



Studies On Co crystallization Of Curcumin: Solid State Characterization

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Abstract

The poor solubility and dissolution rate is major constrain in oral delivery of most of drugs. The most of drug synthesized nowadays are BCS class II and IV drugs. Many scientific investigators have utilized various approaches for dissolution rate enhancement of drug. The formulation of cocrystals is recently explored way for solubility enhancement of drug. Curcumin is naturally obtaining drug used in management of various disease. The poor solubility is major limitation associated with oral delivery of curcumin. Thus, present study has planned to formulate curcumin cocrystals. The cocrystals of curcumin were prepared using various cofomer by solvent evaporation method. The formulated cocrystals showed enhanced saturation solubility than pure drug and more drug release than pure drug. Thus, cocrystals could be promising alternative for delivery of drug.

Keywords: Curcumin, Solubility enhancement, Cocrystals, Solvent evaporation

Introduction

The poor aqueous solubility and dissolution rate of API is one of the main challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase. According to the Biopharmaceutics Classification System (BCS), a drug compound is poorly soluble if the highest dose strength is not soluble in 250 ml aqueous media over the pH ranges at 37°C. Therefore, one of the major challenges of the pharmaceutical industry is to apply strategies that improve the dissolution and/or apparent solubility of poorly soluble drugs to develop such problematic compounds into orally bioavailable and therapeutic effective drugs [1].

Recently cocrystals have gained much importance owing to their amenability to design and their ability to tailor physicochemical properties [2]. The development of cocrystals was resulted by designing crystals with a purpose, as the properties of a compound depend on the arrangement of the atoms in the crystal structure which helps in modifying its properties. The first cocrystals to be synthesized was Quinhydrone, a 1:1 cocrystal between benzoquinone and hydroquinone and was synthesized by Wohler in 1844. In 1963 Hoogsten synthesized a complex between 1-methyl thiamine and 1- methyl adenine as seen in DNA base pairing and used the term “cocrystal” for the first time [3].

Generally, chemists and engineers in pharmaceutical industry seek to deliver crystalline forms of their active compounds due to inherent stability of crystalline materials. Active pharmaceutical ingredients (API's) can exist in different solid forms, including polymorphs, solvates, hydrates, salts, cocrystals and amorphous solids [4]. Each solid form displays unique physicochemical properties that can influence bioavailability, purification, stability, manufacturability and other performance characteristics of the drug.

Thus, present study has started with an aim to formulate and evaluate cocrystals of curcumin using various cofomers.

Materials and methods

Curcumin was purchased from Himedia Ltd, India. Benzoic acid, acetone, citric acid and itaconic acid were purchased from SD Fine Chemicals Ltd., Mumbai, India. All other reagents and solvents were analytical grade and purchased locally.

Methods

Preparation of curcumin cocrystals

The cocrystals of curcumin with saccharin (SAC), maleic acid (MA), itaconic acid (IA) and benzoic acid (BA) were prepared in 1:1 stoichiometric ratio by solvent evaporation (SE) technique [6].

To prepare curcumin-SAC cocrystal by this method, 323.24 mg of curcumin and 183.19 mg of SAC were dissolved in 10 ml of acetone by stirring. Stirring was continued till a clear solution was obtained. The system was covered with an aluminium foil and about 5- 6 fine holes were pierced in the foil. Solvent from the clear solution was allowed to evaporate at a slow constant rate at room temperature with constant stirring. The process was continued till solid cocrystals were obtained. The obtained cocrystals were dried at room temperature and evaluated.

Characterization of curcumin cocrystals prepared by solvent evaporation and melt fusion method**Visual morphology**

The photographic images of plain curcumin, benzoic acid, itaconic acid and developed cocrystals were taken using Canon Digital camera and organoleptic characteristics were studied and compared.

Melting point

Melting point of cofomers (SAC, IA and BA) and obtained cocrystals were determined by using Expo Hi-Tech Melting point apparatus (India).

In vitro drug release

The *in vitro* release profiles of cocrystals was studied using USP Dissolution Apparatus II (Paddle Type) and dissolution experiments were performed in triplicates [7-9]. 80 mg of curcumin and an amount of curcumin cocrystals equivalent to 80 mg of curcumin were weighed and placed in hard gelatin capsules size 1. The hard gelatin capsules were clamped using sinkers and placed in 900 ml of phosphate buffer pH 7.4. Dissolution was performed at 100 rpm at $37 \pm 0.5^\circ\text{C}$. Aliquots of 10 ml were taken at 5, 10, 15, 30, 45 and 60 minutes and filtered through Whatman filter paper. 1 ml of the resulting solution was diluted 10 times with phosphate buffer pH 7.4. The absorbance of resultant solutions was measured using UV-Visible spectrophotometer (Jasco 530V, Japan). Sink conditions were maintained by replacing 10 ml of the aliquot sample with phosphate buffer pH 7.4. The standard equation obtained by plotting a standard plot of curcumin in phosphate buffer pH 7.4 was used for calculating the drug release. All the measurements were performed in triplicates.

