Delivery of Drugs from Laminar Co-Extrudates Manufactured by a Solvent-Free Process at Room Temperature

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ABSTRACT: This work aims to design and manufacture laminar co-extrudates as a new dosage form for the delivery of drugs. Co-extrudates made of lipid-based materials with a laminar shape were manufactured at room temperature in the absence of solvents and assessed over time for their mechanical properties (bending strength, deformation, stiffness, and elasticity), density, porosity, thermal behavior and main mechanism of drug release. The study has shown that the extrusion force at steady state increased with the extrusion rate and with the number of layers. The bending strength and stiffness of extrudates increased over time. Laminar co-extrudates with higher number of layers presented a decreasing dissolution efficiency of $38.3 \pm 0.6\%$, $23.0 \pm 0.2\%$, and $12.3 \pm 0.2\%$, for mono-, bi-, and trilayer, respectively. After 90 days, the density, the deformation, and elasticity decreased: trilayer extrudates were the denser and the ones to present the lowest ability to deform and the highest elasticity, whereas monolayer extrudates were the less dense presenting the highest ability to deform. Changes were more evident in the first days after manufacture leading to stabilization over time. Laminar (co-)extrudates have been confirmed as an innovative dosage form for tailored delivery of drugs made without solvents at room temperature. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3501–3510, 2014

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INTRODUCTION

Co-extrusion involves the separate preparation of two or more mixtures of excipients with drug(s), which are conveyed separately into a die where they come together as a co-extrudate with a predefined number of layers and shape (e.g., laminar, tubular, rod, or cylindrical)[1] depending on the extruder features, particularly on the extrusion die.[2,3] In the last decade, the technology of co-extrusion has been applied in several areas, namely in the ceramics, food, metallurgy, and polymer industries, and, also, in the manufacture of medical devices and pharmaceutical products.[4]

In drug delivery, multilayered extrudates can be used for modulating the release of drugs either by producing a multimodal release[5] or by allowing a higher fine-tuning ability on controlling the release of a drug[6] by imposing different release kinetics to each layer, depending on the composition of individual layers.[7] Furthermore, co-extrusion can be considered for the combined delivery of drugs in the same dosage form (even if incompatible), which can be present in different layers.[1] Traditionally, extrusion and co-extrusion of materials is accomplished by either using a solvent (e.g., wet masses[8]) or in the absence of solvents (e.g., hot[1] or cold melt extrusion[3]).

Lipid-based materials such as fatty acids, mixtures of fatty acids with polyethylene glycols, triglycerides, and glyceride bases (e.g., glyceryl palmitostearate, glyceryl trimyristate, or glyceryl dibehenate) have been proven as suitable excipients for extrusion at room temperature,[9–12] which can be considered a green technology. However, the use of these materials represents an important challenge to the formulator, as their composition, particularly their chemical and physical variability and complexity, can greatly influence the properties of the extrudates due to their ability to crystallize or suffer polymorphic changes.[13] Therefore, a deep knowledge of the properties of these lipid-based starting materials is essential for better predicting and understanding the properties of the extrudates manufactured and their stability (i.e., aging over storage[13]). For instance, a higher fraction of lipid-based materials with a heterogeneous composition can lead to more relevant changes in the physical stability of the extrudates over time with a negative impact on their performance, particularly on the release rate of the drug.[13]

This study aimed at the manufacture of laminar extrudates and co-extrudates (with one, two, or three layers) in the absence of solvents and at room temperature with the potential for the delivery of a model drug by the oral or topical routes of administration, and to assess the stability of their properties over storage.

MATERIALS

Glyceryl dibehenate (Compritol™ 888 ATO; Gattefossé, Saint-Priest, Lyon, France), hard fat (Witocan™ 42/44; Sasol, Hamburg, Germany), a mixture of polyethylene glycol with glycerides (Gelucire™ 33/01; Gattefossé, Saint-Priest, Lyon, France), a mixture of polydimethylsiloxane with silicon dioxide (Simethicone™ Q7-2243 LVA; Dow Corning, Seneffe, Belgium), and lactose (SpheroLac™; Meggle Pharma, Wasserburg

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Table 1. Density of Raw Materials and Composition of Individual Laminar Extrudate Layers

Materials	Density (g/cm^3)	Layer (%)	
Polyethylene glycol glyceride	0.944 ± 0.001	4	4
Hard fat	0.999 ± 0.001	33	33
Glyceryl dibehenate	1.021 ± 0.000	33	33
Polydimethylsiloxane–silicon dioxide mixture	0.956 ± 0.000	20	20
Lactose	1.543 ± 0.001	–	10
Coumarin	1.380 ± 0.001	10	–

am Inn, Germany) were used as starting materials for the manufacture of the extrudates and co-extrudates. Coumarin particles (0–90 μm) milled from coarse coumarin (Sigma–Aldrich, Munich, Germany) in an analytical grinder (A10 Yellow Line; IKA, Königswinter, Germany) were sieved (Vibratory Sieve Shaker, AS 200 digit; Retsch GmbH, Haan, Germany) before considering as a model drug.

