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## ภาคผนวก

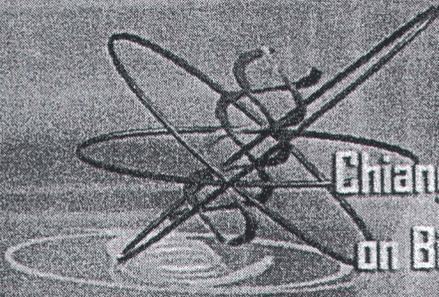
### Outputs

#### งานประชุมระดับนานาชาติ

Sungthongjeen S, Puttipipatkachorn S. Comparison Between Ethylcellulose Aqueous Colloidal Dispersion and Ethylcellulose Ethanolic Solution as Rupturable Coating Materials for Pulsatile Release Tablets. บทคัดย่อและนำเสนอโปสเตอร์ในงานประชุมวิชาการ Chiang Mai International Conference on Biomaterials & Applications (CMICBA 2011), Aug 9-10, 2011, The Empress Hotel, Chiang Mai, Thailand. (ได้รับรางวัล Poster Presentation Award (1<sup>st</sup> Prize))

Sungthongjeen S, Puttipipatkachorn S. Development of Pulsatile Release Tablets Using Ethylcellulose Aqueous Colloidal Dispersion as Rupturable Coating. บทคัดย่อและนำเสนอโปสเตอร์ในงานประชุม 8<sup>th</sup> World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (2012), March 19-22, 2012, Istanbul, Turkey.

Abstracts Book



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**COMPARISON BETWEEN ETHYLCELLULOSE AQUEOUS COLLOIDAL DISPERSION AND ETHYLCELLULOSE ETHANOLIC SOLUTION AS RUPTURABLE COATING MATERIALS FOR PULSATILE RELEASE TABLETS**

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**Abstract**

Pulsatile release dosage forms which time of drug release can be determined have shown advantages for various drugs such as chronopharmacological drugs and drugs with high first pass metabolism. The pulsatile release tablets consisting of drug-containing cores coated with inner swelling layer containing a superdisintegrant (croscarmellose sodium (Ac-Di-Sol®)) and outer rupturable layer (ethylcellulose (EC)) were previously developed. In this study, two different types of EC coating membrane, EC ethanolic solution (ECS) versus EC aqueous colloidal dispersion (ECD), were compared. Propranolol HCl was used as a model drug. Effect of rupturable coating level on lag time and drug release was investigated. The results demonstrated that using ECS could provide the pulsatile release tablets with obviously longer lag time than ECD. With ECS, increasing of rupturable coating level increased lag time of the pulsatile release tablets because of the lowered water uptake. In addition, rapid drug release after the predetermined lag time was achieved in the pulsatile release tablets using ECS. However, the pulsatile tablets with ECD ruptured within a few minutes even high levels of rupturable coating were used. It was suggested that the different performance of the pulsatile release tablets with different types of EC might be related to the discrepancy in physical properties of the obtained EC membrane.

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**FABRICATION OF DENTAL CERAMICS FROM SILICON NITRIDE CORE WITH BOROSILICATE GLASS VENEER**

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**Abstract**

Silicon nitride ceramic is a potential material for clinical indications due to its high fracture toughness, strength, and non-cytotoxicity. For this reason, Si<sub>3</sub>N<sub>4</sub> ceramic is interested to apply for dental core. The superiority of Si<sub>3</sub>N<sub>4</sub> ceramic is the low coefficient of thermal expansion (CTE) which is lower than that of zirconia and alumina ceramics that are popular in this field. In this study, borosilicate glass powder with 5 wt% of zirconia addition was prepared by melting at 1450 °C for 1 h. The glass melt was quenched and was then ground to be a powder and mixed with polyvinyl alcohol solution to be a paste. The Si<sub>3</sub>N<sub>4</sub> specimens coated with the veneer were fired in electrical tubular furnace at 1100 °C for 15 min. The appearance of these specimens shows smooth, glossy without defect and crazing. The veneer has thermal expansion coefficient as 3.05x10<sup>-6</sup> °C<sup>-1</sup> and the Vickers hardness as 4.0 GPa which is close to the human teeth. The specimens were tested by human gingival and periodontal ligament fibroblasts (HGF and HPDLF) and cytotoxicity by MTT assay. The results indicated that Si<sub>3</sub>N<sub>4</sub> ceramic and borosilicate glass can used as dental materials.

