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DEVELOPMENT AND EVALUTION OF CO-CRYSATALS OF RIFAMPICIN TO IMPROVE SOLUBILITY

Sourabh P. Jadhav* Dr. Indrayani S. Bandgar
RAJARAMBAPU COLLEGE OF PHARMACY, KASEGAON (MS) INDIA

ABSTRACT

BCS class II drug Rifampicin has high permeability and low solubility. categorized as an NSDAI. Novel co-crystal forms of Rifampicin with generic GRAS(generally recognized as safe) molecules were created via crystal engineering. Salicylic acid and other GRAS compounds were used to create pharmaceutical co-crystals of rifampicin in a 1:1 ratio. Rifampicin co-crystals were produced via solvent drop grinding and solvent evaporation methods. to confirm the production of Co-crystals and their purity. Every formed crystalline form was analyzed using FTIR, DSC, and XRD. Differential scanning calorimetry provìded information on changes in thermal behavior and co-crystal formation, while X-ray crystal data provided information on hydrogen bonding and the ways in which the medication and the coforms. Every co-crystal disintegrated faster than the parent medication based on evaluations of physical and chemical characteristics such as solubility and rate of dissolution. FPN-FA cocrystals had the maximum solubility of any crystalline form.

Key words : Rifampicin, Co-crystals, Salicyclic acid, Solvent drop Grinding, Solvent Evaporation, etc.

INTRODUCTION

The therapeutic efficacy and manufacturing costs of solid dosage forms are significantly influenced by the physico-chemical characteristics of Active Pharmaceutical Ingredients. This setting emphasizes the importance of factors including compatibility, taste, hygroscopicity, solubility, stability, particle size, and powder flow properties.[1] The pace at which medication molecules dissolve and become soluble has a significant effect on the GI tract's nutritional absorption in oral drug administration methods. Unfortunately, 90% of recently discovered chemical entities and 40% of already marketed medications fall under the Biopharmaceutical Classifícation System (BCS) Class II & IV, which has problems with low solubility and

poor bioavailability. This eventually affects the therapeutic use of medications by reducing drug absorption within the gastrointestinal system.[2]

It is well known that the physical-chemical characteristics of pharmacėuticals solids greatly impact the efficacy of medicinal goods. It is commonly known that atomic packing & crystal lattice of given crystalline substance directly affect its qualities. Thus, by changing the crystal packing patterns, one may change the physicochemical characteristics of a solid medication that has been created.[3]

A minimum of one of these compounds is an API, and the remaining substances are pharmaceutically acceptable substances. Pharmaceutical co-crystals is defined as crystals with more discrete neutral compounds arranged in a ratio that is stoichiometric and bonded through non-covalent bonding (such as a hydrogen bond as well as van der Waals & stacking interactions).[4]

Selection of Co-formers:

Before creating pharmaceutical co-crystals, it's crucial to analyze conformer compatibility and drug suitability. Conformer screening helps identify suitable co-formers that can be combined with a drug to form a co-crystal. After selecting the best candidate, its pharmacological and physicochemical properties are investigated. To ensure safety, USFDA's generally recognized as safe(GRAS) list is often used for co-former selection, as these substances do not impact the drug's pharmacological effects. In summary, this process guarantees the development of safe and effective co-crystals for pharmaceutical applications.[7]

MATERIALS AND METHODS

Materials

Lupin Goa gave me a sample of Rifampicin as a gift. Global Calcium provided L-Lysine, L-Arginine, and Urea. Ethanol and methanol are the solvents utilized to create cocrystals. Every item utilized was exactly as received.[31]

Co-crystal preparation:

Cocrystal preparation is a crucial process in pharmaceuticals to improve API properties and formulations. Various techniques are employed, including solvent evaporation, solution reaction crystallization, solid-state grinding, Slurry Conversion, and Hot Melt Extrusion. The choice of method depends on empirical judgment between solution-based and solid-based approaches.[10]

Solution-based methods:

The ideal condition for cocrystal formation is when the mixture is super-saturated with the API and coformer, and the reactants are either saturated or undersaturated. The critical factor is adjusting the concentration of API and coformer to modify the degree of super-saturation. A phase diagram is necessary to guide cocrystal production, ensuring that the resulting crystals are thermodynamically stable and avoiding the crystallization of pure reactants within the stable zone. Solubility of the reactants is an important factor influencing the zones of thermodynamically stable cocrystals.[19]

Solvent evaporation technique :

Solvent evaporation is a reliable method for generating co-crystals. It involves dissolving a medication and coformer in a suitable solvent, then allowing the solvent to evaporate at room temperature. The choice of solvent depends on the API and coformer's solubility. This method can produce co-crystals with increased stability and solubility, and is effective for creating multi-drug co-crystals.[12]

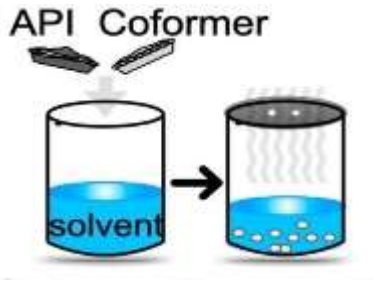


Fig.no.1.1 Solvent Evaporation Method

Anti solvent crystallization:

Anti solvent crystallization is a method for creating high-quality co-crystals. It involves supersaturating the drug-containing medium by adding a liquid, such as a buffer or organic [35]

Slurrying:

In the slurry Cocrystallization process, an appropriate coformer and an Active Pharmaceutical Ingredient(API) are mixed with Solvent based on their solubility. The chosen solvent allows co-crystal formation upon adding the coformer and stirring. Co-crystals are then created as the solvent evaporates at room temperature, which can be characterizes using Powder X-ray Diffraction(PXRD)[18].

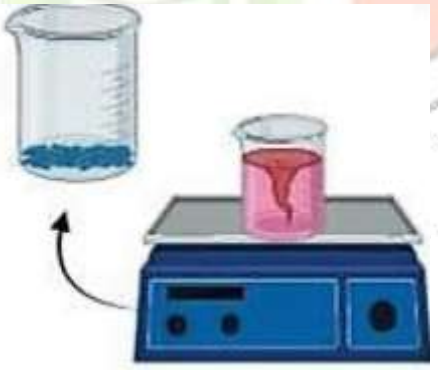


Fig.no1.2 Slurry Conversion Method

Reaction Co-crystallization:

Cocrystallization is effective for creating cocrystals when components have different solubilities. Mixing reactants with non-stoichiometric proportions forms highsaturated solutions, leading the Co-crystals precipitation. The reactants' ability to lower crystal solubility controls nucleation & crystals incressed. the reaction crystallization approach, indomethacin and saccharin cocrystals have been produced.[26]

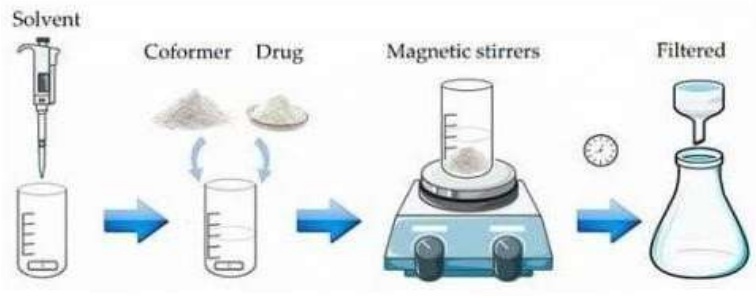


Fig. no.1.3Reaction Cocrystallization

Neat grinding:

