Hot-Melt Extrusion (HME) formulations of Albendazole for increasing dissolution properties

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INTRODUCTION

Hot-Melt-Extrusion (HME) is a flexible process that uses high temperature and pressure conditions to pump raw materials such as an Active Pharmaceutical Ingredient (API) and a pharmaceutical grade polymer through a barrel. The material is conveyed and mixed using intermeshing co-rotating twin-screws and then pushed through a die to form a well-shaped strand. Due to the high mixing degree provided by the twin-screws, the drug is transformed from crystalline to amorphous form. The use of twin-screw extruders is currently being implemented within continuous manufacturing platforms (Crowley, 2007).

Moreover, HME processes have been widely studied in areas such as plastics, food industry and more recently, in the pharmaceutical industry. Main focus comprises the development of immediate and sustained release dosage forms and more recently, the enhancement of oral bioavailability of poorly water soluble drugs.

In this study, amorphous solid dispersions of a BCS Class II drug, Albendazole (ABZ), were achieved by HME technique using different hydrophilic carriers. Previous amorphous solid dispersions of ABZ were performed by Torrado et al., (1996) and Leonardi et al., (2009) using the solvent evaporation method. By the application of a cutting edge technique such as HME that can be applied in a continuous and more efficient manner, we developed a new successful application to produce amorphous solid dispersions of ABZ.

METHODOLOGY

Preparation of amorphous solid dispersions

Albendazole (ABZ) (Sigma-Aldrich Company Ltd., Gillingham, Dorset, United Kingdom) and polymeric carriers such as Polyvinylpyrrolidone K12 (PVP K12 PF, BASF, Cheshire, United Kingdom) and Polyethylene glycol 6000 (PEG 6000, Croda International, Yorkshire, United Kingdom) were used.

Polymer was sieved to assure particle size homogeneity and then drug and polymer were blended using a Turbula® T2F mixer (Glen Mills Inc., New Jersey, United States).

A Thermo Scientific® Process 11 co-rotating twin-screw extruder (40L/D) (Karlsruhe, Germany) with a 2mm diameter die was used to produce the extruded materials. Formulations comprising ABZ and polymer content of 1/99, 5/95, 10/90 and 20/80 % (w/w) were produced using different processing conditions. Material strands were subsequently cooled at room temperature and stored in glass sealed containers for a total period of 6 months at 25 and 50ºC.

Characterisation techniques

Miscibility studies

The miscibility properties of ABZ with each of the polymeric carriers were assessed theoretically by applying Hansen solubility parameter calculations and experimental evidence was also shown by Hot-Stage Microscopy (HSM).

Surface characterisation techniques

A Hitachi SU 6600 high-resolution analytical FE-SEM (New York, United States) and a Bruker high-resolution X-ray Micro-CT SkyScan 1272 (Kontich, Belgium) were used to provide information regarding material properties such as porosity, homogeneity and drug content uniformity within the extruded materials.

Evaluation of amorphous behaviour

The physicochemical properties of the extruded materials were characterised using a Bruker AXS D8 advanced transmission diffractometer (Karlsruhe, Germany) and a Mettler Toledo DSC 822^e (Greifensee, Switzerland) differential scanning calorimeter to evaluate the formation of amorphous solid dispersions.

Dissolution profile studies

Dissolution curves were obtained under non-sink conditions using the Sirius T3 measurement system (East Sussex, United Kingdom) and dispersions exhibited an increased dissolution rate compared to pure ABZ. Other main properties such as water content and API quantification were obtained by Karl-Fisher method and High-Performance Liquid Chromatography (HPLC).

RESULTS

Miscibility Studies

The excellent miscibility properties of ABZ with each carrier were proven by Hansen solubility parameter calculations where values below 7MPa were obtained.

Further assessment was performed by the application of HSM under different temperature conditions to establish the initial melting temperature in each system.

Scanning Electron Microscopy (SEM)

All extruded materials, physical mixtures (PM) and pure ABZ were characterised by SEM analysis where the amorphous state and also certain porosity degree were observed.

Computed Tomography (Micro-CT)

Homogeneity, content uniformity and porosity properties of the extruded materials can be successfully determined by Computed Tomography (Micro-CT) (Sinka, 2004). In our study, it was observed that the higher the drug content, the higher porosity degree achieved in the case of ABZ – PVP K12 formulations (Figure 1). Further studies will be performed in order to decrease the porosity degree.

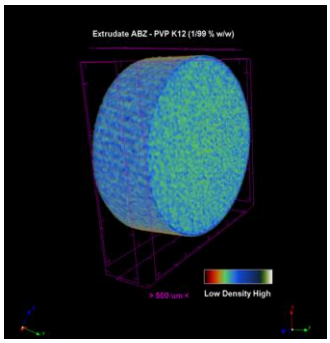

Figure 1. Micro-CT image of ABZ – PVP K12 extruded material at 1/99 % (w/w)

X-Ray Powder Diffraction (XRPD)

Extruded materials, PM drug-polymer and pure ABZ patterns showed absence of crystalline material and therefore confirmed the presence of amorphous ABZ (Figure 2).

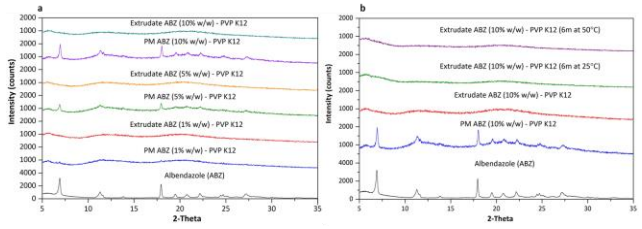

Figure 2. Diffractograms of (a) ABZ – PVP K12 formulations at time zero and (b) ABZ – PVP K12 at 10/90 % (w/w) after 6 months storage

Differential Scanning Calorimetry (DSC)

DSC thermograms of the extruded materials, PM and pure ABZ supported the information provided by XRPD data, where amorphous solid dispersions were observed. Characteristic Tg events of the extruded materials were identified and extruded materials proved to be stable over time, as no endothermic peaks due to re-crystallisation events were shown.

Dissolution profile studies

Dissolution profiles of the extruded materials showed a great increase of drug released (%) over time compared to physical mixtures (PM) and ABZ alone. In the case of ABZ-PVP K12 formulations at 10/90 and 20/80 % (w/w), supersaturated dissolution profile curves were achieved.

CONCLUSIONS

Amorphous solid dispersions of ABZ in PVP K12 and PEG 6000 were obtained by HME technique, in comparison to previous studies where classical methods were employed. Extruded materials showed a great increase in drug dissolution rate in comparison to pure ABZ and also stability studies showed promising results that may lead to further oral bioavailability studies.

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