# Comparison Between Ethylcellulose Aqueous Colloidal Dispersion and Ethylcellulose Ethanolic Solution as Rupturable Coating Materials for Pulsatile Release Tablets

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## INTRODUCTION

Pulsatile release drug delivery systems have recently been great interest in pharmaceutical field to improve therapeutic efficacy particularly for drugs having a high first pass metabolism or specific chronopharmacological needs [1, 2]. The system releases the drug rapidly after a predetermined lag time [3]. In this study, a pulsatile release tablet consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated. Ethylcellulose (EC) was used as rupturable coating because it formed a mechanically weak which could rupture easily upon exposure to the dissolution medium and the resultant internal pressure developed within the tablet cores [4]. EC can be applied either as an organic solution or as an aqueous colloidal dispersion (pseudolatex). Because of safety and environmental considerations and a lower viscosity at the same solids content, aqueous ethylcellulose dispersions (ECD) are preferred [5], however, both an organic solution and an aqueous colloidal dispersion of EC were used as rupturable layer and compared in this study.

## OBJECTIVES

- To prepare and evaluate a pulsatile release tablets with swelling and rupturable coatings
- To compare two different types of EC coating membrane, EC ethanolic solution (ECS) and EC aqueous colloidal dispersion (ECD), used as rupturable coating

## EXPERIMENTAL

### Materials:

Core tablets - microcrystalline cellulose (Avicel® PH 102)  
 - spray dried lactose monohydrate (Flowlac® 100)

Model drug - propranolol HCl (40 mg/tablet)

### Swelling layer

- croscarmellose sodium (AcDiSol®), ADS: swelling agent
- polyvinyl pyrrolidone (Kollidon® 90F): binder

### Rupturable layer

- EC ethanolic solution (ECS)- ethylcellulose 10 (Ethocel® 10)
- EC aqueous colloidal dispersion (ECD)- Aquacoat® ECD
- dibutyl sebacate (DBS): plasticizer

### Methods:

#### Core tablets:

Direct compression method

#### Coating:

Core tablets were double-layer coated with an inner swellable and outer rupturable layers by using a perforated pan coater (NR-COTA18®). The coating levels were expressed in mg/cm<sup>2</sup>.

#### Lag time and drug release:

USP paddle dissolution apparatus (900 ml of 0.1 N HCl, 37 °C, 50 rpm).

## RESULTS

Swelling layer (ADS)      Rupturable layer (EC)



Fig.1 The design of the pulsatile release tablet

When the system is placed into the medium, water starts to penetrate into the coated tablet through the barrier coating. The water influx and the subsequent volume expansion of the swelling substance cause the rupture of the membrane. The drug is then released rapidly.

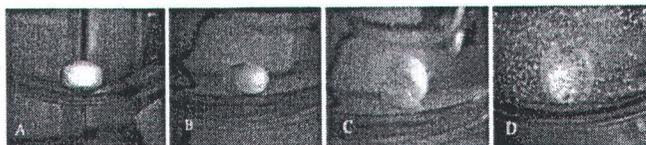


Fig.2 Rupture sequence of pulsatile tablet in dissolution medium

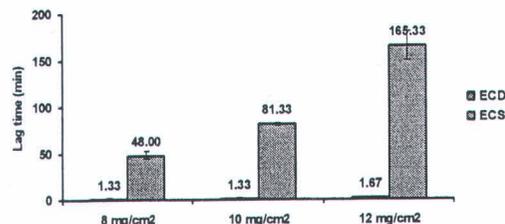


Fig.3 Lag time of pulsatile tablets using different EC coating membrane types and rupturable coating levels (swelling coating level; 22.5 mg/cm<sup>2</sup>, 5%/w/w DBS)

