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Dual Mechanism of Microenvironmental pH Modulation and Foam Melt Extrusion to Enhance Performance of HPMCAS Based Amorphous Solid Dispersion

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Abstract

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is an excellent polymeric carrier for melt extrusion amorphous solid dispersion. However, its pH-dependent solubility limits its application, especially for narrow absorption window drugs. The current study proposed a novel dual approach of foam extrusion and microenvironmental pH modulation to overcome this limitation. Sodium bicarbonate was used as a blowing agent and the remaining sodium carbonate acted as an internal pH modifier. Compared with conventional extrusion, foam extrusion dramatically lowered the extrudate physical strength (breaking force and hardness decreased by 20-fold; breaking energy and deformation energy decreased by more than 30-fold). Milling efficiency of foam extrudate was largely improved compared with that of conventional extrudates, demonstrating smaller particle size, larger specific surface area, and ability to pass through a smaller milling screen. The foam extrudate could generate a supersaturation concentration up to 8-fold higher than the solubility of the pure drug. It also significantly enhanced drug dissolution in a two-step biorelevant medium ($p < 0.05$). This novel approach improved both manufacturing processability and dissolution of HPMCAS-based solid dispersions.

Graphical Abstract

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Keywords

Foam melt extrusion; Amorphous solid dispersion; Supersaturation; pH modulation; Hydroxypropyl methylcellulose acetate succinate (HPMCAS); Felodipine

1. Introduction

It is estimated that approximately one third of the approved active pharmaceutical ingredients (APIs) and a majority of the drug candidates in the pipeline are sparingly soluble (Vasconcelos et al., 2007, Williams et al., 2013). Therefore, enhancement of dissolution and solubility of poorly soluble compounds is very important to drug product development. Polymeric amorphous solid dispersion (ASD), in which drugs are molecularly dispersed in a polymeric matrix to form a solid solution or a metastable system, is among the most explored and effective approaches to improving sparingly soluble drugs (Van den Mooter, 2012). Polymeric carriers could enhance physical instability of amorphous drugs (Grohgan et al., 2014) and maximize the effect of super saturation. Polymeric matrices can lower the chemical potential and “freeze” API molecules from molecular mobility, which potentially retards the nucleation and crystallization process (Baghel et al., 2016, Theil et al., 2016). In addition, the presence of certain polymers induces a “parachute effect” by preventing nucleation (Baghel et al., 2018), which can prolong the supersaturation status created by amorphous drugs in the non-sink conditions in the gastrointestinal tract (Li and Taylor, 2018, Sarode et al., 2014, Vo et al., 2017). This will ultimately raise the *in situ* concentration (Brouwers et al., 2009) and therefore enhance flux of drug across the intestinal mucosa (Ueda et al., 2012); (Warren et al., 2010).

Hot-melt extrusion (HME) was originally invented for the plastic and rubber industry at the beginning of the 20th century and was first applied to pharmaceutical formulations in the early 1970s (El-Egakey et al., 1971). Since then, HME has been innovatively customized with various functions and has evolved into a green pharmaceutical production platform

(Repka et al., 2013). It has been applied to formulate versatile dosage forms and has become the most efficient tool to formulate amorphous solid dispersions (Repka et al., 2018). Its unique blending geometry promotes highly localized shear force that enables drug molecules to dissolve and/or disperse in molten polymers (Haser et al., 2016). HME is high throughput, continuous, and systematically able to be scaled up (Repka et al., 2013); (Brown et al., 2014). It can be developed into a continuous manufacturing platform with the application of Quality by Design (QbD) and Process Analytical Technology (PAT) real time monitoring (Islam et al., 2015, Vo et al.), in which the manufacturing process is better controlled and the drug quality is more consistent (Chatterjee, 2012). Hydroxypropyl methylcellulose acetate succinate (HPMCAS) has emerged as an excellent candidate for use in melt extrusion to prepare ASD because of its thermal plasticity and supersaturation sustainability. With an ideal T_g varying from 115–125 °C, HPMCAS can be extruded at a relatively low temperature compared with other cellulosic polymers, while it still can maintain a suitable T_g of generated solid dispersions. Even with moderate drug loading of 20–30% w/w, the T_g of its ASDs could be maintained at >90 °C, implying that the solid dispersion morphology is highly stable (Repka et al., 2013). The presence of HPMCAS in dissolution media can prolong the supersaturation state of amorphous drugs in a non-sink condition (Pinto et al., 2018). This will raise the *in situ* drug concentration at the absorption site (Brouwers et al., 2009) and therefore can enhance the absorption rate and drug bioavailability (Ueda et al., 2012); (Warren et al., 2010). The 3 grades of HPMCAS, which are different in acetic and succinic substituent ratios, have different recrystallization inhibition effects (Ueda et al., 2014) and pH values at which the polymer becomes soluble. The parachute effect and minimum dissolvable pH of HPMCAS decrease in the order: H grade > M grade > L grade (Ueda et al., 2014).

Because HPMCAS is soluble in buffer media with pH > 5, the drug only can be noticeably released from an HPMC AS-based solid dispersion when the dosage form enters the intestine segment. Slow release of the API from the polymer matrices might lead to dosage forms having passed the optimum absorption regions with only a small part of the drug released. Therefore, facilitating drug release quickly after leaving the stomach is crucial for immediate release dosage forms. In addition, the inherent properties of the polymers impede the extrudate milling process, an unavoidable step in the formulation of solid dispersions using HME. At a cool temperature, HPMCAS extrudates are quite hard and might require great energy to break. However, when the extrudates absorb energy, the sample temperature will gradually increase, exceeding the system T_g that results in the extrudates becoming soft, disrupting the milling process. To improve the applicability of HPMCAS-based ASD, it is necessary to enhance its dissolution and improve its milling efficiency.

Microenvironmental pH modulation is a popular approach to improve dissolution of APIs of which solubility is pH dependent (Badawy and Hussain, 2007). A weak acid or base (pH modifier) is used to modify microenvironment pH inside matrices, surrounding API particles/domains that favors for drug dissolution (Taniguchi et al., 2014). This approach uses relatively small amount of a pH modifier that does not change the pH of the bulk dissolution media but it could improve *in vivo* dissolution and bioavailability of pH dependent solubility drugs (Hou et al., 2018, Wairkar et al., 2017, Yang et al., 2014).

