Saudi Pharmaceutical Journal xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Development of ternary solid dispersions with hydrophilic polymer and surface adsorbent for improving dissolution rate of carbamazepine

Tanja Vojinović [a], Djordje Medarević [b,*], Edina Vranić [c], Zorica Potpara [a], Marko Krstić [b], Jelena Djuriš [b], Svetlana Ibrić [b]

[a] Department of Pharmacy, Faculty of Medicine, University of Montenegro, Ljubljanska bb, Podgorica, Montenegro
[b] Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, Belgrade, Serbia
[c] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Sarajevo, Zmaja od Bosne 8, Sarajevo, Bosnia and Herzegovina

ARTICLE INFO

Article history:
Received 13 September 2017
Accepted 5 February 2018
Available online xxxx

Keywords:
Solid dispersions
D-optimal mixture experimental design
Surface adsorbent
Poorly soluble drugs
Polymorphism
Polymorphic conversion

ABSTRACT

In this study solid dispersions of carbamazepine in the hydrophilic Kollidon® VA64 polymer, adsorbed onto Neusilin® UFL2 adsorption carrier have been employed to improve carbamazepine dissolution rate. In order to evaluate effects of changing in the proportions of all solid dispersion components on carbamazepine dissolution rate, D-optimal mixture experimental design was used in the formulation development. From all prepared solid dispersion formulations, significantly faster carbamazepine dissolution was observed compared to pure drug. Ternary solid dispersions containing carbamazepine, Kollidon® VA64 and Neusilin® UFL2 showed superior dissolution performances over binary ones, containing only carbamazepine and Neusilin® UFL2. Proportion of Kollidon® VA64 showed the most profound effect on the amount of carbamazepine dissolved after 10 and 30 min, whereby these parameters increase upon increasing in Kollidon® VA64 concentrations up to the middle values in the studied range of Kollidon® VA64 concentrations. Physicochemical characterization of the selected samples using differential scanning calorimetry, FT-IR spectroscopy, powder X-ray diffraction and polarizing light microscopy showed polymorphic transition of carbamazepine from more thermodynamically stable monoclinic form (form III) to less thermodynamically stable triclinic form (form I) in the case of ternary, but not of binary solid dispersion formulations. This polymorphic transition can be one of the factors responsible for improving of carbamazepine dissolution rate from studied solid dispersions. Ternary solid dispersions prepared with Kollidon® VA64 hydrophilic polymer and Neusilin® UFL2 adsorption carrier resulted in significantly improvement of carbamazepine dissolution rate, but formation of metastable polymorphic form of carbamazepine requires particular care to be taken in ensuring product long term stability.

1. Introduction

Increase using of combinatorial chemistry and high throughput screening in the development of new drugs led to development of huge number of compounds with good pharmacological activity, but unfortunately very low aqueous solubility. Since drug dissolution is prerequisite for its absorption, low drug solubility and dissolution rate will limit drug bioavailability after oral administration. Numerous approaches have been applied for improving drugs dissolution rate and bioavailability, including formation of prodrugs (Rautio et al., 2008) and salts (Serajuddin, 2007), particle size reduction (Leleux and Williams, 2014), complexation with cyclodextrins (Loftsson et al., 2005), formulation of solid dispersions (Vo et al., 2013), nanocrystalline systems (Möschwitzer, 2013) and lipid-based drug delivery systems (Feeney et al., 2016). Although application of solid dispersions was in a lot of cases accompanied with improved drug solubility and oral bioavailability, wider commercial application of this approach is very limited due to problems in ensuring long term product stability as a consequence of polymorphic transitions and crystalline-amorphous transitions and difficult further processing of solid dispersions into final dosage form as a result of their sticky

* Corresponding author at: Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia.
E-mail address: djordje.medarevic@pharmacy.bg.ac.rs (D. Medarević).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2018.02.017
1319-0164/

consistency which causes poor flow and compression properties (Serajuddin, 1999; Vo et al., 2013). It has been shown that adsorption of solid dispersions onto inert carriers with high specific surface area is very effective strategy to enable further processing of these systems into final dosage form, with maintaining fast drug release (Gupta et al., 2001, Gupta et al., 2002). Higher drug dissolution rate from these ternary systems is not only consequence of intricate properties of solid dispersions, such as generation of amorphous form of API, improved wetting and decrease in particle size, but also of increased surface area due to using of adsorption carrier (Gupta et al., 2001). In addition, adsorption carrier can further stabilize drug within the solid dispersion matrix, due to specific chemical interactions, as well as prevention of crystal growth due to very confined space inside the carrier pores (Censi et al., 2016). Neusilin® is an amorphous, synthetic form of magnesium aluminometasilicate, available in different grades and is commonly used for pharmaceutical applications as a carrier and filler for improving the quality of tablets, powders, granules and capsules (Censi et al., 2016). Particular success with using of this carrier has been achieved in solidification of self-emulsifying drug delivery systems (Milović et al., 2012; Qi et al., 2014; Williams et al., 2014) as well as solid dispersions (Gupta et al., 2001, 2002).

