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Development of a floating drug delivery system with superior buoyancy in gastric fluid using hot-melt extrusion coupled with pressurized CO_2

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The present study aimed to develop a continuous single-step manufacturing platform to prepare a porous, low-density, and floating multi-particulate system (mini-tablet, 4 mm size). This process involves injecting inert, non-toxic pressurized CO_2 gas (P-CO_2) in zone 4 of a 16-mm hot-melt extruder (HME) to continuously generate pores throughout the carrier matrix. Unlike conventional methods for preparing floating drug delivery systems, additional chemical excipients and additives are not needed in this approach to create minute openings on the surface of the matrices. The buoyancy efficiency of the prepared floating system (injection of P-CO_2) in terms of lag time (0 s) significantly improved ($P < 0.05$), compared to the formulation prepared by adding the excipient sodium bicarbonate (lag time 120 s). The main advantages of this novel manufacturing technique include: (i) no additional chemical excipients need to be incorporated in the formulation, (ii) few manufacturing steps are required, (iii) high buoyancy efficiency is attained, and (iv) the extrudate is free of toxic solvent residues. Floating mini-tablets containing acetaminophen (APAP) as a model drug within the matrix-forming carrier (Eudragit® RL PO) have been successfully processed via this combined technique (P-CO_2/HME). Desired controlled release profile of APAP from the polymer Eudragit® RL PO is attained in the optimized formulation, which remains buoyant on the surface of gastric fluids prior to gastric emptying time (average each 4 h).

1. Introduction

Hot-melt extrusion (HME) is a leading technology for the manufacture of solid dispersions using polymers as matrix-forming carriers; various solid dosage forms can be manufactured using this process (Repka et al. 2007; Patil et al. 2014; Alshehri et al. 2015). One of those solid dosage forms is that of a low-density based floating system (Streubel et al. 2002). Floating drug delivery systems developed by the pharmaceutical industry specialists are readily available (Singh and Kim 2000). The advent of innovative techniques has ushered scientists into an era of increasingly productive and cost-effective manufacturing processes. In order to address the common limitations of conventional methods and to overcome the difficulties in formulating floating systems using these methods (Table 1) (Fordtran et al. 1984; Thomas and Stone 1994; Fukuda et al. 2006; Badawy and Hussain 2007; Forslund et al. 2008), a novel-manufacturing platform has been proposed and was compared with the latest technique for manufacturing Floating Drug Delivery Systems (FDDS) (Patil et al. 2015).

Not only has HME gained increasing attention among industrial pharmacy researchers, recently, injecting pressurized carbon dioxide (P-CO_2) gas during the HME process has also received much attention. Injecting P-CO_2 gas during a solvent-free continuous HME process has an added advantage of being adaptable and portable to a hot melt extruder instrument (Ashour et al. 2015).

Most of the conventional methods for preparing floating systems, such as the microsphere and gel formation floating method, depend on the use of organic solvents such as n-hexane, ethanol, methanol etc. (Thanoo et al. 1993; Choi et al. 2002; Galeska et al. 2005; Silva et al. 2005; Dhaliwal et al. 2008). The residual of these solvents can be hazardous to health upon long-term use. Another approach utilizes lipids as low-density floating devices; however, instability and polymorphism of crystalline lipid matrices limits the use of these agents (Chauhan et al. 2005). Additionally, using excipients such as sodium bicarbonate, while extruding the physical blend, affects the stability and compatibility of floating dosage compositions. This can be explained in terms of buoyancy efficiency. The buoyancy lag time for the device can be up to 3 min (Fukuda et al. 2006).

