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Research Article

Impact of Anti-tacking Agents on Properties of Gas-Entrapped Membrane and Effervescent Floating Tablets

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Abstract. Tackiness caused by the gas-entrapped membrane (Eudragit®RL 30D) was usually observed during storage of the effervescent floating tablets, leading to failure in floatation and sustained release. In this work, common anti-tacking agents (glyceryl monostearate (GMS) and talc) were used to solve this tackiness problem. The impact of anti-tacking agent on the properties of free films and corresponding floating tablets was investigated. GMS was more effective than talc in reducing tackiness of the film. Addition and increasing amount of anti-tacking agents lowered the film mechanical strength, but the coating films were still strong and flexible enough to resist the generated gas pressure inside the floating tablet. Wettability and water vapor permeability of the film decreased with increasing level of anti-tacking agents as a result of their hydrophobicity. No interaction between anti-tacking agents and polymer was observed as confirmed by Fourier transform infrared spectroscopy, powder X-ray diffractometry, and differential scanning calorimetry studies. Increasing amount of anti-tacking agents decreased time to float and tended to retard drug release of the floating tablets. Floating properties and drug release were also influenced by type of anti-tacking agents. The obtained floating tablets still possessed good floating properties and controlled drug release even though anti-tacking agent had some effects. The results demonstrated that the tackiness problem of the floating tablets could be solved by incorporating anti-tacking agent into the gas-entrapped membrane.

KEY WORDS: anti-tacking agent; coating film; controlled release; effervescent floating tablets; Eudragit®RL 30D.

INTRODUCTION

Numerous floating drug delivery systems (FDDS) have been developed to prolong gastric retention time and obtain sufficient drug bioavailability (1-4). This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine (1,2,5), for drugs that are unstable in the intestinal fluid (1,6,7) and for drugs that exhibit poor solubility in the intestinal tract (1,2). The floating systems are also useful for drugs that act locally in the proximal part of gastrointestinal tract (3). In our previous work, the new effervescent multilayer coated floating tablet consisting of a drug-loaded core tablet coated consecutively with a protective layer, an effervescent layer, and a gas-entrapped membrane was developed (8,9). This tablet could float and maintain the buoyancy due to the lowered density resulting from the generated carbon dioxide entrapped in a gas-entrapped membrane. Aqueous acrylic dispersion, Eudragit® RL 30D, was found to be the appropriate gas-entrapped membrane due to its high flexibility and high water permeability (8,9). However, this polymeric film usually caused a problem of tackiness during coating process and storage (10,11). This tackiness can create a tremendous handling problem as the coated substrates stick to each other as well as to the wall of the coating chamber. It also increases number of coating defects and impairs the yield and quality of the coated batch (12-19). In case of the effervescent floating tablets, irreversible agglomeration of the tablets could damage the gas-entrapped membrane when the tablets were separated. This led to failure in floatation and controlled drug release of the systems. Therefore, the incorporation of anti-tacking agents in the gas-entrapped membrane was needed.

An anti-tacking agent is a necessary component in a coating system to prevent tackiness of the dosage forms during the manufacturing process. Commonly, talc was chosen as anti-tacking agent at concentration ranging from

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25 to 100% of dried polymer weight (10,11,17-20). However, the drawback of using high amount of talc in the coating formulation includes sedimentation in the spray lines and clogging spray nozzles during coating (16). Other anti-tacking agents that have been used to reduce the tackiness of polymeric film coating formulations include glyceryl monostearate (GMS) (10,11), magnesium stearate (13,14), and silicon dioxide (16,17). Wesselling et al. (10) and Petereit et al. (21) reported the overcoming tackiness problem of aqueous acrylic polymer film. They reported that the use of GMS at lower amount was sufficient as an anti-tacking agent and GMS was found to be superior to talc.

To date, there are very limited numbers of published reports on the influence of anti-tacking agent on the properties of floating delivery systems. To obtain a clear understanding on the effect of anti-tacking agent on floating and drug release behavior of the floating tablet, an insight study on the changes in physical and mechanical properties of the free polymeric films, including film tackiness, mechanical properties, water vapor permeability, and water contact angle, by anti-tacking agents, was necessary. Furthermore, the interaction between polymer and anti-tacking agent in the film was also investigated. The relationship between the changes in polymeric film properties by anti-tacking agents and the performance of the floating tablets was then discussed. It was expected that the obtained results can be applied for the pharmaceutical industry especially in the production of effervescent floating tablets.

MATERIAL AND METHODS

Materials

Anhydrous theophylline (Lianyungang Foreign Trade Corp., China) was used as a model drug. Microcrystalline cellulose (Avicel® PH102, FMC Biopolymer, Cork, Ireland) and lactose monohydrate (Flowlac® 100, Meggle GmbH, Wasserburg, Germany) were used as components of the core tablets. Colloidal silicon dioxide (Aerosil® 200, Degussa AG, Hanau, Germany) and magnesium stearate (Peter Greven Nederland C.V., Venlo, Netherlands) were used as glidant and lubricant, respectively. Hydroxypropyl methylcellulose, HPMC (Anycoat-C® AN15, Samsung, Korea) plasticized with polyethylene glycol 6000 (PEG 6000, Fluka Chemie, Switzerland) was used as protective layer and also binder of sodium bicarbonate ($NaHCO_3$, Fisher Scientific, UK), a gas forming agent, in effervescent layer. The gas-entrapped membrane used was 30% *w/w* aqueous colloidal polymethacrylate dispersions (Eudragit®RL 30D, Rohm GmbH&Co. Degussa, Germany), a copolymer of ethyl acrylate, methyl methacrylate, and a low content of methacrylic acid ester with quaternary ammonium groups (1:2:0.2). The dispersion was plasticized with diethyl phthalate (DEP), a water insoluble plasticizer (Sigma–Aldrich Chemie GmbH, Steinheim, Germany). Talcum (Yingkou Yahui, China) and GMS (Cognis Thai, Thailand) were used as anti-tacking agents. All other reagents were of an analytical grade.

Study on Free Polymeric Films

Preparation of Polymeric Films

The Eudragit®RL 30D dispersion was mixed with 20% *w/w* DEP (based on polymer solids) and gently agitated for at least 30 min prior to addition with the anti-tacking agent (talc or GMS which was passed through a 60-mesh sieve) dispersions to obtain the polymer dispersions with 5, 10, 20, or 30% (*w/w*) anti-tacking agent (based on polymer solid). The films were produced by using a pneumatic nozzle that continually sprayed the polymer dispersions onto Teflon sheets laid on a pan of perforated pan coater (NR-COTA18, N.R. Industries Co., Ltd., Bangkok, Thailand). The dispersions were stirred continuously when spraying. The following conditions were used: 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 mL/min. After the films were formed on the surface of the Teflon sheets, with an approximate thickness of 160±20 μm, they were further dried in the coating chamber for 30 min and then removed from the Teflon sheets. The films were stored over silica gel in a desiccator until required for further investigations.

Determination of Mechanical Properties

The mechanical properties of the films were measured by a puncture test using a texture analyzer (TA.XT.plus, Texture Analyzer, Stable Micro Systems, UK). A stainless steel puncturing probe with a spherical end (diameter 5 mm) was driven through the film with a speed of 0.1 mm/s. Force-displacement curves were recorded with a 50-N load cell. The load at break and the maximum displacement of the film samples were measured, and then converted to puncture strength (MPa), elongation at puncture (%), and energy at break (MJ/m^3)

$$\text{Puncture strength} = \frac{F}{A_{CS}} \tag{1}$$

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 ($A_{cs}=2rd$, where r is the radius of the hole, d is the thickness of the film).

$$\text{Elongation} = \frac{\sqrt{r^2 + D^2} - r}{r} \times 100 \tag{2}$$

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

$$\text{Energy at break} = \frac{\text{AUC}}{V_C} \tag{3}$$

where AUC is the area under the curve of the load at break and the distance, V_c is the volume of the film ($V_c=\pi r^2 d$, where r is the radius of the hole, d is the thickness of the film).

