Evaluation of Enteric Coated Tablet Sensitive to Pancreatic Lipase. I. *In Vitro* Disintegration Test

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We designed a new enteric coated preparation which is pH independent and functions by pancreatic lipase activity in the duodenum. Triolein (TO) and trilaurin (TL) were selected as lipase sensitive components and ethylcellulose (EC) was used as the support film for TO and TL.

Tablets (330 mg, d = 10 mm) containing a model drug, sulfamethizole (SMZ), were coated with 1% each of TO, TL and EC solution by the fluidized bed coating technique. Disintegration tests were carried out in the media including JPXI 1st fluid (pH 1.2, JP-1), 2nd fluid (pH 6.8, JP-2) and JP-2 with gall powder and pancreatic lipase (JP-2-GL). The lag time of disintegration of the tablet (TOTL-Tab) coated 5—7 mg/tab with TO, TL and EC was about 10 min and all of the tablets disintegrated completely within 30 min in JP-2-GL. However, in the other media, which did not contain lipase, TOTL-Tab did not disintegrate for at least 2 h. It was confirmed that TO and TL in the coating film were digested by lipase. In addition, the tensil strength of the film decreased quickly after incubation in JP-2-GL.

These results suggest that the application of TO, TL and EC to tablet coating is useful for an enteric release preparation sensitive to pancreatic lipase, even if patients have low gastric acidity or are taking antacids.

Keywords enteric coated tablet; triglyceride; triolein; trilaurin; pancreatic lipase; digestion; disintegration; pH independent; tensil strength; ethylcellulose

Enteric coating is used to prevent adverse drug effects such as gastric irritation caused by aspirin[1] or to improve bioavailability.[2,3] Cellulose acetate phthalate[4,5] (CAP), hydroxypropyl methylcellulose phthalate[5] and carboxymethyl ethyl cellulose[6] are widely used as enteric coating materials. These polymers are insoluble in acid media, but are soluble in neutral and alkali media. In general, the gastric pH value is considered to be below 2. However, it has been reported that the gastric pH can rise to near 7 in humans at physiological condition.[7] Also, if a subject has hypo- or anacidity, or is given some antacids or a histamine H_2 blocker such as cimetidine, the pH in the stomach spontaneously increases. Therefore, it is possible that a drug in one of the traditional enteric coated preparations could be released in such stomach conditions, contrary to expectation.

The difference in conditions of the stomach and the small intestine is enzymatic activity other than pH. In the previous work,[8] we reported that a triglyceride sphere made of tristearin and trilaurin was useful for an enteric release dosage form sensitive to pancreatic lipase. Watanabe *et al.* successfully prepared enteric aspirin granules sensitive to lipase by using other acylglyceroles.[9] There has been no reports made about enteric coated tablets being disintegrated by enzymatic digestion in the small intestine.

In the present study, we tried to develop enteric coated tablets which are not influenced by pH, but are sensitive to pancreatic lipase.

Experimental

Preparation of Core Tablets Two hundred (200) g of sulfamethizole (Eisai Co., Japan (SMZ)) and 800 g of lactose (Nacalai Tesque, Inc., Japan) were mixed in a mortar. One hundred and thirty (130) ml of 5% potato starch (Wako Pure Chem., Japan) solution were added and kneaded. The mass was granulated in a wet granulator (Erweka, FRG) and dried at 50 °C for 6 h. Granules between 297—1000 μm in size were used for tableting. The granules mixed with a lubricant, magnesium stearate (0.4% weight of granules), were tableted on an Erweka single punch tablet machine (Erweka, FRG) equipped with a 10 mm punch. The tablet weighed 330 ± 11 mg.

Coating The coating materials studied are as follows: CAP (Wako Pure Chem., Japan), ethyl cellulose (80—120 cps, Nacalai Tesque, Inc., Japan (EC)) and triglycerides (Tokyo Kasei Kogyo Co., Ltd., Japan (TG)), including tricaprylin (TCL), tricaprin (TCP), trilaurin (TL), trimyristin (TM), tripalmitin (TP), tristearin (TS) and triolein (TO).

