Evaluation of Enteric Coated Tablet Sensitive to Pancreatic Lipase. II.1)

In Vivo Evaluation

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Plain tablets containing a model drug, sulfamethizole (SMZ), were coated with triolein (TO), trilaurin (TL) and ethylene cellulose (EC). The biological behavior of the coated tablets (TOTL-Tab), which are pH-dependent and sensitive to pancreatic lipase, was investigated in humans. Results of the administration of the tablets with or without an antacid, under fasting and non-fasting conditions, and at 0.5 h before and 0.5 h after meals, were examined. A comparison of the in vivo behavior of SMZ after the administration of these tablets was done using the following data: the lag time of urinary excretion (\(t_{lag}\)), the total urinary recovery percentage (\(X_u\)), and the mean residence time after \(U_{lag}\) (MRTd). A typical pH-sensitive tablet coated by cellulose acetate phthalate (CAP-Tab) was used as a reference. For the administration of a CAP-Tab alone, the \(U_{lag}\) obtained under both the non-fasting and fasting condition was longer than that of the plain tablet. However, \(U_{lag}\) after the administration of a CAP-Tab with an antacid became considerably shorter. This lag time was about the same as that obtained from the plain tablet, regardless of food ingestion. The obtained CAP-Tab MRTd and \(X_u\) values were not significantly different in comparison to the plain tablets. Under the non-fasting condition, \(U_{lag}\) MRTd and \(X_u\) of TOTL-Tab were not affected by the co-administration of an antacid, and these values were virtually the same as those obtained from a CAP-Tab without an antacid. The urinary excretion data obtained after the administration of TOTL-Tab alone under fasting was analogous to the non-fasting case. When TOTL-Tab was co-administered with an antacid under fasting, the MRTd was the much longer than that of the plain tablet, and the \(X_u\) was almost half that of the plain tablet. These results suggest that TOTL-Tab is useful as an enteric release preparation sensitive to pancreatic lipase in humans, except when antacids are taken under a fasting condition.

Keywords enteric coated tablet; lipase sensitive; human; disintegration; antacid; food

In the previous paper1) in this series, we reported that a tablet coated with triolein, trilaurin and ethylene cellulose (TOTL-Tab) is useful as an enteric release preparation sensitive to pancreatic lipase. This coating film does not dissolve in water, regardless of pH; however, it tears smoothly in a pancreatic lipase solution which is capable of digesting triglycerides. TOTL-Tab did not disintegrate in the 1st fluid (pH 1.2, JP-1) or the 2nd fluid (pH 6.8, JP-2) described according to the JP-XII “disintegration test,” but it did disintegrate quickly in JP-2 containing gall powder and pancreatic lipase (JP-2-GL).

It is known that the pH of the gastro-intestinal lumen and the pancreatic lipase secretions are affected by food ingestion, the administration of antacids, and so on. Therefore, it is possible that the conditions of the disintegration test in vitro for TOTL-Tab is not sufficient for accurately judging an enteric release preparation sensitive to pancreatic lipase in vivo.

In the present study, the disintegration behavior of TOTL-Tab in humans was investigated, and a tablet coated with cellulose acetate phthalate (CAP-Tab), which is a typical pH-sensitive enteric coated tablet, was used as a reference.

Materials and Methods

Materials Sulfamethizole (SMZ) was purchased from Eisai Co., (Tokyo, Japan). Triolein (TO) and trilaurin (TL) were procured from Tokyo Kasei Kogyo (Tokyo, Japan). Ethyl cellulose (80—120 cps, (EC)), diethylphthalate and gall powder were obtained from Nakalai Tesque, Inc. (Tokyo, Japan), lipase (type II) from Sigma (St. Louis, MO, U.S.A.), cellulose acetate phthalate from Wako Pure Chem. (Tokyo, Japan), magnesium oxide from Yamanouch Yakuin (Osaka, Japan) and sodium bicarbonate from Hishiyama Seiyaku (Osaka, Japan). Other chemicals were of a reagent grade.

