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Development of Novel Cefixime Cocrystal with Different Coformers for the Enhancement of Solubility

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ABSTRACT

Cocrystallization is a method that enables an improvement in physicochemical properties. The objective of this research was to establish Cefixime Cocrystals which could result in increased solubility and thus enhanced bioavailability of the drug. Cefixime is a β-lactam third-generation antibiotic and comes underclass (IV) of BCS classification which means low solubility and low permeability. Cocrystallization is a method of formation of mainly hydrogen bonds between the drug molecule and coformer. This research work utilized Cocrystals preparation by solvent evaporation and neat grinding techniques with sodium acetate, benzoic acid, D-mannitol, and soluplus which enlisted as coformer in various proportions (1:1, 1:2, and 1:3) with Cefixime. From both methods, the cocrystals produced were evaluated lying on percentage drug content, FTIR analysis, SEM, and *in-vitro* drug release. The highest drug content was found to be 97.09 % with sodium acetate at 1:1 by solvent evaporation method and 94.52 % with soluplus at 1:3 by the neat grinding method. The FTIR analysis was conducted to eliminate the possibility of incompatibility between drug and excipients used with the analytical method of drug estimation. The SEM analysis shows the cocrystals were formed 100 µm in size and crystalline in shape. The *in-vitro* drug release studies revealed 85.40 % drug release in 60 minutes by the cocrystal as compared to pure drug release i.e 50.72 %. The maximum solubility found i.e 18.5 fold increase with sodium acetate at 1:1 by solvent evaporation method as compared to pure drug.

1. INTRODUCTION

A cocrystal is a multiple-component crystal made up of two or more solid components kept together by non-covalent as well as nonionic interactions in a definite stoichiometric ratio. Cocrystal formation is the product of directional yet poor molecular recognition activities, which are often dependent on hydrogen bonding. Heterosynthons, as well as homosynthons, are two types of intermolecular interactions or synthons[1]. Etter was the first to coin the term "cocrystal" as well as to define design principles for hydrogen bonding in organic cocrystals. Cocrystals have resurfaced as an appealing solid shape alternative for drug production. API's pharmacological activity does not affect via cocrystallization by pharmaceutically acceptable compounds, infect can improve compaction behavior solubility, hygroscopicity like physical properties. Scientists showed that changing drug's physical properties by pharmaceutical cocrystal formation increased the performance of lower solubility drugs[2]. Schmidt placed the idea of crystal engineering into practice in the context of organic solid-state photochemical reactions, which Pepinsky proposed in 1955[3]. The selection of a coformer is an important step in the cocrystal production process. Throughout the design phase, there are various useful reference materials available, including both analytical as well as theoretical tools like Cambridge Structural Database (C.S.D), hydrogen bond models, numerous empirical findings[4]. Any two molecules with complementary hydrogen bond functionalities, regardless of shape or size, may be used to make cocrystals. Types of coformers used, API coformer ratio, solvents used, temperature as well as other aspects all have an impact on an API's capacity to form cocrystal[5]. In cocrystals, solubility is primarily dependent on two factors: strength of crystal lattice as well as cocrystal redemption. Solubility can be improved by lowering lattice energy and/or increasing solvent affinity. Cocrystals have varying degrees of capacity to effect these influences[6]. To increase solubility, the pharmaceutical industry uses amorphous dispersions, cocrystals, or salts. Cocrystals, on other hand, are gaining prominence because they can increase the dissolution of improperly soluble drugs as well as their bioavailability[7]. Cocrystals can be made using several techniques. Figure No. 1 illustrates the proportions of various cocrystal synthesis methods recorded in the literature. Cocrystals are most commonly synthesized by gradual evaporation from solution, as seen in Figure No. 1. However, due to high solvent intake, this approach does not follow green energy criteria[8].

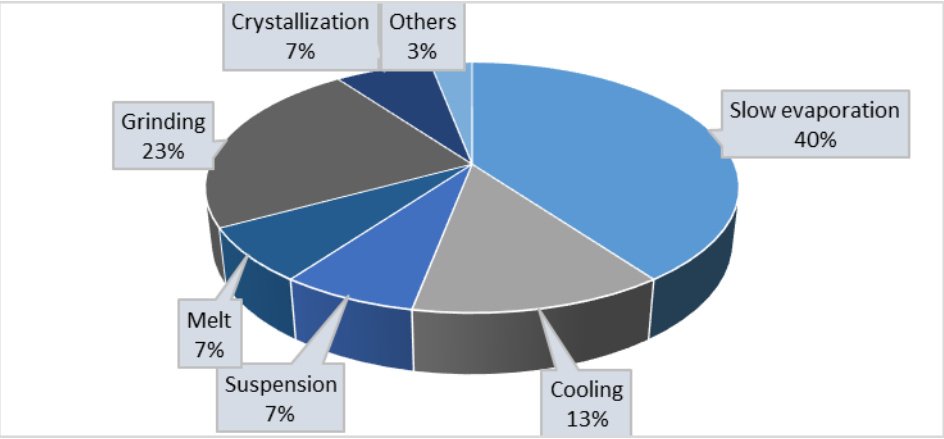

Figure No. 1: The method of cocrystallization used in different ratios.

Cocrystallization by active pharmaceutical ingredients with coformers is a promising approach for enhancing resilience, solubility, the dissolution rate of active pharmaceutical ingredients, and their bioavailability as well as mechanical properties, without needing any chemical modification[9]. Cocrystals are the safe medium that can be used to solve BCS Class II as well as IV drug solubility issues. Furthermore, choosing the right coformer will affect some solid-state issues including physical stability, hygroscopicity, melting point, as well as dissolution rate[10].

2. MATERIALS AND METHODS

2.1 Materials:

Cefixime was purchased from Symed Laboratories (Hyderabad), Potassium di-hydrogen-*o* phosphate was purchased from Signet Chemical Corp. Pvt. Ltd. (Mumbai), Sodium hydroxide was purchased from Fisher Chemical Ltd. (Ahmedabad), Sodium acetate was purchased from Thomas baker Pvt. Ltd. (Mumbai), Benzoic acid was purchased from Central drug house (P)LTD (New Delhi), D-mannitol was purchased from Loba Chemie, Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was purchased from BASF Germany, Methanol was purchased from Fisher Chemical Ltd. (Ahmedabad), Ethanol was purchased from Changshu hongsheng fine chemical co, LTD, Chloroform was purchased from Leonid chemicals PVT. LTD., DMF(N, N-Dimethylformamide) was purchased from Fisher scientific, Acetone and n-octanol was purchased from Avantor performance materials India LTD.

2.2 Preformulation studies

Preformulation trials are an important component of the drug discovery phase. Before the compounding phase, it is an analysis of the drug's physical as well as chemical properties. These experiments concentrate on the drug's physicochemical properties that may influence its performance as well as the production of an effective dosage type. Detailed understanding of these properties can eventually help to justify formulation design or the need for molecular alteration.

2.2.1 Organoleptic properties

Visual experiments were used to conduct organoleptic studies such as general appearance like nature, colour, odour, taste, as well as so on[11].

2.2.2 Determination of absorption Maxima of Cefixime by UV-Spectrophotometer

Absorption maxima (λ_{max}) of the drug were determined by UV spectrophotometer (Shimadzu Pharma. Spec1800). The stock of 0.1 mg/ml was prepared by dissolving 10 mg cefixime in 100 ml of methanol. Appropriate dilutions were scanned for determining λ_{max} from 200-400 nm through a UV spectrophotometer.

- **Preparation of calibration curve of cefixime in methanol**

Dilutions in the range of 4 µg/ml to 32 µg/ml were prepared from a stock solution in methanol. Dilutions were scanned for determining λ_{max} from 200-400 nm through a UV spectrophotometer[12].

