Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 312–319
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Influence of formulation and process parameters on the release characteristics of ethylcellulose sustained-release mini-matrices produced by hot-melt extrusion

E. Verhoeven [a], T.R.M. De Beer [b], G. Van den Mooter [c], J.P. Remon [a], C. Vervaet [a,*]

[a] Laboratory of Pharmaceutical Technology, Ghent University, Gent, Belgium
[b] Department of Pharmaceutical Analysis, Ghent University, Gent, Belgium
[c] Laboratory of Pharmacotechnology and Biopharmacy, University of Leuven, Leuven, Belgium

Received 30 August 2007; accepted in revised form 8 October 2007
Available online 15 October 2007

Abstract

Mini-matrices (multiple unit dosage form) with release-sustaining properties were developed by hot-melt extrusion (cylindrical die: 3 mm) using metoprolol tartrate as model drug and ethylcellulose as sustained-release agent. Dibutyl sebacate was selected as plasticizer and its concentration was optimized to 50% (w/w) of the ethylcellulose concentration. Xanthan gum, a hydrophilic polymer, was added to the formulation to increase drug release. Changing the xanthan gum concentration modified the in vitro drug release: increasing xanthan gum concentrations (1%, 2.5%, 5%, 10% and 20%, w/w) yielded a faster drug release. Zero-order drug release was obtained at 5% (w/w) xanthan gum. Using kneading paddles, smooth extrudates were obtained when processed at 60 °C. At least one mixing zone was required to obtain smooth and homogeneous extrudates. The mixing efficacy and drug release were not affected by the number of mixing zones or their position along the extruder barrel. Raman analysis revealed that metoprolol tartrate was homogeneously distributed in the mini-matrices, independent of screw design and processing conditions. Simultaneously changing the powder feed rate (6–25–50 g/min) and screw speed (30–100–200 rpm) did not alter extrudate quality or dissolution properties.

Keywords: Hot-melt extrusion; Sustained-release; Multiple-unit dosage form; Matrix system; Xanthan gum

1. Introduction

Hot-melt extrusion is a technology used in the pharmaceutical industry to produce matrix formulations into which a drug is homogeneously embedded. Its major advantage over conventional techniques for manufacturing sustained-release matrices is the continuity of the production process as the different steps (mixing, melting, homogenizing and shaping) are carried out on a single machine [1–3]. The excellent feasibility of ethylcellulose, a polymer with thermoplastic properties, for hot-stage extrusion has been established in a variety of applications [4–6]. Previous work has shown that hot-melt extrusion is an appropriate technique to develop mini-matrices using ethylcellulose to sustain the release of ibuprofen: the combination of ethylcellulose and a hydrophilic component (hydroxypropyl-methylcellulose [7–9], xanthan gum [7–10]) offered a flexible system to tailor the in vitro as well as in vivo drug release. Due to the specific drug–matrix interaction, the low-melting ibuprofen (melting point 76 °C) was identified as a plasticizer for ethylcellulose [11]. Consequently, the characteristics of ethylcellulose/hydrophilic polymer mini-matrices containing ibuprofen are not predictive of the extrusion and dissolution properties of ethylcellulose mini-matrices containing non-plasticizing drugs. Therefore, ibuprofen was substituted by a drug with a higher melting point (metoprolol

* Corresponding author. Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, 9000 Gent, Belgium. Tel.: +32 9 2648069; fax: +32 9 2228236.
E-mail address: Chris.Vervaet@Ugent.be (C. Vervaet).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.10.007

tartrate, 123 °C) and a conventional plasticizer was added to the formulation.

In the present study sustained-release mini-matrices were developed by hot-melt extrusion of a metoprolol tartrate/ethylcellulose-mixture with the addition of xanthan gum to tailor drug release. The aim was to examine the effect of different plasticizers on the extrusion behaviour and extrudate quality. After optimization of the formulation (type and concentration of plasticizer, xanthan gum concentration) to obtain zero-order drug release, the effect of extrusion process parameters (screw design, powder feed rate and screw speed) on the quality and drug release properties of the mini-matrices was evaluated.

2. Materials and methods

2.1. Materials

Metoprolol tartrate (MPT) (10 μm) (Esteve Quimica, Barcelona, Spain) was selected as model drug. The matrix consisted of ethylcellulose (EC) (Ethocel® Std 10 FP Premium, particle size of 3–15 μm), kindly donated by the Dow Chemical Company (Midland, USA), and a hydrophilic component: xanthan gum (XG) (Xantural® 75, mean particle size of 75 μm) supplied by CP Kelco (Liverpool, UK). Dibutyl sebacate (DBS), diethyl phthalate (DEP), triethyl citrate (TEC) and triacetin (TA) (Sigma–Aldrich, Steinheim, Germany) were tested as potential plasticizers for ethylcellulose. All other chemicals were of analytical grade.

