

## Drug Release from Hydroxypropyl Cellulose and Polyethylene Oxide Capsules: *In Vitro* and *In Vivo* Assessment

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### ABSTRACT

In this study, hard capsule shells produced using a heat-melting method, which involved heating polyethylene oxide (PEO, with a molecular weight (MW) of 200,000) or hydroxypropyl cellulose (HPC, with MWs of 80,000, 100,000, and 370,000) powder in a mold, followed by inserting a suitably sized pestle in the mold in order to coat the melted shell materials (HPC or PEO) onto the pestle with a certain force. The water uptake and dissolution tests of these capsule shells were evaluated in acidic buffer, basic buffer, and water. Theophylline was selected as the model drug. The drug release rate decreased with increasing viscosity grades of HPC used as the shell material. *In vivo* studies were conducted in rabbits with the novel capsules, and comparisons were made with gelatin capsules. It was found that the pharmacokinetic parameters, including  $AUC_{0-\infty}$  and  $T_{1/2}$ , showed no significant differences among the various capsules. Correlations between the *in vitro*  $T_{D50}$  values and several *in vivo* parameters were established.

**Key words:** Hard capsules; Polyethylene oxide; Hydroxypropyl cellulose; Heat-melting method; Dissolution; Theophylline; Pharmacokinetics.

### INTRODUCTION

Gelatin has been used as a material for hard capsules since the late 19th century.<sup>1</sup> Gelatin is of animal origin, from either bovine bone or porcine skin.<sup>2</sup> Recently, several plant-derived materials have been tested to fully replace or modify gelatin as the shell material of capsules. Most novel capsule materials are based on water-soluble cellulose derivatives, such as methylcellulose<sup>3</sup> and hydroxypropyl methyl

cellulose (HPMC).<sup>4</sup> Other materials such as starch<sup>5</sup> and dextrans<sup>6</sup> have also been examined. It was reported that the dissolution of HPMC capsules in water or gastric fluids at 37 °C was only slightly longer than that of gelatin capsules.<sup>7</sup> Also, theophylline release from HPMC capsules filled with lactose was slower than that from gelatin capsules.<sup>8</sup> In bioavailability studies, it was reported that with the oral administration of ibuprofen filled with lactose in rabbits, there were no significant differences in pharma-

cokinetic parameters.<sup>9</sup>

Non-ionic cellulose derivatives such as hydroxypropyl cellulose (HPC) have been used in controlled-release formulations and as film coatings.<sup>10</sup> In a previous study, different viscosity grades of HPC were used as the material for film coatings, and the drug release lag time was prolonged with increasing viscosity grade in both the *in vivo* dissolution test and the *in vivo* bioavailability study.<sup>11</sup> Polyethylene oxide (PEO) is a water-soluble macromolecular polymer and has been used in formulations of controlled-release products.<sup>12</sup> In this study, we attempted to use both HPC and PEO as capsule shell materials. Previously, we described the application of a heat-melting method for the manufacture of hard capsules from hydroxypropyl cellulose (HPC) or polyethylene oxide (PEO).<sup>13</sup>

For comparative purposes, the *in vitro* dissolution rates and *in vivo* absorption profiles of the new capsules and traditional hard gelatin capsules were evaluated using theophylline as the model drug. Also the characteristics of the drug release performances from HPC or PEO capsules were determined.

## EXPERIMENTAL PROCEDURES

### Materials

Hydroxypropyl cellulose (HPC) with molecular weights of 80K, 100K, and 370K (lots 09604HU, 02705AI, and 12807MU, respectively) and polyethylene oxide (PEO) with a molecular weight of 200K (lot 06725JO) were purchased from Aldrich, USA. Theophylline (lot 80k1367, Sigma, Germany) was used as the model drug. Lactose (lot 421006207, Borculo Domo, Holland) and Avicel 102 (lot 40742, Mintai, Taiwan) were utilized as diluents. No. 2 gelatin hard capsules were provided by Dah Feng Capsule Industry Co. All of the other chemicals were of analytical quality.

