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Research paper

Structural modifications of polymethacrylates: Impact on thermal behavior and release characteristics of glassy solid solutions

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ABSTRACT

Polymethacrylates such as Eudragit® polymers are well established as drug delivery matrix. Here, we synthesize several Eudragit E PO (n-butyl-, dimethylaminoethyl-, methyl-methacrylate-terpolymer) analogues via free radical polymerization. These polymers are processed via hot melt extrusion, followed by injection molding and evaluated as carriers to produce immediate release solid solution tablets. Three chemical modifications increased the glass transition temperature of the polymer: (a) substitution of n-butyl by t-butyl groups, (b) reduction of the dimethylaminoethyl methacrylate (DMAEMA) content, and (c) incorporation of a bulky isobornyl repeating unit. These structural modifications revealed the possibility to increase the mechanical stability of the tablets via altering the polymer T_g without influencing the drug release characteristics and glassy solid solution forming properties. The presence of DMAEMA units proved to be crucial with respect to API/polymer interaction (essential in creating glassy solid solutions) and drug release characteristics. Moreover, these chemical modifications accentuate the need for a more rational design of (methacrylate) polymer matrix excipients for drug formulation via hot melt extrusion and injection molding.

1. Introduction

Hot melt extrusion (HME) has attracted increasing attention as novel drug formulation strategy to produce solid solutions with enhanced oral bioavailability of dissolution-limited drugs [1–7]. Moreover, the combination with injection molding (IM) enables the processing of materials with high dimensional precision [8,9]. This technique relies on obtaining a homogeneous system via a substantial energy input, provided by elevated temperature, high shear force, and pressure during HME and IM. The development of glassy solid solutions, that is, homogeneous one-phase systems with the drug molecularly dispersed in the matrix, is challenging in particular, as such formulations are inherently metastable [10–13]. Due to the substantial energy uptake during the HME/IM-process, followed by a fast cooling of the melt, the obtained glassy solid solution is kinetically trapped resulting in a blend far from its thermodynamic equilibrium.

Several methods have been proposed to decrease the rate of recrystallization and, hence, increase the stability of solid solutions. These methods are often based on molecular interactions between the active pharmaceutical ingredient (API) and the polymer. For instance, Eudragit E PO (EudrE; an n-butyl-, dimethylaminoethyl-, methylmethacrylate-terpolymer) was used as antinucleant agent in ibuprofen containing transdermal polydimethylsiloxane patches [14]. Interactions on a molecular level inhibited drug mobility inside the matrix and reduced recrystallization. An antiplasticizing effect by combining two polymers is also proposed as a stabilizing factor by several authors [15–17]. The use of a polymer with a high glass transition temperature (T_g) provides lower molecular mobility of the drug in a polymer/drug system at room temperature, maintaining the drug in its metastable amorphous state. Sufficient miscibility of the drug in the polymer matrix [18] and the absence of clusters are crucial conditions for this approach. Six et al. [15], for instance, combined Eudragit E PO with PVP-VA64 in order to increase the physicochemical drug stability in a hot melt extruded polymer matrix. Although much research has been performed in terms of molecular interactions between API and polymer or the use of polymer combinations, little attention has been given to the molecular structure of the polymer itself.

In this paper, we report the synthesis of several novel polymethacrylate analogues of Eudragit E PO, with the aim to increase the T_g of the polymers, allowing better processing of drugs into

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glassy solid solutions, based on increased mechanical stability, via HME and IM. Ibuprofen (IBP, a non-traditional plasticizer) was selected as model drug since it challenges the polymethacrylates to a higher extent [19–22]. The second API used in this study was celecoxib (CEL). Eudragit E PO (EudrE) was chosen as carrier to produce glassy solid solutions.

2. Experimental section

2.1. Materials

Ibuprofen 25 (IBP; Fig. 1, left), with a melting endotherm at 76 °C and a T_g of −42 °C, was purchased from Abbott (Ludwigshafen, Germany). Celecoxib (CEL; Fig. 1, right), with a melting endotherm of 162 °C and a T_g of 58 °C, was purchased from Utag (Amsterdam, The Netherlands). Eudragit® E PO, a methacrylate terpolymer based on n-butylmethacrylate (n-BMA), dimethylaminoethylmethacrylate (DMAEMA) and methylmethacrylate (MMA) in a 1/2/1.5-ratio, was supplied by Evonik (Darmstadt, Germany).

2.2. Polymer synthesis

The different monomers tert-butylmethacrylate (t-BMA), DMAEMA, MMA, and isobornylmethacrylate (isoBMA; Sigma Aldrich, St-Louis, USA) were purified to remove the inhibitor via filtration over aluminum oxide (Acros Organics, New Jersey, USA) and subsequently degassed via N_2 bubbling. Free radical polymerization of these monomers in varying ratios (Table 1) was carried out in toluene (Biosolve, Valkenswaard, the Netherlands) under a nitrogen atmosphere at 70 °C for 24 h using azoisobutyronitrile (AIBN, Sigma Aldrich, St-Louis, USA) as initiator. The resulting polymethacrylates were subsequently precipitated (three times) from toluene in hexane (Biosolve, Valkenswaard, the Netherlands), dried for 48 h at 40 °C, and vacuum-dried at 55 °C for 48 h.

