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Solubility of carbamazepine, nicotinamide and carbamazepine–nicotinamide cocrystal in ethanol–water mixtures

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ABSTRACT

Solubility is an important physiochemical property of pharmaceutical compounds, and cocrystallization is one method used to improve the solubility of drugs. Carbamazepine is a drug from class II, according to the biopharmaceutical classification system, and it forms a cocrystal with nicotinamide. Carbamazepine cocrystallized with nicotinamide was synthesized using the solvent evaporation approach, and its characteristics were determined using differential scanning calorimetry and powder X-ray diffractometry. The solubility of various solid phases in ethanol + water mixtures was investigated at different temperatures using the shake-flask method, and the resulting precipitates were characterized. The solubility of carbamazepine was increased with the addition of ethanol up to a mass fraction of 0.8. Nevertheless, maximum solubility of NIC is observed in neat solvent (water). While the solubility of a cocrystal depends on the concentration of the coformer and its stability in the solution.

1. Introduction

Solubility is a crucial physiochemical property in drug discovery and development [1]. Crystal engineering is claimed to be one of the essential strategies of improving drug solubility. Solvates or hydrates, salts, polymorphs, and cocrystals are examples of different crystal engineering strategies. A solid-state structure that contains solvent molecules is known as a solvate, and if the solvent is water, it is called a hydrate [2]. Salt formation is another approach used to alter the physicochemical properties of ionizable drugs [3]. Cocrystals are defined as multicomponent systems containing two components in a stoichiometric ratio that are crystalline single-phase materials. The cocrystals are formed by means of non-covalent interactions (often hydrogen bonding) [4–7].

Cosolvency (mixing solvent with water) is another method for solubilizing and crystallizing pharmaceutical compounds [8]. Solvent mixtures can be used in cocrystalization experiments to thermodynamically suppress solvate formation [9]. Ethanol is a widely used cosolvent in the pharmaceutical industry and includes dosage forms such as parenterals and soft gelatin pharmaceutical formulations for low soluble drugs [10]. It is also one of the main solvent systems in the crystallization of drugs [11]. The amount of water in a crystallization solvent can affect solubility and the crystal habit of the drugs [12]. In addition, solution-mediated phase transformation is a crucial issue in the evaluation of dissolution and bioavailability of drugs [13]. The influence of the ethanol + water composition on the solubility of different drugs such as nevirapine [12], sodium naproxen [14], and carbamazepine (CBZ) [15] was investigated in the literature. In addition, solvent mediated transformation is very important in cocrystal studies, because it can dissociate in solution environments [7] and is a tool used to prepare cocrystal polymorphs [16].

CBZ is an anti-epileptic drug and belongs to the biopharmaceutics classification system (BSC) class II (low solubility and high permeability) [17]. CBZ exists in different crystalline forms with different solubility, dissolution rate, and bioavailability. CBZ is rapidly converted to dihydrate form in water which has a lower solubility than the anhydrate form [18,19]. It is one of the most frequently investigated drugs in cocrystal studies to change physicochemical properties such as solubility [20]. CBZ can form a hydrogen bond with different coformers via its amide group [21]. Nicotinamide (NIC) (or vitamin B_3) is a highly soluble coformer that forms a cocrystal with CBZ [22]. CBZ cocrystal with NIC (CBZ–NIC) is a common model cocrystal in crystal engineering [23,24], and different cocrystal forms of CBZ have different levels of stability. High soluble coformers with CBZ are dissociated in water [25]. The aqueous solubility of CBZ–NIC has no significant difference with that of CBZ according to a recent report [21], whereas significantly different solubility in ethanol was reported [24].

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List of symbols

ΔH	apparent molar enthalpy changes (kJ mol^{-1})
ΔS	apparent molar entropy changes (J mol^{-1} K^{-1})
ΔG	apparent molar Gibbs free energy changes (kJ mol^{-1})
$\%\xi_H$	relative contributions by enthalpy
$\%\xi_{TS}$	relative contributions by entropy
BCS	biopharmaceutics classification system
CBZ	carbamazepine
CBZ–NIC	CBZ cocrystal with NIC
DSC	differential scanning calorimetry
K	equilibrium constant
NIC	nicotinamide
PXRD	powder X-ray diffractometry
R	gas constant
RSD	relative standard deviation
T	temperature (K)
T_{hm}	the mean harmonic temperature

The study of solubility and thermodynamic properties are important issues in crystal engineering as they relate to controlling the phase transformation in pharmaceutical processing and storage. The solubility of drugs as well as their crystal habits and polymorphism can change as a function of solvent composition and temperature [2]. These variables are also crucial in solvent-mediated anhydrate to hydrate transformation of CBZ [26].

