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Quality improvement of melt extruded laminar systems using mixture design

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ABSTRACT

This study investigates the application of melt extrusion for the development of an oral retard formulation with a precise drug release over time. Since adjusting the formulation appears to be of the utmost importance in achieving the desired drug release patterns, different formulations of laminar extrudates were prepared according to the principles of Experimental Design, using a design for mixtures to assess the influence of formulation composition on the *in vitro* drug release from the extrudates after 1 h and after 8 h. The effect of each component on the two response variables was also studied.

Ternary mixtures of theophylline (model drug), monohydrate lactose and microcrystalline wax (as thermoplastic binder) were extruded in a lab scale vertical ram extruder in absence of solvents at a temperature below the melting point of the binder (so that the crystalline state of the drug could be maintained), through a rectangular die to obtain suitable laminar systems.

Thanks to the desirability approach and a reliability study for ensuring the quality of the formulation, a very restricted optimal zone was defined within the experimental domain. Among the mixture components, the variation of microcrystalline wax content played the most significant role in overall influence on the *in vitro* drug release. The formulation theophylline:lactose:wax, 57:14:29 (by weight), selected based on the desirability zone, was subsequently used for *in vivo* studies. The plasma profile, obtained after oral administration of the laminar extruded system in hard gelatine capsules, revealed the typical trend of an oral retard formulation.

The application of the mixture experimental design associated to a desirability function permitted to optimize the extruded system and to determine the composition space that ensures final product quality.

1. Introduction

Melt extrusion is a relatively recent solvent-free pharmaceutical processing technique applicable to both immediate release and sustained release dosage forms (Breitenbach, 2002; Douroumis, 2012). During the process, the mixture of thermoplastic binder, excipients and APIs are fed into the heated barrel, and extruded through the die attached at the end of the barrel (McGinity et al., 2007). The physical shape of the final product depends on the geometrical design of the die, obtaining e.g. cylinders, pipes, laminates, helices or films. In literature, both hollow and solid cylinders are the most studied shape of extrudates (Mehuys et al., 2004; Michalk et al., 2008), even though several authors have investigated the opportunity to change the shape (and hence the specific surface area) to tailor the attributes of the final system (e.g. drug release). Conversely laminar extrudates, being the most "obvious" shape and easiest to produce have been poorly investigated. To our best knowledge, rectangular dies are largely employed in the production of films but the only example of laminar extrudates reported in the literature is that of Pinto and coworkers (Oliveira et al., 2013). These authors have recently successfully produced such kind of extrudates using lipid-based excipients as carriers in absence of solvents and at ambient temperature. Yet, laminar extrudates have a great potential due to their high versatility being suitable for oral, buccal or topical administration. Furthermore, extrudates can be easily cut in different sizes allowing the convenient adjustment of the drug dose. Finally, this shape is suitable as a final dosage form, as well as to be filled in hard gelatine capsules (Müllers et al., 2013).

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The aim of the present investigation is to produce, in a lab scale vertical ram extruder, thin laminar extrudates (7.5 × 0.5 × 5 mm) with a targeted *in vitro* release of theophylline (model drug), ranging from 35% after 1 h and 75% after 8 h (Table 1), with the final purpose of producing a retard formulation for oral administration. The choice of thin laminar extrudates was also based on previous studies dealing with the relationship among surface area and drug release in 3 different helical shapes of extrudates (having 2, 3 and 4 blades) (Hasa et al., 2011), and previous experiences with bi-layered cylindrical co-extrudate (Quintavalle et al., 2008). In this case, in order to ensure a successful formulation development, the design of experiments (DoE) principles were adopted to explore the composition space of the formulation. DoE is one of the most important area in drug development. Design and analysis of experiments are considered useful tools for really optimizing the process performance, identifying interactions among process variables, and reducing the process variation that can affect the quality of the output. DoE methodology can be applied in process development and improvement: screening DoE may be used for process parameter screening and statistical DoE for process parameter range determination.