A mixture of 50 ml 2% solution of EC in ethylacetate and 50 ml 0—4% TG solution in ethylether was used as a coating solution. The tablets were coated by the fluidized bed coating technique. Each of ten tablets in a batch was marked with ink on its surface, and weighed before and after coating for calculation of mean coat weight.

Measurement of Coating Film Thickness Tablets were cut in half by a razor. The core was dyed with 0.1% methylene blue solution, and the thickness of the coating film was determined directly by microscopy.

Disintegration Test Disintegration tests were carried out with modified JPXI disintegration apparatus. Each tablet was tested with a disk in each beaker. An aliquot of test solution was removed at suitable time intervals and SMZ concentration was determined by the diazocouppling method.[10] The following parameters were obtained from the dissolution curves: lag time of disintegration and t_{50} (time required to dissolve 50% of SMZ after lag time). Whether the tablets had disintegrated completely or not was checked by the naked eye at 0.5, 1, 2 and 3 h.

Disintegration Media The media used were 1st (pH 1.2, JP-1) and 2nd (pH 6.8, JP-2) fluids of JPXI disintegration media, and JP-2 in which gall powder (0.4%, Nacalai Tesque, Inc., Japan) and pancreatic lipase (0.4%, type II, Sigma, U.S.A.) were added as a simulated intestinal fluid (JP-2-GL). The digestive capability of JP-2-GL for triglycerides was reported previously.[8] Furthermore, an isotonic sodium chloride solution perfused in rabbit and rat gastrointestinal (GI) tracts was used as the disintegration medium.

Male rabbits (2.5 kg) or rats (Wistar, 240 g) were fasted for 18 h before the experiment. Each animal was anaesthetized with sodium pentobarbitone (50 mg/kg, i.p.). The GI tract was exposed by a central midline incision. Polyethylene tubes were cannulated at the cardia (d = 4 mm) and pylorus (d = 8 mm) for rabbit stomach infusion, and at the duodenum (d = 4 mm) and lower jejunal portion (d = 4 and 8 mm for rat and rabbit, respectively) for the small intestine infusion. Isotonic sodium chloride solution was perfused at the rate of 60 ml/h for rabbits or 20 ml/h for rats from the upper to lower cannula. The outflow solution was collected in a container kept in an ice bath for 3 h and was filtered through a filter paper (Toyo, No. 2), and kept in an ice bath until use.

The disintegration media used are summerized in Table I.

Tensil Strength of EC Film Ten (10) ml of each coating solution was poured onto 5% gelatin gel in a petri dish (d = 9 cm) and the solvent was evaporated at room temperature. The film was peeled, washed with

TABLE I. Property of Disintegration Media Used

Medium	pH	Surface tension (dyn/cm)	Lipase[f] activity
JP-1	1.2	70.1	0
JP-2	6.8	69.9	0
JP-2-GL	6.7	36.0	0.75
JP-2-TW[a]	6.8	35.5	0
JP-2-G[b]	6.8	38.0	0.02
Rabbit-S-Sol[c]	1.7	45.2	0
Rabbit-I-Sol[d]	8.0	44.0	0.36
Rat-I-Sol[e]	7.4	34.5	0.49

a) JP-2 with 0.1% Tween 80. *b*) JP-2 with 0.4% gall powder. *c*—*e*) Isotonic salin perfused in rabbit stomach *c*), and intestine *d*), and in rat intestine *e*). *f*) Lipase activity is expressed as free fatty acid concentration (meq/l) 1 h after incubation of trilaurin tablet (d = 1.4 cm) at 37 °C in 40 ml of each medium (see ref. 8).

