Contents lists available at ScienceDirect

Chemical Engineering Research and Design

journal homepage: www.elsevier.com/locate/cherd

Dissolution and solid state behaviours of carbamazepine-gluconolactone solid dispersion powders: The potential use of gluconolactone as dissolution enhancer

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ARTICLE INFO

Article history:
Received 29 October 2014
Received in revised form 10 February 2015
Accepted 18 April 2015
Available online 12 May 2015

Keywords:
Solid dispersions
Carbamazepin-gluconolactone
Dissolution enhancement
Eutectic mixtures
Mechanistic solid state analysis

ABSTRACT

Solid dispersions are one of the most effective methods for improving the dissolution rate of poorly water-soluble drugs; however, this is reliant on the selection of a suitable carrier and solvent. The present study is the mechanistic evaluation of the changes in polymorphic form of carbamazepine when the type of solvent and the concentration of D-gluconolactone (D-GL) change. The studies reported herein also explore the use of D-GL as a potential hydrophilic carrier to improve the dissolution rate of a poorly water-soluble drug, carbamazepine (CBZ), from physical mixtures and solid dispersion formulations. The effect of using different solvents in the preparation of solid dispersion formulations was also investigated. Different ratios of solid dispersions of the drug and D-GL were prepared using a conventional solvent evaporation method. Different solvents (ethanol, acetone and water) were used as a second experimental variable in the preparation of solid dispersions. Physical mixtures of CBZ and D-GL were also prepared for comparison. The results showed that the presence of D-GL can increase the dissolution rate of CBZ compared to pure CBZ. This study showed that D-GL could be used as a new carrier in solid dispersion formulations and physical mixtures. The interesting solid state behaviour of CBZ in all solid dispersions in the presence of D-GL was fully analyzed using Fourier-transform infrared (FT-IR), X-ray powder diffraction (XRPD), scanning electron microscope (SEM), hot stage microscopy (HSM) and differential scanning calorimetry (DSC). The results showed that depending on the type of solvent and concentration of D-GL used in the preparation of solid dispersions different forms of CBZ (Form I, Form III and dihydrate) can be existed in the formulations.

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http://dx.doi.org/10.1016/j.cherd.2015.04.018

1. Introduction

It is known that the rate of oral absorption of poorly water soluble drugs, particularly class II drugs (poor solubility, high permeability), is often limited by their dissolution rates in the gastrointestinal tract (Lobenberg and Amidon, 2000). This means drugs with a high permeability but low solubility can show low bioavailability hence less drug absorption. This indicates that the solubility and dissolution rate of this class of drugs are important parameters in determining the oral bioavailability of such drugs (Vo et al., 2013). This is true for carbamazepine as it belongs to BCS Class II drugs. Carbamazepine (CBZ) is an antiepileptic drug which exists in different polymorphic forms (Rustichelli et al., 2000), all of which have different dissolution rates leading to irregular and delayed absorption (Bertillson, 1978). CBZ has an experimental log *P* value of 2.45 and is practically insoluble in water (~113 μg/mL at 25 °C) (Sethia and Squillante, 2002). Carbamazepine tablets on the market contains 200 mg CBZ which should dissolved in the fluid available in the gastrointestinal tract and the presence of less fluid in the GIT with poor solubility of CBZ will delay its dissolution leading to a poor performance. Therefore an improvement in the solubility or dissolution can increase the performance of CBZ in vivo. It has been shown that the solubility of CBZ can be increased 10-fold in the presence of 1% sodium lauryl sulphate (SLS) (Lee et al., 2005). CBZ and other drugs (e.g. piroxicam, indomethacin) with low solubility and high permeability belonged to Class II in the Biopharmaceutical Classification System are more likely to display dissolution-dependent oral bioavailability (Lobenberg and Amidon, 2000). Solid dispersion is one of the techniques developed to address the foregoing problems associated with Class II drugs. Solid dispersion systems have been considered, for over 40 years, as a means of increasing the solubility, dissolution, and absorption of poorly water-soluble drugs (Chiou, 1971; Leuner and Dressman, 2000; Al-Hamidi et al., 2009). Moreover, solid dispersions are one of the most promising methods for pharmaceutical formulators because of their ease of preparation and optimization, as well as reproducibility (Chiou, 1971; Goldberg et al., 1966). Poorly water soluble drugs can be dispersed in an inert hydrophilic polymer or matrix by melting, solution formation, or vehicle melting to yield solid dispersions (Chiou, 1971; Leuner and Dressman, 2000). Solid dispersions have some disadvantages such as requiring large amount of carrier to achieve the desirable dissolution profile and also in some cases the conversion from the amorphous to the crystalline form during storage (Kalia and Poddar, 2011). An increase in the dissolution of solid dispersions is mainly reliant on the type of hydrophilic carriers used in the preparation of solid dispersions. D-gluconolactone (D-GL) is an amino sugar which is a naturally occurring, highly water soluble, non-toxic compound (Hunt and Barnetson, 1992) and has the potential to enhance the dissolution of low dose drugs such as piroxicam (Al-Hamidi, 2014). For high dose drugs such as CBZ in most cases the amount of carriers used to enhance the dissolution is too high to be embedded into a capsule. Therefore the aim of the present research is to explore the suitability of D-GL to enhance the dissolution of a high dose drug, CBZ. It should be kept in mind that the type of CBZ polymorphic form is also important as the solubility of CBZ form III was slightly higher than that of CBZ form I (Kobayashi et al., 2000). But opposite results were also reported by Kaneniwa et al. (Kaneniwa et al., 1984) showing the solubility of CBZ form I was higher than form CBZ III. All published data were consistent in showing the least solubility for dihydrate form of CBZ compared to anhydrate forms (forms I and III). It has also been reported that CBZ form I and form III were enantiotropic and that form I was stable below 71 °C (Behme and Brooke, 1991). Therefore, on the basis of this it can be concluded that the solubility of form I should be less than that of CBZ form III.