Saturation solubility studies

Saturation solubility studies of curcumin and cocrystals were performed in phosphate buffer pH 7.4 [10-12]. Briefly, an excess amount of curcumin was taken in the eppendorf to which 1 ml of phosphate buffer pH 7.4 was added. Thereafter, the eppendorf were sealed and shaken for 72 hrs at 37°C in water bath shaker (Remi, CM 101, Mumbai, India). Subsequently, the solutions were filtered through 0.22 μ filter and the supernatant was suitably diluted and curcumin content was quantified on a Jasco-V-530 UV spectrophotometer, using a validated UV spectrophotometric technique. To eliminate the solvent effect on absorbance, phosphate buffer pH 7.4 was used as blank. Saturation solubility studies of cocrystals were performed in a similar way. All the experiments were performed in triplicates.

Determination of drug content

Drug content was determined by dissolving cocrystals quantity equivalent to 80 mg of curcumin in 50 ml of methanol and the volume was adjusted to 100 ml with methanol AR [13-15]. The solution was filtered through Whatman filter paper no 41 and 1 ml of the resulting solution was diluted 100 times with methanol AR. Absorbance of the resultant solution was measured using UV spectrophotometer (Jasco 530V, Japan).

Stability studies of Cocrystals**Introduction**

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light; and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. Stability studies include exposing the drug product to normal storage conditions (long term storage condition) for a period of time sufficient to cover the proposed retest period, also the drug product is subjected to accelerated conditions of temperature and humidity so as to determine the stability of product under accelerated conditions. The studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions are known as accelerated stability studies. The product is evaluated at different time points for various parameters, such as physicochemical characters, drug content and the data obtained from the studies carried out is used to determine the shelf life of a product at a particular storage condition. Shelf life is a period till which not more than 10% of the drug is degraded.

Stability testing as per ICH Guidelines

International conference on harmonization (ICH) has established a guideline for "Stability testing of new drug substances and products Q1A (R2). The guideline recommends the following storage conditions for drug products intended to be stored at room temperature:

Table 1 Storage conditions for stability studies

Study	Storage condition
Long term	$25^\circ\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$
Accelerated	$40^\circ\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$

Results and Discussion**Preparation of curcumin cocrystals by solvent evaporation (SE)**

Curcumin cocrystals were successfully formulated by solvent evaporation technique using various cocrystals. The difference in organoleptic properties of cocrystals and plain drug were observed which indicated conversion of drug into different crystalline form. The organoleptic properties of various cocrystals are represented in table 2. The colour of pure curcumin was white, whereas cocrystals were found to be pale yellow to brown. The cocrystals prepared using maleic acid cofomer were found to be semisolid, which were difficult to process further. Thus, maleic acid cocrystals were not used in further study.

Table 2 Organoleptic characteristics of cocrystals obtained by solvent evaporation

Cocrystals	Appearance
Curcumin-SAC	Pale yellow coloured flaky powder
Curcumin -IA	Pale yellow coloured flaky powder
Curcumin -BA	Yellow-brown coloured flaky powder
Curcumin-MA	Semisolid, orange coloured compound

Characterization of curcumin cocrystals

Melting point

Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase. It is an important property considered during drug development and is a fundamental physical property. Much research work has been done to investigate if melting point of a cocrystal changes with respect to individual components. In the present study melting point of cocrystals of curcumin prepared by solvent evaporation were analysed. All the formed curcumin cocrystals had considerable difference in their melting points when compared to curcumin and cofomers used.

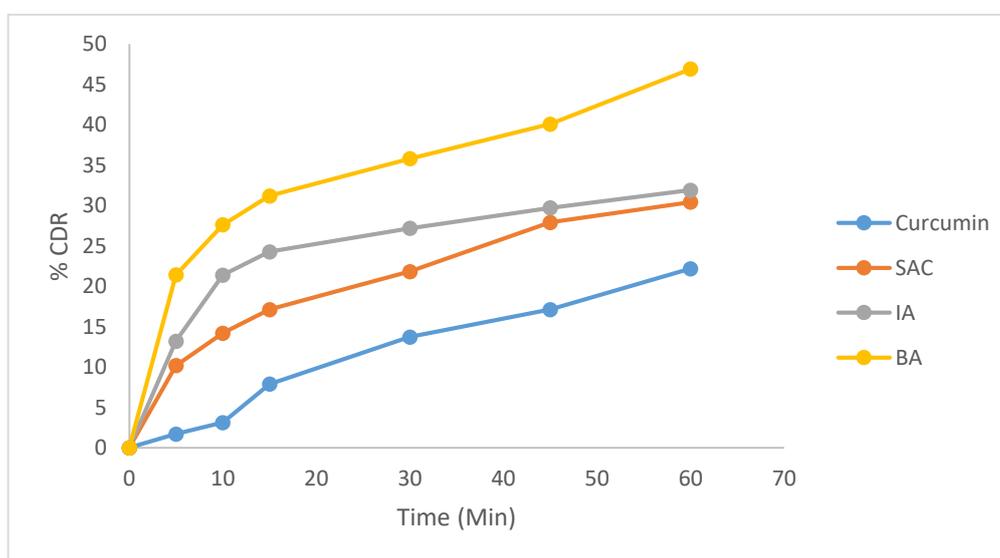
Table 3 Melting point of drug and cocrystals