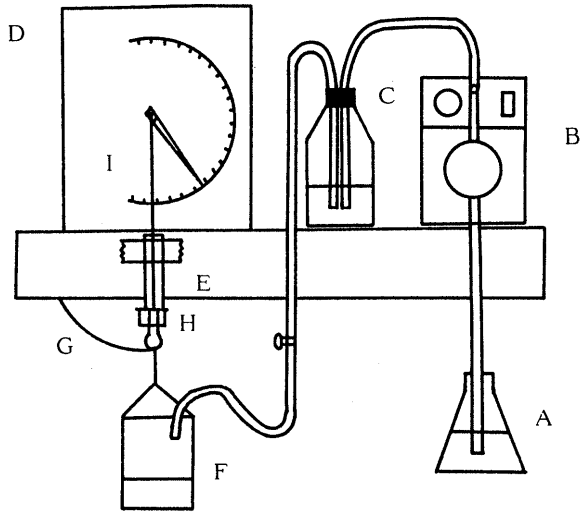

Fig. 1. Schematic Apparatus for Measurement of Tensil Strength

A, distilled water; B, pump (20 ml/min); C, dumper; D, scale for elongation; E, film; F, plastic vessel; G, steel wire as stopper; H, double clip; I, thread.

warm water (45 °C) and then dried at 30 °C for 12 h. The films were kept in a decicator at 4 °C until use.

Cut film (0.5 × 4 cm) was incubated in 30 ml of JP-2 and JP-2-GL at 37 °C. The film was removed from the media at 30 min, washed in 100 ml of distilled water three times, and then dried at 30 °C for 12 h. The tensil strength of the dried film was determined.

The apparatus for measurement of tensil strength is shown in Fig. 1. The upper site of the film was attached by cellophane tape, and a plastic vessel was attached to the lower site of the film by a double clip. The effective length of film was 2 cm. Distilled water was dropped into the vessel (20 ml/min). After the film tore, the vessel was weighed. The tensil strength of the film was expressed in terms of the weight (g/0.5 cm film width).

Results and Discussion

Evaluation of Disintegration Test The requirements for the disintegration test for pH independent enteric coated tablets sensitive to pancreatic lipase are defined in this study as follows: the tablets do not disintegrate in JP-1 and JP-2 for 2 h and disintegrate in JP-2-GL within 1 h. The length of time was set in the same manner as JPXI. It is needless to say that the shorter the disintegration time in JP-2-GL, the better for enteric release preparation.

It is difficult to determine the time of the beginning and end of disintegration by the naked eye. Therefore, the lag time of disintegration, which can be obtained from SMZ release profiles, was used as tentative criterion in order to determine the most suitable formulation for tablet coating. However, the final judgement was done by observation.

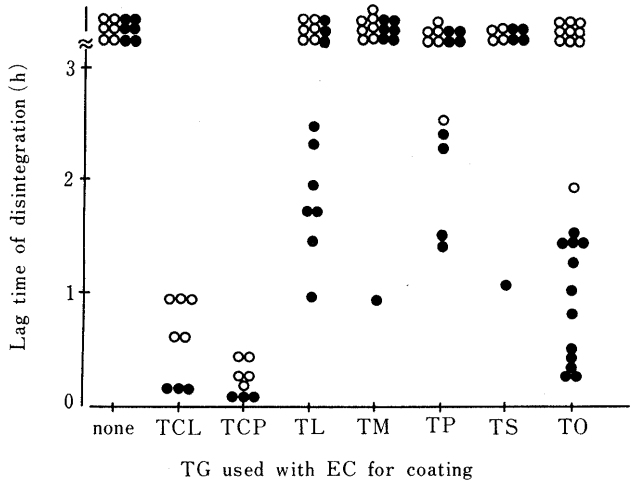

Fig. 2. Effect of Several Kinds of TG on Lag Time of Disintegration of SMZ Tablets in JP-2 (○) and JP-2-GL (●)

Coating media were 1% each of EC and TG solution. TG used and coat weight (the mean ± S.D., mg/tab) are given as follows: TCL, tricaprylin (5.9 ± 0.3); TCP, tricaprin (5.8 ± 0.4); TL, trilaurin (6.1 ± 0.8); TM, trimyristin (6.2 ± 0.6); TP, tripalmitin (5.9 ± 0.6); TS, Tristearin (5.8 ± 0.8); TO, triolein (6.3 ± 0.4).