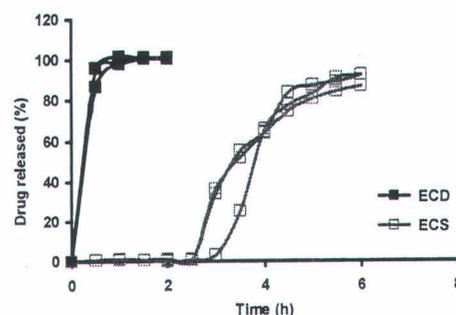


Fig.4 Effect of EC coating membrane type on drug release of pulsatile tablets (swelling coating level; 22.5 mg/cm<sup>2</sup>, rupturable coating level; 12 mg/cm<sup>2</sup>, 5%/w/w DBS)

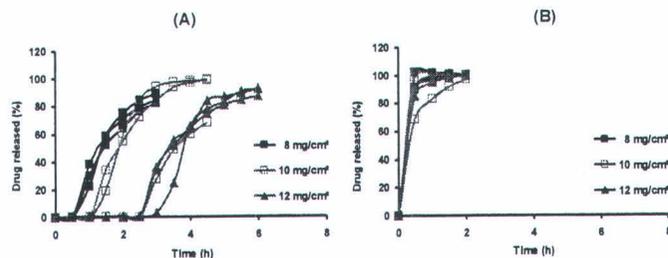


Fig.5 Effect of rupturable coating level on drug release of pulsatile tablets; (A) ECS, (B) ECD (swelling coating level; 22.5 mg/cm<sup>2</sup>, 5%/w/w DBS).

## CONCLUSIONS

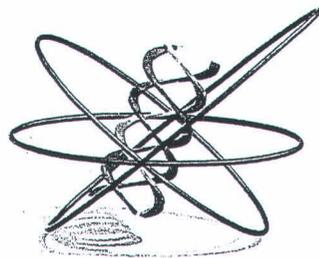
- pulsatile release tablets with swelling and rupturable coatings were prepared and evaluated. The system released the drug rapidly after a certain lag time.
- using ECS could provide the pulsatile release tablets with obviously longer lag time than ECD.
- with ECS, increasing of rupturable coating level increased lag time of the pulsatile release tablets.
- the pulsatile tablets with ECD ruptured within a few minutes even high levels of rupturable coating were used.
- It was suggested that the different performance of the pulsatile release tablets with different types of EC might be related to the discrepancy in physical properties of the obtained EC membrane.

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**COMPARISON BETWEEN ETHYLCELLULOSE AQUEOUS  
COLLOIDAL DISPERSION AND ETHYLCELLULOSE  
ETHANOLIC SOLUTION AS RUPTURABLE COATING  
MATERIALS FOR PULSATILE RELEASE TABLETS**

PRESENTED BY

**SRISAGUL SUNGTHONGJEEN**

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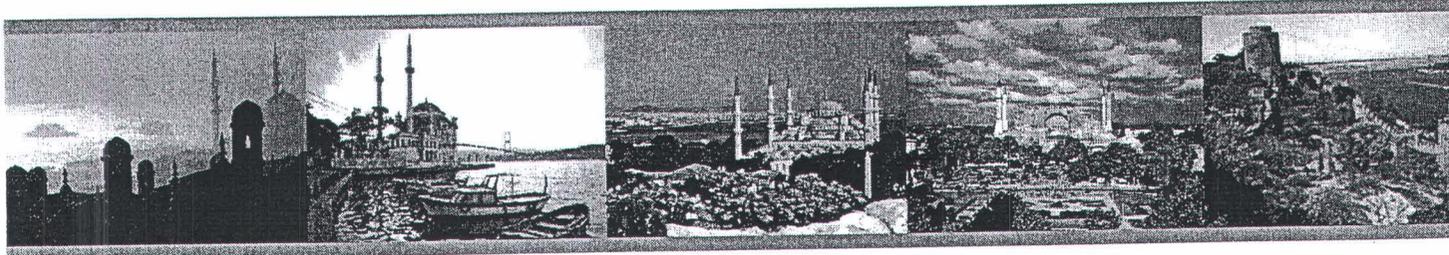
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# DEVELOPMENT OF PULSATILE RELEASE TABLETS USING ETHYLCELLULOSE AQUEOUS COLLOIDAL DISPERSION AS RUPTURABLE COATING