Preparation of Enteric Coated Tablets Enteric coated tablets containing a model drug, SMZ, were prepared by the method described previously.1) A granular mixture of SMZ and lactose was prepared by the wet granulation method using an aqueous solution of starch as a binder. The lubricant, magnesium stearate, was mixed with the dried granulation, and the mixture was compressed into tablets (320 mg, d=10 mm, 66 mg as SMZ). These tablets were coated using the fluidized bed coating technique with 1% each of TO, TL and EC in ethylcellulose-ether (1:1, v/v) solution for TOTL-Tab, or with 3% of CAP and 0.75% of diethylphthalate in an acetone solution for CAP-Tab. The mean coat weights of TOTL-Tab and CAP-Tab were 5.6 ± 0.5 and 5.4 ± 0.3 mg, respectively.

In Vitro Disintegration Test Disintegration tests were carried out with a JP XII disintegration apparatus. Each tablet was tested with a disk in each beaker for 3 h. An aliquot of the disintegration test solution was taken at suitable time intervals and SMZ concentration was determined. Whether the tablets had disintegrated completely or not was checked by the naked eye at 0.5, 1, 2 and 3 h. The disintegration media used were 1st (pH 1.2, JP-1) and 2nd (pH 6.8, JP-2) fluids of JP XII disintegration media, as well as JP-2 to which gall powder (0.4%) and pancreatic lipase (0.4%) were added as a simulated intestinal fluid (JP-2-GL). The digestive capability of JP-2-GL for triglycerides was reported previously.1,2)

In Vivo Study Each of three preparations (plain, TOTL-Tab and CAP-Tab) was given orally to five male subjects (aged 21 to 43 and weighing 53 to 70 kg), along with 100 ml of tap water. Each subject gave informed consent prior to the study. A washout period of at least 4d was allowed between treatments. Subjects were fasted overnight and received a tablet with or without an antacid (powders of 3 g sodium bicarbonate and 0.5 g magnesium oxide) 0.5 h before or 0.5 h after ingestion of a standard breakfast (100 g bread, 10 g butter and 180 ml milk), and also under a fasted condition. All subjects abstained from any other food until 4 h after administration of the tablets. Urine samples were collected at predetermined time intervals for 24 h following administration, and were kept frozen until assayed.

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Assay SMZ concentration in disintegration media and urine was determined by the diazocoupling method.31

Data Analysis The data were evaluated by moment analysis.4,5. The statistical moment parameters for the urinary excretion profiles are defined as follows:

\[ X'_n = \int_0^\infty (dX'_n/dt)dt \]  

(1)

\[ MRT = \int_0^\infty t(dX'_n/dt)dt/X'_n \]  

(2)

where \( X'_n \) is the total amount of SMZ excreted in urine to an infinite time, \( dX'_n/dt \) is the urinary excretion rate, and \( MRT \) is the mean residence time of the urinary excretion–time curves after administration of a preparation. \( MRT \) includes the lag time of urinary excretion. Therefore, Eq. 2 was rewritten as follows:

\[ MRT = U_{lag} + \int_{U_{lag}}^\infty t(dX'_n/dt)dt/X'_n \]  

(3)

\[ = U_{lag} + MRT_{sf} \]  

(3')

where \( U_{lag} \) is the lag time of urinary excretion, which is obtained by extrapolation from the cumulative amount of urinary excretion–time curve, and \( MRT_{sf} \) is the mean residence time after \( U_{lag} \). \( X'_n \) and \( MRT_{sf} \) were calculated by linear trapezoidal integration with extrapolation of the time course curve to infinite time according to a monoeponential equation using a microcomputer program.59

The moments for the dissolution profiles of SMZ from preparations are defined in the same manner as in Eq. 3.

\[ MDT = D_{lag} + \int_{D_{lag}}^\infty t(dX'_n/dt)dt/X'_n \]  

(4)

\[ = D_{lag} + MDT_{df} \]  

(4')

where \( MDT \) is the mean dissolution time of the dissolution profile, \( D_{lag} \) is the lag time of dissolution, which refers to the time dissolution begins, \( D_{lag} \) is the dissolution rate, \( X'_n \) is the final concentration, and \( MDT_{df} \) is the mean dissolution time after \( D_{lag}. MDT_{df} \) represents the intrinsic \( MDT \) for SMZ for each preparation. \( MDT_{df} \) was calculated in the same way as \( MRT_{sf} \).59

Statistical comparison of the mean parameters was performed using the Student's t-test.

