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Development of Micropore-Controlled Release Tablet and *In Vivo* Pharmacokinetic Study

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ABSTRACT

The aim of this work was to develop a micropore-controlled release tablet for theophylline. The tablets were composed of a drug core surrounded by a microporous film. The major components of coating film included a biocompatible semipermeable polymer, cellulose acetate, and a water-soluble pore-forming agent, poly(ethylene glycol). The effect of the coating film composition and the type of excipient incorporated in the drug core on drug release were demonstrated via an *in vitro* release study. The optimized formulation was further investigated *in vivo* of rabbits. The results showed that micropore-controlled release tablets continuously released drug for 24-36 hours depending on the type of excipient in the drug core and the coating film composition. Incorporation of lactose in the drug core enhanced drug release from micropore-controlled release tablets. *In vivo* animal study revealed that the micropore-controlled release tablets reduced the maximum concentration and prolonged the mean residence time of drug.

Key words: micropore-controlled release tablet, theophylline, cellulose acetate, poly(ethylene glycol), pharmacokinetics

INTRODUCTION

Many studies have examined advantages of sustained release dosage forms including employing less drug dose, minimizing side effect, improving therapeutic efficacy, *etc*[1]. Among sustained release systems, orally controlled release systems receive the most attraction due to easy administration and better patient compliance[2]. Cellulose acetate is a well-known semipermeable polymer that is freely permeable for water but not solutes. Cellulose acetate has been applied for transdermal delivery system and as the rate-controlling coating film for osmotic tablets[3-9]. Osmotic systems usually comprise three major components. The first component is the drug reservoir which continuously provides the dissolved or suspended drug. The second component is the semipermeable coating film which allows water penetration into the system. The third component is the orifice to control drug release out of the system. Several variables affect drug release from osmotic-sustained release systems, including the drug type, osmotic agent, plasticizer, channeling agent, composition and the thickness of coating film, and size of orifice. Proper choices of these variables yield the desirable drug release profile and therapeutic efficacy.

The new generation of controlled-porosity osmotic pump has been developed via incorporation of leachable water-soluble small molecules, such as sodium chloride, potassium chloride, urea, sucrose, *etc*., into major components of film[10-13]. These pore-forming agents were leached when contacted with the aqueous medium, and the pores were created on the films to allow drug release. The blending of pore-forming agents avoided using high technique laser to drill the orifice for drug release and eliminated controlling drug release via only one orifice. In addition, it was easily fabricated via a traditional film coating technique instead of high technique laser[14]. Blending a leachable water-soluble polymer instead of small molecules as a pore-forming agent was another feasible choice successfully demonstrated by poly(ε-caprolactone)/poly(ethylene glycol) (PCL/PEG) microporous films[15-18]. There were two major polymers combined in the blended films. PCL was the component remained in the end-used film, while PEG acted as a leachable pore-forming agent to produce porous structure on the film for drug release. Since PCL and PEG were immiscible polymers, blending both of them would cause phase separation. The release of drug from PCL microporous films was completely dominated by the number of pores and the pore size. However, the release rate of drug from PCL microporous films was limited even with high level of the pore-forming agent. One possible reason was that PCL is a highly

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hydrophobic and crystallized polymer that did not allow water to freely penetrate into the drug core initially. This resulted in hindering drug dissolution and further release. In order to improve drug release, the semipermeable polymer might overcome the issue occurred in PCL microporous films.

The aim of this study was to develop micropore-controlled release tablets for theophylline. The tablets were composed of a drug core surrounded by the microporous coating film. The major components of the coating film contained a biocompatible semipermeable polymer, cellulose acetate, and a water-soluble pore-forming agent, poly(ethylene glycol). The effect of the composition of the coating film and the type of excipient incorporated in the drug core on drug release was demonstrated via an *in vitro* release study. Finally, the optimized formulation was applied for animal study, and the pharmacokinetic property of theophylline released from micropore-controlled release tablets was elucidated.

MATERIALS AND METHODS

I. *Materials*

Cellulose acetate (CA, M_n 30,000) was from Aldrich Chemical Co. Ltd. (St. Wisconsin, Milwaukee, U.S.A.). PEG_{4000} and lactose monohydrate were from Wako Pure Chemical Co. Ltd. (Osaka, Japan). Polyvinylpyrrolidone K30 and K90 were from BASF Chemical Company (Ludwigshafen, Germany). Theophylline was from Sigma-Aldrich Chemical Co. Ltd. (St. Louis, MO, USA).

