Original article

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

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A B S T R A C T

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.

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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
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 (Milovic 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 (Cheng 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 (Milovic 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., 2016). 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) (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% ≤ A ≤ 50%, 30% ≤ B ≤ 80%, 0% ≤ C ≤ 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 (Dejaeger 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 (Y1 and Y2) were the amounts of dissolved CBZ (%) from solid dispersions after 10 (Q10) and 30 (Q30) minutes.

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

\[ Y = b_0 + b_1A + b_2B + b_3C \]  
\[ Y = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC \]  
\[ Y = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{123}ABC \]  
\[ Y = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{13}AC + b_{23}BC + b_{123}ABC + \gamma_{12}AB(A - B) + \gamma_{13}AC(A - C) + \gamma_{23}BC(B - C) \]

where \( b_{12}, b_{13}, b_{23}, b_{123}, \gamma_{12}, \gamma_{13}, \gamma_{23} \) 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 scraped 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
performed with paddle rotation speed of 50 rpm. Amount of solid dispersion samples equivalent to single therapeutic dose of CBZ of 200 mg was used in the testing. 4 ml aliquots were taken at predetermined intervals (5, 10, 15, 20 and 30 min), followed by replacement with the same volume of fresh medium. Withdrawn aliquots were filtered through a membrane filter (0.45 μm) and amount of dissolved CBZ was determined by UV spectrophotometry at a wavelength of 287 nm using Evolution 300 UV–Vis spectrophotometer (Thermo Fisher Scientific, Waltham, MA). Results are presented as mean values of three replicates ± standard deviation.

2.2.4. Physicochemical characterization of solid dispersion samples

Based on the results of dissolution testing, formulations F5 (20% CBZ, 80% Neusilin® UFL2), F12 (47.26% CBZ, 32.74% Neusilin® UFL2, 15.87% Kollidon® VA64) and F15 (44.33% CBZ, 39.79% Neusilin® UFL2, 15.87% Kollidon® VA64) were selected as representative for physicochemical characterization. Formulations for physicochemical characterization were chosen based on the observed differences in drug dissolution profiles in order to elucidate possible mechanisms responsible for improvement of CBZ dissolution rate.

2.2.4.1. Differential scanning calorimetry (DSC).

DSC analyses were performed on a DSC 204 F1 Phoenix differential scanning calorimeter (NETZSCH, Germany). Accurately weighted 5–10 mg of samples were placed in pierced aluminum pans, and subjected to heating at 10 °C/min in the range of 25–220 °C under nitrogen purge gas flow of 70 ml/min. An empty pan was used as a reference.

2.2.4.2. Fourier transform infrared spectroscopy (FT-IR).

FT-IR spectra were recorded using Nicolet iS10 (Thermo Scientific, Waltham, MA, USA) FT-IR spectrometer equipped with a single reflection ATR system (Smart iTR, Thermo Scientific, Waltham, MA, USA) with diamond plate and ZnSe lens. The spectra were collected in the frequency range from 4000 to 650 cm⁻¹, with the resolution of 4 cm⁻¹, as an average of 16 scans.

2.2.4.3. Powder X-ray diffraction analysis (PXRD).

PXRD patterns in transmission mode were recorded using Bruker D8 advance diffractometer equipped with focusing Ge-crystal primary monochromator (Johanson type) that generates CuKα1 radiation (λ = 1.541 Å), within 4–45° 20 range in steps of 0.05° and scanning time of 12 s per step.

2.2.4.4. Polarizing light microscopy.

Selected samples of solid dispersions were dispersed in a silicone oil and observed by polarizing microscope (Olympus BX53P, Olympus, Japan) under cross polars. Photos were acquired using cellSens Entry Version 1.14 software (Olympus, Japan).