Solid-state or dry grinding is a method where API and coformers are combined and ground using equipment like ball mills and mortar and pestle. However, this method can be challenging for forming crystals due to poor grinding quality and heat generated during grinding, which can affect the stability of the material. [27]

To overcome these issues, high-melting-point APIs are often used in mechanochemical grinding for co-crystallization[22]

Fig no. 1.4 Neat Grindig

DRUG & EXCIPIENTS

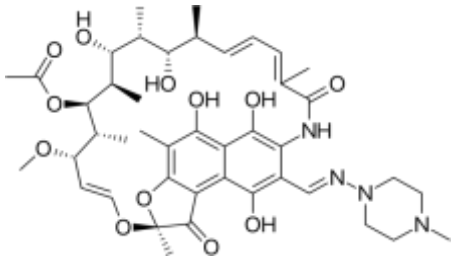
A) Drug Profile:

Rifampicin

1. **BCS Class:** Class II
2. **Appearance:** Red – brown, Crystalline Powder.
3. **Odour:** Odourless
4. **Mol.F:** C43H58N4O12

5. **Mol.Wt.** 822.41 g/mol

6. **Log P value:** 1.086



7. **Structure**

8. **Solubility:** Very slightly soluble in water,Freely soluble in chloroform; Soluble in chloroform,Soluble in ethyl acetate and in methanol

9. **Hydrogen bondacceptor:**12

10. **Hydrogenbonddonor:** 6

11. **Rotatable bondcount:** 5

12. **Meltingpoint:**183 ^{o}C – 188 ^{o}C

13. **pH:** 2.06

14. **Boiling point:**937 ^{0}C

15. **Flash point:** 561.5±3.0 ^{o}C **16.Density:**

1.3±0.1gm/cm3 **17.Refractiveindex:**1.613

18.Molarrefractivity: 213.1±0.5cm^{3}

19.Pharmacokinetics:

Absorption:

- Following oral administration rifampicin is very instantly absorbed.
- Peak plasma concentrations were reached 0.5- 4 hours following oral administration.

Volume of Distribution:

- 14L[HealthyAdultsintheNorm]
- 12L[PatientswithGeriatricArthritis]
- 10 L[PatientswithEnd-Stage RenalDisease]
- 14L[PatientswithAlcoholicCirrhosis]

- 0.12L/kg

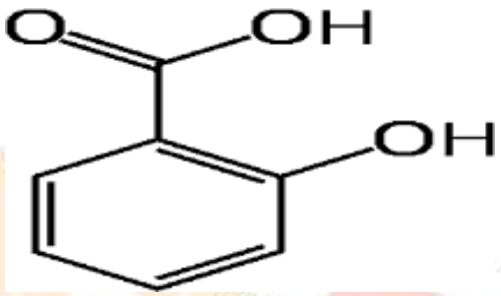
B) Excipients:

Salicylic Acid

1. **Mol.F**:$C_7H_6O_3$

2. **Mol.Wt.**138.1207g/mol

3. **Structure**:



4. **Description** : The substance prepared synthetically and also obtained from the white willow as wellas wintergreen leaves. It effect keratolytic, killing the fungal infection , and bacteriostatic effects. Salicylates,whichareitssalts,areemployedas analgesics.

5. **Odour:**Odourless

6. **Taste**:Sweetish,afterward acrid,taste.

7. **Solubility:**11.3mg/ml

8. **Meltingpoint**:158°C

9. **Boiling point:**211°C.

10. **Hydrogen bonddonor**:2

11. **Hydrogen bondacceptor**:3

12. **Rotatablebondcount**:1

13. **pKa(StrongestBasic):** -6.3

14. **pKa(StrongestAcidic):** 2.79

15. **.Refractiveindex:** 35.3$m^3 \cdot mol^{-1}$

16. **16.LogP:**1.96

RESULTS

Pre formulation study of drug & coformer:

The preliminary formulation of medication and conformer yields the results shown below based on melting point and visual inspection.

Table No:1.1 Result of Organoleptic Properties of Rifampicin

Sr.no.	Identification test	Observed outcome	Reported as per USP
1	Physical state	Solid crystalline	Solid crystalline
2	Colour	Red-orange	Red-orange
3	Odour	Odourless	Odourless

Table No:1.2 Result of Organoleptic Properties of Co former

Sr.No	Coformer	Physical state	Colour	Odour
1	L-Lysine	Solid crystalline	Red-Orange	Odourless
2	L-Arginine	Solid crystalline	Red- Orange	Odourless
3	Salicylic acid	Solid crystalline	Amber	Odourless
4	Urea	Solid crystalline	Pale yellow	Odourless

Melting Point Determination:

Ideally Rifampicin, Salicylic acid, L-Lysine, L-Arginine, Urea melts at 183-188, 158-161, 224- 227, 244-247, 133-137 respectively & practically observedmelting point at 184, 159, 228, 245, 135, °C respectively. It proves that the given powder material is Rifampicin, Salicylic acid, L- Lysine, L-Arginine, Urea all powder substances in pure form.

UV-Spectral Characterization:

Below are the calibration curve and λ max determination for different solvents and buffers:

A) In distilled water:

The 2.5 mcg/ml solution of Rifampicin was analyzed usìng a UV spectrophotomėter (Shimadzu UV-1900) to determine its absorption properties. The maximum absorption was observed in a wavelength 344 nm. In this of pure Rifampicin in water, the concentration range was identified. to be between 1 and 3 g/ml when plotted on a concentration vs. absorbance graph.

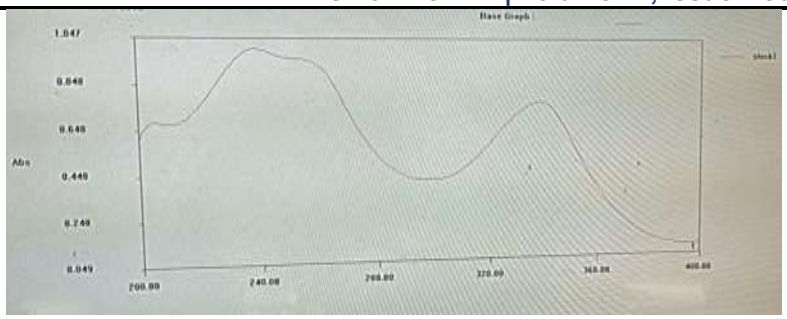
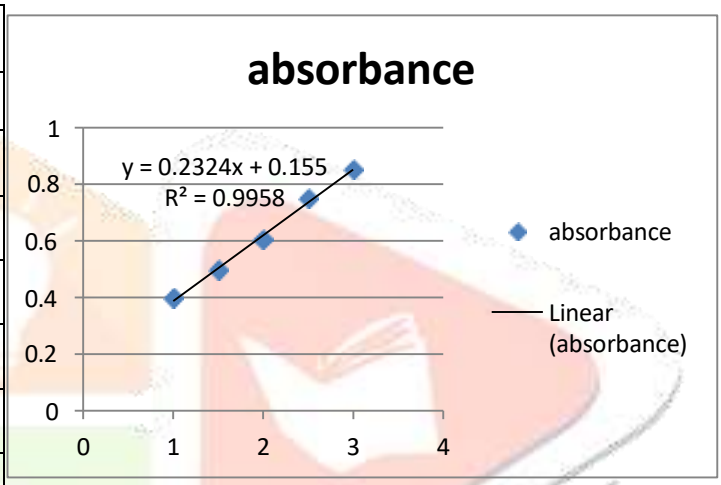


