European Journal of Pharmaceutics and Biopharmaceutics 96 (2015) 125–131

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

Calendering as a direct shaping tool for the continuous production of fixed-dose combination products via co-extrusion

A.-K. Vynckier [a], H. Lin [b], J.A. Zeitler [b], J.-F. Willart [c], E. Bongaers [d], J. Voorspoels [e], J.P. Remon [a], C. Vervaet [a,*]

[a] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium
[b] Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, UK
[c] Unité Matériaux et Transformations, UMR CNRS 8207, Université de Lille1, Lille, France
[d] Bruker microCT, Kontich, Belgium
[e] CONEXUS Pharma, Ghent, Belgium

ARTICLE INFO

Article history:
Received 22 March 2015
Revised 19 July 2015
Accepted in revised form 26 July 2015
Available online 29 July 2015

Keywords:
Calendering
Co-extrusion
Continuous production
Fixed-dose combination product
Sustained release
Immediate release

ABSTRACT

In this study calendering is used as a downstream technique to shape monolithic co-extruded fixed-dose combination products in a continuous way. Co-extrudates with a metoprolol tartrate-loaded sustained-release core and a hydrochlorothiazide-loaded immediate-release coat were produced and immediately shaped into a monolithic drug delivery system via calendering, using chilled rolls with tablet-shaped cavities. *In vitro* metoprolol tartrate release from the ethylcellulose core of the calendered tablets was prolonged in comparison with the sustained release of a multiparticulate dosage form, prepared manually by cutting co-extrudates into mini-matrices. Analysis of the dosage forms using X-ray micro-computed tomography only detected small differences between the pore structure of the core of the calendered tablet and the mini-matrices. Diffusion path length was shown to be the main mechanism behind the release kinetics. Terahertz pulsed imaging visualized that adhesion between the core and coat of the calendered tablet was not complete and a gradient in coat thickness (varying from 200 to 600 μm) was observed. Modulated differential scanning calorimetry and X-ray diffraction indicated that the solid-state properties of both drugs were not affected by the calendering procedure.

1. Introduction

In co-extrusion two or more formulations are simultaneously processed via hot-melt extrusion (HME) through the same die. In addition to the advantages of HME, such as the continuity of the production process, not requiring the use of solvents or water and improving drug bioavailability, this technique offers the opportunity to produce fixed-dose combination (FDC) products with enhanced release characteristics, by making it possible to design multilayered dosage forms that are extruded in the same process step, in order to modulate the drug release from each layer. Although co-extrusion is used to manufacture implants [1] and vaginal rings [2], there are currently no co-extruded dosage forms for oral application on the market. In the literature only a limited number of studies describe co-extrusion of dosage forms for oral drug delivery [3–6]. Recently co-extrusion has been used for the development of multiparticulate fixed-dose combination drug products for oral pharmaceutical application, consisting of a controlled release core matrix and an immediate release coat [7] and to develop sustained and dual drug release formulations for individual dosing [8]. For pharmaceutical applications of co-extrusion, one of the major challenges is the shaping of the final product in a continuous way, as a suitable downstream shaping technique is needed to ensure an efficient manufacturing line. Previously injection-moulding has been used to shape extrudates into solid oral dosage forms in a semi-continuous way [9,10] and even to prepare co-injection moulded matrices [4]. Calendering is a technique that allows in-line shaping of the extruded material in a fully continuous single-step process. Using this technique the freshly-extruded thermoplastic strand is guided through a pair

Abbreviations: HME, hot-melt extrusion; FDC, fixed-dose combination; MPT, metoprolol tartrate; HCT, hydrochlorothiazide; EC, ethylcellulose; PEO, polyethylene oxide; PEG, polyethylene glycol; MDSC, modulated differential scanning calorimetry; XRD, X-ray diffraction; DBS, dibutyl sebacate; MW, molecular weight; USP, United States Pharmacopeia; UV, ultraviolet; *Tg*, glass transition temperature; RCS, refrigerated cooling system; TPI, terahertz pulsed imaging; Micro-CT, micro-computed tomography; BMP, bitmap; ROI, region of interest.

* Corresponding author at: Ghent University, Laboratory of Pharmaceutical Technology, Harelbekestraat 72, 9000 Ghent, Belgium. Tel.: +32 9 264 80 54; fax: +32 9 222 82 36.
E-mail address: Chris.Vervaet@UGent.be (C. Vervaet).

http://dx.doi.org/10.1016/j.ejpb.2015.07.023
0939-6411/

of temperature-controlled rolls containing tablet- or pill-shaped cavities, yielding bands that contain single tablet-shaped cores of the desired shape. Although this technique is already widely established in the plastic and confectionary industry to produce monolithic shapes, only the Meltrex® technology [11] and the continuous extrusion process for the production of sustained release tablets developed by Knoll AG [12] report calendering as a possible shaping tool for pharmaceutical applications.

In this study the use of calendering to continuously shape a multi-layered co-extrudate into a monolithic FDC dosage form was evaluated. In the treatment of cardiovascular disease the FDC of the beta-blocker metoprolol tartrate (MPT) with the diuretic hydrochlorothiazide (HCT) is well established [13]. Therefore co-extrudates consisting of a plasticized ethylcellulose (EC) core, containing MPT and polyethylene oxide (PEO), and a coat of polyethylene oxide (PEO)/polyethylene glycol (PEG) containing HCT were previously developed [14]. After production the cylindrical co-extrudate with concentric coat layer was immediately shaped via calendering, using chilled rolls with tablet-shaped cavities. In this way monolithic dosage forms with a sustained-release core, loaded with MPT as model drug, and an immediate-release coat, loaded with HCT as model drug, were produced and evaluated for *in vitro* drug release, coat thickness and uniformity and pore structure. The impact of the calendering step on the physical state of the drugs in the formulations was characterized using modulated differential scanning calorimetry (MDSC) and X-ray diffraction (XRD).

