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Colon Delivery Efficiencies of Intestinal Pressure-controlled Colon Delivery Capsules Prepared by a Coating Machine in Human Subjects

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Abstract

Large quantities of pressure-controlled colon delivery capsules (PCDCs) were prepared by a Hicoater-mini pharmaceutical coating machine and colon delivery efficiencies were evaluated in man. Caffeine powder as a model drug was suspended with a polyethylene glycol (PEG) 1000 suppository base at 50°C, and was hardened in no. 0- and no. 2-sized capsular shapes. The capsule-shaped suppositories were coated with 5% w/v ethanolic ethylcellulose (7G grade) solution using the coating machine.

By increasing the coating weight of ethylcellulose from 28·6 ± 1·1 mg to 45·3 ± 0·2 mg, the mean coating thickness of no. 0 PCDCs increased from 56 ± 1 μm to 64 ± 1 μm. With no. 2 PCDCs, the mean coating thickness increased from 50 ± 1 μm to 57 ± 1 μm by increasing the coating weight of ethylcellulose from 8·1 ± 0·5 mg to 11·2 ± 0·3 mg. The no. 0 PCDCs, having a mean ethylcellulose coating membrane thicknesses of 56 ± 1 μm (type 1) and 64 ± 1 μm (type 2), as well as no. 2 PCDCs, having thicknesses of 50 ± 1 μm (type 3) and 57 ± 1 μm (type 4), were used for in-vivo evaluation in man. After oral administration of test preparations containing 75 mg of caffeine, saliva samples were obtained and salivary caffeine levels were measured by an HPLC method. The first appearance time, Ti, of caffeine in the saliva was used as a parameter for the estimation of the release time of caffeine from PCDCs in the gastrointestinal tract. The mean Ti values of no. 0 PCDCs were 3·3 ± 0·3 h for type-1 and 5·3 ± 0·3 h for type-2 preparations while the mean Ti values of no. 2 PCDCs were 4·3 ± 0·5 h for type 3 and 5·3 ± 0·3 h for type 4. There were good correlations between ethylcellulose coating membrane thicknesses and in-vivo Ti values. A colon arrival time of 5 h was reported in our subjects by gastrointestinal magnetomarkergraphy.

PCDCs having a mean coating thickness of 64 ± 1 μm for no. 0 capsules and of 57 ± 1 μm for no. 2 capsules were thought to deliver caffeine to the human colon efficiently.

We have been studying a unique colon delivery system in which drug release occurs following the disintegration of a water-insoluble polymer membrane as the result of colon luminal pressure. The system was prepared by coating capsule-shaped suppositories with ethylcellulose solution, where the thickness of the ethylcellulose coating membrane determines tolerability to luminal pressure (Matsuda et al 1996; Takaya et al 1997). Therefore, we called these capsules intestinal luminal pressure-controlled colon delivery capsules (PCDCs). In PCDCs, the drug is dissolved or suspended with a hydrophilic or lipophilic suppository base such as polyethylene glycol (PEG) 1000, Witepsol or Pharmasol. After oral administration, therefore, the system behaves like an ethylcellulose balloon containing drug solution, since these suppository bases dissolve at body temperature. The fluidity inside the upper gastrointestinal tract, is such that the ethylcellulose balloon is not directly subjected to intestinal luminal pressures. However, reabsorption of water occurs in the colon and the viscosity of the luminal contents increases (Digenis & Sandefer 1991; Ritschel 1991; Moës 1993). As a

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result, intestinal pressure due to peristalsis directly affects the ethylcellulose balloon. Since the ethylcellulose balloon cannot tolerate these pressures, it disintegrates in the colon wherein intestinal luminal pressure is high. Therefore, the thickness of the water-insoluble ethylcellulose membrane is the most important factor for the disintegration of the balloon in the colon.

In our previous reports, a new method for preparing PCDCs on a large scale using a coating machine was developed and these PCDCs were evaluated in beagle dogs (Hu et al 1998). Because the ethylcellulose coating membranes obtained were more porous than those produced by conventional methods (Matsuda et al 1996; Takaya et al 1997), it was necessary to perform a human study to optimize the system before application to patients suffering from colon-specific diseases.

