Published in final edited form as:

Eur J Pharm Sci. 2017 May 01; 102: 71–84. doi:10.1016/j.ejps.2017.02.040.

Dual-Mechanism Gastroretentive Drug Delivery System Loaded with an Amorphous Solid Dispersion Prepared by Hot-Melt Extrusion

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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 (KlucelTM MF) and hypromellose (BenecelTM 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 CO₂, which was generated from sodium bicarbonate during the melt-extrusion process. A 2ⁿ 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

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

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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.

Graphical abstract

Keywords

amorphous solid dispersion; supersaturation; melt extrusion; floating; bioadhesion; gastroretentive drug delivery system

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 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 & 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 (Podczek, 2010). This indicates that conventional controlled-release dosage forms might pass through the small intestine, the main absorption site, in $\frac{1}{4}$ to $\frac{1}{3}$ 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 & 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 11TM, 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 under an inert nitrogen flow of 20 mL/min. The thermograms were analysed to detect for thermal events.

2.4 Experimental Design

A two-level full factorial design was applied to address the effects of formulation compositions on pellet characteristics. By using this model, significant input factors and interactions between factors can be identified. Furthermore, the effects of input factors can be mathematically described and outcomes can be predicted for each set value of input factors. The results of the regression are very useful for designing operation spaces in the quality by design (QBD) approach.

The regression equation is expressed as follows:

$$Y_i = b_i + a_{i1}X_1 + a_{i2}X_2 + a_{i3}X_3 + a_{i12}X_1X_2 + a_{i13}X_1X_3 + a_{i23}X_2X_3$$

where Y_i is the response number i , b_i is the constant, and a_{i1} , a_{i2} , a_{i3} , a_{i12} , a_{i13} , a_{i23} are the coefficients of the encoded factors. The significance of the model and effect of factors determined the regression and one-way analysis of variance (ANOVA) performed on Modde 8.0 software (Umetrics Inc., Sweden). Three independent variables were investigated: Drug load, HPMC content, and SCB percentage. The output variables were drug release profiles, porosity, and floating strengths.

2.5 Scanning Electron Microscopy

The pellets were carefully cut to produce flat surfaces for SEM examination. The samples were stuck on aluminium stubs held with a double-sided carbon adhesive film and placed in the coating chamber. The coating was performed in an inert gas environment prepared by removing the air at 40 mmHg, then filling the chamber with high purity nitrogen. The samples were then coated with gold by using a Hummer® 6.2 Sputtering System (Anatech LTD., Battlecreek, MI, USA) in nitrogen environment at 120 mmHg and current of 18 mA.

The coating was triplicated for 45 s each. The pellets' surface topography was examined using a scanning electron microscope (SEM) operating at an accelerating voltage of 5 kV and a magnification of 45× (JEOL JSM-5600; JEOL, Inc., Peabody, MA, USA).

2.6 X-Ray Diffraction

The X-Ray diffraction experiments were performed by using a Rigaku X-ray equipment (D/MAX-2500PC, Rigaku Corporation, Tokyo, Japan) with a copper tube anode and a standard sample holder. The diffractograms were collected at room temperature (20–25°C) with the following parameters: step width of 0.02°/s, scanning range from 5° to 40° on a 2θ scale; generator tension (voltage) 40 kV; generator current 100 mA; scanning speed 10°/min.

2.7 Densities and Porosity

To measure geometric density, uniform straight strands were cut into 10-cm cylinders with flat surfaces on both sides. The diameter (d), an average of 5 different measurements along the length of the cylinder, and length (h) of the cylinders were measured using digital callipers (d=0.01 mm, VWR Digital Calliper, Radnor, PA, USA). The cylinders were weighed (m) using a high precision balance (Analytical Balance XSE 204, Mettler Toledo, Switzerland). The pellet geometric density was calculated using the following equation:

$$D_{\text{geometric}} = \frac{4m}{\pi h d^2}$$

The pellet true density was determined using a gas pycnometer (AccuPyc II 1340, Micromeritics, Norcross, GA, USA) using helium gas. The measurements were replicated five times and the data were processed using the built-in software suite. The results reflected the density of the matrix skeleton, as the helium gas occupied the entirety of the vacuous space within the matrix. The porosity of the floating pellets was calculated using the following equation:

$$P = \frac{V_{\text{void}}}{V_{\text{geometric}}} = 1 - \frac{D_{\text{geometric}}}{D_{\text{skeletal}}}$$

where V_{void} is the total volume of the air pockets inside the pellets, and $V_{\text{geometric}}$ is the volume of the pellet as a whole object. $D_{\text{geometric}}$ and D_{skeletal} are the geometric density and true density of the pellets, respectively.

2.8 Sample Process for Quantitative Analysis

Using a mortar and pestle, the extrudate was ground into a fine powder. It was then accurately weighed to an amount equivalent to 10 mg of FEL and transferred into a 100-mL volumetric flask along with 40 mL acetonitrile and 20 mL methanol. The flask was sonicated for 5 min (Branson 2510, Branson Ultrasonic Corp., Danbury, CT, USA) before adding 30 mL phosphate buffer (pH=3) and continuously shaken for 15 min using a mechanical shaker. The buffer was added to the volume and mixed well. A volume of 5 mL was centrifuged at the relative centrifuge force of 16,000 g for 10 min at 25°C (Centrifuge

5415R, Eppendorf AG, Eppendorf, Germany). The supernatant was diluted five times with the mobile phase and filtered with a 0.45- μ m membrane before loading into the autosampler of the high-performance liquid chromatography (HPLC) system.