Fig. no.2.1 λ max of Rifampicin in water

Table. no.1.3 λ max and calibration curve of Rifampicin in water

λmax	Absorbance
344	0.716
Conc.(µg/ml)	**Absorbance**
1	0.336
1.5	0.458
2	0.569
2.5	0.716
3	0.881



C)In Ethanol :

The 2.5 mcg/ml solution of Rifampicin was analyzed using a UV spectrophotometer (Shimadzu UV-1900) to determine its absorption properties. The maximum absorption was observed at a wavelength of 344 nm. In the pure Rifampicin in Ethanol, the concentration range is found to be between 1 and 3 g/ml when plotted on a concentration versus absorbance graph.

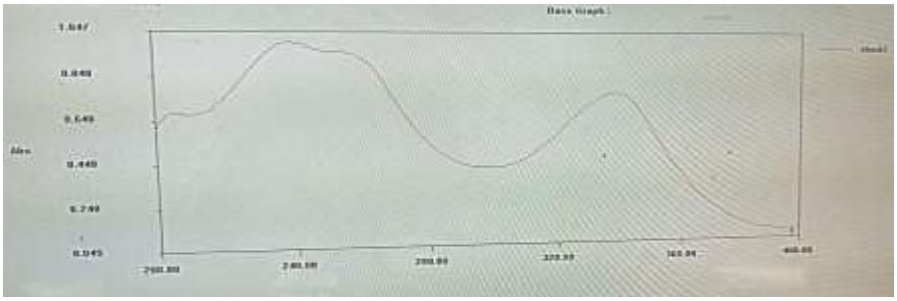
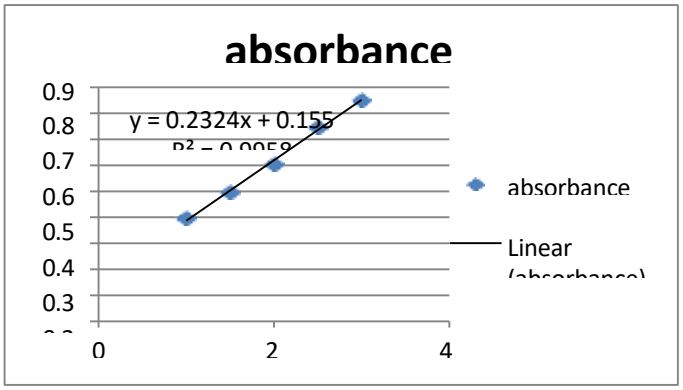


Fig.no.2.2 λ max of Rifampicin in Ethanol

Table.no.1.4 λ max and calibration curve of Rifampicin in Ethanol

λmax	Absorbance
344	0.750
Conc.(µg/ml)	**Absorbance**
1	0.397
1.5	0.496
2	0.605
2.5	0.750
3	0.851



Solubility study:

Solubility study of Rifampicin and Rifampicin cocrystals was performed in different solvents:

Tableno.1.5Solubility of Rifampicin

sr.no.	Solvent	Rifampicin (mg /ml)
1	Water	0.49±0.06
2	0.1N HCl	1.88±0.04
3	PBSpH6.8	7.89±0.03
4	PBSpH7.2	4.86±0.02
5	Methanol	9.55±0.05

Table no.1.6 Solubility study of Rifampicin Co-crystal prepared with different conformer by solvent drop method.

Solvent	Solubility			
	L-Lysine cocrystal	L-Arginine Co crystal	Salicyclic acid cocrystal	Urea cocrystal
Water	4.26±0.13	4.56±0.23	6.23±0.09	5.12±0.23
0.1NHCl	1.27±0.21	1.94±0.16	3.48±0.13	2.24±0.12
PBS pH6.8	8.34±0.28	7.65±0.19	9.79±0.22	8.02±0.26
PBS pH7.2	8.64±0.18	8.14±0.29	9.75±0.32	9.31±0.14
Methanol	9.14±0.24	9.24±0.21	9.94±0.30	9.34±0.23

Table no 1.7 Solubility study of Rifampicin Co-Crystal prepared with different conformer by Solvent Evaporatìon method

Solvent	Solubility			
	L-Lysine Cocrystal	L-Arginine Co crystal	Salicyclic acid Cocrystal	Urea Cocrystal
Water	6.24±0.29	6.46±0.16	9.64±0.33	7.25±0.42
0.1NHCl	4.29±0.32	3.79±0.19	7.13±0.22	4.42±0.38
PBS pH6.8	8.69±0.23	8.67±0.13	9.88±0.27	8.27±0.17
PBS pH7.2	8.96±0.34	9.12±0.29	9.94±0.30	9.39±0.23
Methanol	9.26±0.36	9.45±0.31	9.99±0.35	9.36±0.14

In-vitro drug release study:

Table no. 1.8 In-vitro drug release study of Rifampicin co-crystal by solvent drop method

Sr.No	time (min)	%DR Of L-Lysine	%DR Of L-Arginine	%DR of Urea	%DR Of Salicylic acid
1	0	0	0	0	0
2	10	11.47 ±1.2	12.51 ±0.8	15.37 ±0.5	13.47 ±0.3
3	20	25.47 ±0.9	26.23±0.6	29.47 ±0.8	37.37 ±0.5
4	30	35.0 ±0.3	36.80 ±0.9	42.13 ±0.3	55.37 ±0.7
5	40	42.0 ±1.4	51.56 ±0.4	57.18 ±0.7	69.75 ±1.2
6	50	45.4 ±0.7	64.90 ±0.2	68.80 ±0.9	77.66 ±0.8
7	60	53.28 ±1.1	74.90±0.6	82.61 ±1.2	89.66 ±0.2

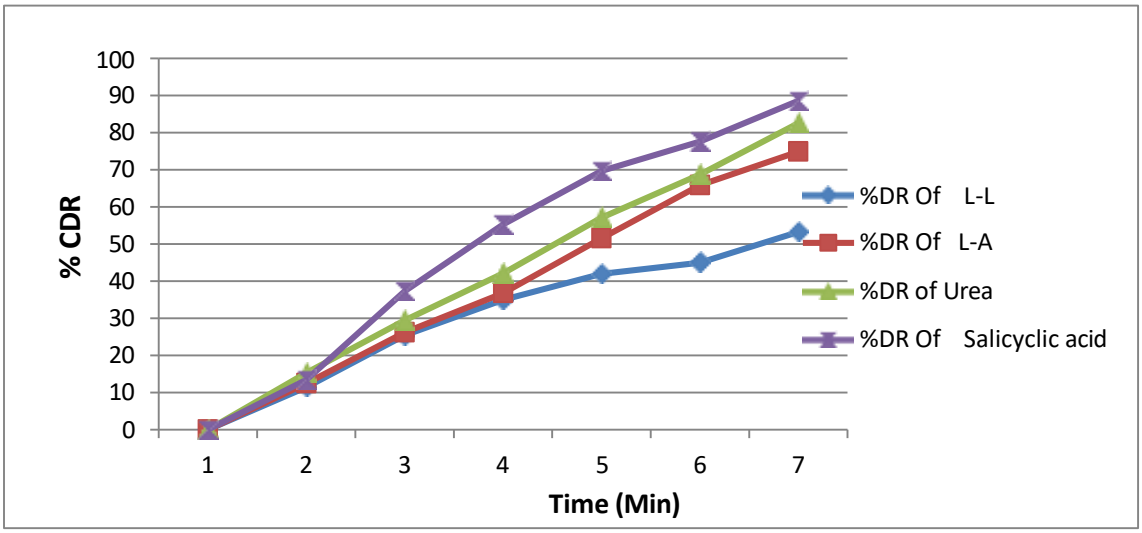


Fig No. 2.3 % drug release

Table no 1.9 In-vitro Drug release study of Rifampicin cocrystal by solvent evaporation method

