Research paper

Design and evaluation of floating multi-layer coated tablets based on gas formation

Srisagul Sungthongjeen a,*, Pornsak SRIAMNORNSAK b, Satit Puttipipatkachorn c

a Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand
b Department of Pharmaceutical Technology, and Pharmaceutical Biopolymer Group (PBiG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand
c Department of Manufacturing Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

Received 11 August 2007; accepted in revised form 25 September 2007
Available online 1 October 2007

Abstract

Floating multi-layer coated tablets were designed based on gas formation. The system consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. The mechanical properties of acrylic polymers (Eudragit® C210 RL 30D, RS 30D, NE 30D) and ethylcellulose were characterized by the puncture test in order to screen a suitable film for the system. Eudragit® C210 RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability. The obtained tablets enabled to float due to the CO2-gas formation and the gas entrapment by polymeric membrane. The effect of formulation variables on floating properties and drug release was investigated. The floating tablets using direct-compressed cores had shorter time to float and faster drug release than those using wet-granulated cores. The increased amount of a gas forming agent did not affect time to float but increased the drug release from the floating tablets while increasing coating level of gas-entrapped membrane increased time to float and slightly retarded drug release. Good floating properties and sustained drug release were achieved. These floating tablets seem to be a promising gastroretentive drug delivery system.

Keywords: Floating tablets; Gastroretentive drug delivery system; Gas formation; Gas-entrapped membrane; Sustained release

1. Introduction

The drug bioavailability of pharmaceutical dosage forms is influenced by various factors. One of the important factors is the gastric residence time (GRT) of these dosage forms [1]. The gastric emptying process from the stomach to small intestine generally lasts from a few minutes to 12 h. This variability leads to an unpredictable bioavailability of an orally administered dosage form. Furthermore, the relatively short gastric emptying time can result in an incomplete release of drug from the drug delivery system, leading to a diminished efficacy of the administered dose [2]. Therefore, an effective control of the placement of a delivery system in a specific region of the gastrointestinal (GI) tract offers numerous advantages, especially for the drugs with specific absorption site in the GI tract or the drugs with stability problem. These considerations have led to the development of the controlled release dosage forms that possess gastric retention capability. Floating drug delivery system (FDDS) is one of gastro-retentive dosage forms that could prolong GRT to obtain sufficient drug bioavailability [3–6]. 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 such as furosemide and theophylline [4,7,8]. It is also useful for drugs that act locally in the proximal part of GI tract such as antibiotic admin-
istration for Helicobacter pylori eradication in the treatment of peptic ulcer [6,9–11], for drugs that are unstable in the intestinal fluid such as captopril [4,12,13], and for drugs that exhibit poor solubility in the intestinal tract such as diazepam [14] and verapamil HCl [15].

Several approaches of non-effervescent and effervescent systems have been used to achieve FDDS to increase GRT. Streubel et al. [16] prepared floating matrix tablets using a low density polypropylene foam powder and matrix-forming polymers. They also developed microparticles based on low density materials, such as edible oils, in the dosage forms has been also reported recently [19,20]. Fukuda et al. [21] investigated floating hot-melt extruded tablets for gastroretentive controlled drug release system. The influence of sodium bicarbonate on physicochemical properties of the hot-melt extruded tablets was determined. The porous internal tablet morphology that contributed to buoyancy was formed by using evolution of CO₂ gas. Wei et al. [22] studied the properties of floating tablets containing hydroxypropylmethylcellulose (HPMC) and sodium bicarbonate. When the tablets were immersed in simulated gastric fluid, the CO₂ gas generated and rendered the tablets buoyant. Xiaoqiang et al. [23] developed floating matrix tablets based on a gas forming agent. HPMC K4M and Carbopol 971P NF were used as hydrogel polymers. These floating tablets consisting of drug, sodium bicarbonate with combined hydrogel polymers were prepared by wet granulation and their properties in vitro and in vivo were evaluated. The use of reservoir-type delivery system of swellable polymers and effervescent compounds is another approach for preparing FDDS. Ichikawa et al. [24] developed FDDS by coating the sustained release 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 [25]. Recently, Sungthongjeen et al. [26] developed a multi-layer coated tablet preparation methods, amount of the gas forming agent layered onto the core tablets, and coating level of the gas-entrapped membrane, on the floating properties and drug release of the floating tablets were evaluated.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Lianyungang Foreign Trade Corp., China) was used as a model drug. Microp crystalline cellulose (Avicel® PH101 or Avicel® PH102, FMC, Philadelphia, USA) and lactose monohydrate (Flowlac® 100, Meggle GmbH, Wasserburg, Germany) were used as components of the core tablets. Colloidal silicon dioxide (Aerosil® 200, Degussa-Hüls AG, Hanau, Germany) and magnesium stearate (Peter Greven Nederland C.V., Venlo, Netherlands) were used as glidant and lubricant, respectively. Povidone K90 or PVP K90 (Kollidon® 90F, BASF, Ludwigshafen, Germany) was used as binder for the core tablets prepared by wet granulation method. HPMC (Methocel® E15LV, Dow Chemical, USA) plasticized with polyethylene glycol 6000 (PEG 6000, Fluka Chemie, Switzerland) was used as protective layer and also binder of sodium bicarbonate (NaHCO₃, Fisher Scientific, UK), a gas forming agent, in gas forming layer. The gas-entrapped membrane used was aqueous colloidal polymethacrylate dispersions (Eudragit® RS 30D, NE 30D or NE 30D, Rohm Pharma, Darmstadt, Germany) or ethylcellulose (Ethocel® Standard 10, Dow Chemical, Midland, MI, USA) plasticized with diethyl phthalate (DEP), a water insoluble plasticizer (Sigma–Aldrich Chemie GmbH, Steinheim, Germany). All other reagents were of an analytical grade.