Determination of Tackiness

A modification of the method reported by Wesseling et al. (10) was applied. The films were cut into pieces (2.0 cm×7.0 cm). Two pieces of tested films were pressed together under a 1,000-g weight and stored at 40°C for 1 h. After treatment, the samples were equilibrated at room temperature (27±2°C) for 10 min. T-peel tests were performed using a texture analyzer, equipped with a 5 N load cell. The films were peeled from each other through one end at a cross-head speed of 15 mm/min. The force–displacement diagram was recorded. The average value obtained from the constant force portions of the diagrams was used to represent the peeling forces. Each sample was tested for four times.

Determination of Water Contact Angle

Water contact angle was measured with droplet of water on the polymeric film surface, using the contact angle goniometer (FTA1000 B Class, Virginia, USA) at 27±2°C. A drop of water was gently placed on the films using a microsyringe. The angle between the tangent line and the film surface from goniometric scale, after 30 s each droplet onto the surface was measured. Six tests were performed for each film sample. The averaged values of contact angle were then used for all subsequent calculation.

Determination of Water Vapor Permeability

An adapted method for water vapor permeation (WVP) measurement as described in the previous study was used (22). The film was placed on open 4-mL glass vial containing 4 g of dried granular calcium chloride, and was then covered by aluminum cap with an opened circular hole diameter of 1.3 cm (test area, 1.33 cm^2). The vials were conditioned in a desiccator containing silica gel for 24 h. The vials were then placed in a desiccator containing a saturated aqueous NaCl solution (75% RH, 27±2°C). The weight change was recorded at predetermined time intervals. The WVP coefficient of at least three cells for all films was then calculated using the following equation:

$$\text{WVP coefficient} = \frac{W \times t}{A \times \Delta P} \tag{4}$$

where W was the amount of water permeated through the film in mg/h, t was the thickness of film (mm), A was test area (mm^2), and ΔP was the vapor pressure difference (mmHg).

Fourier Transformed Infrared Spectroscopy

Fourier transformed infrared (FTIR) spectroscopy was used to determine molecular interaction between the anti-tacking agent and Eudragit®RL 30D. The Eudragit®RL 30D films with and without anti-tacking agents were pulverized, blended with KBr, and compressed to prepare disks. The FTIR spectra of the prepared disks were measured using a FTIR spectrophotometer (Nicolet, 4700 FT-IR, Thermo Scientific, USA).

Powder X-ray Diffractometry

The powder X-ray diffraction (PXRD) patterns of Eudragit®RL 30D films with and without anti-tacking agents were measured by a powder X-ray diffractometer (Rigaku, MiniflexII, Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 30 kV; current, 15 mA and scanning speed 4°/min.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermograms of anti-tacking agent, Eudragit®RL 30D films with and without anti-tacking agents were measured by using a differential scanning calorimeter (DSC822e, Mettler Toledo, Switzerland). The samples of 2–3 mg were accurately weighed into aluminum pans without an aluminum cover. The measurement was performed over 30–450°C at a heating rate of 10°C/min under nitrogen purge.

Preparation and Evaluation of Effervescent Floating Tablets

Preparation of Core Tablets

The core tablets were prepared by a direct compression method. The core components consist of a drug (anhydrous theophylline, 20 mg per tablet), spray-dried lactose monohydrate (Flowlac® 100) (140 mg per tablet) and microcrystalline cellulose (Avicel® PH102) (140 mg per tablet). The core tablet excipients were mixed for 10 min, followed by the addition of magnesium stearate (0.5% *w*/*w*) and Aerosil® 200 (0.5% *w*/*w*). The powder mixture was further mixed for 3 min and compressed into tablets (diameter, 9.53 mm; biconvex; hardness, 9–10 kg; average tablet weight, 300 mg) using a single punch tabletting machine (Model YH06, Yeo Heng Co., Ltd., Thailand).

Coating of the Core Tablets

The core tablets were coated with three successive layers: an inner protective layer (HPMC) (Anycoat-C® AN15), an effervescent layer (sodium bicarbonate), and a gas-entrapped membrane layer (aqueous colloidal polymethacrylate dispersion, Eudragit®RL 30D), respectively. The protective layer contained 5% *w*/*w* HPMC solution plasticized with PEG 6000 (10% *w*/*w* based on the solid content of HPMC). The coating level of the protective layer was 2% *w*/*w*. For effervescent 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. The ratio of sodium bicarbonate to HPMC was 8:2 *w*/*w*. The coating level of effervescent 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. The prepared tablets were then removed from the coating chamber and stored in a closed container. The two-layer coated tablets were subsequently coated with gas-entrapped membrane (Eudragit®RL 30D) to achieve a weight gain of 5 and 10% *w*/*w* to obtain the complete floating tablets. Colloidal polymer dispersion was plasticized with 20% *w*/*w* DEP (based on polymer solids) and

gently stirred for at least 30 min. The anti-tacking agent (e.g., talc and GMS) was passed through a 60-mesh sieve and dispersed in the purified water prior to further mixing with colloidal polymer dispersion to dilute the coating dispersion. The floating tablets were obtained by coating with 15% *w/w* solid content of the coating dispersions. The floating tablets were stored in a desiccator for further evaluation. All 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; and spray rate, 5–8 mL/min. The coating substances 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.

Scanning Electron Microscopy

The dried floating tablets were mounted onto the stages prior to coating with gold to a thickness about 90 nm under vacuum. The surface and cross-section morphology of the gas-entrapped membranes with anti-tacking agents were then observed under scanning electron microscopy (SEM) (Maxim-2000, CamScan Analytical, England).

Determination of Floating Properties

The floating properties of the floating tablets were determined using USP dissolution apparatus II (paddle speed of 50 rpm, temperature of 37±0.5°C, 900 mL of 0.1 N HCl). Three floating tablets were placed in the medium. The time to float and duration of floating (floating time) were determined by visual observation.

Drug Release Studies

The drug release studies were carried out by using 900 mL of 0.1 N HCl as the dissolution medium in USP dissolution apparatus II (VK-7000, Vankel, USA) at 37±0.5°C and 50 rpm. At predetermined time points, samples (5 ml) were withdrawn and replaced with fresh medium to compensate for the loss due to sampling. The amount of theophylline release was determined by UV/visible spectrophotometer (Varian, Australia) at a wavelength of 270 nm using a 1.0-cm quartz cell. A minimum of three replicates were carried out for each formulation.

Data Analysis

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

Analysis of Release Data

The mechanism of drug release from the effervescent floating tablets in 0.1 N HCl was determined using zero-order, first-order, and Higuchi equation. The zero order rate Eq. (5) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (6) describes the release from system where release rate is concentration dependent. Higuchi describes the release of the drugs from matrix as a square root of time dependent process based on Fickian diffusion Eq. (7).

$$C = k_0 t \tag{5}$$

where k_0 is zero order rate constant expressed in units of concentration/time and t is the time.

$$\mathrm{Log}\, C = \mathrm{Log}\, C_0 - \frac{kt}{2.303} \tag{6}$$

where C_0 is the initial concentration of drug and k is first order constant.

$$Q = k\sqrt{t} \tag{7}$$

where k is the constant reflecting the design variables of the system.