Determining drug solubility is a time-consuming process, but fitting the solubility data to the mathematical model can confirm the accuracy of data points and detect possible outlier data points [8]. In this study, the van't Hoff equation was used to fit the solubility data of drugs in a mono-solvent at different temperatures [27]:

$$\log x_T^{Sat} = A + \frac{B}{T/K} \quad (1)$$

In this model x_T^{Sat} is solubility of drugs in mole fraction unit. T is temperature in Kelvin unit, A and B are constants of the model.

Thermodynamic properties, such as apparent molar enthalpy (ΔH), entropy (ΔS), and Gibbs energy (ΔG) changes, can be calculated using a modified version of the van't Hoff equation [28,29]:

$$\log x_T^{Sat} = -\frac{\Delta H}{R}\left(\frac{1}{T/K} - \frac{1}{T_{hm}/K}\right) \quad (2)$$

where R is the gas constant using (8.314 J K^{-1} mol^{-1}) and T_{hm} is the mean harmonic temperature that can be calculated using:

$$T_{hm}/K = \frac{n}{\sum_{i=1}^{n}(1/(T/K))} \quad (3)$$

where n is the number of temperatures studied

ΔG and ΔS are computed by the following equations:

$$\Delta G = -RT_{hm} \quad \text{intercept} \quad (4)$$

$$\Delta S = \frac{\Delta H - \Delta G}{T_{hm}} \quad (5)$$

Relative contributions by enthalpy ($\%\xi_H$) and entropy ($\%\xi_{TS}$) of CBZ, NIC and CBZ–NIC solutions in ethanol + water mixtures can be calculated by Eqs. (6) and (7), respectively.

$$\%\xi_H = 100\frac{|\Delta H|}{|\Delta H| + |T\Delta S|} \quad (6)$$

$$\%\xi_{TS} = 100\frac{|T\Delta S|}{|\Delta H| + |T\Delta S|} \quad (7)$$

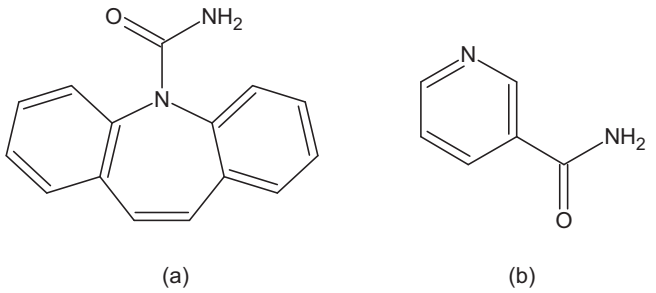

Fig. 1. Chemical structure of (a) CBZ, and (b) NIC.

The main objectives of this study are to determine and compare the solubility of CBZ, NIC and CBZ–NIC in ethanol + water mixtures at different temperatures and the solid state of CBZ and CBZ–NIC after dissolution.

2. Experimental

2.1. Materials

CBZ (Fig. 1a) (IUPAC name: dibenzo[b,f]azepine-5-carboxamide) (0.99 mass fraction) was purchased from the Arasto Company (Tehran, Iran), and NIC (Fig. 1b) (IUPAC name: pyridine-3-carboxamide) (0.99 mass fraction) was purchased from the Zahravi Pharmaceutical Company (Tabriz, Iran). Anhydrous ethanol (0.99 mass fraction) for preparation of solutions and ethanol (0.935 mass fraction) for dilution of the samples were obtained from Scharlau Chemie (Barcelona, Spain) and Jahan Alcohol Teb (Arak, Iran), respectively. Chemicals were used as received from the companies without further purification. Distilled water was used to prepare the solutions. Table 1 lists a summary of chemicals used in this work and their source and purity.

2.2. Preparation of CBZ–NIC

The CBZ–NIC was prepared using the solvent evaporation approach following a published method with minor modifications [21]. A 1:1 mixture of CBZ (2.363 g, 0.01 mol) and NIC (1.221 g, 0.01 mol) was dissolved in 20 mL absolute ethanol, heated, and stirred for 30 min; then the mixture was left at 303.2 K for 72 h for evaporation.

2.3. Characterization of CBZ–NIC

The X-ray diffraction pattern of the drug powders, the synthesized cocrystals, and the solid state of the saturated solutions were determined using powder X-ray diffraction (PXRD) (Siemens-850, Munich, Germany) within a range of 2θ (4–40°) with steps of 0.05°. The thermal properties of the solid phase were also studied using differential scanning calorimetry (DSC) (Shimadzu, Kyoto, Japan). The 5 mg samples were analyzed using aluminum pans and heated at a rate of 10 K min^{-1} to 308.2–473.2 K.

Table 1
Source and purity of chemical used in this study.

Component	Supplier	Mass fraction purity
CBZ	Arasto Pharmaceutical Chemicals Inc.	0.99
NIC	Zahravi Pharmaceutical Company	0.99
Anhydrate ethanol	Scharlau Chemie	0.99
Ethanol	Jahan Alcohol Teb	0.94
Distilled water	Lab made	–