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Development and Mathematical Simulation of Theophylline Pulsatile Release Tablets

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ABSTRACT Theophylline pulsatile release tablets consisting of a fast-swelling core with a water-insoluble ethylcellulose were developed. Effects of coating material, the amount of the plasticizer, subcoating, the type of the disintegrant, and coating level on the release profiles were investigated. Results showed that ethylcellulose was the best candidate polymer for pulsatile release tablets. Rupture time increased with increasing the amount of the plasticizer, but 15% plasticizer provided the best release profiles. Tablets with Methocel® E50 as subcoating was most optimal in order to achieve a long lag time and followed by a rapid release. The lag time of tablets containing different disintegrants increased in the following order: croscarmellose (Ac-Di-Sol®)<sodium starch glycolate (Explotab®)<low-substituted hydroxypropyl cellulose (L-HPC)<crospovidone (Kollidon® CL). And the rupture time increased with higher coating level. A mathematical model was presented to predict the lag time prior to rupture. Results of the water uptake experiment were used to estimate the apparent diffusion coefficient of the coating tablets. The prediction of the lag time based on the presented model is in good agreement with the experimental results.

KEYWORDS Pulsatile release, Theophylline, Lag time, Fick's law, Diffusion

INTRODUCTION

A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release, which is advantageous for many drug therapies, such as asthma, hypertension, rheumatoid arthritis, etc. Numerous patents and articles have been published in this field (Freichel & Lippold, 2000; Göpferich, 1997; Krögel & Bodmeier, 1998; Ross et al., 2000; Schultz & Kleinebudde, 1997; Schultz et al., 1997; Ueda et al. 1989).

Pulsatile release systems can be classified into multiple unit and single unit systems (including tablet and capsule systems). Bussemer et al. (2003a, 2003b) developed a pulsatile drug delivery system based on drug-containing hard

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gelatin capsules, which were coated with a swelling layer and an outer insoluble, water-permeable polymeric coating. An inner pressure was developed by the swelling layer resulted in the rupture of the outer coating. One advantage of Bussemer's system over the Pulsincap (Wilding et al., 1992) was that the Bussemer's system was made of approved substances. Sungthongjeen et al. (2004) prepared a tablet system consisting of cores coated with two layers, an inner swelling layer containing a superdisintegrant (croscarmellose sodium), and an outer rupturable layer of ethycellulose. Krögel and Bodmeier (1999) developed a pulsatile tablet consisting of a drug-containing effervescent core and a polymer coating consisting of acrylic and cellulosic polymers. It was shown that the core composition and the mechanical properties of the film influenced the release behavior. Kok et al. (2001) developed a multi-particulate delayed release system consisting of a water-soluble core coated with a water-insoluble ethylcellulose coating. Kok, also gave a mathematical description with the Maxwell-Stefan theory on this system. Results of water sorption experiments were used to estimate the Maxwell-Stefan diffusion coefficients of water in the coating. It was shown that the predicted release time was in good agreement with the experimental findings. But the model broke down at the prediction of the lag-time with a core in which a swelling agent was incorporated.

The lag time prior to release due to rupture of coating is mainly controlled by: 1) the permeation and mechanical properties of the polymer coating, and 2) the water uptake and the swelling behavior of the swelling layer. In this paper, we present the development of a pulsatile system consisting of a fast-swelling tablet core coated with a water-insoluble ethylcellulose layer. A mathematical model is also presented to predict the lag time which integrated the effect of the permeation and mechanical properties of the coating and the swelling behavior of tablet core.

THEORY

The Fick's Law and Its Numerical Solution

The rate of diffusion through a plan with unit surface area was established by Fick to be proportional to the concentration gradient measured normal to the plan, as described as Fick's first law in the following equation (Liang, 1979):

$$J = -D\frac{\partial C}{\partial x} \tag{1}$$

If concentration gradient exists only along the x-axis of a three-dimensional element, the rate of concentration increase of the diffusant in the element can be described by differentiating Fick's first law to result in Fick's second law as described in Eq. 2:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \tag{2}$$

where C is the concentration of the diffusing substance, being a function of time t at position x. And D is the diffusion coefficient of the substance.

