ORIGINAL ARTICLE

Enhancement of Solubility and Dissolution Rate of Lumefantrine by Pharmaceutical Cocrystals

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Abstract

Purpose: The solid-state properties of drug compounds, such as solubility and dissolution, can be changed by cocrystallizing the drug with coformers. The purpose of the current effort was to identify potential coformers and then develop, formulate, and assess the lumefantrine cocrystal. **Methods:** Lumefantrine cocrystals were created using the solvent evaporation process. The crystalline phase's melting temperature and solubility were established. DSC, IR, and XRPD were used to characterize the putative cocrystal. Evaluations were also conducted on solubility and dissolution rate, two additional medicinal qualities. **Results and Discussion:** Lumefantrine-adipic acid cocrystals showed a range in solubility and melting points. Adipic acid and the cocrystals were combined in a 1:1 ratio. The infrared research clearly showed that the lumefantrine distinctive bands were changing. A notable variation in the 2θ of the strong peaks and the crystallinity of cocrystals were indicated by the X-ray powder diffraction pattern. Cocrystal's differential scanning calorimetry spectra revealed changed melting point endotherms. Due to cocrystallization, the cocrystals showed a higher rate of dissolution, as seen by an increase in the extent of dissolution. **Conclusion:** The lumefantrine cocrystal with modified properties was prepared with adipic acid having greater solubility and dissolution rate of the drug.

Key words: Cocrystal, dissolution, lumefantrine, solubility

INTRODUCTION

In recent years, a large number of drugs with low water solubility have been discovered. About 60–70% of the molecules in these recently identified medications fall within BCS Classes II (low solubility/high permeability) and IV (low solubility/poor permeability). Due to the drug's poor solubility in water and low bioavailability, many active pharmaceutical ingredients (APIs) have not yet been developed. The gastrointestinal (GI) tract has different pH values in different parts, so drugs administered orally have different solubility in GI fluid at different pH values, which often leads to the variable, non-linear absorption, and effectiveness, and cannot fully evaluate the safety of the drug. Therefore, the limited aqueous solubility of active drug molecule is a serious problem in the development of oral dosage forms. In the market, most preferred formulations are oral formulations due to their ease of administration. Drugs that are administered orally should have good solubility into the GI medium for its good absorption. Nowadays, in pharmaceutical industries, NCE obtained has poor water solubility-related issues so that cause erratic oral absorption, and ultimately, it affects the bioavailability. It is a major challenge during formulation development in pharmaceutical industries. According to BCS classification, drugs that are poorly soluble in water are included under BCS class II and class IV.[1-3]

Cocrystals

Cocrystals are crystalline material composed of multiple components. It includes mainly two components API and cocrystal former (Coformers). API is a molecule that has some issues such as stability, solubility, and bioavailability which

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affect on its pharmacokinetic profile and result in minimal efficacy. Coformers, also known as cocrystal formers, are typically accepted as safe molecules. These two elements are linked together in cocrystal systems by non-covalent bonding such as hydrogen bonding, van der Waal's interaction, and pi-pi stacking. Coformers are selected based on properties that have to be modified. The properties modified are solubility, stability, dissolution, and bioavailability. Cocrystals can improve drugs with poor physicochemical properties.[4,5]

MATERIALS AND METHODS

Materials

Lumefantrine was provided by Jay Jalaram Enterprise, Gujarat. Adipic acid, benzoic acid, and salicylic acid were obtained from Loba Chem Pvt. Ltd., Mumbai. Other resources utilized were of an analytical caliber and came from our organization (MESCOP, Sonai).