In particular, in this study to better ensure the desired product quality, the influence of formulation factors was analyzed by developing quantitative regression models. Being the examined factors ingredients of a formulation, their amount cannot be varied independently, since their proportions sum up to 100%. Thus an experimental design for mixtures (Voinovich et al., 2009) was employed. This strategy has been previously applied to the preparation of hot melt extruded systems by Rambali et al. (2003) and recently by Djuris et al. (2013). To go into more details, several ternary mixtures (composed of theophylline, lactose and wax) according to an experimental design for mixtures were prepared and subjected to melt extrusion, and the influence of formulation composition on the *in vitro* drug release from such extrudates (after 1 h, experimental response Y_1 and after 8 h, Y_2) was estimated. The experimental design for mixtures was hence associated to a desirability function, to optimize the extruded system and to ensure confidence in the attainment of the required level of quality in the final product. Inside the composition zone defined by desirability function one formulation was selected for *in vivo* studies and hence administered orally in hard gelatine capsules to healthy volunteers. Finally, the *in vivo* performance was studied by performing the pharmacokinetic analysis.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (theo), with a particle mean diameter (±S.D.) of 56 (±18) μm, was obtained from Polichimica s.r.l. (Bologna, Italy). Monohydrate lactose Flowlac®100-Meggle (lac) (having the following particle size distribution: <32 μm ⩽ 10%, <100 μm ⩽ 20–45%, <200 μm ⩽ 80%) was a gift from Faravelli (Milan, Italy). Microcrystalline wax (or paraffinic wax, complex blends of mineral hydrocarbon waxes marketed as Paracera P, wax), with a particle mean diameter (±S.D.) of 204 (±95) μm and a melting range of 58–62 °C, was kindly donated by Paramelt (Heerhugowaard, Netherlands). Solvents of HPLC grade were purchased from Carlo Erba (Milan, Italy).

Table 1
Design of the mixture study for the drug release optimization.

Associated variable	Factors: formulation components	Lower limit (%)	Upper limit (%)
x_1	Theophylline	55	65
x_2	Monohydrate lactose	5	15
x_3	Microcrystalline wax	28	32
	Responses	Target values	
y_1	Drug release after 1 h	35%	
y_2	Drug release after 8 h	75%	

2.2. Preparation of laminar extrudates

The extrudates were prepared using a vertical lab scale ram extruder (Thalassia®, Trieste, Italy) described into details in a previous work (Grassi et al., 2003). Briefly, the movement of the stainless steel ram in this extruder is promoted by an oleodynamic cylinder driven by an electric pump (max pressure 150 bar). The cylindrical nickel plated brass barrel has a capacity of 66 cm^3 and an internal diameter of 25 mm. The die attached at the end of the barrel can be changed on demand: in this case a rectangular die (with a flat entry, 0.5 mm × 5 mm cross section) was used. The barrel, acting as a powder reservoir, can be thermo-stated with an electrically heated jacket (max temp. ~ 120 °C). In this case, based on previous experiences with analogous mixtures (Hasa et al., 2011), a temperature of 50 °C was chosen.

Prior to extrusion, the powdered materials (ternary mixtures of theo, lac and wax in different proportions according to Table 2) were mixed in 2.81 high shear mixer (Rotolab, Zanchetta®, Lucca, Italy) for 10 min at 120 rpm. Then, batches of 50 g of each mixture were packed to a constant volume into the barrel, by applying hand pressure, and equilibrated for 1 h at 50 °C. Then, the mass was extruded through the rectangular die using a constant pressure. The laminar extrudates were collected and, after cooling at ambient temperature, were sliced up manually by use of a hot cutter in unities of length (7.5 mm) suitable to have a drug content for dissolution studies in sink conditions.

At the end of the extrusion procedure, the samples were subjected to X-ray Powder diffraction analysis in comparison to pure compounds and physical mixtures prepared in the same weight ratios to check the drug solid state in the samples. These data (not shown) attested that the drug still retains its crystalline state after extrusion, probably thanks to the high content of drug in the laminar extrudates and to the low extrusion temperature, below

Table 2
Design point coordinates in the constrained region inside the factor space given by three blend components, along with experimental results (two replications for experiments 1–13).

Design points	Formulation factor (%)			Experimental response (%)	
	x_1	x_2	x_3	y_1	y_2
1	55.0	13.0	32.0	23.0, 25.0	67.0, 70.0
2	65.0	7.0	28.0	31.0, 33.0	73.0, 78.0
3	55.0	15.0	30.0	27.0, 29.0	74.0, 69.0
4	57.0	15.0	28.0	35.0, 38.0	81.0, 83.0
5	65.0	5.0	30.0	24.0, 21.0	64.0, 67.0
6	63.0	5.0	32.0	20.0, 17.0	72.0, 68.0
7	55.0	14.0	31.0	23.0, 26.0	69.0, 70.0
8	59.0	9.0	32.0	21.0, 17.0	71.0, 70.0
9	61.0	11.0	28.0	34.0, 36.0	84.0, 80.0
10	65.0	6.0	29.0	27.0, 30.0	71.0, 73.0
11	56.0	15.0	29.0	32.0, 37.0	76.0, 73.0
12	64.0	5.0	31.0	21.0, 22.0	68.0, 70.0
13	60.0	10.0	30.0	26.0, 24.0	78.0, 77.0
14[a]	57.5	11.5	31.0	26.0	70.0
15[a]	62.5	8.5	29.0	30.0	73.0
16[a]	57.5	12.5	30.0	26.0	71.0
17[a]	58.5	12.5	29.0	35.0	75.0
18[a]	62.5	7.5	30.0	25.0	71.0
19[a]	61.5	7.5	31.0	23.0	74.0

[a] Checkpoints.