2.2.3 Solubility Studies

For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned culture flasks containing 5 ml of different solvents (Methanol, Ethanol, Acetone, Chloroform, pH 6.8 phosphate buffer, 0.1N HCl, water, Dimethyl Formamide) as well as test tubes were tightly closed. These test tubes were shaken on a water bath shaker for 24 hours at 37±0.5 ^{0}C. After 24 hours, each sample was centrifuged for 15 minutes at 15,000 rpm as well as was suitably diluted and determined spectrophotometrically[13].

2.2.4 Partition Coefficient of Drug

- **Shake flask method**

The partition coefficient determination study was performed by using the shake flask method. Excess amounts of drugs dissolved in 5 ml of two solvents (n-octanol: Water) together (1:1) as well as placed for 24 hours. After 24 hours, two layers were separated as well as centrifuged for 15 minutes at 15,000 rpm. Absorbance was taken in UV spectrophotometer at respective λ_{max} after appropriate dilution[14].

2.2.5 Drug as well as excipient compatibility study by FTIR spectroscopy

Infrared Fourier transforms for purpose of identifying specific compounds, spectroscopies of various compounds were conducted. KBr pellets were used to conduct FT-IR spectroscopy on pure drugs as well as polymers. FT-IR Continuum peaks were viewed to distinguish various classes in the configuration of pure drugs as well as their mixtures. Any physicochemical interactions between various materials may also be investigated as well as predicted using FT-IR spectroscopy[15].

2.3 Preparation of Cocrystals of Cefixime

Pharmaceutical cocrystal of Cefixime was prepared with different coformers using solvent evaporation method as well as neat grinding method.

Solvent evaporation method: This is the most popular method for making cocrystals. In typical solvent methanol, compounds, as well as coformer, are dissolved in various molar ratio ratios. (1:1, 1:2, 1:3) as well as completely evaporated by slow heating. After evaporation cocrystals are formed[2].

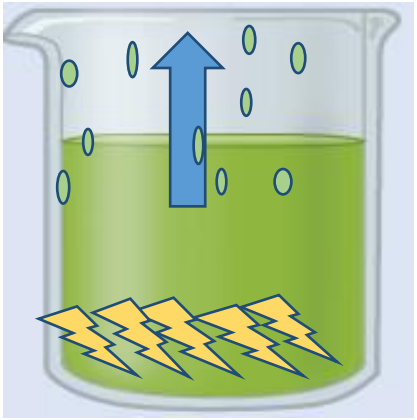

Figure No. 2: Solvent Evaporation Method.

Drug coformer cocrystals were prepared with four different polymers i.e., sodium acetate, benzoic acid, D-mannitol as well as soluplus in four different molar ratios with each enlisted coformer.

Table No. 1: Composition of Cocrystals by Solvent Evaporation method.

Sr. No.	Formulation Code	Molar Ratio (Drug:Coformer)			
		Sodium Acetate	Benzoic Acid	D-Mannitol	Soluplus
1	F1	1:1	-	-	-
2	F2	1:2	-	-	-
3	F3	1:3	-	-	-
4	F4	-	1:1	-	-
5	F5	-	1:2	-	-
6	F6	-	1:3	-	-
7	F7	-	-	1:1	-
8	F8	-	-	1:2	-
9	F9	-	-	1:3	-
10	F10	-	-	-	1:1
11	F11	-	-	-	1:2
12	F12	-	-	-	1:3

Neat grinding method: Neat grinding, also called dry grinding or solid-state grinding. The drug, as well as conformer, are taken in a stoichiometric ratio in mortar and pestle and triturated. After trituration cocrystals are formed as well as collected[16].

Figure No. 3: Solid-state or Neat grinding Technique.

Table No. 2: Composition of Cocrystals by Neat Grinding Method.

Sr. No.	Formulation Code	Molar Ratio (Drug:Coformer)			
		Sodium Acetate	Benzoic Acid	D-Mannitol	Soluplus
1	N1	1:1	-	-	-
2	N2	1:2	-	-	-
3	N3	1:3	-	-	-
4	N4	-	1:1	-	-
5	N5	-	1:2	-	-
6	N6	-	1:3	-	-
7	N7	-	-	1:1	-
8	N8	-	-	1:2	-
9	N9	-	-	1:3	-
10	N10	-	-	-	1:1
11	N11	-	-	-	1:2
12	N12	-	-	-	1:3

3. EVALUATION OF COCRYSTALS

3.1 Optical Microscopy

Microscopic examination of Cefixime cocrystals with various coformers produced through solvent evaporation as well as neat grinding methods have been performed. Photographs of microscopic pictures viewed at a magnification of 10X were obtained[17].

3.2 Percentage Yield

To determine the percent yield or efficacy of the process, percentage functional yield of Cefixime cocrystals with sodium acetate, benzoic acid, D-mannitol, as well as soluplus prepared by solvent evaporation method as well as the neat grinding method was determined. The following equation was used to calculate the percentage of cocrystals.

$$Percentage\ Yield = \frac{Practical\ Yield}{Theoretical\ Yield} \times 100 [18]$$

3.3 Solubility studies

The solubility of cefixime, as well as cocrystal in different media, was investigated. Excess cocrystals were applied to culture flasks comprising 5 ml of the medium as well as stirred at 50 rpm on a magnetic stirrer for 24 hours at 37.5°C. The solution was then centrifuged for 15 minutes at 15000 rpm, as well as concentration was measured spectrophotometrically at 288 nm[19].

3.4 Drug content

Samples of cocrystals equivalent to 200 mg Cefixime were dissolved in 100 ml of methanol to assess drug content. The absorbance of resulting solutions was calculated at 288 nm using a double beam UV Visible Spectrophotometer after sufficient dilution.

$$\% \ Drug \ Content = \frac{Practical \ Yield}{Theoretical \ Yield} \times 100 [20]$$

3.5 Optimized Formulation (FTIR)

The cocrystal's FT-IR (Fourier Transform Infrared) spectrum was examined for details about groups found in that compound. FTIR was used to scan samples (F1) on a 400-4000 cm^{-1} scale.

3.6 SEM (Scanning Electron Microscopy)

The diameter of the cocrystal was measured using scanning electron microscopy. On the glass stub, a fragment of cocrystal was vacuum dried. Sample stub was analyzed microscopically at a voltage of 10 kV after being put in a scanning electron microscope chamber as well as covered with gold-palladium. kV[21].

3.7 *In-vitro* drug release studies

In-vitro dissolution studies were carried out in a USP Dissolution apparatus using dissolution medium (0.1N HCl). Dissolution media was filled to 900 mL and pure drug, as well as cocrystal equal to a 200 mg dosage, was put in it, the temperature was held at 37.5°C, as well as speed was set to 75 rpm (USP II). Whatman filter paper was used to filter the solution after 5.0 ml samples were withdrawn at different time intervals of 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 45 minutes, and 60 minutes. Then UV spectrophotometer was used to analyze the filtered sample at 288nm[18].

3.8 Drug release kinetic studies

The percent drug release, as well as release kinetics of cefixime from cocrystals, were calculated using raw data from *in vitro* release experiments that were fitted to different equations as well as kinetics models as Higuchi's model, zero-order equation, first-order equation, Korsmeyer-Peppas equation as well as Hixson Crowellmodel[22,23].

4. RESULTS AND DISCUSSIONS

Organoleptic properties of the drug

Organoleptic properties of cefixime were found to be as per I.P. monograph (1).

Table No. 3: Organoleptic properties of the drug.

Sr. No.	Properties	Inference
1.	Colour	Yellowish-white
2.	Odour	Odourless
3.	Form	Crystalline
4.	Taste	Bitter

The purity of the drug is performed by UV spectroscopy, melting point, and FTIR (Figure No. 4). The melting point was found to be 220.333 ± 1.527°Cwhich comes under the standard melting point range.