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## INTRODUCTION

Pulsatile release drug delivery systems have recently been great interest in pharmaceutical field to improve therapeutic efficacy particularly for drugs having a high first pass metabolism or specific chronopharmacological needs [1, 2]. The system releases the drug rapidly after a predetermined lag time [3]. In this study, a pulsatile release tablet consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated. Ethylcellulose (EC) was used as rupturable coating because it formed a mechanically weak membrane which could rupture easily upon exposure to the dissolution medium and the resultant internal pressure developed within the tablet cores [4]. EC can be applied either as an organic solution or as an aqueous colloidal dispersion (pseudolatex). Because of safety and environmental considerations and a lower viscosity at the same solids content, aqueous ethylcellulose dispersions (ECD) are preferred [5]. Effects of plasticizer (dibutyl sebacate, DBS) amount and rupturable coating level on lag time and drug release of pulsatile release tablets were investigated. Types of EC coating membrane, i.e. EC aqueous colloidal dispersion (ECD) and EC ethanolic solution (ECS), were also compared.

## EXPERIMENTAL METHODS

### • Materials

Propranolol HCl (40 mg/tablet) was chosen as a model drug. Microcrystalline cellulose (MCC, Avicel<sup>®</sup> PH102) and lactose monohydrate (Flowlac<sup>®</sup> 100) were used as components of the core tablets. Croscarmellose sodium (Ac-Di-Sol<sup>®</sup>, ADS) and polyvinyl pyrrolidone (Kollidon<sup>®</sup> 90F) was used as a swelling agent and a binder of swelling layer respectively. The rupturable coating used was ECD (Aquacoat<sup>®</sup> ECD) or ECS (Ethocel<sup>®</sup> Standard 10) with DBS as a plasticizer.

### • Preparation of pulsatile release tablet

The core tablets (425 mg/tablet) were prepared by direct compression and coated with an inner swelling layer and an outer rupturable layer by using a perforated pan coater (NR-COTA18<sup>®</sup>). The coating levels were expressed in mg/cm<sup>2</sup>.

### • Evaluation of pulsatile release tablets

The lag time which is defined as the time when the rupturable coating starts to rupture and drug release were evaluated in 0.1 N HCl using USP paddle apparatus (900 ml of media, 37 °C, 50 rpm).

## RESULTS AND DISCUSSION

### Design of the pulsatile release tablet

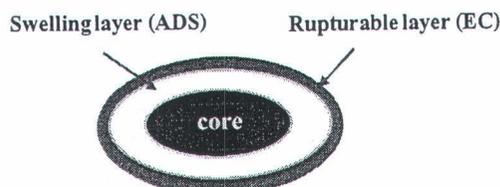


Figure 1. Design of the pulsatile release tablet

Pulsatile release tablets consisted of a core tablet containing drug (Propranolol HCl) coated with inner swelling layer containing a superdisintegrant (croscarmellose sodium (Ac-Di-Sol<sup>®</sup>)) and outer rupturable layer (ethylcellulose (EC)) as shown in Figure 1. When the system is placed into the medium, water starts to penetrate into the coated tablets through the rupturable coating. The water influx and the subsequent swelling of the pressure inducing agent cause the rupture of the coating. The drug is then released rapidly after a certain lag time. The rupture sequence of the pulsatile tablet at different times is shown in Figure 2.

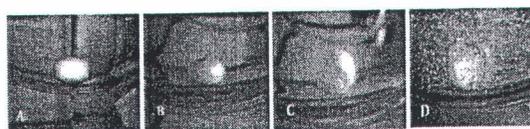
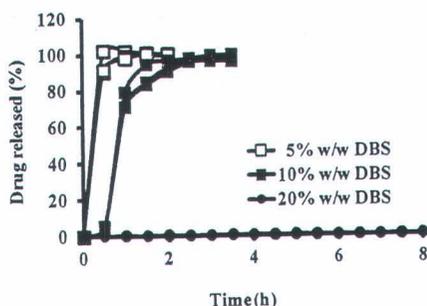


Figure 2. Rupture sequence in 0.1 N HCl of a pulsatile tablet.

