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Co-amorphous drug systems of carbamazepine: intrinsic dissolution rate improvements

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Abstract – Co-amorphous systems is one of the attractive strategies used to enhance the dissolution rates of poorly soluble drugs. This strategy has an additional advantage as it has the ability to overcome stability issues that may arise from the conversion of a crystalline drug into its amorphous form. In this study, quench cooling was used to prepare co-amorphous forms of carbamazepine (CBZ) with saccharin (SAC), lactose (LAC) and gluconolactone (GLU) as carriers. Analytical techniques such as P-XRD, DSC and SEM were used to confirm the conversion to the amorphous state. In addition, the intrinsic dissolution rates (IDR) of the new drug forms were also investigated. Co-amorphous systems of CBZ as a parent drug with SAC, LAC and GLU were successfully formulated. CBZ-LAC had the highest IDR (0.339 mg/min/cm^2) when compared to the untreated CBZ (0.091 mg/min/cm^2). P-XRD and DSC showed CBZ-SAC and CBZ-LAC to be stable after storage at room temperature (22 ± 1 °C) for 30 days and relative humidity of 35–47 %. However, CBZ-GLU started to crystallize on storage and as such may require other excipients to stabilize its co-amorphous form.

Keywords – Co-amorphous, quench-cooling, carbamazepine, saccharin, lactose, gluconolactone

1. Introduction

The oral route is the most preferable route of drug delivery to the patient. Solid dosage forms such as tablets are more popular to use due to advantages in safety and convenience in its administration [1]. The administered drug must therefore be dissolved and released in the gastrointestinal (GI) fluid before it can get into the systemic circulation to reach the action site. However, many active pharmaceutical ingredients (API) belong to the Biopharmaceutical Classification System (BCS) class II group which means they are poorly soluble [1, 2]. Carbamazepine (CBZ), the model drug used in this study, is a BCS Class II drug. It is practically insoluble in water (~ 0.12 mg/mL) but has good permeability in the GI tract [3, 4]. CBZ has become one of the most frequently prescribed drugs as a first-line anticonvulsant drug used in the treatment of partial and generalized tonic-clonic seizures, treatment of trigeminal neuralgia and bipolar depression [5]. A high dose of CBZ is required due to slow dissolution rates, unpredictable drug absorption which leads to low oral bioavailability [3, 6]. As such, improving the solubility and dissolution rate of the drug should lead to a higher bioavailability. Several methods such as co-crystal formation, micronization, salt-formation, prodrugs, solid dispersions, nano-suspensions, self-emulsification, exploitation of the meta-stable form, cyclodextrins, amorphous and co-amorphous systems have been reported to improve the solubility of APIs [5, 7-25].

In recent years, the generation of amorphous forms of drugs (second generation solid dispersions) has been used to enhance the solubility of drugs. However, there are stability concerns as the amorphous drug tends to recrystallize during manufacturing or storage under various conditions [15, 20, 22]. Inhibition of drug re-crystallization in an amorphous system is quite challenging and several strategies that have been used to prevent this which include, solid polymer solutions, low molecular weight molecules being used as stabilizers, co-amorphous systems consisting of two excipients, co-amorphous systems consisting of two suitable drugs or API plus excipient [15, 26-32].

In this study we report the characterization of co-amorphous systems of CBZ using X-ray powder diffraction (P-XRD) and differential scanning calorimetry (DSC) with gluconolactone (GLU), saccharin (SAC) and lactose (LAC) as carriers. As intrinsic dissolution rate (IDR) is an important parameter in early stage drug development that helps to predict API behaviour *in vivo*, the effect of the various excipients on the IDR was also determined.

2. Materials and Methods

2.1. Materials

CBZ (molecular weight, 236.3 g/mol), SAC (molecular weight, 183.2 g/mol), and GLU (molecular weight, 178.14 g/mol) were purchased from Sigma (UK). LAC (molecular weight, 342.3 g/mol) was a kind gift from DFE pharma, Goch (Germany) and sodium dodecyl sulfate (SLS) was purchased from Fluka (Germany). The API and excipients

used are depicted in Figure 1. Sodium lauryl sulfate (SLS) was purchased from Sigma, UK.