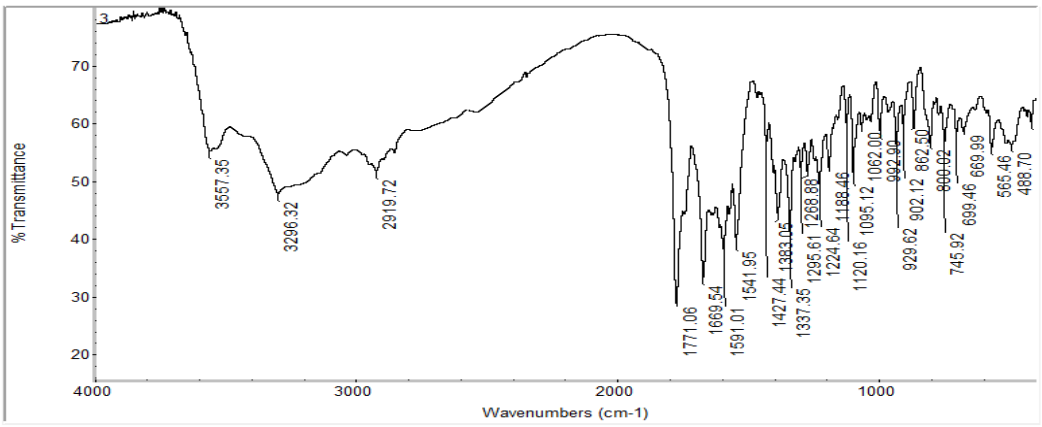

Figure No. 4: FTIR spectrum of *Cefixime*.

UV Visible Spectrophotometric analysis of Cefixime

The Stock solution of Cefixime was processed with methanol. A sample containing the drug (5 µg/ml) was scanned between 200-400 nm. It was found that the λ_{max} is 288 nm.

Standard Calibration Curve of Cefixime in Methanol

The standard calibration curve of cefixime was determined as per methodology. The results obtained are shown below in Table No. 2 as well as graphically shown in Figure No. 5.

Table No. 4: Standard calibration curve data of Cefixime in methanol.

Concentration (µg/ml)	Max. Absorbance	Statistical data
4	0.142 ± 0.001	R^2 value= 0.9969 Regression equation y = 0.0272x + 0.0448
8	0.258 ± 0.000	
12	0.361 ± 0.001	
16	0.506 ± 0.007	
20	0.607 ± 0.001	
24	0.689 ± 0.001	
28	0.794 ± 0.002	
32	0.908 ±0.001	

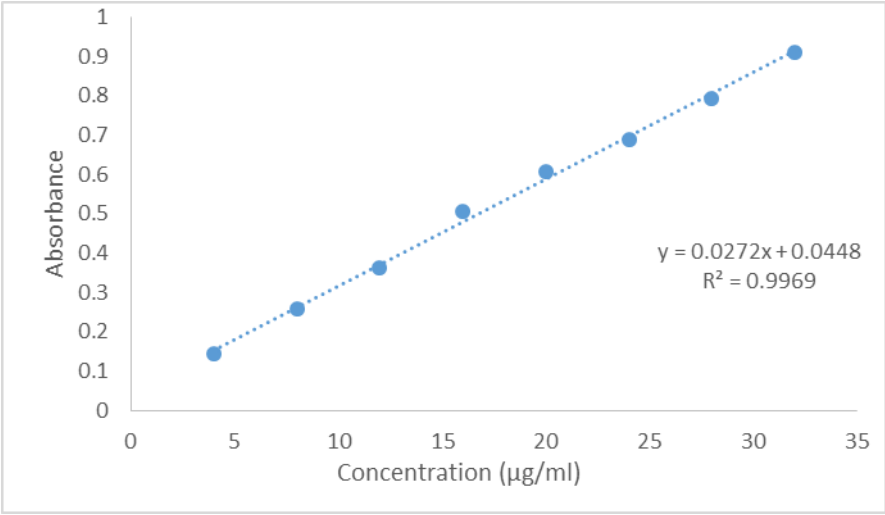

Figure No. 5: Standard calibration curve of Cefixime in methanol.

The standard calibration curve of Cefixime as shown in the graph indicated regression equation Y = 0.0272x + 0.0448, as well as R2 value, is 0.9969, which shows good linearity.

Solubility studies

The solubility profile of cefixime in different solvents has been given in Table No. 3 and graphically shown in Figure No. 7.

Table No. 5: Solubility profile of cefixime in different solvents.

Sr. No.	Name of Solvents	Solubility of Cefixime (mg/ml)
01.	Chloroform	0.134 ± 0.002
02.	Water	1.509 ± 0.013
03.	Phosphate buffer pH 6.8	1.767 ± 0.015
04.	0.1N HCL	2.677± 0.007
05.	Ethanol	5.019 ± 0.021
06.	Dimethylformamide	33.352 ± 0.036
07.	Acetone	47.867 ± 0.367
08.	Methanol	148.725 ± 0.561

(Mean ± SD, N=3)

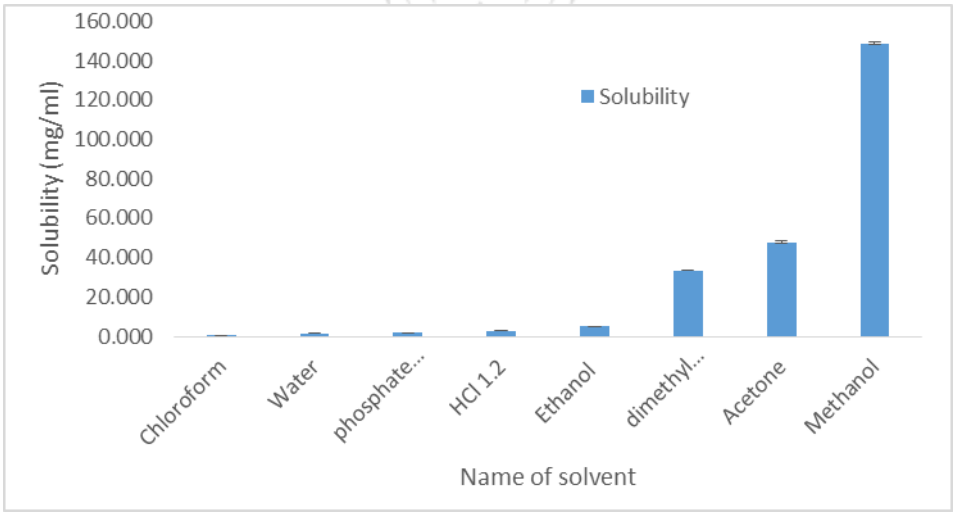

Figure No. 6: Solubility profile of *cefixime* in different solvents.

The drug ***cefixime*** was highly soluble in methanol followed by acetone as well as dimethylformamide. However, the drug was partially soluble in chloroform, water as well as phosphate buffer pH=6.8

Partition coefficient determination

The partition coefficient determination study was performed by using the shake flask method.

Table No. 6: Partition coefficient of *Cefixime*.

Drug	**Solvent System**	**Log P Values**	**Reference**
Cefixime	n-octanol: water	3.370 ± 0.032	3.55

(Mean ± SD, n=3)

The partition coefficient of ***cefixime*** in n- Octanol: Water was found to be 3.370 ± 0.032 which was similar to the reported partition coefficient. This indicates that the drug ***cefixime is lipophilic***.