II. *Preparation of Coated Tablets*

Theophylline without or with 20% of five types of excipients (*e.g.*, KCl, lactose, starch, PVP K30 and PVP K90) were weighed in a 3-mm diameter of die and compressed directly by IR compressor under 2,200 pounds force for 10 seconds. The theophylline tablets were further coated. The coating solution was prepared by dissolving various compositions of cellulose acetate and PEG_{4000} in a blended solvent of acetone, ethyl acetate, and ethanol in the volume ratio of 6 : 6 : 1. Each core tablet with or without excipient was coated by polymer solution via a dip-coating method and dried in the oven. Table 1 lists the compositions of drug core, coating film and the related symbols for micropore-controlled release tablets.

III. *In Vitro Release Study*

The release of theophylline from film-coated tablets was conducted according to the USP XXXII basket method. De-ionized water was used as the dissolution medium and maintained at 37 ± 0.5°C. The stirring speed was set at 50 rpm. Samples (1 mL) were withdrawn at specific time points, and the same volume of fresh dissolution medium was replaced. The concentration

Table 1. The compositions of drug core, coating film and the related symbols for micropore-controlled release tablets

Symbol	Film composition	Core composition		
Tablet	CA/PEG	Theophylline	Excipient	
	(%w/w)	(mg)	type	weight (mg)
TH	–	30	–	
TH-A_0	100 : 0	30	–	
TH-A_5	95 : 5	30	–	
TH-A_{10}	90 : 10	30	–	
TH-A_{20}	80 : 20	30	–	
TH-A_{30}	70 : 30	30	–	
TH-A_{40}	60 : 40	30	–	
TH-A_{50}	50 : 50	30	–	
TH-Sta-A_{50}	50 : 50	24	Starch	6
TH-KCl-A_{50}	50 : 50	24	KCl	6
TH-Lac-A_{50}	50 : 50	24	Lactose	6
TH-K30-A_{50}	50 : 50	24	Kollindon® 30	6
TH-K90-A_{50}	50 : 50	24	Kollindon® 90	6
TH-Lac	–	24	Lactose	6

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of theophylline in each sample was determined by UV spectrophotometer (Hitachi U-2000, Japan) at 272 nm. In all cases three runs were carried out for each formulation. The accumulative amount of drug released at each sampling point was corrected with the volume of the dissolution medium. The release of drug from coated tablets was further fitted by equation (1)[19].

$$\left[\frac{M_t}{M_\infty}\right] = Kt^n \quad (1)$$

where M_t: the amount of drug released at time *t*
M: total amount of drug in each tablet
K: the release rate constant
n: exponent constant

IV. *Morphology of Porous Films*

The microporous film was collected at the end of release study and dried in the oven. They were mounted on the stage and coated with gold/palladium under an argon atmosphere. The surface and the cross section morphology were observed with a scanning electron microscope (JEOL JSM-6300, Japan).

V. *HPLC Condition*

Theophylline was assayed with a high performance liquid chromatography equipped with a reverse-phase column (Hypersil BDS C18, 250 × 4.6 mm, 5 μm) and a UV spectrophotometer at 272 nm (Shimadzu SPD-6AV). The mobile phase of acetonitrile and 0.2 M acetate buffer solution (pH 4.5) in the volume ratio of 6.5 : 93.5 (%, v/v) was applied at a flow rate of 1.0 mL/min. The intra- and inter-day precision and accuracy of the HPLC analytical method were validated before sample analysis.

VI. *Pharmacokinetic Study in Rabbits*

Male rabbits were used in this study. They were obtained from National Taiwan University Experimental Animal Center. All procedures were examined by the Ethics Committee on Animal Experiment at National Taiwan University, and the animal experiment was in accordance with "Guide for the Care and Use of Laboratory Animals" published by the National Institute of Health. Each rabbit received intravenous injection of theophylline solution, orally administered an uncoated tablet (TH-Lac) and a coated tablet (TH-Lac-A_{50}), respectively. Blood samples were collected at specific time points. Plasma concentrations of theophylline were analyzed with a validated HPLC method. The pharmacokinetic parameters were calculated by using WinNonlin software (Version 5.2, Pharsight, U.S.A.), and statistically compared by *t*-test ($\alpha = 0.05$). The relationship between the percentage of drug released *in vitro* and the percentage of drug absorbed *in vivo* was further correlated.