### Preparation of the HPC Capsule Shells

PEO (200K) and HPC (80K, 100K, and 370K) were melted by heating them to above their respective melting temperatures. Hard HPC or PEO capsule shells were prepared by the same melting method for which we previously had been granted a US Patent.<sup>13</sup> The apparatus used in this study consisted of two major parts, as shown in Fig. 1: (1) a mold, which contains an opening shaped as a capsule cap, and (2) a capsule-forming pestle also shaped as a capsule cap or a capsule body, but its diameter was slightly smaller than the mold opening. Both the mold and the capsule-forming pestle were made of stainless steel. A hard capsule shell was prepared by the following procedures. About 60 mg of HPC or PEO was added to the opening of the mold; the diameter of the opening of the mold corresponds with intended capsule shell size. The mold and a capsule-forming pestle with a diameter equal to the internal diameter of a no. 2 capsule shell were heated. The pestle was inserted into the mold while the polymer was in a melted condition, with pressure so that the melted polymer was evenly coated onto the pestle. The pestle was withdrawn from the mold, by a pulling device connected to the pestle. (3) After the capsule-forming composition had cooled on the pestle, the dried capsule was removed from the pestle.

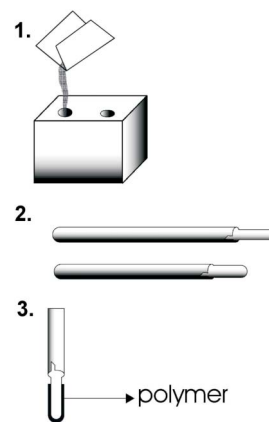


Fig. 1. Capsule-forming devices. (1) Mold; (2) pestle of the capsule cap and body; (3) pestle coated with polymer.

### Water Uptake and Swelling of Capsule Shells

Water uptake by the empty capsule was determined using an equilibrium weight gain method. The study was performed in the various media including acid medium of 0.1 N HCl (pH 1.2), basic medium of 0.1 N tris-(hydroxymethyl)-aminomethane buffer (pH 6.8), and water at  $37 \pm 0.5$  °C.<sup>14</sup> The water uptake percentage was calculated according to the following equation:

$$\text{Water uptake (\%)} = \frac{W_t - W_o}{W_o} ;$$

where  $W_t$  is the weight of the swollen capsule at time,  $t$ , and  $W_o$  is the initial weight of the capsule. The saturation time was obtained by determining the point at which no more water was taken up.

### *In vitro* Dissolution Tests

Drug dissolution from the HPC, PEO, and gelatin capsules was carried out in a dissolution tester with an automatic sampler device (Model VK 7000E, Van-Kel Industries) using a U.S.P paddle method with 900 mL of dissolution medium (including 0.1 N HCl (pH 1.2)), tris(hydroxymethyl)-aminomethane buffer (pH 6.8), and water at a temperature of  $37 \pm 0.5$  °C. The rotation speed was set at 50 rpm. The dissolution medium was automatically withdrawn, and the results were determined at set intervals. The dissolution samples were monitored by a UV spectrophotometer at a wavelength of 273 nm for theophylline. The lag time was defined as the intersection on the time axis of the portion of the straight line of the dissolution curve extended to the time axis, and the dissolution rate of theophylline was calculated from the slope of the linear portion.

### *In vivo* Experiments

New Zealand rabbits weighing 2.1~3.0 kg were

used in this study. Animals were starved for 24 h prior to administration of the drug. Each rabbit was given a single dose of 10 mg/kg theophylline with lactose in a capsule, which was ingested with 20 mL water orally through a catheter. Water was provided ad libitum during starvation and throughout the experiment. Blood samples (1.5 mL each) were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, and 36 h from the rabbit ear vein following drug administration. Plasma was separated with a centrifuge (Heraeus Instrument, Biofuge Primo, Germany) at 4000 rpm for 20 min and then stored at -20 °C until being assayed.

