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Design of porous Eudragit® L beads for floating drug delivery by wax removal technique

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ABSTRACT

The aim of this study was to design porous matrix beads for floating drug delivery using enteric polymer, Eudragit® L and various amounts of waxes (0, 0.1, 0.5, 1, 2 and 3% w/w). In this study, wax containing cetyl alcohol and white petrolatum was utilized to produce pores using a wax removal technique. To prepare the beads, Eudragit® L, metronidazole and wax were dissolved in acetone and then extruded into dichloromethane. The effect of the amount of wax on the floating and drug release behavior of the Eudragit® L beads was determined. After the extruded product was immersed in dichloromethane, wax dissolved out from the formed beads, resulting in a porous structure. The prepared beads could float in simulated gastric fluid for more than 10 hours. Different amounts of wax had an effect on the drug release. We found that when the percentage of wax increased, the drug release was higher while the beads remained floating. The results suggest that Eudragit® L beads could be used as a carrier for an intragastric floating drug delivery system.

Keywords: Porous beads Floating Wax removal Eudragit® L

1. Introduction

Oral delivery is the preferred route for drug administration due to its ease of use, low cost, and high patient compliance. Most of the conventional oral drug delivery systems have shown some limitations related to fast gastric emptying time and poor bioavailability of certain drugs due to incomplete absorption and degradation in the gastrointestinal tract [1]. A controlled drug release delivery system has therefore been developed to...
provide predetermined drug release at a predictable and controlled rate [2,3]. Nevertheless, differences in gastrointestinal (GI) physiology, such as pH and motility, result in subject variability, demonstrating significant effects on drug delivery behavior. To overcome this obstacle, retention of drug delivery systems have been discovered to prolong the overall GI transit time, thereby resulting in improved oral bioavailability of poorly water-soluble drugs [4]. Furthermore, gastric retention with drug release may be an advantageous strategy for Helicobacter pylori eradication in the stomach mucosa [3]. Various GI targeting and retaining dosage forms such as intragastric floating systems [5], mucoadhesive systems, swelling or expanding systems [6], magnetic systems and unfoldable systems, have been developed to overcome these limitations [5].

One of the thriving trends in enhancing drug residence in the stomach is the floating drug delivery system (FDDS). Several approaches have been used to encourage buoyancy of the dosage form in the stomach. The principal rule is to provide a density lower than the gastric fluid so that they are capable of floating on the gastric juice in the stomach. Based on the buoyancy mechanism, FDDS may be roughly grouped into: hydrodynamically balanced systems, gas-generating systems, raft-forming systems and low-density systems [7,8]. Numerous polymers such as polycarbonate, Eudragit® S, cellulose acetate, calcium alginate, agar and low methoxylated pectin are commonly used as drug carriers in FDDS [9]. Among several FDDSs, low-density system (density < 1 g/cm³) offers immediate floating on the stomach contents. This can eliminate the problem of premature evacuation of FDDS through the pyloric sphincter. However, one disadvantage of this technique is the high initial burst release associated with this type of system [10]. Moreover, the efficacy of the system is dependent on the presence of enough liquid in the stomach, requiring frequent drinking of water [11].

In order to overcome the drawbacks mentioned above, floating beads have been developed via many techniques including solvent evaporation, incorporation of a gas-forming agent (such as CaCO₃) or porous structural elements in the system [5]. In this study, poly(methacylic acid-co-methyl methacrylate) or Eudragit® L (referred to as EL) was used as a drug carrier in the form of spherical EL beads. The EL beads are a multiple-unit form of spherical EL beads. The EL beads are a multiple-unit system, which may be more beneficial than single-unit systems by circumventing all-or-none emptying from the stomach during houskeeper waves. This study aimed to fabricate porous EL beads containing metronidazole (MTZ), an antibiotic used for eradication of H. pylori [12]. The pores were produced using a wax removal technique after dispersing wax, either cetyl alcohol or white petrolatum, into the EL beads during bead formation process. The effects of various amounts of cetyl alcohol and white petrolatum as well as curing time on floating behavior and drug release in gastric fluid were also investigated.