RESULTS AND DISCUSSION

Effect of Anti-tacking Agents on Free Polymeric Film Properties

Mechanical Properties

The effervescent floating tablet was composed of a drug-loaded core coated consecutively with a protective layer, an effervescent layer and a gas-entrapped membrane. The floating mechanism of this system can be explained by carbon dioxide generated from neutralization reaction between sodium bicarbonate with HCl in acidic medium. The gas-entrapped membrane played a vital role to entrap the generated CO_2 gas to cause the system density less than 1.0 g/mL. Consequently, the floating tablets floated and maintained the buoyancy. Regarding mechanical properties of gas-entrapped membrane, the polymer films should be flexible and strong enough to withstand CO_2 pressure of the system to avoid rupture of the coating. The mechanical properties of polymeric films incorporating with anti-tacking agents were investigated to obtain the suitable gas-entrapped membrane. The puncture strength, elongation, and energy at break of Eudragit®RL 30D films with and without anti-tacking agents were determined by puncture test, and the results are shown in Table I. The results exhibited that the films with anti-tacking agents showed lower puncture strength, elongation, and energy at break when compared to the films without anti-tacking agents. GMS could reduce the mechanical properties of the film at higher extent than talc especially at high concentration (20–30% w/w). When the higher amount of the anti-tacking agents was incorporated, the higher degree in reduction of both puncture strength and elongation values was obtained. The energy required to break the films decreased with addition and increasing amount of anti-tacking agents. It can be explained that the presence of the anti-tacking agents could cause discontinuities in the network of the polymeric film. This resulted in a weak link in the film structure (17,23) and a decrease in the film mechanical

Table I. Mechanical Properties of Eudragit®RL 30D Films Using Different Types and Amounts of Anti-tacking Agents (S.D. in parentheses; n=5) (film thickness 160±20 μm)

Anti-tacking agents (% based on solid polymer)	Mechanical properties					
	Puncture strength (MPa)		Elongation (%)		Energy at break (MJ/m^3)	
	Talc	GMS	Talc	GMS	Talc	GMS
0	6.74 (0.99)	6.74 (0.99)	79.34 (6.45)	79.34 (6.45)	5.65 (0.42)	5.65 (0.42)
5	5.54 (0.61)	5.36 (0.57)	48.66 (4.09)	60.63 (9.20)	4.78 (0.42)	2.78 (0.38)
10	4.48 (0.35)	4.99 (0.42)	47.47 (13.49)	58.22 (7.15)	4.06 (0.34)	2.53 (0.15)
20	5.15 (0.18)	2.66 (0.22)	45.94 (6.98)	40.29 (6.18)	4.34 (0.62)	1.05 (0.14)
30	4.66 (0.45)	2.47 (0.34)	42.71 (7.84)	35.37 (7.60)	3.05 (0.57)	0.75 (0.17)

properties. This finding is consistent with the previous study, where a magnesium stearate was incorporated to aqueous ethylcellulose film (23). Felton and McGinity (20) suggested that the decrease in the elasticity of the polymeric film was probably due to the filler particles physically impeding the mobility of the polymer phase or the filler-polymer interaction stiffening the molecular chains of the polymer and reducing segmental mobility.

Tackiness

To solve the tackiness problems in coatings with acrylic polymer, different types and amount of common anti-tacking agents were incorporated to the Eudragit®RL 30D films. T-peel test adopt form Wesseling et al. (10) was used to measure the tackiness of the films. The force required to peel the pressed films from each other could exhibit the level of the film tackiness. Figure 1 represents the effect of type and amount of anti-tacking agents on the tackiness of polymeric films. Peeling force of the film without anti-tacking agents exhibited the highest value at 1.96 N. Addition of 5% *w*/*w* GMS dramatically reduced peeling force of the films and showed more significant effect than talc. These findings are in accordance with previous studies which reported that GMS was effective at much lower concentrations than talc (10). Nimkulrat et al. (11) suggested that GMS could decrease more polymer contact area than talc; thus, the ability in reducing film tackiness of GMS is more powerful. However, when increasing amount of anti-tacking agent to 10% *w*/*w*, there was no significant effect on peeling force between the films with two different anti-tacking agents. Increasing amount of anti-tacking agent (at higher level than 10% *w*/*w*) slightly decreased peeling force of the films. The reduction in tackiness of both GMS and talc-containing films could not be improved by increasing the concentration from 10 to 30% *w*/*w*. This result is consistent with that reported by Wesseling et al. (10). The decrease in tackiness of the films depended on capability of anti-tacking agents in reducing the contact area between the polymers (11, 16). Addition of 10% *w*/*w* of anti-tacking agent seemed to almost reach the capability in reduction of film tackiness, and further addition of anti-tacking agent from 10 to 30% *w*/*w* could not improve the reduction in film tackiness. Another reason was due to an increasing hydrophobicity of the film with added anti-tacking agents. Cervera et al. (14) revealed that the mechanism of anti-sticking agents was based on their strong capability to reduce hydrogen bonds existing in the film and to form simultaneously an increased number of competitive hydrophobic bonding in the system. These implied that the mechanism of anti-tacking agents might be not only reducing contact area between the film surfaces but also increasing hydrophobicity of the polymeric film.

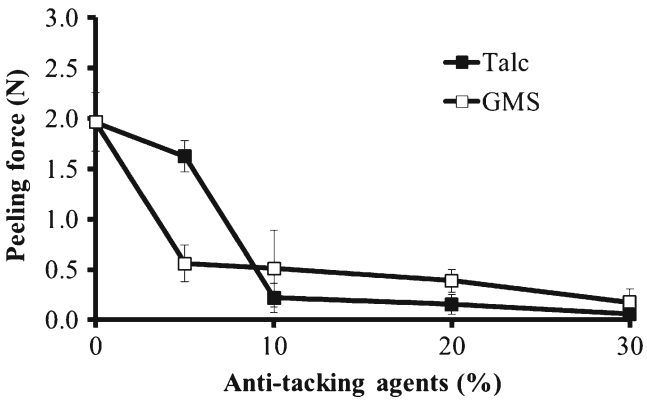

Fig. 1. Effects of type and amount of anti-tacking agents on tackiness of Eudragit®RL 30D films (film thickness 160±20 μm)

Water Contact Angle

Wettability of gas-entrapped membrane is crucial for the effervescent floating tablet because it is related to time to float. Generally, the tablet should have low-density system within few minutes after contact with gastric fluids. The fast

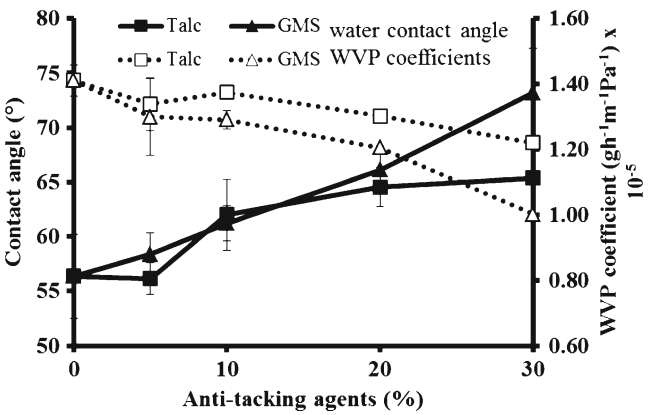

Fig. 2. Effects of type and amount of anti-tacking agents on water contact angle (*solid lines*) and WVP coefficients (*dotted lines*) of Eudragit®RL 30D films