Preparation of cocrystals

The method of gradual solvent evaporation was used to accomplish cocrystallization. Lumefantrine and coformers in the stoichiometric ratio (1:1) were placed into the glass beaker then added 25 mL methanol and stirred with a magnetic stirrer until dissolved. The glass beaker was covered with aluminum foil and given small holes. The solution in a glass beaker was allowed at room temperature for slowly evaporation of the solvent. The solid mass was obtained, then crushed, and characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and Fourier transform infrared (FTIR) and further examined by solubility and dissolution test.[6]

Characterization of cocrystals

Melting point

The melting temperature of lumefantrine and its cocrystals was determined by the simple capillary method using melting point apparatus. The average melting point in triplicate was made and compared with the standard values.[7]

Micromeretics properties

Characterization of lumefantrine and its cocrystals performed for various pharmaceutical processing properties such as angle of repose, bulk density, tapped density, cars index, and Hausner ratios were studied.[8]

FTIR spectroscopy

The likelihood of a contract between the medication and the coformer was evaluated using IR spectroscopy. The samples were dispersed in a KBr pellet and scanned using a Shimadzu IR spectrophotometer between 4000 and 400 cm^{-1} with the resolution of 4 cm^{-1}.[9]

DSC

The thermal behavior of the drug alone and cocrystal was determined by DSC studies by Mettler Toledo DSC 822e Module. Weighed samples were heated in aluminum pans at a rate of 5°C/min, from 0 to 300°C temperature range, under a nitrogen stream. The instrument was calibrated using indium and the empty aluminum pan was used as a reference.[10]

PXRD

The silicon sample holders were utilized to get diffraction patterns of pure lumefantrine and cocrystal (Bruker D8 Advance Diffractometer). Each sample was put on a motorized goniometer head that allowed it to spin while collecting data and the apparatus was fitted with a fine-focus X-ray tube.[11]

Solubility Study

In distilled water, lumefantrine's solubility was tested. The vials containing 10 mL of distilled water had an excessive amount of lumefantrine added to it. The vials underwent rotary shaking and were let to stand for 24 h for equilibrations. After 24 h, the samples were filtered, diluted with distilled water, and subjected to UV spectrophotometer analysis at 267.5 nm.[12]

Dissolution study

Utilizing a USP type II dissolve test apparatus (TDT-08L, Electrolab, Mumbai, India) for 60 min at 37 ± 0.5°C and 50 rpm, dissolution tests were carried out in 0.1 N HCl (900 mL). For the trial, a cocrystal and pure medication with a 10 mg equivalency each were employed.[13]

Drug efficiency

Cocrystals of lumefantrine with adipic 10 mg were precisely weighed and transferred to a volumetric flask (10 mL). It was dissolved properly in methanol and diluted up to the mark with methanol to obtain a final concentration of 1000 µg/mL and used as a stock solution (Stock Solution I). 1 mL of stock solution I was withdrawn and further diluted by methanol to give 10 µg/mL. This solution was scanned in the UV region of 400–190 nm. The spectrum was obtained to determine the maximum absorbance. They were analyzed by UV–Visible spectrophotometer by measuring the absorbance at 250 nm.[14-18]

RESULTS AND DISCUSSION

Melting point and solubility

The melting points of pure drug and cocrystals are determined and recorded in Table 1. Melting temperatures of cocrystals were lesser than the lumefantrine. The depression of melting temperatures revealed a multicomponent system and designated formation of cocrystals. The interaction between lumefantrine and coformers, a shift in the crystallinity of the molecules, or a changed packing arrangement could all be responsible for the modified melting points of cocrystals. This contact causes a modification in the molecular arrangement, resulting in a new crystal structure with altered solubility and/or melting point.

Micromeritics properties

Hausner ratio and Carr's index are indirect methods of assessing the flow properties of granulates. For the Hausner ratio, values >1.6 are indicative of poor flowability while values ~ 1.25 show good flowability. In the case of Carr's index, values ≤16% indicate good flowability, while values >23 % demonstrate poor flowability. The values of the Hausner ratio and Carr's index obtained in this study showed that the lumefantrine and cocrystal possessed good flowability. However, the angle of repose of 32.08 and 24.90 for lumefantrine and cocrystal, respectively, confirm good flowability.