Equations for diffusion into or release from a planar matrix can be derived based on the initial and boundary conditions. For sorption of water into a planar matrix, the initial condition and the boundary conditions are:

$$C(x, 0) = 0 \tag{3}$$

$$C(0, t) = C_0 \tag{4}$$

Eq. 2 can be solved to result in the following equation (Liang, 1979):

$$C(x, t) = C_0 erfc\left(\frac{x}{2\sqrt{Dt}}\right) \tag{5}$$

Calculation of Diffusion Coefficient

For Eq. 2, it is assumed that diffusion coefficient, D, is constant at a given temperature and pressure. An analytical solution for sorption by diffusion into a planar system is given as follows (Crank & Park, 1986),

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2} \times \exp\left[-\frac{D(2n+1)^2\pi^2 t}{d^2}\right] \tag{6}$$

where M_t is the sorption mass in the film at time t, M_∞ is the equilibrium sorption attained after infinitive time, and d is the thickness of film.

For the early uptake, such as $M_t/M_\infty \leq 0.5$, approximation can be given by Eq. 7,

$$\frac{M_t}{M_\infty} = \frac{4}{d}\left(\frac{D}{\pi}\right)^{1/2} t^{1/2} \quad (7)$$

Hence, the diffusion coefficient can be determined by measuring the slope of the linear sorption curve M_t/M_∞ against $\sqrt{t}$.

Calculating Lag Time

Water uptake at different intervals was obtained by weighing. With Eq. 7, diffusion coefficients were calculated. In order to perform the numerical calculation according to Eq. 5, water concentration at rupturing point has to be measured. Water uptake could be known by weighing. Then, water molar concentration is calculated by summation of the volume of water and the volume of the polymer. The constant volume of coating is assumed compared with the volume of water (Sungthongjeen et al., 2004).

MATERIALS AND METHODS

Materials

The following materials were obtained theophylline (Shijiazhuang Pharmaceuticals Co., Hebei Province, China), croscarmellose sodium (CC-Na, Ac-Di-Sol®, FMC, Princeton, NJ, USA), sodium starch glycolate (CMS-Na, Vivastar, JRS, Rosenberg, Germany), crospovidone (PVPP, Kollidon® CL, BASF, Ludwigshafen, Germany), low-substituted hydroxypropyl cellulose (L-HPC, LH® 21, Shin-Etsu, Tokyo, Japan), polyvinyl pyrrolidone (PVP, Kollidon® 30, BASF, Ludwigshafen, Germany), microcrystalline cellulose (MCC, Avicel®PH101, FMC, Princeton, NJ, USA), ethylcellulose (EC, Ethocel® Standard 10cp, Dow Chemical, Midland, MI, USA), hydroxypropylmethylcellulose (Methocel® E15, E50, Dow Chemicals, Midland, MI, USA), Eudragit RS 100 (Röhm Pharma, Darmstadt, Germany), cellulose acetate (CA, Eastman Chemicals, Jefferson, PA, USA), dibutyl sebacate (DBS, Shanghai Chemical, Shanghai, China). All other reagents were of analytical grade and were used without further purification.

Preparation of Pulsed Tablets

Preparation of Core Tablets

A manually granulated mixture of theophylline, MCC, and a type of superdisintegrant was combined with 10% PVP water solution as a binder. Following drying in the oven at 60°C and sieving, magnesium stearate was added and then compressed. The tablets (diameter, 8 mm; convex-shaped; weight, 170 mg; hardness, 50 N) were compressed with a single punch press (TDP-I, Jianxiang, China).

Coating of Tablets

The tablets were coated in a modified-traditional coating pan and the process conditions were as follows: inlet temperature: 60°C, product temperature: 35–40°C, batch size: 0.7 kg, pan speed: 30 rpm, atomizing pressure: 1 bar, spraying rate: 2 g/min.