Drug excipient compatibility study by FTIR spectroscopy

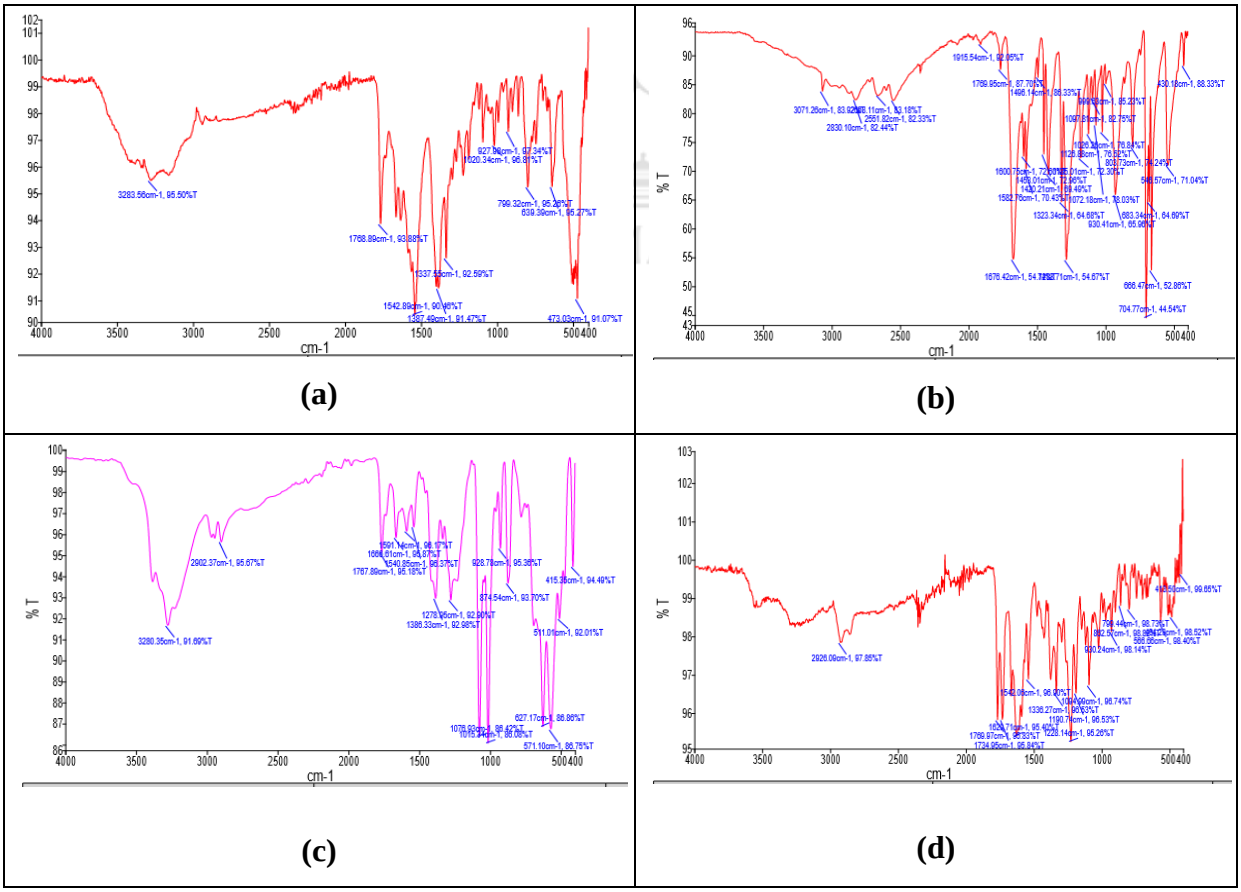

Figure No. 7: FTIR Spectrum of Physical Mixture of (a) Cefixime + Sodium Acetate, (b) Cefixime + benzoic acid, (c) Cefixime + D-mannitol, (D) Cefixime + soluplus.

FTIR was used to rule out the probability of drug-excipient interactions by using the empirical approach of drug estimation. Cefixime, as well as sodium acetate, have IR peaks of 1337.55 cm^{-1} (C=N stretching aromatic), 1768.89 cm^{-1} (C-H banding), 799.32 cm^{-1} (C-C stretching), as well as 1542.89 cm^{-1}, respectively (C-O stretching). The principal IR peaks of cefixime, as well as benzoic acid, were observed 1676.42 cm^{-1} (C-O stretching), 1323.34 cm^{-1} (C-O stretching), 930.41 cm^{-1} (O-H out of plane banding), 704.77 cm^{-1} (C-C stretching). The principal IR peaks of cefixime, as well as D-mannitol, were observed 1666.61 cm^{-1} (C-O stretching), 1540.85 cm^{-1} (C-C stretching), 3280.35 cm^{-1} (O-H vibration with intermolecular hydrogen bond), 2902.37 cm^{-1} (C-H stretching), and the Cefixime, as well as soluplus IR peaks, were 1734.95 cm^{-1} (Carbonyl stretching), 1769.97 cm^{-1} (C-H banding), 1542.06 cm^{-1} (C-C stretching), as well as 1228.14 cm^{-1} (C-C stretching) (C-O stretching for ether). Both spectrum peaks showed that the drug's corresponding peaks, as well as excipient peaks, are present in the above spectra. As result, there was no interaction exhibited with these mixtures.

Evaluation of cocrystals

Optical Microscopy

The cocrystals were observed under an optical microscope.

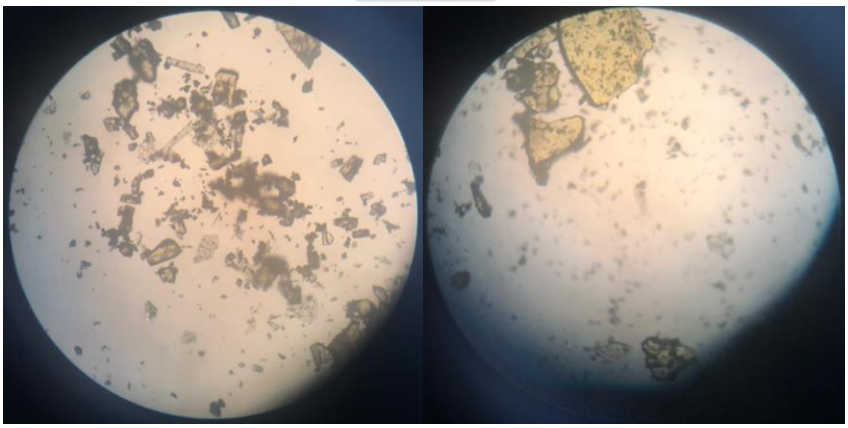

Figure No. 8: Optical Photomicrographs of a cocrystal of Cefixime.

Optical microscopic revealed cocrystals were formed with crystalline structure exhibiting glass-like morphology.

Percentage Yield

The percentage yield of all formulations is given below.

Table No. 7: Percentage yield of different cocrystals of cefixime by Solvent Evaporation Method.

Sr. No.	Formulation Code	Percentage Yield
1.	F1	38.090 ± 0.188
2.	F2	11.740 ± 0.257
3.	F3	13.599 ± 0.168
4.	F4	47.287 ± 0.172
5.	F5	56.837 ± 0.256
6.	F6	57.362 ± 0.195
7.	F7	69.157 ± 0.168
8.	F8	82.727 ± 0.157
9.	F9	2.857 ± 0.089
10.	F10	5.750 ± 0.188
11.	F11	1.621 ± 0.187
12.	F12	18.030 ± 0.147

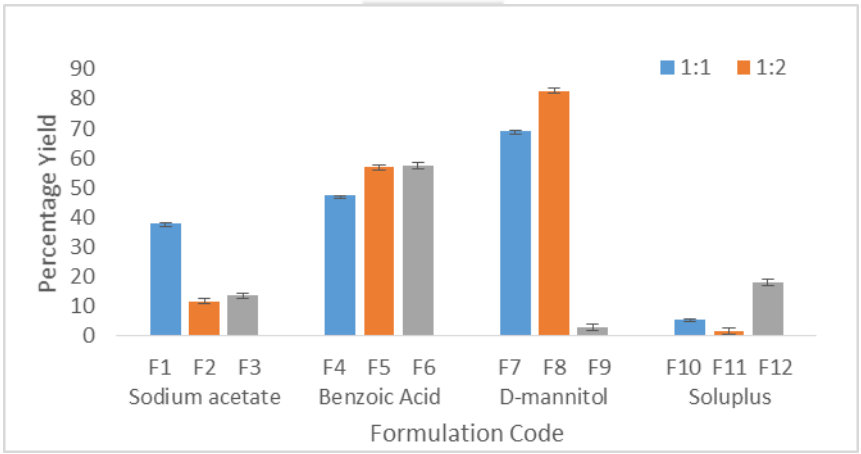

Figure No. 9: Percentage Yield of different cocrystals of cefixime by Solvent Evaporation Method.