FTIR spectroscopy of lumefantrine and cocrystal

The IR spectrum for pure drug and cocrystal was recorded and shown in Figures 1 and 2, respectively. The principle bands were identified and associated changes were recorded. The IR spectra of Lumefantrine show the presence of the characteristic peaks which were recorded at 903.48 cm^{-1} for C-Cl Stretching, N-C stretching at 2305.48 cm^{-1}, and C-C stretching at 2305.48 cm^{-1}. The IR spectra of the cocrystal revealed an absorption band at 3565.74 cm-1 which can be assigned to O-H stretching. In addition, COOH and C-H stretching bands were recorded at 1700.91 cm^{-1} and 1456.96 cm^{-1}, respectively. These spectra are in good agreement with the published data. In compared to the pure drug and coformer, the IR bands in the cocrystal dramatically shifted, showing drug and coformer interaction. This indicates cocrystal formation as the peak shifted slightly and became broader in the cocrystal. The cocrystal spectra showed numerous additional peaks that supported the cocrystal's development. As a result, the alterations noted in the study can be interpreted as a hint that the medication and coformers are coforming crystals.

Table 1: Micromeritics properties of cocrystals

Parameters	Lumefantrine	Lumefantrine cocrystal with adipic acid
Melting point	125–131°C	103–107°C
Angle of repose	32.08	24.19
Bulk density	0.5172 g/cc	0.3043 g/cc
Tapped density	0.73 g/cc	0.4 g/cc
Hauser's ratio	1.4147	1.13144
Carr's index	21.28%	9.57%

DSC thermogram of lumefantrine cocrystal with adipic acid

Lumefantrine and lumefantrine-adipic acid cocrystals were characterized by DSC. The lumefantrine and coformer showed a characteristic endothermic peak at 136.08°C and 162.94°C, respectively, corresponding to their melting point. Similar thermal behavior was reported for the drug. The cocrystal showed a substantial difference in the melting point (152.40°C) in comparison to the pure drug (136.08°C) and coformer (162.94°C). In addition, the peak onset for the pure drug was recorded, suggesting that a cocrystal may have formed. The absence of the peak associated with coformer fusion in the cocrystal's DSC indicates its creation and the absence of a physical mixing. The change in the thermal properties was reported as evidence for the development of the cocrystal. Hence, the present investigation denotes the formation of cocrystal. The DSC spectrum of lumefantrine, adipic acid, and lumefantrine-adipic acid cocrystals is depicted in Figures 3-5.

XRD analysis of lumefantrine and cocrystal

The PXRD patterns for lumefantrine and cocrystal are depicted in Figures 6 and 7, respectively. The materials in the powder state give distinctive peaks of varying intensities at certain positions. The diffractogram of the lumefantrine showed characteristic diffraction peaks at different 2θ values (19.98, 20.62. 21.05, 22.11, 22.69, 23.62, 25.65, 26.02, 26.33, 26.57, and 27.30) indicating the crystalline nature. The PXRD pattern of the cocrystal was distinguishable from its components and some additional diffraction peaks were appeared which did not exist in the pure drug. The additional diffraction peaks for cocrystal were obtained at 2θ values of 21.36, 22.12, 22.55, 24.03, 24.94, 25.51, 26.48, 26.91, 28.10, 29.15, 29.72, and 31.08. The appearance of new diffraction peaks in the diffractogram of cocrystal shows the formation of a new crystalline phase (cocrystal). Based on the PXRD pattern, which displayed new peaks distinct from the peaks corresponding to its input components, the development of cocrystals had previously been well-documented.

Solubility study of lumefantrine and their cocrystal

The solubility of cocrystals (49.81 µg/mL) was increased with each coformer but remarkably improved (29.30 folds)

