Therapeutic-Polymer-Cyclodextrin Composite Processing with Dense Gas Antisolvent Technology

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Abstract. Low solubility prevents around 60-70% of bioactive compounds to be further developed as therapeutic agents. One strategy to overcome this drawback is to formulate the therapeutic agent with polymers to form composites. In this study, a hydrophobic therapeutic agent has been incorporated into a polymer-cyclodextrin using dense gas anti-solvent processing. Econazole nitrate, a poorly water solubility compound has been co-processed with polyvinylpyrrolidone and methyl-β-cyclodextrin to form binary and ternary composites. The processing employed dense gas of CO_2 as antisolvent and acetone-ethanol mixtures as solvent. Analysis of morphology and thermal property assessments indicated an intimate mixing of the active ingredient in the polymer and/or the cyclodextrin. Improvement of econazole nitrate solubility in aqueous medium as high as 25 times was reached, when both excipients were used.

Keywords: Pharmaceuticals; polymer; cyclodextrin; dense gas; CO_2 technology

Introduction

It is estimated that 60-70% of new drug candidates exhibit low aqueous solubility(3). Drug compounds in this category usually possess solubility less than 100 µg/mL. Low solubility has become a major problem for drug development, since it may have a direct consequence on low dissolution rate and bioavailability. As a result, high dosages may be required to obtain therapeutic concentration levels, which may increase the possibility of side effects of the therapy(3).

Formulation of polymeric systems is frequently proposed as one strategy to improve the physics. Polymers have been pivotal in drug formulation due to their versatile and vast properties. Some polymeric composites have been useful to increase drug solubility and dissolution rate, while others may facilitate a modification of the release profile(1).

In particular, composites of polymers with cyclic oligomers of glucose, known as cyclodextrins, have been quite interesting since they provide the potential for significant solubility enhancement with controlled release profiles(1,7). Cyclodextrins are commonly

used to include hydrophobic compounds, to increase solubility and stability through molecular complexation. Furthermore, cyclodextrin inclusion may be able to provide improved bioavailability of the included compounds(2).

Incorporation of drugs into polymeric-cyclodextrin matrices has commonly been conducted in organic solvent based methods. The disadvantage of the method has been obvious since the solvent may interfere and weaken cyclodextrin-polymer interactions with the hydrophobic guest molecules. Some studies further suggest that the removal of solvent residue, such as acetone, from the cyclodextrin based products, can be challenging(1). Others have applied a more environmentally friendly aqueous based method to perform polymeric-cyclodextrin drug inclusion(5). However time-consuming methodologies are usually the downside.

In this study, the incorporation of the poorly soluble drug of econazole nitrate (EN) in polymeric-cyclodextrin matrices was carried out in a dense gas antisolvent of CO_2 based method. Water soluble polymer of polyvinylpyrrolidone (PVP) and methyl beta cyclodextrin (MβCD) were co-processed in binary, as well as ternary mixtures with the drug. The aim of the study was to assess an alternative method to formulate polymer-cyclodextrin composites with therapeutic agents. In addition, the application of dense gas methodology may provide the ability to manipulate particle morphology design and thereby provide a synergistic strategy for formulation, with the end result being improved drug performance.

Methodology

Materials

Econazole nitrate (Mw = 444.4) was purchased from Australian Pharmaceuticals (AP). Polyvinylpyrrolidone (PVP) with Mw = 55000 was purchased from Sigma Aldrich. Methyl Beta Cyclodextrin (MβCD) (Mw = 1331) was obtained from Cavasol Wacker. Acetone and ethanol (HPLC grade) were purchased from Ajax Finechem. CO_2 purchased from BOC Gases Australia (>99.5% purity) was used as the anti-solvent.