2.2. Study on free films

2.2.1. Preparation of polymeric films

An aqueous colloidal polymethacrylate dispersion (Eudragit® RL 30D or RS 30D) was plasticized with 20% w/w DEP (based on polymer solids) and gently agitated for at least 30 min prior to an appropriate dilution with purified water to achieve 15% w/w solid content. Eudragit® NE 30D can form film without a plasticizer and thus diluted with water without the incorporation of a plasticizer. To prepare ethylcellulose solution, ethylcellulose was dissolved in 95% v/v ethanol at a concentration of 12.5% w/w and plasticized with 20% w/w DEP (based on polymer solids). The polymeric films were prepared by casting the resulting dispersions/solutions onto the Teflon sheets mounted on a leveled glass plate (area of casting: 14 × 14 cm²). The films were dried for 24 h at room temperature under a special cover with reduced solvent evaporation to ensure smooth homogeneous films. The dried films were peeled from the Teflon surface, cut into 6.5 × 6.7 cm² test sections, incubated in the oven at 40 °C for 24 h and kept in a desiccator overnight prior to further investigations. The thickness of dry films (180–220 μm) was
determined in five positions with a thickness gauge (Mini-test 600, Erichsen, Hemer, Germany).

2.2.2. Evaluation of mechanical properties

The mechanical properties of the films in the dry or wet state were measured by a puncture test with a texture analyzer (TA.XT.plus Texture Analyzer, Stable Micro Systems, UK) which was previous by described [27,28]. A stainless puncturing probe with a spherical end (diameter 5 mm) was driven through the dry film with a speed of 0.1 mm/s. Force–displacement curves were recorded with a 50-N load cell. The holder with the film was immersed into 0.1 N HCl at 37 °C and further puncture test was performed with the wet films at 4 h. The load at break and the maximum displacement of the film samples were measured, and then converted to puncture strength (MPa) and elongation at puncture (%). The puncture strength and %elongation were calculated using the following equations:

\[
Puncture\ strength = \frac{F}{A_{cs}}
\]

where \( F \) is the load required for puncture, \( A_{cs} \) is cross-sectional area of the edge of the dry film located in the path of cylindrical opening of the film holder \( (A_{cs} = 2\pi r \delta, \text{where} r \text{is the radius of the hole, } \delta \text{is the thickness of the film}).

\[
\%\ Elongation = \frac{\sqrt{r^2 + D^2} - r}{r} \times 100
\]

where \( r \) is the radius of the film exposed in the cylindrical hole of the film holder, \( D \) is the displacement of the probe from point of contact to the point of film puncture.

2.3. Preparation of the floating tablets

2.3.1. Preparation of core tablets

The core tablets were prepared by a direct compression or a conventional wet granulation method. The core components consist of a drug (anhydrous theophylline 20 mg per tablet), spray dried lactose monohydrate (Flowlac® 20 mg per tablet), spray dried lactose monohydrate or a conventional wet granulation method. The core tablet excipients were sieved and mixed in a mortar by geometric dilution technique. The mixtures were placed in a Kitchen Aid® (model KPM5, United Instrument Co., Ltd., USA) and mixed with PVP K90 solution as a binder (10% w/w in distilled water) to obtain damp mass. The damp mass was granulated through sieve No. 14 (mesh size 1.41 mm) and dried at 50 °C in an incubator for 8 h. The dried granules were passed through sieve No. 18 (mesh size 1.00 mm) again and mixed with magnesium stearate (0.5% w/w) and Aerosil® 200 (0.5% w/w) in the cube mixer for 5 min. The core tablets (diameter, 9.53 mm; biconvex; hardness, 80–90 N; average tablet weight, 303 mg) were compressed using a single punch tabletting machine.

