European Journal of Pharmaceutical Sciences 102 (2017) 71–84

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Dual-mechanism gastroretentive drug delivery system loaded with an amorphous solid dispersion prepared by hot-melt extrusion

Anh Q. Vo [a], Xin Feng [a], Manjeet Pimparade [a], Xinyou Ye [a], Dong Wuk Kim [a], Scott T. Martin [c], Michael A. Repka [a,b,*]

[a] Department of Pharmaceutics and Drug Delivery, School of Pharmacy, The University of Mississippi, University, MS 38677, USA
[b] Pii Center for Pharmaceutical Technology, The University of Mississippi, University, MS 38677, USA
[c] Material Chacterization, Thermo Fisher Scientific, Tewksbury, MA 01876, USA

ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form 13 February 2017
Accepted 27 February 2017
Available online 28 February 2017

Keywords:
Amorphous solid dispersion
Supersaturation
Melt extrusion
Floating
Bioadhesion
Gastroretentive drug delivery system

ABSTRACT

In the present study, we aimed to prepare a gastroretentive drug delivery system that would be both highly resistant to gastric emptying *via* multiple mechanisms and would also potentially induce *in situ* supersaturation. The bioadhesive floating pellets, loaded with an amorphous solid dispersion, were prepared in a single step of hot-melt extrusion technology. Hydroxypropyl cellulose (Klucel™ MF) and hypromellose (Benecel™ K15M) were used as matrix-forming polymers, and felodipine was used as the model drug. The foam pellets were fabricated based on the expansion of CO_2, which was generated from sodium bicarbonate during the melt-extrusion process. A 2^n full factorial experimental design was utilized to investigate the effects of formulation compositions to the pellet properties. The melt-extrusion process transformed the crystalline felodipine into an amorphous state that was dispersed and "frozen" in the polymer matrix. All formulations showed high porosity and were able to float immediately, without lag time, on top of gastric fluid, and maintained their buoyancy over 12 h. The pellet-specific floating force, which could be as high as 4800 μN/g, increased significantly during the first hour, and was relatively stable until 9 h. The sodium bicarbonate percentage was found to be most significantly effect to the floating force. The *ex vivo* bioadhesion force of the pellets to porcine stomach mucosa was approximately 5 mN/pellet, which was more than five times higher than the gravitation force of the pellet saturated with water. Drug release was well controlled up to 12 h in the sink condition of 0.5% sodium lauryl sulphate in 0.1 N HCl. The dissolution at 1, 3, 5, and 8 h were 5–12%, 25–45%, 55–80%, and ≥75% respectively for all 11 formulations. In biorelevant dissolution medium, a supersaturated solution was formed, and the concentration was maintained at around 2 μg/mL, approximately 10-folds higher than that of the pure felodipine. All input factors significantly affected dissolution in the first 3 h, but afterwards, only drug load and hypromellose (HPMC) content had significant effects. The prepared drug delivery system has great potential in overcoming low and fluctuating bioavailability of poorly soluble drugs.

Chemical: Felodipine (PubChem CID: 3333); hypromellose (PubChem CID: 57503849), hydroxypropyl cellulose (PubChem CID: 71306830), sodium bicarbonate (PubChem CID: 516892); sodium carbonate (PubChem CID: 10340).

1. Introduction

Owing to its many inherent advantages, oral administration is the most preferable route of medicinal administrations, and thus has a prominent role in therapy. However, it is also known as an unpredictable and fluctuating treatment route, especially with regard to active pharmaceutical ingredients (APIs) that have poor solubility, slow dissolution, low intestinal permeability, and narrow absorption window. Frequent problems of oral drugs include fluctuating pharmacokinetics, low bioavailability, and poor treatment efficiency. Most of the encountered problems stem from the low solubility of APIs, as well as the physiological fluctuations.