Sr.no.	Time (min)	%DR Of L-Lysine	%DR Of L-Arginine	%DR of Urea	%DR Of Salicyclic acid
1	0	0	0	0	0
2	10	11.47±0.9	16.90±0.3	16.32±0.6	31.66±0.5
3	20	25.47±1.2	31.47±0.7	35.47±0.8	52.13±1.2
4	30	35.09±0.7	42.13±1.5	42.61±1.1	67.94±0.4
5	40	42.04±0.4	55.85±1.1	55.09±0.5	76.51±0.6
6	50	45.47±1.1	74.42±0.9	65.18±0.9	83.37±0.2
7	60	53.28±0.6	76.80±0.4	83.09±0.3	94.32±0.7

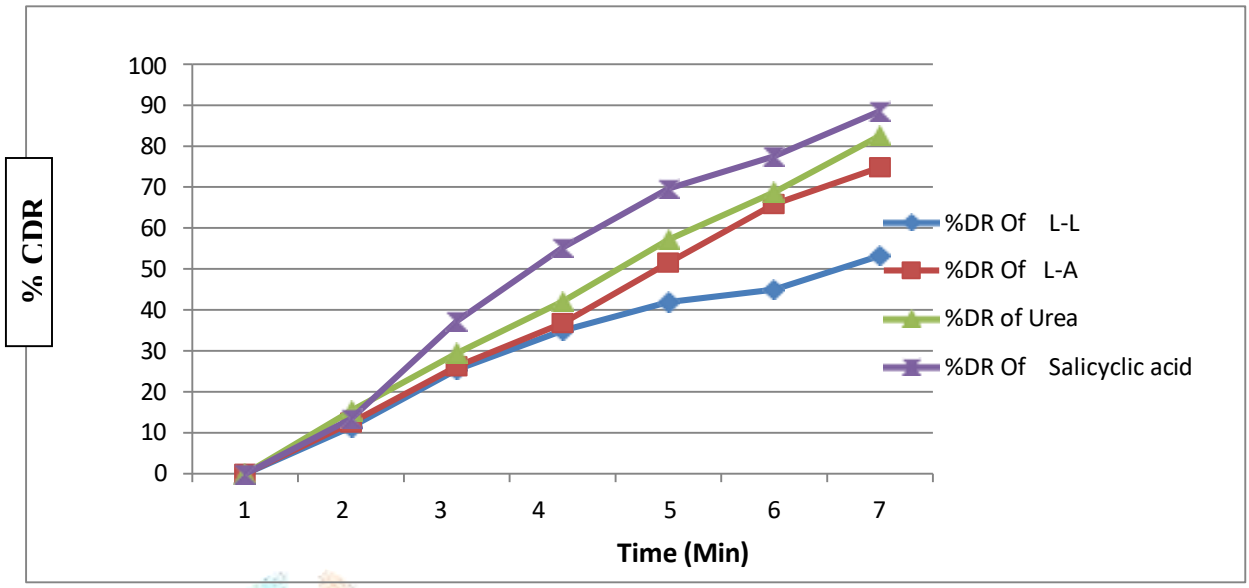


Fig No. 2.4 % drug release

FTIR:

A) Rifampicin

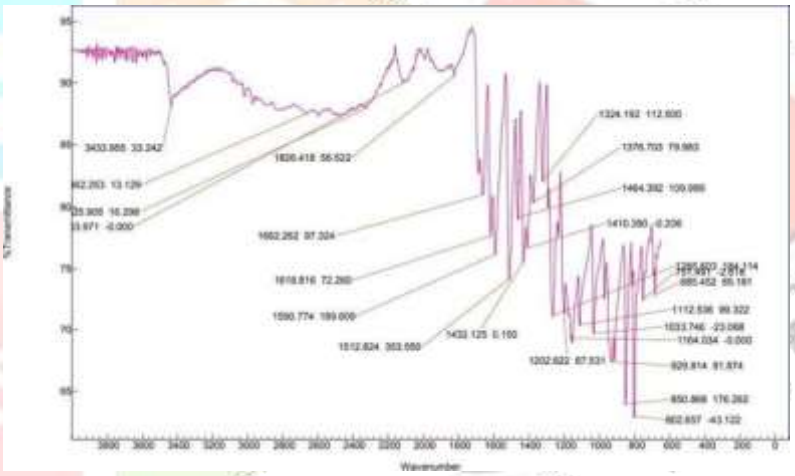


Fig. no.8.8 FTIR of Rifmpicin

The IR spectrum of Rifampicin shows peaks corresponding to the following functional groups:

* Methyl group (-CH3): 1432 cm-1

* Aromatic C-H bond: 802 and 850 cm-1

* Carboxylic acid group: 2590 cm-1 (O-H stretch), 1662 cm-1 (C=O), and 1265 cm-1 (C-O stretch)

* Primary amine group: 3433 cm-1 (N-H stretch)

These peaks help identify the functional groups present in the Rifampicin molecule.

B) Salicylic acid

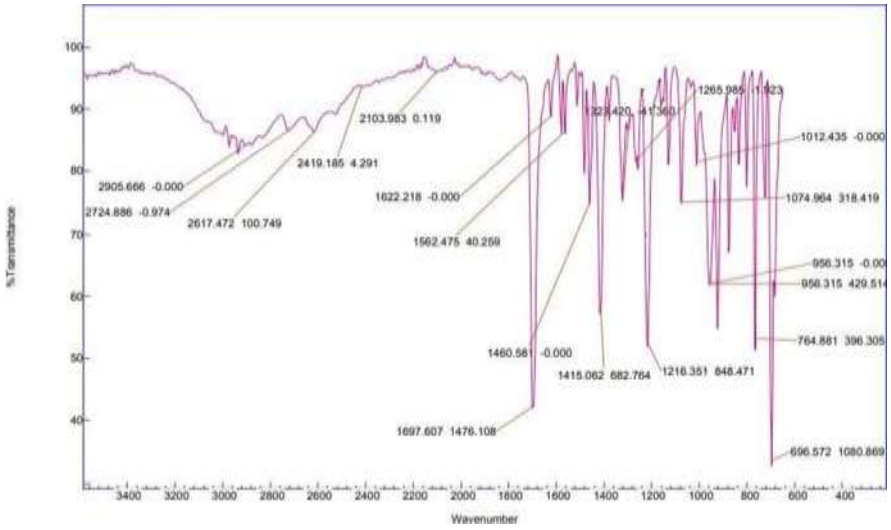


Fig.no.2.5FTIR of Salicyclic acid

Here is a concise summary of the characteristic peaks of salicylic acid:

1. C-H (-CH3): 1415 cm-1 (methyl group's C-H bond)
2. C-H (aromatic): 696 & 764 cm-1 (aromatic C-H bond stretching)
3. O-H (carboxylic acid): 2724 cm-1 (carboxylic acid group)
4. C=O (carboxylic acid): 1697 cm-1 (carbonyl group in carboxylic acid)
5. C-O (carboxylic acid): 1074 cm-1 (C-O bond in carboxylic acid group)

C) Physical Mixture

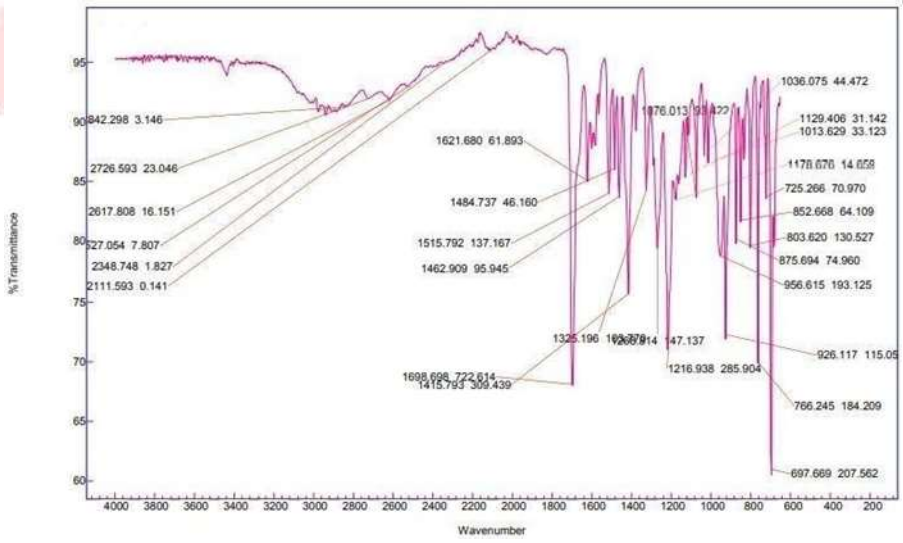


Fig.no.2.6 FTIR of Physical Mixture

In the analysis of the IR spectra, the majority of the peaks remained unchanged when the substances were physically mixed. However, some minor peak shifts occurred due to weak Van Der Waals forces. The affected peaks are:

* C-H (-CH3) at 1462 cm-1
* C-H stretch (aromatic) at 696 & 765 cm-1
* O-H stretch (carboxylic acid) at 2726 cm-1
* C=O (carboxylic acid) at 1698 cm-1
* C-O (carboxylic acid) stretch at 1075 cm-1
* N-H (primary amine) at 3423 cm-1

These peaks help identify the primary functional groups in the physical mixture.

D) **Cocrystal by Solvent evaporation method:-**

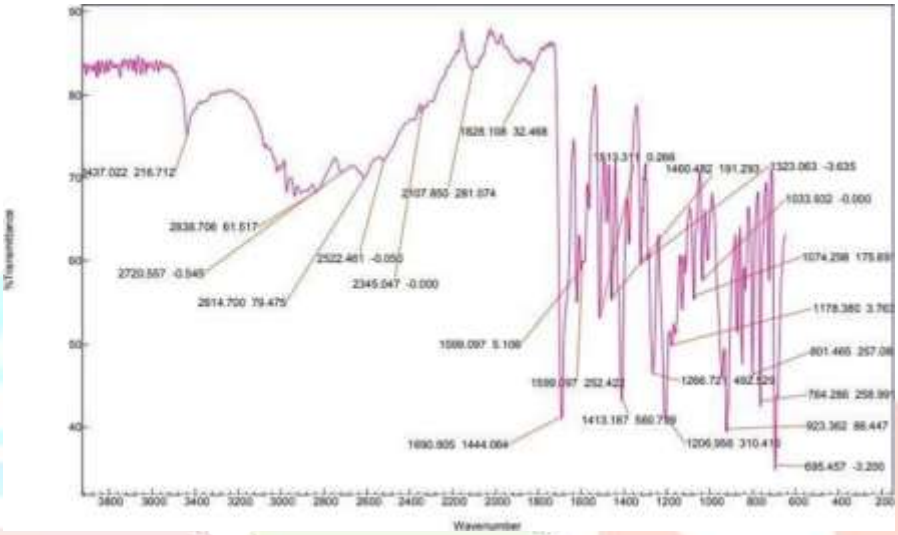


Fig. no.2.7 FTIR of Co-crystal by Solvent Evaporation

When Rifampicin and Salicylic acid co-crystallize, the following changes are observed:

* The O-H peak of Rifampicin shifts to the C=O peak of Salicylic acid.

* The O-H peak of Salicylic acid shifts to a slightly higher range (2724-2726 cm-1).

* Broad peaks in the 2500-3000 cm-1 range indicate O-H stretching and suggest hydrogen bonding.

* Peaks in the 3400-3500 cm-1 range hint at N-H interactions, increasing the probability of synthon formation at the N atom.

These changes suggest that the two molecules form hydrogen bonds and interact through nitrogen-hydrogen interactions, leading to the formation of a stable crystal structure.

E)Co-crystal prepared by solvent drop method:

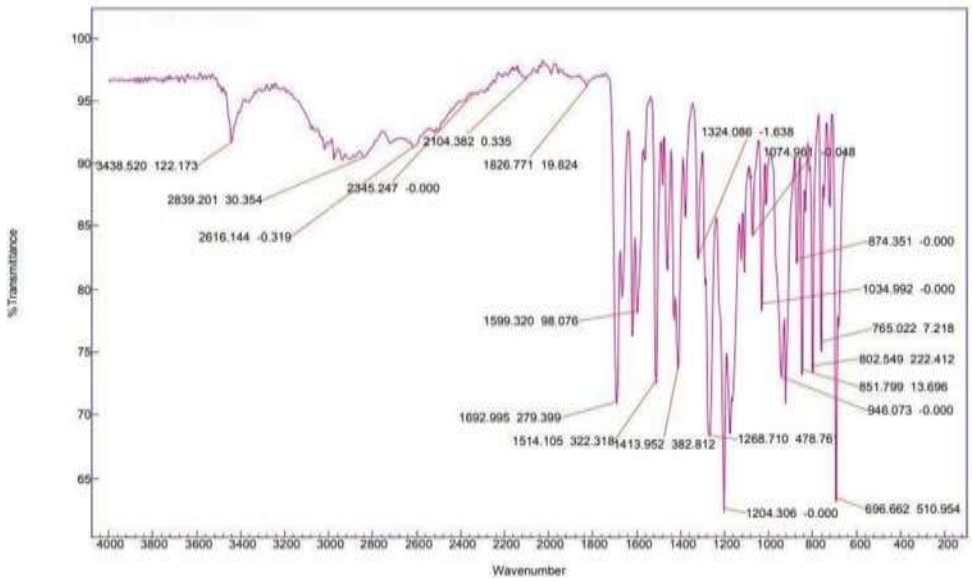


Fig. no.2.8 FTIR of Co-crystal by drop

* Rifampicin and salicylic acid have distinct peaks in their FTIR spectra:

+ Rifampicin: 2724 cm-1 (O-H stretch), 1697 cm-1 (C=O stretch), 3438 cm-1 (N-H stretch)

+ Salicylic acid: 1662 cm-1 (C=O stretch), 3334 cm-1 (O-H stretch)

* When combined in a co-crystal, the O-H peak of salicylic acid shifts from 2424 cm-1 to 2726 cm-1, and the C=O peak of salicylic acid shifts from 1662 cm-1 to 1692 cm-1

* The N-H peak of rifampicin also shifts from 3435-3438 cm-1

* The presence of broad peaks in the 2500-3000 cm-1 range indicates O-H stretching and hydrogen bonding, and peaks in the N-H range suggest nitrogen-hydrogen interactions, increasing the likelihood of synthon formation at the N atom.

