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ORIGINAL ARTICLE

Crystal engineering to improve physicochemical properties of mefloquine hydrochloride

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Abstract

Background: Pharmaceutical cocrystallization is a promising alternative for improving the solubility and dissolution rate or manipulating other physical properties of active pharmaceutical ingredients. The objective of this investigation was to study the effect of cocrystallization with different cocrystal formers on physicochemical properties of mefloquine hydrochloride. *Method:* Cocrystals were prepared by solution crystallization method – mefloquine hydrochloride (414.8 mg, 1 mmol) and different cocrystal formers (1/2 mmol) were dissolved in 20 mL of ethanol with warming. Solution was cooled in ice bath for 6 hours. The crystals were isolated by filtration through a membrane (0.45 μm) and dried in the air. The pure drug and the prepared cocrystals were characterized in terms of saturation solubility, drug content, infrared spectroscopy, differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy, in vitro dissolution studies, and stability studies. *Results:* The cocrystals showed enhanced solubility and dissolution rate. The cocrystals were found to be stable over the period of 6 months confirmed from stability studies. *Conclusion:* Cocrystals resist the conversion of anhydrous form of drug into its hydrate which is responsible for the drugs less solubility and dissolution rate.

Key words: *Cocrystals; dissolution; slurry crystallization; solubility; stability*

Introduction

Active pharmaceutical ingredient (API) can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, cocrystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug[1]. Solid form discovery and design depend on the nature of the molecule of interest and the type of physical property challenges faced in its development. The preferred solid form is generally the thermodynamically most stable crystalline form of the compound[2]. However, the stable crystal form of the parent compound may exhibit inadequate solubility or dissolution rate resulting in poor oral absorption, particularly for water-insoluble compounds. In this case, alternative solid forms may be investigated. For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability[3,4]. Many technological methods of enhancing the dissolution characteristics of slightly water-soluble drugs have been reported in various literatures[5]. These include reducing particle size to increase surface area[6,7], solubilization in surfactant systems[8], formation of solid dispersions[9–11], use of polymorph[12], solubilization of drugs in cosolvents and micellar solutions, complexation with cyclodextrins[13,14], the use of lipidic systems for the delivery of lipophilic drugs[15], drug derivatization, and manipulation of solid state of drug substance to improve drug dissolution, that is, by decreasing crystallinity of drug substance[16] and spherical crystallization[17]. Although these techniques have been shown to be effective at enhancing oral bioavailability, the success of these approaches is dependent at times on the specific physicochemical nature of the molecules being studied. Crystal form can be crucial to the performance of a dosage form[18,19]. This is especially true for compounds that have intrinsic barriers to

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drug delivery, such as low aqueous solubility, slow dissolution in gastrointestinal media, low permeability, and first-pass metabolism.

The dissolution of drugs is a prime determinant in the absorption of poorly water-soluble drugs and also serves as a rate-limiting step[20]. Pharmaceutical cocrystallization is a promising alternative for improving the solubility and dissolution rate or manipulating other physical properties of APIs. Pharmaceutical cocrystals are formed with an API (neutral or in the ionic form) and a benign cocrystal former that is solid under ambient conditions. The cocrystals are designed from the first principles of crystal engineering by evaluating the robustness of the potential intermolecular interactions (supramolecular synthons or hydrogen-bonding motifs) and following general hydrogen-bonding rules.

Crystal form can be crucial to the performance of a dosage form. This is especially true for compounds that have intrinsic barriers to drug delivery, such as low aqueous solubility, slow dissolution in gastrointestinal media, low permeability, and first-pass metabolism. According to the biopharmaceutics classification system[21,22], the nature of the physical form and formulation tends to exhibit the greatest effect on bioavailability parameters of water-insoluble compounds that need to be given orally in high doses such as mefloquine hydrochloride (MFL). Crystal engineering approach can modify the physicochemical properties of drugs and can help in overcoming these problems. By using crystal engineering, many successful attempts were made previously to improve physicochemical properties such as solubility[22,23], dissolution rate[23], and stability. This improvement was also confirmed through the enhancement of bioavailability[23–36]. Crystal engineering approach was also successfully applied in the improvement of mechanical properties such as compressibility in case of methyl gallate[33].

MFL is a blood schizonticide used for combating drug-resistant-falciparum malaria[34]. Plasma protein binding is about 98% and long elimination half-life is 2–4 weeks. It is very slightly soluble in water and showed polymorphism[33,35]. MFL can crystallize in at least eight anhydrous forms (A, B', E, and M), solvate forms (B and I), and hydrate forms (C and D). The forms present in commercial tablet formulation were found to be forms E and C. When the tablets were stored at 60°C, 75% RH, form E was transformed into form D, but form C did not undergo a significant change[36]. This might be the possible reason for the poor dissolution performance of the drug when formulated into tablets. These observations also matched with the results obtained in a study carried out to assess the bioequivalence between generic tablet of mefloquine (Mephaquine M1) and the reference one (Lariam M2) in healthy volunteers in a randomized two-way cross over study. The observed differences in C_{max}, t_{max}, and area under the curve are consistent with a slower rate and lower extent of mefloquine absorption after the administration of M1. Statistical evaluation of these kinetic data showed that the M1 tablet is not bioequivalent to the M2 tablet[37]. As Mefloquine is present as hydrochloride salt, no significant attempts had been made for the enhancement of solubility. Because of high molecular weight (414.8) and high melting point (255–260°C), inclusion complexes with cyclodextrin have not been tried[38].

