European Journal of Pharmaceutics and Biopharmaceutics 98 (2016) 108–121

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research Paper

A novel floating controlled release drug delivery system prepared by hot-melt extrusion

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ARTICLE INFO

Article history:
Received 10 June 2015
Revised 19 October 2015
Accepted in revised form 23 November 2015
Available online 28 November 2015

Keywords:
Hot-melt extrusion
Foamed extrudate
Floating drug delivery system
Controlled release
Eudragit® RSPO
Chemical imaging
Theophylline

ABSTRACT

Floating dosage forms are an important formulation strategy for drugs with a narrow absorption window and low intestinal solubility, and for localized gastric treatment. Novel floating pellets were prepared using the hot-melt extrusion (HME) technology. Uniformly foamed strands were created by liquid injection pumping and screw configuration modification. The ammonio methacrylate copolymer (Eudragit® RSPO) foaming structure was formed by a liquid–vapor phase transition inside the strand upon die exiting resulting from the sudden decrease in external pressure, vaporizing the liquid ethanol and vacating the extruded material. This generated uniform vacuous regions in the extrudate. The pellets' internal structure was investigated using scanning electron microscopy (SEM). The formulation constituents' and processing parameters' effects on the drug release profiles, floating force, and the pellets' micromeritic properties were evaluated by design of experiments: all formulations showed zero lag time and excellent floating strength, indicating immediate-floating pellet formation. The pellets' drug release profiles were controlled by multiple independent variables at different time points (⩽24 h). Drug loading significantly affected drug release within the first hour, the hydroxypropyl methylcellulose (HPMC) content thereafter. Understanding the variables' effects on the formulations allows for the tailoring of this delivery system to obtain various drug release profiles.

1. Introduction

Solid oral controlled-release dosage forms are the most preferred and reliable dosage forms because of their inherent advantages, such as the reduction of side effects, unassisted administration, improvement of patient compliance, treatment cost reduction, and their flexible drug delivery system design. However, biological variations are challenging factors in controlling the dosage form. Among these, individual variations in the gastrointestinal tract-transition times, which can vary from minutes to hours [1], are most likely the primary source of these fluctuations.

The drugs most susceptible to these fluctuations are those with either a narrow absorption window in the upper part of the gastrointestinal tract [2], those that are locally active in the stomach, unstable in the intestinal or colonic environment, or those with a low solubility in a relatively high pH environment [3]. Such drugs need to reside in the stomach for an extended period to gradually deliver the appropriate amounts of the active pharmaceutical ingredient (API) to the absorption site, to promote the desired effect(s) in the stomach region itself, or to be dissolved completely before entering an environment where further dissolution is necessary. A substantial increase in the stomach residence time of the dosage form is possibly the single most significant strategy when attempting to overcome the above-mentioned drawbacks of conventional dosage forms. Gastro-retentive drug delivery systems (DDS) offer several advantages over the conventional dosage forms, such as a continuous, controlled drug supply to the absorption sites, reduced drug plasma concentration fluctuations, and improved bioavailability [4]. Numerous approaches can prolong the retention time of DDS in the stomach [2,5] including (a) floating DDS, which have a relatively low density and float atop

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http://dx.doi.org/10.1016/j.ejpb.2015.11.015
0939-6411/

the existing gastric fluid, (b) a muco-adhesive system that can attach itself to the gastric epithelium to avoid gastric emptying events, (c) swelling DDS, which have been shown to efficiently absorb the gastric fluid and become larger than the pyloric sphincter, thereby preventing the physical forcing of the dosage form through the pyloric orifice, and (d) high-density DDS that sink to the lower part of the stomach and remain there because of the combination of the dosage form's density and its location relative to the pyloric sphincter. Among these, floating DDS are considered the most favorable as they do not interfere with the physiological activity of the gastro-intestinal tract, nor are they likely to be removed because of a temporary elevation of the dosage form. It has been previously reported that the floating dosage forms significantly prolong the gastro-retention time [6–9] and also improve bioavailability [10,11]. Therefore, floating DDS are suitable dosage forms for controlled-release oral dosage forms [12].

Floating DDS can be further sub-classified as either monolithic or multi-unit DDS. Though most of the marketed gastro-retentive drug products are monolithic, multi-unit systems are more advantageous than their counterparts [13]. The monolithic dosage forms are unreliable and lack reproducibility when attempting to extend the gastric residence time because of their "all-or-nothing" presence with regard to the gastric emptying process. In contrast, multi-unit systems can reduce the intersubject absorption variability and lower the probability of dose-dumping [12]. Additionally, the small size of floating units has been speculated to be superior in extending the residence time in the stomach [14]. This would certainly minimize the risk of treatment failure and enhance the safety of the dosage form. Moreover, multi-unit dosage forms not only enhance formulation flexibility, but also allow for a tailored drug release profile and the incorporation of various APIs into a single dosage form.