Experiments

The processing was carried out in dense gas conditions using the ASES (The Aerosol Solvent Extraction of System) method. The equipment used is shown schematically in Fig. 1. Experiments were conducted at 100 bar and 25^{o}C. Feed solution of binary mixtures of EN-PVP, EN-MBCD and ternary mixtures EN-PVP-MBCD with equal weight ratio (1:1

w/w and 1:1:1 w/w respectively) were used in the study. Feed with initial concentration of 10-40 mg/mL in acetone-ethanol 3:1 v/v was sonicated for 10 minutes before processing. The flow rate of the solution was 0.1 ml/min, and the CO_2 gas flow rate was kept around 10 – 15 ml/min by the use of an ISCO-syringe pump. Spraying was carried out through a 1.6 mm ID and 20 cm long nozzle. Approximately 300 – 400 ml of CO_2 was used for final washing, at the end of the experiments.

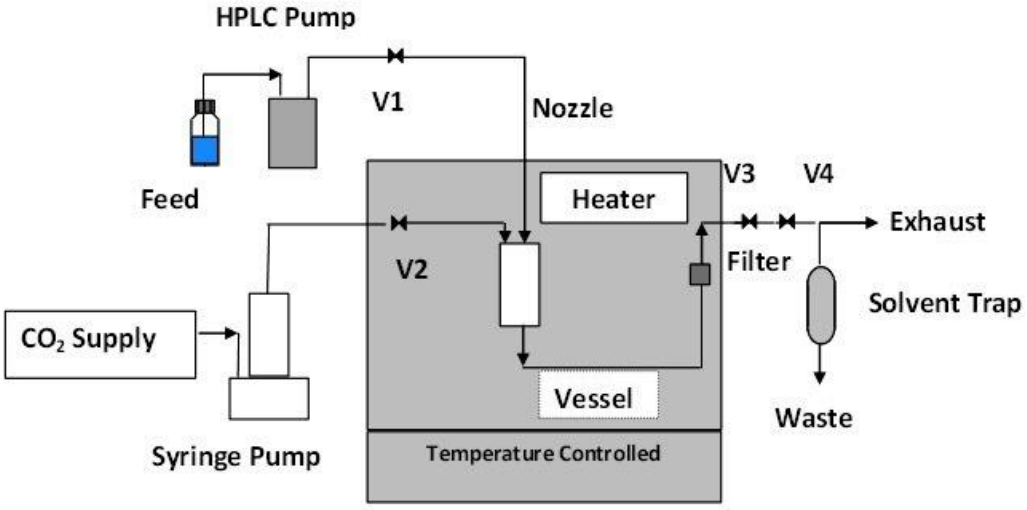


Figure 1. The ASES equipment set up (4).

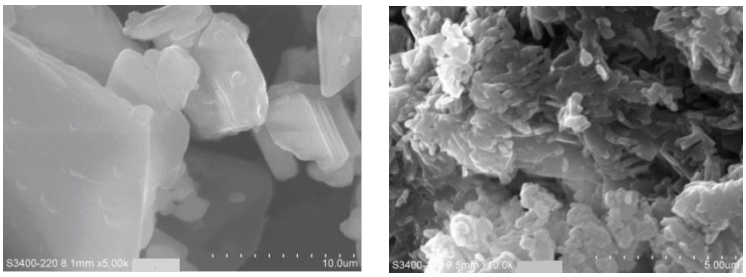
Analysis

The morphology and particle size of the composites were assessed by Hitachi S-3400 Electron Microscopy. The differential scanning calorimetry (DSC) analysis using TA 2010 instrument was carried out to examine any thermal properties changes in the products. Drug content and solubility were calculated using UV-Visible Spectrophotometer Hewlett–Packard (UV Spec-HP 8453-10833B).

Results and Discussion

Morphology

Scanning electron microscopy (SEM) was used to examine the morphology of the solid products. The SEM images are shown in Fig. 2, and indicate crystalline flakes of econazole nitrate could be reduced to more regular micron crystals, after being processed with dense gas of CO_2.



(a) (b)

Figure 2. SEM images of econazole nitrate (a) unprocessed (b) processed.

The processing of binary mixtures of both drug-polymer and drug-cyclodextrin could have reduced econazole nitrate crystallinity. When both polyvinylpyrrolidone and methyl-beta cyclodextrin were co-formulated in the composite, the crystal appearance was almost invisible from the sample image, as indicated in Fig. 3.