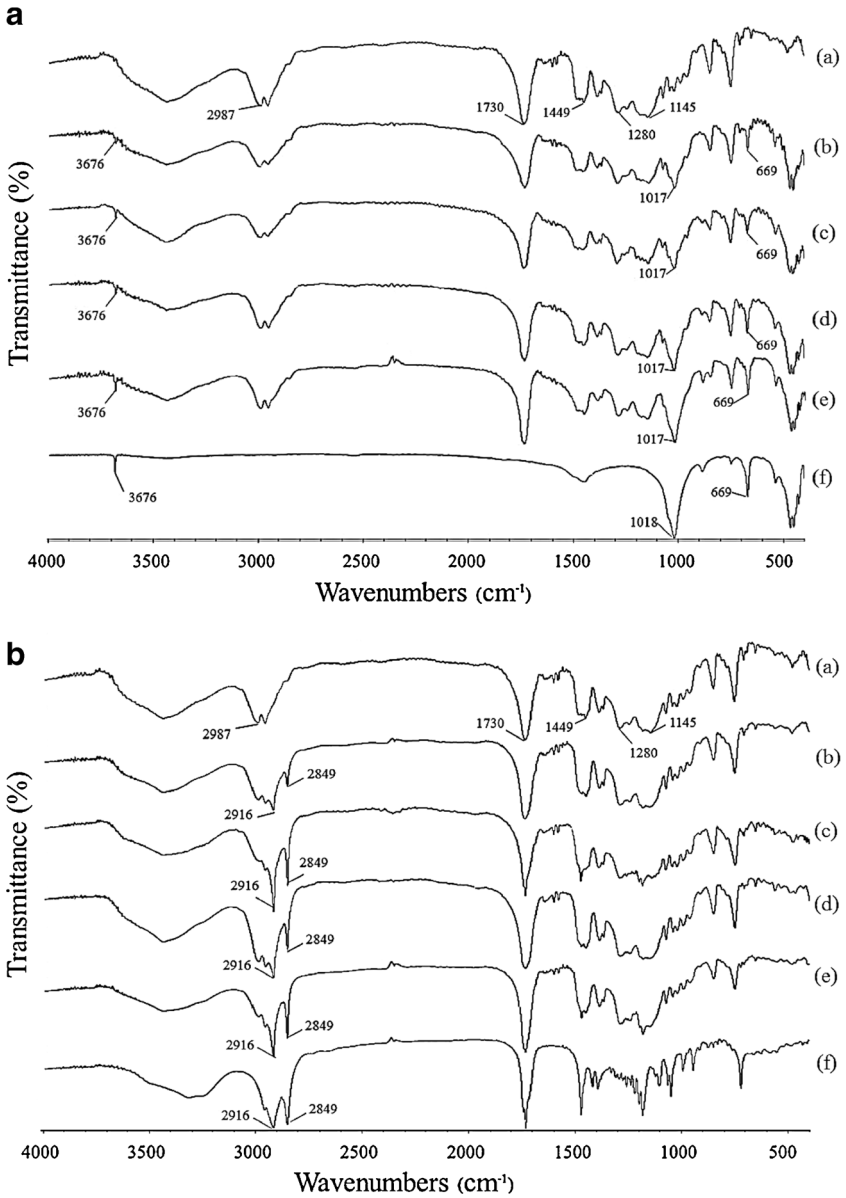

Fig. 3. FTIR spectra of Eudragit®RL 30D films with different type and amount of anti-tacking agents: **a** talc, **b** GMS, Key: (*a*) 0%; (*b*) 5%; (*c*) 10%; (*d*) 20%; (*e*) 30%; *w/w* of anti-tacking agents; and (*f*) anti-tacking agent powder

hydrated film permits a rapid water penetration into the floating tablet leading to a fast gas generation and consequently a short time to float (8, 9). Addition of anti-tacking agents resulted in the higher water contact angles (lower wettability) compared to the film without anti-tacking agents (Fig. 2, solid lines). The films with GMS showed higher contact angle value than those with talc especially at the level of 30% *w/w*. This suggested that the film with GMS had more hydrophobicity. The water contact angles increased with increasing GMS content in the Eudragit®RL 30D films from 5 to 30% *w/w*. However, addition of talc showed noticeable increase in water contact angles at a level of 10% *w/w*, and then the contact angle gradually increased when talc was incorporated from 10 to 30% *w/w*. These results suggested that incorporation of the anti-tacking agents resulted in lower water wettability of the films. It seemed probable because anti-tacking agents enhanced the hydrophobic nature of the Eudragit®RL 30D film (14). The obtained results on enhanced hydrophobicity were in agreement with Leterme et al. (24) study which reported that incorporation of talc particles exhibited higher values of water contact angles and hence lower values of total surface-free energy. The authors explained that siloxane (Si-O-Si) bonds of talc could not form strong hydrogen bonds with water leading to an increase of film hydrophobicity and consequently resulting in a decrease of film wettability (24, 25).

Water Vapor Permeability

An ideal coating membrane for a floating system should be highly water permeable. Rapid effervescent reaction and

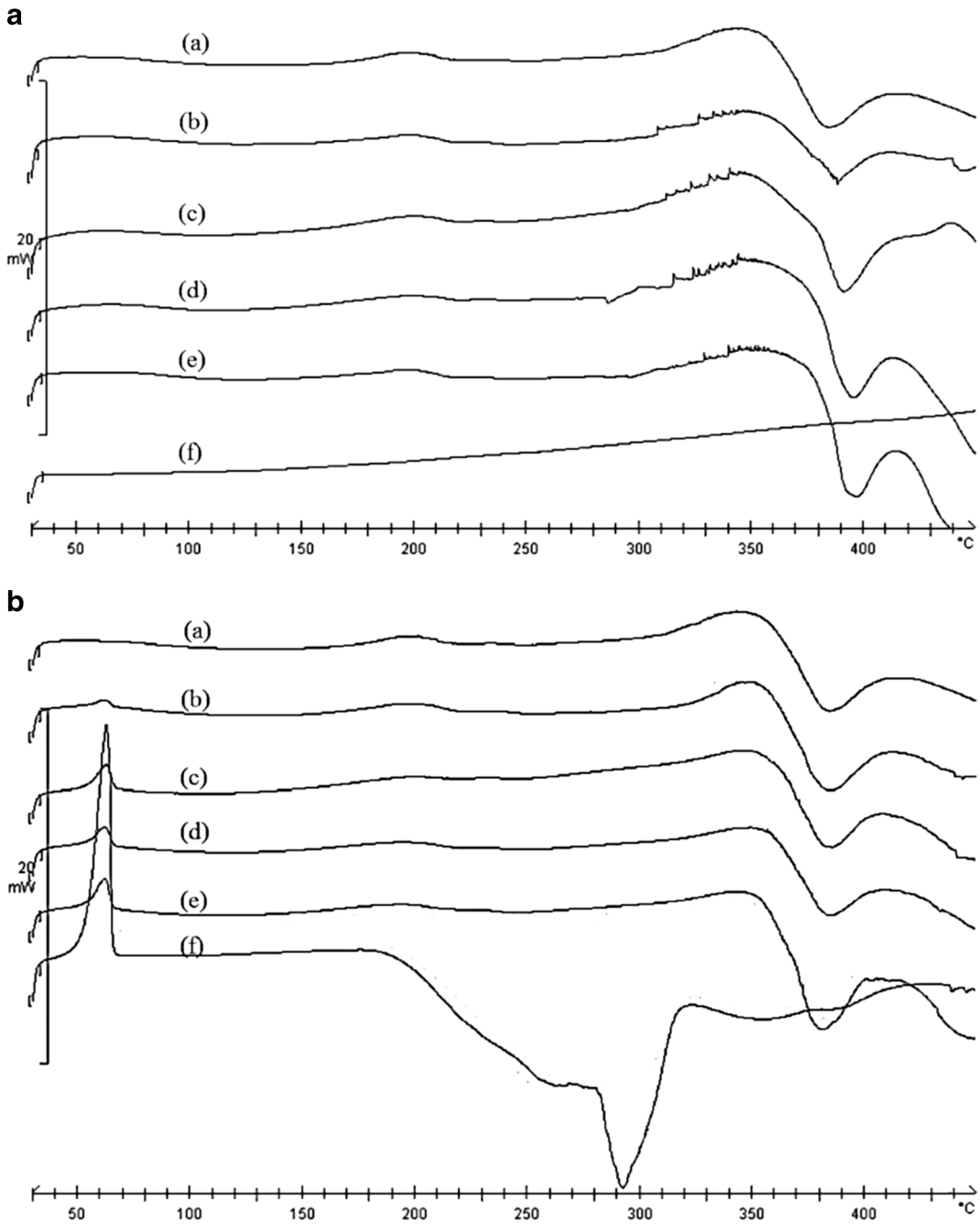

Fig. 4. DSC thermograms of Eudragit®RL 30D films with different type and amount of anti-tacking agents: **a** talc and **b** GMS, Key: (*a*) 0%; (*b*) 5%; (*c*) 10%; (*d*) 20%; (*e*) 30%; *w*/*w* of anti-tacking agents; and (*f*) anti-tacking agent powder