TABLE II. Effect of TO and TL Concentrations in Coating Medium on Disintegration of Tablets

Formulation No.	Concn. (%)[a]			JP-2	JP-2-GL		Judgement[d]
	EC	TO	TL	L.T.[b]	L.T.[b]	t_{50}[c]	
1	1	0	0	> 180	> 180	—	F
2	1	0.5	0.5	150 ± 33	21 ± 7	26 ± 12	F
3	1	0.5	1	> 180	20 ± 5	18 ± 8	P
4	1	1	0.5	> 180	14 ± 2	12 ± 6	P
5	1	1	1	> 180	9 ± 1	13 ± 4	P
6	1	2	2	132 ± 50	10 ± 3	12 ± 3	F

Each value represents the mean ± S.D. (n = 4—7). Coat weights (the mean ± S.D., mg/tab) of each formulation are as follows: No. 1, 6.0 ± 0.5; No. 2, 5.9 ± 0.5; No. 3, 5.9 ± 0.5; No. 4, 6.0 ± 0.4; No. 5, 5.8 ± 0.3; No. 6, 6.2 ± 0.6. *a*) Concentration of each component in coating medium. *b*) Lag time (min). *c*) Time (min) required to release 50% of SMZ from tablet. *d*) Judgement of disintegration test for enteric coated tablet sensitive to pancreatic lipase: F, fail; P, pass.

Selection of Triglyceride Various kinds of TG were used to coat the SMZ tablets in order to find the most suitable TG for an enteric film component. Tablets were coated with 1% each of EC and TG solution by the fluidized bed technique until weight-increase reached about 6 mg/tab (see the caption in Fig. 2). The coated tablets were subjected to the disintegration test and the lag times were determined in JP-2 and JP-2-GL. The results are shown in Fig. 2. The lag times of tablets, which did not show any disintegration within 3 h, were plotted above 3 h for convenience.

As shown in Fig. 2, no combination of EC and TG satisfied the requirements of the enteric film. However, it is found that the difference of lag times between JP-2 and JP-2-GL for the tablets coated with EC with TO or TL were relatively larger compared with other tablets. It seems that TL and TO are good candidates to use for the enteric film.

The lag times in JP-2-GL vary widely from 1 to over 3 h and from 0.25 to 1.5 h for the tablets coated with TL and TO, respectively. One of the causes of this variation may be due to the inconsistency in coat weight, but the

correlation between the lag time and the coat weight is not clear since each tablet was not weighed.

The Effect of TO and TL Concentration in Coating Medium on Disintegration Time Based on the results in Fig. 2, the effect of the combination of TO and TL was investigated. The disintegration data, which are summerized in Table II, were obtained when both TL and TO were used together as components of the coating media. The durability of coating film in JP-2 was almost enough except for formulations No. 2 and No. 6. On the other hand, the lag time in JP-2-GL of formulation No. 5 was the shortest of all the formulations. It was confirmed by the naked eye that all the tablets of formulation No. 5 disintegrated completely within 30 min. It was suggested that the most suitable formulation sensitive to lipase was No. 5 (TOTL-Tab), which used 1% each of EC, TL and TO solution as a coating medium.

Effect of Coating Weight on Disintegration for TOTL-Tab In order to decide the acceptable range of coat weight for an enteric release preparation, disintegration tests were carried out for TOTL-Tabs with varying coat weights. The relationship between coat weight and lag time of disintegration for TOTL-Tab and results of the tests were shown in Fig. 3. Lag time of TOTL-Tabs, of which coat

