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Preparation and in vitro evaluation of a multiple-unit floating drug delivery system based on gas formation technique

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Abstract

A multiple-unit floating drug delivery system based on gas formation technique was developed in order to prolong the gastric residence time and to increase the overall bioavailability of the dosage form. The system consists of the drug-containing core pellets prepared by extrusion–spheronization processes, which are coated with double layers of an inner effervescent layer (sodium bicarbonate) and an outer gas-entrapped polymeric membrane of an aqueous colloidal polymer dispersion (Eudragit® RL 30D, RS 30D, NE 30D). Only the system using Eudragit® RL 30D as a gas-entrapped polymeric membrane could float. The time to float decreased as amount of the effervescent agent increased and coating level of gas-entrapped polymeric membrane decreased. The optimum system could float completely within 3 min and maintained the buoyancy over a period of 24 h. The drug release was sustained and linear with the square root of time. Increasing coating level of gas-entrapped polymeric membrane decreased the drug release. Both the rapid floating and the sustained release properties were achieved in the multiple-unit floating drug delivery system developed in this present study.

Keywords: Floating drug delivery system; Pellets; Effervescent agent; Polymeric membrane; Sustained release

1. Introduction

It is widely known that gastric residence time (GRT) is one of the important factors affecting the drug bioavailability of pharmaceutical dosage forms (Desai and Bolton, 1993). Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system (DDS) above the absorption zone (stomach or upper part of small intestine), leading to a diminished efficacy of the administered dose (Chueh et al., 1995; Iannuccelli et al., 1998). Floating drug delivery system (FDDS) is one of gastroretentive dosage forms which could prolong GRT to obtain sufficient drug bioavailability (Whitehead et al., 1998; Singh and Kim, 2000; Arora et al., 2005; Bardonnet et al., 2006). The system basically floats in the gastric fluid because of its lower bulk density compared to that of the aqueous medium. FDDS is desirable for drugs with an absorption window in the stomach or in the upper small intestine (Rouge et al., 1996; Sato et al., 2004a). It is also useful for drugs that act locally in the proximal part of gastrointestinal (GI) tract such as antibiotic administration for *Helicobacter pylori* eradication in the treatment of peptic ulcer (Cooreman et al., 1993; Yang et al., 1999; Umamaheshwari et al., 2003; Bardonnet et al., 2006) and for drugs that are poorly soluble or unstable in the intestinal fluid (Singh and Kim, 2000; Jain et al., 2005).

Most of the floating systems previously reported are single-unit systems such as tablets and capsules. A drawback of these systems is the high variability of the GI transit time due to their all-or-nothing emptying processes (Ichigawa et al., 1991; Kawashima et al., 1991; Streubel et al., 2003; Umamaheshwari et al., 2003; Talukder and Fassihi, 2004; Jain et al., 2005). On the other hand, the multiple-unit dosage forms may be an attractive alternative since they have been shown to reduce the inter- and intra-subject variabilities in drug absorption as

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well as to lower the possibility of dose dumping (Bechgaard and Ladefoged, 1978; Bechgaard and Nielson, 1978; Vervaet et al., 1995). Various multiple-unit floating systems have been developed in different forms and principles such as air compartment multiple-unit system (Iannuccelli et al., 1998), hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method (Sato et al., 2003, 2004a,b; Jain et al., 2005), microparticles based on low-density foam powder (Streubel et al., 2002, 2003), beads prepared by emulsion–gelation method (Talukder and Fassihi, 2004; Sriamornsak et al., 2005). Use of swellable polymers and effervescent compounds is another approach for preparing multiple-unit FDDS. Ichigawa et al. (1991) developed FDDS by coating the sustained release pills or granules with tartaric acid layer, sodium bicarbonate layer and polymeric film consisting of polyvinyl acetate and shellac. The floating system using ion exchange resin loaded with bicarbonate and then coated by a semipermeable membrane was also proposed (Atyabi et al., 1996). Recently, Choi et al. (2002) prepared floating alginate beads using gas forming agents (calcium carbonate and sodium bicarbonate).

