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Comparison of metoprolol tartrate multiple-unit lipid matrix systems produced by different technologies

Aleksandar Aleksovski [a,e], Pieter-Jan Van Bockstal [b], Robert Roškar [c], Tamás Sovány [d], Géza Regdon Jr. [d], Thomas De Beer [b], Chris Vervaet [a], Rok Dreu [e,*]

[a] Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[b] Laboratory of Pharmaceutical Process Analytical Technology, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[c] Department of Biopharmacy and Pharmacokinetics, Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia
[d] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Szeged, Eötvös 6, 6720 Szeged, Hungary
[e] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

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ABSTRACT

The aim of this study was to develop, evaluate and compare extended release mini-matrices based on metoprolol tartrate (MPT) and either glyceryl behenate (GB) or glyceryl palmitostearate (GPS). Mini-matrices were produced by three different techniques: hot melt extrusion, compression of melt granulates and prilling. Hot-melt extrusion and compression of granules obtained from melted material proved to be reliable, robust and reproducible techniques with aim of obtaining extended release matrices. Prilling tended to be susceptible to increased melt viscosity. Direct compression was not applicable for mini-matrix production due to poor powder flow. In general MPT release from all matrices was affected by its loading and the size of the units/particles. Processing of GB–MPT mixtures by different techniques did not lead to different drug release rates and patterns, while in case of GPS differently obtained matrices provided diverse MPT release outcomes. Matrices based on GB tended to have higher porosity compared to ones composed of GPS and thus most of the GB-based formulations showed faster drug delivery. FT-IR analysis revealed no interactions between primary components used for matrix production and Raman mapping outlined uniform MPT distribution throughout the units. DSC and X-ray studies revealed significant changes in the crystallinity of glycerides after storage under room conditions (GPS samples) and at increased temperature (GB and GPS samples), which was correlated to the changes seen in drug release rate and pattern after storage. Media composition in general tended to insignificantly affect GB matrices, while in case of GPS matrices increasing the pH and presence of biorelevant compounds induced faster drug release.

1. Introduction

Extended drug release (ER) provides API delivery in a continuous fashion and subsequently benefits from constant plasma concentration levels and reduced dosing frequency. Formulating product as multiple unit drug delivery system (MDDS) gives advantages such as broad gastro-intestinal distribution, insignificant "all-or-nothing release effect", possibility of combining different API's and different release kinetics in one system and improved swallowing. Combining ER and MDDS platforms is a viable approach towards designing solid dosage forms with added value. (Aulton, 2007; Abdul et al., 2010; Aleksovski et al., 2015a; Aleksovski et al., 2015b; Qui et al., 2009; Ranade et al., 2004; Wen and Park, 2010). Mini-tablets (MT; tablets with d ≤ 3 mm) are emerging as a promising basis for designing MDDS offering modified drug delivery and also improved swallowing and flexible dosing regarding age/weight/health condition. MT are produced on standard tableting presses equipped with multi-tip punches and multi-bore dies. Production of MT has special requirements with regard to very good powder flow properties, limited particle size and process/press assembly control in terms of obtaining acceptable product and avoiding tooling damage. (Aleksovski et al., 2015b; Klingmann et al., 2013; Klingmann et al., 2015; Spomer et al., 2012; Tomson et al., 2009)) Hot-melt extrusion (HME, combined with uniform extrudate cutting in post processing stage) and prilling are emerging as continuous, robust, simple, less demanding (with regard to flow properties and compressibility) and solvent free techniques for producing of extended release mini-matrices and thus become reliable alternatives to mini-tablet production. HME is a process where powdered material is introduced into a heated barrel equipped with one or two rotating screws which provide melting, mixing, kneading and forcing the material to an end-plate die, which determines the shape of the extruded material. Prilling is a technique where a liquid-molten system is forced through a pre-heated narrow nozzle, creating a liquid jet which is broken up into

* Corresponding author.
E-mail address: rok.dreu@ffa.uni-lj.si (R. Dreu).

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droplets by vibrational energy or periodic nozzle valve movement. These droplets are subsequently cooled down by falling through a tempered cooling tower and gathered as spheres with narrow size distribution. Main drawback of HME and prilling is the requirement of higher processing temperatures, which are in general not suitable for thermo-labile compounds (Ceowley et al., 2007; Lang et al., 2014; Maniruzzaman et al., 2012; Pivette et al., 2012; Repka et al., 2007; Repka et al., 2012; Sequier et al., 2014; Vervaeck et al., 2013). Pharmaceutically approved lipids are excipients suitable for production of solid oral dosage forms by melting technologies, due to their biocompatibility, low-toxicity, compatibility with many active compounds, moderate melting temperatures and low cost. High hydrophobicity of some of the lipids is making them suitable for design of extended release systems. However, the main drawback of pharmaceutical lipids is their physical instability, which is correlated with changes of their crystallinity during processing and storage (Reitz and Kleinebudde, 2007a; Rosiaux et al., 2014; Vithani et al., 2013).

