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Design and evaluation of double coated floating capsules based on gas formation

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ABSTRACT

The purpose of this work was to create double coated floating capsules using gas formation. Theophylline was used as a model drug. Theophylline and hydroxypropyl methylcellulose (HPMC) were physically blended and filled in hard capsules. Then, they were coated with a layer of a gas producing agent ($NaHCO_3$) and a gas-entrapped membrane (i.e., EuRL30D, EuRS30D). The impact of types of gel-forming polymers, and gas-entrapped membrane's coating types and levels on floating characteristics and drug release from the floating capsules was investigated. Optimum formulations could float immediately and maintain buoyancy longer than 8 h. The increased viscosity of the high molecular weight HPMC in the floating capsules resulted in a delayed drug release, compared to the low molecular weight HPMC-containing capsules. The floating capsules coated with EuRS30D released the drug more slowly than those coated with EuRL30D. Due to EuRS30D demonstrated relatively low drug release, EuRL30D appeared to be a promising option for gas-entrapped membranes. Drug release was decreased as the gas-entrapped membrane's coating level was increased, resulting from a thicker film. The floating capsules with good floating abilities and sustained drug release were obtained in this investigation.

Keywords: double coated floating capsules; floating abilities; sustained drug release; coating; gas producing layer

1. INTRODUCTION

One of the key factors influencing the drug bioavailability of pharmaceutical dosage forms is gastric residence time (GRT). Insufficient drug release from drug delivery systems above the absorption zone (stomach or upper region of the small intestine) can lower the efficiency of the administered dose due to variation and a short GRT. Numerous techniques, such as mucoadhesive systems (Kumar et al., 2022), expanding systems (Melocchi et al., 2019), high density systems (Sharma et al., 2018), and floating systems (Sriamornsak et al., 2022), have been developed to enhance the retention of an oral dosage form in the stomach (Amrutkar et al., 2012; Moes, 1993). Some of these systems, meanwhile, appear to be less effective and/or less suggested than others. Depending on the drug's ulcerogenic properties, drug-induced injuries, which can range from local irritation to perforation, may originate from mucoadhesive systems. Expandable gastroretentive dosage forms that accumulate in the stomach could have harmful effects on the patient. For this specific use, rapid biodegradation would enhance the safety profile of such gastroretentive dosage formulations (Klausner et al., 2003). Among the various techniques for prolonging GRT of the dosage form, some researchers stated that only the floating and swelling techniques provided

clinical evidence for prolonged stomach residence duration at fed state (Kim et al., 2018; Chen et al., 2013; Oth et al., 1992).

The floating drug delivery system (FDDS) is one of the gastroretentive drug formulations that could extend GRT to achieve better drug bioavailability (Patil et al., 2022; Singh and Kim, 2000). The device basically floats in the gastric fluid because it has a lower bulk density than an aqueous medium. FDDS is useful for drugs with a window of absorption in the stomach or the upper part of the gastrointestinal tract, such as lansoprazole (Rajput et al. 2022), theophylline (Singh and Kim, 2000; Rouge et al., 1996), and furosemide (Meng et al., 2022). It is also desirable for locally acting drugs in the stomach, such as curcumin to treat *Helicobacter pylori*-related peptic ulcers (Treesinchai et al., 2019; Uboldi et al., 2022), for drugs that have limited solubility in the small intestine, such as verapamil HCl (Munday, 2003), and for drugs that are unstable in the intestinal fluid, such as captopril (Seta et al., 1988; Tripathi et al., 2021). Two completely different technologies based on the principle of buoyancy have been developed in the development of FDDS, effervescent and non-effervescent systems.

This study aimed to develop a double coated floating capsule based on gas formation. The system consisted of a core capsule containing gel-forming polymer (hydroxypropyl methylcellulose, HPMC) coated with two successive layers as a gas producing layer and a gas-entrapped membrane. The layer of gas producing was composed of sodium bicarbonate ($NaCHO_3$), a gas producing agent, while aqueous colloidal polymethacrylate dispersion formed the gas-entrapped membrane. The floating abilities and drug release of the produced floating capsules were examined in relation to the gas-entrapped membrane's types and coating levels, as well as the grades of gel-forming polymers.

