral or ionic) and a neutral coformer, bound together through non-covalent, reversible interactions". A pharmaceutical cocrystal requires that at least one of these components is a drug, and the other is a pharmaceutically acceptable solid coformer. Rapid onset and improved bioavailability are desirable for analgesics. Hence, there is strong scientific and clinical need to prepare novel forms of mesalamine possessing modified solubility and dissolution rate which can be formulated for oral administration. Hence, it was selected for solubility enhancement via cocrystallization.

4. Materials and Methods

Table 1: Drug and Coformers

Sr. No.	Drug and Coformer	Manufacturer
1.	Mesalamine	Pi Chemicals
2.	Nicotinamide	SRL Chemicals
3.	L-Glutamine	Ottokemi chemika biochemika reagents
4.	Ascorbic Acid	Ozone International
5.	Sodium Acetate	SRL Chemicals
6.	Urea	Research lab
7.	Mannitol	Aarati chemicals
8.	Saccharine Sodium	Loba Chemicals
9.	Acetonitrile	Research lab

4.2 Equipment

Table 2: List of Equipment used

Sr. No.	Name of Equipment	Supplier
1.	Weighing Balance	Contech CA233
2.	Water Bath Shaker	REMIRSB-12
3.	Sonicator	Oscar103
4.	UV Spectrometer	Systronic UV 2102
5.	Tablet Punching Machine	Karnavati 12 Station Tablet Compression Machine
6.	Friabilator	Electrolab
8.	Dissolution Apparatus	Electrolab
9.	FT-IR	Bruker Alpha II
10.	DSC	Mettler Star SW 12.10
11.	XRD	Ultima IV, Riga Corporation, Japan

4.3 Liquid Assisted Grinding Method for preparation of cocrystal

Mesalamine and coformers at 1:1 stoichiometric ratio was grounded in acetonitrile for 10 minutes using a mortar and pestle and left it for solvent evaporation to obtain free flowing cocrystal.

Table 3: drug and cocrystal quantity in formulation of cocrystals

Mesalamine Quantity(mg)	Coformers	Coformer Quantity(mg)	Volume of Acetonitrile(ml)
15.3	Nicotinamide	12.21	2
	Ascorbic Acid	17.6	2
	Sodium Acetate	8.2	2
	Resorcinol	11	2
	Mannitol	18.2	2
	Urea	6	2
	Saccharin Sodium	20.5	2
	Benzoic acid	12.2	2

4.4 Formulation of pure mesalamine tablet

Composition for the formulation of pure mesalamine tablets were presented in table. The accurately weighed ingredients were mixed and were directly compressed to form tablet.

Table 4: Formulation of pure mesalamine tablet

Sr No	Ingredient	Manufacturer	Quantity per tablet
1	Mesalamine	Pi chemicals	400 mg
2	Microcrystalline cellulose	Ozone International	32 mg
3	Magnesium Starate	Milton Chemicals	20 mg
4	Talc	Milton Chemicals	8 mg

4.5 Formulation of mesalamine cocrystal tablet

Composition for the formulation of pure mesalamine: Saccharin sodium (cocrystal with highest solubility) cocrystal tablets were presented in table.

Table 5: Formulation of mesalamine cocrystal tablet

Sr No	Ingredient	Manufacturer	Quantity per tablet
1	Mesalamine Saccharin Cocrystal	Pi Chemicals	935mg
2	Microcrystalline cellulose	Ozone International	75 mg
3	Magnesium Starate	Milton Chemicals	48 mg
4	Talc	Milton Chemicals	19 mg

4.6 Analysis of solubility and evaluation of cocrystals:

4.6.1 Analytical Method Development

The UV method was developed in water and phosphate buffer pH 6.8. The mesalamine solution was scanned in the 200-400 nm range in order to obtain the absorption spectrum.

Calibration Curve of Mesalamine in Distilled Water

The standard stock solution of mesalamine was prepared in distilled water and phosphate buffer pH6.8 to produce the concentration of 100 µg/ml by dissolving accurately weighed quantity of drug.

Preparation of Working Solutions

Series of working solutions were prepared in the range 10-100 µg/ml by appropriate dilutions of the standard stock solution.

Construction of Calibration Curve

The calibration curve was created by recording the absorbance of the working solutions and plotting the absorbance against concentration.

4.6.2 Saturated solubility study

The solubility was determined by dissolving excess quantity of pure drug and cocrystal in the 10 ml vials containing water. The vials were subjected to agitation on rotary shaker for 6 hrs and allowed to stand for equilibration. The samples were filtered after 1 hr using Whatman filter paper, diluted with distilled water and analysed by UV Spectrophotometer at 330 nm.

4.6.3 Fourier Transform Infrared Spectroscopy (FTIR)

IR spectroscopy was employed for the characterization of cocrystal. The samples were scanned using Bruker Alpha II IR Spectrophotometer.

4.6.4 Differential Scanning Calorimetry

DSC analysis of mesalamine and cocrystal was done using METTLER TOLEDO DSC1 STARe System. About 3 mg of sample was taken in aluminium pans and sealed using lids. The event was run within the temperature range of 100-350°C at a ramp of 10°C/min, under a nitrogen atmosphere with a flow rate of 50 mL/min.