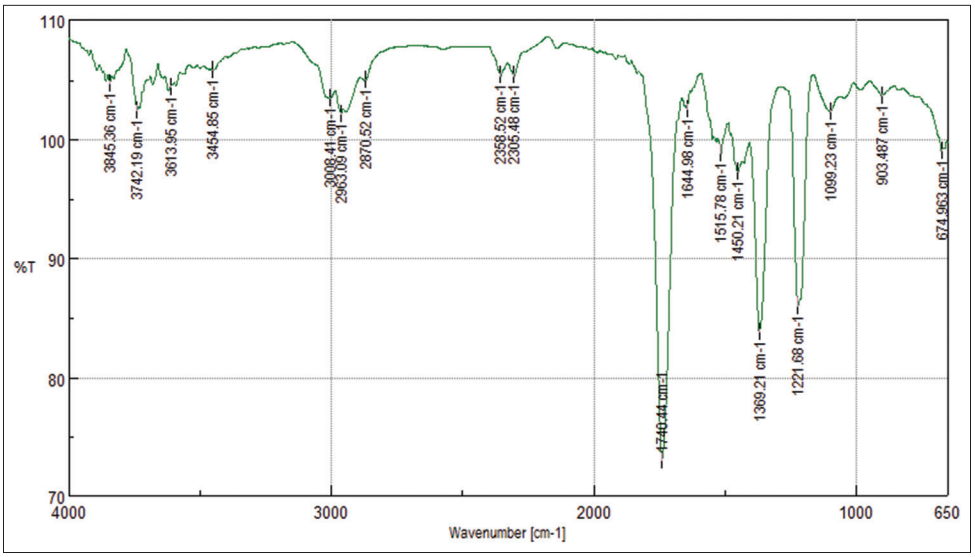

Figure 1: Fourier transform infrared spectrum of lumefantrine

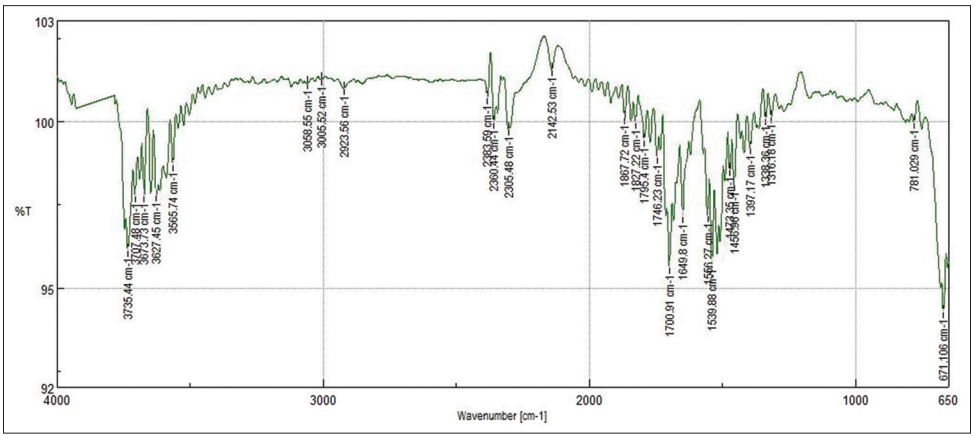

Figure 2: Fourier transform infrared spectrum of cocrystal with adipic acid

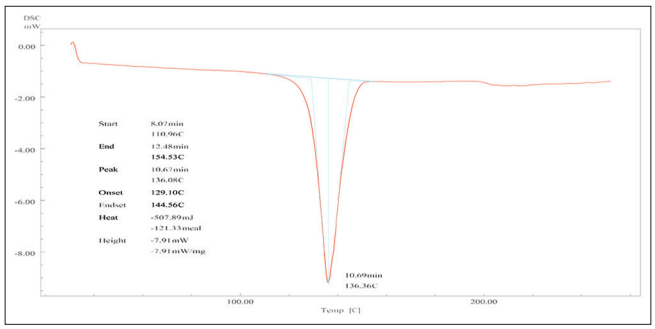

Figure 3: Differential scanning calorimetry thermogram of lumefantrine

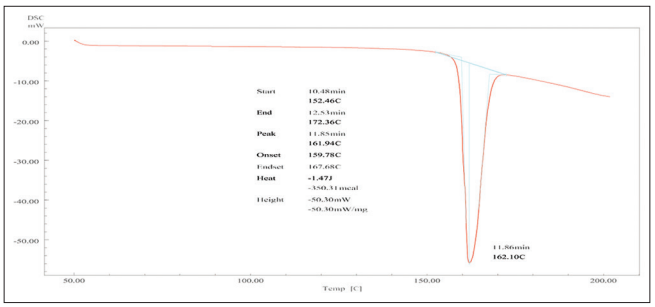

Figure 4: Differential scanning calorimetry thermogram of adipic acid

with adipic acid. This indicates the successful interaction of lumefantrine with coformers and the formation of cocrystals. The studies pertaining to solubility enhancement were reported with cocrystals of fluoxetine hydrochloride, niclosamide, meloxicam, etc. Based on the results, the lumefantrine-adipic acid cocrystal was further characterized. The solubility of lumefantrine and lumefantrine with adipic acid cocrystal is depicted in Table 2.

Dissolution study

The dissolution rate plays a crucial role in the bioavailability of active drugs with poor solubility. The cocrystal and pure medication were used in the dissolution experiment. Figure 8 depicts the dissolution profile of the created cocrystal and the pure medication. The dissolution outline of the pure drug indicates a slow dissolution rate with only 21.54% of the drug being dissolved in the first 5 min.

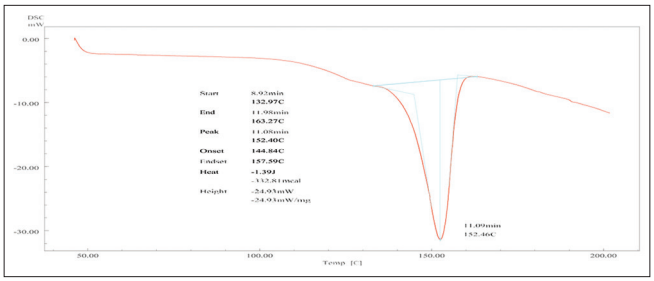

Figure 5: Differential scanning calorimetry thermogram of cocrystal with adipic acid