2.3.2. Coating of the core tablets

The core tablets were coated with three successive layers; an inner protective layer (HPMC), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane layer (aqueous colloidal polymethacrylate dispersion, Eudragit® RL 30D), respectively. The protective layer was 5% w/w HPMC solution plasticized with PEG 6000 (10% w/w based on the solid content of HPMC). The coating level of protective layer was 2% w/w. For gas forming layer, sodium bicarbonate was incorporated into HPMC solution plasticized with PEG 6000 (10% w/w based on the solid content of HPMC) and then layered onto the core tablets. 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 gas forming layer was 12% weight gain and the solid content of coating solution was kept constant at 10% w/w.

The coating solution was sprayed onto the core tablets in a perforated pan coater (NR-COTA18®, N.R. Industries Co., Ltd., Bangkok, Thailand). The conditions for layering protective and gas forming layers were given as follows: batch size, 1 kg; preheating temperature, 50 °C; preheating time, 30 min; inlet temperature, 48–50 °C; outlet temperature, 38–40 °C; atomizing air pressure, 1.1 bar; spray rate, 5–10 mL/min. The layered tablets were further dried in the coating chamber for additional 30 min at 50 °C to evaporate the residual moisture. The prepared tablets were then removed from the coating chamber and stored in a closed container for further experiments.

The two-layer coated tablets were subsequently coated with aqueous colloidal polymethacrylate dispersion (Eudragit® RL 30D) to achieve a weight gain of 5% and 10% w/w to obtain the complete floating tablets. A plasticizer (DEP; 20% w/w based on polymer solids) was added into the colloidal polymer dispersions and the dispersions were gently stirred for at least 30 min prior to an appropriate dilution with purified water and subsequent coating. The solid content of the coating dispersions was 15% w/w. The coating conditions were as follows: batch size, 1 kg; preheating temperature, 50 °C; preheating time, 30 min; inlet temperature, 48–50 °C; outlet temperature, 39–41 °C; atomizing air pressure, 2.5 bar; spray rate, 5–8 mL/min. The floating tablets 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.
2.4. Evaluation of the floating tablets

2.4.1. Floating properties

The floating properties of the floating tablets were determined in the closed medium-filled flasks placed in a horizontal shaker (model OS1473VBA, Revco Scientific Inc., USA) (medium: 150 mL of 0.1 N HCl, 37 °C, 50 rpm). Ten floating tablets were placed in the medium and the time to float and duration of floating (floating time) were determined by visual observation.

2.4.2. Drug release studies

The drug release studies were carried out using USP dissolution apparatus II (Vankel Model VK-7000, Vankel, USA) equipped with paddles which was operated at the speed of 50 rpm. Nine hundred milliliters of 0.1 N HCl (pH 1.2), as the dissolution medium, was placed in the glass vessel, assembled the apparatus, and equilibrated the dissolution medium to 37 ± 0.5 °C. The amount of drug release was measured at predetermined time intervals and was then assayed with UV/visible spectrophotometer (Varian, Australia) at a wavelength of 270 nm using a 1.0 cm quartz cell. Each in vitro release study was performed in triplicate.

2.5. 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 (α = 0.05).

3. Results and discussion

3.1. Mechanical properties of free polymeric films

To develop the floating multi-layer coated tablets based on gas formation, 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 action. The effect of the preparative parameters such as a core preparation method, an amount of the gas forming agent layered onto the core tablets, and a coating level of the gas-entrapped membrane, on the floating properties and the drug release of the floating tablets were evaluated. The mechanical properties of free polymeric films were also investigated to get the suitable gas-entrapped membrane.

Concerning mechanical properties of the gas-entrapped membrane for FDDS, the polymer films should be flexible enough in a wet state to withstand CO₂ pressure of the system and avoid rupture of the coating. The widely used polymers in coating of solid dosage forms such as aqueous colloidal polymethacrylate dispersions (Eudragit® RL 30D, RS 30D and NE 30D) and ethylcellulose were investigated in this study. The puncture strength and elongation of dry and wet polymeric films were determined by puncture test and the results are shown in Table 1. In dry state, films prepared from ethylcellulose showed slightly lower puncture strength and much lower elongation value when compared to the aqueous colloidal polymethacrylate dispersions (Eudragit® RL 30D, RS 30D and NE 30D). This indicated that ethylcellulose was a mechanically weak and brittle polymer. It was not flexible and could be easily ruptured under pressure according to CO₂ formation. The bubble would release rapidly after the burst of the coat. According to the results, ethylcellulose was not a suitable candidate for floating drug delivery system.