2.9 HPLC Analysis

Felodipine was analysed using a Waters 600 HPLC system (Waters Corp., Milford, MA, USA) equipped with an autosampler, UV/VIS detector, and a Phenomenex[®] Luna C18 column (5 μ m, 250 mm $\times$ 4.6 mm). The HPLC program was developed after referencing the USP Felodipine extended release tablet monograph. The mobile phase was a mixture of acetonitrile: methanol: phosphate buffer (6.9 g mono basic sodium phosphate in a 1000 mL solution, adjusted with phosphoric acid to pH 3) at a ratio of 3:2:1 (v/v). The elution was performed at a flow rate of 1.0 mL/min in an isocratic mode. The injection volume was set at 10 μ L for the assay samples, and 50 μ L for the dissolution samples. The signal was detected at a wavelength of 362 nm. Two linear calibration curves were established, one ranging from 0.4375 μ g/mL to 28 μ g/mL ($R^2 = 0.9998$), which was used to analyse the assay samples and dissolution in sink condition samples. The other ranged from 0.0252 μ g/mL to 3.220 μ g/mL ($R^2 = 0.9983$), which was used to quantify the dissolution in fasted state simulated gastric fluid (FaSSGF) samples.

2.10 In Vitro Drug Release

Floating pellets (10 mg FEL) were subjected to dissolution testing in a sink condition and biorelevant dissolution medium. The sink condition dissolution medium consisted of 900 mL 1% SLS in 0.1 N HCl solution. The un-sink dissolution media was the FaSSGF whose composition was described by Margareth Marques (Marques *et al.*, 2011) and Ekarat Jantratid (Jantratid *et al.*, 2008). The paddle method and USP dissolution apparatus type 2 (Hanson SR8; Hanson Research, Chatsworth, CA, USA) were used with a setting temperature of $37 \pm 0.5^\circ\text{C}$ and paddle rotation speed of 100 rpm. At predetermined time points, a volume of 2.0 mL dissolution media was withdrawn and 2.0 mL fresh dissolution media was added. The samples were subsequently filtered through 0.2 μ m, 13 mm PTFE membrane filters (Whatman, Inc., Haverhill, MA, USA). Samples of the dissolution test in biorelevant media were diluted with an equal volume of an acetonitrile: methanol (2:1) mixture before injection into the HPLC system. A volume of 10 μ L (assay test) or 50 μ L (dissolution test) was injected into the HPLC system for analysis by the above method.

2.11 Floating Strength Determination

The pellet floating force was determined via resultant-weight, which was measured based on the lever principle. The apparatus, operation, and calculation were described previously (Vo *et al.*, 2016). The five-point calibration curve was established by measuring the resultant weight of known counterpoise weights. Using a USP dissolution apparatus II (Hanson SR8), 1000 mg of the pellets were placed in 900 mL FaSSGF at $37 \pm 0.5^\circ\text{C}$ and continuously stirred at 50 rpm. At predetermined time points, the vessel was removed from the dissolution system and was carefully placed on a vessel holder. The vessel holder was then slowly lifted to collect all floating pellets under a perforated cone. A basement was used to support the holder and keep the system steady. The resultant weight was read as the value on the balance. After measuring, the vessel was placed back into the dissolution system, with

stirring, until the next measurement. The floating strength was calculated by plugging resultant weight values into the regression equation of the calibration curve.

2.12 *Ex Vivo* Bioadhesion Force Measurement

Fresh porcine stomachs were taken from the slaughterhouse, processed, and used within 1 day. The stomachs were opened and gently rinsed with 0.9% NaCl solution. They were then mounted onto a flat surface, and the outer muscle layer was removed using a surgical knife. The remaining portion with the mucosa was then cut into suitably sized pieces and kept in 0.9% NaCl solution before experimentation.

The bioadhesion force was measured using a Texture Analyzer Stable Micro Systems (TA-TXi2, Texture Technologies Corp. UK) equipped with Exponent V 6.1.5.0 data processing software. One portion of stomach mucosa was fixed firmly onto the instrument basement and another was mounted tightly onto the probe (3×3 cm, flat surface). The pellets were placed in FaSSGF at 37°C for at least 5 min before testing. Twenty saturated pellets were placed evenly onto the mucosa surface, which was fixed onto the instrument basement. Both mucosa on the basement and the probe were moistened with FaSSGF prior to experimentation. Operation parameters were set as following: pretest and test speed of the probe were 1 mm/s, trigger force was 0.05 N, applied force was 0.1 N, and contact time was 120 s. The adhesion force was determined as the peak on generated force-time plots. The experiment was conducted five times for each formulation.