It is estimated that approximately 40% of marketed APIs have problem with dissolution, and the majority of drug candidates currently in development are poorly soluble, and their absorption sites limited to the upper small intestine (Vasconcelos et al., 2007; Williams et al., 2013). Therefore, ensuring that drugs are completely dissolved and ready for absorption before passing through the small intestine is very crucial. To date, solid dispersion (SD) is one of the most successful

* Corresponding author at: Department of Pharmaceutics and Drug Delivery, Pii Center for Pharmaceutical Technology, School of Pharmacy, The University of Mississippi, University, MS 38677, USA.
E-mail address: marepka@olemiss.edu (M.A. Repka).

http://dx.doi.org/10.1016/j.ejps.2017.02.040
0928-0987/

strategies that enhances the dissolution and/or solubility of poorly soluble APIs. More advanced than conventional SD, amorphous SD can significantly enhance the apparent solubility (Taylor and Zhang, 2016), and therefore create a supersaturated solution in a non-sink condition. This ultimately raises the *in situ* drug concentration at the absorption site (Brouwers et al., 2009), and thus is potential to enhance the drug absorption (Ueda et al., 2012), (Warren et al., 2010).

The gastrointestinal (GI) tract comprises many segments that are starkly different in both anatomy and internal environment, which crucially influences the *in vivo* dissolution and absorption of drugs. Ideally, drugs are completely dissolved and absorbed before they reach the colon, as small intestine is the main absorptive region with surface area approximately 120 times higher than the total area of all other parts of the GI tract (Rouge et al., 1996). However, the drugs' retention time largely fluctuates depending on meals, dosage forms, and inter- and intra-subjective variations (Newton, 2010); (Van Den Abeele et al., 2016). The gastric retention time may vary from several minutes to 3 h in the fasted state and from 1 to 10 h in the fed state. Meanwhile, the intestinal transition time, which is believed to be less variable, can be as short as 1 h or as long as 7 h, or even longer (Weitschies et al., 2010). This ultimately results in large pharmacokinetic fluctuations and unpredictable treatment efficacy. Residing dosage forms in the stomach is a potential approach overcoming these drawbacks.

A gastroretentive drug delivery system (DDS) can facilitate a more predictable release and allow for more complete absorption. Because *in vivo* dissolution is limited in the stomach, drug release tends to be more controlled (Taupitz et al., 2013). Furthermore, drug concentration surrounding the dosage forms is maintained low, since the dissolved drug is continuously transported away from them, downward the intestine. This is very important with regard to low solubility drugs, as a pseudo-sink condition is created and *in situ* recrystallization is prevented. In addition, drugs gradually enter the absorption site as free molecules ready for absorption which is practically meaningful to drugs with narrow absorption window and unpredictable bioavailability (Streubel et al., 2006). Finally, such a formulation maximizes the absorption area as the whole GI tract surface for all drug molecules. Since the drugs always release at the first segment, they all have the potential to be absorbed at any point throughout the tract. In contrast, for conventional DDSs, absorption area decreases significantly along with their downward movement. Therefore, taken as a whole, the gastroretentive amorphous SD is a viable solution to the pharmacologic problems of narrow absorption window, low solubility, and poor absorbability.

The short gastric retention time of conventional dosage forms might limit the advantages of controlled-release DDSs, which usually prolong drug release up to 12 h or longer. It is estimated that the average drug retention time in the stomach is around 30 min (Newton, 2010), and in the small intestine it is around 3 h (Podczeck, 2010). This indicates that conventional controlled-release dosage forms might pass through the small intestine, the main absorption site, in 1/4 to 1/3 of their lifespans, resulting in incomplete drug absorption. Therefore, they might only be suitable for APIs that can be absorbed well in the colon. Otherwise, the gastroretentive DDS is a viable approach to the controlled release drugs.