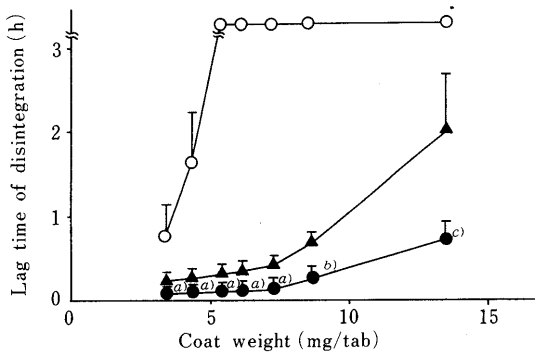

Fig. 3. Effect of Coat Weight on Lag Time of Disintegration for TOTL-Tab

○, lag time in JP-1 and JP-2; ●, lag time in JP-2-GL; ▲, (lag time+t_{50}) in JP-2-GL. Each point represents the mean±S.D. (n=4—6). *a*) All the tablets disintegrated completely within 1 h. *b*) One of 6 tablets did not disintegrate completely within 1 h. *c*) Five of 6 tablets did not disintegrate completely within 1 h.

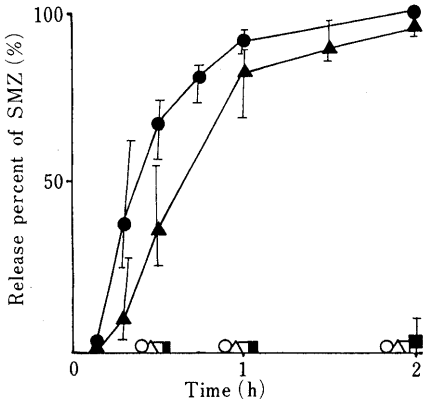

Fig. 4. Effect of Disintegration Media on SMZ Release Profiles from TOTL-Tab

Media: △, JP-1; ○, JP-2; ●, JP-2-GL; ▼, Rat-I-Sol; □, JP-2 with 0.1% Tween 80; ■, JP-2 with 0.4% gall powder. Coat weights were 5.5±0.4 mg/tab. Each point represents the mean value and the vertical bars indicate maximum and minimum values (n=3—6).

weights were in the range of 5 to 7 mg/tab, were less than 20 min in JP-2-GL and all of these tablets disintegrated completely within 1 h in JP-2-GL. But they did not disintegrate in JP-1 and JP-2 in 3 h. The standard deviation of coat weight used was within 10% of the mean value. It is suggested that TOTL-Tabs, with a coating weight of about 6 mg/tab, are useful as an enteric coated tablet without exception. The coating film thickness of these suitable tablets was in the range of 15 to 20 μm.

Effect of Media on Disintegration Disintegration tests of the TOTL-Tab were carried out in several kinds of media. Typical dissolution profiles of SMZ from the tablets are shown in Fig. 4. The release of SMZ from the TOTL-Tab was not detected in JP-1, JP-2, and JP-2 with Tween 80 (0.1%) or gall powder (0.4%) up to 2 h. Only in JP-2-GL and Rat-I-Sol (see Table II), which have digestive capability for lipid, were the tablets rapidly disintegrated and SMZ was released into these media. These results suggest that the destruction of coating film was caused by lipase, but not by solubilization ability, improvement of wettability or penetration of water by the surfactants, gall powder and Tween 80.

Tensil Strength of EC Film Containing TO and TL In order to confirm the above results, the effect of lipase digestion on tensil strength of EC films containing different amounts of TO and TL was investigated. Results are summarized in Table III.

The tensil strength of film without incubation was not affected by adding TL, but decreased to about a half by adding TO. At the same time, tensil elongation of each film was measured; 14%, 11%, 56% and 51% for EC, EC with TL, EC with TO and EC with TOTL, respectively. These results suggested that TO functions not only as a substrate for lipase but also as a plasticizer for film.

The incubation in JP-2 and JP-2-G for 30 min had no influence on the tensil strength of the film tested, while the tensil strength of the film incubated in JP-2-GL decreased significantly. In particular, the film containing EC, TO and TL (1 : 1 : 1 weight ratio, TOTL-film), which was the same as the coating material of the TOTL-Tab, was so weak after incubation for only 10 min in JP-2-GL, it could not be removed from the incubation medium. These results supported the finding of the disintegration behaviour in the TOTL-Tab in JP-2-GL.