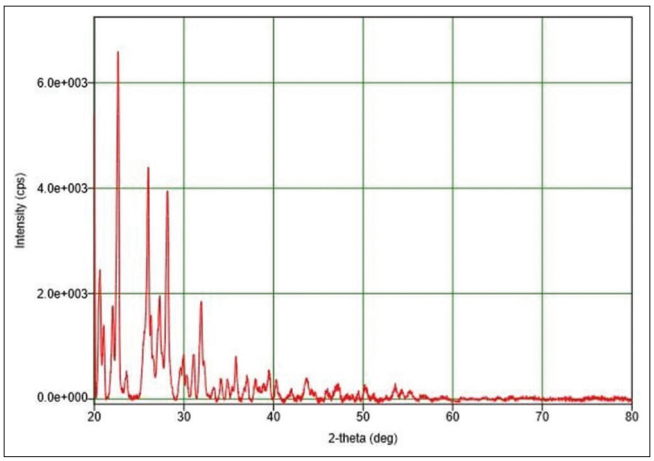

Figure 6: X-ray diffraction analysis of lumefantrine

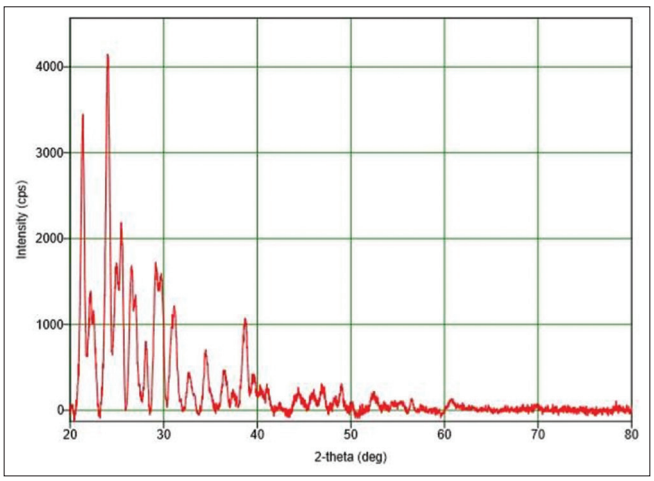

Figure 7: X-ray diffraction analysis of cocrystal with adipic acid

The amount of drug dissolved in 30 min was 30.22%. However, the cocrystal of the lumefantrine resulted in a significant increase in the dissolution rate. The amount of drug dissolved in the first 10 min was 42.64% and the total amount dissolved was 86.88% with a dissolution efficiency of 97.91%. The increased dissolving rate can be interpreted as indicating the cocrystal's poorer crystalline structure. Moreover, greater dissolution of lumefantrine from cocrystal can be attributed to changed crystallinity pattern, size, shape, and crystal habit of cocrystal that

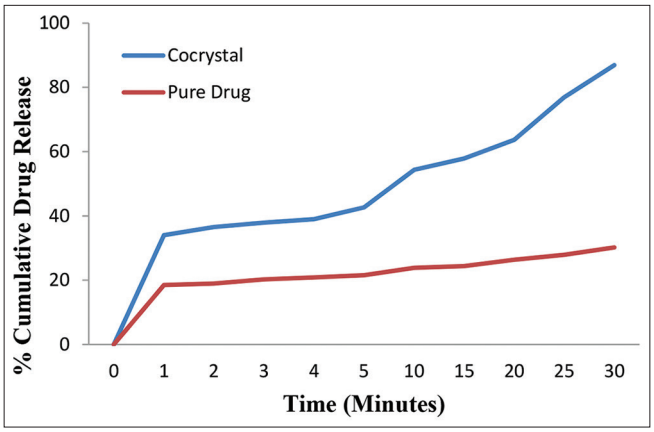

Figure 8: Percentage cumulative drug release for cocrystal and pure drug

Table 2: Solubility of lumefantrine cocrystal with adipic acid

S. No.	Cocrystal	Ratio	Solubility Conc. µg/mL
1.	Lumefantrine		0.00278
2.	Cocrystal lumefantrine	1:1	49.81 (29.30 Fold)
3.	Cocrystal lumefantrine	1:2	43.67
4.	Cocrystal lumefantrine	1:3	42.50
5.	Cocrystal lumefantrine	1:4	40.23
6.	Cocrystal lumefantrine	1:5	39.16

Table 3: Percentage cumulative drug release of lumefantrine and cocrystal

Time in minutes	Lumefantrine: Adipic acid (1:1) (%)	Lumefantrine (pure drug) (%)
1	34.00	18.51
2	36.55	19.00
3	37.89	20.30
4	38.99	20.88
5	42.64	21.54
10	54.38	23.83
15	57.86	24.38
20	63.67	26.36
25	76.92	27.91
30	86.88	30.22

leads to enhanced solubility of cocrystal in the dissolution media. Cocrystallization had been well-documented as a competent technique for dissolution enhancement. It was clearly reflected that there was a significant increase in the dissolution of lumefantrine due to cocrystal formation and complete inhibition of dihydrate formation. The % cumulative drug release of lumefantrine and cocrystal is depicted in Table 3.

CONCLUSION

It was found that all formed cocrystals were in stoichiometric ratios with lumefantrine depending on the difference in their structures and the ability to form bonds. The formation of new phases was confirmed by DSC and P-XRD analysis. The cocrystals showed enhanced solubility and dissolution rate. The results of SEM images concluded that the cocrystals prepared were uniform in size and shape, larger in size than the pure drug, uniformly distributed thus having good flow properties, and has good solubility than the pure drug. The choice of solvent system is extremely important for the synthesis of cocrystals. The choice of solvents system is extremely Important for the synthesis of Lumefantrine cooyrstals. Thus, one can apply the ideology of crystal engineering to improve the physicochemical properties of API's while simultaneously retaining its activity. Finally, we might, therefore, say that the coformer technique is a useful technique in improving the physical and chemical properties of the drug, solubility, and dissolution rate.

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ETHICS APPROVAL

None to declare.

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