3. Results and discussion

3.1. CBZ dissolution from solid dispersions

Dissolution profiles of CBZ from the samples of pure drug and prepared formulations are shown on Fig. 1. From the presented dissolution profiles, it can be observed that pure CBZ dissolves slowly and incompletely, with less than 30% of dissolved drug after 30 min of testing. Dissolution of CBZ from all prepared dispersions was faster relative to pure CBZ. The fastest CBZ dissolution rate was achieved from the formulation F15 (44.33% CBZ, 39.79% Neusilin® UFL2, 15.87% Kollidon® VA64), with 73.25% of dissolved CBZ after 30 min of testing. While about 15% of pure CBZ was dissolved from the samples of pure drug within the first 10 min, more than 40% of CBZ was dissolved from 11 of 20 of the prepared solid dispersion formulations during the same time period. The slowest CBZ dissolution was observed from the formulations of binary solid dispersions and ternary solid dispersions (Q10 below 50%).

| Mixture components (%) | Responses |
|------------------------|-----------|
|                        | Q10 (%)   | Q30 (%)   |
| CBZ (%)                | Neusilin® UFL2 (%) | Kollidon® VA64 (%) |
| F1  50.00              | 39.47     | 10.53     | 48.38 | 63.45 |
| F2  42.99              | 57.01     | 0.00      | 18.65 | 34.94 |
| F3  50.00              | 39.47     | 10.53     | 48.08 | 61.80 |
| F4  26.15              | 68.82     | 5.04      | 46.61 | 57.76 |
| F5  20.00              | 80.00     | 0.00      | 17.03 | 28.29 |
| F6  34.53              | 45.52     | 19.94     | 31.10 | 46.18 |
| F7  20.00              | 80.00     | 0.00      | 16.20 | 28.51 |
| F8  27.15              | 54.54     | 18.32     | 43.91 | 52.45 |
| F9  20.00              | 63.59     | 16.41     | 43.61 | 53.69 |
| F10 34.72             | 58.21     | 7.07      | 42.07 | 52.00 |
| F11 41.61             | 48.30     | 10.09     | 47.52 | 59.02 |
| F12 47.26             | 32.74     | 20.00     | 36.99 | 48.15 |
| F13 20.00             | 63.59     | 16.41     | 43.36 | 52.56 |
| F14 47.26             | 32.74     | 20.00     | 36.79 | 50.57 |
| F15 44.33             | 39.79     | 15.87     | 54.89 | 73.25 |
| F16 34.94             | 51.99     | 13.07     | 36.74 | 47.35 |
| F17 22.61             | 66.19     | 11.20     | 39.20 | 45.54 |
| F18 20.00             | 60.00     | 20.00     | 42.51 | 55.64 |
| F19 42.57             | 52.44     | 4.99      | 54.77 | 68.09 |
| F20 33.86             | 62.73     | 3.41      | 39.55 | 50.77 |

Table 1

The composition of the prepared solid dispersions with the obtained values of the dependent variables according to D-optimal mixture experimental design matrix.

* Replicated experiments.
tain only CBZ and Neusilin® UFL2 (area on the plot marked in blue). On the other hand, the fastest CBZ dissolution was observed when CBZ proportion is on the upper limit of the studied range (50%), with presence of 10–15% of Kollidon® VA64 (yellow and orange areas on the plot). Trace plots show the effect of changing in the proportions of individual components on the response values. These plots (Fig. 2b and e) show the most pronounced effect of changing in the proportion of Kollidon® VA64, where the amount of dissolved CBZ increases up to some optimal concentration of Kollidon® VA64, than reach plateau and start to decrease. From the two component mix graphs (Fig. 2c and f) it can be observed that optimal ratio of CBZ:Kollidon® VA64 that provides the fastest CBZ dissolution from the evaluated ternary solid dispersions is 3–3.5:1. From the presented trace plots, it seems that Neusilin® UFL2 negatively affect CBZ dissolution rate, i.e. amount of dissolved CBZ decreases with increasing proportion of this adsorption carrier. However, this effect can be rather attributed to highly pronounced increase of CBZ dissolution rate with increase in both proportions of CBZ and Kollidon® VA64 and the slowest CBZ dissolution rate from the formulations that contain high amount of Neusilin® UFL2, but not Kollidon® VA64.