XRD:

A) Rifampicin:

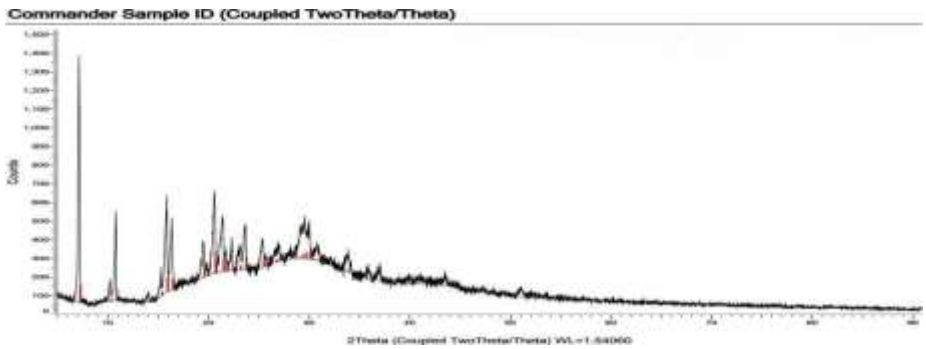


Fig no 2.9 XRD of Rifampicin

Table no.1.10XRD of Rifampicin

Sr. No	2Θ	Relative intensity

1	7.14	1386
2	10.79	553
3	15.84	638
4	20.56	662

B)Co-crystal Prepared by Solvent Evaporation Method:

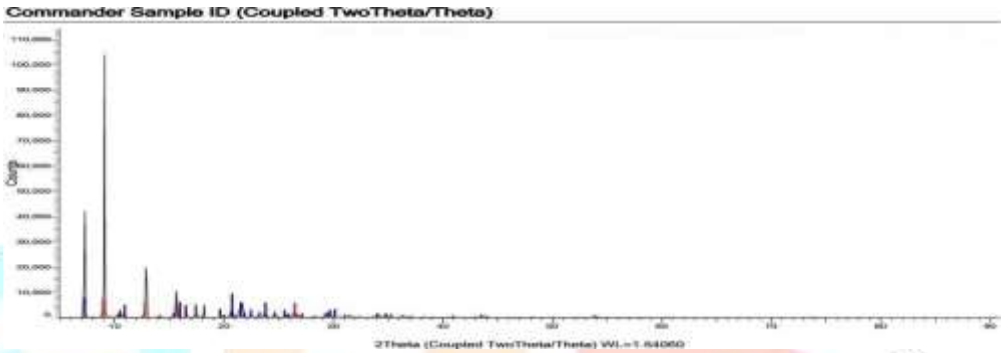


Fig.no.2.11Co-crystals by solvent evaporation

Table no.1.11 Co-Crystals by Solvent Evaporation

Sr.no.	**2Ɵ**	**Relative intensity**
1	7.27	42159
2	9.08	103870
3	10.92	3748
4	12.79	3338
5	12.88	19903
6	15.69	10624
7	21.70	5370

C)Co-crystal prepared by solvent drop method:

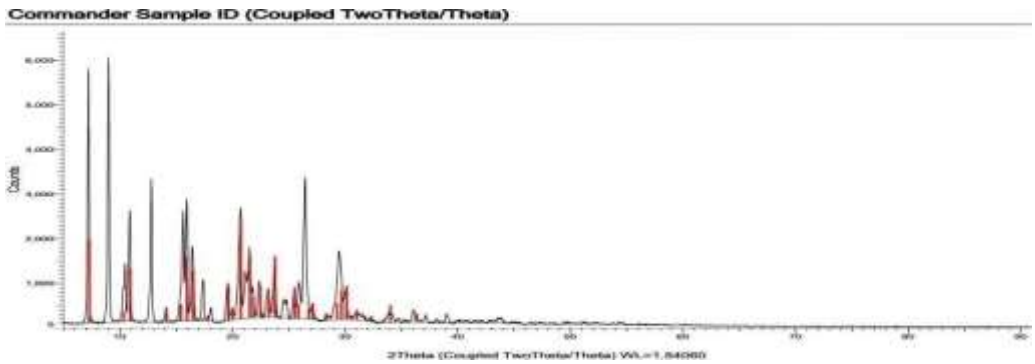


Fig.no.2.12 Cocrystal by solvent drop method

Table no. 1.12 Co-crystals by solvent drop method

Sr. no	2Ɵ	Relative intensity
1	7.23	5818
2	9.01	6057
3	10.86	2616
4	12.79	3338
5	15.62	2636
6	26.45	3389

DSC :

A)Rifampicin:

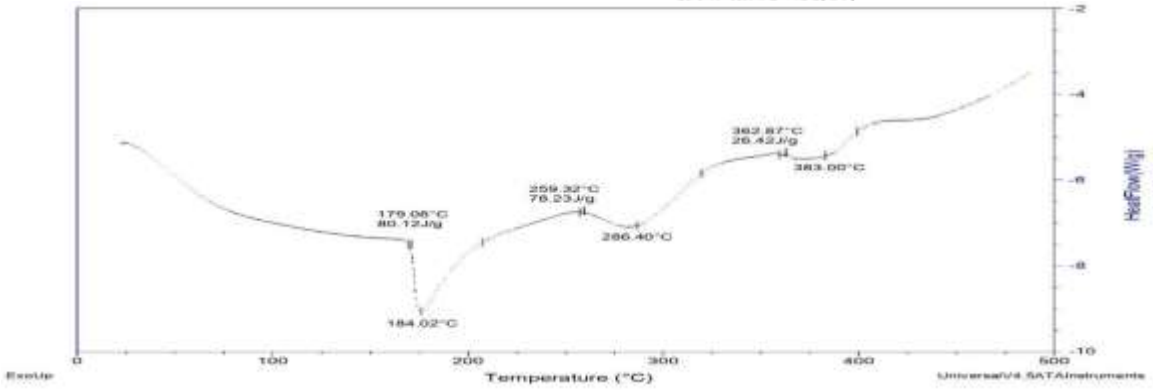


Fig. no. 2.13 DSC of Rifampici

Differential Scanning Calorimetry (DSC) was used to analyze the thermal behavior of Rifampicin, an antibiotic.