### Analysis of Theophylline in Plasma

Plasma samples were assayed for theophylline according to a modified high-performance liquid chromatographic (HPLC) method.<sup>15</sup> After thawing at room temperature, an aliquot of each sample (200 µL) was pipetted into a glass tube, and 20 µL of  $\beta$ -hydroxyethyl theophylline (100 µg/mL) was added as the internal standard. Then 100 µL of trichloroacetic acid (60 mg/mL) was added to each sample and vortexed again for 60 s. After centrifuging for 20 min at 4000 rpm, 100 µL of the supernatant was injected into the HPLC system. The HPLC system consisted of a pump (Hitachi model L7100) HPLC, an autosampler (Hitachi model L-7400), and a UV detector (Hitachi model L7200) set at 273 nm. The chromatography for the separation and determination of the drug was carried out by applying the samples to a Purospher®star C18 (5 µm, 4.6 × 250 mm) column (Merck, Germany). The mobile phase consisted of an isocratic mixture of a 0.1% acetic acid aqueous solution and acetonitrile (6.5:93.5, v/v, pH = 3.4), and a flow rate of 1.0 mL/min was found to be adequate for the analysis of the samples. The limit of quantification was 0.2 µg/mL, and the standard curve was linear over the range of 0.2 to 20.0 µg/mL.

### Pharmacokinetic Parameters

The plasma theophylline concentration data were analyzed using the WinNolin program. Parameters evaluated included the time to the maximum concentration ( $T_{\max}$ ) and the maximum value of the plasma concentration ( $C_{\max}$ ). The area under the concentration-time curve from time zero to time  $t$  ( $AUC_{0-t}$ ) was calculated using the linear trapezoidal rule. The area from time  $t$  to infinity was estimated by  $Ct/Kel$ , where  $Ct$  is the serum theophylline concentration observed at the last time point,  $t$ , and  $Kel$  is the apparent elimination rate constant of theophylline obtained from the slope of the log linear portion of the curve by a least squares regression analysis. Moreover, the percent of the drug absorbed was calculated by Nelson's analysis:<sup>16</sup>

$$\text{Percent absorbed} = \frac{C(t)}{Kel \times AUC_{0-\infty}} + AUC_{0-t} \times 100.$$

The relative bioavailability ( $F$ ) was evaluated as the ratio, expressed as a percentage, of the dose-corrected AUC from zero to an infinite time for orally administered gelatin capsules *vs.* that of the PEO 200K, HPC 80K, HPC 100K, and HPC 370K capsules.

### Statistical Analysis

The correlation coefficients of the regression lines between the *in vitro* dissolution parameters and the *in vivo* parameters were obtained by the linear least squares method. The correlation coefficients

were examined for their significance with a  $t$ -test.  $p$  values lower than 0.05 were considered significant. Where mean results are given, the values shown are the mean  $\pm$  standard deviation (s.d.). Comparisons were made using analysis of variance (ANOVA) procedures appropriate to the final balance of each study. Results were judged to be significant based upon a 95% probability ( $p \leq 0.05$ ).

### RESULTS AND DISCUSSION

The main physical characteristics of the various capsules are shown in Table 1. There were no significant differences in the lengths of the caps and bodies, or wall thicknesses among all kinds of capsules evaluated. The water contents of the PEO 200K, HPC 80K, HPC 100K, and HPC 370K capsules were all below 8.2%. It was reported that the water content of commercial gelatin capsules are about 14%.<sup>17</sup> Obviously, the water content of the PEO and HPC capsules were significantly lower than that of hard gelatin capsules. A lower water content can minimize problems when using moisture-sensitive drugs. The hardness values of the various capsules were measured, and the rank of the hardness of these capsules was in the order of HPC 370K > PEO 200K > HPC 100K > HPC 80K. The hardness of the HPC capsules increased with the molecular weight of the HPC. Among all capsules, the HPC 370K capsules possessed the highest hardness.

Polymer capsules such as HPMC capsules usu-

**Table 1. Physical characteristics (mean  $\pm$  s.d.) of various capsule**

Parameter	PEO 200K	HPC 80K	HPC 100K	HPC 370K
Mean length of body (mm)	15.12 $\pm$ 0.24	15.0 $\pm$ 0.22	15.25 $\pm$ 0.37	15.14 $\pm$ 0.38
Mean length of cap (mm)	9.28 $\pm$ 0.37	9.17 $\pm$ 0.37	9.19 $\pm$ 0.36	9.27 $\pm$ 0.34
Thickness (mm)	0.10 $\pm$ 0.01	0.10 $\pm$ 0.01	0.11 $\pm$ 0.01	0.10 $\pm$ 0.01
Hardness (N)	6.5 $\pm$ 0.2	5.0 $\pm$ 0.2	5.3 $\pm$ 0.1	8.0 $\pm$ 0.2
Moisture (%)	8.2 $\pm$ 1.5	8.1 $\pm$ 0.4	7.8 $\pm$ 0.9	7.6 $\pm$ 0.5
Dissolution lag time (min)	3.7 $\pm$ 0.5	4.5 $\pm$ 0.2	5.9 $\pm$ 0.8	20.8 $\pm$ 2.9