In this study, a new multiple-unit FDDS based on gas formation technique was developed. The spherical drug-containing core pellets was prepared by extrusion–spheronization process followed by coating of the pellets with effervescent component (sodium bicarbonate) using hydroxypropyl methylcellulose (HPMC) as a binder and gas-entrapped polymeric membrane (Eudragit® RS 30D, RL 30D, NE 30D), respectively. Anhydrous theophylline, which is predominantly absorbed in the upper part of GI tract (Singh and Kim, 2000), was used as a model compound. The effect of the preparative parameters, e.g., amount of the effervescent agent layered onto the core pellets, and type and coating level of the gas-entrapped polymeric membrane, on the floating ability and drug release properties of the multiple-unit FDDS were evaluated.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Lianyungang Foreign Trade Corp., China) was chosen as a model drug. Microcrystalline cellulose (Avicel® PH 101, FMC, USA) was used as a pelletization aid of the core pellets. Sodium bicarbonate ($NaHCO_3$, Carlo Erba, Italy) was used as an effervescent agent with HPMC (Methocel® E15LV, Dow Chemical, USA) plasticized with polyethylene glycol 6000 (PEG 6000, Fluka Chemie, Switzerland) as a binder. The gas-entrapped polymeric membrane used was aqueous colloidal polymethacrylate dispersion (Eudragit® RL 30D, RS 30D or NE 30D, Rohm Pharma, Darmstadt, Germany) plasticized with diethyl phthalate (DEP), a water insoluble plasticizer (Eastman Kodak Co., NY, USA). All other reagents were of analytical grade.

2.2. Preparation of the multiple-unit FDDS

2.2.1. Preparation of core pellets

Drug-containing core pellets were prepared by extrusion–spheronization process. The drug (theophylline; 40%, w/w) and the pelletization aid (Avicel® PH 101; 60%, w/w) were mixed in a tumbling mixer (Rotomixer®, Foster Equipment Co., England) for 20 min. The dry powder mixture was then loaded into a mixing container. Sufficient amount of distilled water was slowly added in the powder mixture to achieve a consistency of the damp mass suitable for further extrusion–spheronization processes. The prepared damp mass was immediately passed through a radial basket extruder (Caleva Model 25, G.B. Caleva, England) using 2-mm diameter screen. The extrudate uniform in size was produced with the extruder speed set at 15 rpm. The extrudate was then spheronized in a spheronizer (Caleva Model 250, G.B. Caleva, England) with a rotation plate of regular cross-hatch geometry for 15 min at a rotation speed of 1500 rpm. The resultant pellets were dried at 50 °C in a fluidized bed apparatus (Uni-Glatt, Glatt, GmbH Process Technology, Germany) for 45 min.

2.2.2. Coating of the core pellets

The core pellets were coated with two successive layers; an effervescent substance (sodium bicarbonate) as an inner effervescent layer and aqueous colloidal polymethacrylate dispersion (Eudragit® RL 30D, RS 30D or NE 30D) as an outer gas-entrapped polymeric membrane. An effervescent agent was incorporated into HPMC solution plasticized with PEG 6000 (10%, w/w based on the solids content of HPMC) and then layered onto the core pellets. On a dry solid basis, the ratios of sodium bicarbonate to HPMC were 2:8, 5:5 and 8:2 w/w. The coating level of effervescent layer was 12% weight gain and the solids content of coating solution was kept constant at 12% (w/w).

The coating solution was sprayed onto the core pellets (1.41–1.68 mm) in a fluid bed coater (Uni-Glatt, Wurster insert, Glatt GmbH Process Technology, Germany). The conditions for layering were shown as follows: bead charge, 500 g; preheating temperature, 50 °C; preheating time, 20 min; inlet temperature, 50 °C; outlet temperature, 40–42 °C; atomizing air pressure, 25 lb/in.^{2}; spray rate, 8–10 ml/min. The $NaHCO_3$-layered pellets were dried in the coating chamber for 30 min at 50 °C to evaporate the residual moisture. The prepared pellets were then removed from the coating chamber and stored in a closed container for further experiments.

The $NaHCO_3$-layered pellets were subsequently coated with an aqueous colloidal polymethacrylate dispersion (Eudragit® RL 30D, RS 30D, or NE 30D) to achieve a weight gain of 5 and 10% (w/w) to obtain the complete multiple-unit FDDS. A plasticizer (DEP; 20%, w/w based on polymer solids) was added into the colloidal polymer dispersions (Eudragit® RL 30D, RS 30D) and the dispersions were gently agitated for at least 30 min prior to an appropriate dilution with purified water and subsequent coating. Eudragit® NE 30D can form film without the need of a plasticizer and thus diluted with water without the incorporation of a plasticizer. The solids content of the coating dispersions was 15% (w/w). The coating conditions were as follows: bead charge, 500 g; preheating temperature, 45 °C; preheating time, 20 min; inlet temperature, 45 °C; outlet temperature, 40–42 °C; atomizing air pressure, 25 lb/in.^{2}; spray rate, 3–5 ml/min. The pellets were further dried in the coating

chamber for 30 min after the coating was finished in order to evaporate the residual moisture in the polymeric coatings prior to storage.