The aim of this investigation was to study the effect of cocrystallization with different cocrystal formers on physicochemical properties of MFL.

Materials and methods

Materials

MFL was a gift sample from McLeod pharmaceuticals Ltd. (Mumbai, India). All the other chemicals and solvents were analytical grade procured from Merck (Mumbai, India) and Loba Chemie (Mumbai, India).

Preparation of cocrystals

MFL (414.8 mg, 1 mmol) and different cocrystal formers (1/2 mmol) were dissolved in 20 mL of ethanol with warming[30]. Solution was cooled in ice bath for 6 hours. The crystals were isolated by filtration through a membrane (0.45 μm) and dried in the air.

Saturation solubility and drug content

Saturation solubility studies were performed in triplicate according to the method reported by Higuchi and Connors[39]. For saturation solubility, an excess quantity of MFL cocrystals was placed in the vials containing 10 mL of different media. The vials were agitated in incubator shaker (100 agitations/min) for 24 hours at room temperature. The solution was then filtered through a membrane (0.45 μm) and the amount of the drug dissolved was analyzed spectrophotometrically (UV-1700; Shimadzu, Tokyo, Japan) at 283.5 nm. For the determination of drug content, prepared crystals (10 mg) were triturated with simulated gastric fluid (SGF) (pH 1.2)[40] and finally the volume was made up to 100 mL with the same. The solution was filtered through a membrane (0.45 μm) and analyzed spectrophotometrically for drug content after sufficient dilution with SGF (pH 1.2). The study was performed in triplicate.

Infrared spectroscopy

Infrared (IR) spectroscopy was conducted using a Shimadzu Fourier transform infrared spectroscopy (FTIR) 8300S Spectrophotometer (Shimadzu), and the spectrum was recorded in the wavelength region of

4000–400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone, mixture of drug and polymer, or prepared cocrystals) in KBr and compressing into discs by applying a pressure of 5 t for 5 minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded. All spectra were collected as an average of three scans at a resolution of 2 cm^{-1}.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed using DSC-60A (Shimadzu) calorimeter to study the thermal behavior of drug alone and prepared cocrystals. The samples were heated in hermetically sealed aluminum pans under nitrogen flow (30 mL/min) at a scanning rate of 10°C/min from 50°C to 300°C. Empty aluminum pan was used as a reference.

Powder X-ray diffraction

The X-ray diffraction (XRD) patterns of pure drug and the optimized crystals formulation were recorded using Philips analytical X-ray diffractometer (Model: PW 3710) (Philips, Almelo, the Netherlands) with a copper target over the interval of 5–70° $2\theta^{-1}$. The conditions were voltage 40 kV; current 30 mA; scanning speed 2°/min; temperature of acquisition, room temperature; detector, scintillation counter detector; and sample holder, nonrotating holder.

Scanning electron microscopy

The surface characteristics of the pure drug and prepared crystals were studied by scanning electron microscopy (SEM) (JEOL, JSM 50A, Tokyo, Japan) at 1600 × magnification. The samples were mounted on double-sided adhesive tape that has previously been secured on copper stubs and then analyzed. The accelerating voltage was 10 kV.

In vitro dissolution studies of cocrystals

The in vitro dissolution studies were carried out in triplicate using eight-station USP type II dissolution apparatus (Model Disso 2000 Tablet dissolution test apparatus; Lab India, Mumbai, India). Dissolution studies were carried out using 900 mL of SGF and simulated intestinal fluid (SIF) at 37 ± 0.5°C and 100 rpm. A sample of 5 mL was withdrawn after suitable time interval and replaced each time with 5 mL of fresh medium. The solutions were immediately filtered through 0.45-mm membrane filter, diluted, and the concentration of MFL was determined spectrophotometrically at 283.5 nm.

Stability studies of cocrystals

After the determination of drug content, the optimized crystals were charged for the stability studies according to ICH guidelines (30 ± 2°C and 65 ± 5% RH) for a period of 6 months in stability chamber (Thermo Lab, Mumbai, India). The samples were placed in USP type-1 flint vials and hermetically sealed with bromo butyl rubber plugs and aluminum caps. Five milligrams of the stored crystals (n = 3) were taken out at 0, 30, 60, 90, and 180 days and evaluated for the drug content and physical changes.