The gastric pH in some patients fluctuates and can reach a pH of up to 7.0, as seen in fasted achlorhydric subjects (Russell et al. 1992; Mathias et al. 2015). Prescribing a floating tablet to these patients would result in an increased lag time owing to the release of CO_2 from the traces of sodium bicarbonate (Fukuda et al. 2006). Consequently, there is a risk that the floating device will escape out of the pyloric sphincter. Further, it will be expelled out of the stomach with chyme during gastric emptying (Hwang et al. 1998; Wei et al. 2001). Other techniques that implement effervescent systems have a drawback, as the system does not float immediately after swallowing the dosage form, since the process of gas generation has a delayed lag time of up to 20 min. Therefore, they could be cleared from the stomach

Table 1: Limitations of former approaches

Approach	Limitation(s)
FDDS prepared by hot-melt extrusion process with the aid of sodium bicarbonate	Patients on salt restriction diets or have congestive heart failure, kidney function impairment, and high blood pressure are on risk by chronic use of these formulations because of high sodium content. Sodium bicarbonate by thermal effect while extruding in conventional extrusion process converts to CO_2, sodium carbonate and water. Therefore, sodium carbonate and water might have an impact on drug stability or drug-excipient incompatibility over period of time.
FDDS that utilize effervescent system	Acid reflux and irritation of esophagus through esophagus sphincter can be caused by these gas-generating systems. Sodium bicarbonate can act as an alkalizer and increase the microenviromental pH by microenvironmental pH modulation that causes some limitations in terms of dissolution aspects especially the APIs that dissolve in acidic media. Gastric rupture caused by excess gas release (when combined with gastric acid).
FDDS that utilize low density lipid	Stability and lipid polymorphism issues.
Microsphere and gel rafting system	Residual Organic solvent in the final product.

before becoming functionally effective (Streubel et al. 2006). Most of these systems are single unit devices (Hwang et al. 1998). Therefore, they lose their benefits early before they have a chance to function as a floating system in gastric media due to their all-or-nothing emptying from the stomach. In order to address the aforementioned issues, a multiparticulate-unit floating system has been developed (Kawashima et al. 1991).

Acetaminophen (APAP) was selected as a model drug in the present study, since it is not a thermolabile active pharmaceutical ingredient (API) and it has been extensively used previously in developing various formulations via the HME technique (Qi et al. 2008). Furthermore, it has a narrow absorption window and is absorbed in the upper intestinal segment (Davis 2005) and it is also prescribed to patients to alleviate abdominal pain after surgical procedures (Hyllested et al. 2002). All these properties make APAP a suitable candidate for developing floating systems. Eudragit® RL PO (EUD), is one of the polymers that have been widely used in HME processing (Zheng et al. 2004; Zhu et al. 2006; Saerens et al. 2011). It is a copolymer that has quaternary ammonium groups. These groups function as salts, increasing the permeability of dissolution media and make this hydrophobic carrier highly permeable. This permeability characteristic makes this polymer a good candidate to comply USP-NF monograph for the extended release preparations of APAP extended release profile specifications.

In the current study, the HME/P-CO_2 approach was used to develop a FDDS based on low-density devices. This single-step, cost-effective, continuous, and efficient combination method for manufacturing floating gastric devices overcomes the limitations of conventional methods. In this process, API and pH-independent polymer are used along with the injection of an inert P-CO_2 gas. This study aimed to investigate the effect of injected inert CO_2 gas on the physico-mechanical properties of the controlled-release hot-melt extrudates to obtain mini-tablets, using EUD as a release-retarding carrier which resulted in optimal buoyancy required for a floating device, compared to the devices prepared by the existing approach.

2. Investigations, results and discussion

2.1. Extrudates physical appearance and milling efficiency

Extrudates were found to be intact for all formulations (Fig. 1) except for the formulation containing 4% and 10% sodium bicarbonate, wherein deformations and dents in some portions of extrudates (non-intact extrudates) were observed. This was owing to thermal effects while extruding the blends and the higher percentage of sodium bicarbonate present in the blend, which resulted in the excess CO_2 release. This, in turn, affects the quality of extrudates for further processing, i.e. mini-tablet pelletization and a variation in the size of the mini tablets would occur. Milling efficiency was significantly enhanced in case of the formulations prepared by injecting P-CO_2 gas (F2 and F5). Therefore, there is a decrease in milling time and increase in milling efficiency.