In this report, five kinds of PCDCs of sizes no. 0 and no. 2 were prepared by a coating machine and the colon delivery efficiency was evaluated in human subjects using caffeine as a model drug.

Materials and Methods

Materials

Gelatin capsules (no. 0 and no. 2) were obtained from Shionogi Qualicaps Co. Ltd (Yamato kouriyama, Japan). Caffeine and ethanol were obtained from Kanto Chemical Co. Ltd (Tokyo, Japan). Polyethylene glycol (PEG) 1000 and starch were obtained from Nacalai Tesque Inc. (Kyoto, Japan). Ethylcellulose (7G grade) was a gift from Nisshin Chemical Industrial Co. Ltd (Osaka, Japan). Magnesium silicate was obtained from Kyowa Chemical Co. Ltd (Tokyo, Japan). All other materials used were of reagent grade and were used as received.

Preparation of PCDCs by a coating machine

Preparation of capsule-shaped PEG-1000 suppositories containing caffeine Two kinds of caffeine suspensions were prepared. For no. 0 capsules, 9·4 g of caffeine was suspended with 100 g of PEG 1000 at 50°C and the suspension was introduced into a stainless-steel mold which was the same size as the no. 0 gelatin capsule. Similarly, 17·9 g of caffeine was suspended with 100 g of PEG 1000 and enclosed in a stainless-steel mold of the same size as the no. 2 gelatin capsule. A steel stick (1 mm o.d., 25 mm length) was inserted into the mold to make an air space to prevent volume changes which occur during melting of the suppository base. After the caffeine suspension in PEG 1000 was hardened at 10°C in a refrigerator, PEG 1000 capsules were removed from the mold. Thereafter, the steel stick was withdrawn and a small solid mass of PEG 1000 was used to seal the surface. Diameters of PCDCs were $7{\cdot}0 \pm 0{\cdot}1$ mm for no. 0 and $5{\cdot}5 \pm 0{\cdot}1$ mm for no. 2, lengths were $20{\cdot}7 \pm 0{\cdot}2$ mm for no. 0 and $17{\cdot}0 \pm 0{\cdot}2$ mm for no. 2 and weights were $812{\cdot}8 \pm 13{\cdot}9$ mg for no. 0 and $455{\cdot}0 \pm 11{\cdot}1$ mg for no. 2. The content of caffeine was $75{\cdot}0 \pm 0{\cdot}5$ mg per capsule.

Ethylcellulose membrane fabrication The capsule-shaped suppositories made of caffeine and PEG 1000 were incorporated into ethylcellulose membranes. The coating machine used in this study was a Hicoater-mini (Freund Ind. Co. Ltd, Tokyo, Japan). The operating conditions of the coating machine were as follows: blower temperature was 45 ± 2°C, exhaust temperature was 25 ± 1°C, spray pressure was $2\,\mathrm{kg\,cm^{-2}}$, air-flow rate was $30\,\mathrm{Nl\,cm^{-2}}$ and rotating speed of coating pan was $20\,\mathrm{rev\,min^{-1}}$. The concentration of the ethylcellulose coating solution was 5·0% w/v in ethanolic solution. The flow rate of the ethylcellulose coating solution was basically $2{\cdot}0\,\mathrm{mL\,min^{-1}}$. One batch of coating contained 20 capsule-shaped suppositories and 100 dummies in which starch was introduced to make weights equal to the actual suppositories. As the ethylcellulose coating solution might dissolve the PEG 1000 suppository base, the capsule-shaped suppositories were treated with magnesium silicate powder before the coating process. For one batch of coating, 1 g of magnesium silicate powder was mixed well with the capsule-shaped suppositories and the mixture was treated within the coating machine for 3 min before beginning the actual coating process to whisk away excessively adhered magnesium silicate powder. The ethylcellulose solution was sprayed onto the surface of the caffeine–PEG 1000 capsule-shaped suppositories, on which magnesium silicate was sprinkled, to form an ethylcellulose membrane. The conditions for the coating process were the same with both sizes of PCDCs.

