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Evaluation of Gastrointestinal Transit Characteristics of Oral Patch Preparation Using Caffeine as a Model Drug in Human Volunteers

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Summary: Salivary caffeine excretion rate test has been proposed for the evaluation of gastrointestinal transit characteristics of an oral patch preparation after administration to human volunteers instead of measuring the plasma or serum concentration in the early stages of formulation development. Patches having a diameter of 3.0 mm and containing caffeine as a model drug were prepared. The patches consisted of 1) the backing layer made of a water-insoluble polymer, 2) the drug-carrying layer composed of caffeine and a gel-forming polymer, and 3) the enteric polymer membrane. These three layer patches were filled into enteric capsules. Caffeine solution in an enteric capsule was used as the control preparation. After oral administration of each preparation to human volunteers at a dose of 50 mg of caffeine in a cross-over study with a wash-out period of two weeks, saliva samples were collected over 1 min at every sampling time for 12 h and salivary caffeine concentration was determined by a HPLC assay method. Salivary caffeine excretion rate (ER) was used for pharmacokinetic analysis. Mean residence time (MRT) and first-appearance time of caffeine into the saliva (Ti) were determined. To characterize the pharmacokinetics of caffeine, MRT-Ti values of patch and solution preparations were compared. Patch preparations had a Ti value of 2.33 ± 0.33 h and showed significantly longer MRT-Ti, 3.87 ± 0.21 h, as compared to the control preparation (MRT-Ti = 1.04 ± 0.38 h) under fasting condition (p < 0.05). Food intake prolonged the gastric emptying time (GET) of the preparations with Ti values of 5.00 ± 1.15 h for control preparation and 4.67 ± 1.20 h for patch preparation. The MRT-Ti values were 0.62 ± 0.20 h (control) and 2.45 ± 0.73 h (patch). The results of this study indicate that the parameter, MRT-Ti, was useful in characterizing the transit characteristics of oral patch preparations than MRT itself and the presence of food affects the performance of the patch system.

Key words: small intestinal transit; pharmacokinetics; patch preparation; oral preparation; caffeine; human saliva

Introduction

Many novel oral drug delivery systems such as once-a-day sustained release preparations1) and bioadhesive preparations2) are under investigation. As a targeting type preparation, we have been studying two types of colon delivery capsules, i.e. intestinal pressure-controlled colon delivery capsule (PCDC) and time-controlled colon delivery capsule (TCDC).3,4) In our previous study,5) a patch preparation was formulated using recombinant human granulocyte colony-stimulating factor (G-CSF) as a model drug to improve the oral bioavailability of the peptide. By means of this patch preparation, a pharmacological availability (PA) of 23% was obtained for G-CSF as compared to the iv injection of the same dose of G-CSF in dogs. This was the highest value obtained among the other delivery systems, namely, colon delivery system and enteric effervescent system.5,6) The mucoadhesive efficiency of the patch preparation was studied in rats, where the retention and the transit of the patches in the small intestine were directly observed by abdominal incision.7) The study demonstrated that patches adhered to the rat small intestinal wall with a retention time of more than 2.0 h. These studies suggest that patch preparation is a potential delivery system for the oral delivery of...
peptide/protein drugs. However, the physiological characteristics of the gastrointestinal (GI) tract of experimental animals such as dogs and rats differ from those of humans. For example, the length of the small intestine in dogs is approximately 2.5 m whereas in humans it is 7.0 m. Hence, to develop patch preparation as a new oral delivery system, the performance of the system must be evaluated in human subjects.

A biomagnetic measurement system (BMS) using a superconductive quantum interference device (SQUID) was developed for the evaluation of colon delivery efficiency of PCDC in human subjects. As this method needs an expensive equipment, it is difficult to use it for routine evaluation of formulations in humans. Instead of SQUID method, we have been trying to use caffeine excretion rate test for the evaluation of small intestinal transit characteristics of oral preparations. Caffeine excretion rate test is used in the clinical pharmacokinetic studies to determine the phenotype of CYP 1A2. However, this test has not been reported for the evaluation of new dosage forms. In the present investigation, pharmacokinetic studies were carried out to confirm whether salivary caffeine excretion rate could be used for the evaluation of intestinal transit of oral patch preparation in healthy human subjects under both fasting and fed conditions.

