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Hot-melt co-extrusion for the production of fixed-dose combination products with a controlled release ethylcellulose matrix core

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ABSTRACT

In this study, hot-melt co-extrusion was evaluated as a technique for the production of fixed-dose combination products, using ethylcellulose as a core matrix former to control the release of metoprolol tartrate and a polyethylene oxide-based coat formulation to obtain immediate release of hydrochlorothiazide. By lowering the concentration of the hydrophilic additive polyethylene oxide in the plasticized ethylcellulose matrix or by lowering the drug load, the in vitro metoprolol tartrate release from the core was substantially sustained. The in vitro release of hydrochlorothiazide from the polyethylene oxide/polyethylene glycol coat was completed within 45 min for all formulations. Tensile testing of the core/coat mini-matrices revealed an adequate adhesion between the two layers. Raman mapping showed no migration of active substances. Solid state characterization indicated that the crystalline state of metoprolol tartrate was not affected by thermal processing via hot-melt extrusion, while hydrochlorothiazide was amorphous in the coat. These solid state characteristics were confirmed during the stability study. Considering the bioavailability of metoprolol tartrate after oral administration to dogs, the different co-extruded formulations offered a range of sustained release characteristics. Moreover, high metoprolol tartrate plasma concentrations were reached in dogs allowing the administered dose to be halved.

1. Introduction

The need for novel combination therapies, primarily focusing on fixed-dose combinations (FDC), has been reported by various authors and is seen as a driver for innovative drug development (Woodcock et al., 2011; Zhang et al., 2011). Besides their benefits in life cycle management, FDC products have shown to improve patient adherence by decreasing the number of required pills and thus reducing the complexity of the medication regimen (Pan et al., 2008). Fixed-dose combinations offer benefits to a lot of drugs due to the additive nature of therapeutic effect and the reduced level of side-effects associated with the use of complementary drugs (Hiremath et al., 2011). The application of oral sustained release formulations has improved patient compliance due to a lower dosing frequency and a reduced incidence of adverse side effects. Sustained release formulations have been shown to offer many other advantages over conventional drug products, such as the controlled administration of a therapeutic dose at a desired delivery rate in order to gain more constant plasma concentrations of the drug. Moreover, the production of sustained release multiparticulate dosage forms is advantageous since in vivo the subunits spread into the gastro-intestinal tract as soon as the dosage unit, e.g. capsule or tablet, disintegrates. Since high local drug concentrations are avoided, less inter- and intra-subject variability and a decreased risk of dose dumping can be expected (De Brabander et al., 2003).

While hot-melt extrusion (HME) has proven to be a successful processing technique used in pharmaceutical industry to produce drug products in a continuous way, co-extrusion is quite new in pharmaceutical applications (Dierickx et al., 2012; Quintavalle et al., 2008). Nevertheless co-extrusion of polymers is widely applied in the plastics and packaging industry. The pharmaceutical co-extrusion process consists of the simultaneous hot-melt extrusion of two or more drug loaded formulations creating a multi-layered extrudate. HME as a continuous manufacturing technology has shown some other major advantages over conventional techniques, like improving the bioavailability of poorly water soluble drugs via molecular dispersions (Breitenbach and Magerlein, 2003), without the requirement for processes based on organic

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solvent or agueous spray drying. Moreover via HME matrix formulations can be manufactured using polymers that act as drug depots (Crowley et al., 2007). The added value of co-extrusion is that it allows to modulate the release of each drug independently, to enable simultaneous administration of non-compatible drugs and to produce fixed-dose combinations in a continuous single-step process. By processing the co-extrudate into mini-matrices that can be easily filled into gelatin capsules a multi-particulate formulation is created. A specific challenge during co-extrusion is to establish a core/coat polymer combination fit for purpose considering required release characteristics of the incorporated drugs, similarity in extrusion temperature and appropriate adhesion between the layers. So far, no co-extruded dosage forms for oral use are on the market. In this study a contribution is made to enable the use of co-extrusion in pharmaceutical industry for the production of oral FDC drug products that offer multiple release profiles.

The aim of this study was to evaluate the use of co-extrusion for the manufacturing of a fixed-dose combination drug product for oral application, using a core matrix former that offers a range of controlled release profiles for highly water soluble drugs. For this purpose ethylcellulose, a thermoplastic polymer that has been intensively used as a matrix former in hot-melt extrusion (Follonier et al., 1994; Verhoeven et al., 2009), was combined with polyethylene oxide as a hydrophilic additive and metoprolol tartrate as model drug. The combination of this beta-blocker with the diuretic hydrochlorothiazide is well known (Lewanczuk and Tobe, 2007). It offers the opportunity for a co-extrudate with hydrochlorothiazide incorporated in the coat as immediate release model drug and metoprolol tartrate incorporated in the core as model for a highly water soluble drug. The in vitro performance of the different formulations was assessed. The solid state of the model drugs in the formulations was characterized using modulated differential scanning calorimetry (MDSC), X-ray diffraction (XRD) and Raman spectroscopy. Furthermore, the physical stability of the co-extruded mini-matrices was monitored during 6 months storage at 25 °C/60%RH and 40 °C/75%RH. Finally, the bioavailability of the different formulations was evaluated after oral administration to dogs and compared to a commercially available fixed-dose combination product.