Physical test of the capsules

In-vitro hardness studies The hardness of the PCDCs was determined after the PEG 1000 suppository base was melted to liquid at 37°C. A hardness tester, Digital force gage FGN-2 produced by Simpo Co. Ltd (Kyoto, Japan), was used to

measure the hardness of these pre-treated PCDCs at 37°C.

In-vitro thickness studies The thickness of the ethylcellulose coating membrane was measured after the suppository base was melted and wiped off. The film of capsule was cut into six portions (four portions in the capsule body and two portions in the capsule head and bottom) and the thickness of the ethylcellulose membrane was measured using a digital micrometer, SONY μ-mate (Tokyo, Japan).

Pharmacokinetic studies Eight healthy male subjects, aged 21–26 years (mean 22·8 years), participated in the trial. Xanthine beverages, alcohol and smoking were avoided for 12 h before each study and throughout the study day. Subjects joined the study after receiving an explanation of the study protocol, and informed consent was obtained from each subject before entering the trial.

Volunteers were fasted overnight for at least 12 h. All experiments were carried out at the same time of day, in the morning, to exclude the influences of circadian rhythm. Free access to water was allowed during this experiment. At 10 00 h, test preparations were administered orally in the fasting state with 150 mL of water. At 30 min before the test capsules were administered, blank saliva samples were collected over 1-min intervals. As a stimulant of saliva production, 1 g of parafilm was used at each sampling occasion (Haeckel & Hanecke 1996). Saliva samples were collected hourly thereafter over 1-min intervals up to 10 h. The subjects took lunch and supper at 14 00 h and 20 00 h, respectively. After measuring the volume of saliva, the sample was immediately centrifuged at 13 000 rev min^{-1} for 10 min at 4°C and the clear supernatant was transferred into clean tubes and stored at −20°C until analysed by HPLC.

Saliva caffeine assay
The concentration of caffeine in the saliva samples was determined by an HPLC method that was described in detail in our previous report (Muraoka et al 1998). The human saliva samples were deproteinized by heating at 80°C for 5 min. After centrifugation for 10 min at 4000 rev min^{-1}, the supernatant was obtained. The saliva samples were adjusted to 200 μL with a saturated sodium chloride solution, 5 mL of chloroform was added and caffeine was extracted. Four millilitres of the organic phase was evaporated to dryness under a flow of nitrogen gas. The residue was dissolved with 200 μL of the mobile phase and 100 μL of the reconstituted sample was injected into the HPLC system. A set of six or seven calibration standards was run with each series of unknown samples. The standard curve of caffeine added to each human subject' s saliva was linear over the range of 0·05–2·0 μg mL^{-1} and passed through the origin.

Pharmacokinetic analysis
Pharmacokinetic parameters were determined from the salivary caffeine excretion rate vs time data. The time when saliva drug concentration reached its maximum concentration, T_{max}, and the maximum salivary caffeine excretion rate, R_{max}, were determined from the authentic salivary excretion rate vs time data. The first appearance time, Ti, of caffeine into the systemic circulation was also obtained from the authentic salivary excretion rate vs time data. The area under the salivary excretion rate vs time curve (AUC) and the area under the first-moment curve (AUMC) after oral administration of the test preparation were calculated using the linear trapezoidal rule up to the last measured saliva excretion rate (Yoshikawa et al 1998). The mean residence time (MRT) after oral administration was calculated by AUMC/AUC.

Statistics
All values are expressed as mean ± s.e.m. Statistical differences were assumed to be reproducible when $P < 0{\cdot}05$ (one-sided t-test).

Results and Discussion

Coating conditions for capsule-shaped suppositories
Initially, coating conditions including the concentration and flow rate of ethylcellulose coating solution and the coating temperature, were studied. As ethylcellulose is a water-insoluble polymer, it was dissolved in a mixture of methylene chloride and methanol (1 : 1) which was used in our previous reports (Muraoka et al 1998). Although methylene chloride was the preferred organic solvent, residual solvent in the final product is a potential safety concern when PCDCs are used in clinical studies. Therefore, ethanol was selected as the solvent for ethylcellulose, despite the fact that the boiling point of ethanol is higher than methylene chloride and methanol. The melting point of PEG 1000 is 27°C. Optimum coating temperature was investigated in preliminary experiments, and an exhaust temperature of 25 ± 1°C and blower temperature of 45 ± 2°C were chosen as optimum. Since the Hicoater-mini could not control the temperature inside the coating pan, the temperature of the exhaust air from the machine was monitored.