4.6.5 Crystal Structure Determination From PXRD

The crystal structure was determined from its PXRD pattern using Ultima IV, Rigaku Corporation, Japan. The silicon sample holders were used to obtain diffraction patterns of pure mesalamine. The instrument was equipped with a fine focus X-ray tube (X-ray Source: Cu K-α) and each sample was analysed at X-ray wavelength of 1.5406 Å.

4.6.6 Scanning Electron Microscopy SEM

Mesalamine and M+SacchSod cocrystal was subjected to evaluation by SEM to study the surface morphology and result is depicted. Due to greater solubility and considering analytical evaluation only M+SacchSod cocrystal was evaluated by SEM. However remarkable change

was observed in the M+SacchSod 1:1 cocrystal as structure was observed in the SEM image.

4.6.7 Pre-Compression studies

1. Bulk Density

Bulk Density of compound varies substantially with the method of crystallization, milling or formulation. Bulk density was determined by placing powder mix into a graduated cylinder via a large funnel and measuring its volume and weight.

$$\text{Bulk Density} = \frac{\text{weight of powder}}{\text{bulk volume of powder mixed}}$$

2. Tapped Density

Tapped density was determined by placing powder mix into a graduated cylinder via large funnel and tap the cylinder 50 times and measuring its volume and weight.

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{Tapped volume of powder mixed}}$$

3. Angle of Repose

The method used to find angle of repose is to pour the powder through funnel on flat surface and measure the inclined angle with the horizontal.

$$\text{Tan } \theta = \frac{\text{Height of the heap}}{\text{Radius of the heap}}$$

4. Hausner's Ratio

It indicates the flow properties of the powder and ratio of tapped density to the bulk density of powder.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density of powder mixed}}{\text{bulk density of powder}}$$

5. Compressibility index

Compressibility index was measured using the values of bulk density (BD) and tapped density (TD). The following equation was used to find the compressibility index.

$$\text{Carr's index} = \frac{(\text{TD} - \text{BD}) \times 100}{\text{TD}}$$

4.6.8 Post compression tests of tablets

1. Hardness

Hardness is force required to break a tablet in diametric compression. Hardness of tablet was determined by Monsanto hardness tester. The tablet hardness of 5 kg is considered as suitable for handling the tablets.

2. Tablet Size and Thickness

The thickness of the tablet was measured by vernier calipers scale. The thickness of tablet is related to the tablet hardness and can be used as initial control parameter. Tablet thickness should be controlled within range ±5%

3. Friability

The test was performed to evaluate the ability of tablet to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets was taken and these were placed in friabilator, rotating at 25 rpm for 4 min. the difference in weight is noted and expressed as percentage. It should be preferably between 0.5% to 1.0%.

$$\% \text{ friability} = \frac{(\text{weigth of tablet before test} - \text{weigth of tablet after test}) \times 100}{\text{weight of tablet before test}}$$

4. Weight Variation Test

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits. 20 tablets were taken randomly and weighed accurately. The average weight was calculated by using formula,

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

5. Disintegration test

To test disintegration, one tablet was placed in each of the six disintegration, one tablet was placed in each of six disintegration tube of basket

rack assembly which was kept in one liter beaker of phosphate buffer pH6.8, simulated intestinal fluid maintained at 37°c.

4.7 Dissolution Studies

Drug dissolution study was carried out in 900 ml of phosphate buffer pH6.8 at 37°c, using USP paddle method at stirring speed of 50 rpm. At regular time interval of 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110 min, 5 ml of samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium. Dissolution profile was compared with that of mesalamine tablet.

6. Results and Discussion

6.1 Analytical Method Development

The analytical method for mesalamine was developed and validated for the quantification of drug in the bulk and pharmaceutical formulation according to ICH Q2R1 guidelines. The method was developed in the distilled water and phosphate buffer pH 6.8. The results are given in table. The calibration curve for the piroxicam in distilled water and phosphate buffer pH 6.8 is represented in fig. 1. The absorption spectrum of mesalamine in water and phosphate buffer pH 6.8 is given in figure.