RESULTS AND DISCUSSION

I. *Drug Release from Micropore-Controlled Release Tablets*

Figure 1 shows the cumulative release of theophylline from micropore-controlled release tablets coated by various compositions of CA/PEG. The uncoated theophylline tablet was completely dissolved within 2.5 hours. However, a sustained-release character was observed for tablets coated by CA/PEG. Less than 1% of drug was released from 100% CA-coated tablet (TH-A_0) within 36 hours, implying that theophylline cannot directly diffuse through CA. Incorporation of PEG into CA films facilitated theophylline release from coated tablets, and the release rate was prominently enhanced as the level of PEG increased from 5% to 50% in the coating films. This result revealed that the release of theophylline from micropore-controlled release tablets was critically dominated by the extent of micropores after PEG leaching out. Figure 2 shows the SEM micrographs of 100% CA film and $CA_{50\%}/PEG_{50\%}$ microporous films after PEG leaching out. The 100% CA film had a smooth surface without pinholes on it. However, porous structure was observed on CA-porous films and many micropores and inter-connected channels were present while PEG leached out. The $CA_{50\%}/PEG_{50\%}$ formed a less-barrier film with a porous structure and inter-connected channels, which definitely facilitated drug release (Figure 2). The release data up to 60% drug release was further fitted by equation (1), and the release rate constants *K* and *n* values were obtained in the range of 0.07 ± 0.01 - 7.23 ± 0.29 $\%h^{-n}$ and 1.16 ± 0.04 - 0.82 ± 0.02, respectively. The release rate constants of coated tablets were smaller than uncoated tablets by 5-500 folds dependent of the level of PEG blended in the CA films. In other words, increase in blending level of the pore-forming agent created more porous morphology of coating films that further

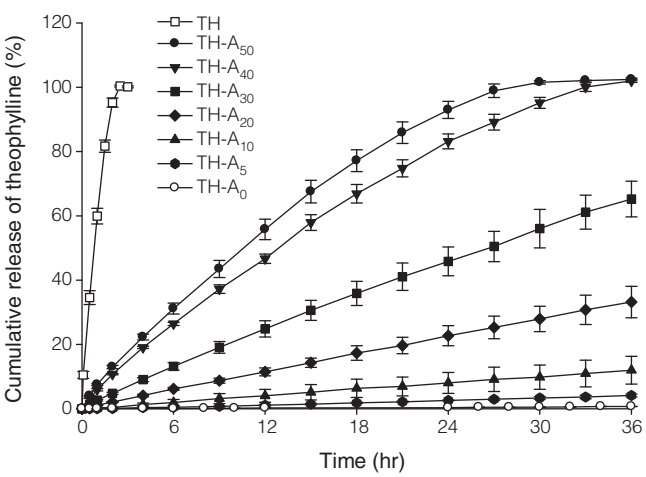

Figure 1. The release of theophylline from tablets coated by various compositions of CA/PEG.

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enhanced drug release from microporous-controlled release tablets. The possible release mechanism of drug from coated tablets was further elucidated based on the *n* values. The result showed that a zero-order constant release pattern was switched to an anomalous release pattern while increasing the level of PEG in the CA films.