3.2. Differential scanning calorimetry (DSC)

DSC thermogram of CBZ (Fig. 3a) showed two characteristic endothermic peaks separated by one exothermic peak. First endothermic peak at 178°C corresponds to melting of CBZ polymorphic form III, which confirmed that CBZ raw material contains this polymorphic form, which is the only one acceptable by the European Pharmacopoeia. Following exothermic peak at 180°C is attributed to recrystallization of polymorphic form I from the melt. Recrystallized form I further melts at 195°C, giving sharp endothermic peak (Grzesiak et al., 2003). Broad endotherms on the DSC curves of Neusilin® UFL2 and Kollidon® VA64 (Fig. 2b) correspond to loss of absorbed and adsorbed water, as well as glass transition of these amorphous materials. Presence of endothermic peaks in the thermograms of all analysed solid dispersion samples (Fig. 3c) indicates on presence of CBZ in the crystalline state. First endothermic peak exhibits broad shape due to progressive melting of some amount of CBZ upon heating, or CBZ dissolution within the Kollidon® VA64 due to progressive heating. Second endothermic peak, present on the thermograms of formulations F5 (194°C) and F12 (192.5°C), indicates the presence of some amount of polymorphic form I in the samples that can be present initially, or form during heating in the DSC analysis, like in the case of pure CBZ (Fig. 3a). Although this peak was not present on the thermogram of sample F15 (44.33% CBZ, 39.79% Neusilin® UFL2, 15.87% Kollidon® VA64), presence of CBZ polymorphic form I in this sample cannot be excluded due to possible dissolution of the considerable amount of CBZ within the Kollidon® VA64 upon progressive heating applied in the DSC procedure. Additionally, in the case of sample F5 (20% CBZ, 80% Neusilin® UFL2), where the second peak was the most pronounced, there is no Kollidon® VA64 present, which can dissolve some CBZ crystals during heating or prevent recrystallisation of polymorphic form I via intermolecular interactions. The results of DSC analysis proved that CBZ was present in the crystalline form in all analysed solid dispersion samples. Since the changes of polymorphic form of CBZ due to heating during DSC analysis are possible, DSC is not reliable technique to identify CBZ polymorphic form present in the sample. Therefore, identification of polymorphic form of CBZ was performed using PXRD technique under ambient temperature.

3.3. Powder X-ray diffraction analysis (PXRD)

Diffractograms of raw materials and prepared formulations, obtained by PXRD analysis are presented on Fig. 4. PXRD pattern of pure CBZ showed characteristic peaks at 13.15°, 14.25°, 15.36°, 15.9°, 19.55°, 23.45°, 25.0° and 27.7° 2θ, which corresponds to previously reported PXRD pattern of polymorphic form III of CBZ.
Both Neusilin® UFL2 and Kollidon® VA64 exhibit diffusive broad pattern, without any diffraction peaks, due to amorphous nature of these excipients. Diffractograms of all three analysed formulations showed diffraction peaks indicating crystalline or partially crystalline nature of CBZ within these solid dispersion samples. On the diffractogram of formulation F5, containing CBZ at the lowest level in the study (20%) and Neusilin® UFL2 (80%), without Kollidon® VA64, most of CBZ diffraction peaks disappeared, while remaining peaks showed considerable reduction of intensity. This indicates that CBZ in this formulation partially transformed into amorphous form. Position of three distinguishable peaks on the diffractogram of this formu-
CBZ peaks showed significant shifting in the diffractograms of formulations F12 (47.26% CBZ, 32.74% Neusilin® UFL2, 20% Kollidon® VA64) and F15 (44.33% CBZ, 39.79% Neusilin® UFL2, 15.87% Kollidon® VA64), with appearance of two new peaks, positioned at 5.05° and 8.8° 2θ. Observed PXRD changes proved that some amount of CBZ transformed from starting monoclinic form III to triclinic form I, as previously reported by Martins et al. (2012) for similar ternary solid dispersion system prepared with CBZ, Gelucire® 50/13 and colloidal silicone dioxide. Based on the results of PXRD analysis, it can be concluded that during preparation of ternary solid dispersions with CBZ, Neusilin® UFL2 and Kollidon® VA64, polymorphic transition from polymorphic form III into polymorphic form I occurred. Although the results of PXRD analysis is not in agreement with the results of DSC, definitive conclusion regarding polymorphic form of CBZ present in the sample was drawn from the results of PXRD, due to absence of heating in this technique, which can induce undesired polymorphic transition.

