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Solubility and dissolution rate of a carbamazepine–cinnamic acid cocrystal

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ABSTRACT

Synthesis of cocrystals is one of the methods to alter physicochemical properties of drugs. A cocrystal of carbamazepine (CBZ) and cinnamic acid (CIN) was synthesized using solvent evaporation and was characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FT-IR). The kinetic solubility, powder dissolution rate and stability of CBZ in aqueous solution were compared with those of cocrystal form (CBZ–CIN). Quantification of CBZ was evaluated using a UV-spectrophotometric technique in the presence of CIN that their spectrums are highly overlapped. Therefore, a recently developed net analyte signal standard addition method (NASSAM) was applied for determination of CBZ in the presence of CIN. The PXRD, DSC and FT-IR studies confirm that the cocrystal formation between CBZ and CIN and the developed NASSAM method can be used to quantitative determination of CBZ concentration in presence of CIN. The powder dissolution rate of cocrystal of CBZ–CIN is higher than CBZ and the kinetic solubility study show that the cocrystal is stable in dissolution medium and the aqueous solubility of CBZ–CIN is higher than CBZ. These findings show that formation of CBZ–CIN cocrystal is a suitable method to increase dissolution rate and solubility of CBZ and NASSAM is a valuable analytical method to quantitative determination of drugs in the presence of coformer in cocrystal studies.

1. Introduction

Solubility and dissolution rate are among the most important physicochemical properties of active pharmaceutical ingredients (API). These parameters are known to impact all stages of drug discovery and development [1], for example, preparation of liquid dosage and semi-solid forms of drugs [2], crystallization [3], absorption and bioavailability [4], synthesis [5], extraction [6], in vitro assays [7] and analytical methodology [8].

Various methods to improve solubility and dissolution rate from a processability and formulatability standpoints include: cosolvency, using surface active agents, pH control, salt formation, complexing agents which these techniques were reviewed by Myrdal and Yalkowsky [9], hydrotropism [10], particle size reduction or nanosizing [11], prodrugs [12], ionic liquids [13], preparation of liquidsolids [14], solid dispersions [15], lipid-based formulations [16], inorganic matrices [17] and crystal engineering [18].

Cocrystal formation has emerged as an alternative form of solid modification in order to improve solubility and dissolution rate [19,20]. Much work and research have been conducted in this area in recent years, and this has led to the FDA releasing guidelines regarding cocrystals in 2011 [20]. In most cases cocrystals show improved solubility and dissolution rate, however in some instances no improvement is seen as a result of rapid conversion to the free form of the API [21].

One of the most important studied API's in crystal engineering is carbamazepine (CBZ) with different crystalline forms [22] and it can form cocrystal with different coformers [23]. CBZ is categorized as BCS (biopharmaceutical classification system) class 2 compound [14], that is, the absorption and bioavailability are solubility/dissolution rate-limited.

The physicochemical properties and bioavailability of CBZ polymorphs have been well characterized [22]. The various cocrystals of CBZ have been documented and reported in the literature [21,23]. These cocrystal forms have different physicochemical properties and stabilities in aqueous solutions. As a general rule, soluble coformers with CBZ form soluble cocrystals, however they are not thermodynamically stable in aqueous solutions and freely crystallize and convert to the dihydrate form of CBZ [23]. For example nicotinamide (NIC) is a highly soluble coformer (its aqueous solubility is 500 mg/mL) and the solubility and dissolution rate of CBZ–NIC cocrystal did not show significant differences due to the instability of the cocrystal

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in water and its conversion to the dihydrate form [24]. Recently the powder dissolution rate of CBZ–NIC cocrystal showed no significant difference when compared to a physical mixture of CBZ and NIC, despite the cocrystal having a lower dissolution rate in the first 60 min [25]. Cocrystals composed of low soluble coformers display more stability in aqueous solutions [23], therefore they can be used to improve the dissolution rate of drugs. Cinnamic acid (CIN) is a pharmaceutically acceptable coformer forming cocrystals with different drugs [26]. CIN is slightly soluble whereas CBZ is very slightly soluble drug. The possibility of cocrystal formation between CBZ and CIN has been reported earlier [27]. However, data on its solubility, dissolution rate, and stability in aqueous solutions could not be found.

Analytical methodology is critical for determining drug concentration in solubility, dissolution rate, and formulation studies [28]. The most common way of analysis for two different components with overlapping UV spectra is HPLC analysis [29]. These methods are complex, time consuming, costly and need more skilled investigators. Chemometrics can be used to determine analyte in the presence of an interferent [30]. Pharmaceutical cocrystals, composed of two components, require determination of solubility in the presence of different quantities of conformer from a processability standpoint. Chemometrics can be a useful analysis tool along with simple spectroscopic methods for the assay of common drugs in the pharmacopeia. Different multivariate calibration methods were developed such as principal components analysis and partial least square in which the calibration and prediction sets are required for developing these methods and consequently, they can affect the performance of the designed method. In addition, these methods have very complex algorithms [31].