3. Result and Discussion

In the present study, we first aimed to fabricate a hydrophilic matrix because the model drug was a poorly soluble compound, and we hypothesized that such a matrix would help enhance drug dissolution. HPMC is the most important hydrophilic polymer in the formulation of controlled-release DDSs. It can swell to form an erodible hydrogel that controls drug release from the matrix (Siepmann & Peppas, 2001). In addition, HPMC is an excellent carrier for amorphous drugs owing to its high T_g (> 180°C) and ability to maintain the supersaturation of drugs in aqueous media (Konno *et al.*, 2008); (Yang *et al.*, 2015). However, it is not a good candidate for HME because HME generates high pressure, high torque, and requires a high processing temperature that is close to HPMC's degradation temperature. Thus, HPC was chosen as the secondary polymer to enable the HME process because it has a chemical structure very similar to that of HPMC; thus, it is potentially able to be melt-miscible with HPMC. Furthermore, its low T_g can be used to modulate the T_g of the polymer blend according to the Gordon-Taylor equation (Forster *et al.*, 2001).

The foamed strands were formed as the extrudate exited the die based on the expansion of CO₂ generated from thermal degradation of NaHCO₃. We hypothesized that the processing temperature would be higher than the degradation temperature of the foaming agent, but simultaneously low enough to ensure the stability of formulations during processing. The optimum processing temperature was chosen based on the DSC experimental results as shown in Fig. 2. The degradation process reached its peak at approximately 150°C and finished below 170°C. Therefore, the processing temperature was chosen to be 165°C, the lowest temperature where the foaming effect of SBC could be maximized. This temperature

was also higher than the melting temperature of the API, facilitating API dispersion into the polymer matrix.

A series of preliminary experimentations were conducted to determine the parameters for experimental feasibility. The screw configuration was redesigned as shown in the Fig. 1 to enhance the performance of the foamed extrusion process. A small reverse mixing zone was set at the second barrel zone to create a temporary melting seal to prevent gas leakage. In addition, all three mixing zones were moved forward towards the barrel end, and the first two mixing zones were simplified to enable the materials to be conveyed into the tight area more quickly. To compensate the first two small mixing zones, the last mixing zone was increased in size and designed more complexly to ensure a good homogeneity effect. The feeding rate was fixed at 5 g/min and screw speed was set at 200 rpm to satisfy various requirements, such as the ability to fill the barrel, to synchronize with the strand conveyance, and to generate a suitable foamed strand.

The design of experiment (DOE) was used to elucidate the effects of formulations on the properties of the pellets. The HPMC content, drug load, and SBC percentage were chosen as independent factors with their variable ranges shown in Table 1. HPC was considered a compensated variable. From the preliminary study, the variation range of HPMC content ranged from 25% to 35%. If it was higher than 40% the torque would increase and the extrudate would be too hard that did not allow for the formation of foamed strands (Fig. 3B); if it was lower than 25%, the extrudate was too soft, and the strands would burst and ultimately shrink, such that the foam structure could not be maintained (Fig. 3A). The SBC range of 5–9% was chosen such that a suitable foamed structure could be obtained. If the SBC was out of the range, either the pellets would have too low porosity to enable them float, or they would be too porous to be effective. The drug load varied around 10%, based on the presumption that the drug and polymers would be completely miscible and physically stable.

All 11 DOE formulations were successfully prepared. Within the experimental ranges, the system worked smoothly and uniformly foamed strands were obtained. When a steady state was established, the torque and die pressure remained relatively stable around 2.5 Nm (25%) and 26 bars, respectively. Even though the operation temperature was lower than the T_g of HPMC, the torque was quite low because HPMC was miscible with the softened HPC and was able to form a polymer blend with lower T_g. In addition, it is possible that the melted FEL plasticized and/or produced a lubricant effect that further decreased the torque. The total retention time of the formulations in the barrel and die was approximately 80 s.

3.1 Micromeritics Properties

Eleven DOE formulations (Table 2) were fabricated and characterized. The SEM images of the pellets' cross-sectional surfaces revealed vacant spaces inside the pellets created by the expanded CO₂ in all 11 formulations. The size and distribution of vacant spaces depended on the HPMC content and SBC percentage. Generally, the SBC percentage had a covariant effect on the size and degree of vacant spaces, and HPMC content had a contravariant effect, as shown in Fig. 3.

The micromeritics properties of the pellets are presented in Table 3. The density of all 11 formulations was lower than 1 g/cm^3 , allowing them to immediately float on top of the gastric fluid (Fig. 4), additionally confirming their foamed structure. The extrudate drug load ranged from 97.70–100.16% compared to theoretical values, which implies that the drug was stable during processing. The loss on drying (105°C for 15 min) of the samples was considerably low (1.18–1.86%) compared to their respective physical mixtures. Under the high processing temperature, most of water evaporated once the extrudate exited the die. Since water would largely effect on molecular mobility via decreasing the T_g of SD, low water content would significantly increase the physical stability of an amorphous SD.

Because the pellet true density (or skeletal density) of all 11 formulations was almost the same, the pellet porosity was proportional related to the pellet geometry density. Hence, the porosity proportionally reflected the initial floatability of the pellets, which could not be measured because of large fluctuations. The regression result confirmed that the model used was suitable for describing the relationship of the input factors to pellet porosity ($R^2 = 0.984$, $Q^2 = 0.746$). While drug load did not significantly affect pellet porosity, both the HPMC content and SBC percentage had significant effects ($p < 0.01$). The SBC percentage positively affected pellet porosity, as it controlled the amount of temporary blowing agent generated. In contrast, HPMC content inversely affected pellet porosity. It moderated the softening of the hot polymer matrix, and thus matrix expansion. Its high T_g also helped to preserve the foamed structure by quickly hardening the extrudate when it exited the die. However, the SBC percentage effect was three times higher than that of HPMC content.

