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ภาคผนวก

Outputs

งานประชุมระดับนานาชาติ

Kriangkrai W, Puttipipatkachorn S, Sriamornsak P, Pongjanyakul T, **Sunghongjeen S**. Magnesium Stearate as Anti-tacking Agent in Acrylic Polymer Films Intended for Gas-entrapped Floating Delivery System. บทความคัดย่อและนำเสนอโปสเตอร์ในงานประชุมวิชาการ Chiang Mai International Conference on Biomaterials & Applications (CMICBA 2011), Aug 9-10, 2011, The Empress Hotel, Chiang Mai, Thailand.

Sunghongjeen S, Kriangkrai W, Sriamornsak P, Pongjanyakul T, Puttipipatkachorn S. Effect of Anti-tacking agent (Talc) on Effervescent Floating Tablets. บทความคัดย่อและนำเสนอโปสเตอร์ในงานประชุม 8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (2012), March 19-22, 2012, Istanbul, Turkey.

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**MAGNESIUM STEARATE AS ANTI-TACKING AGENT IN
ACRYLIC POLYMER FILMS INTENDED FOR GAS-
ENTRAPPED FLOATING DELIVERY SYSTEM**

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Abstract

In development of effervescent-based floating tablets, acrylic polymer is used to prepare a gas-entrapped membrane of the system. The tackiness of this acrylic polymer film causes tablet agglomeration, leading to failure in floatation. Thus, the aim of this study was to investigate the effect of magnesium stearate (MS) used as anti-tacking agent on mechanical and wetting properties of the acrylic polymer (Eudragit® RL 30D) films. Incorporating MS resulted in the films with a slight lowered puncture strength, a high lowered elongation and an increased contact angle. These results indicated that flexibility and wettability of these films were reduced by addition of MS. Furthermore, the film tackiness measurement by peel test showed that 5% (w/w) of MS could significantly decrease the tackiness of the films. It was demonstrated that MS was a promising candidate to be used as an anti-tacking agent for effervescent-based floating tablets.



**ORAL BASES CONTAINING CENTELLA ASIATICA
EXTRACT: FORMULATIONS AND EVALUATIONS**

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Abstract

Centella asiatica (Buabok) was reported to heal wounds, burns and ulcerations, the aim of this project was to formulate the oral pastes for the treatment of aptus ulcers in mount cavity. Oral bases containing 4% W/W C. *asiatica* extract were prepared using polyethylene glycol (PEG), Carbopol 940, poloxamer, polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC). The preparations were evaluated for the physical properties: pH, viscosity and physical stability. The buccal mucoadhesive properties were also evaluated through porcine buccal mucosa using texture analyzer. Bases containing PEG and Carbopol showed suitable properties. Addition of dry powder polymers (pectin, acacia and tragacanth) enhanced the viscosity and adhesion effects in some preparations. The release of asiaticoside, one of the active triterpenoid components, from the formulations were also detected via HPLC.

MAGNESIUM STEARATE AS ANTI-TACKING AGENT IN ACRYLIC POLYMER FILMS INTENDED FOR GAS-ENTRAPPED FLOATING DELIVERY SYSTEM



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INTRODUCTION

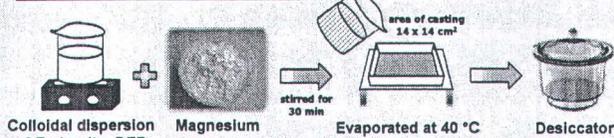
The effervescent-based floating tablets have been developed. The system consisted of the drug-containing core tablets coated with an inner protective layer, a gas forming layer and a gas-entrapped membrane, respectively [1]. Aqueous acrylic dispersion, Eudragit® RL 30D, was used as gas-entrapped membrane. The tackiness of this acrylic polymer film causes tablet agglomeration, leading to failure in floatation. Therefore, anti-tacking agent was needed. Talcum is commonly used. However, some adverse effects have been reported, high amount of talcum causes nozzle clogging and sedimentation [2, 3]. Magnesium stearate is another substance using as anti-tacking agent. From the previous reports, incorporating of magnesium stearate exhibited significant decrease of the tackiness [4]. Nevertheless, addition of anti-tacking agent influences the film properties such as mechanical properties, film hydrophobicity and water vapor permeability. These might have an effect to floating and drug release properties of effervescent-based floating tablets.