2.2. SEM investigations

The SEM images as noticed in Fig. 2 (a) of the formulation processed by conventional extrusion method (i.e. with neither P-CO_2 nor incorporating sodium bicarbonate) clearly showed small open pores of approximately 66 μm in size. Since APAP is hygroscopic in nature, an evaporation process inside the barrel of extruder results in the formation of small-opened pores. Usually while processing the formulation at around 100 °C the water molecule droplets present in APAP will evaporate and converted into a gaseous state and in this rapid movement, it generates small pores. In contrast, when the only pure polymer is extruded (i.e. no hygroscopic API), no pores were observed as noticed in Fig. 2 (f). In addition, the mini-tablets obtained using a P-CO_2 approach contained many closed pores of approximately 200 μm in size, covered with a thin layer, as seen in Fig. 2 (b). These covered pores with thin layer has the size of around 200 μm, but still these mini-tablets have more retarding release behavior, because they are less dense. Therefore, they are less immersed and part of them is exposed to the air on the surface of the media. In case of sodium bicarbonate formulation Fig. 2 (c,d), they are all opened small oval pores, and the more retarding release is because they are less dense and more exposed to the air on the top of the media. Interestingly, as noticed in Fig. 2 (e) the pores are larger than 200 μm in size and this explain the more floating period (168 h) in formulation 5 as described in Table 3.

2.3. Density and porosity measurement

Porous extrudates were obtained with the aid of P-CO_2, and these had a relatively lower density and higher porosity, than the formulations prepared using sodium bicarbonate and the

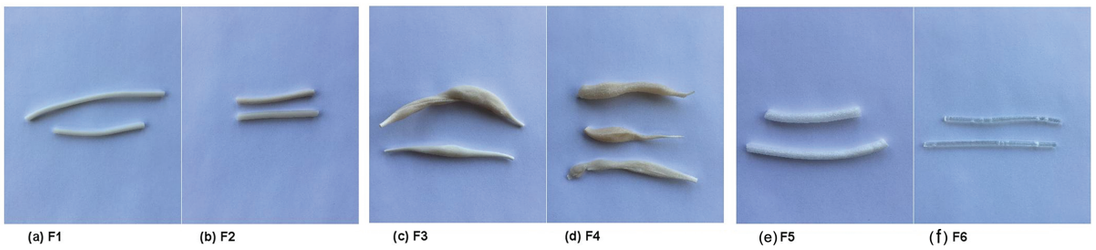

Fig. 1: Digital pictures of the extrudate strands (a) F1: prepared using conventional HME process (control formulation), (b) F2: prepared using HME process with P-CO_2 injection, (c) F3: prepared using conventional HME process with sodium bicarbonate (4%), (d) F4: prepared using conventional HME process with sodium bicarbonate (10%), (e) F5**:** HME process for pure polymer (EUD) with P-CO_2 injection and no sodium bicarbonate, (f) F6**:** conventional HME process for pure polymer (EUD) with no P-CO_2 injection or sodium bicarbonate.