ally dissolve evenly across the shell.<sup>8</sup> The dissolution of both PEO and HPC capsules showed a similar mechanism to that of HPMC capsules. The swelling of the polymer shell depends on the rate of water penetration into the shell. The water penetration measurement has primarily been used to evaluate polymer-penetration interactions that enable the capsule shell to dissolve. The water saturation time for all kinds of capsules showed no significant differences among the acidic buffer (pH 1.2), the basic buffer (pH 6.8), and water. A faster water uptake rate of capsules resulted in a shorter water uptake saturation time. The results showed that the rank of water uptake saturation times was in the order of HPC 370K ( $10.4 \pm 1.2$  min) > HPC 100K ( $2.9 \pm 0.5$  min) > HPC 80K ( $1.6 \pm 0.4$  min) > PEO 200K ( $1.3 \pm 0.3$  min) > gelatin capsule shells ( $0.6 \pm 0.1$  min). The HPC 370K capsule shell possessed the longest water saturation time. This indicates that while HPC 370K had the highest molecular weight, and it also had the longest saturation time of water uptake compared to the other types of HPC capsules.

Fig. 2 shows the release patterns of theophylline from capsules prepared with lactose as the excipient filled in the gelatin, PEO 200K, HPC 80K, HPC 100K, and HPC 370K capsules. Dissolution tests were performed in acidic medium (pH 1.2), ba-

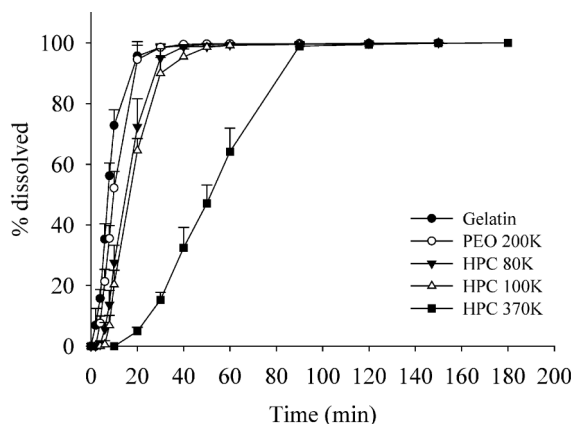


Fig. 2. Release patterns of theophylline prepared with lactose as the excipient in acidic (pH 1.2) medium.

sic medium (pH 6.8), and water. Gelatin capsules achieved 50% release at about  $7.5 \pm 0.4$  min; those for HPC 80K, 100K, and 370K capsules were about  $15.3 \pm 1.6$ ,  $16.8 \pm 0.8$ , and  $51.7 \pm 3.7$  min, respectively; and that for PEO 200K capsules was about  $9.8 \pm 0.7$  min. Complete dissolution of gelatin and PEO 200K capsules took about 40 min, and for HPC 80K, 100K, and 370K capsules took about 50, 60, and 90 min, respectively.

Table 2 shows the release parameters of the model drugs from the gelatin, PEO 200K, HPC 80K, HPC 100K, and HPC 370K capsules. Theophylline was completely released from all kinds of capsules in 40 min except that from HPC 370K. The release rate of theophylline from these capsules did not appear to be markedly affected by the gastrointestinal pH. It was reported that the higher the viscosity of the gel present, the more resistant the gel is to being diluted or eroded; hence, the dissolution of the HPC hard capsule shells is a rate-limiting factor in drug release.<sup>11</sup> The water uptake saturation time and lag time of HPC capsules indicated that these parameters increased with increasing viscosity grade. Because a higher viscosity film forms a stronger barrier, the rate of drug release becomes slower. HPC 370K had the largest molecule weight and higher viscosity of all three kinds of HPC. It was shown that the HPC 370K capsules had the longest lag time and the slowest drug release rate among the three types of HPC capsules.