Hot-melt extrusion (HME) has recently emerged as a novel processing technology in the development of molecular dispersions in polymer and lipid carriers for the preparation of controlled, modified, extended, and targeted drug delivery [15–18]. This processing approach may be an excellent alternative to other more conventional techniques, such as roll spinning and spray drying [19]. Additionally, HME has significant potential as a continuous process, the value of which has been recognized globally in the pharmaceutical industry [20]. The processing flexibility of an HME with various functions and customization potential enables it to be used innovatively and for special or particular purposes.

In this study, floating pellets were prepared by HME in conjunction with liquid–vapor phase transitions and polymer expansion at elevated temperatures. Ammonio methacrylate copolymer (Eudragit® RSPO), stearic acid, and hydroxypropyl methylcellulose (HPMC) K15M were used as an insoluble matrix former, a processing aid, and to control the drug release from the matrix, respectively. The pellets' physicochemical properties, such as their dissolution profiles, buoyancy strength, specific surface area, polymorphism of the API, and drug distribution within the matrix were determined. Furthermore, the strand cross cut was imaged by using SEM. Design of experiments (DoE) was used to elucidate the effects of the formulation constituents and critical processing parameters on the physicochemical properties.

2. Materials and Methods

2.1. Materials

Anhydrous theophylline (THEO) and stearic acid were purchased from Acros Organic (Thermo Fisher Scientific, NJ, USA). Ethyl cellulose N7, polyethylene oxide (Polyox WSR 301), and hyproxypropyl methylcellulose (HPMC K15M) were kindly provided by Colorcon, Inc. (Harleysville, PA, USA). Ammonio methacrylate copolymer type B (Eudragit® RSPO, Eudragit® RLPO) was gifted by Evonik Corporation (Parsippany, NJ, USA). Polyvinyl acetate/polyvinyl pyrrolidone (Kollidon® SR) was generously supplied by BASF Corporation (Florham Park, NJ, USA). Hydroxypropyl cellulose (HPC MF) was gifted by Ashland, Inc. (Lexington, KY, USA). All other reagents used in the study were of analytical grade and were purchased from Fisher Scientific (Pittsburgh, PA, USA).

2.2. Extrusion processing

The system used for preparing the foamed strands is illustrated in Fig. 1. The main module is a twin screw extruder (Process 11™, Thermo Fisher Scientific, Odessa, TX, USA). The die was equipped with a 1.5 mm circular insert. The peristaltic pump (IPC, Ismatec IDEX Corp., Glattbrugg, Switzerland), chiller, feeder, and conveyor belt were assembled as a synchronized and continuous system. The screw speed, feeding rate, barrel temperature profile, die pressure, die temperature, and torque were monitored by the control unit.

Initially, all materials were sieved (USP #35 mesh) to remove potential aggregates in the material. For each formulation, 100 g of the physical mixture was weighed and geometrically diluted until a homogenized mixture was obtained.

A modified screw configuration (Fig. 2) was used for the experiment. The liquid injection port was set at zone 3. The zone temperature on the barrel from the hopper to the die was set to 10, 30, 30, 30, 50, 80, 100, and 110 °C for zone 1 to zone 8, respectively. The die temperature, screw speed, feeding rate, and the liquid injection rate were investigated in the ranges as shown in Table 1.

Prior to processing, the system was allowed to heat-soak to attain the thermal equilibrium. To ensure that the extruder had reached a steady state prior to collecting samples, the first 30 g of the extrudate was discarded. The conveyor speed was adjusted to synchronize with the extruder's throughput to obtain uniformly cylindrical extrudates. The strands were subsequently manually cut to 1.5–2.0 mm long cylinders and preserved in amber glass bottles at ambient temperature. The schematic diagram (Fig. 3) represents the overall process of the floating pellet formation.

2.3. Preformulation

Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) were used to confirm the compatibility of the API and the excipients as well as their thermal stability during extrusion. The pure components, their binary mixtures (1:1), and complete physical mixtures were subjected to TGA (Pyris 1 Perkin Elmer, Waltham, MA, USA). Samples weighing 5–10 mg were heated from 25 °C to 200 °C at a ramp rate of 10 °C/min in a platinum pan under an inert nitrogen atmosphere at a flow rate of 20 mL/min. The samples were held at 200 °C for 5 min.

DSC (Diamond Perkin Elmer, Waltham MA, USA) was used to confirm the TGA results. Samples weighing 4–5 mg were placed in hermetically sealed aluminum pans and placed under an inert nitrogen atmosphere at a flow rate of 20 mL/min. The heating cycles were 25–200 °C at a ramp rate of 10 °C/min; the temperature was maintained at 200 °C for 5 min, and finally the samples were cooled to room temperature at the same rate. The thermograms were analyzed for unanticipated thermal events.

2.4. Design of experiments

DoE was used to address factors that have major effects on the characteristics of the floating pellets and was based on the Plackett–Burman model, which is particularly useful when assessing the main effects for further investigation [21]. The most significant