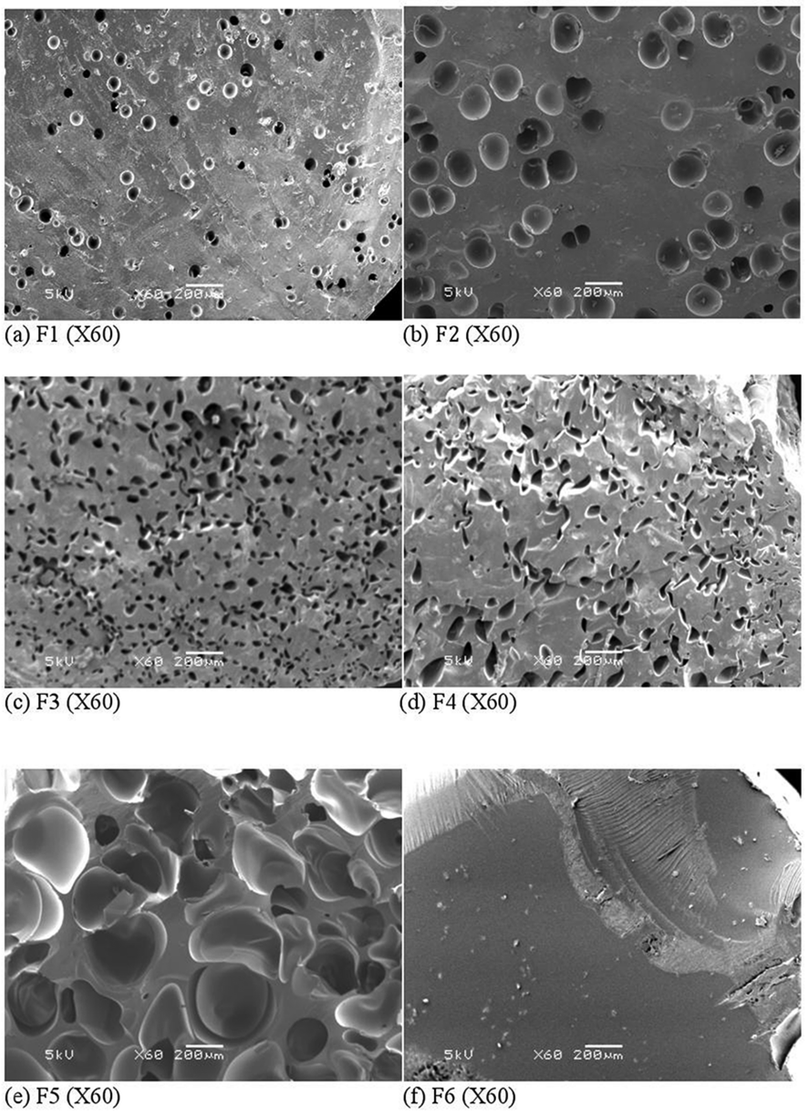

Fig. 2: SEM images of mini tablets. (a) F1: prepared using conventional HME process (control formulation), (b) F2: prepared using HME process with P-CO_2 injection, (c) F3: prepared using conventional HME process with sodium bicarbonate (4%), (d) F4: prepared using conventional HME process with sodium bicarbonate (10%), (e) F5: HME process for pure polymer (EUD) with P-CO_2 injection and no sodium bicarbonate, (f) F6: conventional HME process for pure polymer (EUD) with no P-CO_2 injection or sodium bicarbonate.

Table 2: Formulation compositions

Components	F1	F2[a]	F3	F4	F5[a]	F6
APAP %(w/w)	30	30	30	30	N/A	N/A
Eudragit® RL PO %(w/w)	70	70	70	70	100	100
Sodium bicarbonate %(w/w)	N/A	N/A	4	10	N/A	N/A

[a]Formulation prepared by injecting P-CO_2 gas in Zone 4.

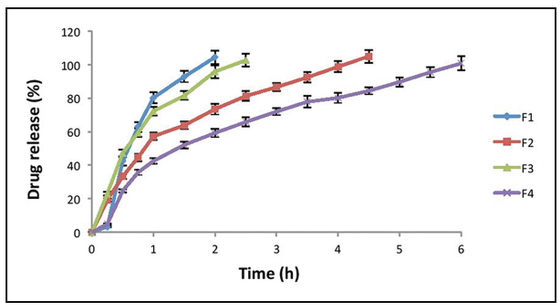

Fig. 3: Drug release % in 0.1 N HCl. F1: prepared using conventional HME process (control formulation), F2: prepared using HME process with P-CO_2 injection, F3: prepared using conventional HME process with sodium bicarbonate (4%), F4: prepared using conventional HME process with sodium bicarbonate (10%).

