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The Use of Binary Polymeric Networks in Stabilizing Polyethylene Oxide Solid Dispersions

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ABSTRACT

The objective of this study was to determine if a high T_g polymer (Eudragit® S100) could be used to stabilize amorphous domains of polyethylene oxide (PEO) and hence improve the stability of binary polymer systems containing celecoxib (CX). We propose a novel method of stabilizing the amorphous PEO solid dispersion through inclusion of a miscible, high T_g polymer, namely, that can form strong inter-polymer interactions. The effects of inter-polymer interactions and miscibility between PEO and Eudragit S100 are considered. Polymer blends were first manufactured via hot-melt extrusion at different PEO/S100 ratios (70/30, 50/50, and 30/70 wt/wt). Differential scanning calorimetry and dynamic mechanical thermal analysis data suggested a good miscibility between PEO and S100 polymer blends, particularly at the 50/50 ratio. To further evaluate the system, CX/PEO/S100 ternary mixtures were extruded. Immediately after hot-melt extrusion, a single T_g that increased with increasing S100 content (anti-plasticization) was observed in all ternary systems. The absence of powder X-ray diffractometry crystalline Bragg's peaks also suggested amorphization of CX. Upon storage (40°C/75% relative humidity), the formulation containing PEO/S100 at a ratio of 50:50 was shown to be most stable. Fourier transform infrared studies confirmed the presence of hydrogen bonding between Eudragit S100 and PEO suggesting this was the principle reason for stabilization of the amorphous CX/PEO solid dispersion system.

Introduction

The use of combinatorial chemistry and high-throughput screening has resulted in a significant number of poorly water soluble drugs within pharmaceutical development pipelines.[1,2] More than 40% of marketed drugs have been estimated as either poorly soluble or water insoluble.[3] It is well accepted that addressing this problem is one of the most significant challenges being faced within the development of oral drug products.[4,5] The slow drug dissolution rate and low drug solubility in the gastrointestinal fluids may result in incomplete and variable bioavailability. An enabling strategy that can be used to overcome this problem is to increase the drug solubility or dissolution rate via the development of solid dispersions.[6] The drug can either be molecularly dispersed, dispersed as an amorphous form or as small crystals in an inert hydrophilic carrier.[7] Often, amorphous drugs have higher solubility than their crystalline counterparts.[8] Although the development of solid dispersions continues to be explored, the commercial success of dosage forms containing amorphous drugs is still limited due to poor physical stability and scale up difficulties.[6] The low physical stability of amorphous drugs and their tendency to re-crystallize rapidly negate their solubility advantage. Polymers used in solid dispersions can stabilize amorphous drugs either by their anti-plasticization effects[9] or strong interactions with drugs.[10-13] Therefore, the rational selection of polymeric excipients is very important in producing stable amorphous solid dispersions.[14,15]

Solid dispersions can generally be prepared using melt or solvent methods. In the solvent method, the drug and carrier are dissolved in a mutual solvent followed by solvent removal. In the melting method, the drug and carrier solid dispersions are prepared by co-melting and cooling. The problems associated with the organic solvents—for example, toxicity, safety hazards, and solvent residuals—make melting the method of choice despite the potential problem of thermal degradation of drugs and carriers. Over the last decade, hot-melt extrusion (HME) has gathered renewed interest, particularly with regard to production of solid dispersions.[16-19]

Polyethylene oxide (PEO) is a semi-crystalline, non-ionic, thermoplastic polymer exhibiting a low melting point, rapid solidification rate, and low toxicity making it suitable for HME.[20] Due to

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their hydrophilic character and ability to form solid dispersions, lower molecular weight PEOs have been widely used as carriers to enhance the solubility and dissolution properties of poorly soluble drugs.[21-23] Melting of PEO followed by solidification on cooling may decrease PEO crystallinity, and hence increase the amorphous fraction within the polymer structure.[24] Molecular dispersions of drugs within semi-crystalline polymers can be formed by dissolution of drug molecules within the amorphous domain of these polymers rather than in the crystalline fraction.[11,25,26] In previous studies, it has been shown that the dissolution of ketoprofen within the amorphous domains of PEO resulted in the formation of a solid dispersion.[23] Additionally, drug-polymer miscibility may result in a decrease of PEO crystallinity thus leading to dissolution of an increased amount of drug. This effect has been extended to other drug compounds in a study by Janssens et al.,[25] wherein the crystallinity of a polymeric carrier has been shown to significantly influence the solubility of itraconazole. However, PEO is highly crystallizable and hence a rapid decrease in its amorphous fraction can occur with time.[26] This decreases the drug solubility and may eventually lead to phase separation and drug re-crystallization (unstable solid dispersion) despite the apparent high solubility or miscibility of drug in the amorphous region of PEO.[21,23] Therefore, stabilizing the amorphous fraction of PEO may result in increased stability of drug-PEO solid dispersions.