Therefore, the actual temperature of the coating pan was most likely higher than the exhaust temperature of 25°C.

The concentration of ethanolic ethylcellulose coating solution was also studied. In the case of 10% w/v solution, the viscosity was so high that a coated ethylcellulose membrane of uniform thickness could not be fabricated and the resulting membranes had microporous structures. Due to the porous structure of the ethylcellulose coating membrane, it was thought that the colon luminal pressure would easily destroy these membranes. When 2·5% w/v ethanolic ethylcellulose solution was used for coating, a great deal of time was required because of the low concentration of the coating solution. Therefore, the concentration of the ethylcellulose coating solution was increased to 5·0% w/v and both good handling and coating efficiencies were obtained.

The flow-rate of the coating solution also affected the coating process. In particular, when the flow-rate was high, the solvent in the ethylcellulose coating solution did not immediately evaporate at the coating temperature used, 25 ± 1°C. As a result, the suppositories were dissolved by non-evaporated ethanol and stuck to each other.

From these preliminary experiments, the optimum coating conditions for the capsule-shaped suppositories were determined to be a concentration of ethanolic ethylcellulose solution of 5% w/v, a flow-rate of 2–3 mL min^{-1}, a blower temperature of 45 ± 2°C and an exhaust temperature of 25 ± 1°C.

Suitability of caffeine as model drug for the evaluation of PCDC

Evaluation of the PCDCs prepared on a large scale by a coating machine was performed in man using caffeine as a model drug. To study the absorption rate of caffeine from the gastrointestinal tract into the systemic circulation, plain gelatin capsules containing 75 mg of caffeine were administered to the subjects. Short Ti (0·5 h) and MRT ($2·5 \pm 0·4$ h) values were obtained in these studies. This indicated that caffeine was absorbed quickly from the gastrointestinal tract into the systemic circulation after oral administration. In PCDCs, caffeine was suspended with PEG 1000 and melted at body temperature during passage through the gastrointestinal tract. Therefore, the liberation of caffeine from PCDCs was thought to occur immediately once the PCDC disintegrated in the gastrointestinal tract due to the intestinal luminal pressure resulting from peristalsis. This fast liberation of drug from the system is one of the important characteristics of PCDCs.

In general, pharmacokinetics studies require many blood samplings (i.e., 10–15 samples). Frequent salivary samples can be obtained more easily and safely than blood samples from human volunteers. Several studies have been performed with the salivary excretion of caffeine. Zuidema & van Ginneken (1983) reported that caffeine was excreted into the saliva by a passive transport process with high extraction ratio. Zylber-Katz et al (1984) showed that there was a good correlation between the salivary caffeine concentration and plasma caffeine concentration. Based on these considerations, pharmacokinetic studies on the salivary transport of caffeine are a valuable method for the evaluation of the biological fate of PCDCs in the gastrointestinal tract after oral administration to man.

Relationship between ethylcellulose coating weight and hardness

The physical properties of the PCDCs prepared in this study are shown in Table 1. The ethylcellulose coating membrane thickness was dependent on the coating time with both sizes of PCDCs. By increasing the coating time of the no. 0 PCDCs from 65 min to 80 min, the mean ethylcellulose coating weight increased from $28·6 \pm 1·1$ mg to $45·3 \pm 0·2$ mg and the mean ethylcellulose coating membrane thickness increased from 56 ± 1 μm to 64 ± 1 μm. Using no. 2 PCDCs, the mean ethylcellulose coating weight increased from $8·1 \pm 0·5$ mg to $11·2 \pm 0·3$ mg and $17·2 \pm 1·2$ mg as the

Table 1. Physical properties of prepared PCDCs.