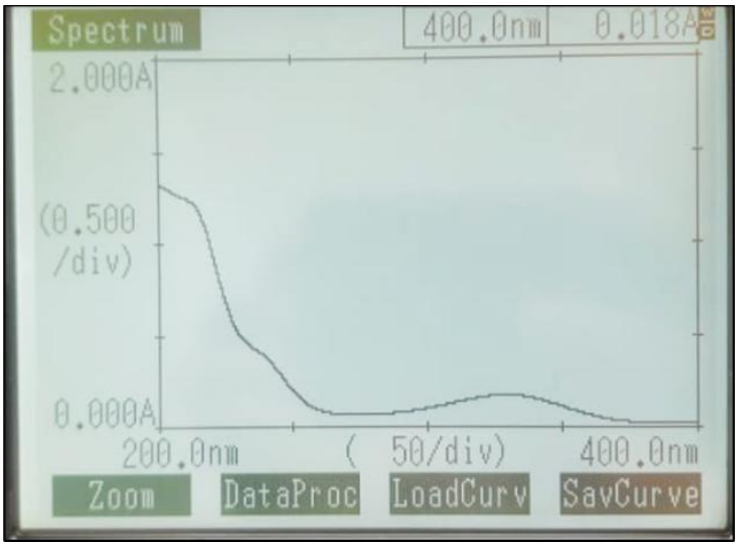

Fig 1: Absorption spectrum of mesalamine in distilled water

Table 6: Concentration and absorbance of mesalamine in distilled water

Concentration (µg/ml)	Absorbance
10	0.279
20	0.427
30	0.581
40	0.693
50	0.86

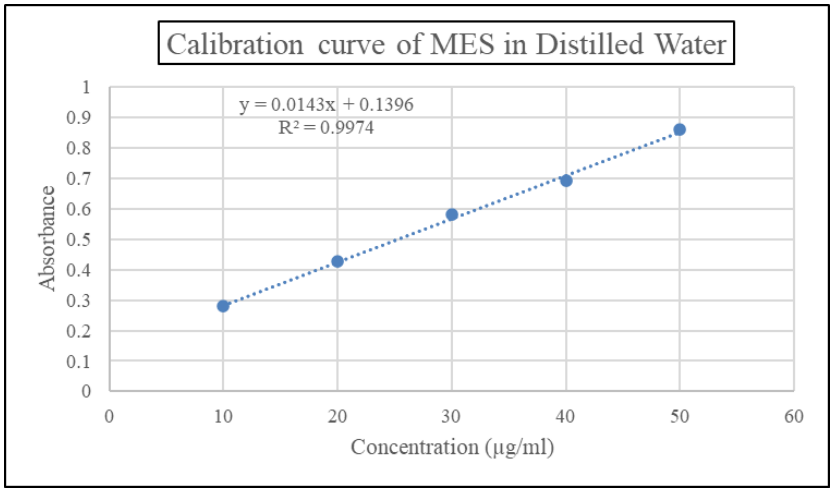

Fig 2: Calibration curve of mesalamine in water

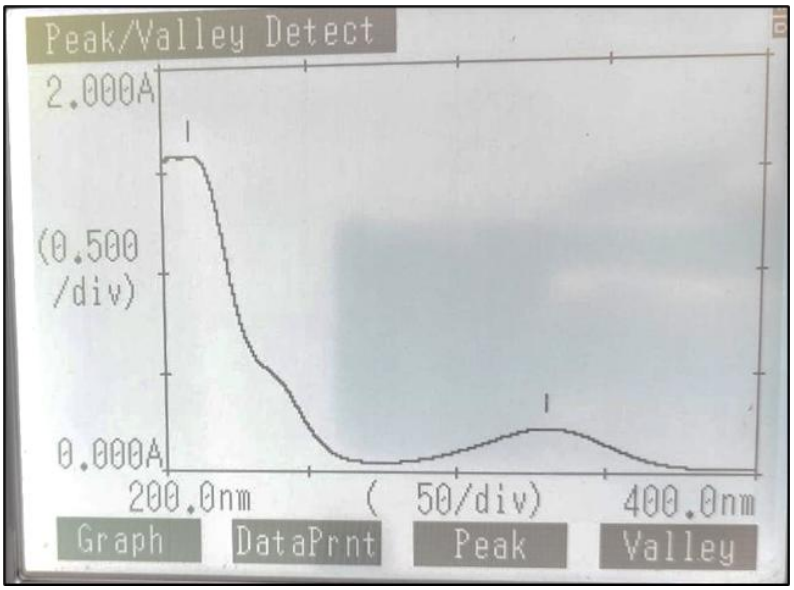

Fig 3: Absorption spectrum mesalamine in phosphate buffer pH6.8

Table 7: Concentration and absorbance of mesalamine in phosphate buffer pH6.8

Concentration (µg/ml)	Absorbance
10	0.222
20	0.404
30	0.591
40	0.784
50	0.969

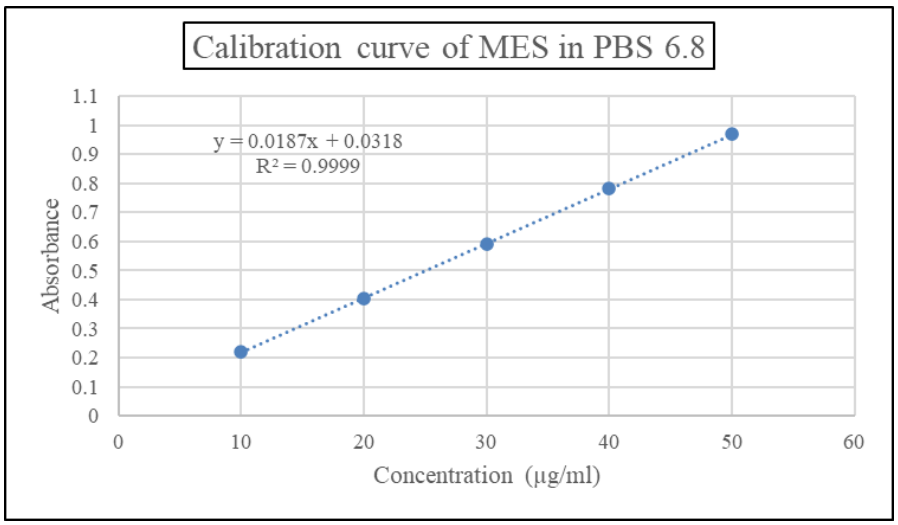

Fig 4: Calibration curve of mesalamine in phosphate buffer pH6.8

6.2 Saturation Solubility study of pure drug and cocrystal

Cocrystal of mesalamine with Ascorbic Acid, Sodium Acetate, urea, Saccharine sodium was observed with more solubility enhancement almost more than 40%. so are selected for further analysis DSC, XRD, SEM, etc. which will confirm the formation of cocrystals.,