**Materials and Methods**

**Materials:** Methacrylate copolymer (Eudragit L100®) was obtained from Röhm GmbH & Co. KG (Darmstadt, Germany). Hydroxypropylmethylcellulose phthalate (HP-55®) and carboxyvinyl polymer (Carbopol® 974P-NF) were procured from Shin-etsu Chemical Industry Co., Ltd. (Tokyo, Japan) and Chugai Boyeki Co., Ltd. (Tokyo, Japan), respectively. Ethylcellulose (Ethocel Premium, 100 cps) (EC) was obtained from Nisshin Kasei, Co., Ltd. (Osaka, Japan). Polyoxymethylene, 60 mol, hydrogenated castor oil derivative (HCO-60®) was procured from Nikko Chemicals Co., Ltd. (Tokyo, Japan). Citric acid (CA), caffeine, sodium salicylate, sodium hydrogen carbonate, disodium hydrogen phosphate, potassium dihydrogen phosphate and polyethylene glycol (PEG) 400 were purchased from Nakalai Tesque Inc. (Kyoto, Japan). All other chemicals used were of reagent grade and were used as received without further purification. Hard gelatin capsules (#00 and #0) were obtained from Yoshida Co., Ltd. (Himeji, Japan). The film spreading apparatus (Bakerapplicator®) and the heat-sealing punching equipment were developed in our laboratory in technical collaboration with Imoto Seisakusho Co., Ltd. (Kyoto, Japan).

**Preparation of patch:** The backing layer made of EC was prepared by a solvent evaporation technique. EC solution (20% w/v) was prepared using a mixture of methylene chloride and methanol (4:1) as solvent. Bakerapplicator was used for spreading EC solution on a Teflon plate (30 cm × 30 cm) and the film was obtained after solvent evaporation at room temperature for 5 min. The mean thickness of the EC film obtained was 31.0 ± 1.8 (S.E.) μm. Enteric polymer film was also prepared by the same method as described above for EC layer using Eudragit L 100 solution (20% w/v). The solvent used was a mixture of methylene chloride and methanol (1:1) and PEG 400 was used as a plasticizer at a concentration of 20% w/w of dry polymer. The thickness of the enteric polymer membrane was 23.7 ± 2.6 μm. The drug-carrying layer was prepared by dissolving sodium salicylate (40 mg) in deionised (DI) water (400 μL) followed by caffeine (50 mg) and HCO-60 (150 mg). Thereafter, 0.5 N NaOH solution (100 μL) and Carbopol (50 mg) were added and mixed in a mortar. After mixing well, the mixture (790 mg) was weighed and was uniformly spread on the surface of the EC film (backing layer) (4.1 × 4.1 cm) and covered with Eudragit L 100 film (enteric polymer membrane). The three-layered preparation was sealed and cut into 240 pieces of patches, 3 mm in diameter, by a heat-sealing punching equipment. The pieces of patches, 120 each, were filled into an enteric capsule (HP-55) of size #00 along with 200 mg of effervescent powder made of a mixture of citric acid and sodium hydrogen carbonate (5:5:4.5). As a control, immediate-release enteric preparation was made by filling a solution composed of caffeine (50 mg), sodium salicylate (40 mg), DI water (400 μL) and 0.5 N HCl (100 μL) into an enteric capsule made of HP-55.

**In vitro dissolution studies:** The in vitro dissolution tests on test preparations were performed using a JP XIII paddle apparatus (50 rpm) with 900 mL of 1/15M phosphate buffer, pH 7.4, maintained at 37 ± 0.5°C as the dissolution medium. Samples of 5.0 mL were collected for 2 h at 5, 10, 20, 30, 60 and 120 min intervals for patch preparation and at 1, 3, 5, 7, 10, 20, 30, 60 and 120 min intervals for control preparation, and were replaced with 5.0 mL of fresh dissolution medium. All the experiments were carried out in triplicate. Samples were measured spectrophotometrically (Shimadzu UV-1500, Japan) at 275 nm for caffeine content suitable dilution. Mean dissolution time (MDT) of caffeine from the oral preparation was calculated by a moment analysis method.