2.3. Size exclusion chromatography (SEC)

SEC measurements were performed in an Agilent 1260-series equipped with a 1260 ISO-pump, a 1260 Diode Array Detector (DAD), a 1260 Refractive Index Detector (RID), and a PSS Gram30 column in series with a PSS Gram1000 column inside a 1260 Thermostated Column Compartment at 50 °C. The used solvent was DMA containing 50 mM of LiCl (flow rate of 1 mL min^{-1}). The molar masses were calculated against polymethyl methacrylate standards.

2.4. ^1H nuclear magnetic resonance (^1H NMR) spectroscopy

Polymer composition was determined through ^1H NMR spectroscopy on a Varian Mercury 300 NMR Spectrometer (Vernon Hills, Illinois, USA). Samples were dissolved in deuterated methanol. ^1H NMR (300 MHz, CD_3OD) δ = 4.12 (br, $COOC\underline{H_2}CH_2N(CH_3)_2$), 3.64 ($COOC\underline{H_3}$), 2.68 (br, $COOCH_2C\underline{H_2}N(CH_3)_2$), 2.35 (br, $COOCH_2CH_2N(C\underline{H_3})_2$), 2.21–1.75 (br, $C\underline{H_2}$ backbone), 1.45 (br, $COOC(C\underline{H_3})_3$, 1.30–0.8 (br, $C\underline{H_3}$). More apolar samples were dissolved in deuterated chloroform. ^1H NMR (300 MHz, $CDCl_3$) δ = 4.34 (br, $COO\underline{C}HC_9H_{16}$), δ = 4.08 (br, $COO\underline{CH_2}CH_2N(CH_3)_2$), δ = 3.60 ($COO\underline{CH_3}$), δ = 2.59 (br, $COOCH_2\underline{CH_2}N(CH_3)_2$), δ = 2.31 (br, $COOCH_2CH_2N(\underline{CH_3})_2$), 2.11–1.65 (br, $C\underline{H_2}$ backbone), δ = 1.41 (br, $COOC(\underline{CH_3})_3$), 1.30–0.7 (br, $C\underline{H_3}$).

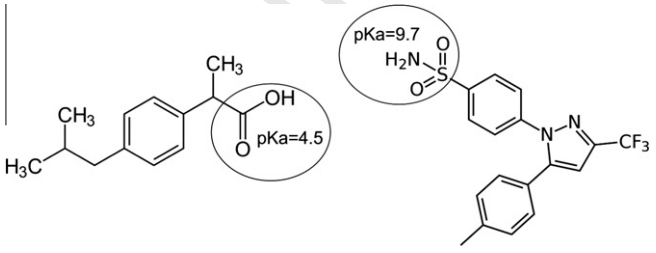

Fig. 1. Chemical structure of ibuprofen (left) and celecoxib (right) with a p*Ka* of 4.5 and 9.7, respectively.

2.5. Thermal analysis

Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was used to investigate the thermal stability of the polymers. The samples were equilibrated at 30 °C and heated (10 °C/min) to 500 °C under an N_2 atmosphere.

The T_g and melting point (T_m) of pure components, physical mixtures (homogenized using mortar and pestle), and injection molded tablets were analyzed by modulated differential scanning calorimetry (MDSC Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2 °C/min. The modulation period and amplitude were set at 1 min and ± 0.318 °C, respectively. Dry nitrogen at a flow rate of 50 ml/min was used to purge the MDSC cell. A heating/cool/heat cycle was run between −70 °C and 120 °C. All results were analyzed using the TA Instruments Universal Analysis 2000 software. The thermoanalytical investigations in terms of interaction were surveyed in the first heating cycle by analyzing the melting enthalpy, Tmelt-max (i.e., inflection point of melting endotherm), and Tmelt-onset (i.e., start of melting endotherm).

2.6. Hot stage microscopy (HSM)

Polarized light microscopy images were recorded on a Leica DM2500P microscope equipped with a 10× objective and a DFC 425 CCD camera. Polymer samples were subjected to controlled heating using a Linkham THHS 600 heating stage.

2.7. X-ray diffraction (XRD)

The crystallinity of the samples was determined via X-ray diffraction using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 kV and current of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

2.8. Fourier-transform infrared (FTIR) spectroscopy

Attenuated total reflectance (ATR) FTIR spectroscopy was used to evaluate the solid-state of the injection molded tablets. Spectra were collected from the pure amorphous components (Supporting information, Fig. S3) (after melting and quenching in liquid nitrogen), the physical mixtures and the injected molded tablets. The ATR-FTIR spectra were collected with a Bruker Vertex 70 FT-IR spectrometer, equipped with a DTGS detector and a PIKE accessory, equipped with a diamond ATR crystal (4 cm^{-1} resolution, 32 scans).

2.9. Production of injection-molded tablets

Physical mixtures, homogenized using mortar and pestle, of drug (IBP, CEL) and polymer (with a drug content varying from 30 to 50 wt.%) were extruded at 100–120 °C using a co-rotating twin-screw extruder at 100 rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karslruhe, Germany). Biconvex tablets (diameter: 10 mm/height: 5 mm) were produced via injection molding (Haake MiniJet System, Thermo Electron). The injection