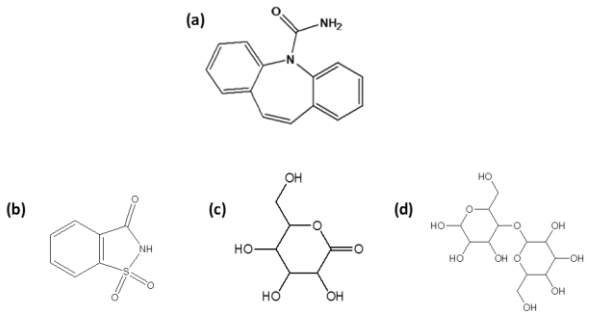

Figure 1: Chemical structures of (a) carbamazepine, (b) saccharin, (c) gluconolactone and (d) lactose

2.2. Preparation of co-amorphous CBZ

The weighed samples of 1:1 equimolar ratios of CBZ and appropriate carrier/excipient (1.66 g CBZ with either 1.29 g SAC, 2.40 g LAC or 2.5 g GLU) was molten on a hot plate at 240 °C, 250 °C, and 200 °C respectively, for 10 min. Liquid nitrogen was then poured on the molten samples and immediately transferred on a phosphorus pentoxide desiccator to prevent the moisture sorption onto the samples [22]. The obtained dried samples were then gently milled to break down the particulates and stored for up to 30 days at room temperature (22 ± 1 °C) and 35–47 % RH to assess their stability under these storage conditions.

2.3. CBZ X-ray powder diffraction (XRPD)

The P-XRD patterns of CBZ, SAC, LAC, GLU and their corresponding co-amorphous samples were obtained using a Bruker D2 Phaser diffractometer. P-XRD patterns were also obtained for the co-amorphous systems after 30 days of storage to evaluate their stability under these storage conditions. The samples were scanned from 5 °to 30° 2ϑ at a rate of 1.5° min^{-1}.

2.4. Differential scanning calorimetry (DSC)

Samples (3-6 mg) of CBZ, SAC, LAC, GLU, their co-amorphous counterparts and stability samples were placed in standard aluminium pans (40 µL) with a vented lid. The crimped aluminium pans were heated from 20 to 250 ˚C at a scanning rate of 10 °C/min using nitrogen gas as a purge gas in a DSC 1 (Mettler-Toledo, Switzerland). The enthalpy and melting points of the samples where appropriate were obtained using the software provided.

2.5. Scanning electron microscopy (SEM)

Electron micrographs of CBZ, SAC, LAC, GLU and the co-amorphous samples were obtained using a scanning electron microscope (Jeol JSM-6060CV SEM) operating at 10 kV. Each sample was mounted on a metal stub with double-sided adhesive tape and was sputter-coated with an ultra-thin coating of gold/palladium (80:20) for 60 s using a Quorum SC7620 Sputter Coater under vacuum with gold in an argon atmosphere prior to observation. Micrographs with different magnifications were taken to facilitate the study of the morphology of the solid dispersions.

2.6. Content uniformity determination

In order to determine the exact amount of CBZ in the co-amorphous samples, a calibration curve of CBZ was obtained. Stock solution of CBZ (200 µg/ml) was made by dissolving 10 mg of CBZ in 50 ml of 1 % SLS solution. A series of CBZ concentrations was prepared by diluting the stock solution and the CBZ measured by a UV spectrophotometer at 281 nm to generate a calibration curve with an R^2 value of 1.

The co-amorphous samples (25 mg) was weighed, dispersed in 100 ml of 1 % SLS solution and diluted to a final concentration 20 µg/ml. The CBZ content of this solution was measured and the equation of the calibration curve was used to calculate the amount of CBZ present in these samples.

2.7. Intrinsic dissolution rate (IDR) determination

CBZ and the co-amorphous samples were compacted as tablets containing 150 mg of CBZ. The weights of the co-amorphous powders used were calculated based on their drug content. The measured powder was placed in the 13 mm die and compressed with the tableting punch at 2 tons of pressure for 30 seconds (Specac, UK). The thicknesses, diameter, and the weight of the tablets were measured to enable the calculation of the surface area of the drug which was exposed to the dissolution medium. A fixed-disc system was used in this study. The tablets and its edges were fixed in the round cup shape disc using liquid paraffin. The discs were placed below the dissolution vessel and the paddles were rotated at 100 rpm. 900 ml of a 1 % SLS solution was used as the dissolution medium and was equilibrated at 37 °C ± 0.5 °C. Samples were withdrawn at selected time intervals (5, 10, 15, 20, 25, 30, 60, 90 and 120 min) using an automated system and the concentrations of CBZ in the samples determined by UV spectrophotometer at 281 nm. All dissolution tests were carried out in triplicate.