conventional method and the data for porosity measurement are presented in Table 3. It has been concluded that the higher %porosity values are with the formulations prepared by P-CO_2 (F2 and F5) in a reproducible manner among batches. However, the porosity was not reproducible with the formulations of sodium bicarbonate (F3 and F4), which appeared to be variable. These data are in a good agreement with buoyancy efficiency in these formulations. P-CO_2 gas generates regular rounded and well-ordered pores and intact extrudate strands, whereas the extrudates prepared by incorporating sodium bicarbonate suffuse and liberate some carbon dioxide molecules, resulting in smaller, random, oval pores in some portions of extrudates and produce clumsy and non-intact extrudate strands. Thus, thermal decomposition of sodium bicarbonate inside the barrel results in liberation of CO_2, water molecules, and anhydrous sodium carbonate in the softened polymer (Fukuda et al. 2006). This might be a problematic issue in the term of formulation stability over a period of time.

2.4. Buoyancy efficiency and dissolution profile

As shown in Table 3, the lag time for the proposed approach (HME/P-CO_2) is 0 sec, compared with that of the traditional HME approach (approximately 2 min, $P < 0.05$). The optimized formulation developed using a HME/P-CO_2 approach had a floating period of around 54 h. Also, it had an efficient floating behavior with an optimal drug release pattern. Formulations containing sodium bicarbonate (F3 and F4) displayed a more extended floating period owing to traces of CO_2 in the manufactured mini-matrices. These traces are released gradually upon contact with gastric media, forming new pores that are neither filled nor saturated with gastric media, thereby extending the buoyancy of the preparations. The density of formulation F5 was low (data not shown) owing to the absence of API, resulting in a longer floating period than that observed for F3 and F4. Additionally, F5 did not disintegrate even after 7 days. In contrast, in the case of (F2), the saturated mini-matrices increased the weight of the mini tablets, until they eventually sank and disintegrated.

In vitro release profiles of injected P-CO_2 mini-tablets in acidic media have given the optimal sustained-release profile that meets USP-NF specifications after 3 h i.e. not less than 85% of APAP should be released. In this study, the *in vitro* release profile of optimized formulation F2 was approximately 86.5%, in 3 h (Fig. 3). Interestingly, F4 gave the most retarding release behavior and this is because of the new born pores that formed when contacted to the media upon time through the traces of sodium bicarbonate that has not liberated the CO_2 by thermal effect while extruding the blend. Therefore, less immersed in the media and most parts of mini tablets are exposed to the air. These data in a good agreement with extended buoyancy efficiency data in F4. In contrast, in F2, CO_2 might be entrapped in the closed pores, and the glassy, transparent thin layer covers the pores. These covered pores hold, embed and incorporate the API firmly. Therefore, the gradual release of API takes place upon contact with gastric media after swelling of this hydrophobic thin layer. Therefore, results demonstrate that this floating device is safe in regard of burst and faster or immediate release of the drug as

Table 3: Process parameters and floating properties

	Process-related measurements				Floating properties-related measurements		
Formulation	Screw speed (rpm)	Temperature °C	Torque %	% Porosity	Lag time (s)	Floating periods (h)	Drug release percentage after 1 h
F1	100	90	70-81	53.66	Rotated and sank	N/A	80.2
F2[b]	100	110	83-86	63.85	0	54	57.2
F3	100	110	69-78	54.00	120	72	72.1
F4	100	110	67-79	55.13	32	144	42.5
F5[b]	100	165	82-86	66.50	0	168	N/A
F6	100	150	74-79	53.62	Sank	N/A	N/A

[b]Formulation prepared by injecting P-CO_2 gas in Zone 4.