OBJECTIVE

To investigate the effect of magnesium stearate used as anti-tacking agent on mechanical and wetting properties of the acrylic polymer (Eudragit® RL 30D) films.

METHODS

Preparation of polymeric films:



Evaluation of mechanical properties:

The mechanical properties of the films were measured by a puncture test with a texture analyzer (TA.XT. plus, Texture Analyzer, UK)

$$\text{Puncture strength} = \frac{F}{A_{cs}}$$

where F is the load required for puncture, A_{cs} is cross-sectional area ($A_{cs} = 2rd$, where r is the radius of the hole, d is the thickness of the film)

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

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.

Tackiness of the films:

Two test films were pressed together under a 1000-g weight and tested at 40 °C for 1 h. T-peel tests were performed using a texture analyzer. The force-displacement diagrams were recorded.

Determination of contact angle:

Water contact angles were measured by contact angle goniometer (FTA1000 B Class, USA). The water was gently dropped on the films. The angle between the tangent line and the film surface from goniometric scale was measured.

RESULTS

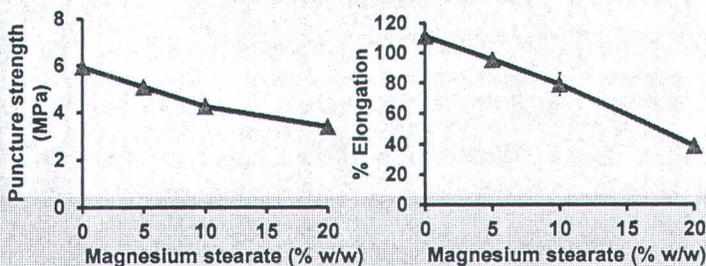


Fig.1 Effect of magnesium stearate on mechanical properties of Eudragit® RL 30D films (n = 5)

Table 1 Effect of magnesium stearate on the tackiness of Eudragit® RL 30D (n = 4)

Magnesium stearate	Force (mN)
0% w/w	770.9 (48.3)
5% w/w	166.8 (71.8)
10% w/w	52.5 (36.0)
20% w/w	55.2 (8.9)

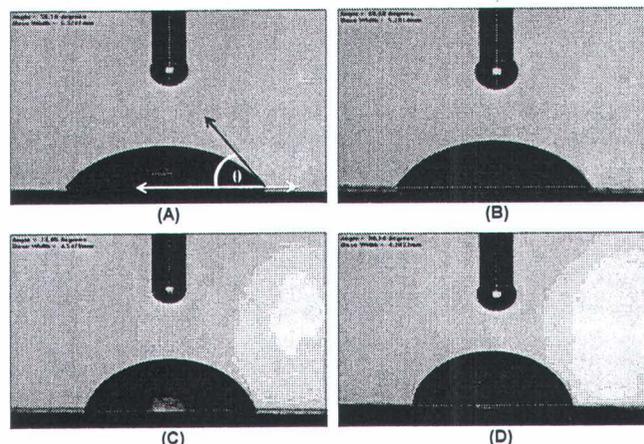


Fig.2 Water contact angles on films containing magnesium stearate : (A) 0%, (B) 5% (C) 10%, (D) 20% (w/w) bases on solid polymer

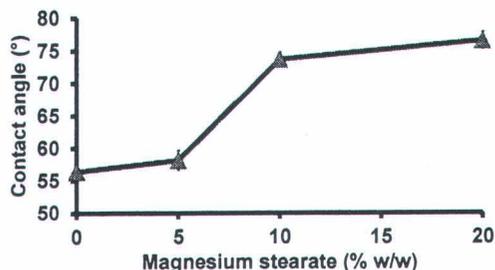


Fig.3 Effect of magnesium stearate on the water contact angle of Eudragit® RL 30D films (n = 6)

CONCLUSIONS

1. Incorporating magnesium stearate in the Eudragit® RL 30D films lowered the film mechanical properties. Both puncture strength and elongation of the films decreased with increasing amount of magnesium stearate.
2. Magnesium stearate has strong ability to reduce the film tackiness for effervescent-based floating tablets.
3. Increasing magnesium stearate amount in Eudragit® RL 30D films increased contact angle. This indicates that film wettability was reduced by the addition of magnesium stearate.