Table No. 8: Percentage Yield of different cocrystals of cefixime by Neat Grinding Method.

Sr. No.	Formulation Code	Percentage Yield
1.	N1	53.834 ± 0.123
2.	N2	34.928 ± 0.242
3.	N3	29.788 ± 0.125
4.	N4	76.460 ± 0.145
5.	N5	86.526 ± 0.145
6.	N6	90.403 ± 0.113
7.	N7	80.279 ± 0.201
8.	N8	87.852 ± 0.175
9.	N9	89.545 ± 0.079
10.	N10	82.695 ± 0.188
11.	N11	89.030 ± 0.124
12.	N12	86.110 ± 0.097

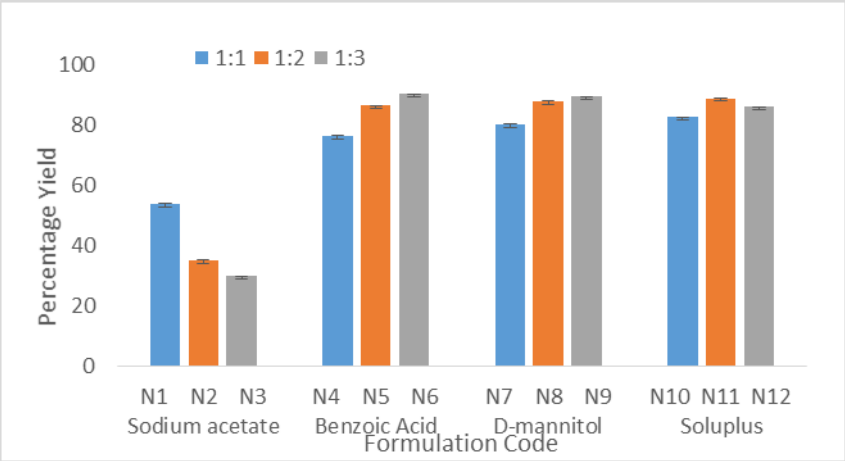

Figure No. 10: Percentage Yield of different cocrystals of cefixime by Neat Grinding Method.

The percentage yield of the formulation, which was discovered to have crystalline morphology, was determined. Yields measured ranged from 2.8570.089 to 82.7270.157 in case of solvent evaporation as well as 29.7880.125 to 90.4030.113 in case of neat grinding, with F6 formulation having the highest yield of 90.4030.113.

Solubility Studies

The saturation solubility studies of all formulations are shown below.

Table No. 9: Saturation Solubility of Cocrystals of Cefixime by the solvent evaporation method.

Sr. No.	Formulation Code	Solubility (mg/ml)
1.	F1	28.058 ± 0.097
2.	F2	14.529 ± 0.132
3.	F3	10.546 ± 0.036
4.	F4	2.982 ± 0.003
5.	F5	5.963 ± 0.036
6.	F6	6.625 ± 0.036
7.	F7	7.654 ± 0.036
8.	F8	4.921 ± 0.056
9.	F9	3.279 ± 0.036
10.	F10	2.537 ± 0.003
11.	F11	2.135 ± 0.011
12.	F12	1.171 ± 0.003

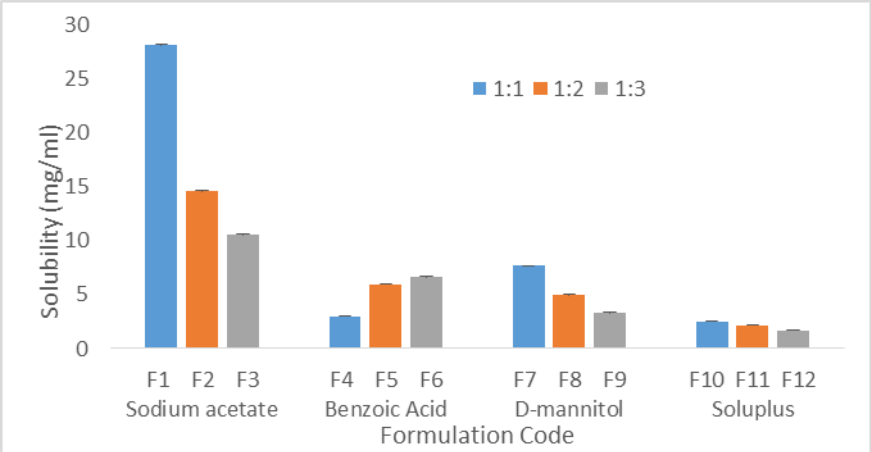

Figure No. 11: Saturation Solubility of cocrystals of Cefixime by the solvent evaporation method.

Table No. 10: Saturation Solubility of cocrystals of Cefixime by Neat Grinding Method.

Sr. No.	Formulation Code	Solubility (mg/ml)
1.	N1	14.235 ± 0.036
2.	N2	12.727 ± 0.036
3.	N3	11.723 ± 0.021
4.	N4	4.529 ± 0.036
5.	N5	3.316 ± 0.003
6.	N6	4.296 ± 0.056
7.	N7	9.137 ± 0.021
8.	N8	8.058 ± 0.036
9.	N9	7.617 ± 0.036
10.	N10	7.36 ± 0.036
11.	N11	5.681 ± 0.021
12.	N12	3.806 ± 0.021

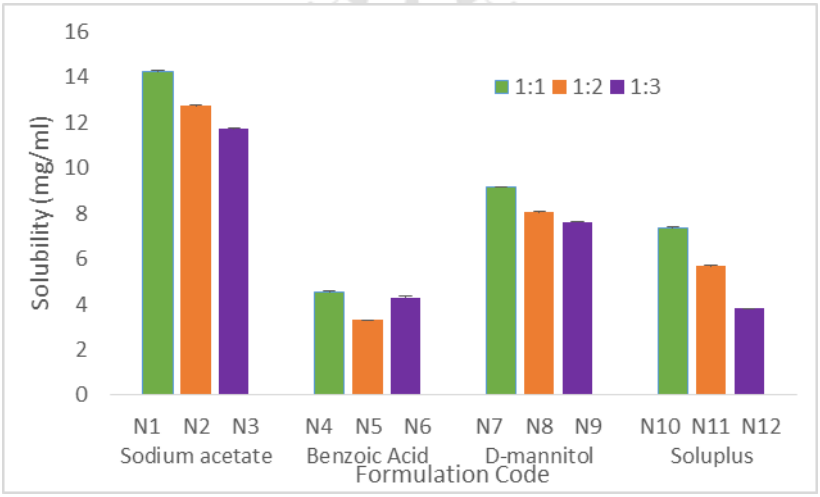

Figure No. 12: Saturation Solubility of cocrystals of Cefixime by the neat grinding method.

Cocrystals grown in presence of different coformers such as sodium acetate, benzoic acid, d-mannitol, as well as soluplus while used in different molar concentrations showed increases in solubility up to 28.058 mg/ml with the solvent evaporation method. With such formulation, F1 has the highest 18.5 fold improvement in solubility.

Drug Content

The percentage drug content of all formulations is given below.

Table No. 11: Percentage Drug Content of cocrystals of Cefixime by the solvent evaporation method.