**In vivo Pharmacokinetic studies:** Three healthy human volunteers, aged 23–33 years (mean 27.0 ± 5.29 years), participated in the study according to the Declaration of Helsinki. Xanthine beverages, alcohol and smoking were avoided 12 h before each study and throughout the study day. The subjects were participated in the study after receiving an explanation of the study protocol, and informed written consent was ob-
tained from each volunteer. The experiments were carried out at the same time of the day (in the morning) to exclude the influence of circadian rhythm and a washout period of at least two weeks separated each study. Volunteers were fasted overnight for at least 12 h. Water was allowed ad libitum during the entire period of the study. The dose of caffeine per subject was 50 mg, which is less than the dose usually used in clinical therapy (200 mg/day). This dose also is less than the amount present in a single drink of beverage, e.g. a cup of coffee contains about 100 mg of caffeine. Therefore, it was considered that there would be no side effects. At 30 min before the administration of test preparation, blank saliva samples were collected for 1 min. As a stimulant for saliva production, 1 g of parafilm was chewed at each sampling occasion. At 9.30 a.m., test preparation was administered orally with 200 mL of water under the fasting or fed state. In the fasting state study, the subjects were provided with lunch and supper at 13.30 p.m. and 20.30 p.m., respectively. In the fed state study, each subject took a standardized breakfast at 9.00 a.m. which was modified from the menu proposed by Melandar et al. The breakfast consisted of 100 mL of low fat milk, 100 mL of orange juice, one egg, a slice of bread, 5 g of margarine, 20 g of orange marmalade and 100 mL of water and the subjects were provided with lunch and supper at 13.30 p.m. and 20.30 p.m., respectively. The saliva samples were collected for 1 min at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after the administration of the test preparation. After measuring the weight of saliva, the sample was centrifuged at 3000 rpm for 10 min and the clear supernatant was transferred to a clean tube and stored at −20°C until analysis.

**Caffeine assay in the saliva samples:** The concentration of caffeine in the saliva samples was determined using a HPLC system (Shimadzu LC-10AS Liquid chromatography and Shimadzu SPD-10A UV-VIS detector). The analytical column used was Chemcosorb 5-ODS-H and was maintained at 50°C. The detection wavelength was 275 nm. A mixture of 5 mM phosphate buffer (pH 3.5) and acetonitrile (80:20 v/v) was used as mobile phase and the flow rate was maintained at 0.8 mL/min. For the extraction of caffeine from saliva samples, 200 μL of saturated sodium chloride solution was added to 200 μL of saliva sample. Thereafter, 5 mL of chloroform was added, mixed for 10 min on a mechanical shaker and centrifuged for 10 min at 3000 rpm. The organic phase (4.0 mL) was transferred to a fresh tube and evaporated to dryness. 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 seven calibration standards was run with each series of unknown samples. The standard curve of caffeine added to each subject’s saliva was linear over the concentration range of 0.1–5.0 μg/mL. The salivary caffeine excretion rate (ER) was obtained by multiplying the salivary caffeine concentration with saliva volume, where the density of the saliva was assumed to be unity.

**Pharmacokinetic analysis:** The time when salivary caffeine ER reached to its maximum, T_max, the maximum salivary caffeine ER, ER_max, and the first appearance time of caffeine into the saliva, T_a, were obtained from the authentic salivary caffeine ER vs. time data. The areas under the salivary caffeine ER vs. time curve (AUER) after oral administration of the test preparations was calculated using trapezoidal rule up to the last measured point. The mean residence time (MRT) was calculated from the ratio of the AUER (area under the first moment of the ER vs. time curve) to the AUER. By comparing the MRT values of the two preparations, it was found to be difficult to distinguish the difference in the transit kinetics of the two test preparations in the gastrointestinal (GI) tract. The time required for the transfer of preparation to small intestine and subsequent drug release and absorption, which was equivalent to T_a, was subtracted from MRT to get a parameter (MRT-T_a) for transit characteristics of test preparations. The difference in transit characteristics of both the preparations was more evident when MRT-T_a values were compared than with MRT values.