3.4. Polarizing light microscopy

Distinct crystal morphology between CBZ polymorphs allows using of polarizing microscopy for identification of possible polymorphic transitions (Rustichelli et al., 2000). Appearance of needle shaped crystals in the micrographs of formulations F12 (47.26% CBZ, 32.74% Neusilin® UFL2, 20% Kollidon® VA64) and F15 (44.33% CBZ, 39.79% Neusilin® UFL2, 15.87% Kollidon® VA64) (Fig. 5b and c) indicated that CBZ changed polymorphic form from monoclinic form III (prismatic shaped) to triclinic form I (needle shaped). However, needle shaped crystals were not observed on the photomicrographs of formulation F5 (20% CBZ, 80% Neusilin® UFL2) (Fig. 5a), indicating that there was not polymorphic conversion from form III to form I. Characteristic particle shape of CBZ polymorphs I and III, observed under polarizing microscope, agree with PXRD pattern of all three analysed formulations. Visual observation also confirmed that using of DSC for identification of CBZ polymorphic transition in the case of these formulations gives misleading conclusions.

3.5. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectroscopy was used to detect presence of possible interactions between CBZ, Kollidon® VA64 and Neusilin® UFL2, that, if present, should result in shifting of the absorption bands.
characteristic for functional groups, which take part in the interaction. FT-IR spectra of raw materials and prepared solid dispersion formulations are shown on Fig. 6. FT-IR spectra of CBZ showed characteristic absorption bands at 3463 cm$^{-1}$ ($\alpha$NH valence vibration), 1674 cm$^{-1}$ ($\alpha$CO$\alpha$R vibration), 1593 cm$^{-1}$ and 1605 cm$^{-1}$ (range of $\alpha$C$\equiv$C$\alpha$ and $\alpha$C$\equiv$O vibration and $\alpha$NH deformation), which is in line with the spectra previously reported in the literature (Rustichelli et al., 2000; Grzesiak et al., 2003). Considerable shifting of the major absorption bands of CBZ has been observed on the spectra of all three analysed formulations. On the spectrum of formulation F5 (20% CBZ, 80% Neusilin UFL2), sharp absorption peak of CBZ, positioned at 3463 cm$^{-1}$, changed to broad absorption band positioned around 3460 cm$^{-1}$, while absorption band positioned at 1674 cm$^{-1}$ shifted to 1652 cm$^{-1}$. Other absorption bands of CBZ became indistinguishable. Formulations F12 (47.26% CBZ, 32.74% Neusilin UFL2, 20% Kollidon VA64) and F15 (44.33% CBZ, 39.79% Neusilin UFL2, 15.87% Kollidon VA64) showed very similar IR spectra. These spectra are characterised with broad absorption band, with small peak at 3481 cm$^{-1}$ and sharp absorption bands at 1682, 1733, 1591 and 1603 cm$^{-1}$. It is obvious that CBZ peaks positioned at 3463 cm$^{-1}$ ($\alpha$NH valence vibration) and 1674 cm$^{-1}$ ($\alpha$CO$\alpha$R vibration) on the spectra of raw material exhibited the highest extent of changes, indicating significant intermolecular interactions, possible hydrogen bonding, between amide group of CBZ and carbonyl group of Kollidon VA64 and/or silanol group of Neusilin UFL2.

The results of physicochemical characterisation of the selected samples of solid dispersions showed polymorphic transition of CBZ from more thermodynamically stable monoclinic form (form III) to less thermodynamically stable triclinic form (form I) in the case of ternary solid dispersion formulations. It has been previously shown by Kobayashi et al. (2000) that form I exhibits faster initial dissolution rate, which is further diminished by its rapid conversion to dihydrate form. Therefore, formation of metastable polymorph is also one of the factors that contribute to improve CBZ dissolution rate from tested ternary solid dispersions, in addition to improved wetting, high specific surface area of adsorption carrier, reduce CBZ particle size and reduce particle agglomeration.
4. Conclusion

In the present study, formulation of ternary solid dispersions with Neusilin® UFL2 as a high specific surface area adsorption carrier and Kollidon® VA64, as a hydrophilic polymer was successfully applied to improve dissolution rate of CBZ. It was demonstrated that CBZ dissolution rate from the prepared solid dispersions is sensitive on the changing of the proportions of all ingredients, which highly supports using of in silico modelling techniques, such as experimental design in the systematic development of these systems. Comprehensive solid state characterisation of ternary solid dispersions showed polymorphic transition from stable monomeric form III of carbamazepine to metastable form I, which was not observed for binary solid dispersions that contain only CBZ and Neusilin® UFL2. Although conversion into metastable polymorph of CBZ resulted in significant improvement of its dissolution rate, particular attention should be paid in ensuring long-term stability of these systems and avoiding reconversion into initial stable polymorph. This issue will be subject of further research.

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