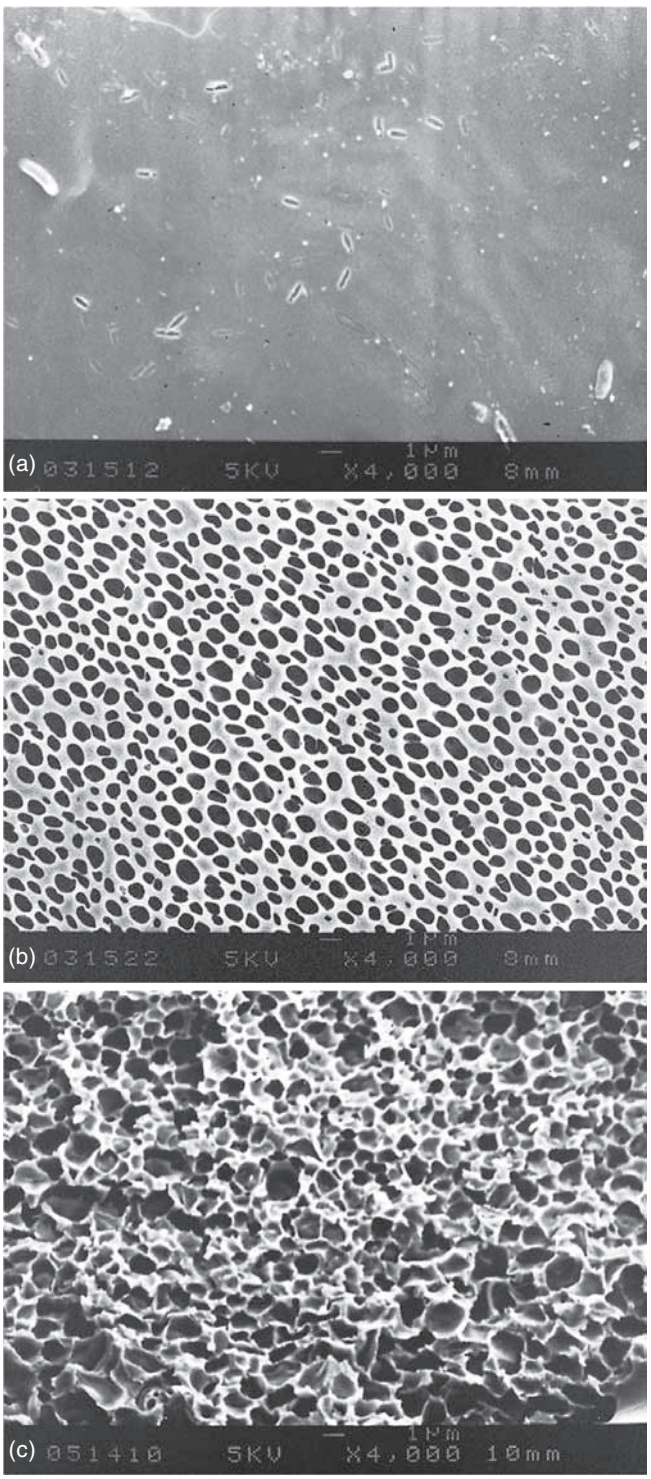

Figure 2. The SEM micrographs of (a) $CA_{100\%}$ (surface morphology), (b) $CA_{50\%}/PEG_{50\%}$ microporous film (surface morphology), and (c) $CA_{50\%}/PEG_{50\%}$ microporous film (cross section morphology).

This change could be due to faster release of drug from more porous films resulting in decrease of driving force across the microporous films. Therefore, the micropore-controlled release tablet could not continuously provide a constant concentration gradient across the porous film.

Figure 3 shows the cumulative release of theophylline from $CA_{50\%}/PEG_{50\%}$ coated tablets composing different types of excipients in the drug core. The

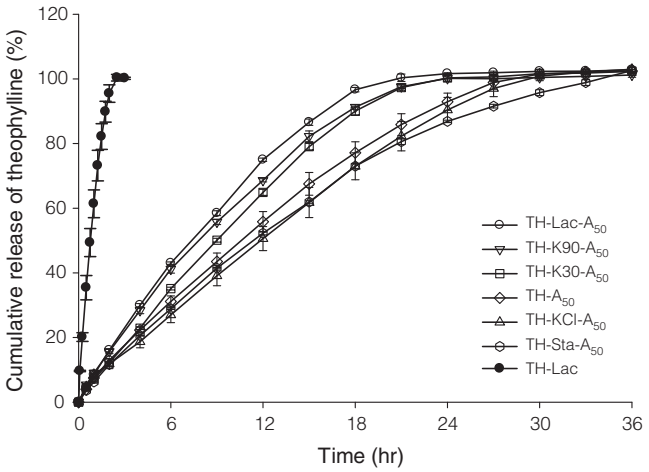

Figure 3. The release of theophylline from $CA_{50\%}/PEG_{50\%}$ coated tablets in the presence of different excipients in the drug core.