2.2. Preparation of co-evaporates and hot-melt extruded samples

The glass transition temperature (T_g) of EC in EC/plasticizer co-evaporates (containing 0%, 10%, 20% and 30% (w/w) DBS, DEP, TEC or TA), in hot-melt extruded EC/DBS mixtures (ratio: 95/5, 80/20 and 66/33 (w/w)) and in hot-melt extruded MPT/EC/plasticizer (30/50/20, w/w/w) mixtures was determined via differential scanning calorimetry (DSC).

2.2.1. Co-evaporates

Co-evaporates were prepared by dissolving the plasticizer and EC in ethanol. The polymer solution (total solid content: 0.5 g in 150 ml) was transferred into a Teflon flask and a rotavapor (Büchi Rotavapor R-200, Flawil, Switzerland) was used to remove the solvent under reduced pressure at 70 °C. The films were peeled from the perfluoroalkoxy surface of the flask and stored in an oven at 70 °C for 2 days to ensure complete removal of ethanol. Subsequently the films were pulverized in a mortar using liquid nitrogen, further dried and stored at 40 °C before subjecting the samples to thermal analysis.

2.2.2. Hot-melt extruded samples

Hot-melt extruded EC/DBS samples were prepared at a powder feed rate at 6 g/min, screw speed of 30 rpm, using the standard screw configuration and different extrusion temperatures (range: 50–200 °C with 25 °C intervals). Hot-melt extruded MPT/EC/plasticizer mixtures were processed at 65 °C. Additionally, the influence of MPT on the T_g of EC is measured in an extruded sample having an EC/MPT ratio of 33.3/30 (w/w) (i.e. the lowest EC/MPT ratio in the formulations tested thus offering the highest interaction possible).

2.3. Optimization of plasticizer

To select a suitable plasticizer EC was combined with different plasticizers (DBS, DEP, TEC and TA) in a ratio of 2.5/1 (w/w). The MPT content of these formulations was 30% (w/w). The components were blended in a planetary mixer (15 min, 90 rpm) (Kenwood Major Classic, Hampshire, UK) and incubated overnight at room temperature to achieve sufficient interaction between EC and plasticizer. The mixture was passed through the screws of the powder feeder of the extruder and recycled into the powder reservoir to grind the MPT/EC/plasticizer mixture prior to hot-melt extrusion. Hot-melt extrusion was performed using a laboratory-scale intermeshing co-rotating twin-screw extruder (MP19TC-25, APV Baker, Newcastle-under-Lyme, UK) having a length-to-diameter ratio of 25/1. The machine was equipped with a Brabender twin-screw powder feeder, a screw with two mixing sections and a densification zone (the geometry of the screws is illustrated in Fig. 1). The die block (2.6 cm thickness) was fixed to the extruder barrel, and additionally, an axially mounted die plate (1.9 cm thickness) was attached to the die block, with a cylindrical hole of 3 mm diameter for shaping the extrudates. The following extrusion conditions were used: a screw speed of 30 rpm, a powder feed rate of 6 g/min and a temperature of 65 °C for the five heating zones along the barrel. After cooling down to room temperature, the extruded rods ($\varnothing = 3$ mm) were manually cut, using surgical blades, into mini-matrix of 2 mm length. The influence of the plasticizer type on drug release was evaluated via in vitro dissolution testing.

To optimize the extrudate quality and mini-matrices properties, formulations with variable DBS concentrations were processed (EC/DBS ratio: 5/1, 3/1, 2/1 and 1.4/1, w/w). The MPT and XG content were 30% and 10% (w/w), respectively. The mini-matrices were manufactured using the same process as described above, except for the temperature: the initial extrusion temperature was set at 80 °C and was lowered in steps of 10 °C until shark skinning of the extrudate occurred. The surface properties of the extrudates were visually inspected for any defects and evaluated for their suitability to be cut into mini-matrices (deformation due to cutting, smoothness of the cutting surfaces and the edges) using a digital camera (C3030 Olympus) linked to an image analysis system (analySIS®, Soft Imaging System, Münster, Germany) (magnification 9.5×).