This method of measuring the tensil strength is very simple and accurate and it is expected that it might become a useful technique for development of pH-independent coating film

Table III. Tensil Strength of EC Film

Film components[a]			Tensil strength (g/0.5 cm)			
			Pre-incubation	After incubation[b]		
EC	TO	TL		JP-2	JP-G[c]	JP-2-GL
1	0	0	216±43	193±48	169±29	179±22
1	0	1	203±18	220±36	185±11	99±39
1	1	0	127±27	121± 7	118±14	19±16
1	1	1	124±43	112±36	105±10	0[d]

Each value represents the mean±S.D. (n=4—6). *a*) Weight ratio in film. *b*) Film was incubated for 30 min in each medium, then dried. *c*) See Table I. *d*) Film torn during incubation.

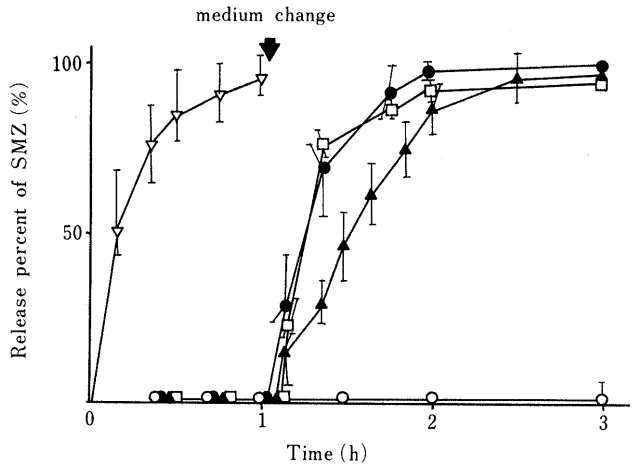

Fig. 5. Effect of Medium Change on Release Profiles of SMZ from TOTL-Tab and CAP-Tab

▽, plain tablet, JP-1; □, CAP-Tab, JP-1 to JP-2; ○, TOTL-Tab, JP-1 to JP-2; ●, TOTL-Tab, JP-1 to JP-2-GL; ▲, TOTL-Tab, Rabbit-S-Sol to Rabbit-I-Sol. Coat weights of TOTL-Tabs were 5.5±0.4 mg/tab. Each point represents the mean value and the vertical bars indicate maximum and minimum values ($n=2$—6).

like TOTL-film as lipase sensitive material.

Comparison with CAP Coated Tablets The disintegration behaviour of the TOTL-Tab was compared with tablets coated with CAP (CAP-Tab). CAP was selected as a reference because it is used extensively in the market. The result is shown in Fig. 5. CAP-Tab, which is a typical pH sensitive enteric coating tablet, did not disintegrate in JP-1, but did disintegrate quickly after changing the medium to JP-2. On the other hand, the change of medium from JP-1 to JP-2 did not affect the TOTL-Tab. When the medium was changed from JP-1 to JP-2-GL or from Rabbit-S-Sol to Rabbit-I-Sol, rapid disintegration of the TOTL-Tab was observed.

The disintegration of the TOTL-Tab was caused by lipase, but not by pH. Therefore, it is concluded that TOTL-coating is useful for pH independent enteric release tablet sensitive to pancreatic lipase. Even if the TOTL-Tab is coadministered with some antacids including sodium bicarbonate or with an inhibitor for secretion of gastric juice such as cimetidine, a drug contained in the tablet could be released at the duodenum.

It is well known that the lipase secretion increased after ingestion of fatty foods. Therefore, digestion in the small intestinal tract is not constant. The possibility that the TOTL-Tab will not disintegrate at the suppresive condition of lipase secretion must be considered. However, this was not investigated in the present study. The effect of foods on drug release from the TOTL-Tab should be studied using animals and human volunteers in the future.

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