Foam extrusion is an innovative approach to assist the melt extrusion process, enhance API dissolution from extrudate and formulate floating dosage forms (Chauvet et al., 2016). CO₂ is the most popular blowing agent which is injected into the extruder barrel in the form of critical fluid or pressurized gas. It could be dissolved into the polymer matrices and played as a plasticizer or a processing aid agent (Sauceau et al., 2011). Ethanol and sodium bicarbonate have also been used as blowing agents in foam extrusion based on liquid/vapor phase transition and thermal degradation, respectively. Foam extrusion using these blowing agents is more controllable than it could be utilized to develop floating drug delivery (Fukuda et al., 2006, Vo et al., 2016). Foam extrusion could also significantly enhance surface area of the extrudate as well as facilitate the post extrusion processing (A. Ashour et al., 2016).

In the current study, performance of HPMCAS-based ASD was improved by a dual mechanism of HME foam extrusion and microenvironmental pH modulation. The foam extrudate milling efficiency was improved significantly because of its loose structure and high brittleness. Meanwhile, the alkaline microenvironment inside the extrudate could speed up the disruption of the polymer matrix when the extrudate made contact with the simulated intestinal environment. A supersaturation was observed with all formulations, and a supersaturating concentration up to 8fold higher than drug solubility could be obtained. This novel approach is a viable method to overcome the disadvantages of HPMCAS-based ASD prepared by hot melt extrusion.

2. Materials and Methods

Materials

The chemical structure of the model drug and polymer was presented in Fig. 1. The United States Pharmacopeia (USP) standard Felodipine (FEL) was procured from Ria International LLC (East Hanover, NJ, USA). HPMCAS L, M, and H grades (USP/NF standard) were kindly gifted by Ashland, Inc. (Lexington, KY, USA). Sodium bicarbonate (SBC) (USP/NF standard) was purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA, USA). Methanol, acetonitrile HPLC grade, and other analytical grade reagents were purchased from Fisher Scientific (Pittsburgh, PA, USA) or VWR (Radnor, PA, USA).

Extrusion processing

Before performing extrusion, the API was screened through a USP #30 mesh sieve, and excipients were separately sieved through a #20 mesh to break aggregates and clumps. A 50-g physical mixture of each formulation was manually mixed by using mortar and pestle according to the equal weight principle until a homogenous mixture was obtained.

The foamed strands were prepared using a twin conical screw counter rotating extruder (Minilab™, Thermo Fisher Scientific, Waltham, USA) equipped with a rectangle die opening of 4×2 mm. The screw length, diameter at the beginning, and diameter at the screw end were 110 mm, 13 mm and 5mm, respectively. The extruder was set to a temperature of 165 °C and a screw speed of 100 rpm. The formulations were manually fed into the feed hopper at the rate of 2 g/min using a sample pusher. The system was started and allowed to equilibrate for 10 min prior to processing. The first 10 g of the extrudate was discarded to

ensure that the samples were collected when the extruder was operating at a steady state. The extrudates were stored in tight glass bottles at 20–25 °C for further processing and characterization.

2.3. Milling process

After extrusion, the obtained extrudate was kept in a cool room at a temperature of 10–15 °C for at least 24 h. It was then milled by using a laboratory grinding mill machine (L1A FitzMill, Fitzpatrick, Illinois, USA) equipped with a round perforations screen (size was 0.51, 0.84, or 1.01 mm). The impact-edged mode (hammer mode) of the blades was utilized, and the blade rotating speed was set at 6000 rpm. The milling process was performed at room temperature (20–25 °C). Extrudate samples were fed manually with the feed rate around 10g/min. The extrudate was broken during collision with the rotating blades. Particles under a certain size limit would pass through the screen and go to the sample collection chamber while the rest would stay in the milling chamber for further milling. The milled extrudate was collected and stored in tight glass vials for further examination.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was utilized to investigate polymorphisms and examine the compatibility of the API and the excipients. The pure API, excipients, their binary mixtures, physical mixtures and formulations were subjected to DSC experimentation (Diamond DSC Perkin Elmer, Waltham, MA, USA). An amount of 2–5 mg sample (for pure compounds) or 8–12 mg (for physical mixtures) were put into a crimped aluminum non-hermetic pan and loaded in the sample chamber of the DSC system. An empty pan with a lid was used as a reference. An inert environment of the sample chamber was maintained by a nitrogen flow of 20 mL/min purging through the system. Samples were kept at equilibrium by holding at a temperature of 40 °C for 2 min and then heated from 40 °C to 200 °C at a heating rate of 20 °C/min. The graph of heat flow over time was recorded for thermal event analysis. The experiment was repeated 3 times for formulations and physical mixtures while a single run was applied for pure materials.

Fourier transform infrared spectroscopy analysis

The extrudate samples were gently ground into a powder form by using a mortar and pestle. Infrared spectra were collected using a Fourier Transform Infrared (FTIR) spectrometer system (Agilent Technologies, Cary 660; Agilent, Santa Clara, CA, USA) fitted with a MIRacle ATR sampling accessory (Pike Technologies, Madison, WI, USA), which was equipped with a single bounce diamond-coated ZnSe internal reflection element. A small amount of sample was placed on top of the diamond crystal and pressed with the MIRacle High-Pressure Clamp. The spectrum was collected from 900 to 4000 cm^{-1} , with 32 scans, and a resolution of 4 cm^{-1} . The experiment was triplicate for each sample.

Scanning electron microscopy (SEM)

The strand cross section or milled extrudate was stuck on aluminum stubs by using carbon patches with dual adhesion sides and placed in the sample coating chamber. The samples were coated in a nitrogen environment that was created by vacuuming the coating chamber

at 40 mmHg followed by filling the chamber with ultra-high purity nitrogen. The samples were coated with an electrically conductive layer (ultrathin gold layer) by using a Hummer® 6.2 Sputtering System (Anatech LTD., Battlecreek, MI, USA) in a reduced pressure environment of nitrogen (120 mmHg) and a sputtering current of 18 mA. The coating duration was 45 s and was repeated 3 times. The samples' topography was examined, and the images were captured using a scanning electron microscope (SEM) (JEOL JSM-5600; JEOL, Inc., Peabody, MA, USA) running at a 5 kV accelerated voltage at 45 x magnification. Three examinations were performed for each sample.