Result

In Vitro Disintegration and Dissolution Disintegration tests stated in the previous paper35 were carried out for the tablets in JP-1, JP-2 and JP-2-GL. It was confirmed by the naked eye that CAP-Tab did not disintegrate until 3 h in JP-1, but disintegrated within 0.5 h in JP-2. The disintegration of CAP-Tab was not affected by adding gall powder and lipase to each media. The requirements for the disintegration test for pH sensitive enteric coated tablets are defined in JP XII as follows: the tablets must not disintegrate in JP-1 for 2 h and must disintegrate in JP-2 within 1 h. It was confirmed that the CAP-Tab used in this study fulfilled the above requirements. By contrast, TOTL-Tab did not disintegrate until 3 h in either JP-1 or JP-2, but disintegrated within 0.5 h in JP-2-GL. The dissolution patterns of SMZ following the disintegration of various tablets are shown in Fig. 1. And \( D_{lag} \) and \( MDT_{df} \) are summarized in Table I.

In Vivo Disintegration and Dissolution The accumulative amount of urinary excretion–time curves following the administration of CAP-Tab and TOTL-Tab 0.5 h after a meal, with or without an antacid, are shown in Fig. 2. According to Fig. 2, \( U_{lag} \) was obtained 2.3—5.0 h (mean ± S.D., 3.3 ± 0.9 h) and 0.1—0.6 h (0.3 ± 0.2 h) after the administration of a CAP-Tab alone and with an antacid, respectively. There is a significant difference between these two values. However, taking an antacid did not affect the urinary excretion profiles following the administration of TOTL-Tab: that is, 2.7—4.9 h (3.6 ± 1.0 h) and 1.5—4.7 h (3.0 ± 1.1 h) were obtained as the \( U_{lag} \) values in the cases with and without an antacid, respectively.

All of the urinary excretion data for plain tablets, CAP-Tab and TOTL-Tab are summarized in Tables II, III and IV, respectively.

When the plain tablet was administered, \( U_{lag}, MRT_{sf} \) and \( X'_n \) were almost same under fasting and non-fasting conditions, before and after meals, and they were not affected by the co-administration of an antacid (Table II). \( MRT_{sf} \) and \( X'_n \), calculated from urinary excretion profiles following the administration of CAP-Tab, were not affected by food or antacids, but the \( U_{lag} \) obtained from the cumulative curves of SMZ following the administration of an antacid was much shorter than that after no administration of an antacid in the cases of both fasting and non-fasting, as shown in Table III.

The \( U_{lag}, MRT_{sf} \) and \( X'_n \) values for TOTL-Tab in non-fasting (before and after meals) subjects were not affected by the administration of an antacid (Table IV). However, the urinary excretion data of the fasted subjects did show a difference between those cases with or without an antacid. When TOTL-Tab was administered alone and then with an antacid, \( MRT_{sf} \) of the fasted subjects were 2.7 ± 0.6 and 9.0 ± 7.8 h, respectively. The \( X'_n \) following
Fig. 2. The Effect of an Antacid on SMZ Urinary Excretion Profiles after Administration of TOTL-Tab and CAP Tab
One SMZ tablet was administered with (●) and without (○) antacid 0.5 h after breakfast.