2. Materials and methods

2.1. Materials

Metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) and hydrochlorothiazide (HCT) (Utag, Amsterdam, the Netherlands) were used as sustained and immediate release model drugs, respectively. As excipients ethylcellulose (Ethocel® std 10, Colorcon, Dartford Kent, United Kingdom), dibutyl sebacate (DBS) (Sigma–Aldrich, Bornem, Belgium), polyethylene oxide (PEO) 1M (MW: 1,000,000 g/mol, Sentry™ Polyox® WSR N12K, Colorcon, Dartford Kent, United Kingdom), PEO 100K (MW: 100,000 g/mol, Sentry™ Polyox® WSR N10, Colorcon, Dartford Kent, United Kingdom) and polyethylene glycol (PEG) 4K (MW: 4000 g/mol, Fagron, Waregem, Belgium) were used. All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Co-extrusion

Co-extrusion was carried out using two co-rotating Prism Eurolab 16 mm twin-screw extruders (ThermoFisher Scientific, Karlsruhe, Germany), connected to a co-extrusion die (Guill, West Warwick, USA). In the calendering set-up the co-extrusion die was adapted to fit the diameter of the co-extrudate with the dimensions of the calender cavities, shaping a cylindrical co-extrudate consisting of a core with a diameter of 4 mm and a concentric coat with a thickness of 2 mm. To produce the multiparticulates, a cylindrical co-extrudate with an inner diameter of 3 mm and an outer diameter of 4 mm was manufactured. The heating zones of both extruders were heated to 80/90/100/100/100/100 °C from feed opening to die-end. The co-extrusion die was heated to 100 °C. Both premixes were fed separately into an extruder by a Brabender Flexwall® loss-in-weight powder feeder (Brabender, 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 and 150 rpm was used for the extruder producing the outer layer and the inner layer, respectively.

2.2.2. Downstream processing

Calendering was performed with a Collin 60 mm calender (Dr. Collin, Ebersberg, Germany), coupled to a compressed air supply and a Coolenergy chiller (Plastima, Breda, The Netherlands), which cooled the calender rolls to a temperature within the range of 4–8 °C. The speed of the calender rolls was set at 1.5 rpm. Immediately after leaving the co-extrusion die the co-extruded strand was guided between a pair of chilled pressurized rolls that contained tablet-shaped cavities, yielding tablets with a diameter of 8 mm and a thickness of 5 mm.

To test the effect of cooling on the MPT release a core extrudate was prepared using the same process parameters as for the core in the co-extrudate. Part of this material was cooled at room temperature, while the remaining part was quench-cooled by dipping the core extrudate in liquid nitrogen immediately after extrusion.

Multiparticulates were obtained by manually cutting a cylindrical co-extrudate with an inner diameter of 3 mm and an outer diameter of 4 mm into mini-matrices of 2 mm length after cooling the co-extruded rod to room temperature.

2.2.3. In vitro drug release

In vitro dissolution was performed using United States Pharmacopeia (USP) dissolution apparatus 1 (baskets) on an Evolution 6300 dissolution system (Distek, New Brunswick, New Jersey, USA), coupled with an Evolution 4300 automatic dissolution sampler (Distek, New Brunswick, New Jersey, USA). The temperature of the dissolution medium (900 ml) was kept at 37 ± 0.5 °C and the rotational speed of the baskets was set to 100 rpm. For the first hour a 0.1 N solution of hydrochloric acid (pH 1) was used as the dissolution medium. Afterwards the baskets containing the mini-matrices or tablets were transferred to vessels filled with phosphate buffer pH 6.8 (USP) as the dissolution medium. 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 HCT concentration in the first dissolution medium and at 1, 2, 4, 6, 8, 12, 16, 20 and 24 h for the determination of MPT concentration in the second dissolution medium. The core layer was analysed separately to cover for the MPT release during the first hour. Samples were analysed spectrophotometrically at 316.6 and 222.0 nm, using a UV-spectrophotometer, type UV-1800 (Shimadzu, Deurne, Belgium) and applying an appropriate calibration curve for quantification of HCT and MPT, respectively. Each experiment was performed in triplicate.

2.2.4. Modulated differential scanning calorimetry

The solubility of HCT in the coat of the tablet was studied by cyclic heating of an oversaturated sample, containing 70% HCT, followed by annealing at a different temperature for each cycle in order to reach the maximum solubility at each temperature. After the annealing step the sample was quenched and heated again to determine the glass transition temperature (*Tg*). These cycles were performed for different annealing temperatures in between the melting point of polymer matrix and drug, and the shift in *Tg* was monitored using a differential scanning calorimeter Q200, equipped with a refrigerated cooling system (RCS) (TA Instruments, Leatherhead, UK). Nitrogen was used as purge gas through the DSC cell (50 ml/min) and the RCS unit (300 ml/min). Samples (±3 mg) were run in an open aluminium pan with an underlying heating rate of 5 °C/min. The modulation period and amplitude were set at 50 s and 0.663 °C, respectively (heat-only method). Temperature and enthalpy calibration was performed with an indium standard at the same scan rate and with the same