European Journal of Pharmaceutics and Biopharmaceutics 120 (2017) 126–132

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Formation of mannitol core microparticles for sustained release with lipid coating in a mini fluid bed system

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ARTICLE INFO

Keywords:
Methyl blue
Aspartame
Mannitol
Hard fat
Glyceryl stearate
Fluid bed coater
Microparticles
Sustained release
Lipids
Coating

ABSTRACT

The goal of this study was to prepare sustained release microparticles for methyl blue and aspartame as sparingly and freely water-soluble model drugs by lipid film coating in a Mini-Glatt fluid bed, and to assess the effect of coating load of two of lipids, hard fat and glyceryl stearate, on the release rates. 30 g drug-loaded mannitol carrier microparticles with average diameter of 500 or 300 µm were coated with 5 g, 10 g, 20 g and 30 g lipids, respectively. The model drugs were completely released *in vitro* through pores which mainly resulted from dissolution of the polyol core beads. The release of methyl blue from microparticles based on 500 µm carrier beads extended up to 25 days, while aspartame release from microparticles formed from 300 µm carrier beads was extended to 7 days. Although glyceryl stearate exhibits higher wettability, burst and release rates were similar for the two lipid materials. Polymorphic transformation of the hart fat was observed upon release. The lipid-coated microparticles produced with 500 µm carrier beads showed slightly lower burst release compared to the microparticles produced with 300 µm carrier beads as they carried relatively thicker lipid layer based on an equivalent lipid to mannitol ratio. Aspartame microparticles showed a much faster release than methyl blue due to the higher water-solubility of aspartame.

1. Introduction

Many biopharmaceutical drugs require frequent parenteral administration to guarantee a therapeutic level due to their short half-live *in vivo,* which leads poor patient compliance. Consequently, sustained release formulations are of high interest [1–3]. For the parenteral sustained release of biopharmaceuticals, the most commonly used carrier materials are polylactide (PLA) and poly(lactide-co-glycolide) (PLGA) since they can provide sustained release for a range of times from days up to months and are well established for small molecule and peptide drugs [4,5]. However, lactic and glycolic acid result upon PLGA degradation, leading to an increase in osmotic pressure and a significant pH drop within the micro-environment, which can result in a loss of activity with biopharmaceuticals [6,7]. Additionally, harsh microparticle manufacturing conditions like high temperature, high shear forces and organic solvent, may result in detrimental effects on the structure and the activity of protein drugs [6,7]. Triglycerides, which are Generally Recognized As Safe (GRAS), biocompatible, biodegradable and not inherently immunogenic [8], have been successfully used to control sustained release of proteins in form of implants, nanoparticles, as well as microparticles, which are the most suitable and preferred system till today [9–17].

Fluid bed coating for microparticle preparation has been widely used in pharmaceutical industry to control oral drug release [18,19]. The most widespread coating materials, cellulose and polyacryl acid derivates are hardly appropriate for parenteral drug delivery systems as they are not biodegradable or available at adequate quality. An interesting alternative is to utilize lipid coated microparticles as parenteral controlled delivery systems. Lipid film coatings provide several noteworthy advantages: (i) they are plastically deformable and form homogenous films without cracks during the coating process; (ii) the amount of excipient required is generally appropriate; (iii) usually only one lipid is required simplifying the formulation and hence the registration of the drug product with regulatory authorities; and finally (iv) they are relatively inexpensive [8,20,21].

Typically, hot-melt and organic solvent spray coating are used for lipid coating [21,22]. Both high temperature and organic solvent may be critical for use with sensitive biopharmaceutical drugs. In general, also the amount of coating that can be deposited on the surface of the smaller cores compared to oral dosage forms is limited [21,23]. Furthermore, sustained release microparticles are normally suspended in a suitable vehicle and injected by using a conventional syringe with a 18 or 20 G gauge needle, which requires free flowing microparticle powders of less than 250 µm in diameter, ideally less than 125 µm [24].

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http://dx.doi.org/10.1016/j.ejpb.2017.09.003
Received 24 January 2017; Received in revised form 18 April 2017; Accepted 7 September 2017
Available online 08 September 2017
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Lipid coating of such small microparticles is challenging due to the high tendency to agglomerate upon coating with the tacky lipid [25]. Additionally, a small scale process is required for development due to the high costs of protein drugs. Consequently, a new small scale lipid coating process with the potential for manufacturing of sustained release microparticles for biopharmaceutical drugs is highly desirable.

The main objective of this work was to investigate the possibility of using organic solvent fluid bed spray coating to form the lipid-coated microparticles without agglomeration at modest temperature for sustained drug release. Successful loading of polyol and sugar spheres with protein drugs has been demonstrated before and this renders a mini fluid bed system very interesting for loading and lipid coating of starting beads [26]. Mannitol beads were selected as the carrier core providing high water solubility and biocompatibility. Drug release from the lipid-coated microparticles may occur through pores in the coat, which form upon dissolution of the polyol core beads. The target release profile was expected to reach a few weeks. Two kinds of lipids with different lipophilicity and wettability, hard fat (HF) and glyceryl stearate (GS) were tested. Furthermore, the effect of the core bead size on processing and release was studied. Two model compounds, methyl blue (MB) and aspartame (ASP) with different solubility were loaded to investigate the effect of drug type on the release. The resulting process parameters could be subsequently transferred to protein loaded core beads.

