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**KEYWORDS:** Magnesium stearate, Anti-tacking agent, Free film properties, Floating properties, Effervescent-based floating tablets

## INTRODUCTION

In our previous work, the effervescent-based floating tablets were developed [1]. The theophylline core tablet was coated with a protective layer, an effervescent layer and a gas-entrapped membrane. Upon contact of the tablet with the medium (0.1 N HCl), the fluid permeated into an effervescent layer. Carbon dioxide was generated via neutralization reaction and was entrapped in a gas-entrapped membrane. The tablet density was reduced less than the density of the acidic medium. The tablets then floated, maintained the buoyancy and released the entrapped drug. Eudragit® RL 30D, which exhibited high flexibility and high water permeability [1], was used as gas-entrapped membrane. However, the problem that usually occurs is the tackiness of the polymeric film[2], especially with Eudragit® RL 30D. The tackiness of this acrylic polymer film causes tablet agglomeration, leading to failure in floatation. Therefore, anti-tacking agent was needed. An anti-tacking agent is an important substance in a coating system to overcome tackiness of the dosage forms during the manufacturing process. Talc is commonly used as anti-tackiness at concentrations ranging from 25 to 100% based on the weight of dry polymer[2,3]. However, the disadvantage to use high ratio of talc in the coating process includes sedimentation in the spray lines and clogging spray nozzles during coating [4]. From the previous reports, incorporation of magnesium stearate (MS) significantly decreased tackiness of chitosan film-coated pellets[5]. Hence, MS was used as anti-tacking agent. The major aim of this study was to investigate the effect of MS as an anti-tacking agent on floating properties and drug release of the effervescent-based floating tablets. Additionally, the effects of film properties including mechanical properties and water vapor permeability were evaluated.

## MATERIALS AND METHODS

**Preparation of polymeric films:** Eudragit® RL 30D (Rohm Pharma, Darmstadt, Germany) was plasticized with 20% w/w diethyl phthalate (DEP, Sigma–Aldrich Chemie GmbH, Steinheim, Germany) based on polymer solids and gently agitated for at least 30 min prior to addition of MS (Peter Greven Nederland C.V., Venlo, Venlo, Netherlands). The polymeric films were prepared by casting onto the Teflon sheets mounted on a leveled glass plate (area of casting: 14 cm x14 cm). The films were dried in the oven at 40 °C for 24 h. The thickness of dry films (180–220 μm) was determined in five positions with a thickness gauge (Minitest 600, Erichsen, Hemer, Germany).

**Film tackiness:** The films were cut into 2.0 cm×7.0 cm sections. Two test films were pressed together under a 1000-g weight and stored at 40 °C for 1 h. After treatment, the samples were cooled to room temperature (25±1 °C) and T-peel tests were performed using a texture analyzer. The films were peeled from each other through one end at a cross-head speed of 15 mm/min. The force-displacement diagrams were recorded. The average values obtained from the constant force portions of the diagrams were used to represent the peel forces. Each sample was performed in triplicate.

**Water vapor permeability of the film:** An adapted permeation method for water vapor permeation (WVP) study was used according to the method described in the previous study [6]. The films were placed on open 4 ml glass vials containing 4 g of dried granular calcium chloride, and were then covered by cap with an opened circular hole with a 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% R.H., 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 following equation

$$\text{WVP coefficient} = (W \times t)/(A \times \Delta P)$$

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

**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 was 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 is 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 is 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 ratios of sodium bicarbonate to HPMC were 8:2 w/w. The coating level of effervescent layer is 12% weight gain and the solid content of coating solution is 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 MS were 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. 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; 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. The floating tablets were stored in desiccator for further evaluation.

**Floating properties:** The floating properties of the floating tablets were determined using USP paddle apparatus (50 rpm, 37±0.5°C, 900ml, 0.1 N HCl). Five floating tablets were placed in the medium. The time to float and duration of floating (floating time) were determined by visual observation.

**In vitro release studies:** The drug release studies were carried out by using 900 ml of 0.1 N HCl as the medium in USP apparatus II (UDT 804, Logan Instruments Corp, USA) at 37 ± 0.5 °C and 50 rpm. The amount of theophylline release was measured at predetermined time intervals and was then assayed with UV/visible spectrophotometer (Model UV2450, Shimadzu, Japan) at a wavelength of 270 nm. A minimum of three replicates were carried out for each formulation.

