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Development of Floating Pellets Using Low-Density Foam Powder Prepared by Extrusion-Spheronization

Srisagul Sungthongjeen[1,*], Benchamat Chaikla[1], Chatrapee Huaihongthong[1], Nattawut Charoenthai[2,3], Worawut Kriangkrai[1], Satit Puttipipatkhachorn[2,3]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok 65000, Thailand*
[2]*Department of Manufacturing Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand*
[3]*Center of Innovative Pharmacy for Pharmaceutical and Herbal Product Development, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand*

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ABSTRACT

This study's goal was to develop floating pellets using low-density foam powder prepared by extrusion-spheronization. The model drug used was theophylline. Polypropylene (PP) low-density foam powder provided the system with the properties of low density and buoyancy. The system was prepared by mixing theophylline, microcrystalline cellulose, and PP foam powder together using water as a binder to obtain a damp mass, which was then passed through a sieve to get extrudates. The extrudates were then spheronized to obtain spherical pellets in a spheronizer under optimum conditions. Floating pellets were studied for their size, buoyancy, and drug release with regard to formulation variables. The results revealed that pellets without low-density foam powder had a spherical shape and a smooth surface, whereas pellets with low-density foam powder had a rougher surface, which became rougher as the proportion of foam powder increased. An increase in the drug loading and foam powder particle size both increased pellet size. Pellets made with a sufficient amount of foam powder (20% w/w) could float immediately when contacted with dissolution medium (0.1 N HCl) and could remain floating for more than 8 h. The drug release study revealed that increased drug loading, increased foam powder, and decrease pellet size increased the amount of drug released. However, the particle size of foam powder did not significantly affect drug release. According to this study, the optimal formulation of floating pellets exhibited good buoyancy, but still had relatively fast drug release. Further investigations into how to prolong or delay drug release, such as using a polymeric coating, may be required.

***Corresponding author:** sungts2000@yahoo.com **doi:** 10.14456/scitechasia.2023.15

Keywords: Extrusion-spheronization; Floating pellets; Floating properties; Low-density foam powder; Sustained drug release

1. Introduction

One of the most critical parameters influencing drug bioavailability in pharmaceutical dosage forms is gastric residence time (GRT). Incomplete drug release from drug delivery systems (DDS) above the absorption zone might be caused by variation in, and shortness of, the stomach emptying period, resulting in reduced efficiency of the administered dose, particularly for drugs with an absorption window in the stomach. A floating drug delivery system (FDDS), for example, has been developed to increase the retention of an oral dosage form in the stomach. An FDDS is a type of gastro-retentive dosage forms that can increase drug bioavailability by extending the GRT without disturbing the gastrointestinal tract's regular peristalsis [1-3]. This DDS can float in the stomach because its bulk density is lower than that of gastric fluid. FDDSs are advantageous for drugs like furosemide and theophylline that have an absorption window in the stomach or upper part of the small intestine [1, 4]. It is also beneficial for drugs that act locally in the proximal GI tract, such as curcumin for *Helicobacter pylori* elimination in the treatment of peptic ulcers [5, 6], as well as drugs like captopril [7], which are unstable in intestinal fluid, and drugs like verapamil HCl [8], which have low solubility in the intestinal tract.

The development of FDDS has been used in two distinct technologies based on buoyancy mechanisms, namely effervescent and non-effervescent systems. For effervescent systems, the system buoyancy depends on the generation of carbon dioxide gas when it comes into contact with gastric juices. Sodium bicarbonate and citric or tartaric acid, for example, are commonly used as gas-forming agents [1]. However, one drawback of this FDDS system is premature gastric emptying. Effervescent systems are able to be removed from the stomach before they become buoyant since they do not float instantly upon administration [5]. On the other hand, one fascinating technique in FDDS systems is the non-effervescent system, based on low-density materials such as low-density foam powder. The initial density of this floating system is low, allowing it to float without lag time [9]. As a result, it avoids early evacuation through the pyloric sphincter, which is a common issue in effervescent systems [10]. Streubel et al. [9] used low-density polypropylene foam powder with matrix-forming polymers to prepare floating matrix tablets. Good floating performance, as well as the ability to regulate drug release over time, were achieved. Simple formulation factors such as the matrix-forming polymer type, the matrix-forming polymer to foam powder ratio, the inclusion of fillers that are both water-soluble and water-insoluble, and the usage of polymer blends could effectively modify drug release patterns. They also created microparticles based on low-density foam powder prepared by an o/w solvent evaporation process [11], a new type of multiparticulate floating system. In vitro floating behavior was reported to be good. The drug release rate increased as drug loading increased and polymer amounts decreased. The type of polymer used significantly affected the drug release rate. Recently, Treesinchai et al. [5] developed floating beads of curcumin with low-density substances and solubilizers prepared by ionotropic gelation. Polypropylene foam powder and low-density oils were used as low-density materials. The findings showed that by utilizing 1% w/w foam powder, instant-floating beads that float for a long time could be successfully achieved. The addition of low-density oils and solubilizers improved the floating properties as well as curcumin release.