METHODS

Manufacture of Extrudates and Co-Extrudates

For each extrudate or co-extrudate layer, the materials (Table 1) were mixed in a planetary mixer (Kenwood, Hampshire, UK) for 15 min and placed in the respective extrusion chamber, according to the type and position of the layers of each sample (Table 2). The manufacture of laminar extrudates and co-extrudates was carried out using a ram extruder (Lurga, Bobadela, Portugal) with a fixed design of chambers and dies (Fig. 1), at defined extrusion rates, which correspond to specific mass flow rates (Table 2). The ram extruder was fixed to a universal testing machine (LR 50K, Lloyds Instruments, West Sussex, UK) fit with a load cell allowing recording of the force applied and displacement of the ram. The extrudates and co-extrudates obtained were cut into squares (40 × 40 mm^2) immediately after exiting the extrusion die and stored in a desiccator (23°C/30% relative humidity, RH) prior to characterization.

Characterization of Extrudates

Extrusion Profiles and Force at Steady State

For each extrudate and co-extrudate, the extrusion force at steady state (F_{ss}) was calculated as the mean of the force values obtained between 100 and 130 mm of the displacement of the ram.

Morphological Evaluation

Extrudates and co-extrudates were visually inspected to detect any surface defect due to poor process control or formulation inadequacy and observed (surface and cross section) by scanning electron microscopy (SEM) using a DSM 940 scanning electron microscope (Carl Zeiss, Jena, Germany). Previously, the samples were coated with gold in a sputter coater (E 5100; Bio-Rad, Munich, Germany).

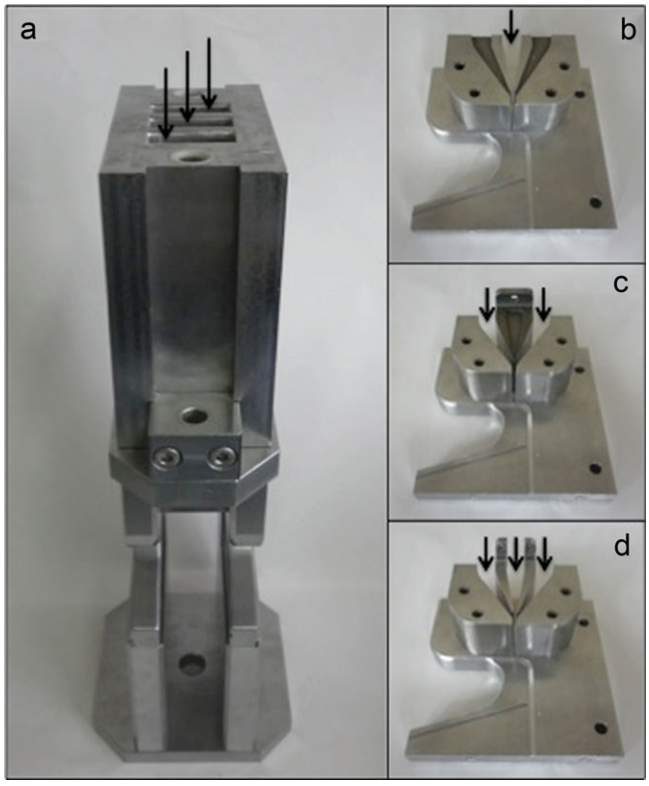

Figure 1. (a) Extruder and extrusion dies used in the manufacture of extrudates with (b) one layer, (c) two layers, and (d) three layers.

Thickness of Extrudates

The thickness of cut extrudates was measured using a caliper ($n = 10$) at five predefined and distinct points to assess thickness uniformity.

Density and Porosity of Extrudates

The densities of both starting materials and extrudates (at 1, 3, 8, 15, 30, 60, and 90 days after manufacture) were determined by helium pycnometry (AccuPyc 1330; Micromeritics, Norcross, GA, USA) at 23 ± 2°C ($n = 3$). The expected densities of the extrudates, calculated from the densities of the starting materials weighted for their fractions in the formulations, allowed the calculation of the porosities of the extrudates.[14]

Table 2. Composition of the Laminar Extrudates and Co-Extrudates, Extrusion Rates, and Mass Flow Rates

Extrudate	Number of Layers	Type and Order of Layers	Extrusion Rate (mm/min)	Mass Flow Rate (g/min)
I	1	A	100	61 ± 3
II	1	A	300	174 ± 8
III	1	A	500	299 ± 7
IV	2	A + B	300	349 ± 12
V	3	B + A + B	300	448 ± 11