Effect of anti-tacking agent on floating and drug release properties of the effervescent-based floating tablets will be investigated in further study.

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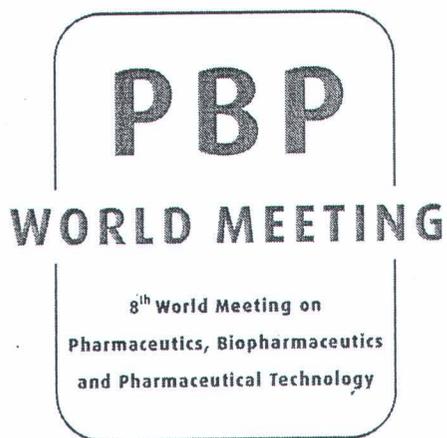
This work was financially supported by the Thailand Research Fund (Grant no. DBG5280007), the Royal Golden Jubilee Ph.D. Program (Grant No. PHD/0340/2551) under the Thailand Research Fund (TRF) and the Research Funds from Yearly Budget, Naresuan University (R2554B059), Thailand.

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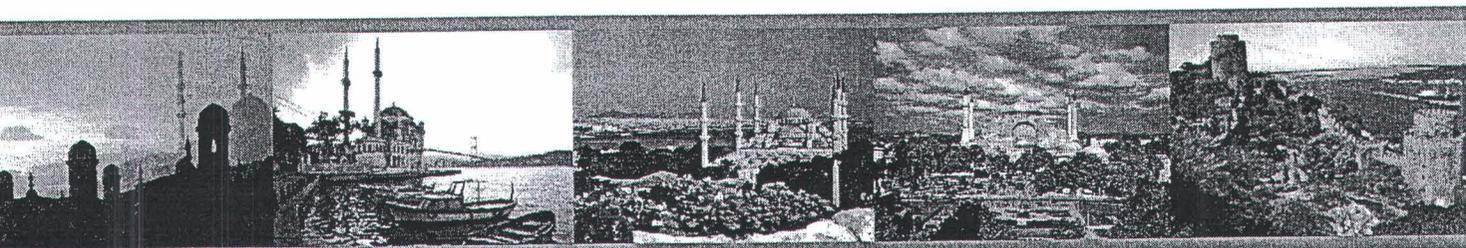
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EFFECT OF ANTI-TACKING AGENT (TALC) ON EFFERVESCENT FLOATING TABLETS

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INTRODUCTION

The effervescent floating tablet was developed in our previous study, the system consisted of the drug-containing core tablets coated with an inner protective layer, a gas forming layer and a gas-entrapped membrane layer, respectively [1]. When the system was placed into the medium (0.1 N HCl), the fluid permeated into a gas forming layer. Carbon dioxide was liberated via neutralization reaction and was entrapped in a gas-entrapped membrane. The swollen tablet with a density less than the medium was then floated, maintained the buoyancy and released the drug. Aqueous acrylic dispersion, Eudragit[®] RL 30D, was used as gas-entrapped membrane. The tackiness problem of this polymer was reported [2]. The tackiness of this acrylic polymer film causes tablet agglomeration. When the tablets were separated, the gas-entrapped membrane was damaged and led to failure in floatation. Therefore, anti-tacking agent was needed. Talc is a hydrophobic substance that is generally added to the coating formulation to reduce the tackiness of the lacquer during the coating process [3]. The aim of this study was to investigate the effect of talc used as anti-tacking agent on mechanical properties and tackiness of the acrylic polymer (Eudragit[®] RL 30D) films. The effect of anti-tacking agent on the floating properties and drug release of the floating tablets were also evaluated.