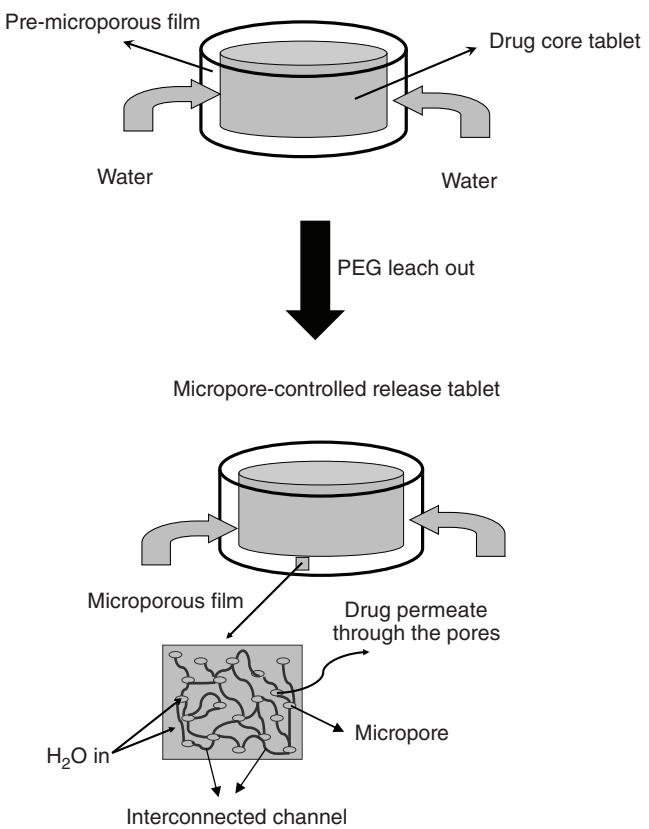

Figure 4. The proposed model for micropore-controlled release tablets.

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Table 2. The pharmacokinetic parameters of theophylline after intravenous injection of solution or oral administrations of uncoated tablets (TH-Lac) and coated tablets (TH-Lac-A_{50}) (n = 5)

Parameter	IV-TH	Oral TH-Lac	Oral TH-Lac-A_{50}
Cmax (μg/mL)	21.15 ± 1.99	14.79 ± 1.36	8.93 ± 1.91
Tmax (hr)	0.25 ± 0.00	3.40 ± 0.55	13.60 ± 1.67
AUC_∞ (μg•hr/mL)	116.54 ± 25.88	146.89 ± 19.42	141.33 ± 27.97
MRT (hr)	7.70 ± 1.16	11.25 ± 1.47	15.65 ± 1.72

dissolution of drug from TH-Lac uncoated tablet was completed within 2.5 hours which was much shorter than the coated tablets. The result showed that the drug continuously released from the micropore-controlled release tablets for 24 - 36 hours dependent of the type of excipient, which was in the order of TH-Lac-A_{50} > TH-K90-A_{50} - TH-K30-A_{50} > TH-A_{50} > TH-KCl-A_{50} - TH-Sta-A_{50}. Lactose enhanced theophylline solubility and increased the osmotic pressure of the drug core which made a positive contribution for drug release. Although potassium chloride produced the highest osmotic pressure in the drug core, the salting-out effect and quick release of KCl from the drug core resulted in slight reduction of drug release. The similar result was also observed with starch as the excipient. Although starch was able to absorb water and allowed tablet disintegration, its low water solubility hindered drug release from micropores. The release data up to 60% drug released were further fitted by equation (1), and the *n* values were in the range of 0.8 - 0.9. The model for drug release from micropore-controlled release tablets was further proposed in Figure 4. CA was a semipermeable membrane which allowed water to penetrate into the drug core at beginning. Simultaneously, the pore-forming agent PEG started to dissolve and leach out of the coating film after contact with the medium, and the micropores were formed in the CA films. These micropores not only enhanced water diffusion into drug core to dissolve drug, but also provided the route for drug release from the micropore-controlled release tablets.