Results and discussion

Solubility and drug content determination

The results of saturation solubility showed that cocrystals prepared form citric acid have highest solubility in all mediums than pure drug. It was observed that there was no significant effect of molar concentration of cocrystal former on the solubility of MFL. This observation may be because of the concept of solution complexation[41,42]. The reason for avoiding high concentrations of cocrystal formers in the preparation of cocrystals was that the cocrystal formers themselves may form chains with hydrogen bonding. This will result in deficiency of cocrystal former for the complexation with the drug[41,42]. Hence, cocrystal phase yield will decrease dramatically along with the impure cocrystalline components. Hence further study was carried out with cocrystals prepared with 1:1 ratio of drug and cocrystal formers (Tables 1 and 2).

The practical yield was 81.26–89.25%. The drug content 98.07–99.76% was found to be good and uniform among the different batches of prepared cocrystals (Table 2). The pH-dependent saturation solubility profile showed that there was no significant difference in the solubility of drug at various pH conditions. But the solubility decreased as pH increased from 1.2 to 4, again increases from 4 to 8, and decreases above pH 8 (Table 3). Solubility curve posses 'S'-shaped curve (Figure 1).

Table 1. Saturation solubility studies of drug.

		Solubility (mg/mL)			
Sample	Temperature (°C)	SGF pH 1.2	FaSSGF pH 1.8	FaSSIF pH 6.5	Deionized water
MFL	37 ± 0.5	0.5346	0.5180	0.5348	0.5381
MFL	37 ± 0.5	0.5312	0.5194	0.5312	0.5399
MFL	37 ± 0.5	0.5334	0.5165	0.5398	0.5423

Table 2. Percentage yield, drug content, and saturation solubility of cocrystals.

Formulation	Yield (%)	Drug content	Solubility (mg/mL)			
			SGF (pH 1.2)	FaSSGF (pH 1.8)	FaSSIF (pH 6.5)	Water
A1 (benzoic 1:1)	87.54	99.76 ± 1.24	0.5530 ± 0.104	0.5081 ± 0.065	0.6882 ± 0.11	0.8014 ± 0.0784
A2 (benzoic 1:2)	83.60	99.23 ± 1.67	0.5134 ± 0.0824	0.5061 ± 0.023	0.6324 ± 0.12	0.6965 ± 0.0356
B1 (citric 1:1)	85.46	98.87 ± 1.34	0.5949 ± 0.0621	0.5081 ± 0.082	0.6899 ± 0.056	0.6893 ± 0.0325
B2 (citric 1:2)	81.26	98.35 ± 1.53	0.5824 ± 0.0302	0.5031 ± 0.0987	0.6458 ± 0.0687	0.6016 ± 0.0562
C1 (oxalic 1:1)	84.65	98.19 ± 2.73	0.4357 ± 0.104	0.5024 ± 0.0647	0.5565 ± 0.0536	0.6765 ± 0.015
C2 (oxalic 1:2)	81.65	98.07 ± 1.56	0.4475 ± 0.094	0.4866 ± 0.0632	0.5124 ± 0.0532	0.5509 ± 0.0214
D1 (saccharin 1:1)	86.35	99.02 ± 2.51	0. 4296 ± 0.034	0.5018 ± 0.0621	0.4312 ± 0.0235	0.5499 ± 0.0658
D2 (saccharin 1:2)	89.25	98.45 ± 1.58	0.4358 ± 0.084	0.4892 ± 0.0452	0.4371 ± 0.0213	0.3754 ± 0.0896
E1 (salicylic 1:1)	88.56	99.25 ± 0.55	0.6173 ± 0.045	0.5363 ± 0.0453	0.5954 ± 0.0123	0.6709 ± 0.0356
E2 (salicylic 1:2)	81.65	99.49 ± 2.17	0.5765 ± 0.089	0.5236 ± 0.0215	0.5513 ± 0.12	0.6072 ± 0.0325
F1 (succinic 1:1)	84.96	99.26 ± 1.34	0.5078 ± 0.101	0.4983 ± 0.085	0.5916 ± 0.10	0.6173 ± 0.0432
F2 (succinic 1:2)	85.62	99.15 ± 1.41	0.5075 ± 0.098	0.4769 ± 0.102	0.5474 ± 0.0213	0.5804 ± 0.0653

At 25°C (mean ± SD, $n = 3$).

Table 3. pH-dependent solubility profile of mefloquine hydrochloride.

S. No.	pH (initial)	pH (final)	pH flux	Solubility (µg/mL)
1	1	0.85	0.15	532.80 ± 1.14
2	2	1.75	0.25	530.50 ± 2.24
3	3	2.78	0.22	529.85 ± 2.04
4	4	3.80	0.20	531.04 ± 2.30
5	5	4.86	0.14	533.34 ± 1.54
6	6	5.68	0.32	535.65 ± 1.31
7	7	6.02	0.98	536.77 ± 1.75
8	8	6.74	1.26	536.21 ± 1.65
9	9	7.38	1.62	534.91 ± 1.23
10	10	8.36	1.64	531.12 ± 1.52

At 25°C (mean ± SD, $n = 3$).