In the present study, the effect of D-GL on the dissolution profile of a hydrophobic and poorly soluble drug, CBZ, was fully investigated. The present research introduces D-GL as a new potential carrier to improve the dissolution rate of CBZ from physical mixtures and solid dispersion formulations. The solid dispersions produced were also characterized by other methods (DSC, HSM, SEM, XRPD and FT-IR) in order to elucidate the mechanisms involved in dissolution enhancement of the formulations.

2. Materials and methods

2.1. Materials

5H-dibenzo[b,f]azepine-5-carboxamide (Carbamazepine, CBZ) was purchased from Sigma (Gillingham, UK). D-(+)-gluconolactone hydrochloride (Sigma, Gillingham, UK) and sodium lauryl sulphate (Fluka, Basel, Switzerland) were used. The organic solvents utilized in this study, acetone and ethanol, were obtained from Fisher Scientific (Loughborough, UK). All solvents, including water, and other chemicals used were of analytical reagent grade. All materials were used as obtained.

2.2. Preparation of solid dispersions of CBZ:D-GL

Solid dispersions of CBZ and D-GL were first prepared using the solvent evaporation technique at ratios of 2:1, 1:1, 1:2 and 1:4 (w/w, drug: carrier) by the conventional solvent evaporation method. Both the drug and carrier were dissolved in acetone or ethanol under stirring condition (200 rpm) followed by the evaporation of the solvent at room temperature (22 ± 1 °C) and relative humidity of around 50% for 24 h. To complete the drying of the solid dispersions obtained, the resultant powders were kept in an oven for 2 h at 40 °C. The resultant solid dispersions were collected and kept for 2 days at room temperature (22 ± 1 °C). The dispersions were then pulverized using a mortar and pestle, and stored in a desiccator at room temperature for one week before use.

As D-GL is highly soluble in water, so, in the next series of the formulation the drug and the carrier were dissolved separately in acetone or ethanol (30 mL) and distilled water (20 mL), respectively. The carrier solution was then added to the drug solution under the same stirring conditions as described above. The stirring was continued until a complete evaporation of the solvents (acetone–water or ethanol–water). To complete the drying of the solid dispersions obtained, the resultant powder was left in an oven for 2 h at 40 °C. The rest of the procedure to get the solid dispersion powder was the same as describe above.

2.3. Preparation of physical mixtures of drug-carrier

Physical mixtures were prepared by mixing drug and carrier in a turbula blender (Basel, Switzerland) for 10 min at a speed of 80 rpm. Different ratios of drug: carrier (4:1, 2:1, 1:1, 1:2 and 1:4 w/w) were prepared for comparison purposes. After