EXPERIMENTAL METHODS

• Materials

Anhydrous theophylline was chosen as a model drug. Microcrystalline cellulose (Avicel[®] PH101) and lactose monohydrate (Flowlac[®] 100) were used as components of the core tablets. Sodium bicarbonate (NaHCO₃) was used as a gas forming agent added in the core tablets. HPMC (Methocel[®] E15LV) plasticized with polyethylene glycol 6000 (PEG 6000) was used as a protective layer.

The gas-entrapped membrane used was Eudragit[®] RL 30D plasticized with diethyl phthalate (DEP). Talc was used as anti-tacking agent.

• Mechanical properties of free film

The aqueous colloidal polymethacrylate dispersion (Eudragit[®] RL 30D) with or without talc was plasticized with 20% w/w DEP and cast on Teflon plates and dried. The mechanical properties of the films in dry state were measured using puncture test with a texture analyser. Puncture strength, elongation and energy at break were determined.

• Tackiness of the films

Two test films were pressed together under a 1000-g weight and stored at 40°C for 1 hour. The samples were cooled to room temperature and T-peel tests were performed to determine peel force using a texture analyzer.

• Preparation of floating tablets

The drug-containing core tablets were prepared by direct compression method. The core tablets were then coated with a protective layer, a gas forming layer and a gas-entrapped membrane, respectively, using a perforated pan coater (NR-COTA18[®]).

• Evaluation of floating tablets

Floating properties (time to float and floating time) and drug release of the floating tablets were performed in USP paddle dissolution apparatus (900 ml of 0.1 N HCl, 37 °C, 50 rpm).

RESULTS AND DISCUSSION

Table 1. Mechanical properties of Eudragit[®] RL 30D films with different amounts of talc (S.D. in parentheses; n = 9) (film thickness 191-212 μm).

Anti-tacking agent, talc (%w/w)	Puncture Strength (MPa)	Elongation (%)	Energy at break (MJ/m ²)
0	5.97 (0.22)	110.54 (5.79)	3.94 (0.25)
5	6.16 (0.74)	89.72 (24.73)	3.45 (1.02)
10	6.66 (0.22)	88.49 (4.05)	3.65 (0.20)
20	5.58 (0.24)	72.11 (6.74)	2.67 (0.18)
30	5.09 (0.17)	63.16 (4.06)	2.25 (0.16)

Table 1 showed that addition and increasing amount of talc in the films tended to decrease puncture strength, elongation and energy at break. A possible explanation could be the inhomogeneous film forming when the films were added by the insoluble substance.

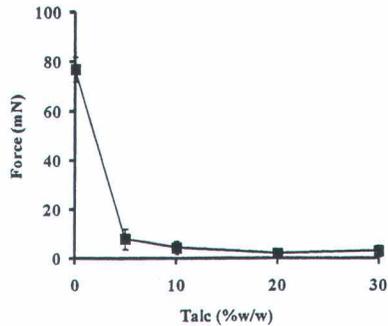


Figure 1. Effect of talc amount on the tackiness of Eudragit[®]RL 30D films

Addition and increasing amount of talc in Eudragit[®]RL 30D films decreased the tackiness of the films. The efficiency of the materials in reducing the tackiness of the films is related to their capability in reducing the contact area between the polymers.

Table 2. Floating properties of floating tablets using different formulation variables in 0.1 N HCl (n = 3).