The resulting thermogram showed an endothermic peak at 184.2°C, which corresponds to the melting point (MP) of Rifampicin. This information is important for understanding the drug's stability.

B) Salicylic acid :

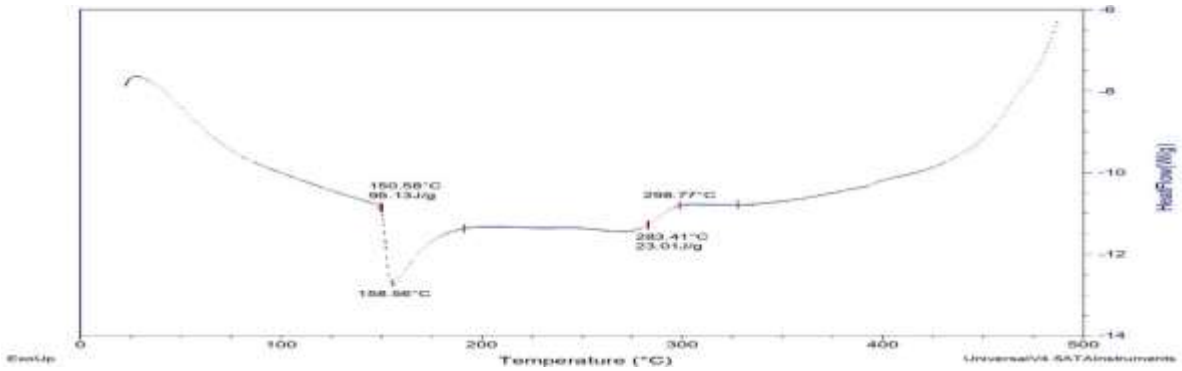


Fig.no.2.14DSC of Salicylic acid

DSC analysis of salicylic acid showed an endothermic peak at 158.56°C, indicating its melting point, which is the temperature at which it transitions from a solid to a liquid state. This information is crucial for understanding the drug's stability, purity, and applications, and can be used to optimize processing conditions, storage requirements, and develop new formulations.

C)Co-crystal by solvent Evaporation method:-

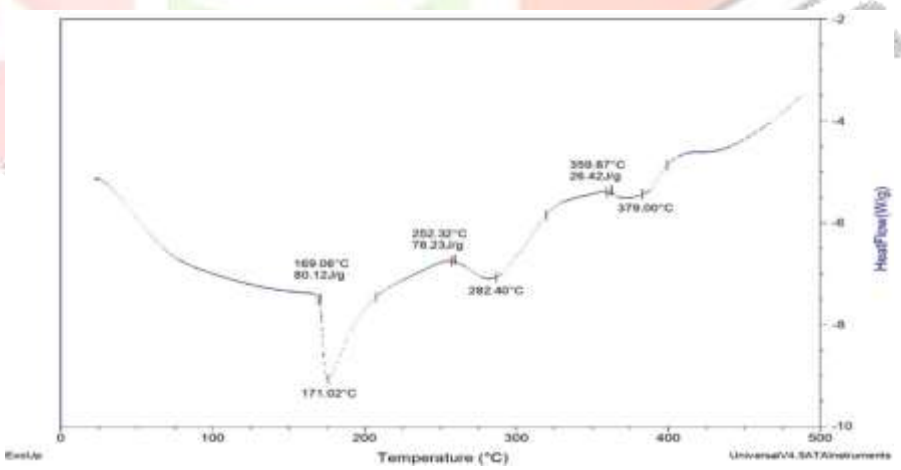


Fig.no.2.15 DSC of Co-crystal by Solvent Evaporation method

Discussion:

The study used Differential Scanning Calorimetry (DSC) to analyze the melting points of Rifampicin and Salicylic acid individually and when combined as co-crystals. The results showed:

* Pure Rifampicin has a melting point of 184.02°C

* Pure Salicylic acid has a melting point of 158.56°C

* The co-crystals of Rifampicin and Salicylic acid showed a strong endothermic peak at a lower temperature.

B) Co-crystal by solvent Drop method:-

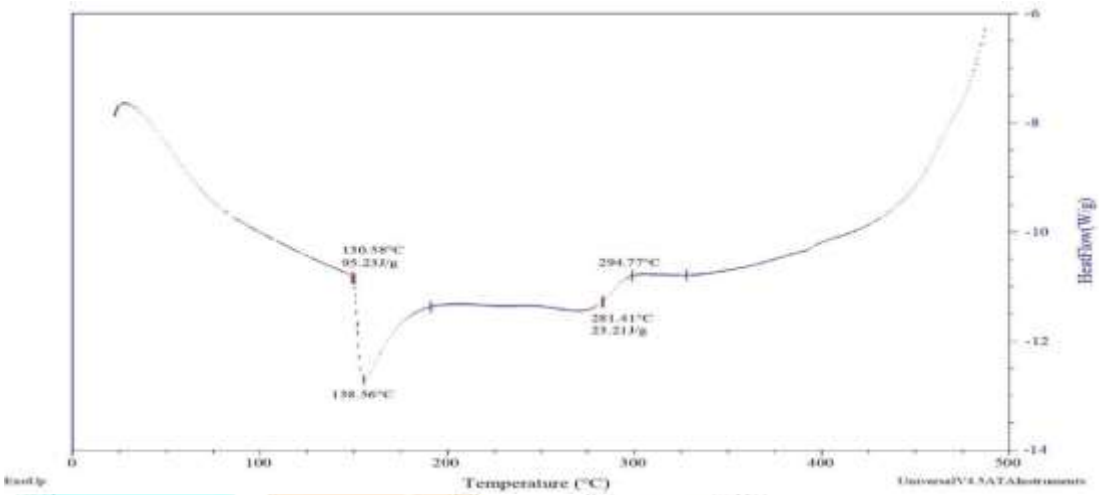


Fig.no.2.16 DSC of Co-crystal by solvent drop method

Discussion:

Researchers developed Rifampicin-Salicylic Acid co-crystals using the solvent Drop method. To confirm the formation of a new crystalline solid form, they analyzed the co-crystals using Differential Scanning Calorimetry (DSC). The DSC thermogram showed an endothermic peak at 138.56°C, which is higher than Rifampicin's melting point and between Salicylic Acid's melting points. This suggests that a new crystalline solid form has been formed, which could potentially lead to improved properties and applications for the individual compounds when combined in this new structure.