2.3. Evaluation of the drug-containing core pellets and the multiple-unit FDDS

2.3.1. Particle size analysis and friability

The particle size distribution of core pellets was evaluated by sieve analysis. Two hundred grams of the core pellets were sieved through a nest of sieves (2.38–0.84 mm) on a vibratory sieve shaker (Retsch® Model AS 200 digit, Retsch, Germany) for 20 min, and the weight distribution was determined.

The friability of the core pellets was determined as the percentage of weight loss after 200 revolutions of 10 g of the core pellets in a friabilator (Erweka, Germany).

2.3.2. Determination of the drug content

The drug content in the drug-containing pellets was determined by extraction with methanol. The core pellets, effervescent-layered pellets or the effervescent-layered pellets coated with gas-entrapped polymeric membrane (complete multiple-unit FDDS) equivalent to about 20 mg of theophylline were accurately weighed, ground, and accurately transferred into a volumetric flask. Methanol was added into the flask and the mixture was stirred overnight to ensure a complete extraction. The solution was filtered through a filter paper, diluted with appropriate amount of methanol and assayed spectrophotometrically at 269 nm (Beckman Model DU600 series, Beckman Coulter, Inc., USA). The analysis was performed where Beer's Law was obeyed over the range of 0–25 μg/ml.

2.3.3. Scanning electron microscopy (SEM)

The dried pellets were mounted onto the stages prior to coating with gold to a thickness about 30 nm under vacuum. The morphology of the pellets was then observed under SEM (model JSM-5410 LV, Jeol, Japan).

2.3.4. Floating ability

The floating abilities of the effervescent-layered pellets and the coated effervescent-layered pellets (complete multiple-unit FDDS) were determined using USP paddle apparatus (50 rpm, 37 ± 0.2 °C, 900 ml, 0.1N HCl). Twenty pellets were placed in the medium; the time to float and duration of floating (floating time) were measured by visual observation. The percentage of floating pellets was calculated by the following equation:

$$\text{floating pellets (\%)} = \frac{\text{number of floating pellets at the measure time}}{\text{initial number of the pellets}} \times 100 \quad (1)$$

2.3.5. Dissolution study

The USP XXIV rotating paddle method (37.0 ± 0.5 °C, 50 rpm, 900 ml, 0.1N HCl, $n = 3$) was used to study the drug release from the multiple-unit FDDS. The weight of pellets used was equivalent to about 20 mg of theophylline. An automated dissolution testing machine comprises a dissolution apparatus (Hanson Model SR8-plus Q-Pak®, Hanson Research Co., USA), eight-channel peristaltic pump (Gilson, France), an UV–vis spectrophotometer equipped with six 1.0 cm quartz cells (Beckman Model DU600 series, Beckman Coulter, Inc., USA). The instrument was programmed to draw the sample automatically at predetermined time intervals by means of a peristaltic pump which delivers the samples to the quartz flow cells of the spectrophotometer operated at 269 nm. The drawn samples are returned to the dissolution vessels.

2.4. Data analysis

The differences in average of data were compared by simple analysis of variance (one-way ANOVA) or independent sample *t*-test. The significance of the difference was determined at 95% confident limit ($\alpha = 0.05$).

3. Results and discussion

3.1. Design of multiple-unit FDDS

Fig. 1 shows the design of multiple-unit FDDS. The system consisted of drug-containing core pellet coated with effervescent layer and gas-entrapped polymeric membrane, respectively. Since sodium bicarbonate itself could not adhere onto the core pellets, HPMC was used as a binder in the inner effervescent layer. An ideal coating material for a floating system should be highly water permeable in order to initiate the effervescent reaction and the floating process rapidly. However, the wet or hydrated coatings should also be impermeable to the generated CO_2 so as to promote and maintain floatation (Krögel and Bodmeier, 1999). Regarding their mechanical properties, the polymeric coatings should be sufficiently flexible in wet state to be able to withstand the pressure of the generated gas and to avoid rupturing. Krögel and Bodmeier (1999) reported that the cellulosic polymers were not suitable candidates for FDDS. Cellulose acetate was too rigid and did not expand sufficiently when in contact with dissolution media, while ethyl cellulose was not flexible and ruptured easily upon CO_2 formation. Gas bubbles were released rapidly after the burst of coating. According to

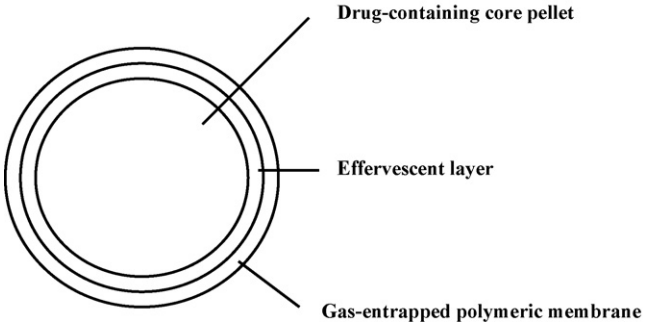

Fig. 1. Design of multiple-unit FDDS.

these reasons, the higher flexibility polymer, an aqueous colloidal polymethacrylate dispersion (Eudragit® RL 30D, RS 30D, or NE 30D), was chosen and investigated as a gas-entrapped polymeric membrane in this study.