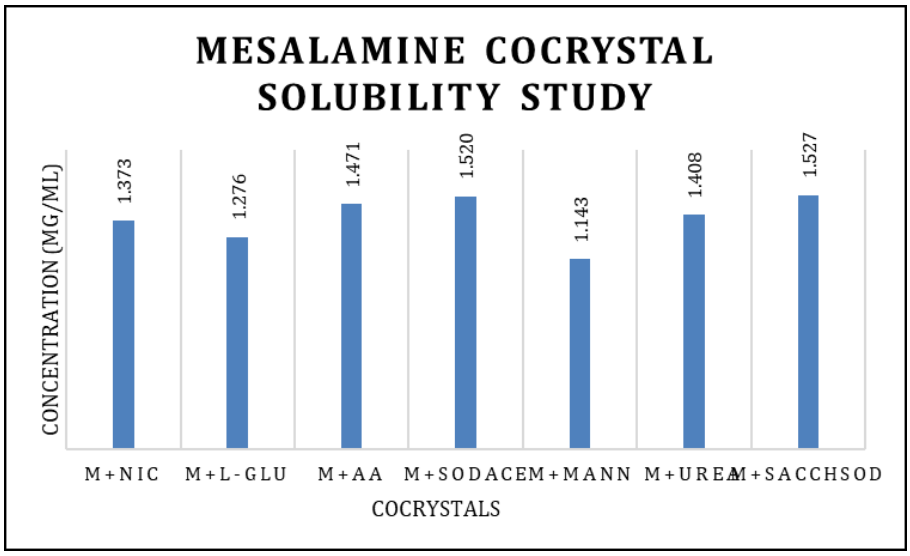

Fig 5: mesalamine cocrystal solubility study in distilled water

Analytical characterization of mesalamine and mesalamine Cocrystal

6.3 Infrared spectroscopy

Comparison of the IR spectrum of drug and cocrystal, clearly indicates that there is hydrogen bond formation between drug and coformer and new supramolecular synthon is formed.

1. **IR Spectrum of mesalamine:**

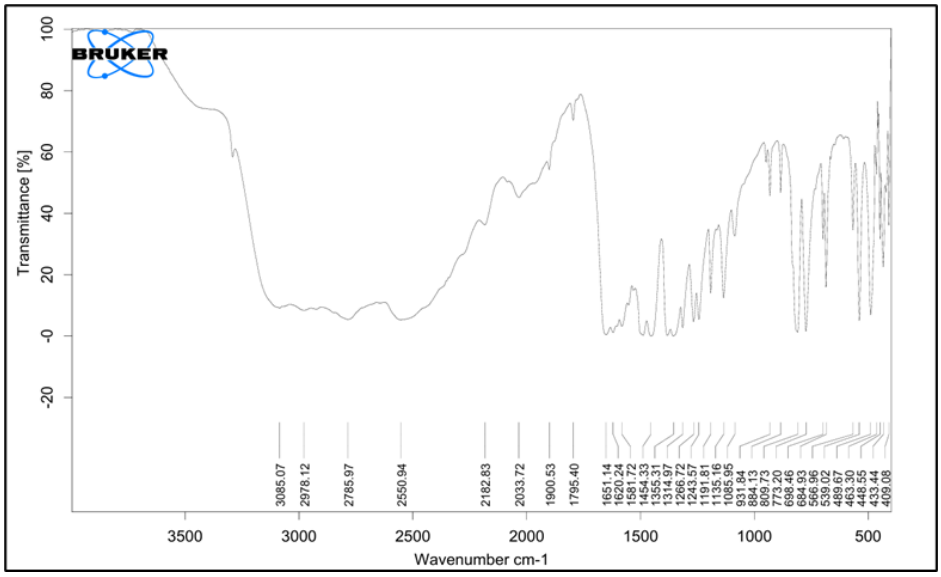

Fig 6: IR Spectra of Mesalamine

Table 8: Characteristic peaks from mesalamine IR

Wavenumber (cm^{-1})	**Functional Group**
3305.07	Broad phenolic O–H stretching
2978.12	Aromatic or Aliphatic C–H stretching
2785.97	N–H stretching
2550.94	Broad Carboxylic acid O–H
1795.40	Sharp C=O stretch

