Solubility of Carbamazepine-Succinic Co-Crystal in Ethanolic Solvent System

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Abstract. Solubility of carbamazepine co-crystal produced from cooling co-crystallization process with succinic acid as a co-crystal former is investigated in this study. Two techniques are used to determine the solubility of the co-crystal which is gravimetric and HPLC. The solubility experiment in ethanol solvent system were conducted at 6 different temperatures (25, 30, 35, 40, 45 and 50^{o}C) while for succinic acid ethanolic solution system were conducted at 5 different concentration ratio. Both of the systems are equilibrated for 72 hours. Result from the experiment has shown that the solubility of co-crystal is depending on temperature. As the temperature increases, the solubility of co-crystal also increased, this situation meets the Second Law of Thermodynamic which heat facilitates the dissolution process by providing more energy to the system.

Introduction

In recent year, there has been an increasing interest in pharmaceutical co-crystal development. Pharmaceutical co-crystallization is an approach that allows binding active pharmaceutical ingredient (API) with one or more components of co-crystal former (CCF) [1] within one periodic crystalline lattice without breaking or making new covalent bond [2]. Co-crystal provides a new approach to tailor the physicochemical properties such drug solubility, dissolution rate, stability, bioavailability, hygroscopicity and mechanical properties while maintaining the biological functions of an API [1-4]. Carbamazepine, (5H-dibenz- (b, f) azepine-5-carboxamide) (CBZ) is an anticonvulsant [5] and mood-stabilizing drug is a water-insoluble drug (>100mg/day) that have been used more than 30 years [6] for treatment of epilepsy, partial seizures [7], bipolar disorder and trigeminal neuralgia. CBZ was of interest because it was one of the water-insoluble drugs; faced issues regarding its poor solubility, bioavailability, stability and mechanical properties [8].

Pharmaceutical co-crystal became main interest of most researchers because it has key for enhances drug performance with dosing and delivery control. Recent evidence been suggests that researches on CBZ are mainly focus on potential CCF selection/synthon development[1], co-crystals screening [3,9] co-crystal characterization, formation mechanism [8] and a few of co-crystals solubility [10]. Most of co-crystal solubility studies were emphasize on kinetic measurements of dissolution [2] which mostly influence by factors such surface area, phase transformation, particles size distribution, and fluid dynamics [10,11]. However, there is only a little attention been paid on the effect of temperature on CBZ and its co-crystal [4,5].

Therefore, this paper will focus on solubility study of Carbamazepine-Succinic acid (CBZ-SUC) in ethanol and ethanolic solution at varies temperature. Succinic acid have been used as CCF with other APIs such picolinic acid[12], adefovir dipivoxil[13], aminopyridine[14] , and a few with CBZ[3,15]. It also have been proved that combination of CBZ with SUC producing co-crystal with various type of co-crystallization processes.

During the formation process, hydrogen bonding interactions occur at both carboxylic acid functional group available in SUC structure as shown in Figure 1. CBZ-SUC co-crystal is prepared using cooling co-crystallization method. The solubility is measured in pure ethanol solvent at 6 different temperatures (25°C -50°C) and with 5 different percentages of CCF in ethanol solution prepared at 25°C. The data collected are discussed.

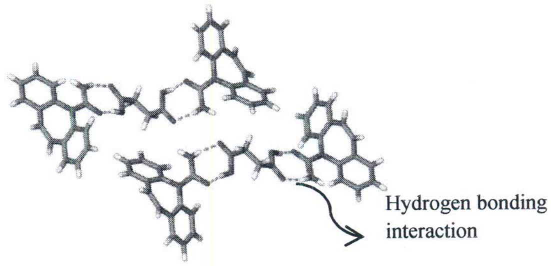

Figure 1. Hydrogen bonding interaction between CBZ and SUC molecules in CBZ-SUC co-crystal.

Experimental

Materials. CBZ and SUC were both purchased from Sigma-Aldrich with 99.0+% of purity. Ethanol and Acetonitrile are both with HPLC grades, also purchased form Sigma-Aldrich. All materials are used as received.

Co-Crystal Preparation. CBZ-SUC co-crystal were crystallized using cooling co-crystallization technique and mixed based on molar ratio of 1:2 (CBZ:SUC). The experiment is carried out in 100ml of ethanol in sealed flask in incubator shaker which heated up to 60 °C and equilibrated for one hour before cooling down until precipitation occurred. The liquid and solid phases are separated using vacuum filter and the co-crystal collected is dried at 30 °C for 3 hours. The dried co-crystal samples are further analyzed for co-crystal characterizations.

Co-Crystal Characterizations. Co-crystal solid properties are characterized using X-Ray powder diffraction (XRPD) analysis, for a range of 5-40° with continuous scan rate of 0.01°/s. Thermal properties are analysed using differential scanning calorimetric (DSC) at 10°C/min heating rate under nitrogen atmosphere (50ml/min).