Fig. 3 shows the correlation between the capsule shell dissolution lag time and time at which 50% of the theophylline had dissolved ( $T_{D50}$ ) in water. Gelatin capsules had the shortest dissolution lag time ( $3.1 \pm 0.4$  min) and  $T_{D50}$  ( $8.2 \pm 0.6$  min). In contrast, HPC 370K had the longest lag time ( $20.8 \pm 0.4$  min) and  $T_{D50}$  ( $50.4 \pm 4.3$  min) among all capsules tested. This indicates that the capsule exhibiting a shorter dissolution lag time has a shorter  $T_{D50}$ .

Water-soluble polymers such as HPC have been

**Table 2. The dissolution parameter of theophylline in various capsules in acidic (pH 1.2), basic buffer (pH 6.8) and water**

	pH 1.2		pH 6.8		Water	
	k (%/min)	T <sub>D50</sub> (min)	k (%/min)	T <sub>D50</sub> (min)	k (%/min)	T <sub>D50</sub> (min)
Gelatin	9.60 ± 0.85	7.5 ± 0.4	9.67 ± 0.63	8.0 ± 0.2	10.00 ± 1.46	8.2 ± 0.6
PEO 200K	7.71 ± 0.42	9.8 ± 0.7	7.84 ± 0.32	10.5 ± 0.5	8.55 ± 0.96	9.6 ± 0.7
HPC 80K	4.75 ± 0.5	15.3 ± 1.6	4.76 ± 0.4	15.8 ± 0.8	4.85 ± 0.76	15.0 ± 1.8
HPC 100K	4.68 ± 0.13	16.8 ± 0.8	4.52 ± 0.26	17.6 ± 0.9	4.74 ± 0.25	16.5 ± 0.8
HPC 370K	1.61 ± 0.16	51.7 ± 3.7	1.65 ± 0.32	53.9 ± 5.2	1.73 ± 0.33	50.4 ± 4.3

utilized for the production of press-coated tablets for many years.<sup>11</sup> Theoretically, a lag time is required for the film barrier to become permeable enough to release drug for press-coated tablets. The lag time is also a function of the thickness and hydration rate on the film barrier as predicted by the Noyes-Whitney equation. The lag time for capsules was also observed upon the dissolution test with various capsules filled with theophylline and lactose. The lag time was defined as the intersection on the time axis of the linear portion of the dissolution curve extended to the time axis. After the lag time, the drug begins releasing from the capsules. Table 1 shows that the rank of the lag times observed was in the order of HPC 370K > HPC 100K > HPC 80K > PEO 200K > gelatin capsule shells in water. The lag time for HPC capsules increased with an increasing vis-

cosity grade of the polymers. Gelatin capsules had a shorter saturation time ( $0.6 \pm 0.1$  min) and dissolution lag time ( $3.1 \pm 0.4$  min), whereas HPC 370K had the longest saturation time ( $10.4 \pm 1.2$  min) and dissolution lag time ( $20.8 \pm 0.4$  min). Fig. 4 shows the statistically significant correlation ( $r^2 = 0.995$ ) between the capsule shell water saturation time and dissolution lag time in water. This indicates that an increasing water saturation time of the capsule leads to an increase in the dissolution lag time.

The mean plasma concentration versus time curves obtained in six rabbits for various types of capsules are shown in Fig. 5. The pharmacokinetic profiles of theophylline absorbed from these capsules was rapid except for that made of HPC 370K. An open one-compartment model best described the disposition of the oral absorption of theophylline

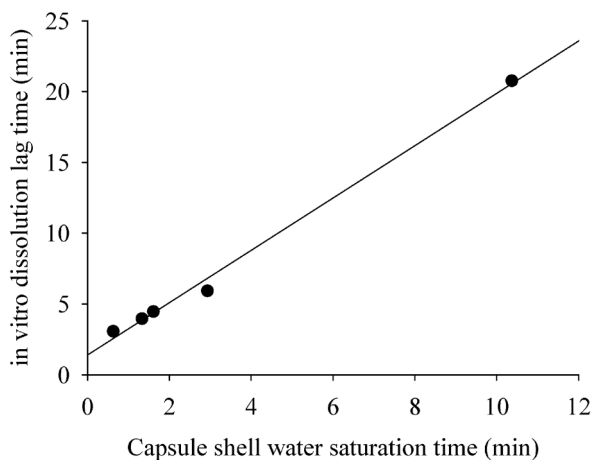


Fig. 3. Correlation between the capsule shell water saturation time and dissolution lag time.