Sr. No.	Formulation Code	Percent Drug Content
1.	F1	97.095 ± 0.486
2.	F2	78.713 ± 0.183
3.	F3	67.990 ± 0.462
4.	F4	82.831 ± 0.333
5.	F5	92.404 ± 0.480
6.	F6	73.897 ± 0.306
7.	F7	72.977 ± 0.306
8.	F8	42.009 ± 0.462
9.	F9	79.937 ± 0.238
10.	F10	24.460 ± 0.561
11.	F11	40.637 ± 0.561
12.	F19	48.937 ± 0.561

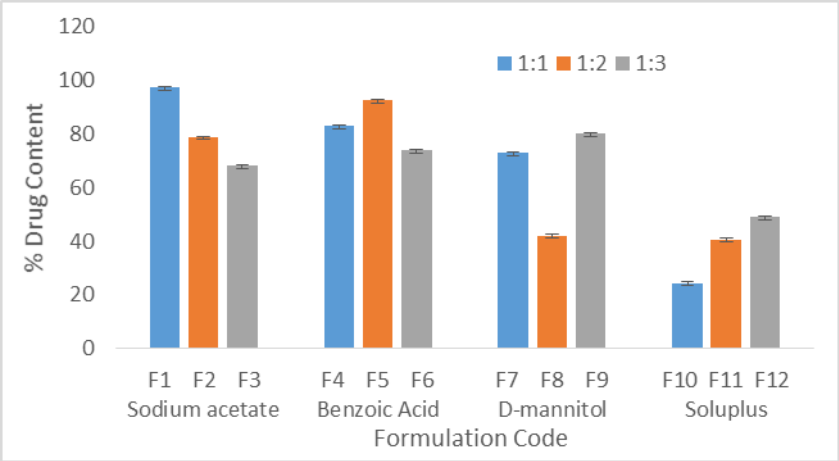

Figure No. 13: Percentage Drug Content of cocrystals of Cefixime by the solvent evaporation method.

Table No. 12: Percentage Drug Content of cocrystals of Cefixime by the neat grinding method.

Sr. No.	Formulation Code	Percent Drug Content
1.	N1	84.963 ± 0.183
2.	N2	73.75 ± 0.183
3.	N3	49.117 ± 0.183
4.	N4	74.301 ± 0.183
5.	N5	92.867 ± 0.183
6.	N6	88.088 ± 0.183
7.	N7	31.164 ± 0.106
8.	N8	29.142 ± 0.106
9.	N9	32.757 ± 0.183
10.	N10	46.176 ± 0.183
11.	N11	26.384 ± 0.106
12.	N12	94.522 ± 0.183

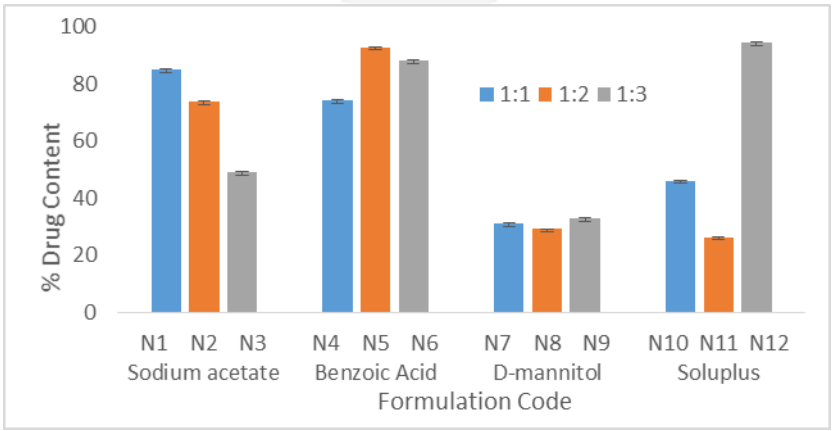

Figure No. 14: Percentage Drug Content of cocrystals of Cefixime by the neat grinding method.

Percentage drug content of both formulations ranged from 24.4600.561 to 97.0950.486 in solvent evaporation process as well as from 29.1420.106 to 94.5220.183 in neat grinding method, with F1 formulation having the highest yield of 97.0950.486. These findings indicate that coformers as well as molar ratios are the important parameters to enhance efficiency.

FTIR analysis of Cocrystals (F1)

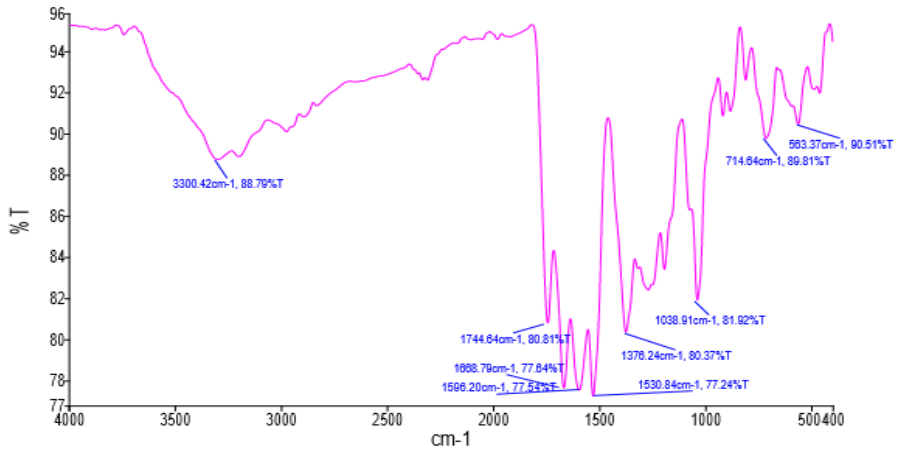

Figure No. 15: FTIR analysis of Cocrystal (F1)

The peaks were obtained at 1668.79 cm^{-1} (C-O stretching), 1744.64 cm^{-1} (C=O stretching), 1530.84 cm^{-1} (C-C stretching), as well as 1596.20 cm^{-1} (C-C stretching) as seen in Figure No.15 some of the cefixime peaks maintained with slight shifting in the FTIR spectra of final formulation (F1).

Scanning electron microscopy (SEM) analysis of cocrystal formulation (F1)

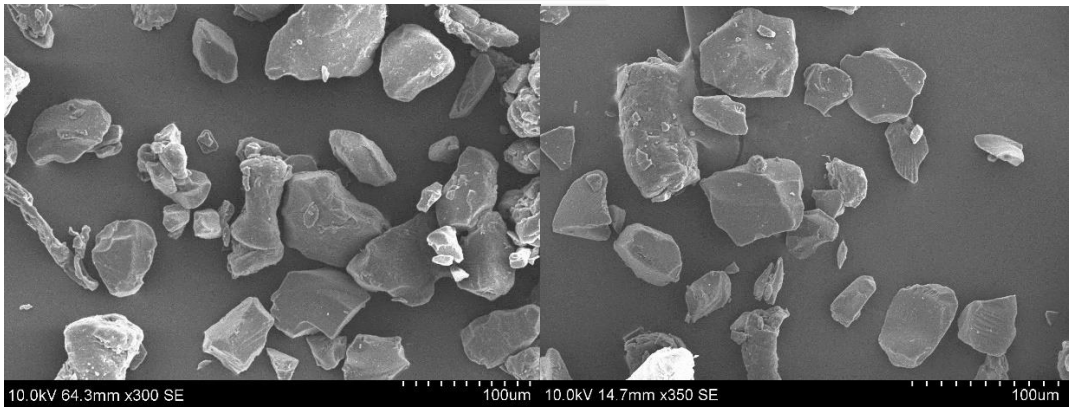

Figure No. 16: SEM micrograph of cocrystal formulation F1.