There are numerous approaches to the fabrication of a gastroretentive dosage form, including floating DDSs, sinking DDSs, expanding DDSs, bioadhering DDS, and magnetic DDSs (Lopes et al., 2016). Among those, floating and bioadhesive DDSs are the most extensively researched as well as developed as marketed products (Pawar et al., 2012). However, the floating DDS can be dislodged by the gastric emptying in an average of every 2 h (Singh and Kim, 2000), while the bioadhesive DDS can be detached from the stomach wall by the mucus turnover that frequently renews the gastric mucosa outer layer (Chen et al., 2010). The combination of the floating and bioadhesive approaches, however, could potentially result in a synergistic effect that could effectively resist the stomach's physiological activities to maintain gastric retention for a suitable period of time.

Hot-melt extrusion (HME) is widely known as a green processing technology in the SD development in which APIs are dispersed and stabilized in polymer and lipid matrixes (Repka et al., 2008); (Sarode et al., 2013). It is an excellent alternative to conventional techniques in the production of SDs (Repka et al., 2007). With the application of the process analytical technology, PAT strategy, it can be systematically scaled up and developed as a continuous process (Tumuluri et al., 2008); (Wahl et al., 2013); (Islam et al., 2015).

In our previous study (Vo et al., 2016), we focused on improving the bioavailability of BCS class I drugs *via* a singular floating approach, which is vulnerable to the dislodgement during the gastric emptying. To enhance applicability, in the present study, we developed a novel dual-mechanism gastroretentive DDS loaded with amorphous SD of a BCS class II drug by utilizing a single step of HME. The prepared DDS can potentially resist the gastric dislodgement *via* the synergistic effect of floatation and bioadhesion. It also can generate and maintain *in situ* drug supersaturation, a viable solution to the problem of poor bioavailability.

2. Materials and Methods

2.1. Materials

Felodipine (FEL) USP was purchased from Ria International LLC (East Hanover, NJ, USA). Sodium bicarbonate (SBC) USP/NF was purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA, USA). HPMC K15M (Benecel K15M) and HPC (Klucel MF) were kindly provided by Ashland, Inc. (Lexington, KY, USA). HPLC solvents and all other reagents used in the study were of analytical grade and were purchased from Fisher Scientific (Pittsburgh, PA, USA).

2.2. Extrusion Processing

Initially, raw materials were separately passed through a USP #35 mesh sieve to remove aggregates and clumps. A mixture of 100 g of each formulation was prepared and physically mixed until a homogenous physical mixture was obtained.

The system used for preparing the foamed strands was comprised a twin screw extruder (Process 11™, Thermo Fisher Scientific, Odessa, TX, USA) equipped with a 1.5 mm circular die insert, a chiller, a feeder, and a conveyor belt that was adjusted to synchronize with the main module. A modified screw configuration (Fig. 1) was used for the experiment. The temperature of all eight zones on the barrel and the die was set at 165 °C. Screw speed and feeding rate was set at a constant 200 rpm and 5 g/min, respectively.

The system was allowed to heat-soak for 10 min to establish thermal equilibrium prior to processing. The first 30 g of the extrudate was discarded to ensure that the samples were collected when the extruder was operating at a steady state. To get a uniformly cylindrical extrudate, the conveyor speed was adjusted to synchronize with the extrudate formation rate. The straight extrudates were subsequently cut into 2.0-mm long pellets and stored in tight glass bottles at 20–25 °C.

2.3. Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) was used to investigate the thermal behaviour of the materials and formulations, as well as to confirm the compatibility of the API and the excipients. The pure components, their binary mixtures (1:1), physical mixtures, and formulations were subjected to DSC experimentation (Diamond DSC Perkin Elmer, Waltham, MA, USA). Samples weighing 2–5 mg (for pure compounds) or 8–12 mg (for physical mixtures) were loaded onto a crimped aluminium pan (non-hermetic pan) and placed in the DSC system. The samples were then stabilized by holding at a temperature of 45 °C for 2 min and followed by heating from 45 °C to 200 °C at a ramp rate of 10 °C/min