3. Results and discussion

3.1. Solid-state analysis

CBZ can exist in up to four polymorphic forms (Grzesiak et al., 2003) and the P-XRD pattern of the CBZ drug shows the CBZ sample used in this study to be a mixture of form I and III (Figure 2a). It has been reported that the polymorphic form of carbamazepine triclinic form I can be identified in XRD with peaks at from 2θ = 7.92°, 9.37°, 12.28° and 19.99° 2θ and form III identified with peaks at 13.14°, 15.36°, 19.56°, 20.56°, 25° and 27.47° 2θ [33]. However, properties of CBZ may vary slightly due to different methods of preparation. The changes in intensities and small shifts in

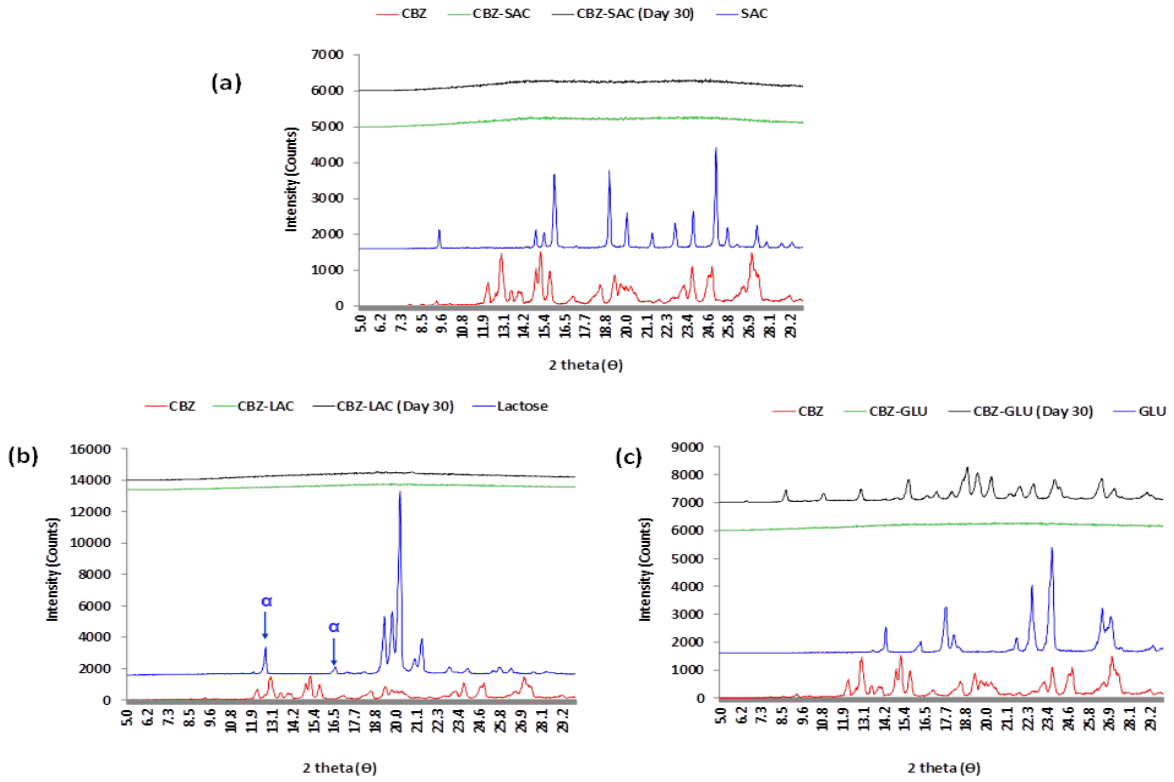

Figure 2: P-XRD patterns for (a) carbamazepine and saccharin and its co-amorphous form b) carbamazepine and lactose and its co-amorphous form (c) carbamazepine and gluconolactone and its co-amorphous form; after preparation and after 30 days storage

