Solubility Enhancement of Poorly Water Soluble Drug using a Novel Polymeric Solubilizer (Soluplus®)

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Abstract

Purpose: To enhance the solubility of a poorly water soluble drug, Carbamazepine (CBZ), using a novel polymeric solubilizer (Soluplus®). Methods: Physical mixtures (PM) of CBZ and Soluplus® (50, 75 and 80% w/w) with a particle size range of 106-500 μm were prepared by blending in a glass vial for 1 hour. Solid dispersions (SD) of CBZ containing various ratios of Soluplus® (5%, 7.5% and 80% w/w) were prepared by solvent casting technique. The SD was dried in an oven at 50°C until the loss on drying is greater than 7%. The SD is then cooled at ~20°C for 1 hour. The SD were gently ground in a mortar and the resulting granules were sieved and the 106-500 μm particle size fraction was obtained using #35 and #140 mesh screen. The solubility study of CBZ, PM and SD were performed in 0.1 N HCl (adjusted to pH 1.2) at room temperature (23 ± 2°C) for 7 days. The UV absorbance values were recorded at a wavelength of 288 nm at the end of 7 days. Results: Solubility of CBZ in pH 1.2 at room temperature was 162 μg/mL. Increases in CBZ solubility were observed in both PM and SD samples as the proportion of Soluplus® is increased. A fourfold increased in solubility were observed in PM and SD containing 50% of Soluplus® where the solubility were 674 and 626 μg/mL, respectively. The solubility of PM and SD containing 75% Soluplus® were 851 and 856 μg/mL, respectively. The greatest increased in solubility was seen in PM and SD containing 80% Soluplus® where the solubility was 1019 and 962 μg/mL. Conclusions: The results demonstrated that Soluplus® (50, 75 and 80% w/w) can be used to enhance the solubility of CBZ where an increased in solubility of CBZ was observed as the Soluplus® proportion is increased.

Introduction

Among the top 200 drugs marketed in US, 60% are classified as BCS class I and III compounds which are considered as highly soluble. However, among the NCES filing, 90% of the NCES are classified as BCS class II and IV compounds which are considered as poorly soluble. Poorly soluble drugs bring many challenges to the industry when trying to formulate these drugs into the solid dosage forms. Some of the drawbacks include: (1) poor, incomplete and variable absorption, (2) difficult in predicting and controlling the pharmacologic and toxic effects of a given dose, (3) causes significant food effects, (4) higher cost of manufacturing and etc. Solid dispersion (SD) is a method widely used to improve the dissolution rate of poorly soluble drugs. Proper selection of the solid dispersion carrier and other excipients that are included in the formulation is important. In the current study, we focused on using a novel polymeric solubilizer (Soluplus®) as the polymer carrier to form SD with a poorly water soluble drug, Carbamazepine (CBZ). Soluplus® is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer with an amphiphilic chemical structure.

Figure 1: Chemical structure of Soluplus®.

Objectives

• Enhancing the solubility of CBZ by forming SD with a novel polymeric solubilizer (Soluplus®)
• Investigate the effect of Soluplus® on the CBZ’s rate of dissolution.
• Investigate the effect of Soluplus® on the CBZ’s equilibrium solubility.

Materials and Methods

Materials: The poorly soluble drug selected for this study is CBZ while the polymer carrier selected is a novel polymeric solubilizer (Soluplus®) developed by BASF Corporation.

Preparation of Physical Mixture (PM): The PMs were prepared by physically mixed in a small sample vial. The PMs were ground in a mortar and the 106-500 μm particle size fraction of the PMs was obtained using #35 and #140 mesh screen. The powders were stored in a screw-cap glass vial at room temperature in a desiccator until further analysis.

Preparation of SD: The SDs were prepared by solvent casting method. The SDs were ground in a mortar and the 106-500 μm particle size fraction of the SDs was obtained using #35 and #140 mesh screen. The powders were stored in a screw-cap glass vial at room temperature in a desiccator until further analysis.

Dissolution: The dissolution profile of CBZ was performed in a USP II dissolution apparatus (paddle method) with 800 mL of 0.1 N HCl (adjusted to pH 1.2) at 100 rpm and 37°C ± 0.5°C. The SDs, PMs, and neat CBZ powders equivalent to 50 mg of CBZ were weighed and introduced to the dissolution medium. The solution was filtered and continuously pumped into a Shimadzu UV 1601 spectrophotometer and the absorbance values were recorded at a wavelength of 288 nm at a 5 minute intervals.

Equilibrium solubility study: The solubility study of CBZ, PMs, and SDs was determined by adding excess drug into 30 mL of 0.1 N HCl (adjusted to pH 1.2) in a glass vial. The glass vial is capped and attached to a wrist shaker in a water bath maintaining the temperature at 37°C±1°C for 7 days with agitation. At the end of the 7 days, 7 mL of the sample was withdrawn and filtered through a 0.45 μm syringe tip filter and the final 2 mL was discarded. The collected sample was again filtered through a 0.22 μm syringe tip filter with first 2 mL discarded. The UV absorbance values of the samples were recorded at a wavelength of 288 nm.

Results and Discussions

Figure 2: Dissolution profile of neat CBZ and PMs with various CBZ weight contain (10%, 20%, 30% and 50% w/w). The dissolution rate of PMs was slow. A decrease of drug dissolution was observed with increasing drug loading while decreasing Soluplus® proportion in the PMs. PMs with 10% and 20% of CBZ (w/w) had faster drug dissolution than the neat CBZ while PMs with 30% and 50% of CBZ (w/w) showed slower drug dissolution.

Figure 3: Dissolution profile of neat CBZ and SDs with various CBZ weight contain (10%, 20%, 30%, 50% and 50% w/w). Neat CBZ shows slowest dissolution where less than 60% was dissolved in 5 minutes. An increase of drug dissolution was observed with decreasing drug loading while increasing Soluplus® proportion in the SDs. All SDs prepared show faster drug dissolution compared to the neat CBZ. SDs containing 20% CBZ (w/w) show rapid drug dissolution where more than 85% of CBZ was dissolved within 15 minutes. The SD with 30% of CBZ was slower where 82% of drug dissolved in 30 minutes. The SD with 50% of CBZ was the slowest where 65% of drug was dissolved in 30 minutes.

Conclusions

The drug dissolution of the PMs containing Soluplus® were slow. PMs with ≥20% of CBZ (w/w) had higher drug dissolution than the neat CBZ while PMs with ≥30% of CBZ (w/w) show slower drug dissolution. When forming SD with the CBZ, Soluplus® markedly increased the rate of drug dissolution. All SDs showed faster drug dissolution than the neat CBZ. An increased in drug dissolution was observed with increasing Soluplus® proportion. In the equilibrium solubility study, Soluplus® was found to increase the solubility of all PMs and SDs formulation with increasing solubility as Soluplus® proportion is increased. Highest solubility increased is seen in SD with 90% of Soluplus® content (w/w) where the equilibrium solubility is increased by more than 5 fold.

References