Dynamic vapor sorption

The milled extrudate of formulations was subjected to the water sorption study by using a dynamic vapor sorption system (DVS, Surface Measurement Systems, London, UK). The sample (30–40 mg) was spread out on the sample holder and placed in the sample chamber, which was continuously purged with ultrahigh purity nitrogen. The relative humidity (RH) and temperature of the environment inside the chamber were well-controlled at predetermined values. The samples were exposed to a stepwise RH profile of 0–60–0% with 10% RH change at each step at the constant temperature of 25 °C. Weight changes were monitored by a highly sensitive balance (CahnD200 ultra-microbalance, ± 0.01 mg mass resolution). Equilibrium states were detected by dm/dt at the limit of 0.001%/min before the instrument started the next step. At the beginning, the sample was exposed to 0% RH until an equilibrium was established, and the equilibrated mass at 0%RH was used as the sample intrinsic mass. The water sorption isotherms were calculated using the equilibrated sample mass from each step.

X-ray diffraction

The samples were subjected to X-ray diffraction (XRD) experiments by using a Rigaku X-ray system (D/MAX-2500PC, Rigaku Corporation, Tokyo, Japan) equipped with a copper tube anode and a standard sample holder. The experiments were performed with the following parameters: step width 0.02°/s; 2θ scanning range from 5° to 40°; generator tension (voltage) of 40 kV; generator current 100 mA; and scanning speed 10°/min. The samples were spread on a sample holder and compressed gently with a clean metal bar. The X-ray diffractograms were collected at room temperature (20–25 °C). The experiment was triplicate for each sample.

Experimental design

In this study, a two-level full factorial design was applied to determine the effects of polymer grade, drug load, and blowing agent content on the characteristics of the extrudates such as drug release profile, porosity, break force, water sorption, and particle size of milled extrudates. This screening design of experiment (DOE) allowed for the identification of critical factors and interactions between factors (if present), and for predicting outcomes of the experiments. It was also useful to determine the variation range or input factors to ensure that predetermined properties of the product would be obtained. The correlation between input and output variables was determined by fitting experimental data to a mathematic model, and the fitness was evaluated by statistical analysis. The regression equation was 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} , and a_{i23} are the coefficients of the encoded factors for response i . One-way analysis of variance (ANOVA) was used to evaluate the suitability of the model and the significance of factors. The experiment planning and data analysis were performed using Modde 8.0 software (Umetrics Inc., Sweden).

Texture analyzer

The straight extruded strands were cut into 5–6 cm segments for texture analysis. The breaking force and hardness (deformation force) of the extruded strands were measured by the three-point bending test and deformation test, respectively. These physical strength measurements were performed using a TA-XT2i texture analyzer (Texture Technologies, Hamilton, MA, USA) equipped with a TA-92 adjustable 3-point bend/snap fixture platform and TA-43 3-mm flat end blade. Briefly, for the breaking force measurement, one extruded strand was placed perpendicularly on the two support ridges adjusted to 25-mm gap. For the hardness measurement, one extruded strand was placed directly on the base of the texture analyzer platform, perpendicularly with the blade. The following parameters were utilized for both breaking force and hardness measurement: blade speed pretest: 2.0 mm/s, blade speed during the test: 1.0 mm/s, and post-test speed: 5 mm/s. The blade was set to return to the original position before the end of the test if the force suddenly decreased (indicating that the strand was broken or deformed). The measurement was triggered by a resistant force 0.5 N. The breaking force (3-point bend test) and deformation force (hardness) were determined as the highest values on the force-penetration distance plots. These two tests were repeated 5 times for each formulation. The data were analyzed using Exponent software version 6.1.5.0 (Stable Micro Systems, Godalming, UK).

Drug content analysis

The extrudate was ground into a fine powder using a mortar and pestle. An amount of sample equivalent to around 5 mg of FEL was accurately weighed and transferred into a 100-mL volumetric flask. Acetonitrile (40 mL) and methanol (20 mL) were added to the flask and sonicated for 5 min (Branson 2510, Branson Ultrasonic Corp., Danbury, CT, USA). Phosphate buffer (30 mL, pH=3) was added and shaking was maintained for 10 min before adjusting the volume and mixing well. Samples were then centrifuged at 13,000 rpm (equal to centrifuge force of $16,000 \times g$) for 10 min at 25°C (Centrifuge 5415R, Eppendorf AG, Eppendorf, Germany) and then filtered through 0.2 µm, 13 mm PTFE membrane filters (Whatman Inc., MA, USA). The filtered solution was diluted 10-fold with the mobile phase before loading into the high-performance liquid chromatography (HPLC) autosampler. The test was triplicate for each sample.

2.12 *In vitro* drug release

The milled extrudates (unit dose equal to 5 mg FEL) were subjected to a two-step dissolution test in biorelevant media. Fasted state-simulated gastric fluid (FaSSGF) and

fasted state-simulated intestinal fluid (FaSSIF) composition described in literature (Jantravid *et al.*, 2008; Marques *et al.*, 2011) was used to prepare biorelevant media for the two-step dissolution test. Briefly, calculate materials needed for 9 L of FaSSGF (M1) and for 10 L of FaSSIF (M2). Subtract the amount of materials in M2 to M1, then add an amount of NaOH needed to neutralize HCL in the M1 that led to mixture 3 (M3). Dissolve M1 in 9 L, adjust to pH 1.6 using HCL 1N or NaOH 1N solution to get FaSSGF dissolution medium. Dissolve M3 in 1 L at 37 °C and keep stirring for at least 2 h (solution A). Withdraw 9 mL FaSSGF and 1 mL solution A prepared above and vortex for 30 s. Monitor amount of HCL and NaOH used while adjusting the pH of the mixed solution to 6.5. From this number, calculate amount of NaOH or HCL needed to add into solution A (solution A adjusted) so that a solution pH 6.5 would be obtained when 450 mL FaSSGF and 50 mL solution A adjusted was mixed.