2. Materials and methods

2.1. Materials

Pearlitol® 500DC-Mannitol and Pearlitol® 300DC-Mannitol (MAN) were kindly provided by Roquette Corporate, Darmstadt, Germany. Methyl blue (MB) and the reagents used for MAN determination were purchased from Sigma-Aldrich, Munich, Germany. Aspartame (ASP) was kindly provided by Salutas Pharma GmbH, Barleben, Germany. Witepsol® E85 (hydrogenated coco-glycerides, HF) and Imwitor® 900 (glyceryl stearate with a monoester content of 40–55%, GS) were kindly provided by Sasol GmbH, Hamburg, Germany. Isopropanol (99.7%) was supplied by the reagent center of the University of Munich, Germany.

2.2. Methods

2.2.1. Preparation of drug-loaded starting cores

0.45 g MB or 1.50 g ASP was dissolved in 45 mL or 150 mL deionized water to get the model drug solution (1.0%, W/W). 30 g MAN microparticles were loaded with the model drug solution in the Mini-Glatt fluid bed (Wurster insert, Glatt GmbH, Binzen, Germany). The detailed operation conditions were as follows: T_{inlet}:40 °C; $p_{process}$:1.0 bar; $p_{atomizing\ air}$:1.0 bar; spray rate:1.0 mL/min; spray nozzle diameter:0.3 mm. After coating, the microparticles were dried for additional 15 min at 40 °C in the fluid bed.

2.2.2. Preparation of lipid-coated microparticles

Lipid was dissolved at 2% w/v in hot isopropanol (70 °C). 30 g drug-loaded microparticles were coated with the lipid solution in the Mini-Glatt fluid bed (Wurster insert) at: T_{inlet}: 40 °C for GS and 30 °C for HF; $p_{process}$: 0.7 bar; $p_{atomizing\ air}$: 0.5 bar; spray rate: 7.0 mL/min; spray nozzle diameter: 0.5 mm. After coating, the microparticles were dried for additional time of 15 min at the same conditions.

2.2.3. Determination of drug loading of lipid-coated microparticles

200 mg of lipid-coated microparticles were dispersed in 50 ml of hot deionized water (70 °C). Approximate 3 mL slurry was filtered through a 0.2 µm filter to remove the lipid after it was cooled down to room temperature. Filtrate was analyzed for drug content present at a 588 nm for MB and 258 nm for ASP using an Agilent 8453 UV–Vis spectrophotometer (Agilent, Waldbronn, Germany). Each experiment was performed in triplicate.

2.2.4. Microparticle morphology

The morphology of microparticles was analyzed with a light optical microscope (Olympus BX50 F4, Olympus, Tokyo, Japan) equipped with a digital camera (HVC 20, Hitachi, Maidenhead, UK). Additionally, the microparticles were visualized by scanning electron microscopy (SEM) using a Jeol JSM-6500 F instrument (Jeol Ltd., Tokyo, Japan) with Inca Software (Oxford instruments, Oxfordshire, UK).

2.2.5. Mannitol determination

The MAN release was determined by a colorimetric method [27]. 10 µL release medium was diluted with 990 µL deionized water, mixed with 1 mL potassium periodate (0.015 mol/L in 0.12 mol/L HCl solution), incubated for 10 min at room temperature, and reacted with 2 mL 0.1% L-rhamnose and 4 mL Nash reagent. The mixture was placed in a water bath at 53 °C for 15 min. After cooling to room temperature the MAN content was quantified at 412 nm using an Agilent 8453 UV–Vis spectrophotometer. Each experiment was performed in triplicate.

2.2.6. In vitro release

In vitro release was studied in phosphate buffer saline (PBS, pH = 7.4) in 37 °C water bath with constant shaking at 30 rpm (Julabo SW21, Julabo GmbH, Seelbach, Germany). Approximate 1.0 g of drug-loaded microparticles suspended in 3 mL buffer were transferred into a dialysis bag with 12 kDa cutoff which was sealed and immersed into a 50 mL disposable plastic tube with 37 mL of PBS release medium containing 0.01% NaN_3. At designated time points, 1 mL release medium was withdrawn and replaced with the same amount of fresh release medium. The model drug content in the release medium was quantified as described above. Each experiment was performed in triplicate.

2.2.7. Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) analysis was performed using a Mettler DSC 821e (Mettler Toledo, Giessen, Germany). DSC scans were recorded at a heating and cooling rate of 5 °C/min. The samples were weighted in 40 µL aluminium pans and cooled down from 25 °C up to 0 °C, kept for 2 mins at 0 °C, heated up to 110 °C, kept at 110 °C for 3 mins, cooled again down to 0 °C, kept for 2 mins at 0 °C and reheated up again to 110 °C, kept at 110 °C for 3 min, cooled down to 25 °C.

3. Results and discussion

3.1. Methyl blue release from HF-coated microparticles

The lipid-coated microparticles prepared in this study consisted of a MAN starter core coated with a model compound and subsequently a lipid layer for sustained release of different thickness. To study the influence of the amount of lipid coat on the release of MB, 30 g drug-loaded MAN microparticles were coated with 5 g, 10 g, 20 g or 30 g HF. The model drug MB migrated into the carrier beads exhibited a homogeneous loading, potentially reducing the contact with organic solvent during the lipid coating process, which is very important for biopharmaceutical drugs. The drug loaded microparticles subsequently coated with lipid maintained their original shape with only minimal agglomeration. MB diffusion into the retarding lipid coat was not observed, which may be beneficial to keep potential burst release low.

Fig. 1a shows the MB release profiles from microparticles coated with different amounts of HF. The microparticles coated with 5 g HF show a high burst release of around 50% followed by subsequent MB release over 14 days. More HF lowers the burst and the release rate. The release period is prolonged to 25 days by coating with 30 g HF. The deceleration of release is also found the MAN core material (Fig. 1b). In

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