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Dissolution improvement of binary solid dispersions of Carbamazepine using Poly (2-ethyl-2-oxazoline) as the hydrophilic carrier.

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SUMMARY

The aim of this study was to design and evaluate the properties of solid dispersions of carbamazepine (CBZ) using poly (2-ethyl-2-oxazoline) (POX) as the hydrophilic carrier. These binary solid dispersions were prepared at varying drug loadings using the solvent evaporation method. The samples were evaluated for their in vitro dissolution, and solid-state properties. There was over 350% increase in dissolution rate of CBZ in samples containing at least 50% POX. This study concludes that POX is an effective hydrophilic carrier for poorly soluble drugs in solid dispersions.

INTRODUCTION

Poly (2-ethyl-2-oxazoline) (POX) is a non-ionic hydrophilic polymer of the pseudo-polypeptide family. Hydrophilic carriers in solid dispersions have been shown to enhance the dissolution rates of poorly water-soluble drugs (Adebisi et al, 2016; 2020). Apart from the hydrophilic nature of this carrier, POX has other properties such as its PEG-like or "stealth" characteristics which may have an impact on muco-penetration of drug particles and formulations.

Carbamazepine (CBZ) is a BCS Class II drug with solubility of 0.12 mg/ml and permeability of 4.3 × 10−4 cm/s respectively (Djuris et al. 2013). It is used as an antiepileptic drug and has four anhydrous polymorphic forms, all of which have variable solubilities, dissolution, and absorption rates. Due to its narrow therapeutic index, it is important that an acceptable and predictable dissolution rate is achieved from CBZ formulations to achieve the desired therapeutic effect. Therefore, the aim of this study was to design and evaluate the properties of CBZ solid dispersions using POX as the hydrophilic carrier to enhance the dissolution rate of the drug. There are limited studies exploring the use of this carrier in solid dispersions and to the best of the authors' knowledge, there is none that has explored its use in enhancing the dissolution rate of CBZ.

MATERIALS AND METHODS

Solid dispersions of CBZ with LMW POX were prepared at varying drug loadings (33-80% CBZ) by the solvent evaporation method. The required quantities of the polymer and drug were dissolved in dimethylacetamide. The solution was dried at 50°C overnight and then transferred to a vacuum oven for another 24h to remove the residual solvent. A control sample was prepared without the carrier. Samples were evaluated for their dissolution properties in phosphate buffer (pH 6.8) such as the dissolution efficiency at 120 min (DE_{120min}) and mean dissolution

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rate (MDR). In addition, solid-state properties such as thermal properties and XRD were also evaluated.

RESULTS AND DISCUSSION

The addition of POX in the SD samples significantly increased the dissolution rate of CBZ as shown in Fig 1. The control CBZ sample that was produced through the same process, had a similar dissolution profile to the unprocessed pure drug (f_2= 71). Addition of POX at a concentration of 20% (0.25POXDM) to the SD led to 68% and 63% increase in DE_{120min} and MDR, respectively. A further increase in POX concentration to 33%(0.5POXDM) led to 101% and 92% increase in DE_{120min} and MDR respectively relative to the pure drug. Further increases in POX concentration at 50% and above led to over 280% and over 350 % increase in DE_{120min} and MDR respectively relative to the pure drug.

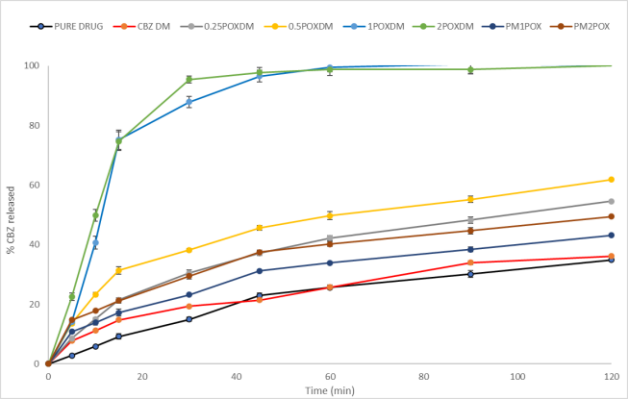

Fig. 1. *Dissolution profile of pure CBZ, control and the various ratios of the SDs.*

The physical mixtures (PM) of the drug with the polymer showed some enhancement in dissolution rates (<7%) but not as much as the SDs (Fig 1), which may give an indication of some interactions between the drug and the carrier in the SDs. XRD diffraction peaks (Fig 2) shows the crystalline nature of the stable CBZ Form III, and these peaks appeared in the samples, showing that there were no polymorphic transitions of CBZ during the process of preparing the SDs. The peaks in the SDs became more diffuse as the proportion of the carrier increased due to dilution and/or decreased crystallinity of the drug. These peaks were almost lost at high carrier concentrations (SD1POXDM and SD2POXDM) which correlated with the enhanced dissolution rates of these samples (Fig 1) suggesting increased amorphization of the drug in the SDs. DSC data (not shown) showed a reduction in melting point of CBZ as the carrier concentration increased, indicating good miscibility between CBZ and POX, likely due to intermolecular interactions which may be responsible for the differences in the properties of the SDs relative to the PMs.

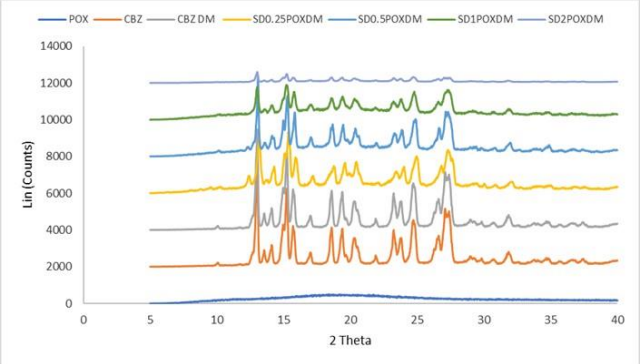

Fig. 2. *XRD scans of POX, pure CBZ, control and the various ratios of the SDs.*

CONCLUSIONS

Poly (2-ethyl-2 oxazoline) was able to increase the dissolution rate of CBZ to achieve complete dissolution within 30 minutes in solid dispersions containing at least 50% of the carrier. This is relative to the 35% dissolution of the pure drug within 120 min. Therefore, this demonstrates the effectiveness of LMW POX as an effective hydrophilic carrier for poorly soluble drugs in solid dispersions.

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