Previously, there were a few published studies on floating dosage forms prepared using HME. Those studies focused on highly soluble compounds, used Eudragit RS as a matrix forming polymer, and owed high risk of dislodgement by gastric emptying. In one study, floating tablets were prepared based on the expansion of CO_2 generated from the reaction of SBC and acetohydroxamic acid (Fukuda *et al.*, 2006); however, the continuous reaction of the residual acid and base during storage is problematic for stability. Recently, gas-generated floating particulates, whose buoyancy depended on gastric pH, were prepared using HME (Malode *et al.*, 2015). However, this process is possibly unpractical for product development because of extremely low throughput and long resident time inside the barrel (9 min). In comparison to the other floating dosage forms, the particulate buoyancy was limited because the lag time ($> 3 \text{ min}$); after 5.5 h and 10.5 h, more than 50% and 90% of the particulates sank, respectively. More recently, floating foamed pellets were prepared by injecting an inert foaming agent into the extruder barrel (Vo *et al.*, 2016). The obtained pellets showed good floating kinetics with no lag time, with floating time greater than 12 h and floating force as high as $5000 \mu\text{N/g}$.

3.2 Thermal Properties

The thermal behaviour of materials and formulations were elucidated using DSC. From the results shown in Fig. 2, no thermal event was detected in the range of $40\text{--}190^\circ\text{C}$ on the thermogram for HPC and HPMC that could confirm the amorphous nature of these two polymers. An exothermic peak at 146°C corresponded to the melting peak of the crystalline FEL raw material. On the thermogram for SBC, a large, broad exothermal event that

noticeably started at 110°C could be interpreted as a thermal degradation peak. CO₂ and H₂O generated from the SBC degradation reaction could evaporate and remove heat from the DSC sample, thus causing the heat to flow to the sample to compensate for the heat lost, resulting in the exothermic peak. There was no detectable thermal event in the thermograms of all 11 formulations. This further suggests that the crystalline FEL was transformed into an amorphous form, and the SBC in the starting formulations had maximized its effect. The amorphous form of FEL in the formulations was confirmed by XRD results. The sharp peaks in the region of 23° to 26° that presented in pure FEL and the low drug load physical mixture could not be detected in the diffractogram of formulations with both low and high drug load (Fig. 5).

During the extrusion process, melted FEL was expected to disperse at the molecular level into the softened polymer matrix. In the experimental concentration range, the formulations were presumed to be either in a solution region (thermodynamic stable) or in a spinodal region (metastable) on the API-polymer phase diagram, thus maintaining the API amorphous state. Moreover, the combination of HPMC and HPC formed a polymer blend whose T_g (calculated using the Gordon-Taylor equation) was remarkably higher than the storage temperature; thus, the drug molecules were able to be frozen into the polymer matrix.

To investigate the physical stability of the formulations, the samples were packed tightly into light-protected glass vials and stored at 40°C for 6 months. At this elevated storage temperature, we hypothesized that the mobility of molecules would increase and accelerate the recrystallization process; therefore, this method could be utilized to detect early physical instability. There was no thermal event detected on the thermograms of all 11 formulations tested for stability, confirming that the amorphous state of FEL was maintained. The experimental data support the hypothesis of a relatively stable amorphous SD.

3.3 Floating Kinetics

A floating dosage form might experience many obstacles that prevent it from maintaining buoyancy for a sufficient period of time. Floating force is the most crucial parameter in evaluating buoyancy, as it shows how well a dosage form can float (Timmermans & Moes, 1990). High floating force enables the dosage form to resist submergence and assists it in refloating when the submergence might temporarily occur.

Owing to their low density ($d < 1.00$), all 11 formulations could float immediately on top of FaSSGF. Upon contact with the gastric fluid, the polymers rapidly absorbed water and swelled, with a gel layer forming to cover the matrix, trapped bubbles, and maintain floatation for over 12 h (Fig. 4). To investigate the floating kinetics, the buoyant force of the pellets in FaSSGF was measured at different time points over 12 h. The floating kinetics greatly varied from one formulation to the other (Fig. 6). The initial floating force could not be measured accurately, as the simultaneous effects of the swelling process and the reaction of sodium carbonate (SC), which was formed from the thermal degradation of SBC and remained in the formulations, with acid from the environment caused the force to continually increase. The increase in the floating force in the first 60 min was proportionally related to the SBC percentage. Afterwards, it became relatively constant up to 9 h, before

dropping off. During the first 9 h, the bubbles escaping from the matrix were compensated by the CO₂ generated from SC, ultimately keeping the floating force stable (Table 4). When the SC was exhausted, the loss of vacant space in the matrix overcame gas generation, that would make the floating force decrease at a rapid rate.