## RESULTS

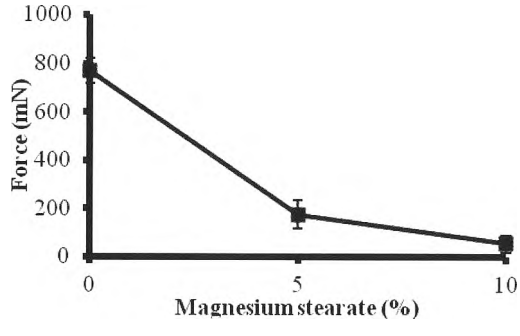


**Figure 1** Effect of magnesium stearate on tackiness of Eudragit® RL 30D films.

**Film tackiness:**

As illustrated in Figure 1, the ability of MS to reduce film tackiness was observed. Incorporating MS in Eudragit® RL 30D film reduced the peeling force significantly. Additionally, with increasing amount of MS as 5% and 10% w/w, the tackiness of polymeric film decreases to 174 mN and 52 mN, respectively.

**Water vapor permeability of film:** The coating membrane for our floating system should be highly water permeable. Rapid gas generation floating process is a major challenge when incorporating MS to reduce the tackiness of Eudragit® RL 30D film. From this consideration, WVP of the films was determined as the results shown in Figure 2. The Eudragit® RL 30D film exhibited highest WVP coefficient at $1.41\times10^{-5}$ $gh^{-1}m^{-1}Pa^{-1}$ and

WVP coefficients of films were slightly reduced by addition of MS. Increasing amount of MS from 5% to 10%, the WVP coefficients were decreased to $1.30\times10^{-5}$ and $1.22\times10^{-5}$, respectively.

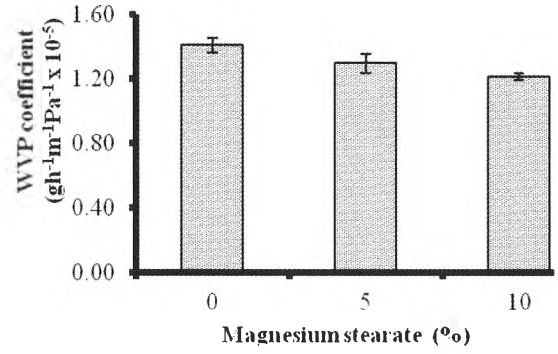


**Figure 2** Effect of magnesium stearate on the WVP coefficients of Eudragit® RL 30D films.

**Floating properties:** Table 1 represents effect of MS on the floating properties. The tablet without MS showed the shortest time to float (around 4.93 and 7.68 min for 5% and 10% w/w gas-entrapped membrane coating level respectively). The MS significantly reduced the time to float of the system. In all formulations, the floating time more than 8 h was obtained.

**Table 1** Floating properties of effervescent-based floating tablets using different amount of magnesium and levels of gas-entrapped coating in 0.1 N HCl (n = 5)

| Formulation | Time to float (min ± SD) | Floating time (h) |
|---|---|---|
| 5% w/w Eudragit RL 30D | | |
| 0% w/w Magnesium stearate | 4.93 ± 0.28 | > 8 |
| 5% w/w Magnesium stearate | 7.62 ± 0.45 | > 8 |
| 10% w/w Magnesium stearate | 8.59 ± 0.73 | > 8 |
| 10% w/w Eudragit RL 30D | | |
| 0% w/w Magnesium stearate | 7.68 ± 0.20 | > 8 |
| 5% w/w Magnesium stearate | 10.00 ± 0.72 | > 8 |
| 10% w/w Magnesium stearate | 11.71 ± 0.77 | > 8 |

**In vitro release studies:** At 5% gas-entrapped membrane coating level (Figure 3A), the floating tablet with 5% w/w MS based on solid polymer exhibited no significant difference in theophylline released comparing to the floating tablet without MS. However, increasing amount of MS to 10% w/w clearly retarded the drug released from the system. At the thicker coating level, 10% w/w based on polymer solid, incorporating and increasing amount of MS significantly decreased the drug release (Figure 3B).