**Statistics:** All values are expressed as their mean ± S.E. Differences in pharmacokinetic parameter values between the two preparations were statistically evaluated by one side Student’s t-test. Statistical differences were assumed to be significant when P<0.05.

**Results and discussion**

Caffeine is a sparingly soluble drug and can be solubilized by complexation with salicylates, benzoates, citrates or cinnamates. In this study, sodium salicylate was used as a complexing agent to improve the solubility of caffeine. Fig. 1 shows the results of the dissolution studies carried out on the enteric capsules containing caffeine patch preparation and caffeine solution. The dissolution rate of caffeine from patch preparation was found to be slower than that from solution. The mean time for the dissolution of 50% of the formulated amount of caffeine (T50%) was 27.0 ± 4.5 min for patch preparation and 12.8 ± 0.5 min for caffeine solution. Approximately 85% of caffeine in the patch preparations was dissolved by 0.5 h and thereafter complete dissolution was obtained within 1 h. The MDTs of caffeine from the preparations were 0.33 ± 0.05 h for patch and 0.10 ± 0.004 h for solution. These results indicated that the dissolution of caffeine was slow from the patch preparation after the dissolution of the enteric surface membrane of the patch.

**In vivo** pharmacokinetic studies were carried out in healthy human volunteers to assess the small intestinal
Fig. 1. The percent release vs. time profiles of caffeine from enteric capsules containing (●) caffeine patch preparation and (●) caffeine solution. Each point shows the mean ± SE (n = 3).

Fig. 2. Salivary caffeine ER vs. time profiles obtained after oral administration of enteric capsules containing (●) caffeine solution and (●) caffeine patch preparation to three human volunteers under fasting condition. The dose of caffeine was 50 mg. Each point shows the mean ± SE of three subjects.

transit kinetics of the two test preparations. Fig. 2 shows the mean salivary caffeine ER vs. time profiles after oral administrations of enteric capsules containing caffeine solution (control) and caffeine patch preparation in three volunteers under fasting condition. The pharmacokinetic parameters of caffeine obtained after oral administration of test preparations under fasting condition are given in Table 1. With the control preparation, the salivary caffeine ER was rapidly decreased after reaching to ER$_{\text{max}}$ at 4 h and high inter-subject variation was observed. On the other hand, ER$_{\text{max}}$ showed less inter-subject variation with the enteric capsule containing caffeine patches, though ER$_{\text{max}}$ with patch preparation was lower than that with the control preparation. However, significantly higher AUER value (11.13 ± 2.95 μg·h/min) and longer MRT-T$_1$ value (3.87 ± 0.21 h) were obtained with patch preparation compared to the control preparation (AUER = 3.79 ± 1.41 μg·h/min, MRT-T$_1$ = 1.04 ± 0.38 h). If caffeine was iv injected to each subject, mean absorption time (MAT) could be obtained. However, caffeine iv preparation is not available as a commercial product. By com-
As enteric capsules were used in this study, long absorption lag-times ($T_i$) were obtained with both the preparations. The $T_i$ of patch preparation was $2.33 \pm 0.33$ h and that of the control preparation was $3.00 \pm 0.58$ h. According to the report of Weitschies et al.,\textsuperscript{15} who studied the GI transit of oral solid preparation in human subjects by gamma-scintigraphy, orally administered solid preparations were transferred to the small intestine within 1 h after administration under the fasting condition. As the patch preparation had an enteric polymer membrane, Eudragit L100, which was designed to dissolve after the dissolution of enteric capsule, a longer $T_i$ value was expected as compared to the control preparation. However, the $T_i$ and $T_{\text{max}}$ of patch preparation were shorter than those of the control preparation, though there was no significant difference between these values. This result was ascribed to the inter-subject and intra-subject variation in the gastric emptying time (GET) of the volunteers and to the rapid dissolution of enteric polymer membrane of patch preparation after reaching the upper part of the small intestine, as the pH of the human duodenum was reported to be 6.0–6.5.\textsuperscript{15}

As caffeine was reported to be metabolized by CYP 1A2 and there are reports of the existence of extensive metabolizers,\textsuperscript{10,16} pharmacogenetic factors influence the pharmacokinetics of caffeine. One more subject was involved in this study but the salivary caffeine ER of this subject was so low that the data was not used for pharmacokinetic analysis. The $ER_{\text{max}}$ was 0.10 $\mu$g/min and AUER was 0.18 $\mu$g·h/min with this subject. Although no pharmacogenetic studies were carried out with this volunteer, the subject was thought to be an extensive metabolizer of caffeine.