fast floating behavior of the floating tablet become a major challenge when anti-tacking agents are used to reduce the tackiness of Eudragit®RL 30D film. From this consideration, WVP of all free films with anti-tacking agents are determined, and the obtained results are shown in Fig. 2, dotted lines. The Eudragit®RL 30D film without anti-tacking agent exhibited highest WVP coefficient at 1.41×10^{-5} gh^{-1} m^{-1} Pa^{-1} compared to the films with anti-tacking agents. The WVP coefficient of the Eudragit®RL 30D film with GMS was lower than that of the film with talc. The WVP coefficient could be related to the hydrophobicity of the anti-tacking agents indicating that GMS is more hydrophobic than talc. Cervera et al. (14) reported that WVP of the film was dependent on the number of available polar groups. The obtained results indicated that incorporation of anti-tacking agents decreased the WVP coefficient. In addition, with increasing anti-tacking agent level from 5 to 30%, the WVP coefficients gradually decreased. This result was due to the enhanced hydrophobicity of the films caused by the incorporation of anti-tacking agent. It is also indicated that the results found in the WVP study were in good agreement with those obtained in the water contact angle test.

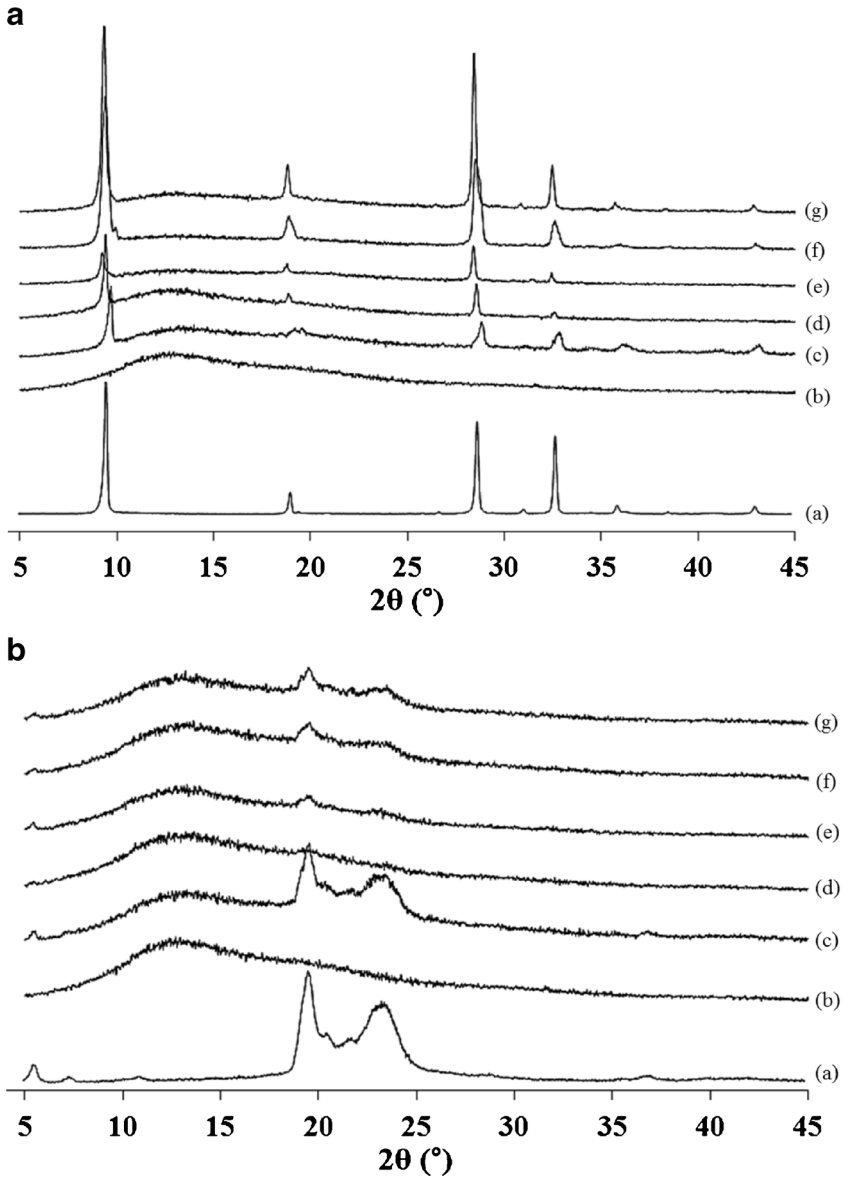

Fig. 5. Powder X-ray diffraction patterns of Eudragit®RL 30D films with different type and amount of anti-tacking agents: **a** talc and **b** GMS, Key: (*a*) anti-tacking agents powder; (*b*) Eudragit®RL 30D film; (*c*) physical mixture; (d) 5%; (*d*) 10%; (*e*) 20%;and (*f*) 30%; *w*/*w* of anti-tacking agents

Interaction Between Polymer and Anti-tacking Agents

It is possible that the interaction between polymer and anti-tacking agent could occur and may subsequently affect the floating properties and drug release of the floating tablets. The FTIR spectroscopy, DSC, and PXRD were used to determine such interaction. The transmission infrared spectra of Eudragit®RL 30D films with talc and GMS are shown in comparison with those without anti-tacking agent (Fig. 3). The Eudragit®RL 30D free film exhibited the characteristic bands of the ester groups at 1,145–1,190 and 1,240–1,280 cm^{-1}, as well as the C=O ester vibration at 1,730 cm^{-1}. In addition, CH_x vibrations can be identified at 1,450 and 2,950–3,000 cm^{-1}. The characteristic peaks of Eudragit®RL 30D was not affected by incorporation of anti-tacking agents both talc and GMS. For example, the characteristic peaks of talc at 669, 1,018, and 3,676 cm^{-1} became evident, only when 5% (*w*/*w*) of talc was added. The FTIR spectra of Eudragit®RL 30D films with talc presented the superposition peaks of talc and Eudragit®RL 30D (Fig. 3a). Also, the higher in intensity of FTIR peaks with increasing amount of talc was observed but no shift of any peaks of Eudragit®RL 30D. This suggested no molecular interaction between Eudragit®RL 30D and talc. Similar results were observed in the Eudragit®RL 30D films with GMS (Fig. 3b) which showed characteristic peaks of GMS at 2,916 and 2,849 cm^{-1}

Thermal analysis is another important evaluation technique to find any possible interaction between the drug and the polymers used. Such interaction can be identified by any change in thermogram. Figure 4a, b are representative of DSC thermograms of Eudragit®RL 30D films with talc and GMS, respectively. No peak was observed in the