Lag time and drug release of the pulsatile tablets were investigated with respect to plasticizer amount (5, 10, 20 %w/w), level of rupturable coating (6, 8, 10, 12 mg/cm<sup>2</sup>) and rupturable coating type (ECD, ECS). Increasing plasticizer amount in rupturable coating (ECD) increased lag time of the pulsatile release tablets (Table 1). The system could release the drug rapidly after a certain lag time (Figure 3).

**Table 2.** Lag time of pulsatile release tablets using different formulation variables in 0.1 N HCl (n = 3).

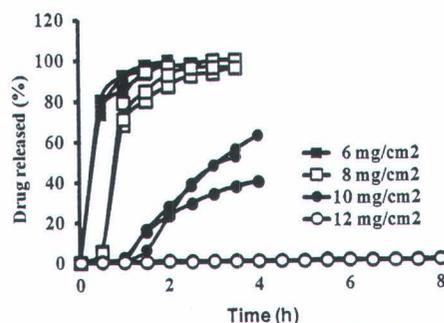
Formulation	Lag time
	(min±SD)
<b>Rupturable coating: ECD</b>	
<b>5% w/w plasticizer (DBS)</b>	
6 mg/cm <sup>2</sup> rupturable coating	3.33 ± 0.58
8 mg/cm <sup>2</sup> rupturable coating	1.33 ± 0.58
10 mg/cm <sup>2</sup> rupturable coating	1.33 ± 0.58
12 mg/cm <sup>2</sup> rupturable coating	1.67 ± 0.58
<b>10% w/w plasticizer (DBS)</b>	
6 mg/cm <sup>2</sup> rupturable coating	11.00 ± 1.00
8 mg/cm <sup>2</sup> rupturable coating	28.00 ± 1.73
10 mg/cm <sup>2</sup> rupturable coating	66.00 ± 13.11
12 mg/cm <sup>2</sup> rupturable coating	> 480
<b>20% w/w plasticizer (DBS)</b>	
6 mg/cm <sup>2</sup> rupturable coating	71.33 ± 10.21
8 mg/cm <sup>2</sup> rupturable coating	> 480
10 mg/cm <sup>2</sup> rupturable coating	n/a
12 mg/cm <sup>2</sup> rupturable coating	n/a
<b>Rupturable coating: ECS</b>	
<b>5% w/w plasticizer (DBS)</b>	
6 mg/cm <sup>2</sup> rupturable coating	27.67 ± 0.58
8 mg/cm <sup>2</sup> rupturable coating	48.00 ± 4.36
10 mg/cm <sup>2</sup> rupturable coating	81.33 ± 1.53
12 mg/cm <sup>2</sup> rupturable coating	165.33 ± 15.57



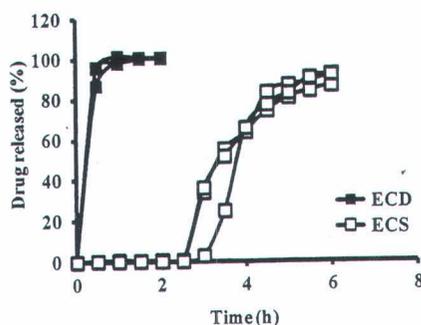
**Figure 3.** Effect of plasticizer amount on drug release from pulsatile tablets in 0.1 N HCl (ADS 22.5 mg/cm<sup>2</sup>, ECD 8 mg/cm<sup>2</sup>)

Increasing of rupturable coating level increased lag time (Table 2) and slightly decreased drug release (Figure 4) of the pulsatile tablets. Higher level of rupturable coating might lower water uptake and rupture quality of the pulsatile release tablets.

At the same plasticizer amount (5%w/w DBS); using ECS as rupturable coating could provide longer lag time of the pulsatile release tablets than that using ECD (Table 2, Figure 5). However, the pulsatile release tablets with ECD ruptured within a few minutes even high levels of rupturable coating were used (data not shown).