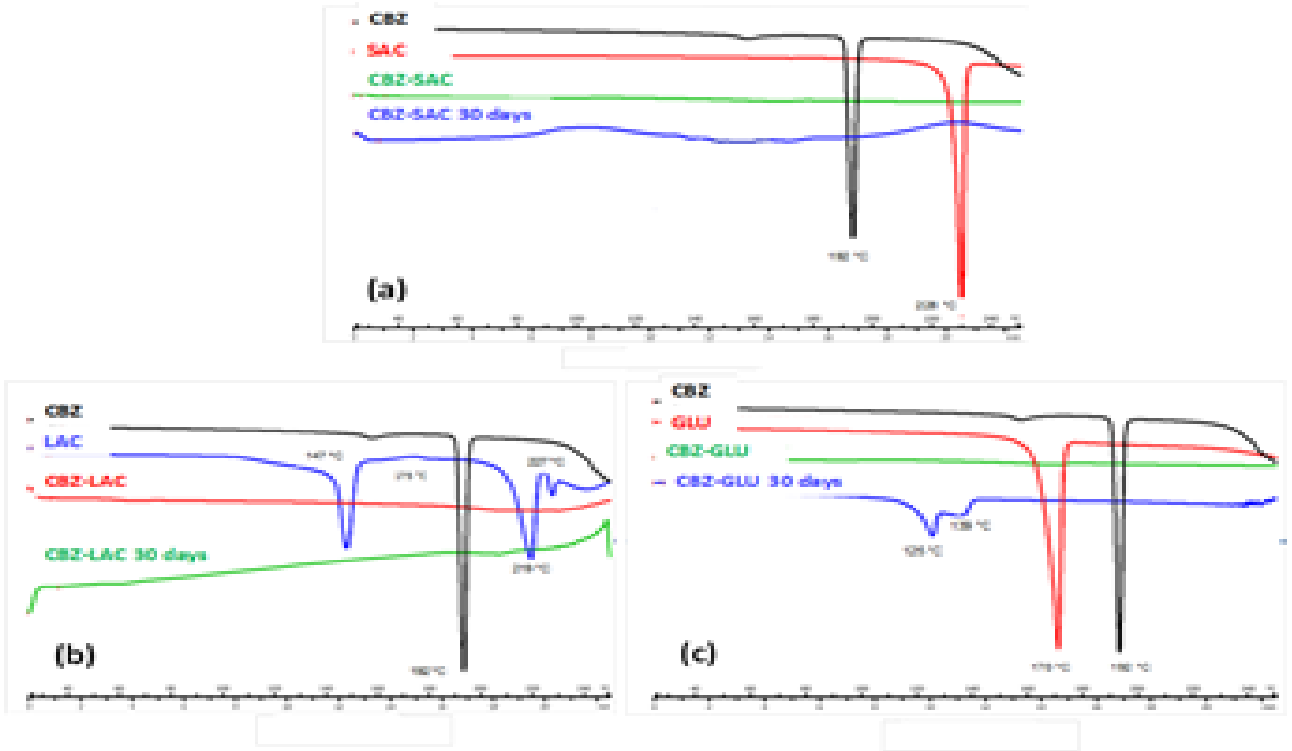

Figure 3: DSC profiles for a) carbamazepine and saccharin and its co-amorphous form b) carbamazepine and lactose and its co-amorphous form (c) carbamazepine and gluconolactone and its co-amorphous form; after preparation and after 30 days storage