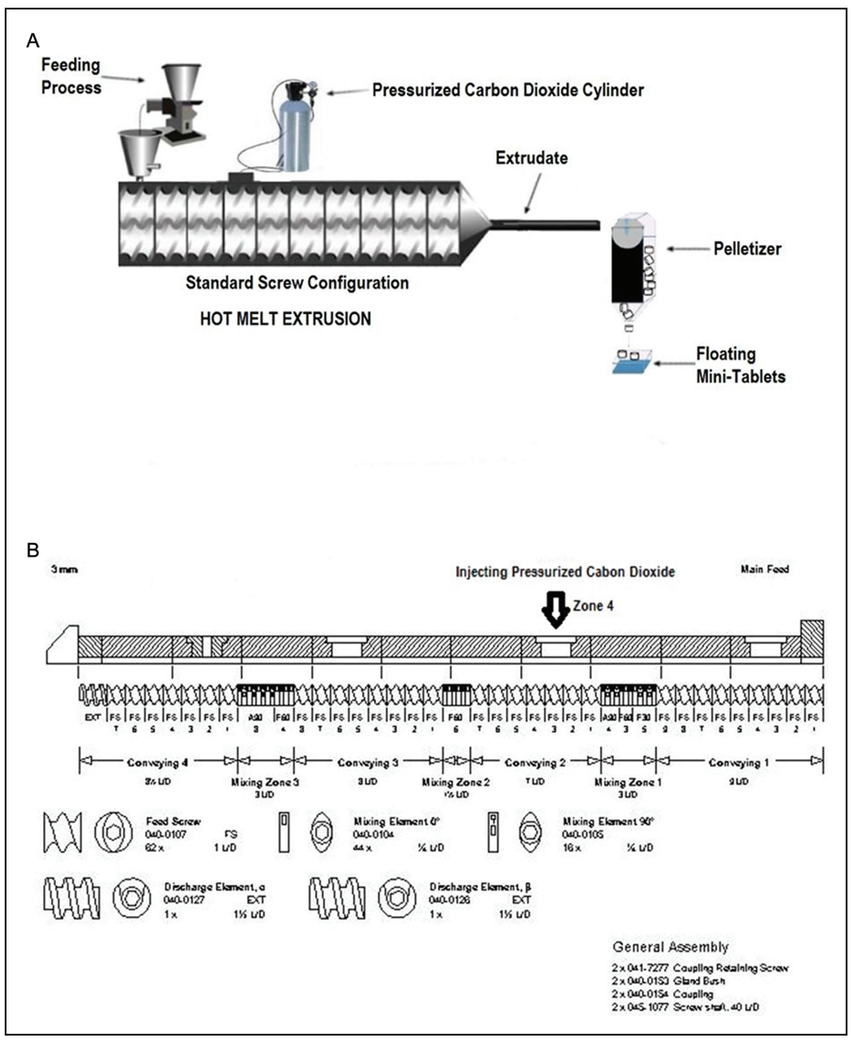

Fig. 4: (a) Schematic representation of preparation of floating mini-tablets using 16-mm hot-melt extruder in conjunction with P-CO_2 injection, (b) Standard screw configuration.

throughout this device there are relatively bigger large, rounded pores. Thus, generating relatively larger rounded pores (super porous) via P-CO_2/HME technology. This approach provides a superior alternative for opening new trends for the manufacturing floating devices with the extended release profiles.

2.5. Conclusion

In conclusion, the floating device formulated in this study by utilizing tasteless/odorless P-CO_2 gas, in conjunction with HME technology, possesses optimal buoyancy. Using this combined technology, low-density floating devices can be easily designed and developed for other APIs/polymers. The combination of injecting P-CO_2 gas and continuous HME process overcomes the existing limitations commonly associated with other conventional techniques for manufacturing floating solid dosage forms. Moreover, the mini-tablets produced using this novel technology, possess superior buoyancy efficiency in terms of lag time and floating period. This study provides an important insight into combining HME/P-CO_2 continuous technology for the development of FDDS, which may be useful for large-scale production of floating devices. However, future studies on other gastric APIs are required for additional applications.