Upon contact with the gastric fluid, the fluid permeated into the effervescent layer through the outer polymeric membrane. Carbon dioxide was liberated via neutralization reaction and was entrapped in the polymeric membrane. After that, the swollen pellets (like balloons) with a density less than 1.0 g/ml floated and maintained the buoyancy; therefore, the drug was released from the system for a long time.

To develop the multi-unit FDDS based on gas formation technique, several studies were necessary to identify the formulation variables providing the desired system properties, rapid expansion and formation of low-density system within minutes after contact with gastric fluids and maintaining the buoyancy in stomach with sustained release. The effect of the preparative parameters such as amount of the effervescent agent layered onto the core pellets, and type and coating level of the polymeric membrane, on the floating ability and drug release of the multiple-unit FDDS were evaluated.

3.2. Pellets characterization

The core pellets containing anhydrous theophylline were prepared by extrusion–spheronization using microcrystalline cellulose as a bulk excipient. The optimum volumes of water for damp mass were around 900–920 ml/kg of the powder mixtures (anhydrous theophylline:Avicel® PH 101, 40:60 w/w). The friability of the formulation was $0.17 \pm 0.04\%$. This indicated that the core pellets were quite hard and able to withstand the mechanical stresses of the subsequent coating process. The distribution of the size fractions, based on the sieve analysis is shown in Fig. 2. The drug-containing core pellets obtained by the extrusion–spheronization showed narrow size distribution and the dominant size fraction was 1.41–1.68 mm. Fig. 3A shows the appearance of the external morphology of the core pellet under SEM. The core pellets were spherical agglomerates with a slightly rough surface. The surface of the effervescent-layered pellet was slightly smoother (Fig. 3B) and the smoothest was the surface of effervescent-layered pellet coated with polymeric membrane (Eudragit® RL 30D) (Fig. 3C). The surface morphology of the effervescent-layered pellets coated with Eudragit® RL 30D as polymeric membrane before and after dissolution test is shown in Fig. 4. After dissolution test, the polymeric membrane of the coated pellets was swelled due to the inner pressure of generated CO_2. However, the swelled membrane in Fig. 4B was collapsed slightly according to the drying process under vacuum before SEM observations.

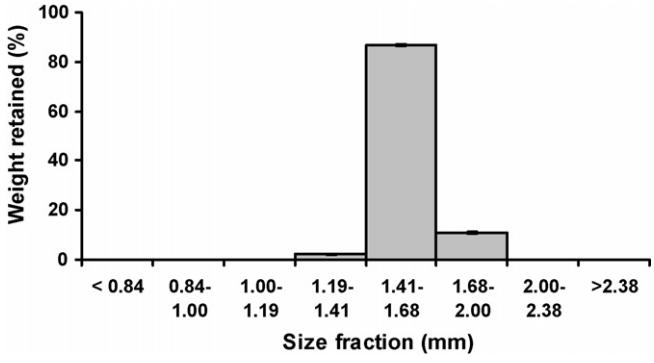

Fig. 2. The size distributions of the core pellets prepared by extrusion–spheronization (determined by sieve analysis).