**Figure 4.** Effect of rupturable coating level on drug release from pulsatile tablets in 0.1 N HCl (ADS 22.5 mg/cm<sup>2</sup>, 10%w/w DBS, ECD)



**Figure 5.** Effect of EC coating membrane type on drug release of pulsatile release tablets (ADS 22.5 mg/cm<sup>2</sup>, rupturable coating level; 12 mg/cm<sup>2</sup>, 5%w/w DBS)

## CONCLUSIONS

- The pulsatile release tablets with swelling and rupturable coatings were prepared and evaluated. The system released the drug rapidly after a certain lag time.
- Increasing amount of plasticizer and rupturable coating level increased lag time of the pulsatile release tablets using ECD as rupturable coating.
- At the same plasticizer amount (5%w/w DBS), using ECS as rupturable coating could provide the pulsatile release tablets with obviously longer lag time than ECD.

## ACKNOWLEDGEMENTS

This work was financially supported by Yearly Budget, Naresuan University (R2554B054), Thailand.

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# DEVELOPMENT OF PULSATILE RELEASE TABLETS USING ETHYLCELLULOSE AQUEOUS COLLOIDAL DISPERSION AS RUPTURABLE COATING

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## INTRODUCTION

Pulsatile release drug delivery system has received much attention because it can improve therapeutic efficacy, particularly for drugs having specific chronopharmacological needs or a high first pass metabolism [1, 2]. Recently, we developed the pulsatile release tablets consisting of cores coated with two layers of swelling and rupturable coating [3]. Ethylcellulose (EC) was used as rupturable coating because it formed a mechanically weak which could rupture easily upon exposure to the dissolution medium and the resultant internal pressure developed within the tablet cores [4]. In this study, ethylcellulose aqueous colloidal dispersion (ECD) was used as rupturable coating membrane in comparison with EC ethanolic solution (ECS). Because of safety and environmental considerations and a lower viscosity at the same solid content, ECD is preferred [5]. Effects of type of EC, plasticizer (dibutyl sebacate, DBS) amount and rupturable coating level on lag time and drug release of the pulsatile release tablets were investigated.

## OBJECTIVES

- To prepare and evaluate the pulsatile release tablets using ECD as rupturable coating
- To investigate the effects of formulation variables on lag time and drug release of the pulsatile release tablets

## EXPERIMENTAL

### Materials:

Core tablets - microcrystalline cellulose (Avicel® PH 102)  
 - spray dried lactose monohydrate (Flowlac® 100)

Model drug - propranolol HCl (40 mg/tablet)

### Swelling layer

- croscarmellose sodium (AcDiSo®), ADS: swelling agent  
 - polyvinyl pyrrolidone (Kollidon® 90F): binder

### Rupturable layer

- EC ethanolic solution (ECS)- ethylcellulose 10 (Ethocel® 10)  
 - EC aqueous colloidal dispersion (ECD)- Aquacoat® ECD  
 - dibutyl sebacate (DBS): plasticizer

### Methods:

#### Core tablets:

Direct compression

#### Coating:

Core tablets were double-layer coated with an inner swellable and outer rupturable layers by using a perforated pan coater (NR-COTA18®). The coating levels were expressed in mg/cm<sup>2</sup>.

#### Lag time and drug release:

USP paddle dissolution apparatus (900 ml of 0.1 N HCl, 37 °C, 50 rpm).

## RESULTS

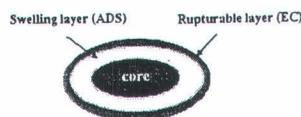


Fig.1 Design of the pulsatile release tablet

When the system is placed into the medium, water starts to penetrate into the coated tablet through the barrier coating. The water influx and the subsequent volume expansion of the swelling substance cause the rupture of the membrane. The drug is then released rapidly.