The test was performed in 450 mL FaSSGF for the first 30 min, then 50 mL solution A adjusted was added resulting 500 mL FaSSIF dissolution medium. Continue the dissolution test with for another 420 min. The USP dissolution apparatus type 2 (Hanson SR8; Hanson Research, Chatsworth, CA, USA) was used with a temperature of $37 \pm 0.5^{\circ}\text{C}$ and paddle rotation speed of 50 rpm. A volume of 2.0 mL dissolution media was withdrawn at each time point and 2.0 mL fresh dissolution media was added for compensation. The samples were subsequently filtered through 0.2 μm , 13 mm PTFE membrane filters (Whatman Inc., MA, USA) and diluted with an equal volume of an acetonitrile:methanol (2:1) mixture for HPLC analysis. Dissolution test was performed on three vessels for each sample.

High-performance liquid chromatography analysis

HPLC analysis was performed 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 μm , 250×4.6 mm). The HPLC 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 3:2:1 ratio (v/v). The HPLC parameters were set as follows: elution rate of 1.0 mL/min, injection volume of 10 μL for the assay samples and 50 μL for the dissolution samples,

and wavelength of 362 nm.

Particle size measurement

The sample size analysis was performed using a Saturn DigiSizer II system (Micromeritics Instrument Co., Norcross, GA, USA). The particle size distribution was determined based on the Mie theory of the relationship between light scattering angle and particle size equivalent to spherical diameter. A pH 4.0 phosphate buffer solution was used as the media for dispersing samples. An amount of 3–5 g milled extrudate was transferred slowly into the ultrasound- dispersing chamber to obtain a beam obscuration from 25–35%. Samples were dispersed for 15 seconds by a build-in sonication probe before measuring the size, and the system was rinsed 3 times before changing the sample. The measurement was repeated 5 times for each sample, and the size distribution was calculated by DigiSizer II software.

Surface Area Measurement

The specific surface area of samples was measured based on the Brunauer-Emmett-Teller (BET) equation of isothermal gas adsorption. The Gemini VII 2390 Surface Area and Porosity system (Micromeritics, Norcross, GA, USA) equipped with a FlowPrep 060 sample degas unit. Prior to the measurement, samples were loaded in a sample tube and purged with ultrahigh purity nitrogen, flow rate 30mL/min, at 40 °C for 60 min. A sample tube was then attached to main unit along with a balance tube loaded with glass beads. Ultrahigh purity nitrogen and helium gas supplies was used to control adsorption and desorption. The adsorption amount at different pressure was measured and data were analyzed using the Gemini VII 2930 software suite (Micromeritics, Norcross, GA, USA). The measurement was repeated 5 times for each sample.

3 Result and discussion

3.1 Foam Extrusion

In the current study, FEL was used as a model drug and different grades of HPMCAS were used as polymeric carriers for ASD. HPMCAS has been demonstrated as an excellent matrix-forming agent for ASD both in terms of maintaining supersaturation and ensuring physical stability. However, HPMCAS is a pH-dependent water-soluble polymer that slowly dissolves in alkaline or neutral pH buffers. This might result in the APIs not dissolving completely when passing through the optimum absorption region.

Sodium bicarbonate was used as a foaming agent. Under the effect of the operating temperature, which was higher than the thermal degradation point of SBC, carbon dioxide was generated and worked as a blowing agent. Inside the barrel, pressure applied to the formulation was relatively high, forcing the generated CO₂ to be dissolved/compressed in the molten mass. Once the extrudate exited, the extruder pressure applied on the extrudate was released, causing CO₂ to expand and blow the molten matrix. Simultaneously, the extrudate temperature dropped below its glass transition temperature making the molten mass hard enough to support the created foam structure. Compared with melt extrusion using physical blowing agents such as ethanol (Vo et al., 2016), supercritical CO₂ (Verreck et al., 2007), and pressurized CO₂ (Verreck et al., 2005), the extrusion system in this study was relatively simple. There was no customized functional module needed, and the extrudate foam structure could be controlled by extrusion parameters utilized when performing a conventional extrusion. In addition, the current extrusion process did not create any risk of fire or explosion.

A series of preliminary studies were conducted to determine the parameters for experimental feasibility. On the DSC thermogram for SBC, a broad exothermal peak started at 110 °C and finished before 170 °C (Fig. 2), its thermal degradation peak. Therefore, the optimal extrusion temperature was determined as 170 °C, which was the lowest temperature ensuring a complete thermal degradation of SBC. The material feeding rate was fixed at 2 g/min, and the screw speed was set at 100 rpm to satisfy various requirements such as feeding material consistently, filling up the barrel with molten mass, generating suitable foamed strands, and homogenizing the drug in the polymer matrix. The DOE was used to elucidate the effects of

formulations on the properties of the extrudate. Drug load, foaming agent content, and polymer grade were chosen as independent factors with variable ranges of 10–20%; 5–10%; and either L, M, or H grade, respectively. HPMCAS content was considered as a compensation variable of the formulations. The SBC range of 5–10% was chosen so that a suitable foamed structure could be obtained.

All 15 DOE formulations and 3 reference formulations shown in Table 11 were successfully prepared. The extrudates of DOE formulations were opaque-white foamed strands, while clear- yellowish glassy strands were generated in the three reference formulations (Fig. 6). Melted FEL exhibited plasticized and/or lubricant effects, which kept the torque relatively low. The retention time of the formulations in the barrel was approximately 1 min.

Mechanical strength and milling efficiency

Milling efficiency is largely dependent on texture properties of the extrudates, which could exhibit hardness and brittleness. A weak and brittle extrudate would ease the milling process. In this study, three-point bending and hardness tests were utilized to determine the break force and deformation force that were related to milling processability of the extrudates. The extrudate breaking energy and deformation energy, which represented the required input energy in a milling process, were also calculated via area under the curve, as shown in Fig. 4 and Fig. 5.