### 2. Materials and methods

#### 2.1. Materials

MTZ, cetyl alcohol and white petrolatum were obtained from P.C. Drug Center Co., Ltd. (Bangkok, Thailand). Eudragit® L (EL) was received from JJ-Degussa Chemical (Thailand) Ltd. (Bangkok, Thailand). Acetone and dichloromethane were purchased from RCI Labscan Ltd. (Bangkok, Thailand). All other chemicals were of standard pharmaceutical grade and were used as received without further purification.

#### 2.2. Floating bead preparation

The drug-loaded floating beads were prepared by dissolving a mixture of EL and MTZ (at a ratio of 4:1) in acetone. The different amounts of the waxes (i.e., cetyl alcohol or white petrolatum) were added to the mixture of EL and MTZ, and then homogeneously mixed by a magnetic stirrer. The dispersion containing wax was placed into a glass syringe and then extruded into dichloromethane. The beads formed were cured by gentle stirring for 5 or 20 min at room temperature and then filtered through filter paper and dried at 37 °C for 12 h. The formulations of the drug-loaded floating beads are presented in Table 1.

#### 2.3. Determination of bead size

The mean diameter of 20 dried beads was determined by optical microscopy (model BH-2, Olympus, Japan). The microscope eyepiece was fitted with a micrometer by which the size of the beads could be determined.

#### 2.4. Morphology of beads

The surface and internal morphology of the bead samples were observed using a scanning electron microscope (SEM; model Maxim-2000, CamScan Analytical, England), under an accelerating voltage of 15 keV. The samples were fixed onto a SEM stub with double-sided adhesive tape and then coated in a vacuum with a thin gold layer before investigation. To study the internal structure of the beads, the beads were cut with a razor blade before being fixed onto the SEM stub.

#### 2.5. Floating properties of the beads

The floating properties of the beads such as floating time and time-to-float were monitored by placing the bead samples (n = 20) into an Erlenmeyer flask filled with 50 mL of simu-
lated gastric fluid USP without pepsin (SGF) test solution. The flask was shaken in a horizontal shaking incubator (model OS1473VBA, Revco Scientific Inc., USA) at 37 °C, 100 rpm. Their buoyancy was observed by visual observation for 24 h [13].

2.6. Drug loading and drug encapsulation efficiency

The drug loading in the EL beads was determined by weighing 35 mg of the beads and then dissolving them in 100 mL phosphate buffer solution (pH 7.4). The MTZ content in the beads was analyzed using a UV–visible spectrophotometer (model U-2000, Hitachi, Japan) at a maximum wavelength of 277 nm (n = 3). The percentage of drug loading was calculated using Equation (1).

\[
\text{Drug loading}(\%) = \frac{\text{Total amount of drug in beads} \times 100}{\text{Weight of beads taken}} \tag{1}
\]

The drug encapsulation efficiency of the EL beads is defined here as the percentage of determined drug loading relative to the nominal (theoretical) loading. The percentage of drug encapsulation efficiency was calculated using Equation (2).

\[
\text{Encapsulation efficiency}(\%) = \frac{\text{Actual drug loading in beads} \times 100}{\text{Theoretical drug loading in beads}} \tag{2}
\]

2.7. In vitro drug release studies

MTZ release from the different formulations of the beads was investigated using a USP dissolution apparatus I (Erweka, Germany) equipped with baskets, which were operated at a speed of 100 rpm. Nine hundred milliliters of SGF (pH 1.2), as the dissolution media, was placed into the glass vessel, the apparatus assembled, and the dissolution medium was equilibrated to 37 ± 0.5 °C. Test fluid (5 mL) was taken at various time intervals, i.e., 15, 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 480 and 600 min. The amount of MTZ released was then analyzed using a UV–visible spectrophotometer at 277 nm. Each in vitro release study was conducted in triplicates.

2.8. Drug release kinetics

The kinetics of drug release were computed by fitting the dissolution curve to standard empirical equations, that is, Korsmeyer–Peppas, Higuchi, zero order kinetics and first order kinetics equations [14,15] by using curve fitting software, KinetDS (free open source software). The data were evaluated according to the following equations:

Zero-order model: \( M_t/M_\infty = kt \)

First-order model: \( \ln(1 - (M_t/M_\infty)) = -kt \)

Higuchi equation: \( M_t/M_\infty = kt^{1/2} \)

Korsmeyer–Peppas model: \( M_t/M_\infty = kt^n \)

where \( M_t/M_\infty \) is the fraction of drug released, \( k \) is a constant incorporating structural and geometric characteristics of dosage form, and \( n \) is the diffusional exponent. The equation was treated logarithmically to determine the value of release exponent, \( n \) [14–16].