The coating solution was applied when the tablet bed in the coating pan reached 60°C. The coating solution was prepared by dissolving ethylcellulose in 90% w/w ethanol, using diethyl-o-phthate of 15% w/w polymer solids as a plasticizer. Coating was continued until the weight gain reached 4.7%, 6%, or 8% calculated using the following equation:

$$\%\ \text{weight gain} = \left(\frac{W_t - W_0}{W_0}\right) \times 100 \quad (8)$$

where W_t is the weight of the tablets after coating, W_0 is the initial weight of tablets. The tablets were dried in an oven at 60°C for 12 h. These tablets were used for the lag time test.

Formulation Screening Studies

For formulation screening studies, different coating materials, such as ethylcellulose, Eudragit RS, and cellulose acetate were used to study the release profiles. The amount of the plasticizer (10%, 15%, and 20% w/w based on polymer solids) was also investigated to optimize the best release. Subcoating was another important factor for pulsatile release tablets. Methocel E15 and methocel E50 were studied as subcoating materials. Different superdisintegrants such as CC-Na, CMS-Na, L-HPC, and PVPP, and coating level of ethylcellulose were also studied.

Study of Films

Preparation of Polymeric Films

The coating polymer EC was dissolved in 95% v/v ethanol at a concentration of 4% w/w. The resulting

solution was cast onto PTFE plates with a round plastic frame (d=12 cm), and dried for 4 h at 40°C under a piece of filter paper, which could reduce solvent evaporation in order to ensure the formation of a smooth homogeneous films. The resulting films were carefully removed, and weighed with an analytical balance.

The films were stored at room temperature at 52% relative humidity (RH) for 48 h and cut into 40 mm × 40 mm. The exact film thickness was measured at ten different points with a micrometer (RSD<15%). For the preparation of wet films, the dry films were put into bags (made from a 40-mesh plastic screen with three sides sewn closed) to avoid sticking and folding of the films in the medium (Krögel & Bodmeier, 1999).

Measurements of Water Uptake by EC Films

The water uptake of the films was determined by immersing the free films into 0.1 N HCl at 37°C, which was the same condition used for dissolution study. At predetermined time intervals, the films were removed from the medium and weighed with an analytical balance after carefully removing the excess medium on the films with paper tissue. The water content at any time was calculated as:

$$\%\ \text{water uptake} = \left(\frac{W_t - W_0}{W_0}\right) \times 100 \qquad (9)$$

where W_t is the wet film weight at time t, and W_0 represents the initial weight of the dry film.

Calculation of Diffusion Coefficient of EC Films

According to Eq. 7, the slope of the sorption curve M_t/M_∞ against $\sqrt{t}$ was measured; then the diffusion coefficient of the water could be calculated.

Evaluation of Pulsed Release Tablets

Scanning Electron Microscopy

A cross-section of the pulsatile tablets was observed under a scanning electronic microscope (Hitachi S-520, Hitachi Ltd., Japan).

Rupture Test

Tablets were tested using a CP 2000 II dissolution apparatus with paddle speed 50 rpm, in 900 mL of 0.1 N HCl at 37°C. Rupture was detected by visual observation. The lag time was defined as the time point, when the coating ruptured due to swelling (n=6).

Water Uptake of Pulsed Tablets Measurements

Water uptake by tablets was determined using the same conditions for rupture test. At predetermined time intervals, tablets were removed from the medium and weighed with an analytical balance after carefully removing the excess water on the surface of tablets with paper tissue. Water content at any time was calculated using Eq. 9, except that the weight of tablets was used for calculation.

The water molar concentration was calculated as follows:

$$\text{Water uptake (mol/L)} = \frac{(W_t - W_0)/18}{V_f + V_w} \qquad (10)$$

where W_t is the wet tablet weight at t time, W_0 is the initial weight of dry tablet, V_f is the volume of tablets, and V_w is the volume of water.