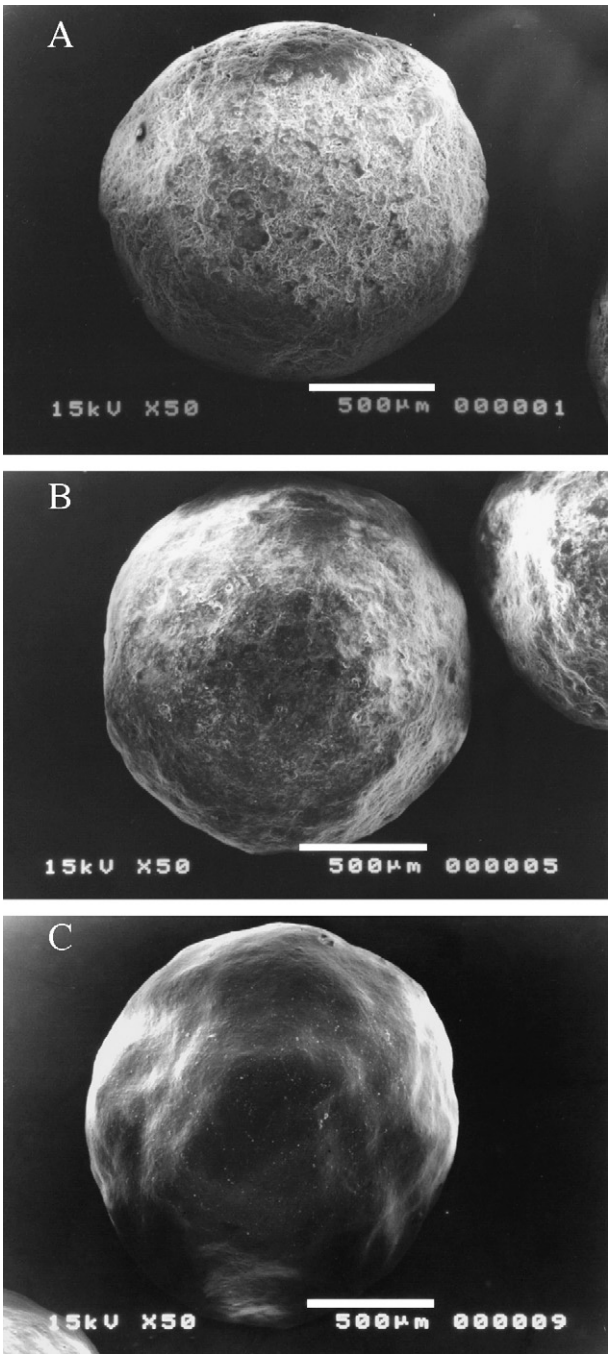

Fig. 3. Scanning electron micrographs of the surfaces of the core, effervescent-layered pellet, and effervescent-layered pellet coated with 5% Eudragit® RL 30D (HPMC:$NaHCO_3$; 2:8 w/w), magnification 50×. Key: (A) core pellet, (B) effervescent-layered pellet, and (C) effervescent-layered pellet coated with Eudragit® RL 30D.

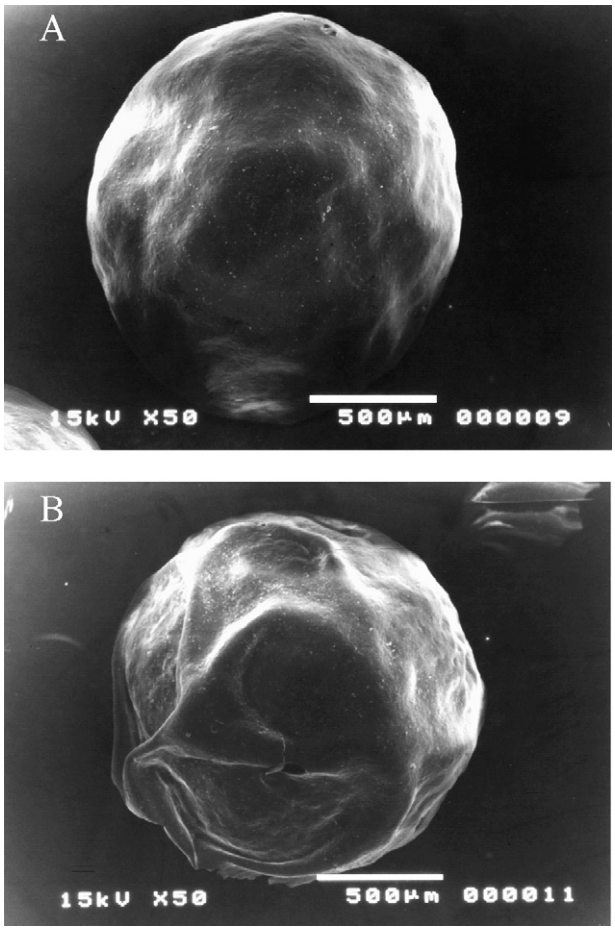

Fig. 4. Scanning electron micrographs of the surfaces of the effervescent-layered pellets coated with 5% Eudragit® RL 30D (HPMC:$NaHCO_3$; 2:8 w/w) before and after exposure to 0.1N HCl. Key: (A) surface before exposure to 0.1N HCl, magnification 50× and (B) surface after exposure to 0.1N HCl, magnification 50×.