2.9. Statistical analysis

Analysis of variance (ANOVA) and Levene’s test for homogeneity of variance were performed using SPSS version 10.0 for Windows (SPSS Inc., USA). Post hoc testing (\( P < 0.05 \)) of the multiple comparisons was performed by either the Scheffé or Games–Howell test, depending on whether Levene’s test was insignificant or significant respectively [17].

3. Results and discussion

3.1. Formation of porous EL beads

The EL beads containing MTZ and wax (either cetyl alcohol or white petrolatum) could be prepared using the solvent diffusion technique as described in previous studies [18]. The wax incorporated into the EL beads was removed by using dichloromethane as a displacement solvent. Dichloromethane was chosen because it is chemically inert in relation to the desired EL beads (poor solvent for the EL) but a relatively good solvent for the wax under the contacting conditions, miscible with the dilution solvent. After wax removal, pores were created inside the EL bead structure. In the meantime, EL beads were solidified in dichloromethane [1]. Curing time of the beads in dichloromethane therefore played a crucial role in the solidification process and porous structure formation. In this study, the effect of curing time, i.e., 5 and 20 min, on the properties of EL beads was investigated.

3.2. Size of EL beads

The mean diameter of the drug-loaded EL beads was observed by microscopic method. The size of the beads ranged from 2.4 to 2.8 mm. The amounts of cetyl alcohol and white petrolatum did not significantly affect the mean size of the prepared beads. The results found here are consistent with a previous report [1]; the portion of used waxes insignificantly influenced the mean diameter of the beads. During bead formation, the solution of EL, MTZ and wax in acetone continuously grew through a needle until its mass achieved a critical value at which moment the droplet detached from the tip of the needle and fell into the dichloromethane. This suggested that the size of the obtained beads principally resulted from the diameter of the extruding needle used in the study [1].

3.3. Morphology of beads

The SEM images of the surface and internal structures of the EL beads and the EL beads containing 1% w/w cetyl alcohol or white petrolatum are presented in Fig. 1. All EL bead formulations showed somewhat spherical beads with a fairly
smooth surface. The internal or cross-sectional structure of the beads demonstrated numerous micropores. This is because the acetone evaporated and diffused from the beads during the bead formation in dichloromethane, which contributed to the porosity of the matrix beads, as discussed above. The pore size of the beads using waxes, cetyl alcohol or white petrolatum, as a pore former was around 3–5 μm which were greater than those of the beads containing no wax (around 2–3 μm). This is because the added waxes gradually dissolved from the beads into the displacement solvent (dichloromethane), resulting in larger internal pores compared with the formulations containing no wax. The higher concentration of waxes also increased the porosity of the matrix beads (data not shown).

3.4. Floating properties of the beads

The MTZ-loaded EL beads with/without different percentages of waxes instantaneously floated in SGF and remained floating for at least 24 h, as illustrated in Fig. 2. Incorporation of various amounts of cetyl alcohol or white petrolatum did
not influence the floating behavior of the beads. Good in vitro floating behavior in SGF was observed in all formulations. The floating properties of the EL beads with/without wax may be attributed to the low apparent density of the porous structured beads, as confirmed by the SEM images. Even though the interior pore size of the EL beads containing wax was greater than that of the EL beads without wax, the fine porous structure generated by the acetone diffusion and evaporation could also maintain the buoyancy of the beads as soon as the beads were immersed in a liquid medium [19]. Moreover, the beads could float for long period (more than 24 h) because EL does not dissolve in an acidic medium; therefore, the porous structure of the beads still remained [20].