Calculation of Diffusion Coefficient of Coating Tablets

The diffusion coefficient of coating tablets could be calculated as described in Calculation of Diffusion Coefficient of EC Films.

Dissolution Testing

Dissolution test was performed using a CP 2000 II paddle apparatus at 37°C in 900 mL 0.1 N HCl with a paddle speed of 50 rpm. Samples were withdrawn after predetermined time intervals and diluted and assayed with a spectrophotometer (Shimadzu UV-2450, Japan) at a wavelength of 272 nm.

RESULTS AND DISCUSSION

Effect of Coating Materials on the Release Profiles

Concerning the mechanical properties (Krögel & Bodmeier, 1999), the polymer films should be weak in the wet state to obtain rupturing of the coating due to the swelling of tablet cores. Three type of coating

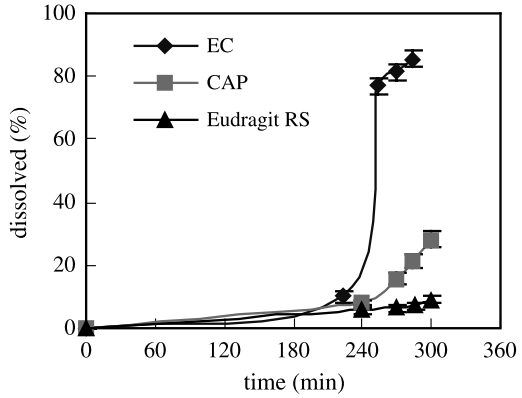

FIGURE 1 **Effect of Coating Materials on the Release Profiles (*n*=6).**

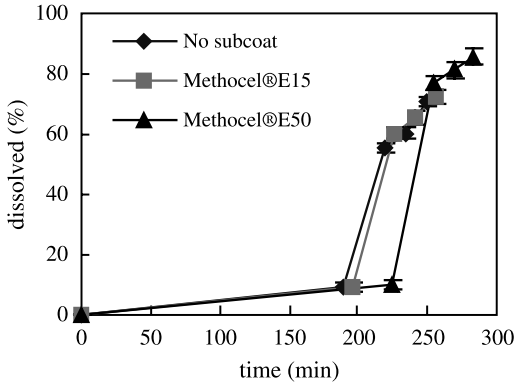

FIGURE 3 **Effect of Subcoating on the Release Profiles (*n*=6).**

materials were screened as candidate. As expected, Eudragit RS film had high flexibility which may be not suitable for pulsatile tablets. Tablets coated with Eudragit RS could not get a pulsatile release profile. Cellulose acetate was too rigid and also couldn't provide pulsatile release. The less flexible polymer ethylcellulose could obtain pulsatile release profile upon tablets swelling (Fig. 1). So, in the next studies, ethylcellulose was chosen as the best coating material for pulsatile release tablets.

Effect of the Amount of the Plasticizer on the Release Profiles

Besides the coating material, the amount of the plasticizer was another important factor influencing the rupturing and drug release. The lag time increased with increasing the plasticizer level. After rupturing, the drug release from the tablets with 15% plasticizer was higher than that from tablets with 10% and 20% plasticizer (Fig. 2). As observed, the drug release after tablets with higher plasticizer (20%) ruptured was hindered because the film wound themselves repeatedly and some tablet core contents were wrapped inside it. But for tablets with 10% plasticizer, films were a little rigid and ruptured leaving only small fissures as pathways for the drug release; more tablet core contents remained inside the ruptured coat. Films with 15% plasticizer ruptured at the edge of the tablet upon swelling and left a wide orifice from which almost all tablet core contents were released and only the empty coating remained.

