Understanding the Performance of Melt-Extruded Poly(ethylene oxide)–Bicalutamide Solid Dispersions: Characterisation of Microstructural Properties Using Thermal, Spectroscopic and Drug Release Methods

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Received 23 May 2011; revised 18 July 2011; accepted 12 August 2011

Published online 8 September 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22748

ABSTRACT: In this article, we have prepared hot-melt-extruded solid dispersions of bicalutamide (BL) using poly(ethylene oxide) (PEO) as a matrix platform. Prior to preparation, miscibility of PEO and BL was assessed using differential scanning calorimetry (DSC). The onset of BL melting was significantly depressed in the presence of PEO, and using Flory–Huggins (FH) theory, we identified a negative value of −3.4, confirming miscibility. Additionally, using FH lattice theory, we estimated the Gibbs free energy of mixing which was shown to be negative, passing through a minimum at a polymer fraction of 0.55. Using these data, solid dispersions at drug-to-polymer ratios of 1:10, 2:10 and 3:10 were prepared via hot-melt extrusion. Using a combination of DSC, powder X-ray diffractometry and scanning electron microscopy, amorphous dispersions of BL were confirmed at the lower two drug loadings. At the 3:10 BL to PEO ratio, crystalline BL was detected. The percent crystallinity of PEO was reduced by approximately 10% in all formulations following extrusion. The increased amorphous content within PEO following extrusion accommodated amorphous BL at drug to polymer loadings up to 2:10; however, the increased amorphous domains with PEO following extrusion were not sufficient to fully accommodate BL at drug-to-polymer ratios of 3:10. © 2011 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:200–213, 2012

Keywords: Extrusion; solid dispersions; amorphous; calorimetry (DSC); dissolution

INTRODUCTION

In light of the increasing number of poorly soluble drug candidates emanating from pharmaceutical development pipelines over the last decade improving the aqueous solubility and hence the oral bioavailability of Biopharmaceutics Classification System (BCS) class II drugs is now considered a significant challenge within the pharmaceutical industry. Consequently, there has been a renewed interest in solid dispersions because they offer an attractive and convenient method to surmount this challenge.[1]

Solid dispersions are an efficient way of dispersing a drug in a hydrophilic carrier and thus improving aqueous solubility. In such systems, the drug may be present in a number of varying forms, existing in a microcrystalline form as part of a eutectic drug–polymer mixture, or more usefully, amorphous drug may be embedded within an amorphous or crystalline carrier.[2] To achieve an intricate blend of drug and polymer, solid dispersions are most often coprocessed using melt extrusion, spray drying or other relevant techniques. Prior to manufacture, it is important to consider the ease by which the polymer–drug blend can be processed, the likelihood of miscibility between the two components and the stability of the amorphous drug during storage and also during dissolution. The ease of processing may be determined from analysis of the polymer–drug thermal properties and through definition of the thermorheological characteristics.[3] Furthermore, the stability of amorphous drug–polymer solid dispersions during long-term storage may be better understood through a fundamental investigation

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Journal of Pharmaceutical Sciences, Vol. 101, 200–213 (2012)

of intramolecular and intermolecular interactions, system viscosity and the thermal/mechanical properties [glass transition temperature (T_g)] of the drug dispersion.[4]

Typical polymeric carriers that have been used to form solid dispersions include water-soluble or water-miscible materials, such as poly(ethylene oxide) (PEO), hydroxypropyl methylcellulose acetate succinate, polyvinylpyrrolidone and low-molecular-weight materials such as sugars.[5] PEO has been used routinely as it is inexpensive, possesses a low melting point and is easily processed using a diverse range of techniques.[6] Traditionally, drug dispersions using PEO have been manufactured by melt, solvent or a combination of both methods. Because of the considerable number of disadvantages associated with these methods (e.g. use of organic solvents, long processing and drying times), they are less attractive to the industry. Hot-melt extrusion (HME) technology by comparison is gaining increasing interest and is being more widely utilised in the pharmaceutical arena for the production of a diverse range of drug containing products including solid dispersions.[7] PEO has been shown to be amenable to the melt extrusion process, although some concerns regarding thermal stability of the polymer have been raised. In a previously published article, the molecular weight of PEO has been shown to significantly decrease following extrusion[8]; although this was dependent upon the molecular weight of PEO, extrusion temperature and the time period, the polymer was maintained at temperatures exceeding the melting point. In a more recent study, the degradation kinetics of PEO has been studied and it has been shown that PEO degrades in a single-step process in the temperature range 330°C–450°C.[9]