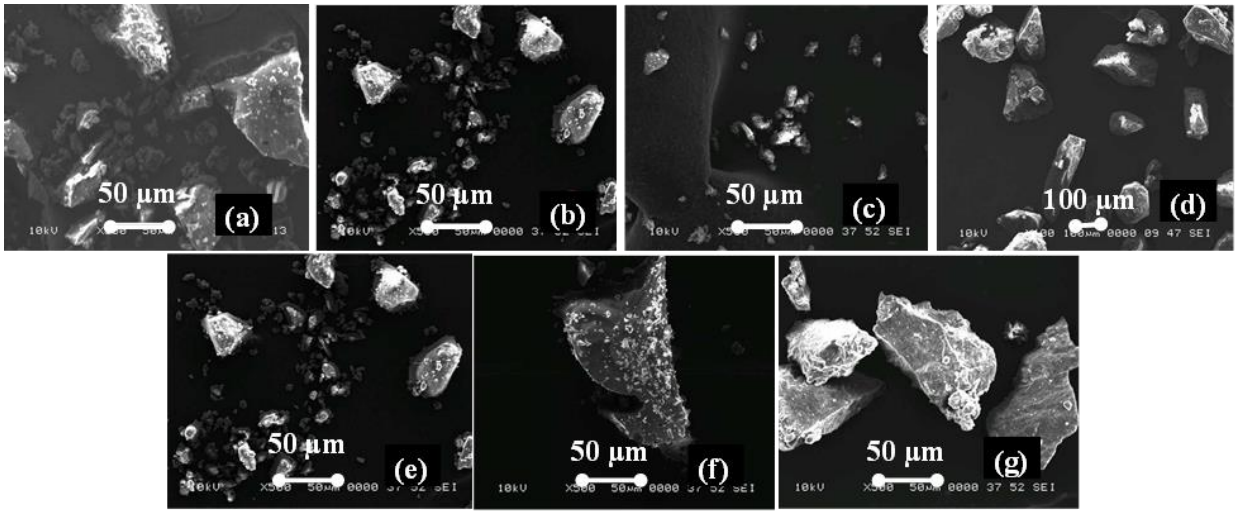

Figure 4: SEM images of (a) carbamazepine, (b) saccharin, (c) lactose, (d) gluconolactone, (e) co-amorphous CBZ-SAC, (f) co-amorphous CBZ-LAC and (g) co-amorphous CBZ-GLU

terms of *2θ* position may be due to the temperature at time of collection and also the preferred orientation of samples in the P-XRD experiment [33].

CBZ melts at temperatures between 190.48 ºC and 191.83 ºC and its melting profile (Figure 3) confirms a combination of form I and III [33], whereas pure SAC (Figure 3a) melts and crystallizes between 228.18 ºC to 229.64 ºC, which is similar to previous studies [34]. The DSC thermograph for LAC (Figure 3b) exhibited the peaks for water dehydration, α-lactose melting and β-lactose melting confirming the typical trace for α-lactose monohydrate [35-37]. GLU (Figure 3b) showed a melting peak around 170 ºC consistent with that reported by Nokhodchi et al.[38]. All these materials were highly crystalline as can be seen in the P-XRD, DSC and SEM images (Figures 2-4).

The CBZ-SAC, CBZ-LAC and CBZ-GLU all formed co-amorphous systems successfully (Figure 3) as evidenced by the absence of any distinct peak or melting due to the fact that there was no crystal lattice to be broken up. However, it was observed that CBZ-GLU started to crystallize under the storage conditions used (Figure 3c) as evidenced by the peaks observed in the diffraction scans. This meant that GLU alone was not enough to stabilize CBZ in their co-amorphous form upon storage.

SEM images of the co-amorphous samples are depicted in Figures 4e-g.

3.2. IDR

The content uniformity analysis showed CBZ content to be 47.4 %, 36.6 % and 43.9 % in CBZ-SAC, CBZ-LAC and CBZ-GLU, respectively. The differences in samples may
be attributed to the interaction of hydrogen bonds between the starting materials during the process, since the functional groups of each molecule can cause differences in the bond interactions [22].

IDR is a measurement of bulk drug substances and excipients in the functionality and characterization under the constant surface area [39]. The IDR of CBZ and the co-amorphous samples are presented in Table 1. CBZ had the lowest IDR value while all the co-amorphous forms had higher IDR values, following the trend CBZ < CBZ-SAC < CBZ-GLU <CBZ- LAC. The CBZ-LAC increased CBZ IDR by 3.7 times. It is known that amorphous forms tend to give higher level of super-saturation, solubility and dissolution rate in aqueous media compared to crystalline forms. This is due to the fact that in the amorphous state there are no crystal lattices, therefore no energy is required for the drug to go into solution [20].

Table 1: Intrinsic dissolution rate values for Carbamazepine and its co-amorphous samples

Formulation	IDR (mg/min/cm^2)
CBZ	0.091 ± 0.001
CBZ-SAC	0.108 ± 0.000
CBZ-LAC	0.339 ± 0.000
CBZ-GLU	0.176 ± 0.001

4. Conclusion

Co-amorphous CBZ was successfully prepared with saccharin, lactose and gluconolactone d using quench-cooling. P-XRD and DSC showed CBZ-SAC and CBZ-LAC to be stable even after 30 days storage at room temperature of 22 ± 1 °C and relative humidity of 35–47 %. However, CBZ-GLU started to crystallize under storage and may require other excipients to stabilize its co-amorphous form. The co-amorphous forms also had an increased IDR value with CBZ-LAC having an almost 4 times increase over the parent drug. This demonstrates that stable co-amorphous systems are attractive alternatives to improving solubility issues faced by BCS class II drugs.

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