According to the reports of Cook et al.,\textsuperscript{17} Zylber-Katz et al.\textsuperscript{18} and Lee et al.,\textsuperscript{19} caffeine was excreted into the saliva and the salivary caffeine ERs were well correlated with the plasma caffeine concentrations. Salivary sampling is also better for subjects than blood sampling because it is safe and not painful. Caffeine ER test was used earlier to evaluate the colonic delivery efficiency of pressure-controlled colon delivery capsule (PCDC) after administration to human volunteers.\textsuperscript{20,21} In those studies, the absorption lag-time, $T_i$, was used as a parameter for colon targeting of drugs. On the other hand, in this study, we tried to evaluate the small intestinal transit characteristics of the patch preparation in comparison with a control preparation using the caffeine ER test. In this study, Eudragit L100 was used as enteric polymer membrane for the patches. As the dissolution threshold pH of Eudragit L100 is 6.0, the surface layer of patches was thought to be dissolved immediately after reaching the small intestine, because the luminal pH of the upper small intestine was reported to be higher than 6.0.\textsuperscript{22} After the dissolution of the surface layer of patch preparation, the drug-carrying gel-layer was expected to get exposed. Mucoadhesive polymers were reported to show their ability to retain drugs in close contact with mucosal membrane for long periods of time.\textsuperscript{2,23-26} Therefore, the increase in AUER and MRT-$T_i$ of caffeine was ascribed to the increased residence time of patch in the small intestine.

If the adhesion of patches to the small intestinal wall is prevented, the residence time of patches in the small intestine is thought to be decreased. Therefore, the effect of food on the pharmacokinetic profile of caffeine...
Table 2. Pharmacokinetic parameters of caffeine after oral administration of enteric capsules containing caffeine solution (control) and patch preparations in human volunteers under fed condition

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>Patch</th>
<th>Control</th>
<th>Patch</th>
<th>Control</th>
<th>Patch</th>
<th>Control</th>
<th>Patch</th>
<th>Control</th>
<th>Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERmax (µg/min)</td>
<td>1.72</td>
<td>3.71</td>
<td>1.28</td>
<td>2.19</td>
<td>0.14</td>
<td>0.68</td>
<td>0.10 ± 0.47</td>
<td>0.19 ± 2.19</td>
<td></td>
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</tr>
<tr>
<td>Tmax (h)</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>5.33 ± 1.20</td>
<td>6.67 ± 1.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ti (h)</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>5.00 ± 1.15</td>
<td>4.67 ± 1.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUER (µg·h/min)</td>
<td>3.47</td>
<td>11.91</td>
<td>3.09</td>
<td>11.48</td>
<td>0.22</td>
<td>2.40</td>
<td>2.26 ± 1.03</td>
<td>8.60 ± 3.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRT (h)</td>
<td>7.50</td>
<td>8.62</td>
<td>6.00</td>
<td>7.90</td>
<td>3.35</td>
<td>4.85</td>
<td>5.62 ± 1.21</td>
<td>7.13 ± 1.16</td>
<td></td>
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</tr>
<tr>
<td>MRT-Ti (h)</td>
<td>0.50</td>
<td>1.63</td>
<td>1.00</td>
<td>3.90</td>
<td>0.35</td>
<td>1.85</td>
<td>0.62 ± 0.20</td>
<td>2.45 ± 0.73</td>
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</tr>
</tbody>
</table>

ERmax: the maximum salivary excretion rate, ER, of caffeine.
Tmax: the time when salivary caffeine ER reached to its maximum value.
Ti: the first appearance time of caffeine into the saliva.
AUER: the area under the salivary caffeine ER vs. time curve.
MRT: mean residence time.
a: significantly different from control preparation (p < 0.05).
b: significantly different from fasted condition (p < 0.05).

