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Production of enteric capsules by means of hot-melt extrusion

Els Mehuys, Jean-Paul Remon, Chris Vervaet*

Laboratory of Pharmaceutical Technology, Ghent University, Harelbekestraat 72, 9000 Gent, Belgium

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Abstract

The aim of this study was to develop an alternative technique for enteric coating consisting of the hot-melt extrusion of coating polymers. An enteric coating polymer (PVAP or HPMC AS), premixed with a plasticizer, was extruded into hollow cylinders. The hollow pipes were filled with a model drug and both open ends of the cylinders were closed, yielding hot-melt extruded enteric capsules. Main advantages of this new technology are the continuity of the process and its application for the formulation of moisture sensitive active ingredients. The enteric capsules showed excellent gastro-resistance, since no drug release was observed after 2 h 0.1N HCl. The influence of wall thickness (0.15, 0.3, 0.5, 0.8, and 1.0 mm) of the capsules on drug release was investigated. Enteric capsules with a wall thickness of 1.0 mm were subjected to a pH gradient dissolution method, simulating passage through the gastro-intestinal tract, in order to evaluate their suitability for ileal or colonic drug targeting. Storing the capsules for 1 month at high relative humidity (RH) (60 and 75% RH) revealed that the HPMC AS capsules were superior to the PVAP capsules. It can be concluded that hot-melt extruded capsules seem suitable as an alternative for enteric coating.

Keywords: Hot-melt extrusion; Enteric coating; Capsules; PVAP; HPMC AS

1. Introduction

During recent years, pharmaceutical coating technology has undergone several fundamental changes. The original sugar-coating technique has been largely replaced by film-coating processes using aqueous or organic solvents. From the point of view of environmental pollution, safety and cost, aqueous-coating systems are preferred. The application of a film coating on a pharmaceutical dosage form comprises several delicate steps. An equilibrium must be established such that the coating material adheres and coalesces properly upon contact with the surface of the substrate, yet it also must dry rapidly so that core penetration of solvent and dissolved coating material is minimized and agglomeration of core material is prevented. To create the necessary environment for such a process to occur, specialised coating equipment, and optimal processing conditions are mandatory. However, the current coating techniques are characterised by several critical process variables such as spray rate of the coating solution, temperature, pressure and volume of the drying air, and equipment dimensions. These critical parameters can cause a non-uniformity of the applied coating layer and up-scaling problems. Moreover, aqueous-coating systems are not applicable for moisture sensitive active ingredients (Mehta, 1996).

To overcome the limitations of aqueous coating and to reduce process time, Obara et al. (1999) developed a dry-coating method. This dry-coating technology involves spraying of the enteric polymer powder (HPMC AS) directly on the dosage form, followed by a subsequent curing and heating step. Pearnchob and Bodmeier (2003) developed a dry-coating method with ethylcellulose to achieve extended drug release. A powder mixture (ethylcellulose plus talc) and a mixture of liquid materials (plasticizer plus binder) were sprayed separately into the coating chamber of a fluidized bed coater, whereafter the pellets were oven-cured (60–80 °C, 2–24 h). Another innovative coating method is the Phoqus Process® consisting of the creation of an electric field, which transfers positively charged powder to earthed tablets, fol-

* Corresponding author. Tel.: +32 9 2648069; fax: +32 9 2228236.
E-mail address: chris.vervaet@ugent.be (C. Vervaet).

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lowed by a curing step to fixate the coating powder onto the tablets (Holroyd, 2004). These alternative coating techniques largely reduced the process time, however they require a heating step making them unsuitable for heat sensitive active agents. Furthermore, the dry-coating technology (Obara et al., 1999; Pearnchob and Bodmeier, 2003) is not completely water free since a small amount of water is still necessary to achieve film formation.

The objective of this study was the development of an alternative technique for enteric coating consisting of the hot-melt extrusion of polymers currently used in coating. The basic idea was to extrude hollow cylinders consisting of an enteric coating polymer, filling these hollow pipes with a model drug and finally closing both open ends of the cylinders, resulting in hot-melt extruded enteric capsules. Main advantages of this new technology are the continuity of the process and its application for the formulation of moisture sensitive active ingredients (such as biomaterials). Two enteric coating polymers were selected based on their low glass transition temperature (T_g), making them suitable for hot-melt extrusion: polyvinyl acetate phthalate ($T_g \sim 78\,^{\circ}C$, Product Information Sheet Colorcon), and hydroxypropylmethylcellulose acetate succinate ($T_g \sim 120\,^{\circ}C$, Product Information Sheet Shin-Etsu).