### Table II. Urinary Excretion Data for SMZ Released from Plain Tablets

<table>
<thead>
<tr>
<th>Cond.</th>
<th>Antacid</th>
<th>(U_{lag}) (h)</th>
<th>(MRT_{af}) (h)</th>
<th>(X_{lag}^o) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before meal</td>
<td>–</td>
<td>0.3 ± 0.2</td>
<td>2.2 ± 0.9</td>
<td>87.5 ± 7.4</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0.2 ± 0.2</td>
<td>2.6 ± 0.5</td>
<td>88.6 ± 11.2</td>
</tr>
<tr>
<td>After meal</td>
<td>–</td>
<td>0.2 ± 0.3</td>
<td>2.2 ± 0.1</td>
<td>86.2 ± 5.2</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0.3 ± 0.3</td>
<td>2.4 ± 0.2</td>
<td>87.9 ± 5.2</td>
</tr>
<tr>
<td>Fasting</td>
<td>–</td>
<td>0.2 ± 0.3</td>
<td>2.5 ± 0.5</td>
<td>91.7 ± 9.8</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0.1 ± 0.1</td>
<td>2.2 ± 0.4</td>
<td>90.8 ± 4.1</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. (n = 4−5). Antacid (+) and (−) represent the addition of an antacid 3 g sodium bicarbonate and 0.5 g magnesium oxide and no such addition, respectively.

### Table IV. Urinary Excretion Data for SMZ Released from TOTL-Tab

<table>
<thead>
<tr>
<th>Cond.</th>
<th>Antacid</th>
<th>(U_{lag}) (h)</th>
<th>(MRT_{af}) (h)</th>
<th>(X_{lag}^o) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before meal</td>
<td>–</td>
<td>2.8 ± 1.7(a)</td>
<td>2.2 ± 0.3</td>
<td>86.5 ± 4.2</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>3.3 ± 1.9</td>
<td>2.8 ± 0.6</td>
<td>84.9 ± 7.5</td>
</tr>
<tr>
<td>After meal</td>
<td>–</td>
<td>3.0 ± 1.1(a)</td>
<td>2.4 ± 0.4</td>
<td>87.2 ± 5.6</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>3.6 ± 1.0</td>
<td>2.3 ± 0.2</td>
<td>89.5 ± 6.9</td>
</tr>
<tr>
<td>Fasting</td>
<td>–</td>
<td>1.2 ± 0.5(a)</td>
<td>2.7 ± 0.6</td>
<td>91.9 ± 4.7(a)</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>3.2 ± 1.0</td>
<td>9.0 ± 7.8</td>
<td>50.1 ± 19.6</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.D. (n = 5). a) Significantly different from coadministration with an antacid (p < 0.01). b) Significantly different from the fasting condition (p < 0.05). c) Not significantly different from CAP Tab in Table II.

### Discussion

In this study, we tried to evaluate the *in vivo* disintegration behavior of TOTL-Tab, which is an enteric release preparation sensitive to pancreatic lipase. The CAP-Tab, a typical pH sensitive enteric coated preparation, was selected as a reference. SMZ is used as a model drug for the evaluation in the *in vivo* disintegration behavior of tablets. It was selected due to its rapid intestinal absorption and urinary excretion in humans. It has already been reported that the biological half-life of SMZ is only 1.1−1.6 h,\(b\) and that 95% of it is excreted unchanged in urine.\(c\) Therefore, it is reasonable to expect that SMZ would appear in the blood and urine within a very short time following the disintegration of the tablets in the gastrointestinal lumen.

Plain tablets prepared in this study disintegrated very quickly and SMZ was released smoothly. \(D_{lag}\) was not observed and the \(MRT_{af}\) was 18.5 ± 4.2 min (Fig. 1 and Table I). The \(MRT_{af}\) of CAP-Tab in JP-2 and of TOTL-Tab in JP-2-GL were 24.3 ± 6.4 and 21.6 ± 3.8 min, respectively. Neither value was significantly different from the \(MRT_{af}\) of a plain tablet. These results suggest that CAP-Tab and TOTL-Tab disintegrate smoothly after \(D_{lag}\), almost the same as plain tablets, and that both tablets were capable of being disintegrated even in the intestinal tract. The \(D_{lag}\) of TOTL-Tab in JP-2-GL (8.6 ± 0.6 min) was longer than that of CAP-Tab in JP-2 (1.3 ± 1.9 min), but was so short that it could be disregarded when compared with the \(U_{lag}\) and \(MRT_{af}\) in Table IV.