The experimental results showed that mechanical strength of the extrudates largely depended on its formulation composition, and foam extrudate was significantly weaker than the corresponding conventional extrudate. The details regarding the extrudate physical strength are shown in Table 2, and statistical analysis of the correlation between the formulation composition and extrudate physical strength are presented in Table 3. All three independent variables significantly influenced the physical strength of the foam extrudate. Blowing agent and drug load had a negative effect on the mechanical strength, or the higher the blowing agent content and drug load, the weaker the resulting extrudate. Even though both variables were significant ($p < 0.05$), the effect of blowing agent was larger than that of drug load, as shown in Fig. 3. In addition, the coefficients of the blowing agent were more than 4 times (effect to break force) and 7 times (effect on hardness) higher than that of drug load (Table 3). Polymer grade had a significant effect on both brittleness and hardness of the extrudate in the order: H grade < M grade < L grade. Using HPMCAS H grade as a polymeric carrier would facilitate the milling process the most among the three polymer grades.

Related to milling ability, foam extrudate could be easily milled through a 0.51 mm screen while 1.01 mm was the smallest screen that the conventional extrudate could be milled through. Even with a 1.01 mm screen, the conventional extrudate tended to stay longer in the milling chamber, which got hotter with milling time. More importantly, the milling screen started to be blocked with softened extrudate at the end of the milling process (25 g milling batch), and this did not happen to the foam extrudates even with a smaller screen of 0.51 mm. This suggested that milling conventional extrudate with a 1.01 mm screen would be disrupted if running for a longer time. The same observation was reported in a study on foam extrusion with HPC using pressurized CO₂ as a blowing agent (A. Ashour et al.,

2016). Obviously, foam extrusion could significantly improve milling efficiency of the extrudate.

Even though the polymer grade largely influenced the physical strength of extrudates, it had an insignificant effect on the particle size of both the foam and conventional milled extrudates. This could be explained by the fact that the particle size was mainly governed by the screen opening and the angle between the extrudate fractures' travel direction and the milling screen. The rotation hammers helped break extrudates and accelerated them before hitting the milling screen for further breaking. The presence of foam was found to largely influence the particle size, with milled foam extrudates were 2-fold smaller than conventional samples, and factors that controlled the foam structure (drug load and blowing agent) significantly influenced the particle size ($p < 0.05$). This indicated that the discrete structure of extrudate created numerous weak points, facilitating extrudate fracture during collision between fractures, fractures with the blades, and fractures with the milling screen.

Micromeritics properties

Conventional extrudates appeared as clear glassy strands, while all the extrudates of DOE formulations were opaque, foam-like strands (Fig. 6 A, B). The conventional extrudates had a solid, consistent internal structure, while DOE formulations exhibited a foam structure with numerous vacant spaces inside resulting from the expansion of CO₂ and H₂O (Fig. 6 C and D). The internally discrete structure of the foam extrudates explained their weak physical strength and therefore higher milling processability. The milled extrudate of the reference formulations exhibited a regular surface while the counterparts had a rough irregular surface (Fig. 6 E and F). With the same milling process (screen size of 1.01 mm), the average particle size of conventional extrudates was more than 2-fold larger than that of the foam extrudates. Drug load and blowing agent were found to significantly influence the particle size ($p < 0.05$), while polymer grade exhibited insignificant effects ($p > 0.7$). Even though the polymer grade largely influenced the physical strength of the extrudates, it had an insignificant effect on the particle size of both foam and non-foam extrudate.

Regarding the specific surface area of milled extrudate (using a 1.01 mm screen), the foam extrudate samples were 1.5–7-fold larger than that of conventional extrudates (Table 4). The increase of specific surface area came from both smaller particle size and irregular surface of the milled extrudates, which resulted from the foam structure of the extrudate. The foam extrudate also possessed numerous capillaries that significantly added up to the surface area.

Saturate water sorption of milled extrudates at 60% RH is presented in Table 4. Compared with conventional extrudates, the foam extrudate had a higher saturated water sorption as a result of the larger surface area. Water sorption also heavily depended on the polymer grade in the order: grade L > grade M > grade H, resembling the hydrophilic order. The regression result shown in Table 5 demonstrated that drug load and polymer grade significantly governed the water sorption of the foam extrudate. These two factors also controlled the hydrophobic properties of the matrices because FEL was a hydrophobic compound, and there was a difference in hydrophobicity of polymer grades following the order: grade L < grade M < grade H. SBC content had significant effects on the size and surface area; however, it might not have been significant enough to create a noticeable effect on water

sorption. The difference between water adsorption and desorption processes of the milled extrudate at RH > 10% shown in Fig. 7 indicated that capillaries were present in the milled extrudate samples. These capillaries were created by volatile CO₂ expansion and evaporation, leaving vacant spaces inside the extrudates during the extrusion process.

Polymorphism of API

The XRD results demonstrated that FEL material and SBC were crystalline, exhibiting multiple narrow characteristic peaks (Fig. 8). Sodium carbonate obtained from thermal degradation of SBC (by curing pure SBC at 170 °C for 15 min) also existed in the crystalline form, showing narrow peaks on its diffractogram. All three grades of HPMCAS were amorphous, inferred from only a broad halo pattern, which was typical for the amorphous form presented on their diffractograms. For the extrudate of DOE formulations, all peaks disappeared and only a broad amorphous halo was observed on their diffractograms, confirming that crystalline FEL underwent amorphous transformation. Sodium carbonate remaining after the extrusion might have molecularly dispersed in the polymeric matrices because there was no crystal trace shown on the diffractograms of the extrudate samples.

The thermal behaviors of materials and formulations were elucidated using DSC. No thermal event was detected in the range of 40–190 °C on the thermogram of all 3 grades of HPMCAS, suggesting their amorphous nature. An exothermic peak at 146 °C presented on the thermogram of FEL material was the melting point of crystalline FEL. There was no melting peak on the thermograms of all extrudate samples (Fig. 2), which further confirmed crystalline FEL was transformed into an amorphous form, and the foaming effect of SBC was maximized.