3.3. Floating ability

The floating ability of the effervescent-layered pellets and the effervescent-layered pellets coated with polymeric membrane (complete multiple-unit FDDS) were investigated respected to amount of the effervescent agent (HPMC:$NaHCO_3$ ratio), and type and level of the polymeric coating. The system should float in a few minutes after contact with gastric fluid to prevent the dosage form from transiting into the small intestine together with food (Iannuccelli et al., 1998). The effervescent-layered pellets floated within 5–10 s after placed in 0.1N HCl. Higher amount of effervescent agent decreased floating time (duration of floating) of the effervescent-layered pellets (Fig. 5). As the coating level of effervescent layer was kept constant at 12% (w/w), amount of HPMC in this layer varied depending on the ratio of HPMC:$NaHCO_3$ used. The prolonged floating time in the pellets layered with lower amount $NaHCO_3$ was attributed to higher amount of HPMC which possessed higher entrapment capacity of the generated CO_2. The floating time of the effervescent-layered pellets was quite short (less than 0.5 h) because HPMC dissolved and there was no polymeric membrane which could entrap the generated CO_2 gas. Therefore, the complete multiple-unit FDDS (effervescent-layered pellets coated with polymeric membrane) was prepared and evaluated for floating ability. Eudragit® RL 30D, RS 30D or NE 30D were used as polymeric membrane. The multiple-unit FDDS using Eudragit® RL 30D as a polymeric membrane floated completely within 3 min in all cases. The time to float of the systems decreased with increasing amount of effervescent agent and increased with increasing level of polymeric membrane coating (Fig. 6). The higher amount of effervescent agent caused faster and higher CO_2 generation (Krögel and Bodmeier, 1999). With increasing level of Eudragit® RL 30D, the floating started later due to the delayed water penetration through the thicker coating. This result was in consistent with the previous studies (Ichigawa et al., 1991; Krögel and Bodmeier, 1999). The duration of floating was longer than 24 h. It was indicated that Eudragit® RL 30D

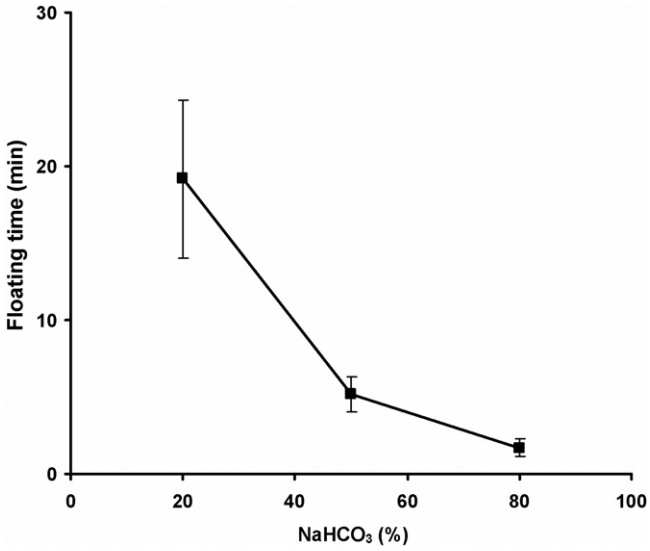

Fig. 5. Effect of % $NaHCO_3$ layered onto the core pellets on floating time of effervescent-layered pellets.

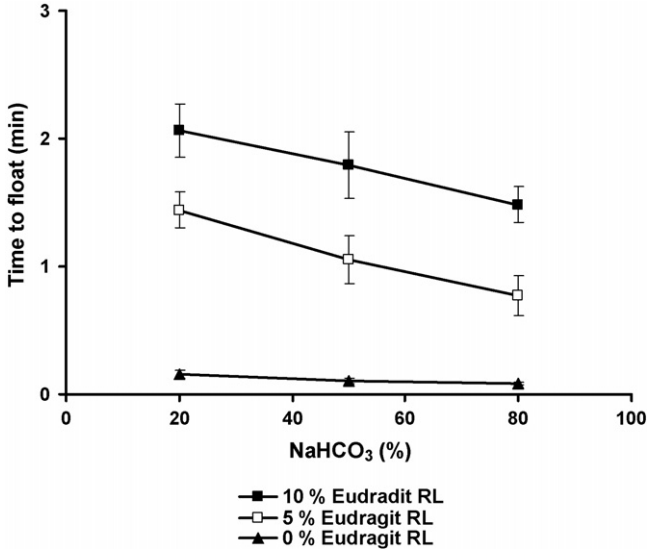

Fig. 6. Effect of % $NaHCO_3$ layered onto the core pellets and coating level of Eudragit® RL 30D on time to float of coated effervescent-layered pellets.