Size	Coating time (min)	Ethylcellulose membrane thickness (μm)	Coating weight (mg)	Hardness (N)
Type 1 (no. 0)	65	56 ± 1	$28·6 \pm 1·1$	$1·51 \pm 0·10$
Type 2 (no. 0)	80	64 ± 1	$45·3 \pm 0·2$	$2·02 \pm 0·12$
Type 3 (no. 2)	35	50 ± 1	$8·1 \pm 0·5$	$1·47 \pm 0·05$
Type 4 (no. 2)	40	57 ± 1	$11·2 \pm 0·3$	$1·83 \pm 0·09$
Type 5 (no. 2)	45	64 ± 1	$17·0 \pm 1·2$	$2·36 \pm 0·09$

Each value represents the mean ± s.e.m. of 6 capsules.

coating time increased from 35 min to 40 and 45 min, respectively. The mean ethylcellulose coating membrane thickness correspondingly increased from $50 \pm 1\ \mu$m to $57 \pm 1\ \mu$m and $64 \pm 1\ \mu$m, respectively. The hardnesses of the prepared PCDCs are also shown in Table 1.

Ethylcellulose has been used in pharmaceutical technology to prepare oral sustained-release preparations and the physicochemical properties of the ethylcellulose membrane formed are dependent on the preparation methods. Ethylcellulose membranes can be prepared by cast methods from ethanolic solutions (Hyppölä et al 1996) or from a chloroform solution (Donbrow & Friendman 1975), or by spraying methods from a pseudolatex coating system (Arwidsson et al 1991; Hutchings et al 1994), from ethanolic solution (Narisawa et al 1994) and from aqueous polymeric dispersions (Obara & McGinity 1994). In our previous studies, ethylcellulose coating of the inner surface of gelatin capsules was performed with 23% w/v ethylcellulose solution prepared in a mixture of methylene chloride and methanol (1 : 1). The results of these previous studies in man on the in-vivo evaluation of PCDCs that were prepared manually demonstrated that the optimum ethylcellulose coating membrane thickness for the disintegration of no. 0 PCDCs in the colon was approximately $40 \pm 1\ \mu$m, and that they had a mean hardness of 1·67 N (Muraoka et al 1998). Because PCDCs were prepared by coating the inner surfaces of gelatin capsules with ethylcellulose solution, the ethylcellulose film was compactly formed inside the capsules. On the other hand, with the spray-coating method, ethanol was used as a solvent for ethylcellulose and was thought to evaporate before it arrived at the surface of the suppositories. Therefore, a porous ethylcellulose membrane was formed on the surface of the capsule-shaped suppositories. If the ethylcellulose membrane coating was performed at the same thickness as we reported in previous studies, the ethylcellulose membrane structure would be fragile when PCDCs were subjected to colon luminal pressures. Ethylcellulose film porosity was one of the factors affecting drug release from the preparation, which was also reported by Narisawa et al (1994). To obtain strong membranes which could tolerate pressures in the small intestine, the membrane thickness must be greater than those present in PCDCs prepared manually.

When nozzles of different sizes are used for the fabrication process, the relationship between ethylcellulose coating membrane thickness and hardness changes. In our previous report (Hu et al 1998), which described a new preparation method for PCDCs using a coating machine, the nozzle size was larger than that used in this study. Because the nozzle size was decreased in this study, the ethylcellulose coating solution was sprayed onto the surface of the suppositories as smaller-sized particles. Although a microporous membrane was formed, the structure of this membrane was tighter than that produced using the larger-size nozzle. Therefore, the ethylcellulose membrane thickness needed for colon delivery of drugs in beagle dogs was approximately 100 μm. Despite the differences in the ethylcellulose coating membrane thicknesses, the hardness of the no. 0 PCDCs produced in this study was around 2·0 N. Our previous reports suggested that a hardness of 2·0 N was necessary for no. 0 PCDCs to deliver caffeine to the human colon. For no. 2 PCDCs, coating time was shorter than that for no. 0 PCDCs and the ethylcellulose membrane thicknesses obtained were $50 \pm 1\ \mu$m (35 min coating), $57 \pm 1\ \mu$m (40 min coating) and $64 \pm 1\ \mu$m (45 min coating). The hardness of these PCDCs were $1{\cdot}47 \pm 0{\cdot}05$, $1{\cdot}83 \pm 0{\cdot}09$ and $2{\cdot}36 \pm 0{\cdot}09$ N, respectively.