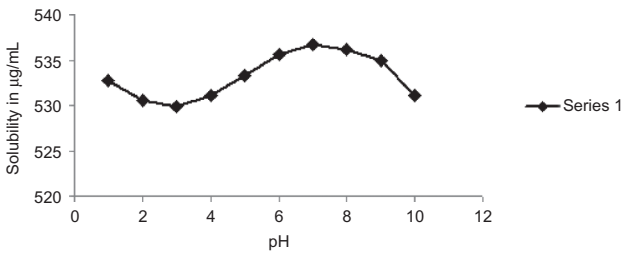

Figure 1. Effect of pH on solubility of mefloquine hydrochloride.

Infrared spectroscopy

The possible interaction between the drug and the cocrystal formers was studied by IR spectroscopy. MFL structural characteristic peaks because of N–H, C–N, O–H, C–O, C–F, C–H, C–X, C–C stretching are shown in Table 4. From the IR spectra (Figure 2), it was observed that all important peaks because of functional groups of drug are present in the cocrystals along with some new peaks. The results revealed considerable changes in IR peaks of MFL in prepared cocrystals when compared to pure drug, thereby indicating the presence of hydrogen bonding that had occurred in cocrystals. Except saccharin

Table 4. FTIR data of mefloquine hydrochloride.

Range	Absorption at (cm^{-1})	Type of bond	Functional groups
3300–3500	3400	N–H stretch	Amine
2500–3100	2700	Weak interaction	Weak bond present
1200–1400	1315	C–N stretch	Aryl NH
3200–3400	3240	O–H stretch	Alcohol
1000–1300	1111	C–O stretch	Alcohol
1500–1600	1515, 1585	C–C stretch	Aromatic ring
3000–3100	3000	C–H stretch	Aromatic ring
600–800	750	C–X	Halogen
1140–1305	1139	C–F	CF_3 groups

all cocrystal formers contain carboxylic acid moiety, and prominent peaks were observed in the range of 1680–1760 cm^{-1}, indicating the presence of C=O stretch, which is a peculiar characteristic of COOH functionality. The C=O stretch in the range of 1000–1300 cm^{-1} was also observed for COOH functional groups. Broad peaks observed in the range of 2500–3000 cm^{-1} are indications of O–H stretch and suggested the presence of hydrogen bonding. These peaks are peculiar characteristic of carboxylic acid dimmers with N–H or O–H groups[23,43,44]. Also there are peaks observed in the range of 400–800 cm^{-1} that are indicative of halogen–hydrogen interactions[23,43,44].

Differential scanning calorimetry

The results of DSC studies are shown in Figure 3. MFL showed an endothermic peak at 269.48 corresponding to its melting point followed by an exothermic peak at 306.32°C. This exothermic peak might convert the drug into more stable but less-soluble form[45]. The peaks of citric, benzoic, and oxalic acid cocrystals were broad, less sharp than drug. This observation showed that the resultant cocrystals were also in the amorphous state although salicylic, succinic acid,

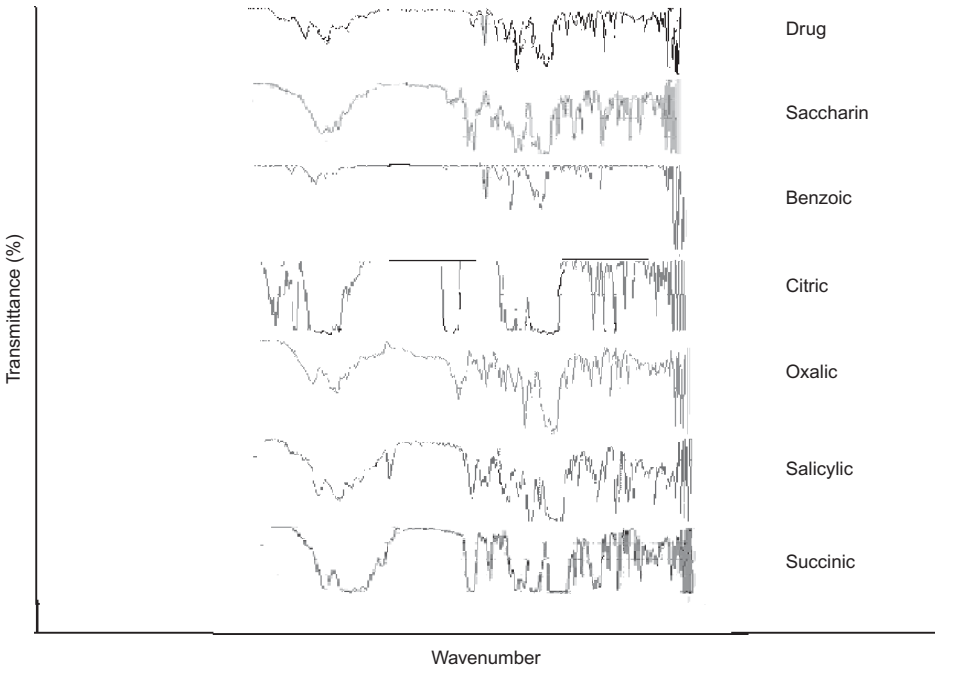

Figure 2. Comparative IR spectra of drug and cocrystals.