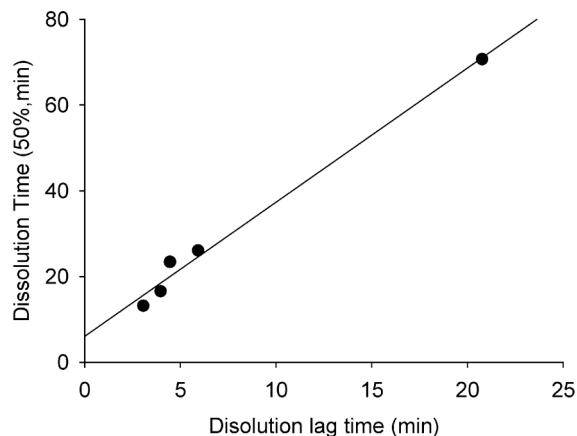


Fig. 4. Correlation between the capsule shell dissolution lag time and theophylline dissolution 50% time (T<sub>D50</sub>).

**Table 3. Pharmacokinetic parameters of theophylline in various capsules in rabbits**

Parameter	Gelatin	PEO 200K	HPC 80K	HPC 100K	HPC 370K
$C_{\max}$ ( $\mu\text{g/mL}$ )	$13.15 \pm 1.64$	$12.25 \pm 1.07$	$12.05 \pm 1.31$	$11.54 \pm 1.20$	$7.19 \pm 0.61$
$T_{\max}$ (h)	$2.12 \pm 0.33$	$2.16 \pm 0.27$	$2.48 \pm 0.54$	$2.53 \pm 0.50$	$6.56 \pm 0.67$
$AUC_{0-t}$ ( $\mu\text{g}\cdot\text{h/mL}$ )	$121.92 \pm 11.46$	$117.07 \pm 6.96$	$120.06 \pm 7.33$	$117.42 \pm 6.47$	$109.61 \pm 9.30$
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{h/mL}$ )	$124.31 \pm 11.24$	$120.01 \pm 7.80$	$122.31 \pm 7.55$	$119.72 \pm 6.69$	$112.02 \pm 9.37$
$T_{1/2}$ (h)	$5.29 \pm 0.41$	$5.49 \pm 0.37$	$5.46 \pm 0.5$	$5.55 \pm 0.40$	$5.68 \pm 0.45$
CL (L/h)	$0.217 \pm 0.017$	$0.214 \pm 0.010$	$0.210 \pm 0.023$	$0.223 \pm 0.026$	$0.233 \pm 0.027$

from these capsules.<sup>18</sup> The results of bioavailability and pharmacokinetic parameters ( $C_{\max}$ ,  $T_{\max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $T_{1/2}$ , and CL) of the various capsules in rabbits are given in Table 3. The plasma level of theophylline in gelatin capsules rose quickly, and the  $C_{\max}$  ( $13.15 \pm 1.64 \mu\text{g/mL}$ ) was reached by  $2.12 \pm 0.33$  h after administration. The plasma level of theophylline in PEO 200K capsules also rose quickly, and the  $C_{\max}$  ( $12.25 \pm 1.07 \mu\text{g/mL}$ ) was reached at  $2.16 \pm 0.27$  h after oral administration. The  $C_{\max}$  values of theophylline from the HPC 80K, 100K, and 370K capsules were  $12.05 \pm 1.31$ ,  $11.54 \pm 1.20$ , and  $7.19 \pm 0.61 \mu\text{g/mL}$  respectively, with  $T_{\max}$  values of  $2.48 \pm 0.54$ ,  $2.53 \pm 0.50$ , and  $6.56 \pm 0.67$  h respectively. The  $C_{\max}$  and  $T_{\max}$  values from gelatin capsules showed no significant differences with the PEO 200K and HPC 80K capsules. The  $C_{\max}$  obtained from gelatin capsules was markedly higher than those of HPC 100K and HPC 370K capsules.