FDDSs have been developed in single-unit and multiple-unit or multiparticulate dosage forms. Because multiple-unit systems avoid "all-or-nothing" stomach emptying, they may be more beneficial than single-unit systems [12–14]. Furthermore, studies have demonstrated that multiple-unit dosage forms minimize drug absorption variability across and among subjects, as well as the dose dumping risk [15].

Only a few researchers had previously studied non-effervescent floating systems based on low-density foam powder. Therefore, the goal of this research was to create a new multiple-unit FDDS: floating pellets that use low-density polypropylene foam powder generated by extrusion-spheronization. Anhydrous theophylline was used as the model drug since it is absorbed mostly in the upper GI tract [1]. The effect of formulation variables on size, floating properties, and drug release of the floating pellets was investigated.

2. Materials and Methods

2.1 Materials

Anhydrous theophylline, a model drug, was purchased from Lianyungang Foreign Trade Corp., China. Microcrystalline cellulose (MCC) (Avicel® PH 101, FMC, USA) was used as a pelletization aid for the pellets. As a low-density material, polypropylene (PP) foam powder (Accurel® MP 1004 and MP 1001, Membrana GmbH, Obernburg, Germany) was used. All other reagents were analytical grade and were used as received.

2.2 Preparation of the floating pellets

Floating pellets using low-density foam powder were prepared by the extrusion-spheronization technique. The 200 g of theophylline (20% w/w), microcrystalline cellulose, and polypropylene foam powder were mixed by geometric dilution. After that, the dry mixture was placed in a mixer (KitchenAid, Benton Harbor, Michigan, USA). A sufficient amount of distilled water (80% w/w, based on the powder mixture weight) was slowly added to the mixture until a consistent and suitable damp mass was obtained for further extrusion–spheronization procedures. Immediately after preparing the damp mass, it was sieved (16 mesh size). The extrudates were produced and subsequently spheronized for 10 min at a rotation speed of 1533 rpm in a spheronizer (Caleva Model 250, G.B. Caleva, England) with a rotating disc of regular cross-hatch shape. The pellets were dried for 12 h in a hot-air oven at 50°C (Model 500, Memmert GmbH, Germany). The floating pellets were stored in a closed desiccator with silica gel at room temperature prior to further investigations. Table 1 shows the composition of floating pellets.

Table 1. Formulations of floating pellets using low-density foam powder prepared by extrusion-spheronization.

Composition (%w/w)	Formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
Theophylline	20	20	20	20	20	10	30	20
MCC PH 101	80	65	62.5	60	57.5	70	50	60
Foam powder MP1004	-	15	17.5	20	22.5	20	20	-
Foam powder MP1001	-	-	-	-	-	-		20
Distilled water	80	80	80	80	80	80	80	80

2.3 Evaluation of the floating pellets

2.3.1 Particle size and morphological analyses

Sieve analysis was used to determine the pellets' particle size distribution. On a vibrating sieve shaker (Retsch® Model AS 200 digit, Retsch, Germany), 100 grams of the pellets were sieved via a nest of sieves (3.35-0.85 mm) to determine the weight distribution.

The surface morphology of the pellets was examined using a stereomicroscope (Model SZ4045, Olympus, Tokyo, Japan) with optical zoom (10x).

2.3.2 Hardness of the floating pellets

Ten floating pellets were measured individually using a texture analyzer (TA.XT. plus Texture Analyzer, Stable Micro Systems, Godalming, UK). The average pellet hardness and standard deviation were calculated.

2.3.3 Friability of the floating pellets

The percentage (%) of weight loss after 200 rotations of 10 g of floating pellets in a friabilator was used to measure the friability of the pellets (Model 45-2200, Vankel, North Carolina, USA).