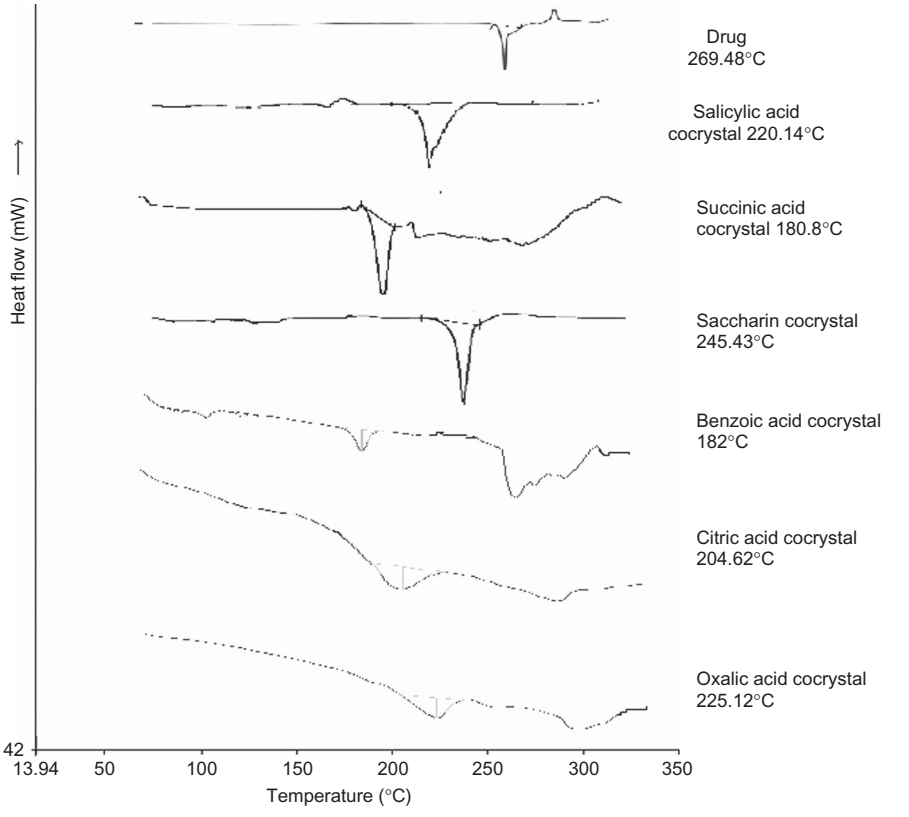

Figure 3. Comparative DSC curves of drug and cocrystals.

and saccharin cocrystals showed sharp endothermic peaks with the depression of melting points. This revealed that cocrystals of these respective cocrystal formers are present in crystalline state. This was also confirmed from powder X-ray diffraction (P-XRD) and SEM analysis.

Table 5. Differential scanning calorimetric analysis of drug and cocrystals.

Name	Reported MP (°C)	Observed or cocrystal MP (°C)
Mefloquine hydrochloride	260–270	269.48
Benzoic acid	122.4	182.11
Citric acid	153	204.6
Oxalic acid	101–102	225.12
Saccharin	228.8–229.7	245.43
Salicylic acid	159	220.14
Succinic acid	185–187	180.08

The endothermic peaks of cocrystals were found to be different than drug and individual cocrystal former, thus confirming the formation of new phases. In case of benzoic acid, citric acid, oxalic acid, saccharin, and salicylic acid cocrystal, melting points of cocrystals were found to be in between the melting points of drug and the respective cocrystal formers. The melting point of succinic acid cocrystal was found to be below the melting points of both the drug and cocrystal former (Table 5). None of the cocrystal showed the exothermic peak like that of drug and thus prevents the conversion of drug into less-soluble form.

Powder X-ray diffraction

The P-XRD pattern of plain MFL showed intense peaks of crystallinity at 21.10°, 34.73°, 33.51°, 29.75°, and 16.88° (2θ) with peak intensities of 169, 137, 81, 67, and 50, respectively, indicating its crystalline nature (Figure 4). Crystallanity was determined by comparing representative peak heights in the diffraction patterns of the cocrystals with those of reference. The relative degree of crystallinity (RDC) of MFL in cocrystals was calculated according to the equation RDC = I_{sam}/I_{ref}, whereas I_{sam} is the peak height of the sample under investigation and I_{ref} is the peak height at the same angle for the reference with the highest intensity[46] (Table 6).