Solubility Determination. The solubility of pure components and co-crystal are analysed using Agilent HPLC (1100, UV-vis spectrophotometer detector) with zorbax Eclipse Plus C18, analytical 4.6x250mm, 5 micron column. The mobile phased used consist of H_2O: ACN (200:800) (v/v), wavelength of 260nm, 1ml/min of flow rate and injection volume of 10µl. Data processing are performed using build-in software from Agilent. Two type of solvent system are used which is pure ethanol and ethanolic solution of CCF prepared at room temperature. For each system, solubility study is carried out at 6 different temperatures from 25-50 °C.

Characterization of CBZ, SUC and CBZ-SUC Co-Crystal. Sample of pure components (CBZ and SUC) and CBZ-SUC co-crystal were analyzed by XPRD to identified the powder samples collected. XPRD pattern profiles produce for all three components are compared to ensure that the co-crystal of CBZ-SUC does not contained any mixture of either pure component of CBZ or SUC. Pattern also compared with the co-crystal structures reported in Cambridge Structural Database (CSD). From the profiles shown in Figure 2, the diffraction peaks for CBZ-SUC does not contain any diffraction peaks of pure components of CBZ and SUC which this confirm that the powder samples measured are co-crystal. Co-crystal sample also matched with structures reported in CSD by ±10% deviation [3,5,19].

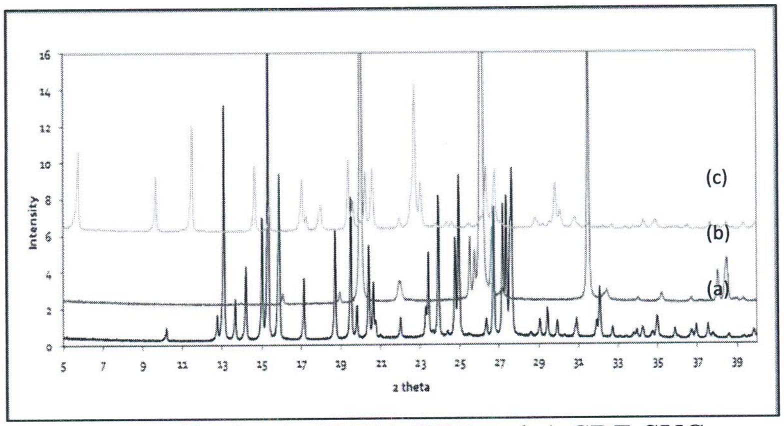

Figure 2. XRPD pattern profile for a) CBZ b) SUC and c) CBZ-SUC co-crystal structure.

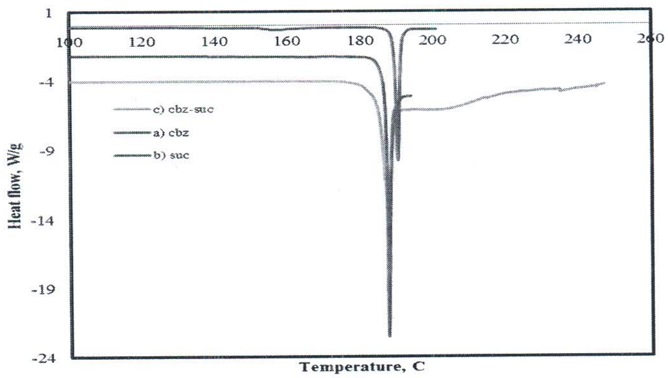

Figure 3. Comparison of melting point between CBZ, SUC and CBZ-SUC co-crystal for heat profiles analyzed by DSC.

Thermal properties of CBZ, SUC and its' co-crystal were obtained from analysis of DSC shown in Figure 3. From the figure, the melting point of CBZ-SUC co-crystal formed is in between of melting points of CBZ and SUC. The melting point, T_m for pure components and the co-crystal are comparable with T_m stated in literature [12,19] , T_{mlit} as tabulated in Table 1 below.

Table 1. Melting temperature and enthalpy obtained from DSC analysis for CBZ, SUC and CBZ-SUC

Samples	T_{mlit},(°C)	T_m,(°C)
CBZ	191.1-192.1	190.26
SUC	188.1-188.7	188.7
CBZ-SUC	182.9-188.9	187.14

Source: T_{mlit} data from Good (2009) and Childs (2008)

Solubility of Pure Component and CBZ-SUC co-crystal in Pure Ethanol. Solubility of pure components/reactants is compare based on both methods which is gravimetric and HPLC analysis. However, there is no chromatograph for SUC component detected in HPLC analysis. Therefore, only data from gravimetric analysis are available. The solubility values of SUC are much higher than CBZ which fit the factor in selecting CCF for APIs compound. Data presented in Figure 4 indicate that the solubility of both components is dependable on the temperature. The solubility of SUC are 3.1-3.5 times higher than CBZ solubility[5] and both of the components exhibit the same profile based on the temperature. The profile also fit with Second Law of Thermodynamic which heat facilitates the dissolution process by providing more energy to the system.