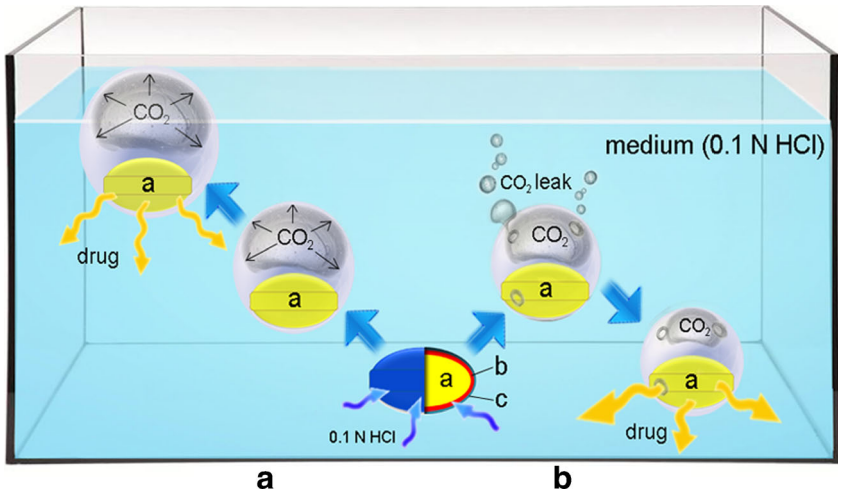

Fig. 6. Floating mechanism of floating tablets without (**a**) and with tackiness problem (**b**). Key: *a* a drug-containing core with a protective layer; *b* an effervescent layer (sodium bicarbonate); and *c* a gas-entrapped membrane

thermograms of pure talc as well as the films with talc. However, higher amount of talc incorporated into Eudragit®RL 30D films seemed to increase thermal stability of the films. The film with talc illustrates slightly shift of degradation peak from 385°C to a higher temperature of 395°C (Fig. 4a). According to high degradation temperature of talc, higher ratio of talc in the film results in retardation of degradation peak. This phenomenon is similar to thermal

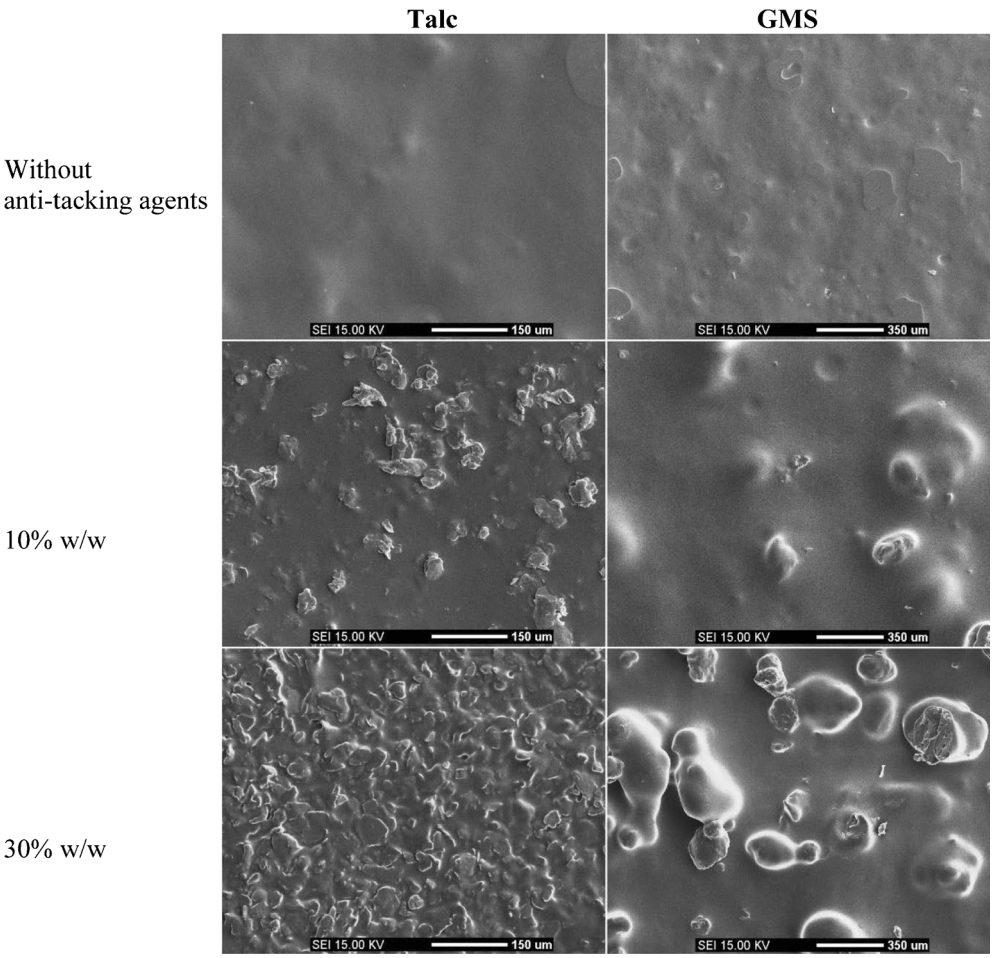

Fig. 7. SEM photomicrographs of surface morphology of sprayed Eudragit®RL 30D films with anti-tacking agents, magnification: Talc ×160, GMS ×80

Table II. Floating Properties of Floating Tablets Using Different Types and Amounts of Anti-tacking Agents in 0.1 N HCl (S.D. in parentheses; $n=4$)

Anti-tacking agents (% based on solid polymer)	Floating properties	
	Time to float (min)	Floating time (h)
No additives	7.68 (0.20)	>8
Talc		
5	7.33 (0.19)	>8
10	7.84 (0.24)	>8
20	10.45 (0.42)	>8
30	12.40 (0.52)	>8
GMS		
5	7.13 (0.57)	>8
10	10.54 (0.42)	>8
20	13.02 (0.26)	>8
30	15.22 (0.33)	>8

behavior of the polymethacrylate film with magnesium aluminum silicate (26). The melting peak of GMS around 72°C was observed (Fig. 4b). Incorporation and increasing amount of GMS into Eudragit®RL 30D films did not change of exothermic peak. The small melting peak of GMS around 72°C was observed in all films containing GMS. The GMS melting peaks were observed more clearly with increasing amount of GMS in the films. These observations indicated that talc slightly affected degradation of Eudragit®RL 30D films whereas GMS had no effect on the thermal behavior of Eudragit®RL 30D films.

To evaluate the effect of anti-tacking agents on the polymorphic structure of the gas-entrapped membrane, powder X-ray diffraction patterns of the films with talc and GMS were measured as shown in Fig. 5a, b, respectively. The diffraction pattern of talc powder showed a crystalline peaks at 9.52°, 19.06°, 28.72°, and 32.76° (Fig. 5a). GMS powder showed a crystalline peak at approximately 19.5° and 23.3° which were specific for α-form (Fig. 5b) (27). Eudragit®RL 30D displayed halo pattern which indicated its amorphous form. When anti-tacking agents were added into Eudragit®RL 30D films, the crystalline peaks of anti-tacking agents were observed and located at the same position with pure anti-tacking agents. The peak intensity increased with increasing anti-tacking agent level. The results from FTIR spectroscopy, DSC, and PXRD studies strongly indicated that there is no interaction between anti-tacking agents and Eudragit®RL 30D. It was suggested that the floating and dissolution behavior of the effervescent floating tablets were not related to this interaction.