Carbamazepine (CBZ) is an antiepileptic drug with poor aqueous solubility which is responsible for its low and irregular oral bioavailability (Sethia and Squillante, 2002). Since CBZ exhibits dissolution-limited bioavailability, numerous approaches have been applied to improve its dissolution rate, including micronisation (Bolten and Türk, 2012), nanocrystallization (Wang et al., 2012), co-crystallization (Chieng et al., 2009; Yamamoto et al., 2012), formulation of binary and ternary solid dispersions (Medarevic et al., 2016a,b; Djuris et al., 2014; Martins et al., 2012) self-emulsifying drug delivery systems (Milović et al., 2012), complexation with cyclodextrins (Jain et al., 2011; Medarevic et al., 2015) and adsorption onto mesoporous silicates (Ambrogi et al., 2008; Van Speybroeck et al., 2009). CBZ is known to exhibit polymorphism, with at least four known anhydrous polymorphic forms, as well as numerous solvates (Kipouros et al., 2006). Since it has been demonstrated that in some of the formulation approaches for improving CBZ dissolution rate, polymorphic transitions occur (Otsuka et al., 1997; Murphy et al., 2002), particular attention should be paid to the comprehensive solid state characterization methods, in order to timely detect these transitions. In this study, ternary solid dispersions containing CBZ and Kollidon® VA 64 (vinyl pyrrolidone/vinyl acetate copolymer at a ratio of 6:4), adsorbed onto Neusilin® UFL2 carrier have been developed to improve dissolution rate of CBZ. Neusilin® UFL2 was included in the formulation due to numerous benefits in solid dispersions formulation, such as increasing of surface area, better dispersing of solid dispersion powder in an aqueous medium, due to lower tendency towards agglomeration, and also facilitation of solid dispersion production process which enables production of powder suitable for further processing into final dosage form. D-optimal mixture experimental design was applied in order to find optimal composition of solid dispersion, which provides the fastest CBZ dissolution. Comprehensive physicochemical characterization was performed in order to evaluate changes in CBZ physical state in the prepared solid dispersions, as well as presence of interactions between CBZ and other solid dispersion components.

2. Materials and methods

2.1. Materials

Neusilin® UFL2 (magnesium aluminometasilicate) (Fuji Chemical Industry, Japan) and water soluble copolymer Kollidon® VA64 (vinyl pyrrolidone/vinyl acetate copolymer at a ratio of 6:4) (BASF, Ludwigshafen, Germany), both kindly donated by the manufacturers, were used as components of solid dispersion matrix. Absolute ethanol (Merck, Darmstadt, Germany) was used as a solvent for solid dispersions preparation. CBZ (Ph. Eur. 9.0), kindly donated by Galenika AD (Belgrade, Serbia), was used as a model of poorly soluble drug.

2.2. Methods

2.2.1. Experimental design and analysis

D-optimal mixture experimental design was used to evaluate the influence of solid dispersion composition on CBZ dissolution rate. The limits for the solid dispersion components proportions were in the following range: $20\% \leq A \leq 50\%$, $30\% \leq B \leq 80\%$, $0\% \leq C \leq 20\%$, where A, B and C are proportions of CBZ, Neusilin® UFL2 and Kollidon® VA64, respectively. D-optimal mixture experimental design was used because setting of the constraints for components proportions in the previous way gave irregularly shaped experimental space, so using of asymmetric types of experimental design is strongly recommended (Dejaegher and Heyden (2011)). Design expert software 7.0.0 (Stat-Ease, Inc., Minneapolis, MN, USA) was used for the development of the D-optimal mixture experimental design matrix that had a total of 20 experimental runs (Table 1).

Independent variables were proportions of CBZ, Neusilin® UFL2 and Kollidon® VA64, while the responses (Y_1 and Y_2) were the amounts of dissolved CBZ (%) from solid dispersions after 10 (Q_{10}) and 30 (Q_{30}) minutes.

Obtained data were fit into the linear (Eq. (1)), quadratic (Eq. (2)), special cubic (Eq. (3)) and cubic (Eq. (4)) Scheffe's models:

$$Y = b_1A + b_2B + b_3C \quad (1)$$

$$Y = b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC \quad (2)$$

$$Y = b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{123}ABC \quad (3)$$

$$Y = b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{123}ABC + \gamma_{12}AB(A - B) + \gamma_{13}AC(A - C) + \gamma_{23}BC(B - C) \quad (4)$$

where b_1–b_{123}, γ_{13}–γ_{23} are coefficients of the mathematical model.

Analysis of variance (ANOVA) test was used to assess statistical significance of the factor effects, where effects with $p < 0.05$ were considered as statistical significant. Obtained polynomial models were visualized as contour and trace plots.

2.2.2. Solid dispersions preparation

Solid dispersions were prepared according to previously defined experimental plan (Table 1). Neusilin® UFL2 was dispersed in ethanolic solution of CBZ and Kollidon® VA64 under stirring on a magnetic stirrer (RCT basic, IKA Labortechnik, Staufen, Germany). Evaporation of ethanol from the prepared dispersions was performed using rotary vacuum evaporator (Büchi Rotavapor®, Büchi Labortechnik AG, Flawil, Switzerland) at a temperature of 70 °C. After evaporation, precipitated material was scrapped off and stored for 48 h in a desiccator. Samples were further pulverized in a mortar with a pestle and afterwards sieved through 300 μm sieve. Until further analysis, samples were kept in sealed glass vials, away from light and moisture.

2.2.3. Dissolution testing

CBZ dissolution rate from the samples of pure drug and prepared solid dispersions was tested using rotating paddle apparatus (Erweka DT70, Erweka, Germany). Distilled water (900 ml) was used as a dissolution medium, since CBZ exhibits pH-independent solubility (Keramatnia et. al., 2015), while test was

Please cite this article in press as: Vojinović, T., et al. Development of ternary solid dispersions with hydrophilic polymer and surface adsorbent for improving dissolution rate of carbamazepine. Saudi Pharmaceutical Journal (2018), https://doi.org/10.1016/j.jsps.2018.02.017