In this work, we have selected PEO as a matrix former for melt extrusion because it has a low melting point (62°C–69°C) enabling extrudates to be formed at moderate temperatures without the need of a thermal plasticizer, especially those of low-molecular weights.[10] In addition, PEO has been shown to form miscible blends through interactions with drugs that contain proton donor groups and thus has the potential to form stable solid dispersions.[11] Moreover, previous work by our group and others in this area has shown that semicrystalline polymers [PEO, Pluronic (copolymer of PEO) and ethylene vinyl acetate] have the potential to accommodate drug molecules within amorphous domains.[12–14] Therefore, within this study, we wanted to examine if extrusion significantly affected the amorphous/crystalline ratio within PEO and if this influenced the ability of PEO to accommodate bicalutamide (BL), thus altering the performance of the extruded drug dispersion. BL was selected as a model BCS class II insoluble drug compound. BL is highly lipophilic (log $P_{octanol/water}$ is 2.92), has a very low aqueous solubility (<5 mg/L) and has shown a significant increase in oral bioavailability following formulation as a solid dispersion.

In this study, we have characterised the physicochemical properties of the BL–PEO solid dispersions prepared by HME technology to determine if stable solid dispersions can be produced using this matrix platform. Moreover, we have examined the effects of extrusion on the crystallinity of PEO and determined if extrusion can be used to facilitate the formulation of PEO dispersions by reducing PEO percentage crystallinity. The effects of drug loading on the solid-state properties of BL within the melt extrudates have been characterised using differential scanning calorimetry (DSC), powder X-ray diffractometry (PXRD) and scanning electron microscopy (SEM). *In vitro* dissolution testing of the melt extrudates was performed and compared with that of the physical mixture (PM) and pure BL, and drug–polymer intermolecular interactions were studied using Fourier transform infrared (FTIR) and Raman spectroscopic analyses.

MATERIALS AND METHODS

Materials

Bicalutamide was purchased from Taresh Chemicals Ltd (Banbridge, Co. Down, UK). PEO (molecular weight 100,000 Da, PEO 100,000) and sodium dodecyl sulfate (SDS) were purchased from Sigma–Aldrich Ltd (Poole, Dorset, UK). All other chemicals used were purchased from BDH Laboratory Supplies (Poole, Dorset, UK) and were of analytical grade or equivalent quality.

Methods

Preparation of Hot-Melt Extrudates

Bicalutamide was mixed with PEO at BL–PEO mass ratios of 1:10, 2:10 and 3:10 (w/w) using a mortar and pestle for 2 min; the prepared PMs were extruded at temperature of 100°C at 80, 60 and 40 rpm for 1:10, 2:10 and 3:10 (w/w) ratios, respectively, using a corotating twin-screw extruder (Minilab, Thermo Fisher Scientific, Winsford, Chesire, UK). Melt extrudates were milled and passed through a 355 μm sieve and stored within glass vials in a dessicator over silica gel at 20°C. A suitable quantity of the PM from each drug loading was kept for analysis to compare with corresponding extrudates.

Thermogravimetric Analysis

Thermogravimetric analysis (TGA) was used to examine the thermal stability of BL and PEO. Experiments were conducted using a Thermal Advantage Model Q500 TGA from TA Instruments (Leatherhead, England, UK). Samples were heated at a rate of 10°C/min from 20°C to 400°C and the remaining mass was