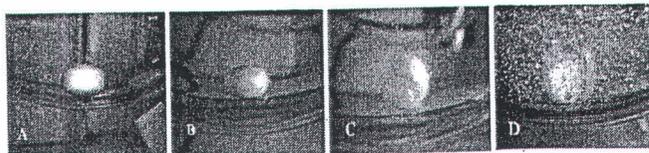


Fig.2 Rupture sequence of pulsatile release tablet in dissolution medium (0.1 N HCl)

Table 1 Lag time of pulsatile release tablets using different formulation variables in 0.1 N HCl (n = 3).

Formulation	Lag time (min)	Lag time (min)	Formulation	Lag time (min)	Lag time (min)
Rupturable coating: ECD			Rupturable coating: ECS		
2% w/w plasticizer (DBS)	1.53 ± 0.34	1.47 ± 0.54	2% w/w plasticizer (DBS)	27.47 ± 0.58	13.33 ± 1.33
4 mg/cm <sup>2</sup> rupturable coating	1.53 ± 0.34	1.58 ± 0.48	4 mg/cm <sup>2</sup> rupturable coating	41.40 ± 0.34	37.47 ± 0.31
8 mg/cm <sup>2</sup> rupturable coating	1.53 ± 0.34	1.88 ± 0.40	8 mg/cm <sup>2</sup> rupturable coating	81.33 ± 1.33	81.97 ± 1.13
12 mg/cm <sup>2</sup> rupturable coating	1.47 ± 0.38	1.98 ± 0.40	12 mg/cm <sup>2</sup> rupturable coating	143.33 ± 10.57	19.33 ± 7.97
10% w/w plasticizer (DBS)					
4 mg/cm <sup>2</sup> rupturable coating	11.90 ± 1.00	10.8 ± 0.90			
8 mg/cm <sup>2</sup> rupturable coating	28.40 ± 1.75	16.35 ± 0.33			
12 mg/cm <sup>2</sup> rupturable coating	64.60 ± 11.11	99.00 ± 0.65			
20% w/w plasticizer (DBS)	> 180	> 180			
4 mg/cm <sup>2</sup> rupturable coating	71.33 ± 10.21	43.33 ± 14.05			
8 mg/cm <sup>2</sup> rupturable coating	> 180	> 180			

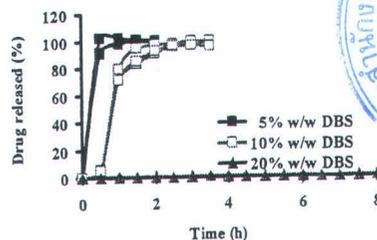


Fig.3 Effect of plasticizer amount on drug release from pulsatile release tablets in 0.1 N HCl (ADS 22.5 mg/cm<sup>2</sup>, ECD 8 mg/cm<sup>2</sup>)

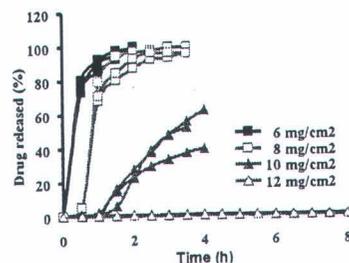


Fig.4 Effect of rupturable coating level on drug release from pulsatile release tablets in 0.1 N HCl (ADS 22.5 mg/cm<sup>2</sup>, 10%w/w DBS, ECD)

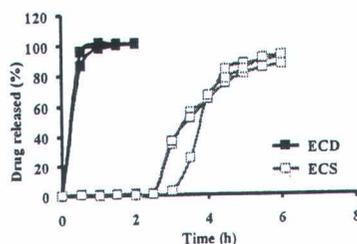


Fig.5 Effect of EC coating membrane type on drug release of pulsatile release tablets (ADS 22.5 mg/cm<sup>2</sup>, rupturable coating level; 12 mg/cm<sup>2</sup>, 5%w/w DBS)

## CONCLUSIONS

- The pulsatile release tablets with swelling and rupturable coatings were prepared and evaluated. The system released the drug rapidly after a certain lag time.
- Increasing amount of plasticizer and rupturable coating level increased lag time of the pulsatile release tablets using ECD as rupturable coating.
- At the same plasticizer amount (5%w/w DBS), using ECS as rupturable coating could provide the pulsatile release tablets with obviously longer lag time than using ECD.

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