Formulation	Time to float (min±SD)	Floating time (h)
5% w/w gas-entrapped membrane		
0% w/w talc	4.93 ± 0.28	> 8
5% w/w talc	4.88 ± 0.36	> 8
10% w/w talc	5.13 ± 0.37	> 8
20% w/w talc	6.24 ± 0.68	> 8
30% w/w talc	8.57 ± 0.82	> 8
10% w/w gas-entrapped membrane		
0% w/w talc	7.68 ± 0.20	> 8
5% w/w talc	7.33 ± 0.19	> 8
10% w/w talc	7.84 ± 0.24	> 8
20% w/w talc	10.45 ± 0.42	> 8
30% w/w talc	12.40 ± 0.52	> 8

The floating properties and drug release of the floating tablets were investigated with respect to amount of anti-tacking agent (talc) in a gas-entrapped membrane and coating level of the gas-entrapped membrane. The results demonstrated that increasing amount of talc in a gas-entrapped membrane tended to increase time to float (Table 1) and decrease drug release (Figure 2). Increasing amount of talc increased hydrophobic bonding in the film. The reduction of film hydrophilicity retarded medium penetration and led to longer time to float and slower drug released. As expected, increasing coating level of gas-entrapped membrane increased time to float (Table 1) and retarded drug release (Figure 3). For floating time of the floating tablets, all floating formulations maintained buoyancy longer than 12 hours.

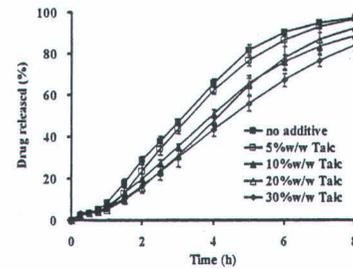


Figure 2. Effect of anti-tacking agent (talc) amount on drug release from floating tablets in 0.1 N HCl (10% w/w gas-entrapped membrane)

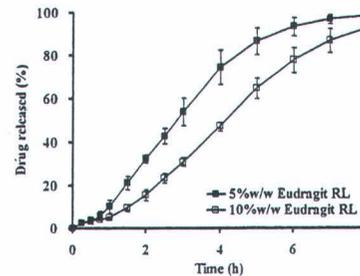


Figure 4. Effect of gas-entrapped membrane coating level on drug release from floating tablets in 0.1 N HCl (20 % w/w talc)

CONCLUSION

Effect of anti-tacking agent (talc) on film and floating tablet properties was investigated. Addition and increasing amount of talc decreased puncture strength, elongation and energy at break as well as tackiness of Eudragit[®]RL 30D films. The floating properties and the drug release from the floating tablets were affected by anti-tacking agent. Increasing amount of talc and level of gas-entrapped membrane increased time to float and retarded drug released of the floating tablets. The tablets with good floating properties (time to float less than 15 minutes, floating time more than 8 hours) and sustained drug release were obtained in this study.

ACKNOWLEDGEMENTS

This work was financially supported by the Thailand Research Fund (Grant no. DBG5280007), the Royal Golden Jubilee Ph.D. Program (Grant No. PHD/0340/2551) under the Thailand Research Fund (TRF) and the Research Funds from Yearly Budget, Naresuan University (R2554B059), Thailand.

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INTRODUCTION

The effervescent floating tablet was developed in our previous study, the system consisted of the drug-containing core tablets coated with an inner protective layer, a gas forming layer and a gas-entrapped membrane layer, respectively [1]. When the system was placed into the medium (0.1 N HCl), the fluid permeated into a gas forming layer. Carbon dioxide was liberated via neutralization reaction and was entrapped in a gas-entrapped membrane. The swollen tablet with a density less than the medium was then floated, maintained the buoyancy and released the drug. Aqueous acrylic dispersion, Eudragit® RL 30D, was used as gas-entrapped membrane. The tackiness problem of this polymer was reported [2]. The tackiness of this acrylic polymer film causes tablet agglomeration. When the tablets were separated, the gas-entrapped membrane was damaged and led to failure in floatation. Therefore, anti-tacking agent was needed. Talc is a hydrophobic substance that is generally added to the coating formulation to reduce the tackiness of the lacquer during the coating process [3].