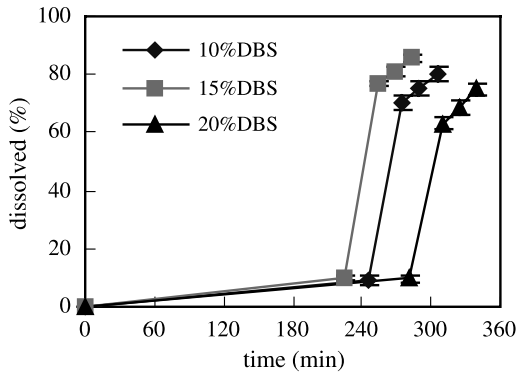

FIGURE 2 **Effect of the Amount of the Plasticizer on the Release Profiles (*n*=6).**

Effect of Subcoating on the Release Profiles

Subcoating was important for film controlled tablets, which was useful for getting intact coating. From Fig. 3, tablets with Methocel® E50 as subcoating got the longest lag time and drug could be released rapidly and completely after lag time, which was most

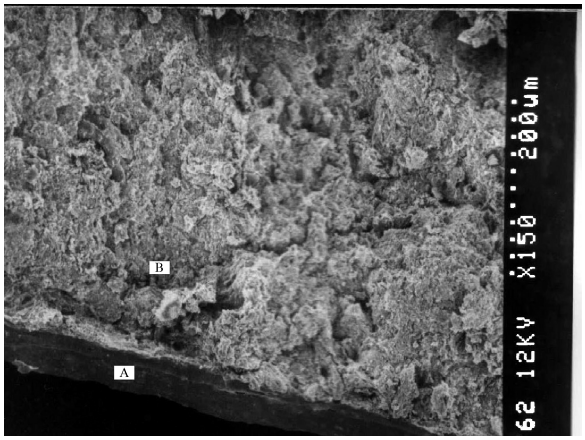

FIGURE 4 **SEM Photograph of a Cross-Section of the Pulsatile Tablets.**

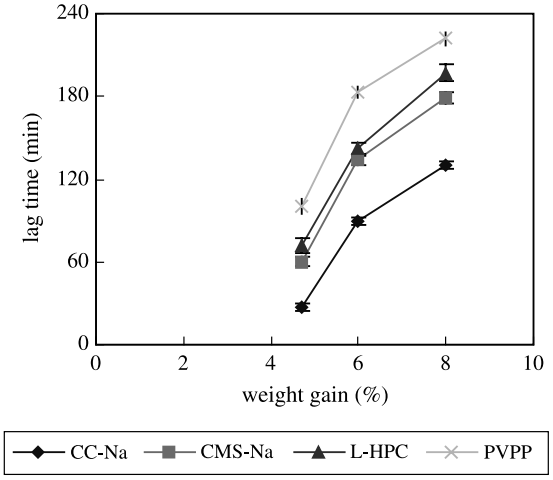

FIGURE 5 **Effect of the Type of the Disintegrant and Coating Level on Lag Time (n=6).**

optimal in order to achieve a long lag time and followed by a rapid release. Tablets with Methocel® E15 and tablets without subcoating had almost the same lag time and release. This could be explained by the fact that films with Methocel® E50 were intact and less water penetrated which was beneficial for disintegrants swelling and coating burst. For tablets without subcoating, films might not be uniform, then water ingressed into tablets and disintegrants swelled gradually and could not get rapidly release after lag time.

Effect of the Type of Disintegrant and Coating Level on the Release Profiles

The lag time of the pulsed tablets was investigated and could be mainly controlled by the disintegrant which has different swelling behavior and coating level which is related to the permeation and mechanical properties of the polymer coating.

Figure 4 showed the photograph of a cross-section of the pulsatile tablets. A is the polymeric coating layer and B is the tablet core. Water ingress and the tablet core expansion caused the rupturing of the ethylcellulose coating and then the drug was released rapidly.