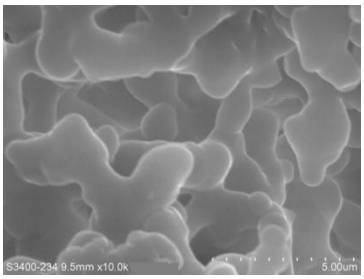
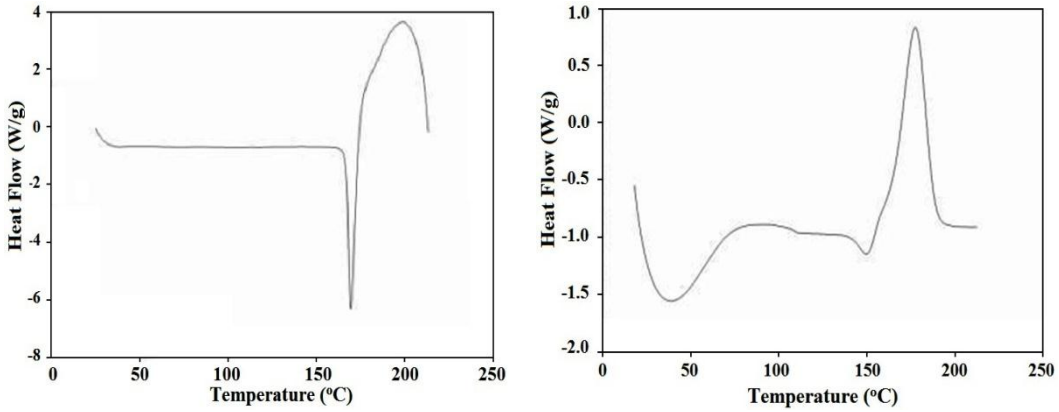


Figure 3. SEM image of the composite of: EN – PVP – MBCD ASES processed at 100 bar and 25^{o}C.

The information that can be drawn from the SEM images is that the composites of polymers, particularly in the ternary system, have surrounded the solid of econazole nitrate. The SEM analysis of composites further suggests that the drug might either be entrapped or included into the cyclodextrin – polymer amorphous matrix structure.

Thermal Analysis

Differential scanning calorimetry (DSC) analysis was carried out to examine the changes in thermal properties (glass, crystallization or melting temperature) of the composites. Thermal analysis indicated that the melting point of unprocessed econazole nitrate could be detected at 169^{o}C. Meanwhile the polymer and cyclodextrin curves (not shown) do not have any sharp peak which suggests an amorphous structure of those materials in the range of temperature examined (0-250^{o}C).



(a) (b)

Figure 4. DSC thermograph (a) Econazole nitrate (unprocessed) (b) Econazole nitrate-polymers (ternary) Composite.

Upon the processing and formulation in dense gas anti-solvent, econazole nitrate might have experienced an evolution in its thermal properties. From the thermographs presented in Fig. 4, it can be observed that the crystalline peak of econazole nitrate has significantly been reduced.

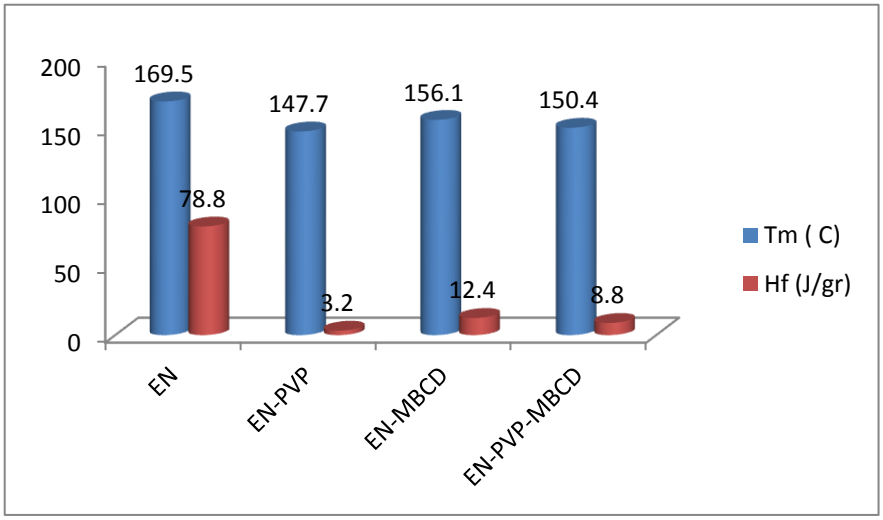


Figure 5. Melting point (Tm) and heat of fusion of the composites.