Evaluation of Gastrointestinal Transit Characteristics of Oral Patch Preparation Using Caffeine

ER into the saliva was studied. Fig. 3 shows the salivary caffeine ER vs. time profiles after oral administration of the control and patch preparations under fed conditions. By comparing to the results in Fig. 2, the salivary caffeine ER vs. time profile of the control preparation showed that ERmax was little decreased but a higher ER than 1.0 µg/min was maintained over 3 h. Table 2 shows that Ti was increased by about 2–3 h as compared to the Ti values obtained under fasting condition. These results indicate that the presence of food prolonged the gastric emptying time (GET) of the enteric capsules.

The prolonged GET was also clearly observed after oral administration of caffeine patch preparation under fed condition as shown in Fig. 3, where the Ti was delayed by about 4 h. High variations in both AUER and MRT-Ti values were obtained after administration of caffeine patch to the subjects. In subject #2, a long MRT-Ti (3.90 h) and a high AUER (11.48 µg·h/min) values were obtained. While, in subject #3, a short MRT-Ti (1.85 h) and low AUER (2.40 µg·h/min) values were obtained. Subject #3 was a heavy-smoker. The effect of smoking on CYP1A2 induction was reported by Zevin and Benowitz.27 The metabolic clearance rate in subject #3 might have increased and consequently the excretion rate of caffeine was lower than the other volunteers. The average data indicate that higher AUER (8.60 ± 3.10 µg·h/min) and longer MRT-Ti (2.45 ± 0.73 h) values were obtained with patch preparation as compared to the control preparation (AUER = 2.26 ± 1.03 µg·h/min and MRT-Ti = 0.62 ± 0.20 h). There was
no significant difference in AUER values, but significant difference in MRT-Ti values of the patch and the control preparations was observed under the fed condition. However, the influence of food on MRT-Ti and AUER of patch preparations was clearly obtained in two volunteers, i.e. subjects #1 and #3. MRT-Ti values were decreased from 4.16 to 1.63 h and 3.47 to 1.85 h and AUER values were decreased from 17.04 to 11.91 µg·h/min and 8.26 to 2.40 µg·h/min in subjects #1 and #3, respectively. From these results it may be assumed that the food intake decreased the adhesive efficiency of patch preparation. Hosny et al. reported that food reduced the bioavailability of drugs from bioadhesive delivery system due to complexation of the mucoadhesive material with food constituents. The increased pH of GI tract after food intake also might have influenced the surface charge of both mucus membrane and the polymer of patch preparation thereby affecting the degree of hydration and viscosity of the mucoadhesive polymer. Consequently, the adhesive strength of the polymer was thought to be decreased. AUER (8.10 µg·h/min) and MRT-Ti (3.97 h) values obtained in subject #2 after administration of patch preparation under fasting condition did not show any difference as compared to fed condition (AUER = 11.48 µg·h/min and MRT-Ti = 3.90 h). However, studies in large number of subjects are needed to establish clearly the effect of food intake on the GI transit kinetics of the test preparations.

Although we did not evaluate the correlation between in vitro dissolution test and in vivo pharmacokinetic study, the relative correlation could be obtained. The slower dissolution rate of the patch preparation was reflected in the longer MRT-Ti than with the control preparation. In order to perform the correlation test, a more suitable dissolution test covering physiological factors, e.g. the fluid condition in the gastrointestinal tract and the adhesiveness in the small intestine and so on, are to be considered. If the dissolution test was performed under more simulated conditions of the gastrointestinal tract, the difference of the MDT value between the control preparation and the patches would be significant. However, the relative tendency could be obtained from the present in vitro dissolution test.

In conclusion, human pharmacokinetic studies using the salivary caffeine ER vs. time data showed that patch preparation increased the residence time of caffeine in the small intestinal tract, since MRT-Ti of the patch preparation was significantly longer than the control preparation under both fasting and fed conditions. However, food intake may affect the efficiency of this system. The MRT-Ti value will be a better pharmacokinetic parameter for the evaluation of the gastrointestinal transit characteristics of a new oral formulation in the explorative human studies.

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