2. MATERIALS AND METHODS

2.1 Materials

Theophylline (anhydrous) was the model drug (Lianyungang Foreign Trade Corp., China). Different HPMC grades, marketed under the name Methocel® (HPMCK100LV, HPMCK4M, Dow Chemical, USA) were utilized as a gel-forming polymer. Talcum performed as the lubrication (China Haicheng Doyo Talc Powder Factory, China). $NaHCO_3$ was purchased from Fisher Scientific (UK). Hard gelatin capsules (size 1) were purchased from S. Charoen Bhaesaj Trading Co., Ltd. (Thailand). HPMC (HPMCE15LV, Dow Chemical, USA), polyethylene glycol 6000 (PEG 6000, Fluka Chemie, Switzerland) was used. Aqueous colloidal polymethacrylate dispersions, marketed under the name Eudragit® (EuRL30D and/or EuRS30D, RohmPharma, Germany) and diethyl phthalate (DEP), (Sigma–Aldrich Chemie GmbH, Germany) were used. The remaining reagents were all of analytical grade.

2.2 Preparation of floating capsules

2.2.1 Preparation of core capsules

The core capsules consisted of drug (anhydrous theophylline, 20 mg/capsule), gel-forming polymer (HPMCK100LV or HPMCK4M, K4M, 260 mg/capsule), and talcum (2% w/w). The drug was weighed and physically blended with other excipients via geometric dilution in a mortar. The mixtures were blended for 5 min and then filled into the hard gelatin capsule (size 1) by a capsule filling machine (Model Panviv A 01, Yiewheng Co., Ltd., Thailand).

2.2.2 Coating of the core capsules

2.2.2.1 Gas producing layer

For the gas producing layer, $NaHCO_3$ was added to an HPMCE15LV solution that had been plasticized with PEG 6000 (based on HPMC's solids content, 10% w/w). On a dry solid basis, the weight ratio of $NaHCO_3$ to HPMCE15LY was 5:5. The coating solution's solid content was kept constant at 12% w/w, and the coating amount of the gas producing layer was set at 12% of the weight gain. The coating solution was sprayed over the core capsules using a perforated pan coater (Model NR-COTA 18, N.R. Industries Co., Ltd., Thailand). The coating parameters are displayed in Table 1. To remove any remaining moisture, the layered capsules underwent additional drying in the coating chamber for 30 min at 50°C. After that, the capsules were taken out of the coating chamber and placed in a closed container for further testing.

2.2.2.2 Gas-entrapped membrane

The gas producing layered capsules were coated with an aqueous colloidal polymethacrylate dispersion (EuRL30D or EuRS30D) to achieve weight gains of 5%, 10%, and 20% w/w in order to create the completely floating capsules. The colloidal polymer dispersions were blended with DEP, a plasticizer (20% w/w based on polymer solids), and the mixture was stirred gently for 30 min before being diluted with distilled water and coated. The coating dispersions contained 15% w/w solid content. The coating conditions are presented in Table 1.

After the coating was completed, the floating capsules were dried in the coating chamber at 50°C for 30 min to evaporate the residual moisture in the polymeric coatings. Prior to further experiments, the coated capsules were equilibrated at room temperature overnight and placed in a closed container.

2.3 Evaluation of the floating capsules

2.3.1 Floating abilities

The USP paddle apparatus (Model VK-7000, Vankel, USA) was used to test the floating abilities of the floating capsules, with the paddle speed set at 50 rpm. At 37±0.5°C, three floating capsules were put in 900 mL of 0.1 N HCl (Treesinchai et al., 2019). The time to start floating (time to float) and the length of flotation (floating time) were determined visually.

2.3.2 Drug release

The USP dissolution apparatus (Model VK-7000, Vankel, USA) equipped with paddles was used in the drug release experiments, which were carried out at a speed of 50 rpm. After putting the equipment together and bringing the dissolution medium's temperature to 37±0.5°C, the dissolution medium (900 mL of 0.1 N HCl) was poured into the glass vessel. At predetermined intervals (0, 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8 h), the amount of drug released was measured with a UV/visible spectrophotometer (Model Cary 1E, Varian, Australia) at a wavelength of 270 nm. The *in vitro* release test was carried out in triplicate.