Because the extrusion temperature (170 °C) was higher than the API melting point (146 °C), the extrusion process followed a miscibilization regime, in which melted FEL is dispersed and miscible with molten HPMCAS to form a molecular dispersion (Repka et al., 2018). In addition, the T_g of HPMCAS was relatively high so that drug molecules would be frozen in the polymer matrix once the extrudate was cooled down to room temperature. The calculation of T_g (Sri et al., 1992) of the prepared ASDs was remarkably higher than the storage temperature, ensuring the formulations were physically stable.

On the FT-IR spectra, there were changes in characteristic peaks related to the amine group ($>N-H$) and carbonyl group ($-C=O$) of FEL (the chemical structures shown in Fig. 1). The strong sharp peak at 3367 cm^{-1} on the FT-IR spectrum of the FEL raw material became lower and broader on the IR spectrum of pure amorphous FEL prepared by melt-quenching crystalline FEL (Fig. 9A). In addition, the peak shifted from 3367 cm^{-1} to 3331 cm^{-1} , resulting from the change in the hydrogen bond of the $>N-H$ group of FEL. Hence, broadening and shifting of the peak at 3368 cm^{-1} was an indication of transformation from crystalline to amorphous of FEL (Konno et al., 2008, Van Eerdenbrugh and Taylor, 2011). On the spectra of all extruded samples, the characteristic peak of crystalline FEL was absent, indicating that FEL was completely amorphized via the extrusion process. This finding was in agreement with the results obtained from XRD and DSC experiments. In addition, the absence of this peak suggested an establishment of hydrogen bonds between the $>N-H$ group of FEL with the $>C=O$ (in COOH) group of HPMCAS.

Similarly, another event observed on the FT-IR spectra was the peak at 1687 cm^{-1} which was typical for the -C=O group of crystalline FEL (Srinivasan et al., 1992). It slightly shifted to 1678 cm^{-1} when FEL transformed to amorphous (Fig. 9A). However, in the ASDs, this peak shifted to around 1695 cm^{-1} (Fig. 9B), indicating a weak interaction between the carbonyl group of FEL and a hydroxyl group of HPMCAS. These API-polymer interactions had potential to physically stabilize the ASDs and to prolong the supersaturation generated by the ASDs in dissolution media.

Physical stability of the formulations was investigated by packing the samples into tight, amber glass vials and storing in a stability chamber at $40\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}/75\%\text{ RH} \pm 5\%\text{ RH}$ for 6 months. The samples were then subjected to DSC and XRD examinations. There was no new noticeable event detected via DSC (Fig. 2) or XRD (Fig. 8) investigation of all stability samples, confirming that the amorphous state of FEL in the solid dispersions was maintained.

Dissolution in biorelevant media

To understand the behavior of the formulations in the gastrointestinal tract environment, a two- step biorelevant dissolution (30 min in FaSSGF followed by 420 min in FaSSIF) was utilized to test the milled extrudates. The dissolution profiles of 15 DoE formulations and crude API are presented in Fig. 11. In the first 30 min, there was no detectable API in the dissolution medium (FaSSGF). In the acid environment, HPMCAS (all three grades) was insoluble; thus, the intact matrix held the API inside, preventing it from release. In the raw material sample, the API slowly dissolved. Once switched to the FaSSIF environment, API started to be released from the extrudates. The dissolution rate was largely different between different formulations. Drug release from samples with HPMCAS L grade was the fastest, followed by the M grade formulations, and H grade formulations were the slowest. The dissolution of all extrudates was higher than that of pure API, and supersaturation was observed with all formulations. A supersaturation as high as $6.5\text{ }\mu\text{g/mL}$ or 8-fold higher than the FEL solubility in FaSSIF ($0.76\text{ }\mu\text{g/mL}$) was observed. Once FEL concentration in the dissolution media reached a certain level ($>6.0\text{ }\mu\text{g/mL}$) it started to decrease slowly, but it was still much higher than the FEL solubility in the test time frame. This confirmed the parachute effect of HPMCAS that has been reported in literature (Curatolo et al., 2009, Laine et al., 2016, Que et al., 2018). Dissolution of all HPMCAS L grade samples demonstrated the fastest decrease after reaching a peak, while the HPMCAS H grade samples did not reach a peak, and the concentration was still increasing at the end of the test.

The regression results showed that all three independent variables significantly influenced ($p < 0.015$) the dissolution at the time point of 60 min (30 min in the FaSSIF). Drug load had a negative effect, blowing agent demonstrated a positive effect, and polymer grade had an increasing effect in the order of H grade $<$ M grade $<$ L grade. The effects of drug load and blowing agent on the drug dissolution are illustrated in Fig. 10, demonstrating that the relative comparison between the effect of these two independent variables depended on the polymer grade. With the HPMCAS grade L, the effect of drug load was more noticeable compared with that of the blowing agent. This indicated that both the hydrophilic property (affected by drug load) and microenvironment pH (governed by remaining sodium

carbonate) were comparably critical to the dissolution at 30 min in FaSSIF. However, in the case of the M grade and H grade, the effect of blowing agent dominated the effect of drug load, or the microenvironmental pH modulation was much more important than hydrophilicity of the matrix. These two polymer grades were soluble in a higher pH buffer and dissolved/swelled slower in the dissolution medium. Therefore, alkaline microenvironment would have more of an effect on speeding up disintegration of the extrudate matrix, resulting in higher dissolution.

Effect of alkaline excipient (remaining sodium carbonate)

During the extrusion process, sodium carbonate was generated from thermal degradation of SBC, and it still remained in the extrudate after extrusion. It could be hypothesized that permeating dissolution media would dissolve the remaining sodium carbonate, creating an alkaline microenvironment inside the extrudate matrix that could speed up the dissolution/disintegration of the HPMCAS matrix.

In the acidic environment of FaSSGF, sodium carbonate on the surface of the extrudates was neutralized and the HPMCAS matrix maintained intact, preventing dissolution medium from penetrating into the matrix. When the extrudate came in contact with FaSSIF (pH 6.5), the outer layer of extrudate matrix would gradually swell and dissolve making it became permeable to dissolution fluid. Therefore, water could penetrate into the extrudate matrix and dissolve the remaining sodium carbonate inside. The alkaline microenvironment created locally by dissolved sodium carbonate could make HPMCAS partly dissolve/swell in advance, which would finally speed up dissolution/disintegration in the dissolution media.