The peak height at 21.10° and 34.73° (2θ) was used for calculating the RDC of cocrystals. The XRD

Table 6. Relative degree of crystallinity of cocrystals.

S. No.	Cocrystals	Angle (2θ)	RDC
1	Citric acid	21.10	Disappeared
		34.73	0.934
2	Oxalic acid	21.10	0.9112
		34.73	0.4087
3	Succinic acid	21.10	Disappeared
		34.73	0.1824
4	Salicylic acid	21.10	1.0177
		34.73	0.4817
5	Benzoic acid	21.16	1.3668
		34.73	0.7737
6	Saccharin	21.10	0.2603
		34.73	0.8686

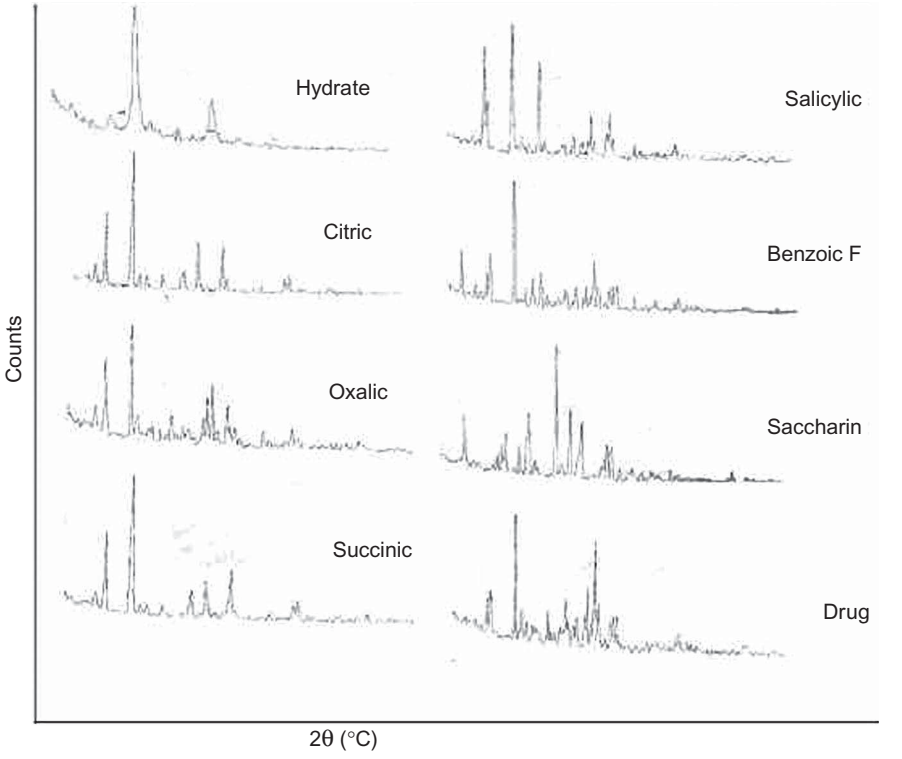

Figure 4. Comparative P-XRD patterns of drug and cocrystals.

pattern of prepared cocrystals exhibited reduction in both number and intensity of peaks compared to MFL at the specific angles indicating the decrease in crystallinity or partial amorphization of the drug in the cocrystals. However, there are some intense peaks observed at angles other than drug-specific angles, which are because of the crystalline nature of the cocrystal formers. In succinic and benzoic acid, particularly intense peaks close to the angle 21.10° were observed. The cocrystals showed better dissolution than pure drug in biorelevant media. This observation suggests the possibility of prevention of anhydrous form of drug from converting into its hydrate form as observed in the Figure 4. The conversion of drug into its hydrate form might be the reason of its poor solubility and dissolution.