SEM:

Rifampicin:

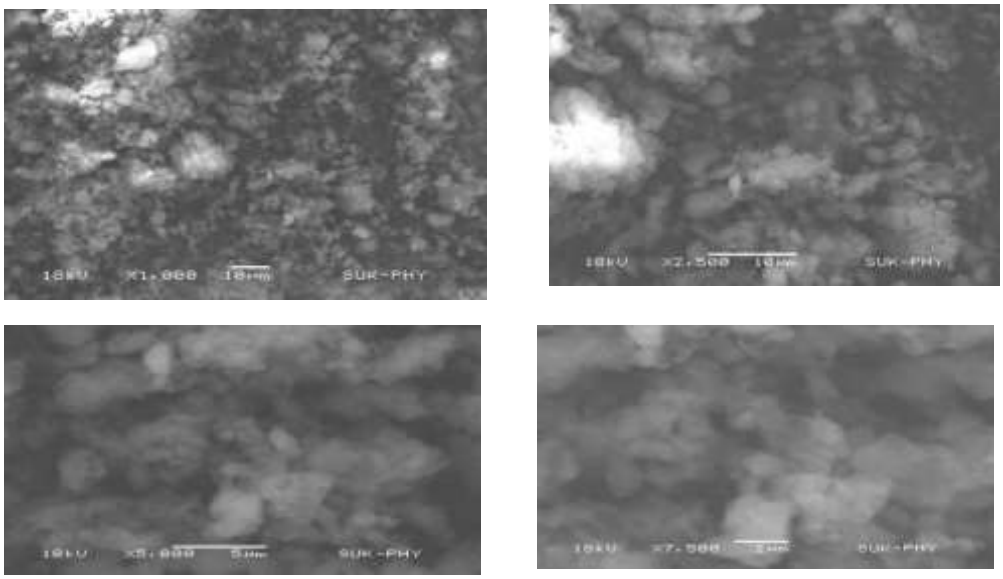


Fig.no.2.17 SEM of Rifampicin

Discussion:

The SEM images of Rifampicin show irregularly shaped, spherical particles with varying sizes and surface patterns, providing information about its physical properties and potential applications.

B) Cocrystal by solvent drop method:

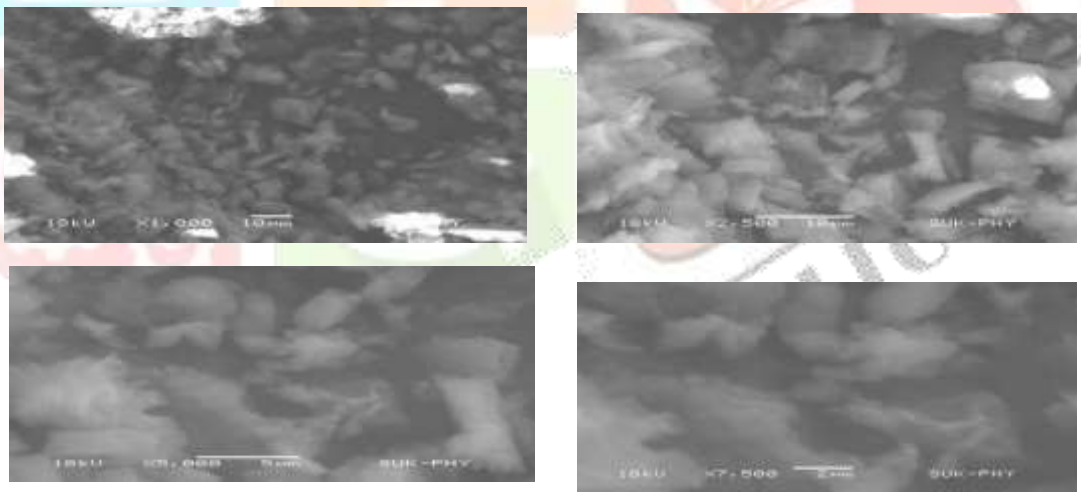


Fig. no.2.18Co crystal by solvent drop method

Discussion:

The novel cocrystal formed through the solvent drop process had a smooth surface morphology and a rod-shaped crystal structure, as observed using scanning electron microscopy (SEM).

Cocrystal by Solvent Evaporation Method:

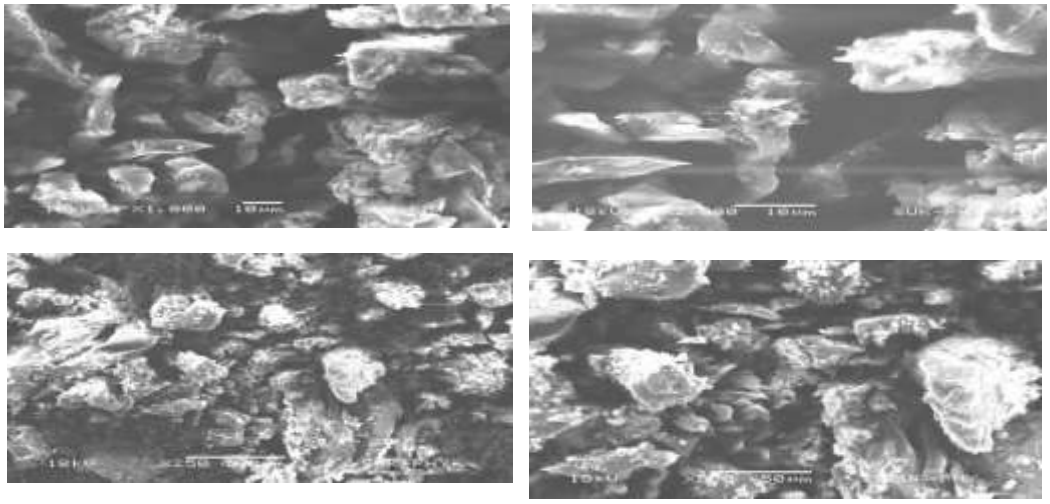


Fig. no.2.19Cocrystal by solvent evaporatíon method

Discussion:

SEM was used to study the morphological differences between pure Rifampicin and a newly developed cocrystal. The cocrystals were created using the solvent evaporation method, resulting in densely packed stick-shaped clusters. This unique formation is attributed to intermolecular hydrogen bonding between Rifampicin molecules and the co-former present in the cocrystal.

Stability study:

Table no. 1.13 Solubility analysis of Co-crystals after stability study.

Storage condition 40±5°C/ 75± 5%RH	**Solubility(mg/ml)**			
	Co-crystal prepared by Solvent drop method		**Co-crystal prepared by Solvent evaporation method**	
	water	**PBSpH7.2**	**water**	**PBSpH7.2**
Initial	6.23±0.53	9.75±0.23	9.64±0.13	9.94±0.47
1month	6.20±0.45	9.69±0.34	9.72±0.29	9.89±0.36
2month	6.26±0.2	9.82±0.41	9.58±0.18	9.96±0.27
3month	6.18±0.32	9.78±0.39	9.68±0.23	9.92±0.43

Table no. 1.14 Intrinsic dissolution rate of Co-crystals after stability study.

Storage condition 40±5°C/75±5%RH	%CDR	
	Solvent Drop Method	Solvent Evaporation Method
Initial	89.66±0.54	94.32±0.92
1month	88.23±0.67	95.12±0.73
2month	90.21±1.2	93.65±0.65
3month	88.87±0.45	94.04±0.32

In the conducted stability study of co-crystals, which lasted for three months,the temperature and humidity were maintained at 40 ± 5°C and 75 ± 5%. Throughout this period, the stability of Co-crystals was monitored, and no significant changes were observed. The study's results are prėsented in Tables and 8.24 show casing the in vitro drug release & solubility profiles, respectively.

CONCLUSION

This research highlights the effectiveness of creating pharmaceutical co-crystals to overcome challenges such as stability, aqueous solubility, and rate of dissolution for drugs like Rifampicin. By employing solvent drop & solvent evaporation methods, the co-crystals exhibit enhanced dissolution & solubility compared to the original compound. The study demonstrates that these Co-crystals can be easily prepared using the mentioned methods. The formed of co- crystals was confirmed through PXRD, DSC & IR analysis. Additionally, the co-crystals maintained stability for three months under accelerated temp & relative humidity conditions.

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