2.3.4 Floating properties

In closed flasks with a medium fill placed in an environmental shaker-incubator (Model ES-20, Biosan, Riga, Latvia) (medium; 150 mL of 0.1 N HCl, 37 °C, 50 rpm), the floating properties of the floating pellets were evaluated. Fifty floating pellets were put in the medium, and visual observation was used to determine the time to float and the floating duration (floating time). The experiments were carried out in triplicate. The data from the visual observation was used to determine the percentage of floating pellets, which was then calculated using Eq. (1) as follows:

$$Floating\ pellets(\%) = \frac{Number\ of\ floating\ pellets\ at\ the\ specific\ time\ point}{Total\ number\ of\ the\ pellets} \times 100. \quad (2.1)$$

2.3.5 Dissolution study

The drug release studies were conducted with a USP dissolution apparatus II (Vankel Model VK-7000, Vankel, USA) equipped with paddles spinning at 50 rpm. The pellets used had a weight equivalent to around 20 mg of theophylline. The dissolution medium, 900 milliliters of 0.1 N HCl, was poured into the glass vessel, assembled in the apparatus, and the dissolution medium was equilibrated to 37 ± 0.5 °C. The amount of drug released was measured at predetermined time intervals and then analyzed using a 1.0 cm quartz cell and a UV/visible spectrophotometer (UV-2450, Shimadzu, Kyoto, Japan). Each in vitro release test was carried out in triplicate.

2.4 Data analysis

To compare differences in the averages of the data (e.g., hardness, dissolution data), simple analysis of variance (one-way ANOVA) or independent sample t-tests were performed using the SPSS Statistics 17.0 program. The significance of the difference was determined using a 95% confidence level ($\alpha = 0.05$).

3. Results and Discussion

3.1 Design of the floating pellets

In this study, the multiple-unit floating pellets using low-density foam powder prepared by the extrusion-spheronization technique were designed and developed. To prevent pellets from transiting into the small intestine and causing early gastric emptying, the floating pellets should float instantly when exposed to stomach fluid [9]. As such, the goal of this research was to create pellets with a density lower than that of gastric fluid (< 1.00 g/cm^3). These pellets initially floated when exposed to the dissolution medium and maintained floating for a long time with sustained drug release. The floating pellets were composed of the model drug (theophylline), pelletization aid (MCC) and low-density PP foam powder that played a key role in the creation of the initial low-density pellets. Distilled water acted as a binder to form the pellets. The design system is shown in Fig. 1. To develop these floating pellets, several variables had to be investigated to achieve the desired system properties that would produce pellets that immediately float when exposed to gastric fluids and maintain buoyancy in the stomach with sustained drug release. The influence of the formulation variables such as the proportion of low-density foam powder, drug loading, and particle size of foam powder and pellets on the floating properties and drug release of the pellets was evaluated.

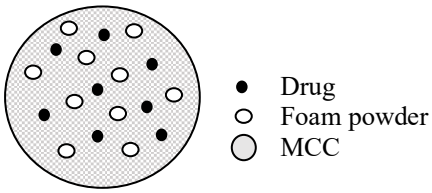

Fig. 1. Design of the floating pellets.

3.2 Morphology, physical and floating properties of floating pellets

Under a stereomicroscope, the oven-dried pellets without low-density foam powder (control, F1) had a spherical shape and a smooth surface (Fig. 2A), whereas pellets with low-density foam powder had a rougher surface, which became rougher as the proportion of foam powder increased (Fig. 2B-2D). Increasing the drug loading and particle size of foam powder increased pellet size. However, increasing the proportion of foam powder did not affect the dominant size fraction of pellets Table 2. The addition of foam powder to the formulations decreased the hardness of the pellets, as shown in Table 2. A higher proportion of foam powder corresponded to a lower proportion of MCC, which might have led to a reduction in the binding properties of the pellets. This is because MCC is the gold standard extrusion–spheronization aid due to its excellent binding properties, which offer cohesiveness to a wetted mass, permitting densification and a larger binding interfacial area inside pellets [16]. The friability of the formulations was quite low and in the range of 0.00 to 0.13%. As evidenced by this, the pellets were relatively hard.