The miscibility and interactions within binary PEO-based polymer blends have been studied extensively in polymer sciences.[27-30] PEO can act as a proton acceptor through the oxygen atom of ethylene oxide monomer.[31] It has been reported that PEO can form miscible polymer blends and complexes through formation of c hydrogen bonding interactions with polymers containing proton donor groups.[29,30,32-34] Inhibition of amorphous PEO crystallization can be achieved either by anti-plasticization effects[31] and through formation of strong specific hydrogen bonding within blends.[29,33] Therefore, we hereby propose the use of a miscible polymer-PEO blend as a viable approach to stabilize amorphous regions of PEO and drug solid dispersions.

The aim of this study was to investigate the potential of binary polymeric matrices composed of a semi-crystalline polymer (PEO) and an amorphous polymer (Eudragit® S100), in stabilizing celecoxib (CX) solid dispersions. HME was used to prepare PEO/Eudragit S100 binary polymer blends and ternary CX/PEO/S100 solid dispersion systems. CX, a poorly soluble non-steroidal anti-inflammatory, was used as a model drug in this study. Eudragit S100, an amorphous copolymer based on poly(methacrylic acid-methyl methacrylate), has been previously used as a polymeric matrix in pharmaceutical HME applications.[35-37] Eudragit S100 has a high T_g and contains free carboxyl groups that can act as a proton donor or acceptor.[38]

Materials and Methods

Materials

CX was a kind gift from Hikma Pharmaceuticals (Amman, Jordan); Eudragit S100 (MW = 135,000 g/mol) was donated by Evonik Röhm GmbH (Darmstadt, Germany); and PEO (MW = 100,000 g/mol) (PEO 100,000), sodium chloride, and potassium bromide were purchased from Sigma-Aldrich Chemie GmbH (Poole, Dorset, UK).

Methods

Preparation of Hot-Melt Extrudates

Melt extrudates containing CX at 30% wt/wt were prepared using different ratios of PEO 100,000/Eudragit S100 (100:0, 70:30, 50:50, and 30:70) using a co-rotating twin-screw extruder (Minilab; Thermo Electron Corporation, Staffordshire, UK) at a temperature of 150°C and a screw speed of 100 rpm. In addition, melt extrudates composed of similar ratios of binary polymeric systems of PEO/S100 without CX were prepared under similar extrusion conditions. The melt extrudates were milled using one cryogenic grinding cycle (5 min, 1 Hz) and one milling cycle (2 min, 20 Hz) (CryoMill; Retsch UK Limited, Hope, UK). The particle size of extrudates ranging from 5 to 180 μm was used for all tests.

Thermogravimetric Analysis

The thermal stability of CX, PEO, and Eudragit S100 was studied using a TA instrument Q500 TGA (thermogravimetric analysis; Leatherhead, UK). Ramp tests were performed at a scan speed of 10°C/min over a range from 20°C to 500°C. Nitrogen was used as the purging gas during all TGA experiments.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of the drugs, polymers, and melt extrudates. DSC analyses were conducted using a Perkin-Elmer DSC 4000 (Cambridge, UK) equipped with a refrigerated cooling system (Perkin-Elmer Intracooler-SP). Data analyses were performed using Pyris Manager software (version 10.1). Samples between 5.0 and 10.0 mg were accurately weighed and placed in crimped aluminum pans. The measurements were conducted at a heating rate of 10°C/min. The DSC was calibrated for baseline correction using empty pans, and for temperature and enthalpy using high purity metal indium and zinc. Nitrogen was used as the purge gas at a flow rate of 20 mL/min.

Melting Point Depression Analysis

Miscibility within melt extruded PEO/S100 binary polymer blends was examined using a melting point depression method. The binary mixtures were also prepared using mortar and pestle and compared with melt extruded samples. The reduction in the melting point of the crystalline phase of PEO as a function of composition and inter-polymer interactions was analyzed using the Nishi-Wang equation[39]:

$$T_m - T_{mb} = \frac{-T_m B V_2 \phi_1^2}{\Delta H_2} \quad (1)$$

where T_m and T_{mb} are melting temperatures of pure crystalline polymer and the blend, respectively; the subscripts 1 and 2 have been used to identify amorphous and crystalline polymer, respectively. B is the interaction energy density between blend components; V_2 is the molar volume of the repeating unit of the crystalline polymer; Φ_1 is the volume fraction of the amorphous polymer in the blend; and ΔH_2 is the heat of fusion of the crystalline polymer per mole of the repeating unit.

The melting points of PEO in the PEO/S100 melt extrudates were determined by DSC and fitted to the Nishi-Wang equation.[39] The B-value was estimated by non-linear regression analysis (GraphPad Prism® version 5.04). V_2 (37.2 cm^3/mol) was calculated by summation of the volumes of the structural groups of the repeating unit of PEO (−CH_2-CH_2-O-).[40] The densities of PEO (1.18 g/cm^3) and Eudragit S100 (1.12 g/cm^3) were obtained from the ratios of molecular weights to molar volumes. The volume fraction of Eudragit S100 (Φ_1) was calculated from the weight fractions and densities of the components. Seven experimental data points were used for this fit. The coefficient of determination (R^2) and randomness of the residuals were used to determine the goodness of fit.