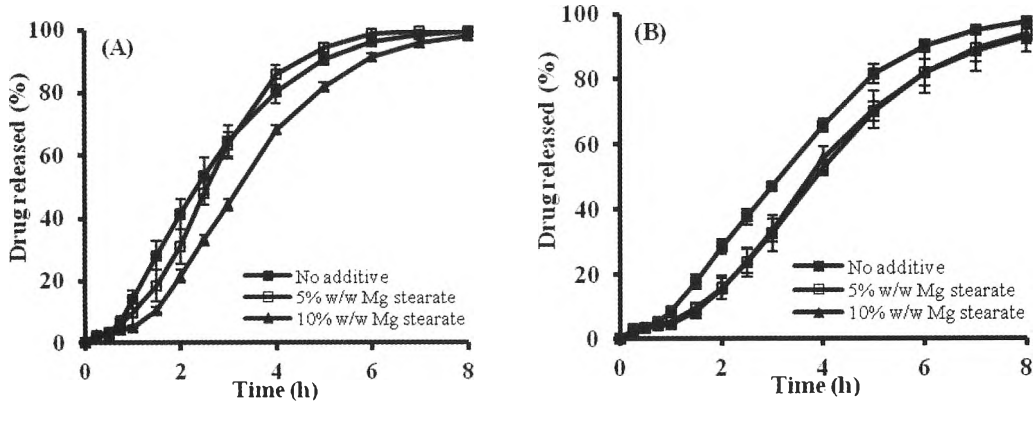


**Figure 3** Effect of magnesium stearate on theophylline released of effervescent-based floating tablets (A: 5% and B: 10% w/w gas-entrapped membrane coating) in 0.1 N HCl (n = 3)

## DISCUSSION

The effervescent-based floating tablets composed of drug-loaded core tablets coated with a protective layer, a gas forming layer and a gas-entrapped membrane. The HPMC was used as protective layer to retard drug release and protect direct contact of drug with effervescent agent. The gas-entrapped membrane was used to entrap the generated $CO_2$ gas which was formed by neutralization of sodium bicarbonate in the effervescent layer. In this study, the MS was used to reduce tackiness of the tablet coating with Eudragit® RL 30D films. The ability of MS to reduce film tackiness is displayed in Figure 1. Addition and increasing amount of MS in Eudragit® RL 30D film decreased the tackiness of the films. Nimkulrat *et al.* [2] explained that the ability of the substance in reducing the tackiness of the films was dependent on their capability in reducing the contact area between the polymers. Since gas-entrapped membrane should be highly water permeable in order to facilitate the effervescent reaction and the floating process. Thus, the WVP of Eudragit® RL 30D films incorporating with MS was determined. As Figure 2, WVP coefficients of films were decreased by adding anti-tacking agent. It can be explained that the presence of MS in the polymeric film caused higher film hydrophobicity. This result was supported by previous study [7], which showed the increasing of film contact angle by incorporating MS in to the film. For floating properties and the drug release of effervescent-based floating tablets, the tablet without MS showed shorter time to float and higher drug release. An obvious increase in time to float was noticed with increasing amount of MS. In addition, drug release was slower when the amount of anti-tacking agent in the film was increased (Figure 3). The results suggest that MS probably enhanced the hydrophobic nature of the Eudragit®RL 30D by increasing number of competitive hydrophobic bondings in the membrane [5] Our results on hydrophobicity also agreed with Leterme *et al.*'s study [8] which reported that incorporation of talc led to higher water contact angles, and hence lower values of total surface-free energy. They suggested that siloxane (Si-O-Si) bonds of talc did not form strong hydrogen bonds with water. The increase in film hydrophobicity resulted in lower medium penetration to interact with sodium bicarbonate and to dissolve the drug.

## CONCLUSION

In free film study, MS has high ability to reduce the film tackiness. Also, incorporation of MS lowered WVP of Eudragit® RL 30D films due to their hydrophobicity. The tackiness of effervescent-based floating tablets seemed to be reduced by incorporating MS in the gas-entrapped membrane. All effervescent-based floating tablets showed good floating properties (time to float less than 15 min, floating time more than 8 h) and controlled drug release. However, the tablets coated with gas-entrapped membrane and MS consequently delayed time to float and drug release due to film hydrophobicity. High hydrophobicity of gas-entrapped membrane with anti-tacking agents was a major reason resulting in delayed acidic medium penetration through the tablets to interact with the effervescent and dissolve the drug out.

## ACKNOWLEDGMENTS

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