Different formulations containing different disintegrants were prepared to characterize their swelling potential. Results in Fig. 5 showed that lag time depended on the type of the disintegrant. The lag time of tablets containing different disintegrants increased in the following order: croscarmellose (Ac-Di-Sol®)< sodium starch glycolate (Explotab®)<low-substituted

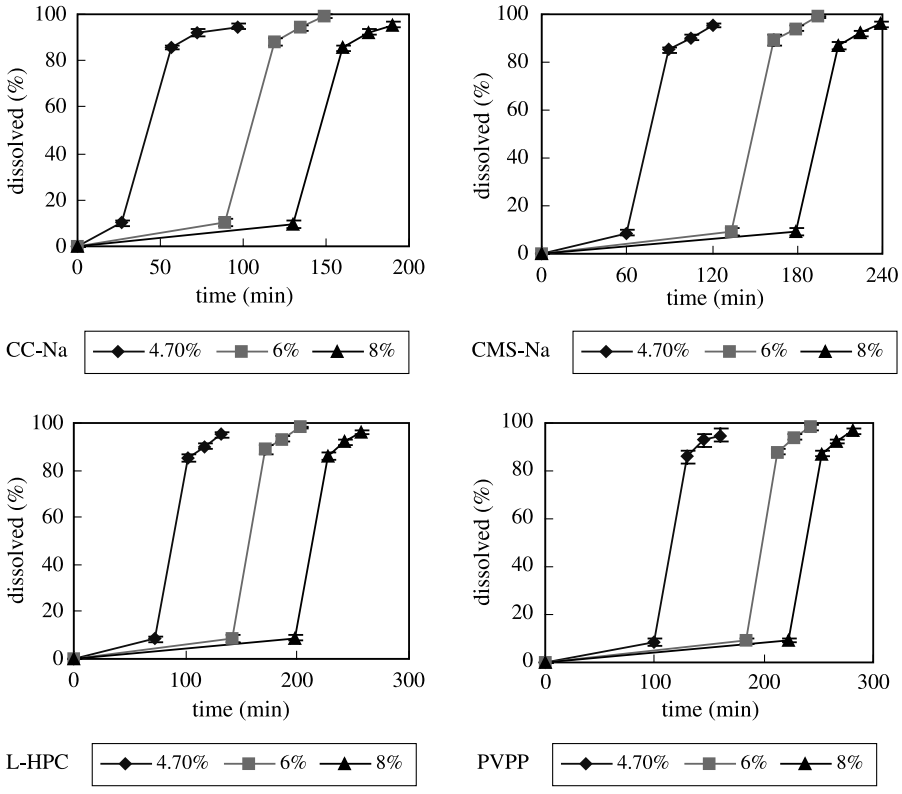

FIGURE 6 **Effect of Different Disintegrants on Drug Release (n=6).**

hydroxypropyl cellulose (L-HPC)<crospovidone (Kollidon® CL), which means CC-Na had a superior effectiveness as a disintegrant when compared with other materials.

The observed trend agrees with the data published in the literature on the swelling of disintegrants. Bussemer et al. (2003a, 2003b) compared the swelling properties of different disintegrants under a load. The swelling energy of several disintegrants decreased in the following order: croscarmellose (Ac-Di-Sol®)> low-substituted hydroxypropyl cellulose (L-HPC)>sodium starch glycolate (Explotab®)>crospovidone (Kollidon® CL). Ac-Di-Sol® showed the highest degree of swelling under load.

As expected, the rupture time increased with higher coating level because of the increased mechanical strength of the coating and the reduced medium permeation rate at higher coating thickness (Fig. 5). A similar trend was observed for all the disintegrants studied.

Release experiments were studied in order to test whether the fast and complete release could be obtained after lag time. Figure 6 shows that theophylline was not released prior to the rupturing of the tablets. After rupture, the drug was released rapidly and completely.

Based on these results, it can be concluded that desired lag time and, hence, pulsatile drug delivery could be achieved by using different disintegrants in combination with different coating levels.