The aim of this study was to develop multiple-unit extended-release systems of a highly soluble model drug (metoprolol tartrate, MPT) based on mixed glycerides (glyceryl behenate (GB) and glyceryl palmitostearate (GPS)) as matrix formers and using different production technologies for lipid matrices: prilling (prills — PR), hot-melt extrusion (mini-extrudates — EX), direct compression (directly compressed mini-tablets — DCMT) and compression of melt granulated material (mini-tablets compressed from granules — GMT). All technologies used for production of the matrices are schematically shown in Fig. 1. Experiments were conducted in order to determine how formulation factors (composition, unit/granule size), production technology, dissolution media and storage conditions affected the drug release and the dosage form characteristics in general. Matrices were evaluated by differential scanning calorimetry (DSC), X-ray diffraction, attenuated total reflection Fourier-transform IR spectroscopy (ATR FT-IR), Raman microscopic mapping and micro-computed tomography (μCT) to characterize solid state, drug-lipid interactions, drug distribution and porosity, and to correlate these characteristics with the drug release properties and final product outcome.

2. Materials and methods

2.1. Materials

Metoprolol tartarate (MPT) was purchased from Esteve Quimica (Barcelona, Spain). Glyceryl behenate (GB, Compritol® 888 ATO) and glyceryl palmitostearate (GPS, Precirol® ATO 5) were obtained from Gattefosse (St. Priest, France). Magnesium stearate (Mg St) was purchased from ABC Chemicals (Wauthier-Braine, Belgium), colloidal silica dioxide (Aerosil® 200 Pharma) from Evonik (Hanau-Wolfgang, Germany), pancreatin from Sigma Aldrich (USA), sodium taurocholate from Prodotti Chimici e Alimentari (Basaluzzo, Italy) and egg phosphatidylcholine (LIPOID E PC S) from Lipoid (Steinhausen, Switzerland). All other reagents were of analytical grade. The quantitative composition of the formulations processed via the four different techniques is given in Table 1.

2.2. Methods

2.2.1. Hot-melt extrusion

Hot-melt extrusion was carried on co-rotating, fully intermeshing, Prism Eurolab 16 mm twin screw extruder (Thermo Fisher Scientific, Karlsruhe, Germany), equipped with a 3 mm cylindrical die. The extruder segments (from powder entrance to die) were pre-heated to temperatures (°C) of 77/75/75/75/72/66 and 57/57/57/55/53/50 for mixtures containing glyceryl behenate and glycerol palmitostearate, respectively. Powder mixtures were fed into the extruder by a Brabender Flexwall® loss-in-weight powder feeder (Duisburg, Germany) at a feed rate of 300 g/h and were further transported, mixed and kneaded along the extruder by screw co-rotation at a speed of 40 rpm. Cylindrically shaped extrudates with a diameter of 3 mm were obtained and were further manually cut into mini-extrudates (EX) of ≈3 mm or 5 mm in length.

2.2.2. Mini-tablet preparation

Powders aimed to be directly compressed were thoroughly mixed for 15 min (with exception of Mg St) in a Paul Schatz principle mixer

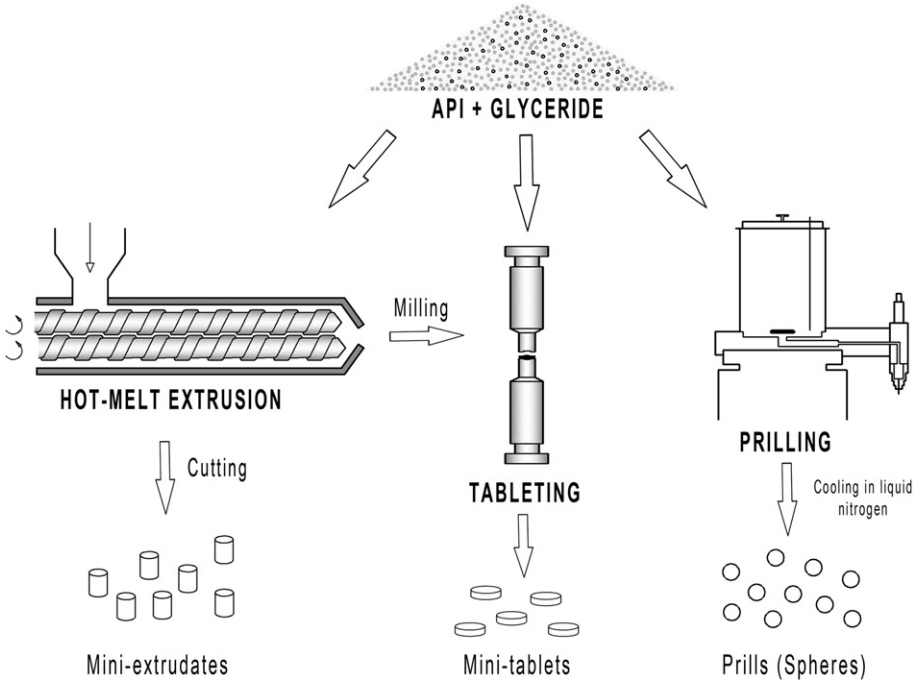

Fig. 1. Schematic presentation of techniques used for production of glyceride matrices.