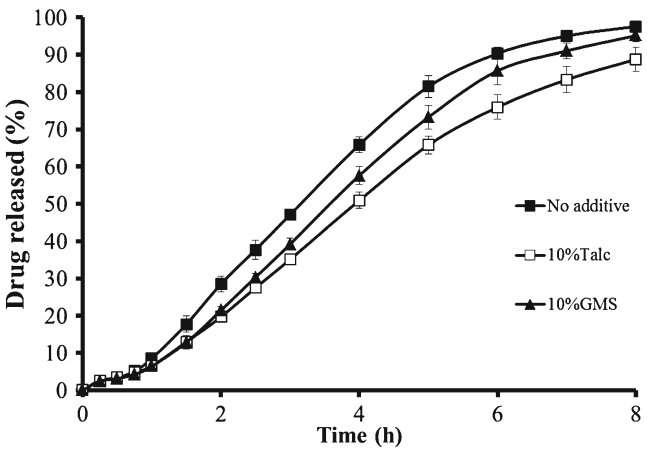

Fig. 8. Effect of anti-tacking agent types on theophylline released from floating tablets coated with 10% *w/w* Eudragit®RL 30D membrane in 0.1 N HCl

Effect of Anti-tacking Agents on Floating Properties and Drug Release of Effervescent Floating Tablets

Floating mechanism of the effervescent floating tablets which are composed of (a) drug-loaded cores coated with a protective layer, (b) an effervescent layer, and (c) a gas-entrapped membrane is shown in Fig. 6a. To achieve system density less than 1.0 g/mL, CO_2 gas was generated via neutralization of sodium bicarbonate in the effervescent layer with HCl in acidic medium. The gas-entrapped membrane was used to entrap the generated CO_2 gas. The system remained buoyant for a prolonged period of time, with the

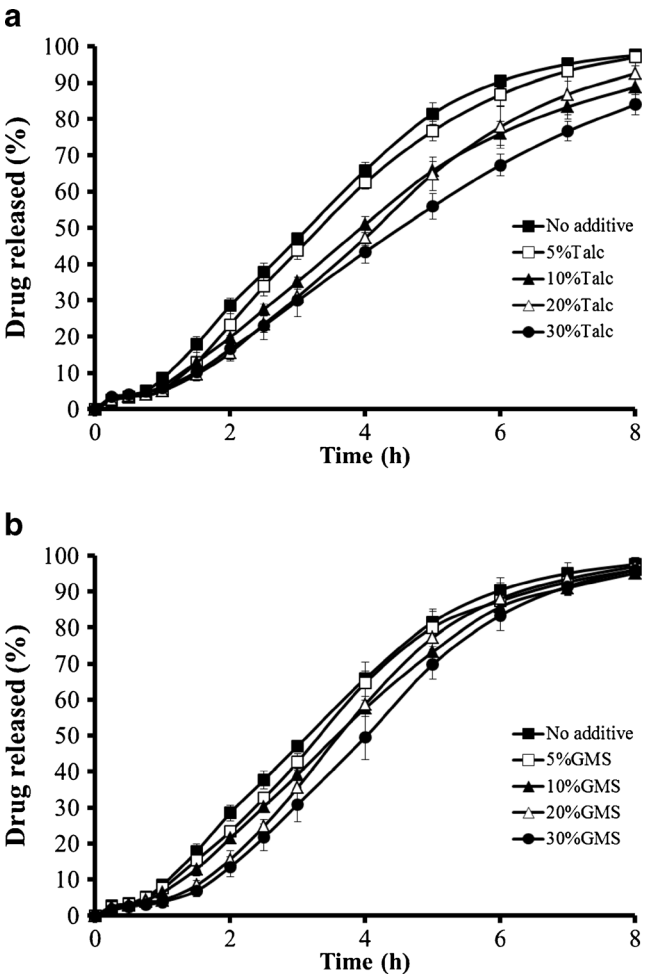

Fig. 9. Effect of amount of anti-tacking agents on theophylline released from floating tablets coated with 10% *w/w* Eudragit®RL 30D membrane in 0.1 N HCl: **a** talc, **b** GMS

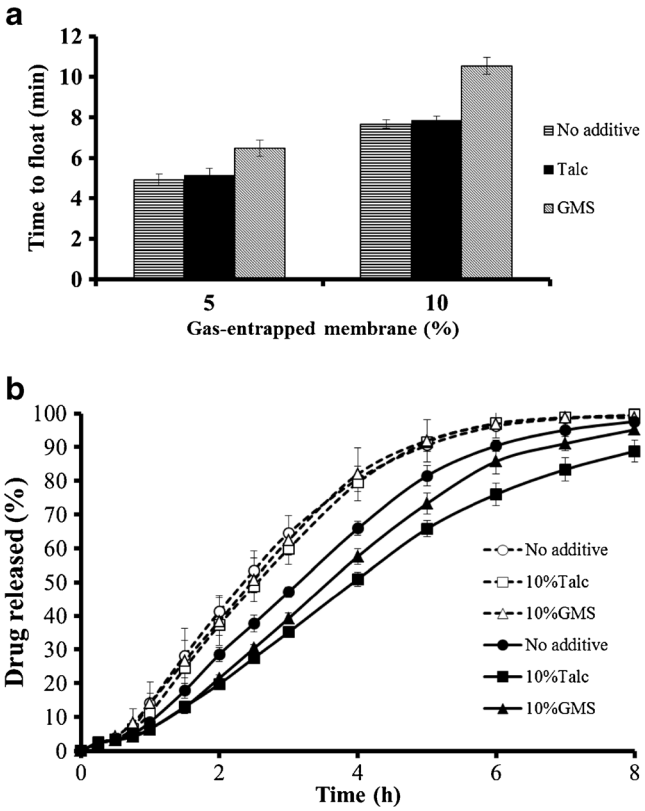

Fig. 10. Effect of coating level of Eudragit®RL 30D membrane (5% *w/w*, *dotted lines* and 10% *w/w*, *full lines*) on time to float (**a**) and drug release (**b**) from effervescent floating tablets with 10% anti-tacking agents in 0.1 N HCl

potential for continuous release of drug. A problem that usually occurs is tackiness of the floating tablet caused by the gas-entrapped membrane (Eudragit®RL 30D). Separation of the agglomerated floating tablets leads to damage the gas-entrapped membrane and causes failure in floatation and controlled release action of the system as shown in Fig. 6b. To overcome this tackiness problem of the gas-entrapped membrane, anti-tacking agents including talc and GMS were incorporated to gas-entrapped membrane. The SEM shown in Fig. 7 demonstrates the surface morphology of Eudragit®RL 30D sprayed films with and without anti-tacking agents. The Eudragit®RL 30D film without anti-tacking agents was smooth and homogeneous. In contrast, the films with talc and GMS had rough surface and discontinuous morphology, which could possibly result from the presence of insoluble particles of anti-tacking agent which was immiscible with the polymeric film. Increasing amount of anti-tacking agents increased the surface roughness of the films (Fig. 7), the results were consistent with previous study of El-Malah and Nazzal (28). They reported that an increase in the amount of talc powder increased the surface roughness of the beads coated with film matrices. In this study, incorporation of anti-tacking agent could reduce tablet agglomeration during coating process and storage which were in agreement with the results obtained in the tackiness study of free polymeric films (Fig. 1). The roughness on the film surface possibly reduced the contact area between the polymeric films (11). Since the good effervescent floating tablets should float in few minutes after contact with a gastric fluid to prevent the dosage forms from transiting into the small intestine and also the system should be a controlled-release function of the polymer films to achieve the slowly and completely release the drug in the stomach (1-3,8,9,29), the influence of anti-tacking agents on floating properties and drug release of the floating tablets must be concerned. The presence of anti-tacking agents in the gas-entrapped membrane caused low wettability and WVP of the films (Fig. 2) and may affect floating properties and drug release of the floating tablets. Thus, effect of anti-