polymeric membrane was impermeable to the generated CO_2 and could maintain the floatation. The multiple-unit FDDS systems coated with Eudragit® RS 30D and NE 30D as polymeric membranes did not float even used high effervescent amount (HPMC:$NaHCO_3$, 2:8 w/w) and low coating level (5% weight gain). The pellets swelled slightly after placed in the medium for 24 h. Eudragit® RS 30D and NE 30D might not be permeable enough for dissolution medium to induce the effervescent reaction and generate sufficient amount of CO_2 to make the pellets floated. Eudragit® RL 30D is a highly water permeable polymer according to its hydrophilic content, quaternary ammonium groups, in the structure (Ghebre-Sellassie et al., 1997; Bauer et al., 1998). It has twice as many quaternary ammonium groups and is more hydrophilic than Eudragit® RS. It therefore hydrated faster and resulted in a shorter time to float (Krögel and Bodmeier, 1999). Based on these results, Eudragit® RL 30D was the polymer of choice as gas-entrapped membrane in this multiple-unit FDDS.

3.4. In vitro drug release characteristics

The release of theophylline from the insoluble matrix core pellets may be described by the following equation:

$$\frac{M_t}{M_\infty} = kt^{1/2} \quad (2)$$

where M_t/M_∞ is the percentage of drug released at time t and k is a release constant which reflects: (a) the shape of the matrix, (b) the internal structure of the matrix as it affects the tortuosity and porosity of the matrix and (c) the drug concentration and solubility (Peppas, 1985; Ford et al., 1991; Sriamornsak et al., 1997). It is applicable if the release of drug is largely governed by diffusion through water-filled pores in the matrix. Fig. 7 shows that the release of theophylline from the core pellets, the effervescent-layered pellets and the effervescent-layered pellets coated with Eudragit® RL 30D as polymeric membrane conforms to Eq. (2) with the correlation coefficient (r^2) of more than 0.97 in each case.

The effect of effervescent level (% $NaHCO_3$) layered onto the core pellets on drug release from effervescent-layered pellets and effervescent-layered pellets coated with Eudragit® RL 30D were investigated. Fig. 8 shows that there is no significant difference in drug release between the core pellets and the effervescent-layered pellets. However, the release of the effervescent-layered pellets with 20% $NaHCO_3$ (HPMC:$NaHCO_3$, 8:2 w/w) was slightly lowered according to the higher HPMC content in the effervescent layer. The drug release of the effervescent-layered pellets coated with Eudragit® RL 30D was lower than that of the uncoated effervescent-layered pellets because the polymeric membrane retarded the water penetration through the effervescent-layered cores. The drug release tended to increase with increasing amount of effervescent agent. However, no significant difference in drug release could be observed. A faster and higher CO_2 generation caused by increasing the level of effervescent (Krögel and Bodmeier, 1999) resulted in higher swelling of polymeric membrane and subsequent drug release. Additionally, the higher level of effervescent agent was corresponded to the lower level of HPMC and this may lead to an increase of drug release according to the easier and faster water penetration through the pellets.

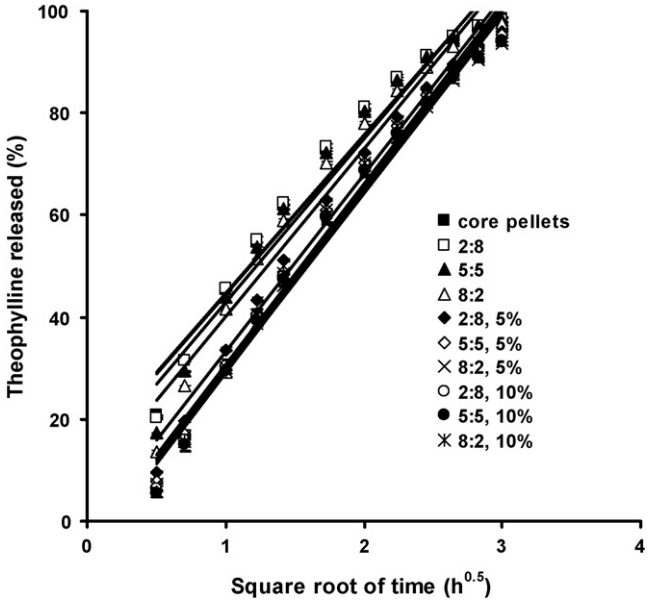

Fig. 7. The release of theophylline from uncoated cores, effervescent-layered pellets and effervescent-layered pellets coated with Eudragit® RL 30D as polymeric membrane in 0.1N HCl, plotted as the cumulative percentage of drug released vs. the square root of time. The means of triplicate data are plotted. *Note*: the value describing each symbol represents HPMC:$NaHCO_3$ ratio and coating level of Eudragit® RL 30D, respectively.