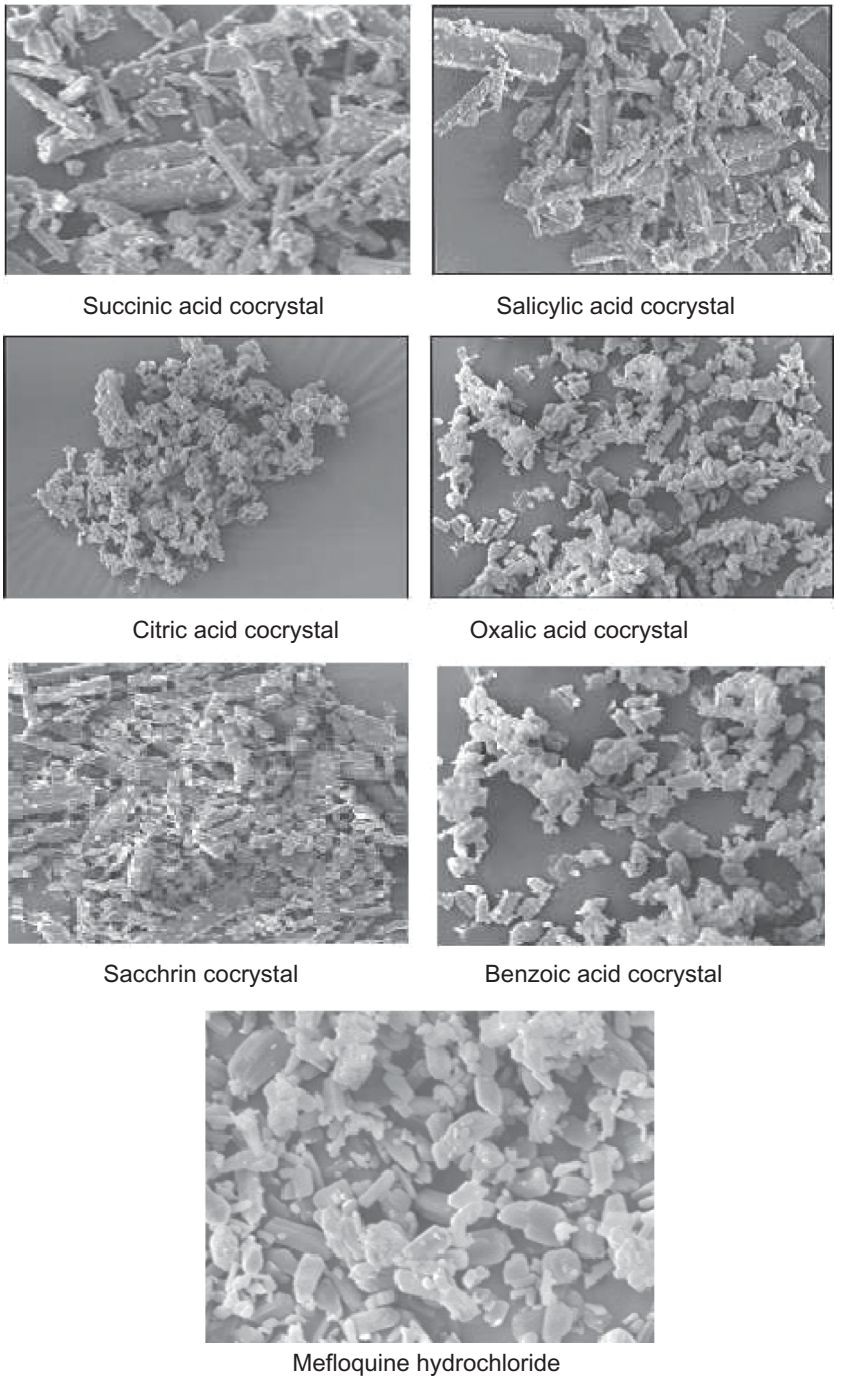

Figure 5. Scanning electron microphotographs of cocrystals.

Scanning electron microscopy

Crystals of bigger size and regular shape with an apparently smooth surface characterized the pure drug (Figure 5). In contrast, cocrystals were present in fine form for citric acid, benzoic acid, and oxalic acid. They were found to be fluffy and possess porous and rough surface, which might have resulted in the enhanced dissolution rate as compared to pure drug. Additionally, the cocrystals of saccharin, salicylic acid, and succinic acid were observed to be more crystalline than drug itself. Thus the process of cocrystallization might retain the crystal nature containing the drug in amorphous form resulting in better dissolution rate.

In vitro dissolution study

In vitro dissolution studies revealed that cocrystals showed enhancement in the dissolution rate. This can be observed from comparative dissolution profiles shown in Figures 6 and 7 and also from the percent released in 15 and 45 minutes (Tables 7 and 8). In case of benzoic acid cocrystal t_{15} values in both SGF and SIF were less than that of drug. But more at 45 minutes; this fact confirms the slow transformation of the cocrystal in the dissolution media. While in case of citric acid, saccharin, and salicylic acid, cocrystal dissolution was found to be superior in SGF but less than the drug in SIF at both 15 and 45 minutes. Succinic acid cocrystal showed superior dissolution in both media in cocrystal

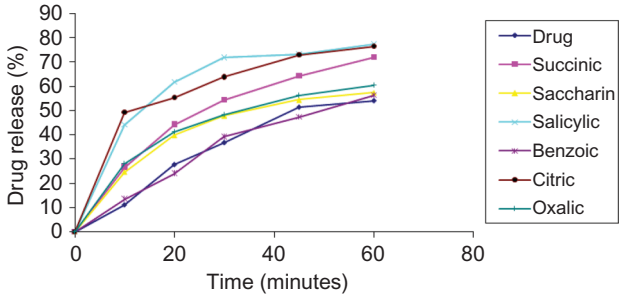

Figure 6. Dissolution studies of cocrystals in SGF pH 1.2.