Scanning electron microscopy was used to examine surface morphology as well as the shape of cocrystals (SEM-Evo, Carl-Zeiss, Germany). Cefixime cocrystals are irregular polyhedrons with a wide distribution range and uneven in size. The majority of particles have a diameter of 100 µm or greater. F1 cefixime cocrystals were shaped with uniform as well as crystalline structure, according to SEM micrographs.

***In vitro* release studies**

The *in vitro* release of pure drug as well as formulation F1 is shown below.

Table No. 13: *In vitro* release profile of pure drug as well as cocrystals containing drug (F1)

Time (min.)	% Drug release of Pure drug	% Drug release of F1 formulation
0.00	0.00	0.00
5	9.135 ± 0.009	82.091 ± 0.095
10	16.560 ± 0.047	72.165 ± 0.095
15	20.2003 ± 0.082	77.625 ± 0.095
20	23.178 ± 0.047	81.430 ± 0.095
25	27.645 ± 0.047	82.091 ± 0.095
30	32.691 ± 0.047	83.415 ± 0.095
45	38.233 ± 0.047	84.408 ± 0.095
60	50.724 ± 0.047	85.400 ± 0.095

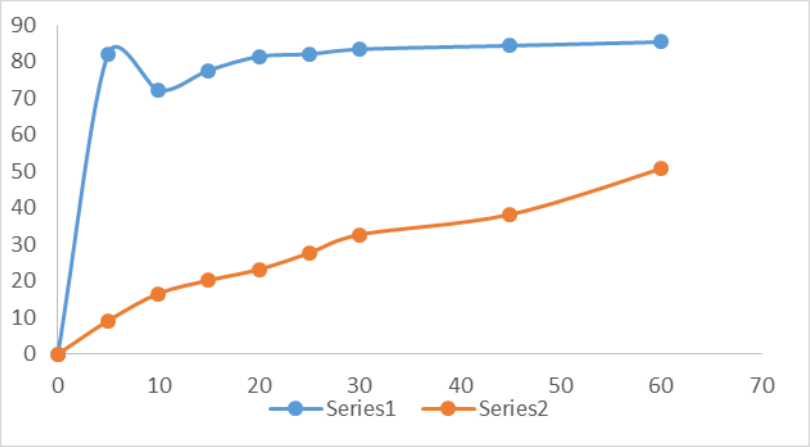

Figure No. 17: Comparative *in vitro* release profile.

The method of *in vitro* dissolution is used to determine the volume of drug released into the system/medium at a given time. Figure No. 18 depicts drug release curves for both pure drug as well as formulation F1. As opposed to the pure drug, formulations containing Cefixime

displayed strong characteristics for control drug release. Within 60 minutes, approximately 85.400 % drug of formulation F1 was released into the medium. Aside from that, *in vitro* release of pure drugs demonstrated 50.724 percent drug release in 60 minutes.

In vitro release Kinetics

In-vitro drug release kinetic study data of formulation F1 is given below.

Table No. 14: Kinetic equation parameter of formulation F1.

Formulation Name	Zero-order		First-order		Higuchi		Peppas		Hixson Crowell	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F1	0.935	0.234	0.977	-0.008	0.972	11.804	0.929	0.978	0.510	0.001

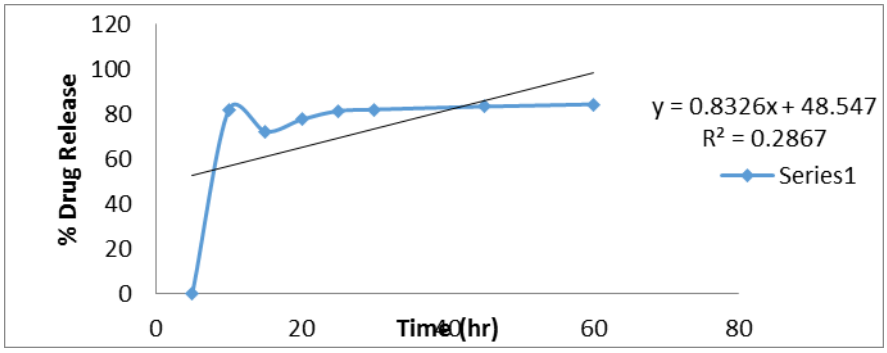

Figure No. 18: Zero-order graph of formulation F1.

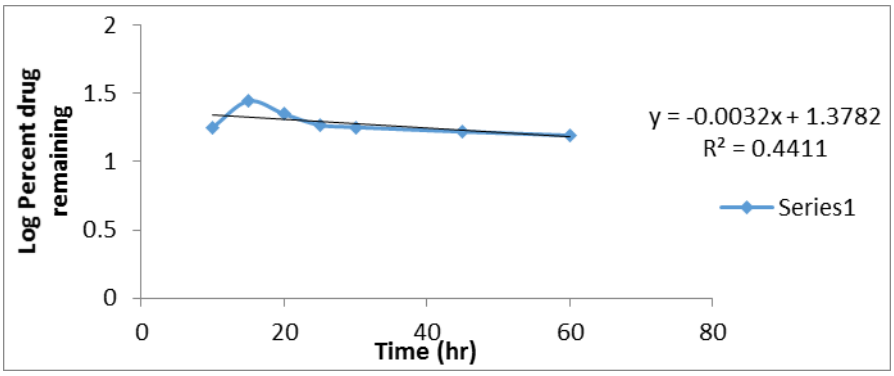

Figure No. 19: First order graph of formulation F1.

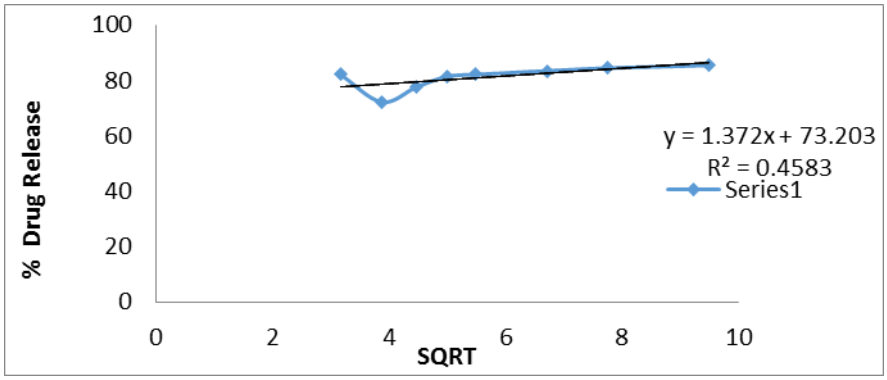

Figure No. 20: Higuchi order graph of formulation F1.

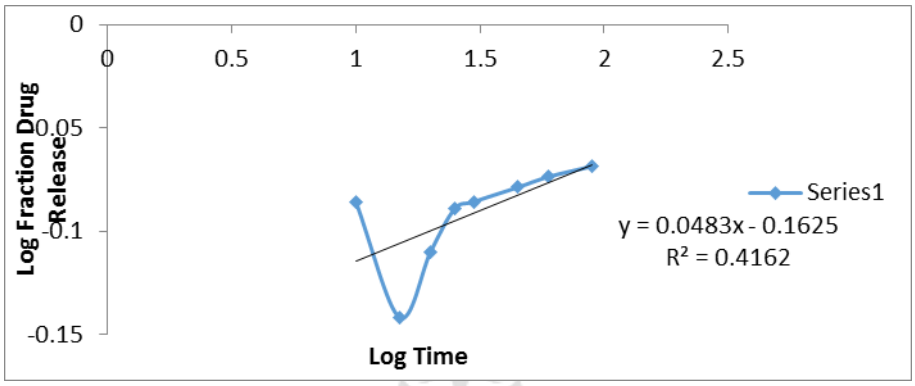

Figure No. 21: Korsmeyerpeppas order graph of formulation F1.