3. Experimental

3.1. Materials

Acetaminophen was purchased from Mallinckrodt (St. Louis, MO, USA) and Eudragit® RL PO was kindly gifted by Evonik industries (Piscataway, USA). Sodium bicarbonate was purchased from Fisher Scientific (Hanover Park, IL, USA). CO_2 gas cylinders (pure clean) were purchased from Airgas (902 Rockefeller St, Tupelo, MS 38801 USA). All other materials and reagents used in this study were of analytical grade.

3.2. Physical blend preparation and HME/P-CO_2 process

EUD was sieved (# 35) and blended with 30% APAP with and without sodium bicarbonate using a V-shell blender (MaxiBlend™, GlobePharma, North Brunswick, NJ, USA). The blends were dried in an oven overnight at 30 °C. The extrudates obtained were in the form of regular rods when only co-rotating twin-screw extruder (16 mm Prism Euro Lab, Thermo Fisher Scientific, Stone, UK) was used. When P-CO_2 gas was injected at zone 4 of the extruder, the extrudates obtained were in the form of porous, foamy rods. With optimal torque (around 80%), all formulations (Table 2) were extruded at an optimal processing temperature (Table 3). Tailoring the ratio of API/polymer in the formulations, along with the appropriate extrusion temperature profile, can be utilized to obtain neat and intact extrudate strands and to be convenient for further downstream procedures (i.e. mini tablet pelletization). P-CO_2 was injected into the barrel of the extruder by means of a high-pressure regulator throughout an injection nozzle located in barrel segment 4 (Fig. 4). CO_2 gas was pressured and injected into the extruder using a high-pressure regulator connected to pliable stainless-steel hose with an armor case ending up in a four-way connection with a pressure gauge,

check valve, and bleed valve connected to the injection port at zone number 4 of the extruder. P-CO_2 gas (120 psi) was metered and regulated using a knob. The obtained extrudates were then cut into mini-tablets (4 mm diameter) using a pelletizer (Type L-001-9482, Thermo Fisher, Stone, UK).

3.3. Scanning Electron Microscopy (SEM)

The surface morphology of the mini tablets was studied by SEM. Samples were mounted on adhesive carbon pads placed on aluminum stubs. Gold was used to coat the samples by a Hummer® 6.2 sputtering system (Anatech LTD, Springfield, VA) in a high-vacuum evaporator. A scanning electron microscope was operated at an accelerating voltage of 5 kV for imaging (JEOL JSM-5600).

3.4. Density measurements and porosity calculation

True density of powdered solid dispersion for all the formulations as well as the pure polymer with and without P-CO_2 has been measured. True density of milled solid dispersion powder was determined utilizing Micromeritics AccuPyc 1330 Gas pycnometer S/N-4011 (Norcross, GA). Prior to each run, calibration was performed. The sample was filled in 10-cm^3 sample cup and the weight of the sample was noted. True density was measured at an equilibration rate of 0.0050 psig/min and the number of purges was set to 10. Bulk density was calculated by measuring the volume of a 5 g milled extrudate in a 10 ml graduated cylinder. Porosity was calculated by the following equation (Joshi et al. 1993):

$$\%\,Porosity = 1 - \frac{Bulk\ density}{True\ Density} \times 100$$

3.5. In vitro buoyancy efficiency and dissolution studies

The buoyancy efficiency of mini-tablets in terms of lag time and the floating period was determined using the dissolution method. Dissolution studies were conducted on USP apparatus II (Hanson SR8) with 900 mL of medium 0.1N HCl, maintained at $37 \pm 0.5\,^{\circ}C$ with a paddle rotation speed of 50 rpm. Data were collected at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, and 6.00 h. All buoyancy tests were performed by visually checking the state of mini-tablets (buoyant, rotated or sunk) every 1 h up to 12 h and the end point of 24 h (Fukuda et al. 2006). Lag time and floating period were determined in seconds and hours, respectively. *In vitro* release studies (n = 3) analysis were performed according to USP using dissolution apparatus II (Hanson SR8), equipped with UV-Vis probes (Rainbow Dissolution Monitor, pION).

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