Net analyte signal (NAS) is a part of mixture spectrum which is orthogonal to the spectrum of all components except the analyte, and recently it is used as a multivariate calibration technique [32–37]. One of the NAS methods is net analyte standard addition method (NASSAM). In this method the concentration of analyte was determined in the presence of the known interferent. Known amounts of an analyte in different concentrations were added to the sample in the presence of a constant concentration of the interferent. The mixtures of spectrums were divided into two parts: 1) NAS which is orthogonal to the spectra of the interferents and 2) the part of the spectrum that was produced by a linear combination of the spectra of the interfering agents. Thus NAS is orthogonal to the part of the spectrum which is only depending on the analyte present in the mixture. This part is called the net analyte signal vector of NAS and can be used for quantitative determination of the analyte (Fig. 1) [34,38–40].

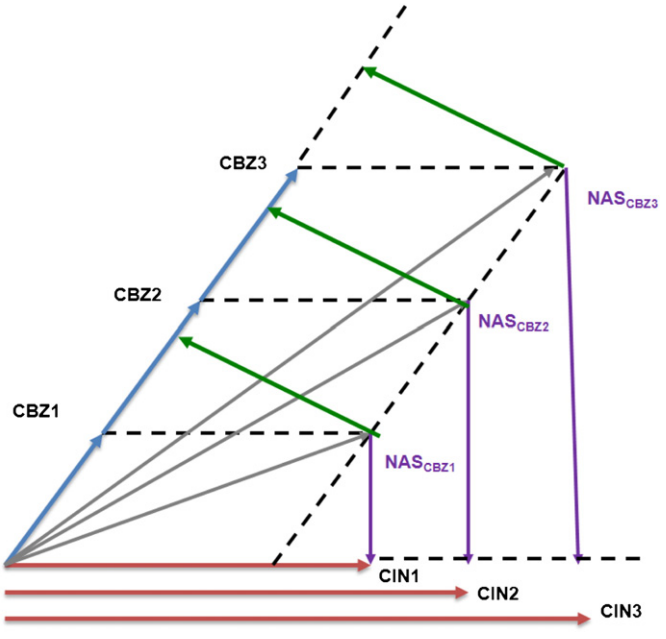

Fig. 1. Schematic representation of NAS vector is orthogonal to the space spanned by the interferent vectors.

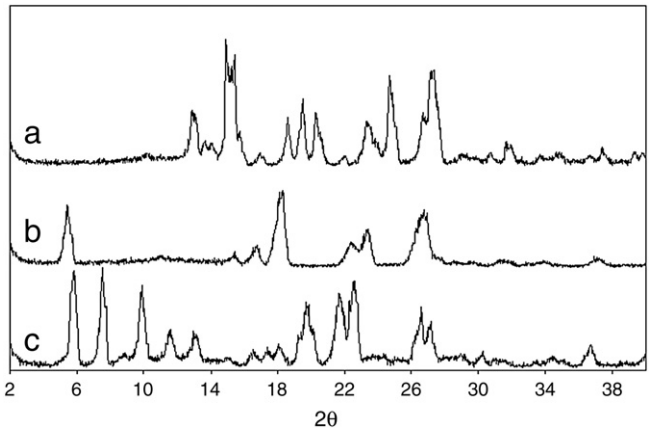

Fig. 2. PXRD patterns of (a) CBZ, (b) CIN (c) CBZ–CIN.

In this study, cocrystal of CBZ–CIN was synthesized and characterized. The kinetic solubility, powder dissolution rate and stability in aqueous solution of this cocrystal were investigated. The quantification of the CBZ in the presence of CIN which have overlapping UV spectra was performed using NASSAM method as a novel analytical technique in these studies.

2. Experimental

2.1. Materials

CBZ was purchased from Arastoo (Tehran, Iran) and CIN from Merck (Darmstadt, Germany), respectively. Based on the powder X-ray diffraction (PXRD) pattern and the reported characteristics for CBZ [22], the used powder was the form I. Anhydrate (absolute) ethanol (99%) for preparation of solutions was supplied by Scharlau Chemie (Barcelona, Spain). Distilled water was used for the preparation and dilutions of the solutions and as dissolution medium.

2.2. Methods

2.2.1. Preparation of CBZ–CIN

The CBZ–CIN cocrystal was prepared using solvent evaporation method. A 1:1 mixture of CBZ (0.236 g, 1 mmol) and CIN (0.148 g, 1 mmol) was added to 20 mL of absolute ethanol, heated and stirred for 5 min, and the resulting clear solution was left at 30 °C for 96 h to allow for solvent evaporation.

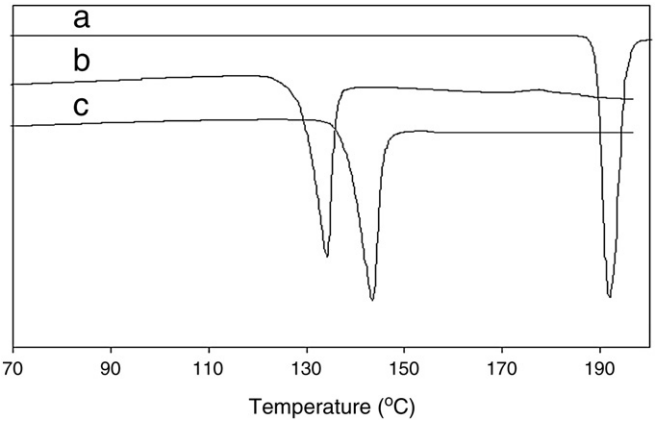

Fig. 3. DSC thermograms of (a) CBZ, (b) CIN (c) CBZ–CIN.