Films prepared from the aqueous colloidal polymethacrylate dispersions (Eudragit® RL 30D, RS 30D and NE 30D) showed comparable puncture strength in dry state. The Eudragit® NE 30D films had the highest elongation values in both the dry and wet state. This polymer dispersion has a low minimum film formation temperature and does not require plasticizers, resulting in flexible films [29]. The films prepared from Eudragit® RL 30D or RS 30D also had a high elongation value indicating their good flexibility. In wet state, the puncture strength of Eudragit® NE 30D films decreased less than those of the films prepared by Eudragit® RL 30D or RS 30D. This could be explained by the hydrophobic character of Eudragit® NE, when compared to Eudragit® RL 30D or RS 30D [30]. Another interesting finding was observed when comparing the dry and wet properties of the prepared films. In the wet state, the values of puncture strength were lower but the values of elongation were higher when compared to those of the dry state. A possible explanation could be the additional plasticizer effect of water when the films were hydrated. The hydration of the polymer and the resulting
interference of water with the interchain hydrogen bonding were responsible for the decrease in puncture strength and the increase in flexibility [30]. According to these results, the high flexibility polymer, an aqueous colloidal poly-methacrylate dispersion (Eudragit® RL 30D, RS 30D, or NE 30D), was interesting candidate to use as a gas-entrapped membrane.

3.2. Design and floating mechanism of floating tablets

The floating tablets composed of drug-loaded core tablets coated with a protective layer, a gas forming layer and a gas-entrapped membrane, respectively (Fig. 1A). In this study, the protective layer was used to retard drug release and protect direct contact of drug with gas forming agent. Since sodium bicarbonate itself could not adhere onto the core tablets, HPMC was used as a binder in the gas forming layer. The gas-entrapped membrane was used to entrap the generated CO$_2$ gas. The ideal membrane should be highly water permeable in order to facilitate the effervescent reaction and the floating process. The wet or hydrated coatings should also be impermeable to the generated CO$_2$ so as to promote and maintain floatation. 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 [29].

The systems coated with Eudragit® RS 30D and NE 30D as a gas-entrapped membrane did not float even when high amount of gas forming agent (12% weight gain of HPMC:NaHCO$_3$, 2:8 w/w) and low coating level (5% weight gain) were used [26]. Eudragit® RS 30D and NE 30D was low water permeable which permit low amount of dissolution medium to induce the effervescent reaction and generate sufficient amount of CO$_2$ to make the systems float. Eudragit® RL 30D is a highly water permeable polymer according to its hydrophilic content and quaternary ammonium groups in the structure [31,32]. It has twice as many quaternary ammonium groups and is more hydrophilic than Eudragit® RS. It therefore hydrated faster and resulted in a faster gas generation [29]. Therefore, only Eudragit® RL 30D was chosen as gas-entrapped membrane in this study.

Fig. 1 shows floating mechanism of the floating multi-layer coated tablets. Upon contact with the acidic medium (i.e. 0.1 N HCl), the fluid permeated into the gas forming layer through the outer gas-entrapped membrane. Carbon dioxide was liberated via neutralization reaction and was entrapped in the polymeric membrane. Consequently, the swollen tablets with a density less than 1.0 g/mL floated and maintained the buoyancy; therefore, the drug was released from the system. The floating sequence of the floating tablet at different times is shown in Fig. 2.

3.3. Effect of formulation variables on floating properties and drug release

Ideally, the floating system should float in a few minutes after contact with a gastric fluid to prevent the dosage forms from transiting into the small intestine [33]. In our preliminary study, the gas forming agent-layered tablets could not float although gas formation was observed. This is due to dissolution of HPMC membrane and no polymeric membrane to entrap the generated CO$_2$ gas, left on the tablet surface. Therefore, the further coating of gas-entrapped membrane was needed. Eudragit® RL 30D was used as gas-entrapped membrane according to the results and reason described above. To obtain the floating tablets which can float in a few minutes after contact with gastric fluid and maintain the buoyancy for a long period with sustained release action, effect of formulation variables on the floating properties and the drug release such as a core preparation method (Section 3.3.1), an amount of gas forming agent (Section 3.3.2) and a level of gas-entrapped polymeric coating (Section 3.3.3) was investigated in this study.