2. Materials and methods

2.1. Materials

Metoprolol tartrate (Esteve Quimica, Barcelona, Spain) and hydrochlorothiazide (Utag, Amsterdam, the Netherlands) were selected as sustained release and immediate release model drugs, respectively. Ethylcellulose (Ethocel® std 10, Colorcon, Dartford Kent, United Kingdom), dibutyl sebacate (Sigma-Aldrich, Bornem, Belgium), polyethylene oxide 1M (MW: 1,000,000 g/mol, Sentry™ Polyox® WSR N12K, Colorcon, Dartford Kent, United Kingdom), polyethylene oxide 100K (MW: 100,000 g/mol, Sentry™ Polyox® WSR N10, Colorcon, Dartford Kent, United Kingdom), polyethylene glycol 4K (MW: 4000 g/mol, Fagron, Waregem, Belgium), polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®, BASF, Ludwigshafen, Germany), poloxamer 188 (Lutrol F68®, BASF, Ludwigshafen, Germany) and an 8:2 blend of polyvinyl acetate and polyvinylpyrrolidone (Kollidon SR®, BASF, Ludwigshafen, Germany) were used as excipients. All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Co-extrusion

Co-extrusion was carried out with two co-rotating, fully intermeshing, Prism Eurolab 16 mm twin screw extruders (ThermoFisher Scientific, Karlsruhe, Germany), both connected to a co-extrusion die (Guill, West Warwick, USA). The co-extrusion die combined both layers into a rod-like co-extrudate consisting of a core and a concentric coat. The five heating segments of both extruders were heated to 80/90/100/100/100 °C from feed opening to die-end. The co-extrusion die was heated to 100 °C. Both formulated premixes were fed separately into the corresponding extruder by a Brabender Flexwall® loss-in-weight powder feeder (Duisburg, Germany) at a feed rate of 200 g/h for the coat and 300 g/h for the core material. A screw speed of 40 rpm for the extruder producing the outer layer and 150 rpm for the extruder producing the inner layer was used. The core of the co-extrudate, with a diameter of 3 mm, was surrounded by a coat with a thickness of 0.5 mm, which led to a total co-extrudate diameter of 4 mm. Four different co-extrudates were manufactured consisting of a specific core and coat formulation, by combining the following components in different concentrations: ethylcellulose (EC), dibutyl sebacate (DBS), polyethylene oxide (PEO), polyethylene glycol (PEG), metoprolol tartrate (MPT) and hydrochlorothiazide (HCT) (Table 1). After cooling down the co-extruded rod to room temperature, the cylindrical co-extrudate was manually cut into mini-matrices of 2 mm length. Those mini-matrices had an average weight of 27.2 mg (SD = 1.8 mg, $n = 20$).

2.2.2. In vitro drug release

In vitro dissolution was performed using USP dissolution apparatus 1 (baskets). The equipment consisted of an Evolution 6300 dissolution system (Distek, New Brunswick, NJ, USA) coupled with an Evolution 4300 automatic dissolution sampler (Distek, New Brunswick, NJ, USA). The temperature of the dissolution medium (900 ml) was maintained at 37 ± 0.5 °C while the rotational speed of the baskets was set at 100 rpm. For the first hour a 0.1 N solution of hydrochloric acid (pH 1) was used as dissolution medium in order to mimic the pH of the stomach. Afterwards the baskets containing the mini-matrices were transferred to vessels filled with phosphate buffer pH 6.8 (USP) as a dissolution medium, to which they were exposed for the next 23 h. Samples (filtered using Distek 45 μm filters) of 5 ml were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min for the determination of hydrochlorothiazide in the first dissolution medium and at 1, 2, 4, 6, 8, 12, 16, 20 and 24 h for the determination of metoprolol tartrate in the second dissolution medium. The inner layer extrudate was analyzed separately to cover for the metoprolol tartrate release during the first hour. Samples were analyzed spectrophotometrically at 316.6 nm and 222 nm by a UV-spectrophotometer, type UV-1800 (Shimadzu, Deurne, Belgium), using an appropriate calibration curve for quantification of hydrochlorothiazide and metoprolol tartrate, respectively. Each experiment was performed in triplicate.

2.2.3. Modulated differential scanning calorimetry

The crystallinity of the drug in the matrices and the thermal behavior of pure compounds, physical mixtures and corresponding extrudates were studied using a differential scanning calorimeter Q2000 V24.8 equipped with a refrigerated cooling system (TA Instruments, Leatherhead, UK). Nitrogen was used as a purge gas through the DSC cell (50 ml/min) and the RCS unit (300 ml/min). Samples (±5 mg) were run in hermetically closed Tzero pans with perforated lid, supplied by TA Instruments, with an underlying heating rate of 2 °C/min. The modulation period and amplitude were set at 60 s and 0.318 °C, respectively (heat-iso method). Mass of sample pan and empty reference pan were taken into account. Temperature and enthalpy calibration was performed with an indium standard, whereas calibration of the heat capacity was performed using a sapphire standard. MDSC data were analyzed using the TA instruments Universal Analysis 2000 V4.7A software. Melting enthalpies were determined in the total heat flow signal.