The regression results of the floating force at 1 h and 9 h (Table 5) confirmed that the model used could accurately describe the effects of input factors on output variables ($p < 0.05$, $R^2 > 0.98$, $Q^2 > 0.485 \approx 0.50$). The floating force was significantly ($p < 0.05$) governed by all three factors in a positive manner. Among the three factors, SBC percentage had the greatest effect on both probability and capability (Fig. 7). This effect on pellet floatability probably acted *via* two different mechanisms; on the one hand, it controls pellet porosity (Table 5), which is proportionally related to the initial floating force and the pellet's intrinsic floating ability. On the other hand, SC in the pellets would react with acid in the gastric fluid and generate CO₂, increasing the floating force. This would explain why the floating force remained relatively stable up to 9 h. As for the role of HPMC, its high viscosity contributed to gel layer density, retarded polymer dissolution, and thus trapped air bubbles in the matrix more effectively. The greater the HPMC content, the higher the floating force observed. FEL, a hydrophobic compound, influenced pellet floatability *via* its contribution to the hydrophobicity of the matrix, retarding water penetration into pellets and positively affecting the floating force. Drug load contributed the least to the pellet buoyancy. With regard to the floating force during the first hour, there was no potential interaction ($p > 0.58$) between input factors, so the regression could be considered a linear regression. However, there was a potential interaction between HPMC content and drug load at 9 h ($p=0.056$), which inferred a possibly significant effect of (drug load * HPMC content) to floating force.

3.4 Bioadhesive Properties

Upon contact with gastric fluid, the pellets would absorb water and swell to produce a highly viscous and sticky hydrogel outer layer. The high viscosity enabled the pellets to initially adhere to the stomach wall. In addition, the HPC and HPMC polymer chains might penetrate into the mucus layer and interlock with the glycoproteins of the mucosa (Varum *et al.*, 2010). Furthermore, upon contact with the stomach mucosa, hydrogen bonding between -OR (R = hydrogen or a short chain hydrocarbon) groups of the polymer and -NH₂ and -COOH groups of the mucosa protein occur (Andrews *et al.*, 2009), further increasing the bioadhesion force of the pellets. Because both HPMC and HPC are rich in -OR groups, the generated hydrogen bonds significantly contribute to the bioadhesion force. The total adhesion force was thus expected to be high enough to keep the pellets attached to the stomach wall during the gastric emptying process, which occurs periodically as a physiological activity of the stomach.

The stomach adhesion potential of the pellets was determined by measuring the bioadhesion force. All 11 formulations were subjected to *ex vivo* bioadhesion force measurement. The bioadhesion force of a single measurement varied from 3.05–6.98 mN/pellet which was over three times larger than gravity of a saturated pellet, which ultimately weighed less than 100 mg even at its heaviest. This could be inferred that every pellet could adhere well onto the

stomach wall to prevent from being dislodged with gastric fluid during gastric emptying stage.

The average bioadhesion force per pellets was in the range of 4.42 ± 1.53 mN to 5.67 ± 1.08 mN (Fig. 8). The differences in bioadhesion force of the 11 formulations were not significant ($p = 0.875$, one-way ANOVA test using SPSS 22). There was no significant difference in the force between any two formulations ($p > 0.926$, Tukey test using SPSS 22). This might be explained by the fact that the chemical structure of HPMC and HPC, the two components that generate the adhesion force, are very similar. Therefore, the hydrogen bond intensity was not significantly affected by the HPMC/HPC ratio in the experimental range.

More interestingly, the average bioadhesion force was found to be relatively stable over the experimental time in the FaSSGF. This can be explained by the following: initially, when the outer polymer layer is not completely saturated, the hydrogel layer is highly viscous and dense, allowing the pellets to adhere more strongly to the stomach mucosa, but the size of the matrix is relatively small, so the contact area of a pellet to the mucosa is also small. Later on, the pellets are more saturated, and the gel layer became less adherent, but the matrix size is increased, so the contact area of the matrix to the mucosa is increased, thus maintaining the adhesion force. The matrix then proceeds into a steady state, in which the balance between the dissolution of polymer molecules at the matrix surface and the gelling of polymer molecules in the inner core is established, and the matrix size and the gel structure are stable enough to keep the adhesion force constant. The steady state was maintained up to 9 h before the polymer-dissolving process exceeded the polymer-gelling process, making the gel layer less adherent and decreasing the adhesion force.

The combination of floating and bioadhesion has the potential to generate a synergistic effect that increases the probability of gastric retention. During the gastric emptying stage (phase 4 of the gastric physiology cycle), the contents of the stomach are pushed forward to the intestine along with gastric fluid; the pellets are expected to stay adhering to the stomach wall, thus ensuring that the pellets would not be pushed out and would remain in the stomach. However, if the pellets did detach from stomach wall because of the mucus shedding process, their buoyancy will keep them in the stomach. A new cycle of mucosal adhesion would start with a new mucosal layer. Therefore, this bioadhesive floating DDS has high potential resistance to gastric biological activities, and is likely to remain in the stomach for a sufficient period of time.

3.5 Drug Release Kinetics

3.5.1 In the sink condition—In the sink condition (SLS 1% in HCL 0.1 N, pH 1.2), drug release could be controlled up to 12 h. Even though dissolution was largely different between formulations, the pattern of the drug release profiles was very similar (Fig. 9) because the release mechanism was similar. HPMC and HPC rapidly swelled once the pellets contacted the gastric fluid, forming an outer gel layer (Fig. 4F). Drug molecules then diffused through the gel layer out to the dissolution medium. Knowing this, the thickness, denseness, and hydrophilicity of the gel layer would control the drug release kinetics. As can be seen from the results of the dissolution regression, drug load, SBC percentage, and HPMC content all affected drug release differently over the time.