To separate the effect of surface area on dissolution enhancement, unfoam extrudates were milled twice, first through a 1.01 mm screen and then through a 0.51 mm screen. The obtained milled extrudates had a smaller average particle size ($128 \pm 12 \mu\text{m}$ for L grade, $124 \pm 18 \mu\text{m}$ for M grade, and $106 \pm 15 \mu\text{m}$ for H grade) and comparable specific surface area ($0.268 \pm 0.0031 \text{ m}^2/\text{g}$ for L grade, $0.256 \pm 0.0062 \text{ m}^2/\text{g}$ for M grade, and $0.298 \pm 0.0087 \text{ m}^2/\text{g}$ for H grade) with that of the DOE formulations. However, dissolution of non-foam extrudates (no alkaline excipient) was much lower than the dissolution of all DOE formulations with the same polymer grade. Fig. 12 shows that the remaining sodium carbonate could dramatically enhance dissolution of the extrudates, confirming the above hypothesis. The hypothesis also agreed with the DOE regression results, which showed that the blowing agent had a significant positive effect ($p = 0.000$). The more SBC presented in the formulation (more remaining sodium carbonate in the extrudate), the higher the dissolution at 30 min that was observed.

4. Conclusion

The HPMCAS-based ASDs were successfully prepared by application of foam extrusion using SBC as a blowing agent. The crystalline FEL was completely amorphized via the melt extrusion process, and the obtained ASDs were physically stable for at least 6 months in an accelerated condition. The foam extrusion improved both milling ability and milling efficiency of the extrudates. Independent variables including drug load, blowing agent, and polymer grade significantly influence the physical strength and dissolution of the extrudates.

The large enhancement of dissolution was a result of increased surface area and microenvironmental pH modulation. A supersaturation 8-fold higher than FEL solubility was generated and maintained for several hours. The novel combination of foam extrusion and internal pH modulation is an efficient approach to enhance performance of HPMCAS-based ASDs.

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Abbreviations:

API	active pharmaceutical ingredient
ASD	amorphous solid dispersion
HME	Hot-melt extrusion
HPMCAS	Hydroxypropyl methylcellulose acetate succinate
PAT	Process Analytical Technology
QbD	Quality by Design

Reference

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Fig. 1:
Chemical structure of felodipine (A) and HPMCAS (B)

Fig. 2:
Thermodiagrams of API, foaming agent and representative high drug load formulations with different polymer grades stored 6 months in accelerated stability condition (40 ± 2 °C/ $75 \pm 5\%$ RH).

Fig. 3: Response surfaces described the effects of drug load and blowing agent to the break force and hardness of the extrudates.

Fig. 4:
Representative plots of force versus penetration distance of extrudate hardness test and the calculation of extrudate deformation energy.

Fig. 5:
Representative texture profiles of 3 points bend test of the extrudate and the calculation of extrudate break energy.

Fig. 6:
Digital images of (A) conventional extrudate and (B) foam extrudate of HPMCAS M grade.
Representative SEM images of cross section of (C) conventional extrudate and (E) its milled extrudate; (D) cross section of foam extrudate N13 and (F) its milled extrudate.

DVS Change In Mass Plot

Fig. 7:

Representative plots of water sorption in response to the environment relative humidity of foam extrudate formulations with A) HPMCAS L grade (N4), B) HPMCAS M grade (N8), and C) HPMCAS H grade (N12).

Fig. 8:
X-Ray diffractograms of API, excipients, and 6 month accelerated stability samples (high drug load formulation with three different HPMCAS grades).

Fig. 9: FTIR spectra of materials and different polymorphisms FEL (A), and representative extrudate formulations with three polymer grades that showed peak shift at 1687 cm^{-1} and peak disappearance at 3367 cm^{-1} (B).

Fig 10: Contours plotted the effect of drug load and blowing agent to dissolution at 30 min in FaSSiF of the extrudate with different polymer grades: A) HPMCAS L, B) HPMCAS M, C) HPMCAS H.

Fig. 11: Dissolution profiles of representative DoE milled extrudates (2 formulations for each polymer grade and the center formulation) compared to that of crude API in the two-step biorelevant medium

Fig. 12:
The effect of microenvironment pH modulation on dissolution of milled extrudates in the two-step biorelevant medium.

Table 1:

Detail of the DoE formulations

Experiment Name	Run Order	Drug load (%)	Blowing agent ratio (%)	Polymer grade
N1	13	10	5	L
N2	2	20	5	L
N3	10	10	10	L
N4	3	20	10	L
N5	1	10	5	M
N6	12	20	5	M
N7	8	10	10	M
N8	4	20	10	M
N9	5	10	5	H
N10	7	20	5	H
N11	9	10	10	H
N12	6	20	10	H
N13	15	15	7.5	M
N14	14	15	7.5	M
N15	11	15	7.5	M
L	16	15	0	85
M	17	15	0	85
H	18	15	0	85

Table 2:

Physical strength of the extrudates (n=5).

Exp. Name	Deformation force (N)		Deformation energy (mJ)		Breaking Force (N)		Breaking energy (mJ)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
N1	207.72	20.48	173.19	13.21	29.91	2.62	6.712	0.457
N2	174.28	11.68	131.56	13.19	28.9	2.22	6.386	0.437
N3	57.98	6.47	21.17	1.64	12.5	1.58	1.406	0.098
N4	30.83	3.24	9.7	0.64	6.35	0.44	0.582	0.033
N5	217.5	17.59	160.19	17.84	28.52	1.44	5.95	0.403
N6	195.35	10.01	128.46	8.29	24.3	2.36	6.27	0.519
N7	41.61	5.15	8.22	0.63	11.68	1.65	1.391	0.088
N8	19.72	1.95	5.34	0.28	6.15	0.63	0.585	0.043
N9	142.23	15.12	56.38	3.05	11.23	1.50	1.84	0.130
N10	125.42	7.89	48.48	2.79	10.41	0.57	1.377	0.100
N11	16.41	1.48	2.55	0.20	3.79	0.56	0.332	0.026
N12	14.55	1.21	4.07	0.32	2.6	0.24	0.22	0.015
N13	118.02	7.41	58.45	3.46	17.47	1.81	3.636	0.320
N14	131.56	16.98	63.75	6.94	17.66	2.54	3.349	0.276
N15	126.76	13.94	61.23	6.74	16.96	0.87	3.535	0.352
Unfoam Grade L	503.78	22.56	383.30	31.93	51.28	5.24	19.475	2.158
Unfoam Grade M	448.46	19.30	347.69	30.17	49.79	6.12	20.281	2.349
Unfoam Grade H	257.69	22.49	158.79	12.87	33.98	4.12	7.146	0.624

Table 3:

Regression result of physical strength.