S. No.	Sample details	Melting point ($^{\circ}$ C)
1	Curcumin	183.66
2	SAC	227-228
3	IA	162-164
4	BA	121-122
5	SAC Cocrystals (Solvent Evaporation)	162-164
6	IA Cocrystals (Solvent Evaporation)	125-127
7	BA Cocrystals (Solvent Evaporation)	110-115

In vitro drug release

Dissolution is an official test used by official compendia for drug release from solid and semisolid dosage forms and it is used in Quality Control (QC) and Research and Development (R&D). The purpose of in vitro drug release studies in QC is to confirm batch to batch consistency and detection of manufacturing deviation while in R&D the focus is to provide some predictive estimate of drug release in respect to the in vivo performance of a drug product.

The dissolution curves of pure drug alone and cocrystals in phosphate buffer pH 7.4 are shown in figure 1. From the graphs it is evident that the cocrystals have significantly improved the dissolution rate of drug compared to the pure drug.

**Figure 1** In vitro release profile of curcumin and curcumin cocrystals prepared by SE

The dissolution profile of curcumin cocrystals prepared by SE depicted significant increase in the dissolution rate of curcumin as compared to plain curcumin. Almost 2.17 fold increase in dissolution rate of curcumin was observed from curcumin -SAC cocrystals prepared by SE whereas it was found to be 3.35 fold and 4.47 fold greater from curcumin -IA and curcumin -BA cocrystals prepared by SE respectively within 5 minutes. Percent cumulative release of 30.43 %, 31.91% and 46.91% were obtained from curcumin-SAC, curcumin-IA and curcumin-BA cocrystals prepared by SE respectively within 60 minutes. Whereas the percent cumulative release of pure drug within the same time was observed to 22.17 %.

Saturation solubility studies

The saturation solubility of 1:1, 1:2 and 1:3 stoichiometric ratios of curcumin -BA and curcumin -IA cocrystals prepared by solvent evaporation were found to be 4.14, 6.18, 7.12, 5.28, 5.14 and 4.13 mg/ml respectively. There was about 3-5 fold increase observed in the solubility of cocrystals prepared by solvent evaporation compared to pure curcumin. Cocrystals prepared by solvent evaporation technique exhibited better enhancement in solubility than those prepared by melt fusion method in saturation solubility studies. This might be because by solvent evaporation technique of cocrystallization the drug and cofomer interact at a molecular level is higher by this technique.

Determination of drug content

Percentage drug contents of prepared cocrystals were found in the range of 89.17±0.04 w/w to 96.17±2.18 w/w.

Table 4 Drug content of cocrystals

Cocrystals	Drug Content (%)
curcumin -BA11	89.17±0.04
curcumin -BA12	96.17±2.18
curcumin -BA13	92.41±2.18

Assessment of stability

Stability studies of optimized Curcumin-BA cocrystals were evaluated according to ICH guidelines. The cocrystals filled in glass vials were stored in 25°C±2°C/60%±5% RH and 40°C±2°C/75%±5% RH. Curcumin cocrystals were sampled after 1 month time point and evaluated for physical appearance and release profile.

Table 5 Organoleptic characteristics of cocrystals before and after stability studies

Cocrystals	Before stability	After stability 25°C/60% RH ± 5% RH	After stability 40°C/75% RH ± 5% RH
Curcumin-BA	Yellow, shiny powder	Yellow, shiny powder	Yellow, shiny powder

Conclusion

The poor oral bioavailability of drug due to poor solubility and less dissolution rate is major constrain in oral delivery of most of drugs. Many scientific experts working in field of solubility enhancement have utilized various approaches for dissolution rate enhancement of drug. The formulation of cocrystals is recently explored way for solubility enhancement of drug. Thus, present study has planned to formulate curcumin cocrystals.

The cocrystals of curcumin were prepared using various cofomer by solvent evaporation method. The formulated cocrystals showed enhanced saturation solubility than pure drug and more drug release than pure drug. Thus, cocrystals could be promising alternative for delivery of drug.

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