The average dissolution at 1, 3, 4, and 8 h (Table 6) was used to correlate the independent factors with dependent variables. From the regression results (Table 7), the three factors of drug load, SBC percentage, and HPMC content significantly affected drug dissolution at 1 h and 3 h ($p < 0.03$). The significance of the (HPMC content*Drug load) and (SBC percentage*Drug load) variables ($p < 0.05$) at 1h indicate that there were interactions between these factors, meaning that the effect of one factor was dependent on the values of the others. On the prediction contour plots, the interactions between factors showed non-straight curves (Fig. 10). Later on, at 5 h and 8 h, SBC lost its significance ($p > 0.098$) and no potential interaction between the factors was observed. Drug release was significantly influenced by HPMC content and drug load ($p < 0.03$).

HPMC moderated the drug release profile by controlling the properties of the gel layer covering the matrix. The HPMC content was covariant with the thickness and denseness of the gel layer, but contra-variant with drug diffusion. The negative effects of HPMC content were described quantitatively by the regression equation. FEL showed a negative effect on drug dissolution, similar to HPMC, but its presence was mostly related to the hydrophilicity of the matrix. An increase in drug load rendered the matrix more hydrophobic, and thus decreased the water absorption rate and drug release (Fig. 10). Unlike HPMC and FEL, which retarded drug release from the matrix, SBC facilitated drug release. It influenced the drug release profile *via* its effects on pellet porosity and matrix hydrophilicity. As SBC percentage was covariant with the pellet porosity, it promoted water absorption into the matrix and created channels for drug release. In addition, SC formed from SBC during the extrusion process is highly soluble, attracting water and making the matrix more hydrophilic. These effects would result in an increase in drug release. However, over the time, the swelled polymers would fill out matrix channels, and SBC would totally dissolve and diffuse out of the matrix, rendering it insignificant.

3.5.2 In biorelevant dissolution medium—Normally, to create a sink condition for dissolution testing of poorly soluble drugs, a high concentration of surfactants (much higher than their CMC) will be added to dissolution medium. It is a simple and popular approach to perform dissolution tests limited to quality control purposes. Such the tests are usually conducted to confirm reproducibility between production batches, which are manufactured with the same formulation and technology. However, such a high concentration of surfactants in dissolution medium would not occur in a biological environment. Therefore, the correlation between *in vitro* dissolution and *in vivo* dissolution is very limited. In contrast, a dissolution test in biorelevant medium would provide more relevant information on the biological conditions of interest and the *in vivo* behaviour of dosage forms.

The dissolution profiles of 11 formulations and crude API in FaSSGF were shown in the Fig. 11. The dissolution profiles of all formulations were significantly different from that of the pure drug at all time points ($p = 0.000$, one-way ANOVA test). From 4 h onward, the drug concentration reached maximum values, which were not significantly different between all 11 formulations ($p > 0.05$, one-way ANOVA test). Drug release was slow during the first hour but increased from 1 to 4 h, before drug concentration peaked at approximately 2 $\mu\text{g/mL}$; this could be considered the drug's apparent solubility. From that time onward, the drug concentration was maintained relatively stable at its apparent solubility. In comparison,

drug dissolution from the crude API was very slow, and its maximum concentration was 10 folds lower than that of the formulations.

Initially, because the polymer had not completely swelled the drug was held in the dense matrix. Water absorption was greater than diffusion outflow, thus impeding drug release from the matrix. After the first stage, the gel layer became less dense, and the balance of water absorption in and diffusion out was established in a manner that drug release increased. This explains why drug release increased from 1 to 5 h, when the drug concentration steadily increased to its limit, the apparent solubility. Dissolution then transitioned into a steady state where the balance between drug release from the matrix and the drug nucleation/crystallization was established such that the drug concentration remained relatively stable at the apparent solubility. An advantage of amorphous drugs compared to their counterparts is that a supersaturation state can be obtained. The increase in the solubility is dependent on the difference in free energy between the amorphous and crystalline form (Murdande *et al.*, 2010). Once dispersed in the polymer matrix, an amorphous SD can further enhance apparent solubility compared to pure amorphous APIs (Jackson *et al.*, 2016), since free drug molecules directly enter the dissolution media along with polymer molecules, which would retard the nucleation process. The presence of polymers generated a parachute effect that would help maintain the supersaturation state (Xie & Taylor, 2016).

The regression results of various output variables can be utilized to design spaces for QBD. On the basis of the predetermined qualities of a finished product and the requirement range of various response variables, the properties of the finished product can be set. On a contour graph of each response variable, a satisfactory region where the response variable meets constraints can be determined. By overlaying all contours, an overlapping space will be generated by all the individual contour plots, called a “sweet spot” region. The “sweet spot” region can be considered a space in which processing parameters can vary without any change in product qualities. It can be considered equivalent to the design space concept of QBD, which is defined as ranges within which parameters can vary without considering as a change in process (Yu, 2008). For example, if the expected quality of the pellets were: $8\% < \text{Dissolution 1 h} < 12\%$, $30\% < \text{Dissolution 3 h} < 45\%$, $45\% < \text{Dissolution 5 h} < 70\%$, $\text{Dissolution 8 h} > 80\%$, floating force at 1 h $> 2500 \mu\text{N/g}$, and floating force at 9 h $> 2500 \mu\text{N/g}$, then the sweet spots would be generated as the red area in the plot at the level of A) 6%, B) 10%, and C) 14% drug load (Fig. 12). Each point on the plot represents a paired value for HPMC content and SBC percentage. If a representative point changes within the sweet spot area, the setting constraints are still satisfied. Applying this principle in production, compositions might vary because of random or systematic errors, but variable limits should be determined to ensure that formula compositions do not fall out of the “sweet spot” area.