Diffusion Coefficient of Films and Coated Tablets

The diffusion coefficient of water through a polymer system, D, is determined from experiments using thin polymer film immersing the water. As the surface of the film is very large compared to its thickness, edge effects could be negligible. The mathematical analysis of water diffusion can be described by the second of Fick's laws, as in Eq. 2. Figure 7 presents the change of water content absorbed by films immersed in water with time. According to Eq. 7, the result of the calculation of the Fick's diffusion coefficients is given in Fig. 8. For different film thickness, the diffusion coefficient, D, is equal to $0.93\ (\pm 0.04)\cdot 10^{-14}\ m^2/s$.

Take the same method, exchange the film into coated tablets, measure the diffusivity, and the result is defined as the apparent diffusion coefficient. In fact, the water transfer into the tablets includes two steps: the influx of water into the film and then the flux of the water from the film into the tablet core. So, the apparent diffusion coefficient of the coating tablets integrates the effect of film and tablet core. Because of the porosity and water uptake property of the core, this coefficient is one hundred times larger than film's, about $10^{-12}\ m^2/s$ (Fig. 9). Water mass transfer would increase more quickly in a film adjacent to the core

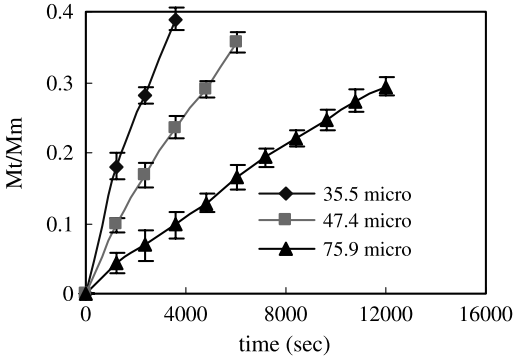

FIGURE 7 **The Change of Water Content Absorbed by Films Immersed in Medium with Time. Error Bars Denote Standard Deviation in Three Experiments.**

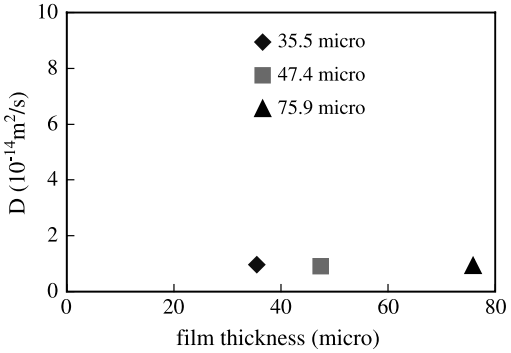

FIGURE 8 **Fick's Diffusion Coefficients for an EC Film as a Function of Film Thickness.**

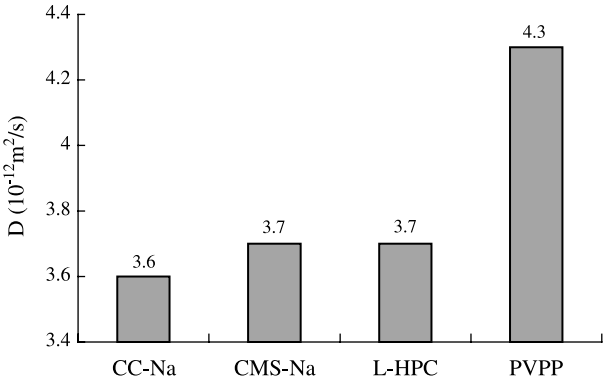

FIGURE 9 **Apparent Diffusion Coefficients for Coated Tablets with Different Disintegrants.**