6.4 IR Spectrum of M+SacchSod cocrystal:

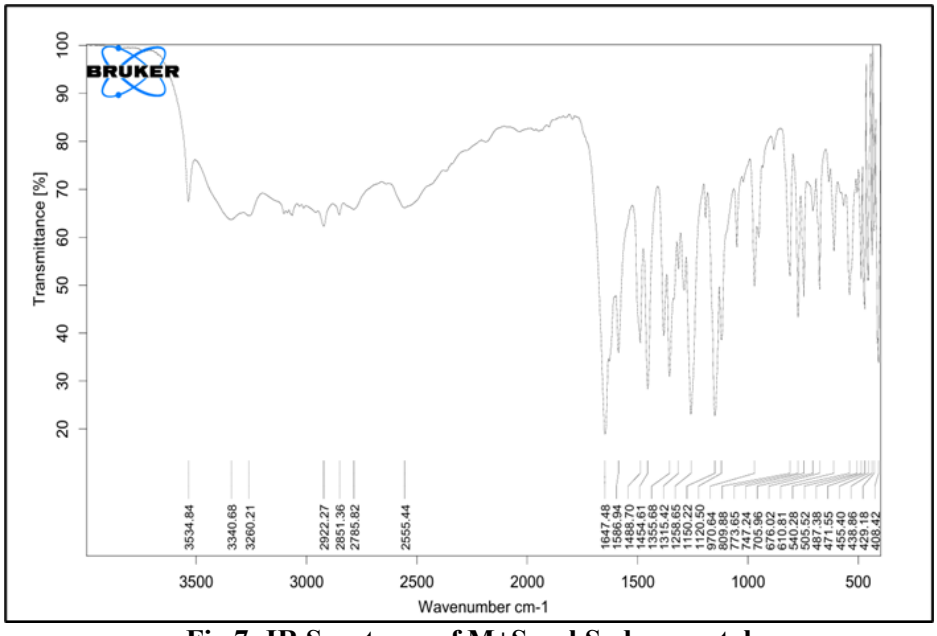

Fig 7: IR Spectrum of M+SacchSod cocrystal

Table 9: Major shifts in absorption peaks of M+SacchSod cocrystal

Wavenumber Region (cm^{-1})		Interpretation
Mesalamine Peaks	**Co-Crystal Peaks**	
3305.07	3260.21	O–H stretching Shifts indicate altered H-bonding
2978.12	2922.27	Aromatic/ Aliphatic C–H stretching
2785.97	2785.82	N–H stretching Shifts indicate altered H-bonding
2550.94	2555.44	Broad Carboxylic acid O–H
1651.14	1647.48	Aromatic C=C and N–H bending

6.5 Differential scanning calorimetry

Mesalamine and cocrystals are characterized by DSC. Pure drug and cocrystal shows characteristic endothermic peak at different temperature corresponding to melting point. This indicates possibility of formation of cocrystal. The change in thermal properties were reported as evidence for the formation of cocrystal.

1. DSC thermogram of Mesalamine

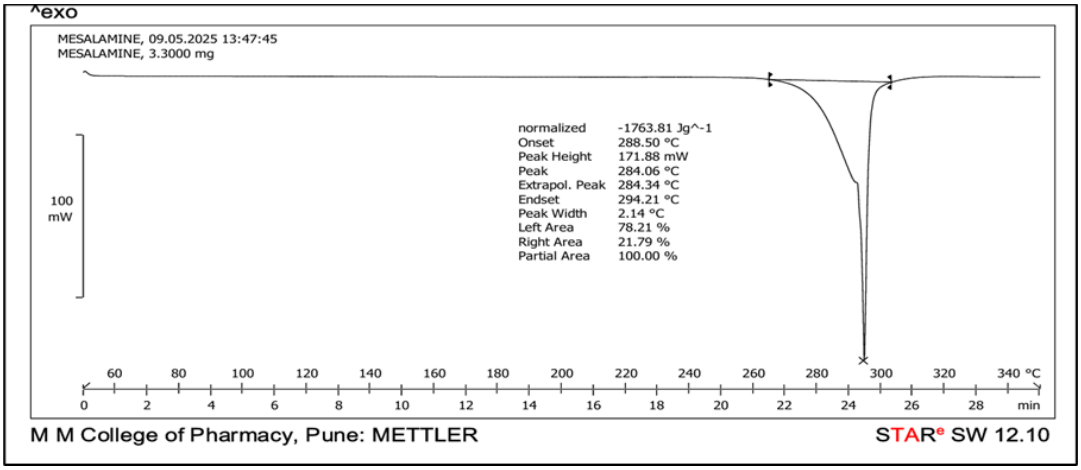

Fig 8: DSC thermogram of Mesalamine

DCS thermogram of M+SacchSod cocrystal:

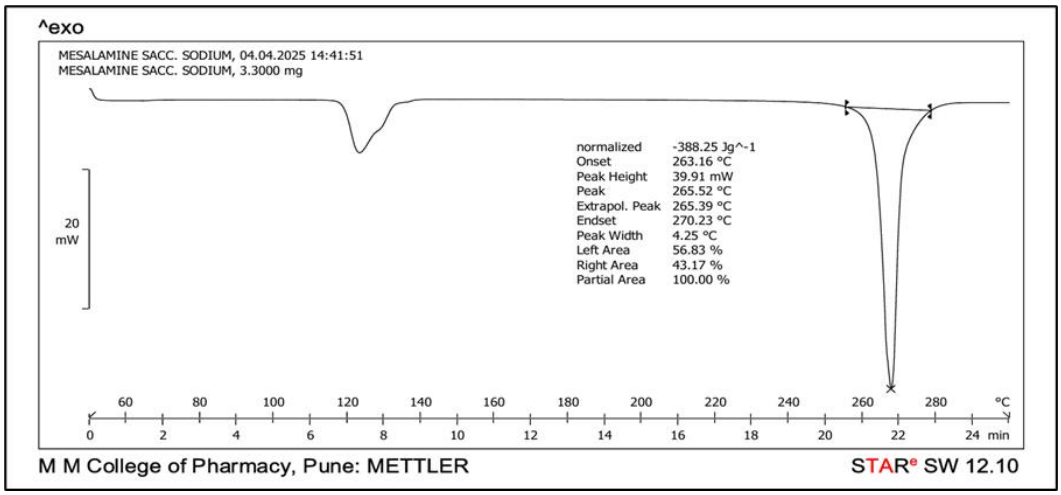

Fig 9: DSC thermogram of M+SacchSod Cocrystal

The cocrystal showed substantial difference in melting point 265.52°Cin comparison to pure drug 284.06°C. moreover, the peak onset for pure drug was obtained at 288.50°C whereas 263.16°C for cocrystal which indicates possibility of formation of cocrystal.

6.6 Powder X-ray diffraction (PXRD)

The PXRD Patterns of cocrystals are shown in figure . Material in powder state give distinctive peak of varying intensity at certain position. The PXRD patterns of cocrystals was distinguishable from components and additional peaks were appeared which did not exist in pure drug. The appearance of new diffraction peak in diffractogram of cocrystals shows formation of new crystalline face.