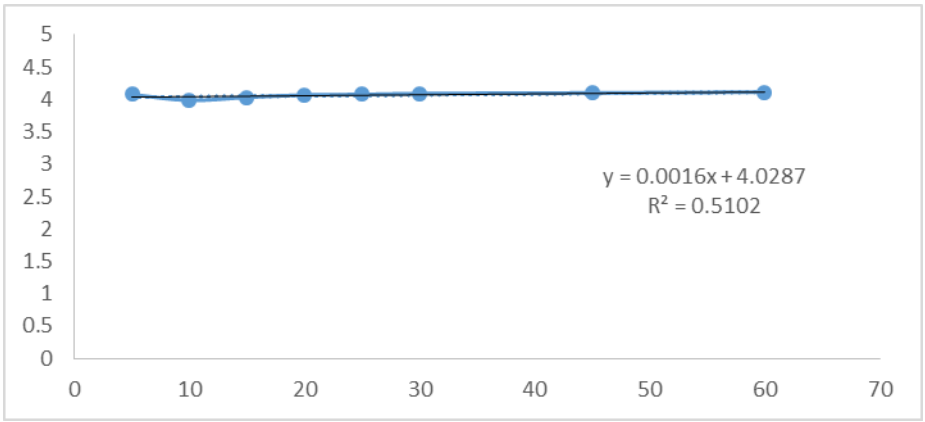

Figure No. 22: Hixson Crowell order graph of formulation F1.

In Table No. 12, *in vitro* release data has shown were fitted into the equation for Hixson Crowell, Higuchi, zero-order, Korsmeyerpeppas, and first-order release models. Meaning of resulting regression coefficients was used to analyze results.

Hixson Crowell was found to be a better match model, with drug release being found to be in an immediate release manner as log fraction drug release Vs log time. Table No. 12 displays

estimated regression coefficients for zero order, first order, Higuchi construct, Korsmeyerpeppas, as well as Hixson Crowell. Hixson Crowell was found to be a better explanation for F1's *in vitro* drug release since the plot had the greatest linearity. For Hixson Crowell, the largest R^2 value was found to be 0.510.

CONCLUSION

Pharmaceutical cocrystallization is a safe as well as an effective way to alter and enhance physical as well as chemical properties of drugs including solubility, dissolution rate, hygroscopicity, and compressibility without affecting their pharmacological activity. To allow for hydrogen bonds or other types of solid contact, cocrystal formation is dependent on functional groups between API as well as coformer. As result, a compound like cefixime, which has low solubility in our environment, could be provided orally after being converted into cocrystals. Cefixime's partition coefficient in n-octanol: water was observed to be 3.370, suggesting that the compound is lipophilic. There was no incompatibility between the drug as well as the coformer based on the FTIR spectroscopy study. The method of preparation of cocrystal was found to be simple and reproducible. Percentage yield varied from 1.621 ± 0.187 to 82.727 ± 0.157 when using solvent evaporation process, as well as from 29.788 ± 0.125 to 90.403 ± 0.113 when using the neat grinding method. Pure drug released 50.724 ± 0.047 percent and drug released from formulation F1 is 85.400 ± 0.095 percent within 60 minutes, according to in vitro results. The maximum solubility found i.e 18.5 fold increase with sodium acetate at 1:1 by solvent evaporation method as compared to pure drug. It was concluded that the cocrystal preparation method is easy, repeatable, as well as provides good efficiency of solubility enhancement.

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REFERENCES

1. Pando C, Cabanas A, Cuadra IA. Preparation of pharmaceutical co-crystals through sustainable processes using supercritical carbon dioxide: a review. RSC advances. 2016;6(75):71134-50.
2. Ancheria RK, Jain S, Kumar D, Soni SL, Sharma M. An Overview of Pharmaceutical Co-Crystal. Asian J Pharma Res Dev. 2019;7(2):39-46.
3. Shan N, Zaworotko MJ. The role of cocrystals in pharmaceutical science. Drug discovery today. 2008 May 1;13(9-10):440-6.

4. Prasad RV, Rakesh MG, Jyotsna RM, Mangesh ST, Anita PS, Mayur PK. Pharmaceutical cocrystallization: a review. Int J Pharm Chem Sci. 2012;1(3):725-36.
5. Sekhon BS. Pharmaceutical co-crystals-a review.
6. Shankar SJ, BH JG, Akshatha RS, Metikurki B. Co-crystallization: A Novel ApproachToEnhance The Dissolution of Poorly SolubleDrugs.
7. Jasud S, Warad S, Rahul S, Jagdale G, Zinjad S. Cocrystal: a novel approach for bioavailability enhancement. World J. Pharm. Sci. 2013;2:4682-97.
8. Perlovich GL, Manin AN. Design of pharmaceutical cocrystals for drug solubility improvement. Russian J Gen. Chem. 2014;84(2):407-14.
9. Yuliandra Y, Zaini E, Syofyan S, Pratiwi W, Putri LN, Pratiwi YS, Arifin H. Cocrystal of ibuprofen–nicotinamide: solid-state characterization and in vivo analgesic activity evaluation. Scientia Pharmaceutica. 2018;86(2):23.
10. Aitipamula S, Vangala VR. X-ray crystallography and its role in understanding the physicochemical properties of pharmaceutical cocrystals. J Ind. Ins. Sci. 2017;97(2):227-43.
11. Ali J, Khar R, Ahuja A," A textbook of dosage form design" Birla publications Pvt Ltd, Delhi; 3rd edition;2008:100-107.
12. Pavia DL, Lampman GM, Kriz GS, Vyvyan JA. Introduction to spectroscopy. Cengage Learning; 2014.
13. Baka E, Comer JE, Takács-Novák K. Study of equilibrium solubility measurement by saturation shake-flask method using hydrochlorothiazide as model compound. J Pharm. Biomed. analysis. 2008;46(2):335-41.
14. Xia XR, Baynes RE, Monteiro-Riviere NA, Riviere JE. Determination of the partition coefficients and absorption kinetic parameters of chemicals in a lipophilic membrane/water system by using a membrane-coated fiber technique. Euro. J pharm sci. 2005;24(1):15-23.
15. Chatwal GR, Anand KS. instrumental methods of chemical analysis, 5th Edn Himalaya Publishing House. Mumbai. 2002:2-149.
16. Rodrigues M, Baptista B, Lopes JA, Sarraguça MC. Pharmaceutical cocrystallization techniques. Advances and challenges. Int. J pharma. 2018 ;547(1-2):404-20.
17. Kang Y, Gu J, Hu X. Syntheses, structure characterization and dissolution of two novel cocrystals of febuxostat. J Mol. Stru. 2017;1130:480-6.
18. Mounika P, Raj SV, Divya G, Gowramma A, Vijayamma G, Rangampet A. Preparation and characterization of novel co-crystal forms of fexofenadine. Int J Innov Pharm Res. 2015;6(1):458-63.
19. Thenge RR, Patond VB, Ajmire PV, Barde LN, Mahajan NM, Tekade NP. Preparation and characterization of co-crystals of diacerein. Indo. J Pharm. 2017;28(1):34.
20. Bhalekar M, Pradhan SB. Scientific Coformer Screening, Preparation, and Evaluation of Fenofibrate Tartaric Acid Cocrystal. J Drug Delivery and Therapeutics. 2019;9(4):406-10.
21. Yuliandra Y, Zaini E, Syofyan S, Pratiwi W, Putri LN, Pratiwi YS, Arifin H. Cocrystal of ibuprofen–nicotinamide: solid-state characterization and in vivo analgesic activity evaluation. Scientia Pharmaceutica. 2018;86(2):23.
22. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010;67(3):217-23.
23. SAFIGHUL IM, Reza S, Rahman H. In vitro release kinetics study of diltiazem hydrochloride from wax and kollidonsr based matrix tablets.