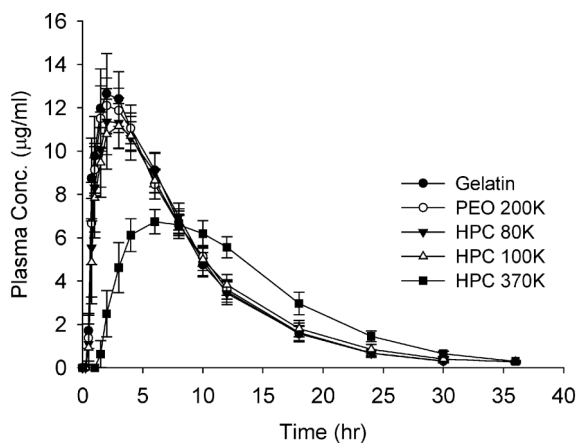


Fig. 5. Mean plasma concentration-time curves for the various capsules.

This also indicates that the rank of the absorption rate observed was in the order of gelatin capsule > PEO 200K > HPC 80K > HPC 100K > HPC 370K capsule. The HPC 370K capsule showed the slowest absorption rate among all capsules. Insignificant differences among those capsules in AUC,  $T_{1/2}$ , and CL values were also shown. It was concluded that these different capsule materials only affected the absorption rate of theophylline from the capsules after oral administration.

The Wagner-Nelson equation provides a means of estimating the cumulative relative fraction of drug absorbed when there is a monoexponential decline describing the elimination of the drug. In the *in vivo* evaluation studies, the percentage of drug absorbed was calculated from the fraction of the area under the curve (AUC) at each time interval. At time  $t$  ( $T_{F0.5}$ ), the fifty percent of drug absorbed was cal-

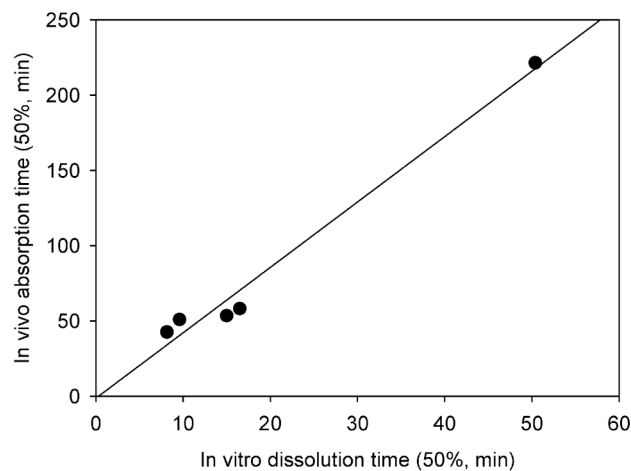


Fig. 6. Correlation between  $T_{D50}$  *in vitro* and  $F_{0.5}$  time of the various capsules in rabbits.

culated using the Wagner-Nelson analysis. Statistically significant correlations between the *in vitro* parameter ( $T_{D50}$ ) and *in vivo* parameters ( $C_{max}$ ,  $T_{max}$ , and  $T_{F0.5}$ ) of various capsules were demonstrated. The *in vivo* parameter,  $C_{max}$ , showed a very high correlation ( $r^2 = 0.989$ ) with  $T_{D50}$  for the five capsules, which were fitted in the equations obtained:  $y = 14.074 - 0.144x$ . The *in vivo* parameters of  $T_{max}$  and  $T_{F0.5}$  also showed very high correlations with the *in vitro* parameter,  $T_{D50}$ , for the three kinds of HPC capsules, which were fitted in the equations obtained:  $y = -2.502 + 4.497x$  and  $y = 0.861 + 0.116x$ , respectively. This indicated that capsules have a 50% faster dissolution time, and thus they can reach the maximum plasma concentration faster and also have a higher  $C_{max}$ . The results suggest that the dissolution process of capsules is the rate-determining step in drug absorption.

## CONCLUSIONS

Two-piece hard capsules made of HPC and PEO were successfully prepared by the heat-melting method. The low water content of the HPC and PEO capsules can overcome problems often encountered with gelatin capsules. Theophylline filled in HPC and PEO capsules showed statistically significant correlations between *in vitro* dissolution test and *in vivo* pharmacokinetic study. PEO and low-molecular-weight HPC capsules might prove to be useful alternatives to their gelatin counterpart.

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