1. Powder X-ray diffraction of Mesalamine

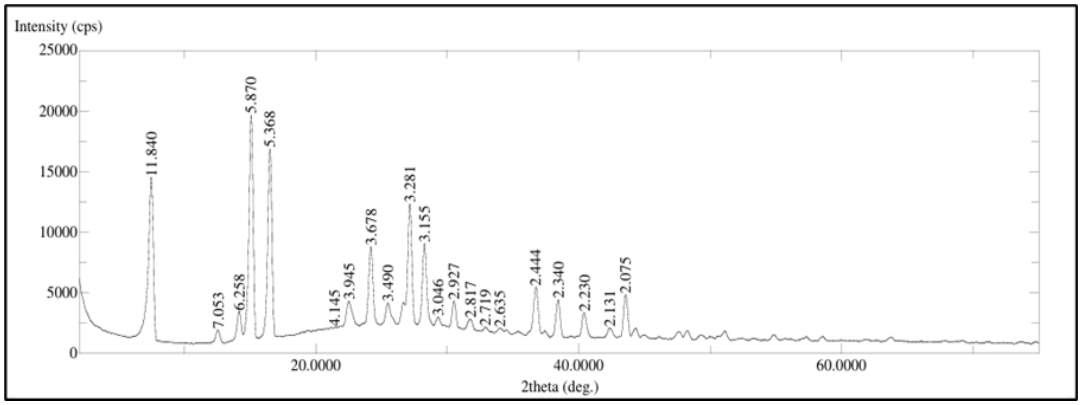

Fig 10: PXRD pattern for Mesalamine

2. Powder X-ray diffraction of M+SacchSod cocrystal:

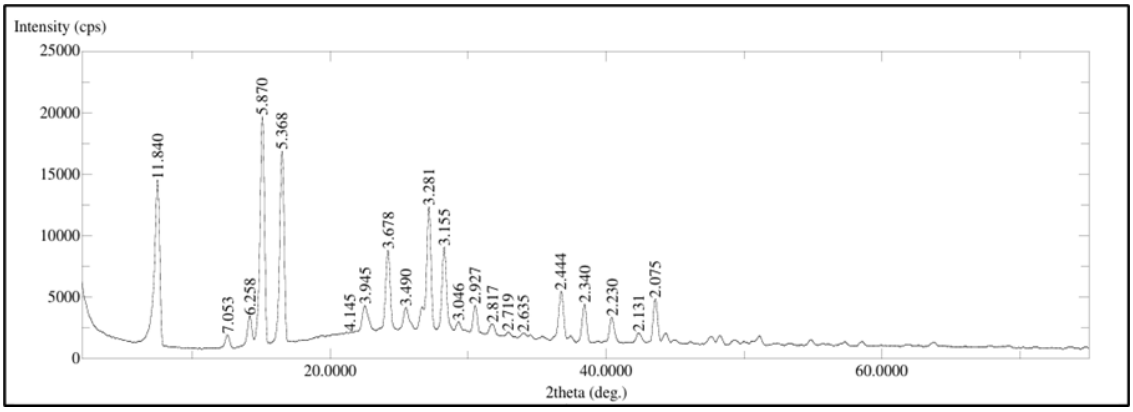

Fig 11: Powder X-ray diffraction of M+SacchSod cocrystal

6.7 Scanning Electron Microscopy SEM

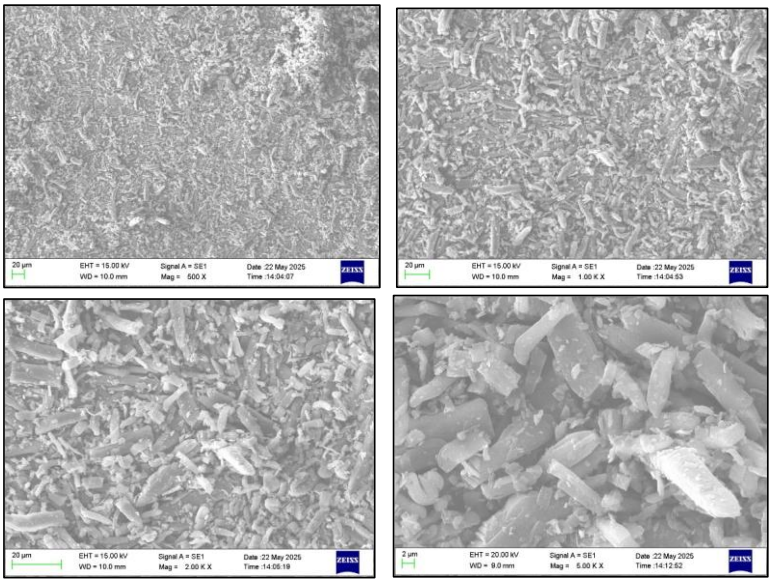

Fig. 12 SEM of Mesalamine

The surface morphology of the Mesalamine was studied by SEM. The scanning electron microscopic images of Mesalamine at 500X, 1000X, 2000X and 5000X magnification shows its crystalline structure.

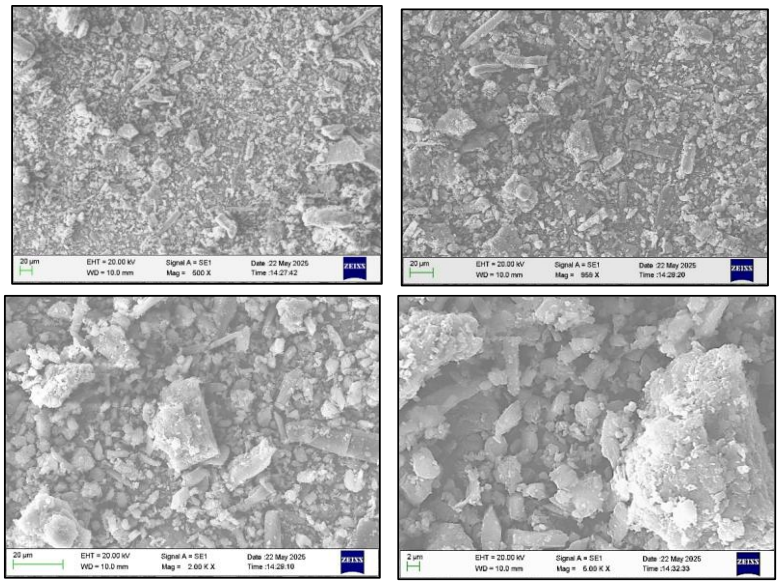

Fig. 13 SEM of M+SacchSod

The Mesalamine, M+SacchSod cocrystal was subjected to evaluation by SEM to study the surface morphology and result is depicted in figure. Due to greater solubility and considering analytical evaluation only M+SacchSod cocrystal was evaluated by SEM. Remarkable change was observed in the M+SacchSod cocrystal. The substantial enhancement in crystallinity supports the formation of cocrystal

6.8 Preformulation Study of Pure Drug and Cocrystal

Table 10: Preformulation study of pure drug and cocrystal

Sample	Angle of repose (°C)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index (%)	Hausner's ratio
Pure drug	30.02	0.383	0.434	11.76	1.133
M+SacchSod Co-crystal	29.03	0.440	0.501	12.14	1.139

The pure mesalamine and M+SacchSod cocrystal were subjected to Preformulation study and results are given in table. The results indicate that bulk and flow properties of cocrystal were improved in comparison to pure drug. This may be due to formation of new crystalline phase with altered particle properties like size, shape etc. Hence cocrystal may provide opportunity to enhance the bulk and flow properties of the API with improved processing properties.

6.9 post-compression parameters of tablet

Table 11: Post-compression parameters of tablet

Parameter	Result	
	Pure Drug	cocrystal
Weight Variation (mg)	460 ±10.2	1077 ±25.5
Hardness (kg/cm2)	2.5	3
Thickness (mm)	4	6.5
Friability (%)	0.8	0.5
Disintegration time (min)	6	8

6.10 Dissolution Studies

The dissolution rate plays crucial role in the bioavailability of drugs with poor solubility. The dissolution experiment was conducted on the tablet of pure drug and cocrystals. The dissolution profile of the pure drug and the prepared cocrystal is shown in Figure 32. The dissolution profile of pure drug tablet indicates slow dissolution rate with only 11.25% of the drug dissolved in the 60 min. The total amount of drug dissolved in 120 min was 49.35%. However, cocrystals of the M+SacchSod cocrystal tablet resulted in significant increase in the dissolution rate. The amount of drug dissolved in first 60 min was 16.70% and. The total amount of drug dissolved in 120 min was 65.24%. Greater dissolution of mesalamine from cocrystal can be attributed to enhanced solubility of cocrystal in the dissolution media.