3.5. Drug loading and drug encapsulation efficiency

Table 2 demonstrates the percentages of drug loading and drug encapsulation efficiency of the prepared EL beads at curing times of 5 and 20 min. MTZ loading in the beads ranged from 7.3% to 12.2% and encapsulation efficiency was between 29.0% and 48.7%. The type of wax, amount of wax and curing time insignificantly influenced the drug loading and drug encapsulation efficiency. This may have been due to the insolubility of MTZ in both cetyl alcohol and white petrolatum. For this reason, the drug loading and encapsulation efficiency of this system did not hinge on the type and amount of the waxes used. On the other hand, MTZ is soluble in acetone and freely soluble in dichloromethane [21]; therefore, some amounts of MTZ could have diffused from the beads, resulting in a decrease in drug encapsulation.

3.6. In vitro drug release studies

The in vitro drug release study was performed in SGF in order to mimic gastric conditions and investigate the suitability of the beads as an intragastric floating drug delivery system. The in vitro drug release profiles of the EL matrix beads containing different percentages of cetyl alcohol are shown in Fig. 3. The MTZ exhibited an initial burst of drug release, followed by a lag phase exhibiting slow release [22]. The initial burst of drug release has been attributed to its tendency to move to the bead surface during the preparation or drying processes. From Fig. 3, it can be seen that drug release from the EL beads without wax was the lowest; the addition of wax during bead preparation and then remove out from the beads could enhance the drug release. This is probably due to the formation of internal pores after wax removing from the beads, as indicated in the bead morphology results. This makes medium diffusing through the beads faster, resulting in rapid drug release [4]. Among the different wax added beads, the drug release is

| Formulation | Drug loading (%) | Drug encapsulation efficiency (%) |
|-------------|------------------|-----------------------------------|
| F1          | 11.9             | 47.8                              |
| F2          | 9.4              | 37.6                              |
| F3          | 7.5              | 29.8                              |
| F4          | 8.6              | 34.4                              |
| F5          | 8.0              | 32.0                              |
| F6          | 7.8              | 31.1                              |
| F7          | 9.9              | 39.4                              |
| F8          | 9.8              | 39.2                              |
| F9          | 12.2             | 48.7                              |
| F10         | 8.7              | 34.8                              |
| F11         | 9.6              | 38.2                              |

Table 2 – Drug loading and encapsulation efficiency of the EL beads.

Fig. 3 – Release profiles of EL beads containing different percentages of cetyl alcohol, using curing time of (a) 5 and (b) 20 min.
not deepened on the portion of the wax. The curing time of the beads in dichloromethane played a vital role on the drug release. The longer curing period (20 min) yielded stronger beads and, consequently, resulted in a slower drug release [23]. Fig. 4 presents the percentage of drug release after 2 h from different EL bead formulations. The drug release from the beads using cetyl alcohol as a pore former was faster than that from the beads using white petrolatum. This might be because cetyl alcohol can be dissolved in dichloromethane faster than white petrolatum, resulting in higher porosity and drug release [1].

3.7. Drug release kinetics

Dissolution data were processed using linear regression analysis for estimation of drug release mechanism or kinetics to test the goodness of fit with zero order, first order, Higuchi and Korsmeyer–Peppas release models. A correlation coefficient (R²) was chosen to define the approximation accuracy of an individual model (Table 3). Acceptable correlation was achieved when R² values were equal to 0.970 or higher [24].

The values of the correlation coefficient of the Korsmeyer–Peppas model, also known as the “power law” model, for the obtained release data of almost all formulations were greater than 0.970, as demonstrated in Table 3. Only F1 (5 min curing time) and F7 (5 min curing time) showed R² values less than 0.970. The Korsmeyer–Peppas model has been used very often to describe the drug release from several different pharmaceutical modified-release dosage forms. There are several simultaneous processes considered in this model, for example, diffusion of water into the beads, swelling of the beads as water entered, formation of gel, diffusion of drug out of the beads, and dissolution of the polymer matrix. In this model, the mechanism of drug release is characterized using the release exponent (“n” value). For a spherical particle, an “n” value of 0.85 corresponds to zero-order release kinetics (case II transport); 0.43 < n < 0.85 means an anomalous (non-Fickian) diffusion release model; n = 0.43 indicates Fickian diffusion, and n > 0.85 indicates a super case II transport relaxational release [14]. The results revealed that most of the release profiles obeyed super case II transport relaxational release, since they fitted well with the Korsmeyer–Peppas model (R² are in range of 0.902–0.985 and exponent values (n) are greater than 0.85) [25]. Super case-II transport refers to drug release by two mechanisms which are diffusion and relaxation of polymer chain [26]. This might be because EL did not dissolve in the SGF. Consequently, MTZ gradually diffused through the relaxed polymer layer.