OBJECTIVES

- To investigate the effect of talc used as anti-tacking agent on mechanical properties and tackiness of the acrylic polymer (Eudragit® RL 30D) films
- To evaluate the effect of anti-tacking agent (talc) on the floating behavior and drug release of the floating tablets

MATERIALS AND METHODS

Model drug: anhydrous theophylline

Core tablets: microcrystalline cellulose (Avicel® PH 102) and lactose monohydrate (Flowlac® 100)

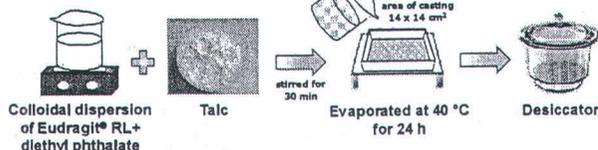
Protective layer: hydroxypropyl methylcellulose (HPMC) (Methocel® E15LV) plasticized with PEG 6000

Gas forming layer: sodium bicarbonate using HPMC as a binder

Gas-entrapped membrane: Eudragit® RL 30D plasticized with diethyl phthalate (DEP)

Anti-tacking agent: talc

Preparation of free films:



Mechanical properties of free films:

The mechanical properties of the films in dry state were measured using puncture test (TA.XT. plus Texture Analyser). Puncture strength, elongation and energy at break were determined.

Tackiness of free films:

Two test films were pressed together under a 1000-g weight and stored at 40 °C for 1 h. T-peel tests were performed using a Texture Analyzer. The force-displacement diagrams were recorded.

Preparation of effervescent floating tablets:

Core tablet preparation: Direct compression

Coating: Core tablets were coated with protective layer, gas forming layer and gas-entrapped membrane, respectively, by using a perforated pan coater (NR-COTA18®).

Floating behavior and drug release: Time to float, floating time and drug release were studied in USP paddle dissolution apparatus (900 ml of 0.1 N HCl, 37 °C, 50 rpm).

RESULTS

Table 1 Mechanical properties of Eudragit®RL 30D films with different amounts of talc (S.D. in parentheses; n = 9) (film thickness 191-212 µm).

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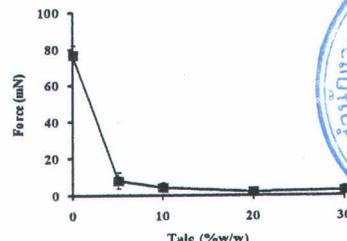


Fig.1 Effect of talc amount on tackiness of Eudragit®RL 30D films (n = 4)

Table 2 Floating behavior of the floating tablets with different formulation variables in 0.1 N HCl (n = 3).

Formulation	Time to float (min±SD)	Floating time (h)
5% w/w gas-entrapped membrane		
0% w/w talc	4.93 ± 0.28	> 8
5% w/w talc	4.88 ± 0.36	> 8
10% w/w talc	5.13 ± 0.37	> 8
20% w/w talc	6.24 ± 0.68	> 8
30% w/w talc	8.57 ± 0.82	> 8
10% w/w gas-entrapped membrane		
0% w/w talc	7.68 ± 0.20	> 8
5% w/w talc	7.33 ± 0.19	> 8
10% w/w talc	7.84 ± 0.24	> 8
20% w/w talc	10.45 ± 0.42	> 8
30% w/w talc	12.40 ± 0.52	> 8

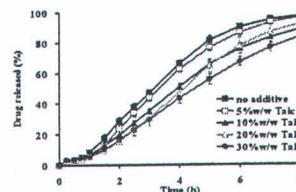


Fig.2 Effect of anti-tacking agent (talc) amount on drug release from floating tablets in 0.1 N HCl (10% w/w gas-entrapped membrane)

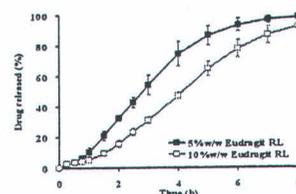


Fig.3 Effect of gas-entrapped membrane coating level on drug release from floating tablets in 0.1 N HCl (20% w/w talc)

CONCLUSIONS

- Addition and increasing amount of talc decreased puncture strength, elongation and energy at break as well as tackiness of Eudragit®RL 30D films.
- Increasing amount of talc and level of gas-entrapped membrane increased time to float and retarded drug released from the floating tablets.
- The tablets with good floating behavior (time to float less than 15 minutes, floating time more than 8 hours) and sustained drug release were obtained in this study.

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