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Research paper

Solid lipid extrusion of sustained release dosage forms

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Abstract

The applicability of the solid lipid extrusion process as preparations method for sustained release dosage forms was investigated in this study. Two lipids with similar melting ranges but of different composition, glyceryl palmitostearate (Precirol ATO 5®) and glyceryl trimyristate (Dynasan 114®), and mixtures of each lipid with 50% or 75% theophylline were extruded at temperatures below their melting ranges. Extrudates were analyzed using differential scanning calorimetry, scanning electron microscopy, porosity measurements and in vitro drug dissolution studies. The possibility of processing lipids by softening instead of complete melting and without subsequent formation of low-melting, metastable polymorphs could be demonstrated. Extrudates based on formulations of glyceryl palmitostearate/theophylline (50:50) and glyceryl trimyristate/theophylline (50:50) showed sustained release properties.

An influence of extrusion conditions on the matrix structure was shown for extrudates based on a mixture of glyceryl trimyristate and theophylline (50:50). Glyceryl trimyristate tended to solidify in porous structures after melting. Exceeding a material temperature of 50.5 °C led to porous extrudate matrices with a faster drug release. The production of novel, non porous sustained release matrices was possible at a material temperature of 49.5 °C. Extrudates based on glyceryl trimyristate/theophylline (50:50) only slight changes in melting enthalpy and stable drug release profiles.

Keywords: Solid lipid extrusion; Lipid matrix; Sustained release; Acylglycerides; DSC

1. Introduction

Solid lipids are advantageous pharmaceutical excipients being low cost, natural and biodegradable products with physiological, non-toxic properties. They are commonly used as lipid matrices with a variety of different functions, that lead to: (1) sustained release of highly soluble drugs, (2) enhancement of bioavailability of poorly soluble drugs, especially with solid dispersions [1], (3) taste masking of bitter tasting drugs [2], (4) floating of dosage forms [3,4] and (5) a decrease of the effect of drugs having gastric irritant properties [5]. Many studies have reported the use of lipids for sustained release matrices [6–12].

The major disadvantage when using lipids in pharmaceutical formulations is the instability of their physical properties during storage. Lipid aging may lead for example to an increase of melting ranges, an increase of melting enthalpy, formation of pores in the surface [3], changes in rheological properties and a decrease in tensile strength [13].

Aging of lipids going along with changes of physical properties is of great significance for sustained release dosage forms, as they contain large doses. A number of studies have demonstrated that lipid matrices may exhibit a change in drug release properties after storage [3,11,13–16]. Moricout et al. [17] reported changes in the melting properties of Gelucires and correlated them to changes in dissolution of incorporated drugs. San Vicente et al. [18] stored different lipid matrices with salbutamol sulphate at room temperature for one year and noticed a decrease in drug release for Gelucire 35/10 and 48/09.

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Sutananta et al. [19] observed an increase in theophylline release for Gelucire 55/18 and 50/13 matrices during storage. Capsules filled with Gelucire 50/02 and 62/05 were stored at different temperatures up to 50 °C. An increase in dissolution of the highly soluble drug was observed after 3 months [20]. In vitro 50% Ketoprofen release from mixtures of Gelucire 50/13 and 50/02 decreased after 28 days storage at 30 °C [21].

The most common preparation methods for lipids are: (1) liquid filling of hard gelatine capsules, (2) hot melt extrusion [12,22], (3) spray-congealing using ultrasound [23], (4) production of tablets by melting or compression and (5) melt granulation.

In most cases the preparation process involves melting of the lipids followed by some method of solidification. On the other hand, it was demonstrated that lipids could be extruded at temperatures below their melting ranges [24,25]. It is common knowledge that the generation of different lipid polymorphic forms is strongly dependent on the presence of nucleating agents [26]. It is also suggested that mechanical treatment, e.g. grinding, accelerates the crystallization of tricaprin, as could be demonstrated by X-ray diffraction [27].

Therefore, the purpose of this work was to obtain physically stable sustained release matrices, prepared by solid lipid extrusion. It represents a production process at preferably low temperatures, in which lipids were treated clearly below their melting ranges. A thermomechanical treatment by moderate pressure and temperature exposure results in plastic mouldability of the lipid mass under conditions of conserving nucleating agents.

In order to prove the applicability of the solid lipid extrusion process at low temperatures, two commercially available powdered lipids were extruded below their melting ranges. The aim of the study was to compare two lipids with different composition, but similar melting range: glyceryl palmitostearate and glyceryl trimyristate were chosen for this purpose. The two lipids possess different constituents and structures which allow the generation of broad information about the dependency between the observed results and the lipid composition. The effect of solid lipid extrusion on the solid state of the lipids was analyzed. The pure lipids and their mixtures with theophylline were used to determine the effect of extrusion conditions on the physical properties of the lipid matrices. Drug release and melting enthalpy of the obtained extrudates were measured in order to analyze their stability during storage influenced by time, structure and storage conditions.

2. Materials and methods

2.1. Materials

The following materials were used as received, theophylline anhydrous powder from BASF AG, Ludwigshafen, Germany, glyceryl palmitostearate powder (Precirol ATO 5®) from Gattefossé GmbH, Weil am Rhein, Germany, and glyceryl trimyristate powder (Dynasan 114®) from Sasol GmbH, Witten, Germany. Physical properties of the used materials are given in Table 1.

2.2. Differential scanning calorimetry (DSC)

Thermal characteristics of the powdered lipids and extrudates were studied with a Mettler DSC 821e (Mettler Toledo, Giessen, Germany) at defined storage times. DSC scans were recorded at a heating rate of 5 °C/min. Samples with an initial weight of approximately 5 mg were heated from 20 to 100 °C or from 20 to 300 °C.

2.3. Evaluation of extrudates

The extrudates were visually analyzed for any apparent defects: shark-skinning, cracks, hairlines, curling or deformation by melting. The absence of defects gave information about the process conditions of good extrudability.

2.4. Extrusion

Powdered lipids of different chemical compositions or mixtures of these lipids with different amounts of theophylline were fed from a gravimetric dosing device into the barrel of a twin-screw extruder (Mikro 27GL-28D, Leistritz, Nürnberg, Germany) with a constant feed rate of 40 g/min. The mass was extruded through a die plate with 23 dies of 1 mm diameter and 2.5 mm length. They were extruded at a constant screw speed of 30 rpm. Material temperature was measured next to the die plate just before the extrusion step. In experiments carried out for Section 3.1 powdered lipids and lipid/drug mixtures were extruded successively at different cylinder temperatures. At each temperature level the different cylinder segments were tempered at the same cylinder temperature. Process parameters were measured and are elucidated in Fig. 1. In experiments carried out for Section 3.3 extrusion parameters were adjusted as listed in Table 2.

Glyceryl trimyristate was processed above its melting range in one experiment (Section 3.3). For this purpose the extruder was loaded with the lipid/drug mass, the screw

Table 1
Physical properties of the extruded materials (manufacturer's specifications)

	Dynasan 114®	Precirol ATO 5®	Theophylline anhydrous
Melting point	55–58 °C	53–57 °C	272 °C
Particle size	95% <125 μm 2% >250 μm	30–40 μm	~110 μm
HLB	2	2	