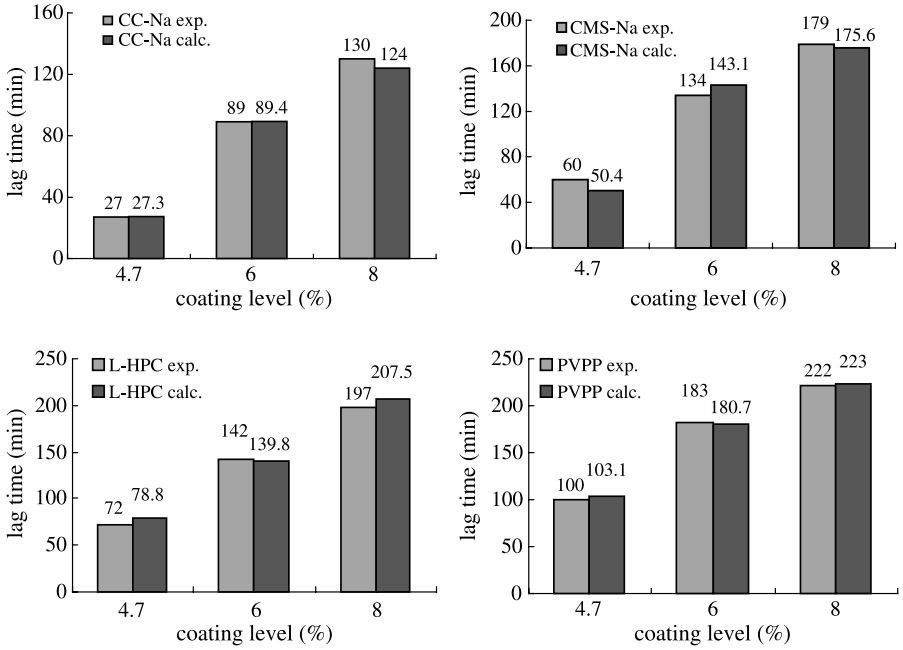

FIGURE 10 **Experimental Lag Time Compared with the Calculated Results (n=6).**

than the single film. It also can be seen that the coating tablets with different disintegrants have different apparent diffusion coefficients. All these tablets have a similar hardness and it was assumed that they have the same porosity, so this difference shows the difference of water uptake property of disintegrants. PVPP is the high hygroscopic material, which drives water move much quicker. CC-Na has the least water uptake property.

Prediction of Lag-Time

We know the weight of water that has to diffuse into the tablet when the coating breaks and therefore could calculate the water concentration in the tablet. We also know the apparent diffusion coefficient, D, listed in Fig. 9. We assume the film thickness as the rupture position. This is allowed because the water influx through the film into the tablets is much faster than the free film, which means water could flux into tablets rapidly as long as the water transfer the film. After that, according to Eq. 5, we could give an estimate of the lag-time. In Fig. 10, the predicted and experimental lag-time for four different formulations is given.

Kok et al. (2001) presented a mathematical description with the Maxwell-Stefan theory on a multiparticulate system, which gave a satisfactory prediction of the lag-time without sub-coating. But the model broke down at the prediction of the lag-time with a core in which a swelling agent was incorporated. In experiment, Kok determined the extension of the coating at breakage under a microscope. The swelling of coated pellets (increase of the core in volume) was regarded as the volume of water into the core at rupturing point. This is reasonable for cores without a swelling agent, but for cores with a swelling agent, this swelling is far lager than the volume of water diffusing into the film.

In our calculation, we measured the apparent diffusion coefficients, which considered the co-effects of the permeation and mechanical properties of the coating and the swelling behavior of tablet core. So from Fig. 10, we can say that the mathematical model gives a good prediction of the lag time of tablets with different disintegrants at different coating levels.

CONCLUSION

The pulsatile release tablets with a fast-disintegrating tablet core coated with EC film were developed, which could release theophylline rapidly and completely after the lag time. Formulation screening studies showed that ethylcellulose was the best candidate polymer for pulsatile release tablets. Tablets with Methocel® E50 as subcoating got the best release profiles. The amount of the plasticizer was important

for drug release after tablets ruptured. The lag time of tablets containing different disintegrants increased in the following order: croscarmellose (Ac-Di-Sol®)<sodium starch glycolate (Explotab®)<low-substituted hydroxypropyl cellulose (L-HPC)<crospovidone (Kollidon® CL). And the rupture time increased with a higher coating level. The lag time could be predicted with the mathematical model based on the Fick's diffusion law. And there is a good agreement between the experimental and calculated results.

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