The pellets prepared without the use of foam powder (F1) did not float in 0.1 N HCl. As stated previously, low-density foam powder was used to provide the initial low density of the pellets, allowing them to float immediately without lag time. Using a sufficient amount of foam powder that would result in the system floating immediately was also important. According to our preliminary study, increasing the amount of foam powder in formulations from 15.0 to 17.5 % w/w raised the proportion of pellets floating immediately from 33.33 to 94.67%. Only pellets containing a sufficient amount of foam powder (20% w/w) could both float immediately when contacted with dissolution medium (0.1 N HCl) (Fig. 3) and retain floating for more than 8 h. As shown in Table 2, most formulations containing 20% w/w low-density foam powder could float instantly and retain buoyancy for more than 8 h except for the formulation containing 10% w/w theophylline, in which 92% of pellets could float instantly.

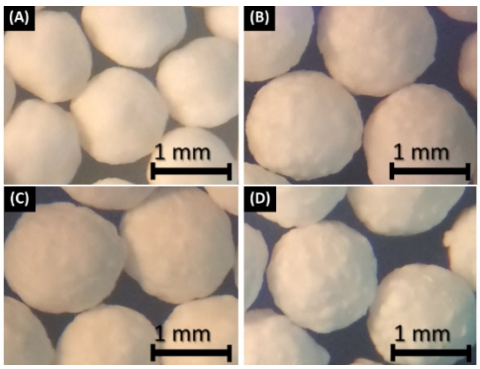

Fig. 2. The morphological surface of floating pellets containing 20% w/w theophylline and MCC, magnification 10x. Key: (A) control (without foam powder), (B) 17.5% w/w foam powder, (C) 20.0% w/w foam powder and (D) 22.5% w/w foam powder.

Fig. 3. Photographs of pellets immediate floating (t=0) in 0.1 N HCl (20% w/w theophylline, 20% w/w foam power MP1004).

Table 2. Physical and floating properties of floating pellets.

Formulation	Hardness (N) (SD)	Friability (%)	d'g (mm)	Dominant size fraction (mm)	Floating pellets (%) (SD)	
					0 h	8 h
20% w/w theophylline						
MCC without foam powder (control, F1)	30.14 (2.16)	0.05	1.16	1.00-1.18	0 (NF)	0
MCC + 15.0%w/w FPMP1004 (F2)	N/A	N/A	N/A	N/A	33.33 (10.07)	6.67 (3.06)
MCC + 17.5%w/w FPMP 1004 (F3)	8.95 (0.74)	0.00	1.45	1.40-1.70	94.67 (4.16)	97.33 (1.15)
MCC + 20.0%w/w FPMP 1004 (F4)	12.88 (1.65)	0.13	1.55	1.40-1.70	100	100
MCC + 22.5%w/w FPMP 1004 (F5)	8.63 (0.83)	0.00	1.40	1.40-1.70	100	100
MCC + 20.0%w/w FPMP 1001 (F8)	11.33 (1.02)	0.00	2.05	2.00-2.36	100	100
10% w/w theophylline						
MCC + 20.0%w/w FPMP 1004 (F6)	5.26 (0.84)	0.00	1.18	1.18-1.40	92.00 (2.00)	91.33 (3.05)
30% w/w theophylline						
MCC + 20.0%w/w FPMP 1004 (F7)	13.31 (0.56)	0.05	2.10	2.00-2.36	100	100

Abbreviation: NF = no floatation, N/A = not applicable, MCC = microcrystalline cellulose and FP = foam powder.

3.3 Effect of formulation variables on drug release

3.3.1 Amount of foam powder

The amount of foam powder sufficient to make the system float immediately was 20% w/w. To determine the optimal formulation of the pellets as a floating drug delivery system, release experiments were carried out on just the pellets floating immediately in the dissolution medium. The effect that foam powder proportion had on drug release was investigated. Pellets without foam powder were used as a control (F1). The addition of foam powder to the pellets increased drug release, as shown in Fig. 4. This finding is consistent with that of Streubel et al. [9]. Since the addition of foam powder reduces pellet hardness by reducing MCC binding properties and lowering pellet density, drug release is increased. Goyanes et al. reported that the co-processed excipients generated by massing MCC with Eudragit® E displayed deposits of acrylic polymer on the surface of the MCC particles. The MCC particles were unable to form bonds over their whole surface due to these deposits, resulting in fewer joints and a weakening of the pellet structure [17]. Higher surface roughness and greater pores at the surface of pellets were also reported to increase drug release [18]. However, increasing the amount of foam powder from 20.0 to 22.5% w/w decreased drug release. The hydrophobicity of the foam powder might play an important role in this effect.