In-vivo evaluation of PCDCs in man

Test PCDC preparations shown in Table 1 were administered (dose of caffeine per subject: $75{\cdot}0 \pm 0{\cdot}5$ mg). Figure 1 shows the salivary caffeine excretion rate vs time profiles. When type-1 PCDCs, which had a mean ethylcellulose coating membrane thickness of $56 \pm 1\ \mu$m, were administered to three subjects, salivary caffeine excretion rates started to increase at about 3 h after oral administration. Therefore, the mean Ti, the time when caffeine first appeared in the saliva after being absorbed from the gastrointestinal tract, was $3{\cdot}3 \pm 0{\cdot}3$ h. Non-compartmental pharmacokinetic analysis was applied to the salivary caffeine

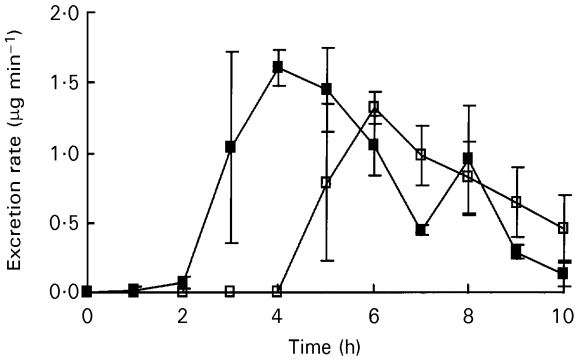

Figure 1. Salivary caffeine excretion rate vs time profiles after oral administration of no. 0 PCDCs to healthy subjects. The mean thicknesses of ethylcellulose coating membranes were $56 \pm 1\ \mu$m (■) and $64 \pm 1\ \mu$m (□). Test preparations were administered at 10 00 h under fasted conditions. Results are expressed as mean ± s.e.m. of three subjects.

excretion rate vs time data and the results are shown in Table 2. The mean MRT values of the type-1 PCDCs was 5·4 ± 0·1 h.

With type-2 PCDCs, of which the mean ethylcellulose coating membrane thickness was 64 ± 1 μm, longer Ti and MRT values were obtained. As shown in Table 2, the Ti values increased to 5·3 ± 0·3 h and the MRT of these PCDCs was 7·0 ± 0·3 h. From the Ti values, we can assume that the type-2 PCDCs were delivered to the colon and released caffeine there. To directly ascertain the colon delivery of PCDCs in our subjects, we developed a gastrointestinal magnetomarkergraphy study using a 129-channel Shimadzu vector biomagnetic measurement system (Hu et al 2000). In that study, we used PCDCs with the same hardness as those used in this study, approximately 2·0 N. By controlling the hardness to 2·0 N, PCDCs disintegrated in the human colon but not in the small intestine. The colon arrival time (CAT) of the test PCDCs in our subjects was determined to be 5 h by the gastrointestinal magnetomarkergraphy study. By comparison with the observed CAT value, we can conclude that type-2 PCDCs were delivered to the colon and released caffeine there.

In general, smaller-sized capsules are preferable for patients taking a drug orally. Therefore, the effect of capsular size on the delivery efficiencies of PCDCs to the colon was studied. Table 2 shows the salivary caffeine excretion rate vs time profile after oral administration of two types of no. 2 PCDCs. When type-3 PCDCs were administered, caffeine started to appear in the saliva at 4·3 ± 0·5 h. Moreover, PCDCs having thicker ethylcellulose membranes were prepared and the in-vivo evaluation was performed in man. As shown in Table 2, the Ti increased to 5·3 ± 0·3 h and MRT was 7·0 ± 0·1 h, respectively. The coating time was further increased to 45 min, and the resulting PCDCs had a mean ethylcellulose coating weight of 17·2 ± 1·2 mg and a mean membrane thickness of 64 ± 1 μm. For these type-5 no. 2 PCDCs, caffeine was not detected in the saliva of the subjects until 24 h after oral administration, because the hardness considerably increased to 2·36 ± 0·09 N, which was too hard for disintegration by colon luminal pressures.