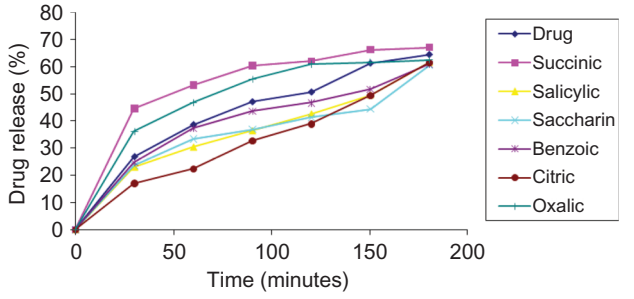

Figure 7. Dissolution studies of cocrystals in FaSSIF pH 6.5.

Table 7. Percent drug released at 15 minutes.

Name	$T_{15\%}$ in SGF of cocrystals	$T_{15\%}$ in SIF of cocrystals
Benzoic acid	20.6	20.12
Citric acid	53.2	12.15
Oxalic acid	35.9	21.23
Saccharin	34.1	14.5
Salicylic acid	56.2	14
Succinic acid	36.7	44.2
Pure drug	21	21.9

Table 8. Percent drug released at 45 minutes.

Name	$t_{45\%}$ in SGF of cocrystals	$t_{45\%}$ in SIF of cocrystals
Benzoic acid	47.8	33.21
Citric acid	72.1	20.15
Oxalic acid	55.4	39.23
Saccharin	53.2	28.44
Salicylic acid	74.4	24.56
Succinic acid	64.6	48.2
Mefloquine hydrochloride	47.7	32.6

form. Oxalic acid cocrystal showed slow transformation behavior in SIF media. The possible mechanism of improvement in dissolution may be due to the hydrotropic action of acids used[47,48]. To study the transformation behavior in detail and predict the correct transformed form, polarization microscopy and online P-XRD studies are necessary[25]. Samples have to be analyzed by P-XRD during the dissolution experiment. But simply by observing the t_{15} and t_{45} values of percent released, one can predict the transformation behavior correctly[24,25]. Upon application of statistics, the best model for these systems was found to be matrix and Peppas one. There was significant difference observed in t_{15} values for percent release in SGF ($P < 0.05$).

Stability studies of cocrystals

The physical stability of cocrystals was compared with the drug for the conversion into its hydrate form. The cocrystals were found to be stable during the study periods. Also the P-XRD patterns of cocrystals showed no significant difference with their previous pattern confirming their stability during storage conditions. The drug content in all the cocrystals was found to be within the limit. The drug content within the formulations is shown in Table 9.

Conclusions

Through a crystal engineering approach, we have developed a method of obtaining multicomponent cocrystals of MFL using pharmaceutically acceptable compounds as guests. This approach is expected to

Table 9. Drug content of formulations after stability studies.

Storage condition 30 ± 2°C/65 ± 5% RH	Drug content (%) of formulations					
	Benzoic acid	Citric acid	Oxalic acid	Saccharin	Salicylic acid	Succinic acid
Time 0 day	99.56 ± 1.14	98.77 ± 1.34	98.19 ± 2.13	99.02 ± 2.51	99.25 ± 0.55	99.26 ± 1.34
Time 90 days	99.46 ± 1.34	98.67 ± 1.44	98.09 ± 2.34	98.82 ± 2.31	99.15 ± 0.48	99.05 ± 1.55
Time 180 days	99.26 ± 1.14	98.47 ± 1.23	97.69 ± 2.01	98.23± 2.11	98.65 ± 0.34	98.25 ± 0.55

Mean ± SD, $n = 3$.

be applicable to variety of pharmaceuticals because large percentages of APIs are capable of existing as crystalline hydrochloride salts. Cocrystallizing the hydrochloride salt of an API presents an opportunity to alter the physical properties of the solid dosage form while simultaneously retaining the hydrochloride salt of the API in the crystal structure. This methodology is illustrated by the rational synthesis, structural characterization, and dissolution properties of six cocrystals of MFL.

It was found that all carboxylic acids except saccharin formed cocrystals in different stoichiometric ratios with MFL depending on the differences in their structures and the ability to form hydrogen bonds. The formation of new phases was confirmed from DSC and P-XRD analysis. The cocrystals showed enhanced solubility and dissolution rate. The cocrystals were found to be stable over the period of 6 months confirmed from stability studies. They resist the conversion of anhydrous form of drug into its hydrate, which is responsible for the drug's less solubility and dissolution rate.

The choice of correct solvent system is extremely important for the synthesis of cocrystals. The concept of solution complexation was studied carefully during this particular work. The effect of solubility of cocrystal former on the formation of cocrystalline phases and the transformation behavior of cocrystals in the dissolution medium was studied. Thus one can apply the principles of crystal engineering to improve physicochemical properties of APIs while simultaneously retaining its activity.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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