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Development of bilayer zein-based matrix tablets for multiphasic drug release kinetics

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Abstract—**Zein has been widely used as a film coating material for controlling the release of drug. However, the role as a matrix forming agent in tablets, especially the extended release dosage forms, was not clearly studied. The objectives of this study were to develop the bilayer tablets with multiple drug release kinetics, and to explore the effect of different zein contents on the mechanism of drug release from matrix tablets. Chlorpheniramine maleate was selected as a model drug. Matrix tablets with various amounts of zein were prepared as bilayer formulations by direct compression method. The first layer was designed for immediate release, and the second layer was aimed to provide a sustained release characteristic. Tableting properties including weight, thickness, diameter, friability, hardness and disintegration were evaluated. The dissolution assay was carried out in 0.1 N HCl (pH 1.2), phosphate buffer solutions with pH of 5.5 and 7.0, respectively. The kinetics of drug release were analyzed using various mathematical models. The results suggested that weight, thickness, diameter, hardness and friability were not significantly different among formulations and well-controlled within the desired range indicating excellent tableting properties. An increase in the amount of zein led to the increased disintegration time exhibiting extended drug release. The first layer without zein component was completely disintegrated and dissolved within 10 min while the second layer consisting of several zein concentrations was not disintegrated. When 60%w/w or more of zein was used, the drug release profile seemed to be sustained over a period of 8 h as influencing by the gel barrier formation of zein after contacting with the aqueous media. The kinetics of drug release in 0.1 N HCl and phosphate buffer solution pH 5.5 were fitted with Higuchi model, whereas the drug release profile in pH 7.0 phosphate buffer solution was followed Hixson-Crowell model. Therefore, the main mechanisms of drug release in acid and basic media were Fickian's diffusion and tablet erosion.**

Keywords—Zein, Chlorpheniramine maleate, Bilayer tablet, Sustained release, Kinetic

I. INTRODUCTION

Oral dosage forms have long been used for drug delivery due to their convenience and flexibility in design of dosage forms. However, the disadvantage of conventional oral dosage forms is the frequency of dosing regimens which might lead to the fluctuation of the plasma drug concentration [1,2]. To improve the patient compliance, several attempts have been made to develop the desired polymers which could provide the barrier of drug release, resulting in the controlled release action. Nowadays, natural polymers have been widely used for controlling of drug release due to their safety. Zein, a natural polymer from corns was also used as a film former and controlled drug release application [3,4].

Different types of controlled release formulations such as matrix tablets, multiple emulsions, osmotic tablets, etc. have been developed to improve the clinical efficacy. Recently, multi-layer tablets seem to be more applicable for controlling of drug release. One or two layers of release retardant polymer are used. After contacting with gastric fluid, the polymer is swollen to a form gel barrier. However, there was few report appeared in the literature on the use of zein as a drug carrier in multi-layer tablets. Therefore, the aim of this study was to fabricate bilayer tablets using zein as a matrix forming agent and investigate the kinetics of drug release.

II. MATERIALS AND METHODS

Materials

Chemicals. Cholrpheniramine maleate (CPM) was purchased from Kongo Chemical Co., Ltd.,

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[Bangkok, Thailand]. Zein was obtained from Sigma-Aldrich [USA]. All other chemicals were of analytical grade.

Methods

Preparation of bilayer zein-based matrix tablets. The bilayer matrix tablets were prepared using a direct compression method with hydraulic press machine (Specac 15011, UK). The composition of bilayer matrix tablets is represented in Table 1. All ingredients were screened through the sieve mesh No. 40#. The CPM and excipients except for colloidal silica and magnesium stearate of each layer were mixed for 5 min. Colloidal silica and magnesium stearate were subsequently added to each powder mixture and blended for 5 min. The powder mixture for first layer was compressed and then the second layer was continuously compressed with 9.53 mm flat faced punch. The total weight and hardness of bilayer tablets were controlled at 500±10 mg and 70±10 N, respectively. All tablets were kept in the ambient temperature before evaluation.

Table 1. The composition of bilayer tablets

Ingredient	Quantity in (mg) present in matrix tablet	
	1st layer (200 mg)	2nd layer (300mg)
CPM	4	8
Zein	-	240
Supertab®	183	44
Ac-Di-Sol®	5	-
Aerosil®	4	4
Magnesium stearate	4	4

Tablets evaluation. The weight variation of tablets was measured by an analytical balance (Sartorius CP224S, Germany). The thickness, diameter, and hardness were comparatively evaluated by a hardness tester (Pharmatest PTB311, Germany). Friability was tested using a friability tester (Erweka TA-10, Germany). The disintegration test was carried out as described in USP 32. The total of 6 tablets were weighed and placed in each tube of a disintegration basket, using a disintegration testing apparatus (Sotax DT3, Switzerland) and immersed in 0.1 N HCl, phosphate buffer pH 5.5 and 7.0 for 120 min, 360 min and 240 min, respectively. The temperature of each media was maintained at 37±0.5° C. The dissolution studies were performed by using dissolution apparatus type II (Pharmatest PTWS3C, Germany). The dissolution testing was conducted at a paddle speed of 50 rpm in continuous medium at37±0.5 °C.The total time of dissolution testing was 12 h. The samples were drawn periodically and replenished with fresh dissolution medium. The amount of drug release was measured by an UV/VIS spectrophotometer (Lambda 2, Perkin Elmer, USA).