3.3.1. Core preparation method

The drug-containing cores were prepared by either a direct compression or a wet granulation method. The core tablets were coated with a protective layer, a gas forming layer and a gas-entrapped membrane, respectively. The floating tablets using direct-compressed cores significantly showed shorter time to float (Table 2) and faster drug release (Fig. 3). It might be explained by the different properties of the cores. The direct-compressed cores had very short disintegration time (less than 1 min) whereas the wet-granulated cores had long disintegration time (about 85 min). The rapid disintegration of the direct-compressed cores was due to the presence of disintegrating direct compression filler, microcrystalline cellulose [34]. The slow disintegration of the wet-granulated cores was attributable to the presence of binder (PVP K90). The results suggested that the dissolution medium could penetrate into the wet-
granulated cores more hardly than the direct-compressed cores, leading to slower gas formation and thus longer time to float (Table 2). Additionally, the slower penetration of dissolution medium led to slower dissolution of drug within the wet-granulated cores and subsequent slower diffusion of drug through polymeric membrane to the bulk medium (Fig. 3). It was also reported that the slower release of theophylline from the wet-granulated pellets resulted from the transformation of anhydrous theophylline to theophylline monohydrate [35]. Thus, the slower release may not be only from the core preparation method but also from the transformation of the drug polymorphic forms.

### 3.3.2. Amount of gas forming agent

Increasing the amount of gas forming agent (NaHCO₃) from 20% to 80% (w/w) did not significantly affect time to float (Table 2) although a faster and higher CO₂ generation was expected to occur. The drug release, however, increased with increasing ratio of gas forming agent to HPMC (Fig. 4). HPMC seemed to play an important role to retard drug release. The higher drug release from the floating tablets coated with higher amount of gas forming agent and lower amount of HPMC resulted from the easier and faster water penetration through the tablets [26]. A faster and higher CO₂ generation caused by increasing of the level of effervescent [29,36] resulted in higher swelling of polymeric membrane according to a higher gas pressure and subsequent faster drug release. Additionally, the faster drug release from the floating tablets with higher amount of gas forming agent is probably explained by their higher porosity or volume inside the polymeric membrane. This may allow the liquid to dissolve the drug more easily, compared to the lower porosity generated from the tablets with low amount of a gas forming agent.

### 3.3.3. Level of gas-entrapped membrane coating

As expected, the time to float was longer with increased coating level of gas-entrapped membrane (Table 2) and was
in agreement with the previous studies [26,29]. The effect of gas-entrapped membrane coating level on the drug release from the floating tablets coated with different coating levels is shown in Fig. 5. The higher level of membrane coating represented the higher thickness of the membrane and caused the lower water permeability of the film. This resulted in the retarded water penetration and slightly decreased drug release. A correlation between level of membrane coating and lag time was observed in the floating tablets containing gas forming agent to HPMC; 8:2 w/w (Fig. 5a). The lag time slightly increased with increasing level of membrane coating which indicated the thickness of the coat. After the lag time, the drug released from the
coated tablets in the different extent. This result agreed with that reported by Beckert et al. [37] who observed the correlation of film thickness and lag time of drug release from pellets that were coated using Eudragit RS 30D.

The obtained results suggested that Eudragit® RL 30D, a highly permeable polymer, has a major influence on the floating properties of the coated tablets and indicated the low CO2 permeability as gas could be entrapped for longer than 8 h, in all cases. However, the effect of the coating level on the drug release was less obvious than the amount of gas forming agent but the time of float depended significantly on the coating level.

4. Conclusions

The floating multi-layer coated tablets were developed. The system consists of drug-containing core tablets coated with a protective layer, a gas forming layer and a polymeric membrane, respectively. The data on mechanical properties of the free polymeric film provided an insight into the selection of gas-entrapped membrane for the FDDS. The polymeric film with high flexibility (Eudragit® RL30D) had high capability to entrapped generated CO2 and subsequent good floating properties. These tablets enable to float due to the formation of CO2 and the entrapment of generated CO2 by the outer polymeric membrane. The floating properties and the drug release from the floating tablets were dependent on the core preparation method, the amount of gas forming tablets and the drug release from the floating tablets were coated using Eudragit RS 30D.

Acknowledgements

The authors gratefully acknowledge J.J-Degussa Chemicals (Thailand) for kindly supplying Eudragit® samples manufactured by Rohm Pharma, Germany. This work was financially supported by Commission on Higher Education, Ministry of Education (Thailand) and The Thailand Research Fund (Grant No. MRG5080162).

References