Table 1. Operating conditions for coating of gas producing layer and gas-entrapped membrane of floating capsules in a perforated pan coater

	Gas producing layer	Gas-entrapped membrane layer
Batch size (L)	1	1
Pan speed (rpm)	15	15
Preheating temperature (°C)	50	50
Preheating time (min)	30	30
Inlet temperature (°C)	48-50	48-50
Outlet temperature (°C)	38-40	39-41
Nozzle diameter (mm)	1	1
Atomizing air pressure (bar)	2.5	2.5
Spray rate (mL/min)	5-10	5-8

2.4 Data analysis

To compare differences, one-way analysis of variance (ANOVA) or independent- sample T-tests were used. The 95% confidence level was used to calculate the significance of the difference ($\alpha = 0.05$).

3. RESULTS AND DISCUSSION

3.1 Design of the floating capsules

The double coated floating capsules consisted of the core capsules containing drug (theophylline) and a gel-forming polymer coated with two successive layers: a gas producing layer and a gas-entrapped membrane. The design of the device is shown in Figure 1. HPMCE15LV was used as a binder in the gas producing layer since $NaHCO_3$ by itself was unable to adhere to the core capsules. The gas-entrapped membrane was used to entrap the generated carbon dioxide (CO_2) gas as well as to control the drug release. To promote the gas producing agent reaction and the floating process, high water permeability is necessary for the ideal membrane. To encourage and maintain floating, the hydrated coatings should also be impermeable to the CO_2 generated (Krögel and Bodmeier, 1999). In terms of mechanical properties, for the polymer coatings to withstand the pressure generated by the gas without rupturing, they must be sufficiently flexible in the wet condition. These reasons led to the decision in this study to choose and investigate an aqueous colloidal polymethacrylate dispersion (EuRL30D or EuRS30D), the higher flexibility polymer, as a gas-entrapped membrane. The fluid passed through the outer gas-entrapped membrane and into the gas producing layer upon contact with the acidic medium. The neutralization reaction produced CO_2, which was entrapped in the gas-entrapped membrane. This enhance floating abilities of the systems, besides swelling and air trapped by the swollen gel-forming polymer. The drug released slowly as a function of time.

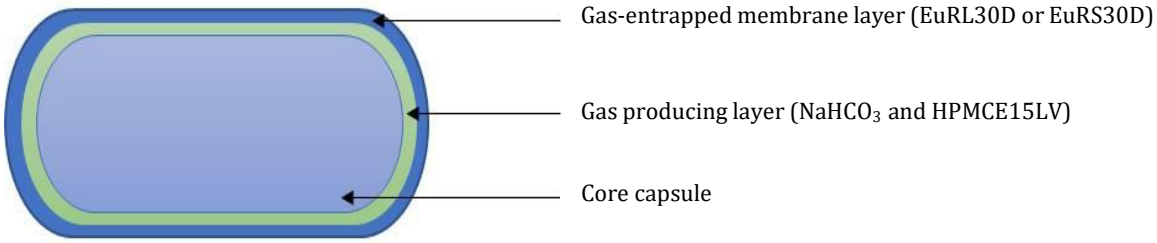

Figure 1. The design of the double coated floating capsule

3.2 Effect of gel-forming polymer type

The most often used matrix polymer for FDDS is HPMC, because it is biocompatible, pH-independent, and accepted by all regulator worldwide (Bera et al., 2016). To produce matrices with better physical properties and the optimal drug release profile, several viscosity grades of HPMC are frequently investigated. In this study, HPMC in the core capsules was used to enhance floating abilities and prolong drug release. All formulations floated instantly and stayed afloat for more than 8 h, as shown in Table 2. The effect of types of gel-forming polymer (HPMC K100LV, HPMCK4M) on drug released from floating capsules is shown in Figure 2. The drug released from floating capsules containing HPMCK100LV was significantly faster than that released from the capsules containing HPMCK4M. It is because HPMCK100LV had a lower molecular weight, which corresponded to its lower viscosity. This is most likely because there may be a reduction in the effective molecular diffusion area due to the degree of entanglement at high molecular weights (Colombo et al., 1995). Escudero et al. (2008) discovered a similar finding that the greater viscosity gel layers of HPMCK100M matrices produced a more tortuous and resistant diffusion barrier, which slowed the release of drugs from these matrices. Bera et al. (2016) also reported that when HPMCK4M was the predominant polymer in the uncoated matrix tablets, the rate of drug (quetiapine fumarate) release was reduced. This could be explained by the potential for HPMCK4M to form a high viscosity gel that surrounds the tablets, thereby preventing drug diffusion. Additionally, because HPMCK4M is a high molecular weight polymer, it can have a better intrinsic

water holding capacity, and the matrices created with this polymer would be less erosive. As the concentration of HPMCE15, a low viscosity grade HPMC, increased in the tablets, the rate of drug release significantly increased, showing that it has a lower drug retarding capacity than HPMCK4M. It most likely occurred because HPMCE15 rapidly eroded when it came into contact with water molecules.