Besides the effect of effervescent level, the effects of polymer type and coating level on drug release were also investigated. Since only the multiple-unit FDDS using Eudragit® RL 30D

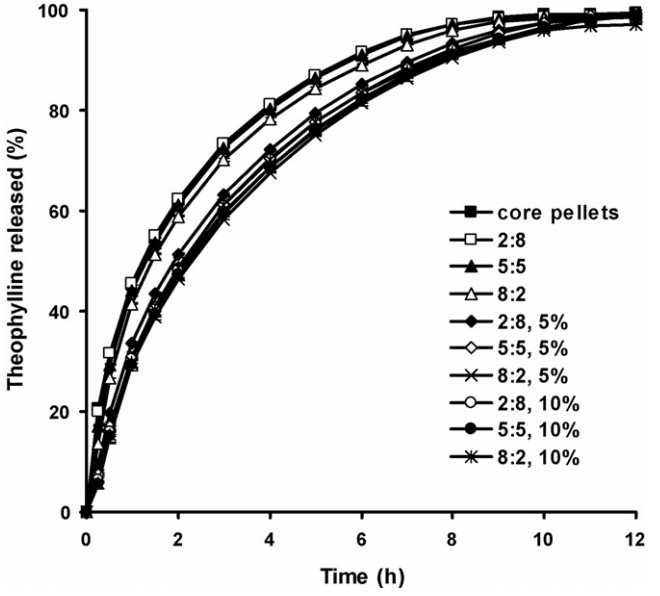

Fig. 8. Effect of % $NaHCO_3$ layered onto the core pellets on drug release of effervescent-layered pellets and effervescent-layered pellets coated with Eudragit® RL 30D as polymeric membrane (HPMC:$NaHCO_3$; 12% weight gain). *Note*: the value describing each symbol represent HPMC:$NaHCO_3$ ratio and coating level of Eudragit® RL 30D, respectively.

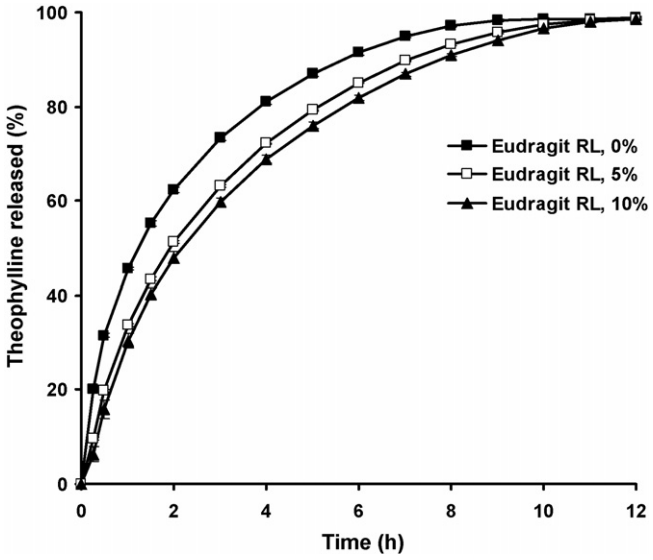

Fig. 9. Effect of gas-entrapped polymeric membrane (Eudragit® RL 30D) coating level on drug release from multiple-unit FDDS (HPMC:$NaHCO_3$, 2:8 w/w).

as a gas-entrapped polymeric membrane could float, the drug release of this system was investigated for further study. Fig. 9 shows drug release results of multiple-unit FDDS with 80% effervescent agent (HPMC:$NaHCO_3$, 2:8 w/w). The drug release decreased with increasing level of polymeric coating from 0 to 10%. The higher membrane thickness retarded water penetration, resulting in decreasing drug release (Ichigawa et al., 1991; Krögel and Bodmeier, 1999). The drug release from the system using Eudragit® RL 30D as gas-entrapped polymeric membrane was linear with the square root of time (as shown in Fig. 7). For high water permeability of Eudragit® RL, the release profile of the multiple-unit FDDS seems to be dominated by drug diffusion through the polymer matrix from the core pellets instead of drug diffusion through polymeric membrane of reservoir system.

4. Conclusions

The multiple-unit FDDS based on gas formation technique was developed. The system consists of drug-containing cores coated with effervescent layer and polymeric membrane. The floating ability and drug release of the system were dependent on amount of the effervescent agent layered onto the core pellets, and type and coating level of the polymeric membrane. Only the system using Eudragit® RL 30D as a polymeric membrane could float as Eudragit® RL 30D had high water- and low CO_2-permeabilities with high flexibility. The system could float completely within 3 min and maintain the buoyancy over a period of 24 h. The multiple-unit FDDS with rapid floating and sustained drug release was obtained and could be a promising gastroretentive DDS.

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