Table III. Mathematic Modeling and Drug Release Kinetics of Theophylline from Effervescent Floating Tablets

Formulation	Correlation coefficient, r^2			Zero order release rate constant, k (%/h)	Lag time (h)
	First order	Higuchi model	Zero order		
5% *w/w* gas-entrapped membrane					
No additive	0.9140	0.9859	0.9989	21.99±0.17	0.74±0.08
5% *w/w* Talc	0.8965	0.9961	0.9933	23.14±0.93	0.82±0.09
10% *w/w* Talc	0.8784	0.9981	0.9958	22.87±0.15	0.87±0.09
20% *w/w* Talc	0.9000	0.9928	0.9992	20.16±1.44	0.89±0.04
30% *w/w* Talc	0.9256	0.9958	0.9973	17.48±1.30	1.22±0.06
5% w/w GMS	0.9438	0.9875	0.9980	25.34±1.79	0.81±0.05
10% *w/w* GMS	0.9378	0.9881	0.9997	24.44±3.59	0.85±0.09
20% w/w GMS	0.9361	0.9935	0.9995	27.07±1.89	0.93±0.08
30% *w/w* GMS	0.9401	0.9884	0.9990	32.28±2.24	1.10±0.15
10% *w/w* gas-entrapped membrane					
No additive	0.9277	0.9965	0.9985	19.15±0.63	1.07±0.11
5% *w/w* Talc	0.9004	0.9988	0.9951	18.50±0.49	1.25±0.16
10% *w/w* Talc	0.9295	0.9944	0.9967	15.91±0.76	1.31±0.06
20% *w/w* Talc	0.9234	0.9919	0.9986	15.21±0.19	1.60±0.09
30% *w/w* Talc	0.9137	0.9954	0.9975	12.68±0.82	1.61±0.09
5% *w/w* GMS	0.9484	0.9897	0.9969	18.20±0.98	1.21±0.09
10% *w/w* GMS	0.9334	0.9941	0.9993	17.38±0.42	1.32±0.06
20% *w/w* GMS	0.9372	0.9836	0.9980	18.94±0.60	1.65±0.09
30% *w/w* GMS	0.8884	0.9952	0.9969	20.33±0.61	1.82±0.08

tacking agents on floating properties and drug release of the floating tablets were investigated in this study.

Type of Anti-tacking Agents

The effervescent floating tablets were prepared by incorporating talc and GMS into the gas-entrapped membrane. The floating properties of the floating tablets coated with films containing anti-tacking agents are shown in the Table II. Clearly, the time to float of the floating tablets increased with increasing level of talc and GMS greater than 10 and 5%, respectively. The floating tablets with GMS presented longer time to float than those with talc at identical level of anti-tacking agent because of the higher hydrophobicity of GMS. This could be explained by the higher water contact angle and lower WVP coefficient of the film containing GMS which was discussed previously. The floating time of all formulations coated with films containing anti-tacking agents were more than 8 h. This indicated that the gas-entrapped membrane with anti-tacking agent is still strong enough to withstand pressure generated by gas formation of the floating tablets even anti-tacking agent reduced mechanical properties of the films. Drug released from the floating tablets was influenced by anti-tacking agents as shown in Fig. 8. Incorporated anti-tacking agents retarded theophylline released from the floating tablets. Since floating properties and drug release of effervescent floating tablets related to water permeability of the gas-entrapped membrane (8), longer time to float and decreased release rates of the floating tablets with anti-tacking agents could be explained by the hydrophobic effect of anti-tacking agents. Addition of anti-tacking agent increased hydrophobicity of the gas-entrapped membrane. This resulted in lower penetration of acidic medium through the membrane to interact with sodium bicarbonate and dissolve the drug. Dissolution retarding action of drug form dosage form with film containing insoluble substances was reported in the previous studies (17,19,20). Unexpectedly, the floating tablet with GMS exhibited the faster drug release compared to that with talc (Fig. 8) although GMS showed higher hydrophobicity than talc as described previously. During dissolution test, the size of the floating tablet with GMS was found to be bigger than that with talc. This indicated that the floating tablet with GMS exhibited slightly higher expansion of the gas-entrapped membrane than that with talc (data not shown). This finding was related to higher film flexibility of the film with GMS (Table I). The higher swelling of gas-entrapped membrane containing GMS caused the thinner film and resulted in higher water penetration and caused faster drug release. This result suggests that the thinner film resulted from higher flexibility plays an important role on drug release from the floating tablets with GMS than the higher hydrophobicity of GMS.

Amount of Anti-tacking Agents

The effect of anti-tacking agent amount on floating properties and drug release are shown in Table II and Fig. 9, respectively. Increasing amount of anti-tacking agents significantly delayed time to float and drug release of the systems. However, there were no statistically significant differences on both time to float and drug release between the floating tablets with and without anti-tacking agents at low amount of anti-tacking agent (5% *w*/*w*). These results suggested that increasing amount of anti-tacking agent in gas-entrapped membrane led to an increase of film hydrophobicity, resulting in retardation of drug release from the floating tablets. This result was similar to the studies of pellets coated with talc-containing acrylic polymer (18, 28).

Coating Level of Gas-Entrapped Membrane

Besides type and amount of anti-tacking agents, the effect of coating level of gas-entrapped membrane with anti-tacking agents on time to float and drug release from effervescent floating tablets was investigated and shown in Fig. 10. Clearly, time to float was longer with increased coating level of gas-entrapped membrane (Fig. 10a). Also, the floating tablets coated with higher coating levels, 10% *w*/*w* based on polymer solid, showed the decrease of theophylline released (Fig. 10b). These indicated that higher coating level of gas-entrapped membrane represented the higher film thickness, leading to the lower water permeability of the film. This resulted in the slower acidic medium penetration and subsequent slower CO_2 generation. Therefore, it decreased time to float and drug release of effervescent floating tablets. These results agreed with previous reports (6,8,9,30) which showed the correlation of film thickness and properties of floatation and drug release from floating systems.

Analysis of Release Data

As illustrated in Figs. 8,9, and 10, the drug release profiles of the effervescent floating tablets had a sigmoidal shape. At initial lag phase, dissolution medium penetrated through gas-entrapped membrane into the core tablet and consequently less than 10% of drug diffused out. Lag time was defined as time interval that less than 10% of drug was released. After the lag phase, drug released gradually until the complete release was obtained. In this phase, three mathematical models (zero-order, first-order, and Higuchi model) were used to determine drug release mechanism. All formulations of effervescent floating tablets were best fitted with the zero-order model (r^2 = 0.9933–0.9997) as presented in Table III. This implied that drug release was controlled by membrane diffusion with lag time. It was indicated that lag time increased with increasing level of anti-tacking agent, especially at a level of 10% *w*/*w* gas-entrapped membrane. In addition, the drug release rate constant of the floating tablet tended to decrease with increasing level of talc but slightly increased with increasing amount of GMS.

CONCLUSIONS

Incorporation of anti-tacking agents to Eudragit®RL 30D, the gas-entrapped membrane, reduced tackiness (decreased peeling force) of the film and could overcome the tackiness problem of the effervescent floating tablets. Addition and increasing amount of anti-tacking agents lowered the mechanical strength of the gas-entrapped membrane; however, the coating films were still strong and flexible enough to resist the generated gas pressure inside the floating tablet. Anti-tacking agents increased hydrophobicity of the film

(decreased WVP and wettability) and resulted in an increase in time to float and retardation of drug release of the floating tablets. GMS seemed to be more effective than talc to reduce peeling force of the film. No interaction between anti-tacking agents and polymer was found as confirmed by FTIR spectroscopy, PXRD, and DSC studies. All formulations of the effervescent floating tablets with anti-tacking agents demonstrated good floating properties and controlled drug release.

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