Variable	Deformation force		Deformation energy		Breaking Force		Breaking energy	
	Coeff	P	Coeff	P	Coeff	P	Coeff	P
Constant	108.00	0.000	2.90	0.000	15.23	0.000	62.18	0.000
Drug	-9.61	0.003	-0.16	0.088	-1.60	0.002	-7.39	0.039
Blow	-70.40	0.000	-1.94	0.000	-7.15	0.000	-52.56	0.000
Grade(L)	7.66	0.014	0.66	0.001	3.16	0.000	15.98	0.003
Grade(M)	15.53	0.001	0.72	0.000	2.65	0.000	8.89	0.026
Grade(H)	-23.19	0.000	-1.38	0.000	-5.81	0.000	-24.87	0.000
Drug*Blow	1.53	0.392	-0.09	0.233	-0.49	0.086	4.90	0.093
Drug*Grade(L)	-3.38	0.158	-0.08	0.383	-0.08	0.785	-3.79	0.254
Drug*Grade(M)	-0.47	0.836	0.05	0.584	-0.63	0.089	-0.53	0.871
Drug*Grade(H)	3.85	0.097	0.03	0.731	0.71	0.042	4.33	0.174
Blow*Grade(L)	1.31	0.549	-0.51	0.002	-1.69	0.002	-9.07	0.027
Blow*Grade(M)	-10.85	0.004	-0.40	0.006	-0.80	0.044	-11.13	0.016
Blow*Grade(H)	9.54	0.004	0.91	0.000	2.49	0.000	20.20	0.001
Goodness of the model	Q2 = 0.713 R2 = 0.997		Q2 = 0.52 R2 = 0.995		Q2 = 0.584 R2 = 0.996		Q2 = 0.483 R2 = 0.991	

Table 4:

Micromeritics properties of the milled extrudates.

Exp. Name	Concentration at 30 min in FaSSIF (µg/ml)		Particle size average (µm)		Surface area (m ² /g)		Water sorption at RH 60% (%)
	Mean *	SD	Mean *	SD	Mean **	SD	Mean
N1	5.021	0.412	361.3	22.4	0.1363	0.0107	3.660
N2	4.077	0.720	320.3	15.9	0.1173	0.0027	3.026
N3	6.573	0.650	256.7	17.0	0.2518	0.0013	4.058
N4	5.469	0.625	206.3	10.6	0.4624	0.0073	3.032
N5	1.571	0.341	352.4	17.0	0.3592	0.0089	3.086
N6	1.332	0.045	297.0	13.7	0.1867	0.0041	2.741
N7	3.521	0.425	280.4	14.7	0.2252	0.0028	3.148
N8	2.955	0.235	260.4	14.4	0.2430	0.0010	2.660
N9	0.224	0.014	344.7	20.9	0.2512	0.0030	2.877
N10	0.206	0.178	279.9	17.4	0.1188	0.0027	2.358
N11	0.452	0.391	251.2	16.0	0.4512	0.0052	3.001
N12	0.391	0.277	251.4	14.8	0.2942	0.0089	2.226
N13	2.194	0.284	292.4	18.3	0.3718	0.0086	2.889
N14	2.249	0.310	259.3	15.1	0.3650	0.0076	3.012
N15	2.171	0.686	274.1	16.1	0.3781	0.0090	2.894
Unfoam Grade L	2.996	0.571	615.7	24.6	0.0676	0.0021	2.328
Unfoam Grade M	1.019	0.539	596.3	33.4	0.0688	0.0015	2.175
Unfoam Grade H	0.083	0.032	526.1	28.7	0.0775	0.0047	1.975

*
: n = 3**
: n = 5

Table 5:

Regression result of micromeritics properties.

Variable	Size		Water sorption		Surface		Dissolution	
	Coeff	P	Coeff	P	Coeff	P	Coeff	P
Constant	285.85	0.000	2.978	0.000	0.281	0.000	2.560	0.000
Drug	-17.23	0.032	-0.278	0.000	-0.026	0.314	-0.228	0.013
Blow	-32.26	0.003	0.022	0.364	0.050	0.083	0.632	0.000
Grade(L)	0.36	0.959	0.352	0.000	-0.029	0.325	2.049	0.000
Grade(M)	1.67	0.800	-0.090	0.012	0.023	0.394	-0.316	0.004
Grade(H)	-2.02	0.759	-0.262	0.000	0.006	0.832	-1.733	0.000
Drug*Blow	6.62	0.259	-0.059	0.029	0.030	0.206	-0.046	0.427
Drug*Grade(L)	-2.68	0.696	-0.068	0.037	0.050	0.108	-0.154	0.068
Drug*Grade(M)	2.07	0.774	0.086	0.020	-0.015	0.599	0.034	0.650
Drug*Grade(H)	0.61	0.924	-0.018	0.463	-0.035	0.203	0.121	0.109
Blow*Grade(L)	-13.02	0.100	0.050	0.094	0.040	0.185	0.023	0.747
Blow*Grade(M)	10.13	0.199	-0.028	0.321	-0.055	0.102	0.210	0.031
Blow*Grade(H)	2.89	0.651	-0.022	0.380	0.015	0.558	-0.233	0.013
Goodness of the model	Q2 = 0.353		Q2 = 0.511		Q2 = 0.308		Q2 = 0.449	
	R2 = 0.915		R2 = 0.989		R2 = 0.807		R2 = 0.996	