Table 2. Floating abilities of double-coated floating capsules

Formulation	Time to float	Floating time (min)
HPMCK100LV		
5% w/w EuRL30D	Float immediately	> 480
10% w/w EuRL30D	Float immediately	> 480
20% w/w EuRL30D	Float immediately	> 480
HPMCK4M		
5% w/w EuRL30D	Float immediately	> 480
10% w/w EuRL30D	Float immediately	> 480
20% w/w EuRL30D	Float immediately	> 480
HPMCK100LV		
5% w/w EuRS30D	Float immediately	> 480
10% w/w EuRS30D	Float immediately	> 480
20% w/w EuRS30D	Float immediately	> 480
HPMCK4M		
5% w/w EuRS30D	Float immediately	> 480
10% w/w EuRS30D	Float immediately	> 480
20% w/w EuRS30D	Float immediately	> 480

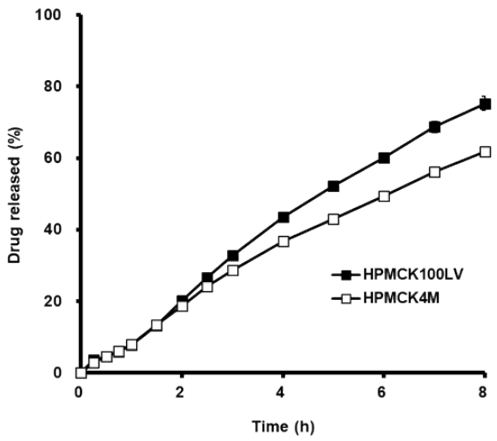

Figure 2. Effect of gel-forming polymer type on drug released from floating capsules in 0.1 N HCl
Note: gas-entrapped membrane: 20% w/w EuRL30D

3.3 Effect gas-entrapped membrane type

In spite of the fact that, in this investigation, the core capsule containing HPMC could float instantly, the erosion of the HPMC as well as the presence of a gas producing agent may cause short flotation. According to Bera et al. (2016), the matrix tablets containing HPMC were covered with an alginate-fenugreek gum gel membrane in order to reduce matrix permeability and erosion, achieve sustained drug release rate, and improve gastroretentive ability. In this study, the gas-entrapped membrane was used to control the amount of drug release, in addition to entrapping the generated CO_2 gas to maintain flotation. As a gas-entrapped membrane EuRL30D and EuRS30D were used. All formulations floated immediately and kept their buoyancy for more than 8 h, as shown in Table 2. The effect of gas-entrapped membrane type was examined in relation to how much drug released from floating capsules coated with 5%, 10%, and 20% w/w coating levels. When compared to those using EuRL30D, the floating capsules coated with EuRS30D released the drugs significantly more slowly (Figure 3). In this investigation, EuRL30D seemed to be a suitable alternative for gas-entrapped membranes because EuRS30D demonstrated relatively low drug release. EuRL30D is a highly permeable polymer because it has hydrophilic content (quaternary ammonium groups) in its structure (Bauer, 1998). In comparison to EuRS30D, it has twice as many quaternary ammonium groups and is more hydrophilic. As a result, it hydrated more quickly, resulting in faster drug release.