As for approximation of experimental results with the Higuchi model, the correlation coefficient ranged from 0.665 to 0.993. This model fits well to data of MTZ release from a few formulations, i.e., F1 (5 and 20 min curing time), F8 (20 min curing time) and F11 (5 min curing time), indicating that the release of MTZ followed the Higuchi release kinetics and diffusion was the dominating mechanism for drug release. It is clearly indicated that the formulations did not follow zero-order and first-order release models because the regression values for all formulations did not show high linearity.

4. Conclusion

The porous EL beads containing cetyl alcohol or white petrolatum were in spherical shape and floated in SGF for more than 24 h. The curing time in dichloromethane, amount and type of wax played a vital role in the drug release. A short curing time and presence of wax during bead preparation could enhance the drug release. Most of the drug release kinetics from the EL beads were super case II kinetics. The results suggested that the bead fabricated by wax removal technique is...
promising for the development of a floating drug delivery system.

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Table 3 – Mathematical modeling and drug release kinetics from EL beads, analyzed by linear regression analysis.

| Formulations | Zero order ($R^2$) | Higuchi ($R^2$) | First order ($R^2$) | Korsmeyer–Peppas ($R^2$) |
|--------------|-------------------|-----------------|---------------------|--------------------------|
| F1           |                   |                 |                     |                          |
| 5 min        | 0.6554            | 0.9760*         | 0.4049              | 0.8762                   |
| 20 min       | 0.6840            | 0.9807*         | 0.4628              | 0.9868*                  |
| F2           |                   |                 |                     |                          |
| 5 min        | 0.6325            | 0.9469          | 0.3016              | 0.9802*                  |
| 20 min       | 0.6606            | 0.9681          | 0.3362              | 0.9830*                  |
| F3           |                   |                 |                     |                          |
| 5 min        | 0.1588            | 0.6465          | 0.1694              | 0.9721*                  |
| 20 min       | 0.5311            | 0.9373          | 0.3388              | 0.9850*                  |
| F4           |                   |                 |                     |                          |
| 5 min        | 0.3362            | 0.8175          | 0.2139              | 0.9757*                  |
| 20 min       | 0.3757            | 0.8489          | 0.2322              | 0.9717*                  |
| F5           |                   |                 |                     |                          |
| 5 min        | 0.2024            | 0.7185          | 0.1864              | 0.9741*                  |
| 20 min       | 0.5756            | 0.9536          | 0.3584              | 0.9864*                  |
| F6           |                   |                 |                     |                          |
| 5 min        | 0.2300            | 0.7447          | 0.1908              | 0.9745*                  |
| 20 min       | 0.4630            | 0.9085          | 0.2888              | 0.9822*                  |
| F7           |                   |                 |                     |                          |
| 5 min        | 0.5251            | 0.9001          | 0.2581              | 0.9021*                  |
| 20 min       | 0.4659            | 0.8976          | 0.2642              | 0.9791*                  |
| F8           |                   |                 |                     |                          |
| 5 min        | 0.3779            | 0.8467          | 0.2272              | 0.9767*                  |
| 20 min       | 0.7451            | 0.9928*         | 0.4581              | 0.9892*                  |
| F9           |                   |                 |                     |                          |
| 5 min        | 0.4139            | 0.8728          | 0.2425              | 0.9783*                  |
| 20 min       | 0.3558            | 0.8451          | 0.2468              | 0.9783*                  |
| F10          |                   |                 |                     |                          |
| 5 min        | 0.4052            | 0.8691          | 0.2417              | 0.9781*                  |
| 20 min       | 0.3558            | 0.8344          | 0.2261              | 0.9763*                  |
| F11          |                   |                 |                     |                          |
| 5 min        | 0.6123            | 0.9713*         | 0.3614              | 0.9826*                  |
| 20 min       | 0.6900            | 0.9653          | 0.3515              | 0.9822*                  |

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