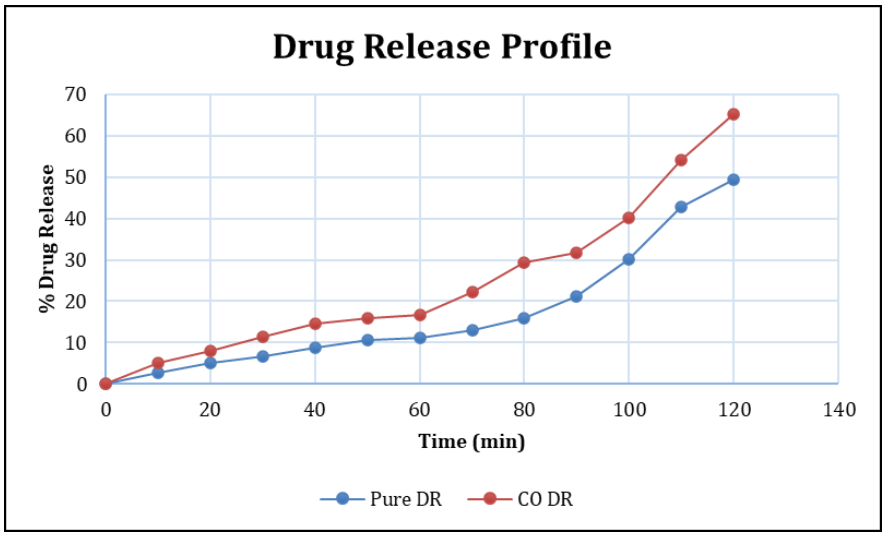

Fig 14: drug release profile of tablet of pure mesalamine and M+SacchSod cocrystal tablet

CONCLUSION

This research aimed to enhance the solubility of mesalamine, a poorly water-soluble BCS Class II drug, through the development of pharmaceutical cocrystals using the liquid-assisted grinding method. Mesalamine is widely used in the treatment of ulcerative colitis and Crohn's disease but suffers from limited oral bioavailability due to poor aqueous solubility. Eleven coformers were initially screened using solubility parameter (Δδ) and ΔpKa calculations. Coformers with $\Delta\delta \leq 7$ MPa 0.5 and $\Delta pKa < 3$ were shortlisted as suitable. Based on this screening and solubility study ascorbic acid, sodium acetate, urea, and saccharin sodium were selected for co-crystal preparation. Cocrystals were synthesized in a 1:1 molar ratio with mesalamine using acetonitrile as solvent and characterized using FTIR, DSC, PXRD, and SEM.

Key Results:

• Solubility Enhancement:

The pure mesalamine exhibited a saturation solubility of 0.982±0.018 mg/mL in water. Among the cocrystals, the M+SacchSod co-crystal showed the highest solubility, increasing to 1.527 mg/ml. Mesalamine-ascorbic acid (M+AA), mesalamine-sodium acetate (M+SodAce), and mesalamine-urea (M+Urea) also showed notable increases to 1.471 mg/ml, 1.520 mg/ml, and 1.408 mg/ml, respectively.

• DSC Analysis:

The melting point of pure mesalamine was observed at 284.06°C. The M+SacchSod co-crystal displayed a distinct melting peak at 265.52°C, indicating the formation of a new solid phase.

• PXRD Patterns:

PXRD of the M+SacchSod co-crystal revealed new diffraction peaks; absent in the spectra of both Mesalamine, confirming the creation of a novel crystalline structure.

• SEM Analysis

The Mesalamine, M+SacchSod cocrystal was subjected to evaluation by SEM to study the surface morphology and result is depicted in figure. Due to greater solubility and considering analytical evaluation only M+SacchSod cocrystal was evaluated by SEM. Remarkable change was observed in the M+SacchSod cocrystal. The substantial enhancement in crystallinity supports the formation of cocrystal

• Flow Properties:

The angle of repose for Mesalamine was 30.02°, indicating poor flow, while M+SacchSod had an improved angle of repose of 29.03°. Hausner's ratio also improved from 1.133 (Mesalamine) to 1.139 (M+SacchSod), showing enhanced compressibility and flow.

• Tablet Formulation:

Tablets containing M+SacchSod passed all pre- and post-compression quality control parameters, including hardness (3 kg/cm²), friability (0.5 %), and disintegration time (8 minutes).

• Dissolution Profile:

Mesalamine tablets released only 49.35% of drug content at 120 minutes in phosphate Buffer pH 6.8. In contrast, M+SacchSod tablets released 65.24% in the same time frame, nearly doubling the dissolution rate.

The study successfully demonstrated that Mesalamine cocrystals, particularly with saccharin sodium, significantly enhanced the Mesalamine solubility, flow properties and Dissolution rate. The use of computational tools such as solubility

parameter analysis and ΔpKa calculations effectively predicted coformer suitability. These findings confirm that cocrystallization is a viable strategy to overcome solubility-related challenges in poorly water-soluble drugs, offering improved formulation performance without altering the Mesalamine molecular structure. The M+SacchSod cocrystal holds strong potential for development into a superior oral dosage form for mesalamine.

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