Table 2. Pharmacokinetic parameter values of caffeine after oral administration with four types of PCDCs to man.

Test preparations	Maximum salivary excretion rate ($\mu g\ min^{-1}$)	T_{max} (h)	Ti (h)	MRT (h)
Type 1	1·88 ± 0·26	4·0 ± 0·6	3·3 ± 0·3	5·4 ± 0·1
Type 2	1·53 ± 0·21	6·3 ± 0·9	5·3 ± 0·3	7·0 ± 0·3
Type 3	1·35 ± 0·39	4·5 ± 0·3	4·3 ± 0·5	6·3 ± 0·01
Type 4	0·90 ± 0·22	5·8 ± 0·3	5·3 ± 0·3	7·0 ± 0·1

Each value represents the mean ± s.e.m. of 3–4 subjects.

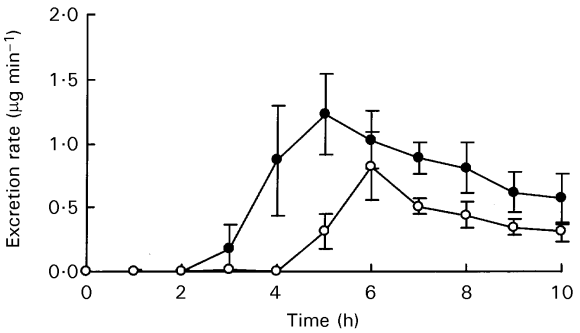

Figure 2. Salivary caffeine excretion rate vs time profiles after oral administration of no. 2 PCDCs to healthy subjects. The mean thicknesses of ethylcellulose coating membranes were 50 ± 1 μm (●) and 57 ± 1 μm (○). Test preparations were administered at 10 00 h under fasted conditions. Results are expressed as mean ± s.e.m. of four subjects.

Type-2 PCDCs, which had a hardness of 2·02 ± 0·02 N, were disintegrated by colon luminal pressure and released caffeine there. However, type-5 PCDCs could not disintegrate in the colon. There were two reasons for this: firstly, type-5 PCDCs were smaller than type-2 PCDCs and it is well known that small-sized PCDCs are more tolerant to pressure than larger PCDCs; secondly, the colon luminal pressure may have intra-site variation, although the maximum pressure might have a limitation of 2·2 N.

By comparing the maximum salivary caffeine excretion rates, Rmax, between no. 0 PCDCs and no. 2 PCDCs, it is apparent that Rmax is dependent on the capsular size. When type-2 no. 0 PCDCs were administered, Rmax was 1·32 ± 0·11 $\mu g\ min^{-1}$. In contrast, an Rmax of 0·82 ± 0·27 $\mu g\ min^{-1}$ was obtained with type-4 no. 2 PCDCs. Since the same dose of caffeine, 75 mg, was formulated in both PCDCs, the larger PCDCs showed the higher bioavailability of caffeine. Water is reabsorbed in the colon and the water content of the stool is an important factor for the absorption of drug from the colon. Hebden et al (1999) showed that water content is an important determinant in colonic drug absorption. With low water content, drug solvent is the most important factor relating to the liberation of drug. In this study, caffeine was introduced into PCDCs with PEG 1000. As the formulated amount of caffeine was the same in both no. 0 and no. 2 PCDCs, the amount of PEG 1000 was thought to affect the absorption of caffeine. By comparing the total weight of the two PCDCs, the weight of no. 0 PCDCs was approximately twice that of no. 2 PCDCs. When the

volume of the solvent, PEG 1000, was increased, the fluidity of the preparation ameliorated the decrease in water content. In other words, the release, and consequently the absorption, of drug were improved by formulation with more base, PEG 1000. Therefore, PEG 1000 was thought to enhance the dissolution of caffeine in the colon and, consequently, higher salivary excretion rates were obtained after absorption from the colon.

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