4. Conclusion

Bioadhesive floating pellets loaded with amorphous SD were successfully fabricated using HME technology. The results of this study showed that the pellets can be utilized as a platform for manufacturing a viable gastroretentive controlled-release DDS. The pellets

were well characterized, and the effects of various factors on pellet properties were regressively correlated. The pellets had excellent bioadhesion, a high and stable floating force, and a capability for controlled drug release up to 12 h. The dual gastroretentive mechanisms of the pellets are highly resistant to stomach physiological activities, which tend to push dosage forms out of the stomach into the intestine. The FEL amorphous SD generated *in situ* supersaturation that would ultimately help the drug absorb more consistently and completely. This study has the potential to systematically scale up by applying the design space QBD concept.

Acknowledgments

This work was partially supported by Grant Number P20GM104932 from the National Institute of General Medical Sciences (NIGMS), a component of NIH. The authors also thank the Pii Center for Pharmaceutical Technology for contributions in this project.

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Fig. 1.
Modified screw configuration used to prepare the foamed pellets loaded with amorphous solid dispersion.

Fig. 2. Thermogram of API, foamed agent, selective formulations, and selective physical mixtures in which sodium bicarbonate was substituted by sodium carbonate (drug load in physical mixture 2 was 6%; and Phys. Mix. 7 was 14%)

Fig. 3.

Representative scanning electron microscope (SEM) images of the pellets' cross-sectional surface. (A) 0% HPMC; (B) 50% HPMC; (C) 25% HPMC and 5% SBC-N1; (D) 35% HPMC and 5% SBC-N2; (E) 25% HPMC and 9% SBC-N7; (F) 35% HPMC and 9% SBC-N8.

Fig. 4. Appearance of the pellets in dissolution medium. (A) Initial. (B) 1 h. (C) 4 h. (D) 8 h. (E) 12 h. (F) Formation of the gel layer after 1 h.

Fig. 5.

XRD diffractogram of crystal FEL, polymers, low drug load physical mixture, and selective formulations with low and high drug load.

Fig. 6.
Specific floating kinetics of the pellets ($\pm$ SD, $n=3$).

Fig. 7. Representative contours describing the effect of the variables on the floating strength of the pellets at (A) 1 h and (B) 9 h.

Fig. 8.
Average bioadhesion force per pellet of the experimental formulations ($\pm$ SD, $n=5$).

Fig. 9. Dissolution profiles of experimental formulations in the sink condition ($\pm$ SD, $n=3$).

Fig. 10.

Regression plots illustrating the effect of the formulation compositions on the drug release kinetics at (A) 1 h, (B) 3 h, (C) 5 h, and (D) 8 h.

Fig. 11. Dissolution profiles of experimental formulations and crude API in FaSSGF ($\pm$ SD, $n=3$).

Fig. 12. Illustration of sweet-spot application in QBD design space. A) Low drug load. (B) Medium drug load. (C) High drug load. (D) Constrained criteria.

Table 1

Experimental Independent Factors and their Variation

Independent Variable	Symbol	Unit	Coded Value		Real Value	
			Upper	Lower	Upper	Lower
HPMC Content	X1	%	+1	-1	35	25
Drug Load	X2	%	+1	-1	14	6
SBC percentage	X3	%	+1	-1	9	5

HPMC: Hypromellose; SBC: Sodium bicarbonate.

Table 2

Experimental Formulation Compositions					
Formulation	Run Order	X1	X2	X3	HPC (%)
N1	11	25	6	5	64
N2	8	35	6	5	54
N3	9	25	14	5	56
N4	4	35	14	5	46
N5	10	25	6	9	60
N6	3	35	6	9	50
N7	6	25	14	9	52
N8	7	35	14	9	42
N9	5	30	10	7	53
N10	2	30	10	7	53
N11	1	30	10	7	53

Table 3Micromeritic Properties of the Foamed Pellets ($\pm$ SD)