II. *Pharmacokinetic Property of Micropore-controlled Release Tablet*

The TH-Lac-A_{50} coated tablet was further applied to *in vivo* animal study, where the lactose was incorporated in the drug core and the composition of coating film was $CA_{50\%}/PEG_{50\%}$. Figure 5 shows the plasma drug concentration after intravenous injection of theophylline solution, oral administrations of uncoated (TH-Lac) and coated (TH-Lac-A_{50}) theophylline tablets respectively. The related pharmacokinetic parameters are listed in Table 2. The highest drug concentration appeared at the beginning followed by quick

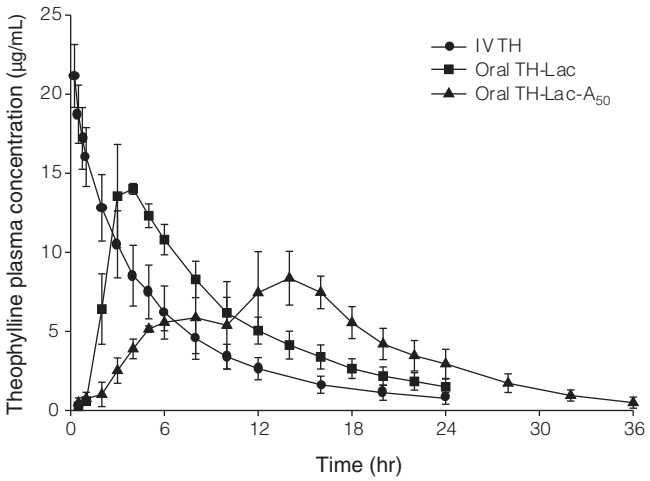

Figure 5. Plasma drug concentrations after intravenous injection of theophylline solution or oral administration of uncoated tablets (TH-Lac) and coated tablets (TH-Lac-A_{50}).

reduction within 24 hours after intravenous injection. Oral administration of uncoated tablet (TH-Lac) reduced the maximum concentration (C_{max}) from 21.15 ± 1.99 to 14.79 ± 1.36 μg/mL. Oral administration of coated tablet (TH-Lac-A_{50}) further reduced the maximum concentration to 8.93 ± 1.91 μg/mL, and the time to reach C_{max} was postponed from 3.40 ± 0.55 to 13.60 ± 1.67 hr. The mean residence time (MRT) was prolonged from 11.25 ± 1.47 to 15.65 ± 1.72 hr after oral administration of coated tablets, but there was no significant difference in AUC_∞ between coated and uncoated tablets. Obviously more lasting and less fluctuation of plasma drug concentrations were observed after administration of coated TH-Lac-A_{50} tablets. The correlation between the percentage of drug absorbed *in vivo* and the percentage of drug released *in vitro* is shown in Figure 6. Both showed a good *in vitro-in vivo* correlation with the equation y = 1.068x - 6.795 with a correlation coefficient of 0.989.

CONCLUSIONS

The micropore-controlled release tablet continuously released drug for 24-36 hours dependent of the type

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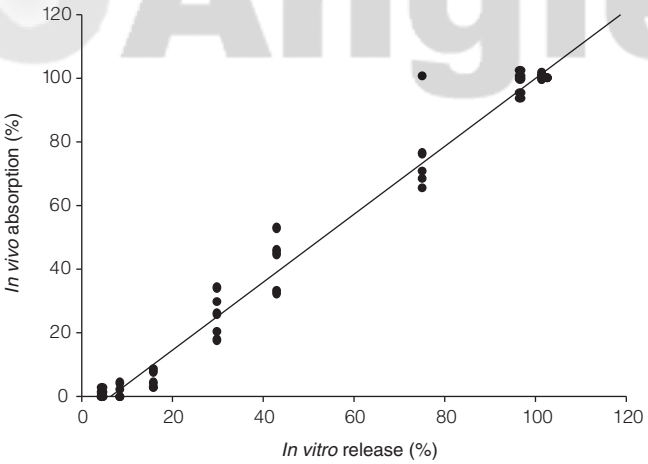

Figure 6. *In vitro-in vivo* correlation of theophylline released from micropore-controlled release tablets.

of excipient in the drug core and the composition of the coating film. Incorporation of lactose in the drug core enhanced drug release from micropore-controlled release tablets. The porous structure built on the CA film dominated theophylline release from the micropore-controlled release tablets. The importance of micropores on the semipermeable CA films not only enhanced water diffusion into drug core to dissolve drug, but also provided the route for drug release from the micropore-controlled release tablets. The animal study showed that TH-Lac-A_{50} micropore-controlled release tablets reduced the maximum concentration, delayed the time to reach C_{max} and prolonged MRT *in vivo*.

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