Table II summarizes the disintegration of a plain tablet, and shows that the dissolution and absorption of SMZ using humans was not affected by either food or antacids.

It is expected that CAP-Tab can be disintegrated in the
intestinal lumen as long as the pH in the stomach is kept at a low value. Therefore, it is obvious that the \( U_{lag} \) obtained by the administration of a CAP-Tab alone showed the gastric transit time for CAP-Tab. Generally, the ingestion of food will lead to some delay in gastric emptying rates.\(^a\) In this study, \( U_{lag} (3.3 \pm 0.9 \text{ h}) \) obtained by the administration of CAP-Tab alone after a meal was also found to be significantly different in comparison to the \( U_{lag} (1.9 \pm 0.4 \text{ h}) \) following fasting, as shown in Table III. The \( U_{lag} (2.4 \pm 1.9 \text{ h}) \) obtained before a meal was slightly longer than that following fasting, although the difference was not statistically significant. However, the \( U_{lag} \) became notably short when an antacid was coadministered with the CAP-Tab, and was virtually same as the \( U_{lag} \) of plain tablets, as shown in Table II. These results suggest that CAP-Tab disintegrated fully in the stomach due to an increase in pH caused by the antacid.

With or without antacid, and under fasting or non-fasting condition, the \( U_{lag} \) obtained after the administration of TOTL-Tab was significantly longer than that of the plain tablets, and the same as the \( U_{lag} \) of CAP-Tab without an antacid. These results suggest that TOTL-Tab did not disintegrate in the stomach, but in the small intestine. The ingestion of food enhances the secretion of pancreatic juice to the duodenum.\(^4,10\) Therefore, the digestive capability of the small intestine of fasted subjects may be relatively low. However, it is shown that TOTL-Tab could disintegrate in the intestine by pancreatic lipase secreted under the fasting condition. In the case of the administration of TOTL-Tab with an antacid to fasted subjects, \( MRT_{st} \) and \( X_{u}\) differed from other cases, as shown in Table IV. It is therefore suggested that the disintegration rate of TOTL-Tab is delayed and disintegration incomplete under the above conditions.

Börgström found that bile acid causes a shift in the optimum pH of pancreatic lipase, from 8—9 down to 6—6.5.\(^11\) It has been reported that the pH values at the duodenum vary from 3.5 to 7.5,\(^12\) and from 2.7 to 6.6\(^3\) depending on various physiological conditions. The pH of the duodenum is decreased by the flow of gastric fluid into the intestine; however, it soon returns to its original pH as the result of the buffer action of a bicarbonate ion (\( \text{HCO}_3^- \)) secreted from the pancreas. Under a fasting condition, gastric juice secretion is suppressed and the gastric emptying rate is relatively faster in comparison with it under a non-fasting.\(^6\) Therefore, when subjects take an excess amount of antacid during fasting, fluid with a high pH will flow into the duodenum, and the pH of the duodenum may then increase and stay higher than the optimal pH of pancreatic lipase. The interference of the disintegration of TOTL-Tab following the administration of an antacid during fasting may be due to the high pH condition created in the duodenum.

Enteric coated tablets are used to prevent adverse drug effects, such as gastric irritation, or to protect drugs from degradation by acid in the stomach. If a subject has anacidity or is given an antacid, the drug may dissolve in the stomach when a pH sensitive enteric coated tablet such as CAP-Tab is administered. In this case, the drug may not be degraded by acid catalysis, but may irritate the stomach. And also, if the duration of the effect of an antacid is shorter than the gastric emptying time of the drug, part of the drug could be degraded in the stomach. Generally, though, it is expected that a drug always dissolves in the small intestine when an enteric coated tablet, such as TOTL-Tab, sensitive to an enzyme in the small intestine is administered.

In conclusion, TOTL-Tab does not disintegrate at any pH value in the stomach, and is useful as an enteric coated tablet sensitive to pancreatic lipase, except in the case of patients taking an excess amount of antacid under a fasting condition.

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