2. Materials and methods

2.1. Materials

Polyvinyl acetate phthalate (PVAP) was a kind gift of Colorcon (Dartford, UK). Hydroxypropylmethylcellulose acetate succinate (HPMC AS) (Aqoat® AS-LG) was donated by Shin-Etsu (Tokyo, Japan). Triethyl citrate, triacetin, and dioctyl phthalate were purchased from Sigma–Aldrich (Steinheim, Germany). Hydralazine (Federa, Brussels, Belgium) was selected as a model drug.

2.2. Methods

2.2.1. Differential scanning calorimetry

The glass transition temperature (T_g) of each plasticizer–polymer mixture was determined by means of modulated DSC (DSC 2920, TA instruments, Gent, Belgium). The samples (5–10 mg in a hermetically closed Al-pan) were heated from 0 to 100 °C at a rate of 2 °C/min with an amplitude of 0.5 °C every 60 s.

2.2.2. Hot-melt extrusion

Prior to hot-melt extrusion, the plasticizer was mixed with the polymer in a Kenwood planetary mixer. The extrusions were performed on a MP 19 TC 25 laboratory scale co-rotating twin-screw extruder of APV Baker (Newcastle-under-Lyme, UK). The machine was equipped with a control panel, a heated barrel containing the two screws, and a twin-screw powder feeder. An annular die (Fig. 1A) was used to extrude hollow cylinders with varying wall thickness (0.15, 0.3, 0.5, 0.8, and 1.0 mm). For the production of the hollow PVAP-cylinders, a mixture of PVAP and plasticizer was extruded at the following extrusion conditions: a screw speed of 25 rpm and a powder feed rate of 0.5 kg/h. A temperature profile of 125–120–115–110–90 °C from the powder feeder to the die was installed. For the HPMC AS-cylinders, a mixture of HPMC AS and plasticizer was extruded at a screw speed of 10 rpm and a powder feed rate of 0.3 kg/h. A temperature profile of 120–120–115–110–107 °C from the powder feeder to the die was installed. After extrusion, the cylinders were left at room temperature for cooling and were cut into pieces

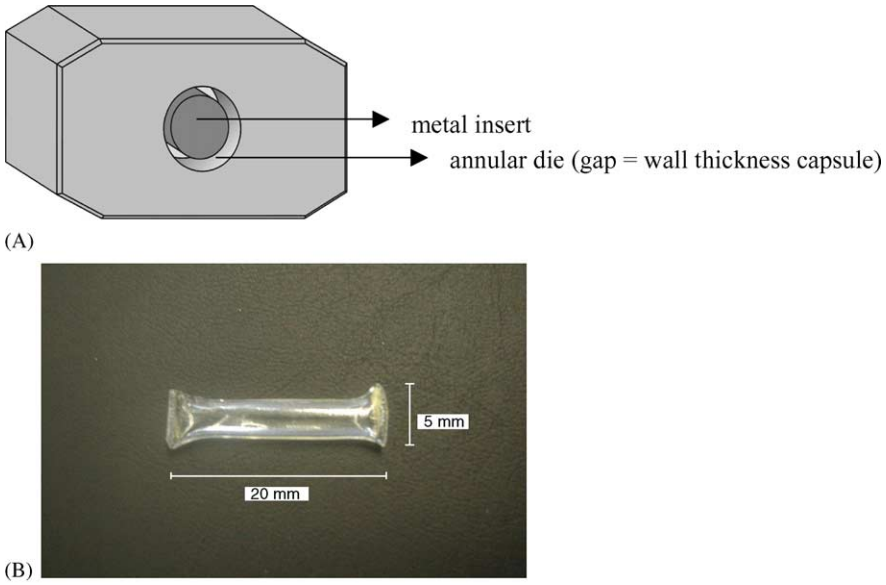

Fig. 1. (A) Schematic drawing of the die used for the extrusion of the capsules and (B) a hot-melt extruded enteric capsule.