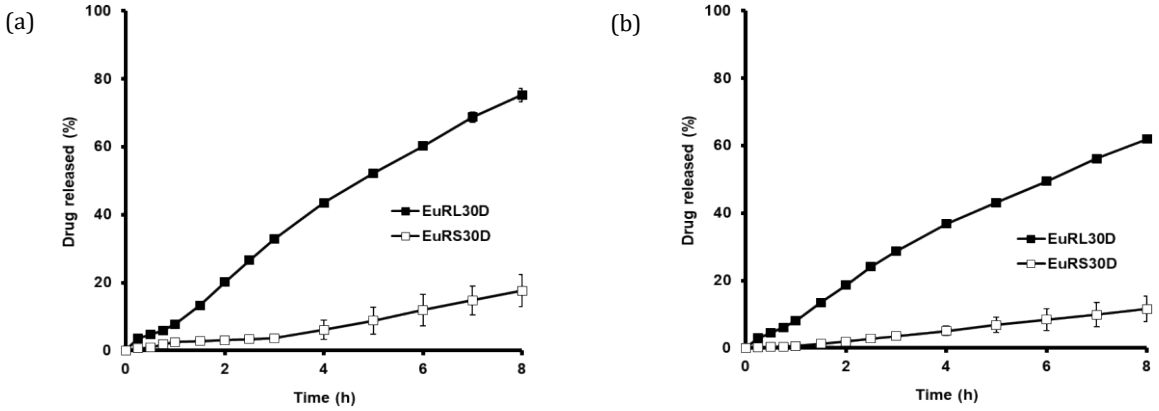

Figure 3. Effect of gas-entrapped membrane types on drug released from floating capsules in 0.1 N HCl
Note: 20% w/w gas- entrapped membrane, using (a) HPMCK100LV and (b) HPMCK4M as gel forming polymer

3.4 Effect of gas-entrapped membrane level

Table 2 displays how the level of coating on the gas-entrapped membrane affected floating abilities. Each formulation floated immediately and maintained its buoyancy for more than 8 h. However, the systems coated with 5% and 10% w/w of both EuRL30D and EuRS30D were broken. These two levels of gas-entrapped membrane may not have enough mechanical strength to withstand the system pressure.

The gas-entrapped membrane coating level effect on the drug release of the floating capsules is shown in Figure 4. The more gas-entrapped membrane coating there was, the thicker the membrane and the lower the water permeability of the film. This led to a slower rate of water penetration and a slightly decreased drug release. From 5% to 20% w/w of gas-entrapped membrane coating, the drug release tended to decrease. Drug release was decreased because of the slower water permeability caused by the thicker membrane (Krögel and Bodmeier, 1999; Sungthongjeen et al., 2006).

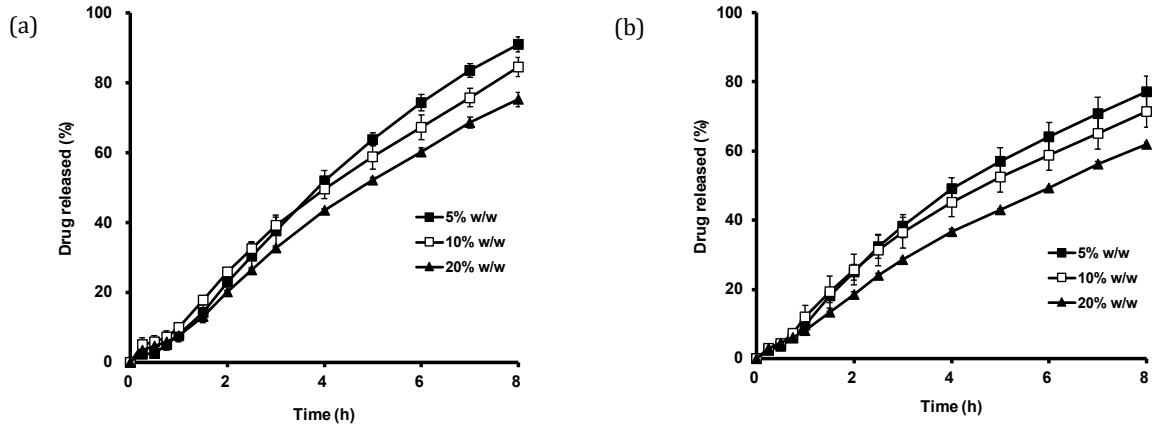

Figure 4. Effect of gas-entrapped membrane (EuRL30D) coating levels on drug released from floating capsules in 0.1 N HCl, using (a) HPMCK100LV and (b) HPMCK4M as gel forming polymer

4. CONCLUSION

The double coated floating capsules based on gas formation with good floating abilities (floated immediately, more than 8 h floating time) and prolonged drug release were successfully developed. Variables in the formulation could modify the floating abilities and drug release of the floating capsules. All of the formulations floated instantly and could stay buoyant for more than 8 h. The floating capsules containing low molecular weight HPMC as a gel-forming polymer and using EuRL30D as a gas-entrapped membrane showed faster drug release than those containing higher molecular weight HPMC and using EuRS30D. An increase in gas-entrapped membrane coating levels of the floating capsules retarded drug release. These results demonstrate that the developed double-coated floating capsule is a promising drug delivery device for gastroretentive systems.

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