Analysis of drug release. To analyze the *in-vitro* drug release profiles, zero order rate (Eq. 1) Higuchi equation (Eq. 2), Hixson-Crowell cube root law (Eq. 3) and Power law equation (Korsmeyer-Peppas equation) (Eq. 4) were used to describe the release kinetics.

$$Q = k_o t. \quad (1)$$

$$Q = Kt^{1/2}. \quad (2)$$

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t. \quad (3)$$

$$M_t / M_\infty = Kt^n. \quad (4)$$

III. RESULTS AND DISCUSSION

Physical properties of bilayer zein-based matrix tablets. The weight variation of the formulation was in the range of 500±10 mg. The average thickness and diameter were in the range of 6.94±0.13 mm and 9.59±0.03 mm, respectively. Based on the results, the average thickness was quite high because of the elastic recovery effect of zein [4]. Tablets containing zein showed good compressibility and less friability. The hardness of bilayer tablets was in the range of 69.10±0.12 N. The friability of bilayer zein–based matrix tablets less than 1%. This could be explained by binding property of zein, resulting in the reduced friability [5]. The data is represented in Table 2.

Disintegration and dissolution studies. The 1st layer of tablet (without zein) was rapidly disintegrated within 1 min in acid media, whereas the disintegration time of the 2nd layer tablet consisting of high zein content was not disintegrated. The tablet was still remained after disintegration test. Fig. 1 represents the percentage weight loss of bilayer zein-based matrix tablets in 0.1 N HCl, phosphate buffer solutions pH 5.5 and 7.0, respectively.

Table 2. Properties of bilayer tablets (n = 20)

Properties	Value (AVG.±S.D)
Weight variation (mg)	507.10±0.02
Diameter (mm)	9.59± 0.03
Thickness (mm)	6.94± 0.13
Hardness (N)	69.10±0.12
Friability (%)	0.29

The tablets were swollen and retained their physical integrity till the end of the 12-h dissolution study. The tri-phasic curve of dissolution was observed. At the beginning, drug release from bilayer tablets was quite rapid. This might be the effect of completed disintegration of the first layer presenting high

content of dissolving drugs. After that, drug release was slightly increased with slow release rate with the effect of good media resistance, and the swollen of zein in the solutions might be a good explanation for the specific release characteristic. However, the curve line was elevated after soaking in a phosphate buffer solution pH 7.0. The erosion of tablet might be the possible explanation.

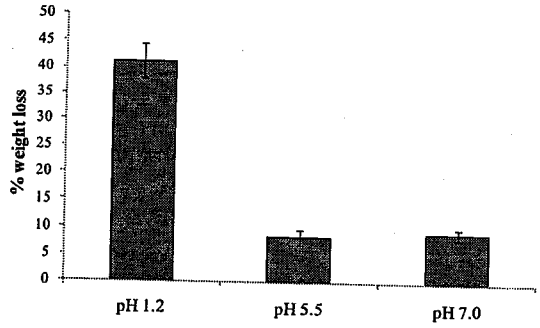

Fig. 1. The percentage weight loss of bilayer tablets (N = 6)

Kinetics of drug release. Based on the analysis of drug release data, the profiles in the low pH media (pH 1.2 and 5.5) was most fitted to Higuchi and power law equation models. The release exponent (n) referring to the mechanism of drug release was followed to Fickian diffusion. At high pH media (pH 7.0), the release mechanism was significantly changed. The drug release profiles were shifted to fit with Hixson-Crowell and power law equation models. The release exponent (n) referring to the mechanism of drug release was followed to errosion process. This might be the effect of zein dissolved in the high pH solvent [5]. Data related with curve fitting is shown in Table 3.

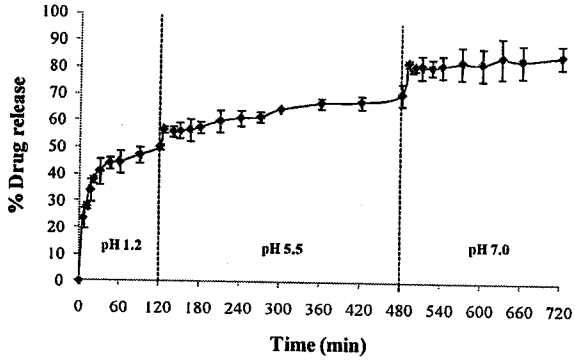

Fig. 2. Drug release profile of bilayer tablets (N = 6)

Table 3. Curve fitting of drug release (n = 6)

Conditions	Zero model	Higuchi model	Hixson-Crowell model	Power law model	
	r^2	r^2	r^2	r^2	n
pH 1.2	0.9318	0.9834	0.9205	0.9802	0.3431
pH 5.5	0.9471	0.9755	0.9334	0.9791	0.4030
pH 7.0	0.9461	0.9349	0.9845	0.9812	1.1009

IV. CONCLUSIONS

The present study was carried out to develop oral bilayer tablets of CPM using zein as a matrix forming agent. The bilayer zein-based matrix tablets were easily fabricated using the direct compression method. The bilayer tablets with zein could immediately release and provide sustained drug release over 12 h. This research could provide the basic knowledge for development of drug containing zein-based matrix tablets.

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