As presented in Fig. 5, the melting point of econazole nitrate has shifted from 169^{o}C to around 150^{o}C in the composite, indicating an occurrence of a molecular inclusion of the drug in cyclodextrin cavity or entrapment in the amorphous matrices. The hypothesis was substantiated from the observation of heat of fusion of the products which significantly decreased as a result of formulation under dense gas condition. The reduction of heat of fusion may relate to inclusion or entrapment of solid crystal in the amorphous structure of

polymer-cyclodextrin matrices (6). The result has been in agreement with the information obtained in the morphology section.

Drug Content and Solubility

The drug content and solubility of the composite were assessed by UV-Spectrophotometry analysis. Solubility was determined by gradually adding distilled water to a certain weight of product sample (typically 4 -5 mg of sample), until complete dissolution was reached. The UV-Spectrophotometry was then used to measure the drug content in the composite.

The presence of both polivinylpyrrolidone and methyl beta cyclodextrin, either in binary or ternary system, increased the solubility of econazole nitrate in water. From the graph in Fig. 6, it can be understood that the ternary system has produced an enhancement of more than 25 times the solubility compared with that of the raw econazole nitrate. The results of the solubility assessments are consistent with those of other studies involving cyclodextrin-polymer systems (5). Most studies have reported that formulation of water soluble polymers along with cyclodextrins may increase solubilities up to tenth times the original values (2, 5). The unique feature in this study is that the formulations, along with the particle formation, has been carried out using dense gas methodology. The employment of a relatively moderate temperature of dense gas CO_2 at 25^{o}C, may facilitate econazole nitrate properties preservation during processing, as it has been pointed out in solubility assessment. In addition, formulations prepared using this methodology confirms that the aim of increasing solubility was achieved.

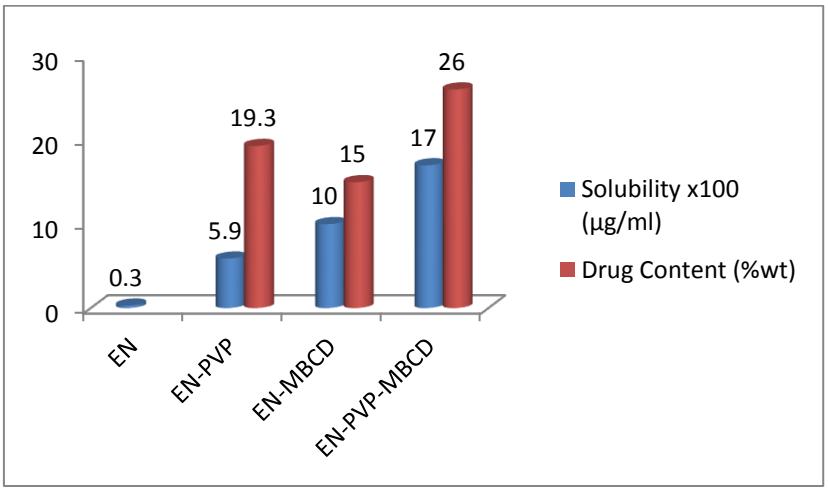


Figure 6. Drug content and solubility of products.

Conclusion

The study has demonstrated how econazole nitrate physicochemical properties can be modified through formulation and processing using dense gas of CO_2 methodology. Co-processing with polyvinylpyrrolidone (PVP) and methyl beta cyclodextrin (MβCD) mixtures has produced composites with the possibility of econazole nitrate entrapment in the excipient matrices. Further assessment also confirms solubility enhancement of the drug when formulation and particle formation were simultaneously carried out using the dense gas approach.

Acknowledgement

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