Form.	Geometric density (g/cm^3) *	True density (g/cm^3) **	Porosity (%)	Physical mixture LOD (%)	Pellet LOD (%)	Drug Load (%) *
N1	0.9136 $\pm$ 0.0174	1.2945 $\pm$ 0.0005	29.18	4.49	1.71	6.03 $\pm$ 0.08
N2	0.9758 $\pm$ 0.0214	1.2884 $\pm$ 0.0001	24.36	4.78	1.86	6.05 $\pm$ 0.02
N3	0.9165 $\pm$ 0.0121	1.2883 $\pm$ 0.0007	28.95	4.15	1.57	14.29 $\pm$ 0.21
N4	0.9537 $\pm$ 0.0197	1.2864 $\pm$ 0.0000	26.07	4.44	1.51	14.38 $\pm$ 0.19
N5	0.7656 $\pm$ 0.0189	1.2924 $\pm$ 0.0004	40.66	4.35	1.48	6.20 $\pm$ 0.02
N6	0.8402 $\pm$ 0.0181	1.2932 $\pm$ 0.0001	34.87	4.61	1.43	6.16 $\pm$ 0.11
N7	0.7878 $\pm$ 0.0193	1.2871 $\pm$ 0.0006	38.93	3.97	1.22	14.55 $\pm$ 0.19
N8	0.8328 $\pm$ 0.0254	1.2943 $\pm$ 0.0002	35.44	4.27	1.18	14.46 $\pm$ 0.14
N9	0.8708 $\pm$ 0.0181	1.2886 $\pm$ 0.0006	32.50	4.39	1.37	10.09 $\pm$ 0.13
N10	0.8726 $\pm$ 0.0057	1.2935 $\pm$ 0.0002	32.35	4.37	1.43	10.03 $\pm$ 0.04
N11	0.8805 $\pm$ 0.0135	1.2878 $\pm$ 0.0006	31.74	4.39	1.38	10.22 $\pm$ 0.07

LOD: Loss on Drying;

*
n = 3;**
n = 5.

Table 4

Floating Efficiency of the Pellets

Form.	Floating Strength ($\mu\text{N/g}$)			
	1 h		9 h	
	Average	SD	Average	SD
F1	1287	360	1334	376
F2	2348	406	1880	298
F3	1619	325	1486	214
F4	2881	476	2287	305
F5	3484	478	3093	416
F6	4072	594	3491	404
F7	3864	345	3086	464
F8	4523	290	4148	284
F9	3093	327	2719	319
F10	3109	510	2756	194
F11	3186	261	2545	358

Table 5

Floating Efficiency Regression Result

Variables	Pellet Porosity		Floating Force at 1 h		Floating Force at 9 h	
	Coefficient	P	Coefficient	P	Coefficient	P
Model		0.002		0.001		0.001
Constant	0.3227	0.000	3042.2	0.000	2620.3	0.000
X1	-0.0170	0.006	373.0	0.004	306.5	0.002
X2	-0.0030	0.395	224.9	0.022	158.1	0.018
X3	0.0462	0.000	876.5	0.000	760.9	0.000
X1 * X2	0.0039	0.244	28.1	0.637	97.5	0.056
X1 * X3	-0.0056	0.121	-26.1	0.660	1.87	0.961
X2 * X3	-0.0016	0.610	-32.8	0.583	18.0	0.648
$R^2 = 0.984$			$R^2 = 0.984$		$R^2 = 0.991$	
$Q^2 = 0.746$			$Q^2 = 0.485$		$Q^2 = 0.555$	

R^2 , goodness of fit; Q^2 , goodness of prediction.

Table 6

Drug Release Kinetics

Form.	Drug Release (%)							
	1 h		3 h		5 h		8 h	
	Average	SD	Average	SD	Average	SD	Average	SD
N1	11.3	1.0	42.8	4.3	75.7	5.6	97.7	4.4
N2	5.6	0.6	28.3	3.2	65.1	4.1	83.0	3.4
N3	5.4	1.0	27.7	1.4	67.2	6.0	89.2	4.8
N4	4.9	0.4	26.5	2.6	58.7	2.3	79.1	3.6
N5	10.9	1.1	44.4	2.1	79.7	4.5	101.3	4.9
N6	6.0	0.5	30.3	5.9	62.0	2.6	83.9	6.9
N7	7.6	1.3	36.4	1.3	72.4	3.2	92.6	2.6
N8	9.2	2.4	34.8	1.6	61.0	4.2	80.7	5.4
N9	8.7	1.4	31.5	3.6	67.4	3.9	90.8	3.7
N10	8.6	0.5	32.4	3.1	67.9	4.3	91.2	4.9
N11	7.9	1.5	31.4	4.7	68.2	3.8	92.4	5.5

Table 7

Dissolution Statistical Analysis and Coefficients of Regression

Variables	% Drug Release 1 h		% Drug Release 3 h		% Drug Release 5 h		% Drug Release 8 h	
	Coefficient	P	Coefficient	P	Coefficient	P	Coefficient	P
Model		0.010		0.006		0.002		0.012
Constant	7.816	0.000	33.306	0.000	67.746	0.000	89.251	0.000
X1	-1.008	0.011	-3.598	0.003	-5.527	0.000	-6.088	0.001
X2	-0.790	0.024	-2.173	0.016	-2.382	0.006	-2.583	0.026
X3	0.738	0.030	2.309	0.013	0.943	0.098	1.049	0.234
X1 * X2	1.171	0.004	2.545	0.006	0.943	0.074	0.945	0.232
X1 * X3	0.216	0.339	0.202	0.695	-0.519	0.256	-0.608	0.416
X2 * X3	0.661	0.029	1.331	0.051	0.325	0.454	0.297	0.681
	$R^2 = 0.958$		$R^2 = 0.967$		$R^2 = 0.980$		$R^2 = 0.954$	
	$Q^2 = 0.664$		$Q^2 = 0.586$		$Q^2 = 0.722$		$Q^2 = 0.623$	

 R^2 , goodness of fit; Q^2 , goodness of prediction