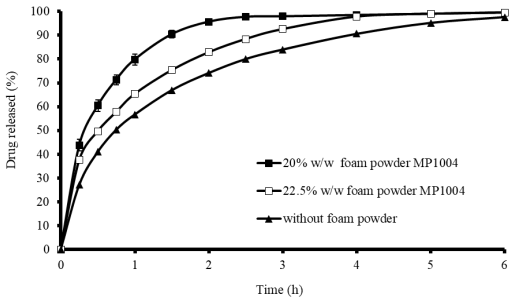

Fig. 4. Effect of foam powder amount on drug release from floating pellets (20% w/w theophylline) in 0.1 N HCl.

3.3.2 Type or particle size of foam powder

There was no significant difference in drug release based on the particle size of the polypropylene foam powder (foam powder MP1001: size 0.4-1.0 mm, foam powder

MP1004: size < 0.4 mm), as shown in Fig. 5. As a result, the size of the foam powder particles has no impact on drug release. The drug release of the floating pellets containing the larger size of foam powder (F8) slightly increased with a slightly decreased pellet hardness from 12.88±1.65 N (F4) to 11.33±1.02 N (F8). This is almost certainly due to an increase in the system's porosity [9].

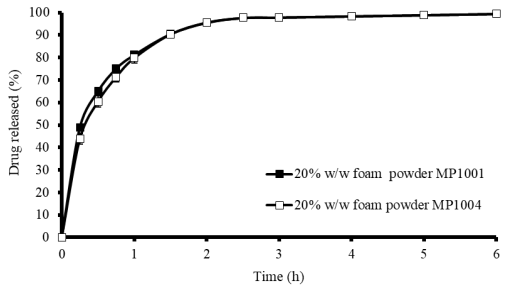

Fig. 5. Effect of foam powder type or particle size on drug release from floating pellets (20% w/w theophylline, 20% w/w foam power) in 0.1 N HCl.

3.3.3 Drug loading

As seen in Fig. 6, drug loading had a significant impact on theophylline release from floating pellets. Increasing drug loading increased drug release. At 10% w/w drug loading, the tablet consists mainly of MCC (70% w/w) which is an insoluble material (the foam powder was kept constant at 20% w/w for the study of this effect). The relative MCC content reduces as the soluble drug loading increases. Consequently, the drug diffusivity and release increase. A similar result was reported in previous work [9].

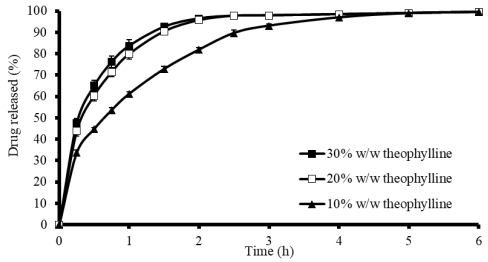

Fig. 6. Effect of theophylline loading on drug release from floating pellets (20% w/w foam powder MP1004) in 0.1 N HCl.

3.3.4 Size of pellets

The release profiles of two sizes of the identical floating pellet formulations (F4) are shown in Fig. 7. It was revealed that when the particle size decreased, the drug release increased. The higher drug release associated with decreasing particle size can be explained by the increase in surface area exposed to the dissolution medium and the decrease in diffusion path length [19].

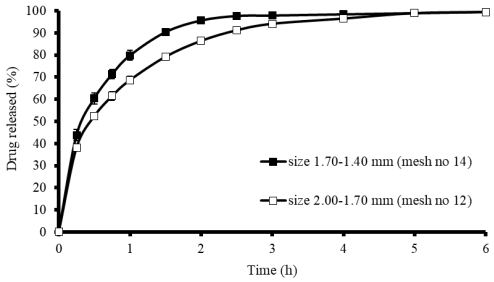

Fig. 7. Effect of pellets size on drug release from floating pellets (20% w/w theophylline, 20% w/w foam powder MP1004) in 0.1 N HCl.

4. Conclusion

Floating pellets using low-density foam powder prepared by extrusion-spheronization were successfully developed. Low-density foam powder of polypropylene provided the system with low density and buoyancy. The floating pellets had a spherical shape and a slightly rough surface. The proportion of foam powder that made the systems float immediately when contacting dissolution medium was 20% w/w. Increasing the drug loading, increasing foam powder, and decreasing pellet size all increased the drug released. The optimal FDDS formulation exhibited good floating properties, but drug release was still relatively fast. More studies on drug release retardation, such as polymeric coating, may be required in order to obtain appropriate formulations for gastroretentive dosage forms.

Acknowledgements

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