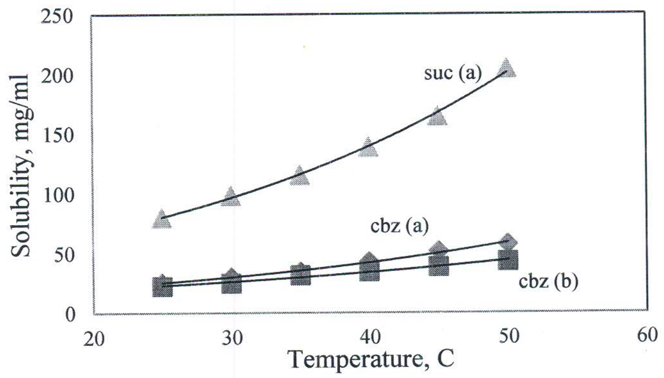

Figure 4. Solubility (g/ml) of CBZ and SUC in ethanol solvent system using (a) gravimetric and (b)HPLC method.

Figure 5 shows the solubility of CBZ-SUC co-crystal is lower than pure CBZ. As mentioned in literature, the formation of co-crystal is believed to enhance the solubility and dissolution rate of API component[3]. However, data achieved from this study shows that the CBZ co-crystal with SUC co-crystal former doesn't increase the solubility values. This scenario might be influence by the solution complexion due to mixing of ethanol solvent with the components.

Solubility of CBZ-SUC Co-crystal in Co-crystal Former Ethanolic Solution. Solubility curves of CBZ-SUC co-crystal in co-crystal former ethanolic solution (solution of ethanol and SUC at 25°C), is shown in Figure 6. Five different percentage of the solution were selected for the solubility study. When the percentage of the saturated solution of SUC increased to 20%, the solubility values decreased rapidly however it slowly decreases afterwards. This situation is influenced by the ethanolic solvent complexion and existence of SUC component inside the solvent mixture. The existence of SUC molecules might leads to the further nucleation with the co-crystal. The concentration of SUC increases as the percentage of the ethanolic solution increased supported the trend of decreasing solubility.

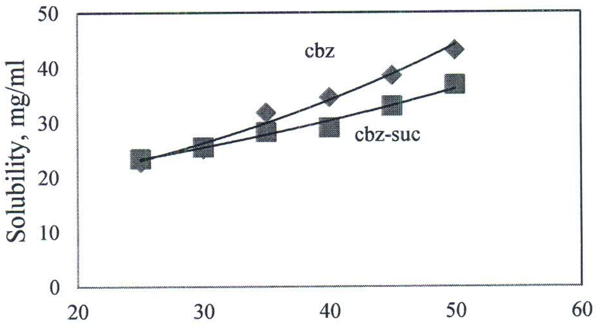

Figure 5. Solubility (g/ml) of CBZ-SUC co-crystal in ethanol solvent system.

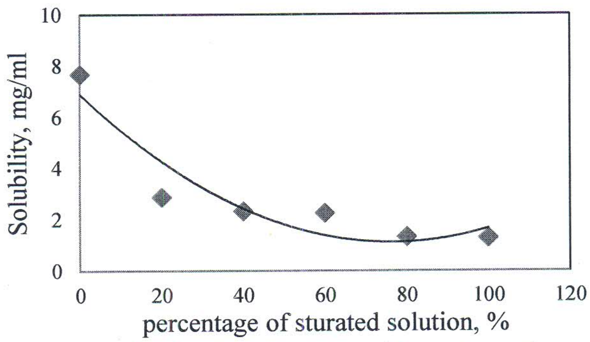

Figure 6. Solubility values of CBZ-SUC co-crystal in ethanolic solution with different percentage of saturated solution of SUC.

Conclusion

In conclusion, the study revealed that the solubility of CBZ, SUC and CBZ-SUC co-crystal does affected by the temperature. As the temperature increased, the solubility of the reactants and co-crystal increased. This situation meets an agreement with Second Law of Thermodynamic which heat facilitates the dissolution process by providing more energy to the system. It have been found that CBZ co-crystal with SUC does not enhance the solubility values of the CBZ since the solubility obtained for CBZ is higher than the solubility of CBZ-SUC co-crystal. In addition, presence of co-crystal former in solution resulting lower solubility of CBZ-SUC co-crystal as the content of the co-crystal former in the solution increases.

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