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Absorption of Diazepam from a Lipid-Containing Oral Dosage Form

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The drug absorption characteristics of a lipid-containing oral dosage form were studied in human subjects and rats. Diazepam was employed as a model drug and medium-chain triglyceride (MCT) was used as a model lipid.

When administered orally to four human subjects, there was no significant difference between diazepam soft capsules and tablets in the average plasma levels of the drug, due to a large intersubject variation. However, when administered to an individual subject repeatedly, the soft capsules showed the tendency of faster drug absorption and superior reproducibility in the plasma level-time curve, suggesting a more uniform drug absorption rate compared with the tablets.

The mechanism of this effect was further investigated in the rat model dosing a small amount (2 μl/rat) of MCT solution or aqueous suspension. After oral administration, the retention of diazepam in the small intestine was quite small compared with that in the stomach, suggesting the importance of the gastric disappearance rate in drug absorption from these preparations. The gastric drug disappearance rate of MCT solution was faster and significantly less variable than that of the aqueous suspension, which was considered to be the main cause of the more uniform drug absorption rate of the oral diazepam-MCT preparations.

It is suggested that diazepam, though it is a weak base, was emptied from the stomach mostly while retained in the lipid, and thus was affected by the movement of MCT in the GI tract.

Keywords——oral dosage form; soft capsule; MCT solution of diazepam; human subject; rat model; uniform drug absorption rate

A solid dosage form containing a poorly water-soluble drug tends to cause bioequivalence problems attributable to formulation factors such as dissolution characteristics. Digoxin has been extensively investigated as a typical drug of this kind.[2]

In our preceding paper[3] it was shown that in the rat, the absorption rate of the lipid-soluble and poorly water-soluble drug 1-cyclopropyl-4-phenyl-6-chlor-2(1H)-quinazolinone (SL-512) from a medium-chain triglyceride (MCT) preparation was less variable than that from an aqueous suspension. One of the advances in this series of studies has been our clarification of the drug absorption characteristics of lipid-containing oral dosage forms in rats[3–5] by reducing the dose level of lipids to a level comparable to the clinical unit dose. It was expected from the above results that the blood level of SL-512 would be less variable compared with solid formulations when MCT soft capsules of SL-512 were administered to human subjects. However, sufficient safety data have not yet been accumulated on SL-512 for studies in man.

1) Location: *Kurakakiuchi 1-3-45, Ibaraki city, Osaka 567, Japan.*
2) G. Mallid, D. Schmidt, and J. Lindenbaum, *Clin. Pharmacol. Ther.*, **18**, 761 (1975); P. Ghirardi, G. Catenazzo, O. Mantero, C. Merotti, and A. Marzo, *J. Pharm. Sci.*, **66**, 267 (1977); M. Allonen, S. Kangas, S. Pynnonen, and M. Salonen, *Acta Pharmacol. Toxicol.*, **41** (Suppl. 4), 39 (1977); P. Reissell, K. Ojala, V. Manninen, and A. Sothman, *Brit. J. Clin. Pharmacol.*, **4**, 235 (1977); C. Longhini, V. Alvisi, B. Bangni, F. Portaluppi, and C. Fersini, *Curr. Ther. Res.*, **21**, 909 (1977).
3) Y. Yamahira, T. Noguchi, T. Noguchi, H. Takenaka, and T. Maeda, *J. Pharm. Dyn.*, **2**, 52 (1979).
4) Y. Yamahira, T. Noguchi, H. Takenaka, and T. Maeda, *J. Pharm. Dyn.*, **1**, 160 (1978).
5) Y. Yamahira, T. Noguchi, H. Takenaka, and T. Maeda, *Inter. J. Pharm.*, in press.

Since diazepam is a weak base, the drug dissolution rate of tablets in the stomach is dependent on the pH of the surrounding fluid. As a matter of fact, it was reported that dissolution profiles of diazepam tablets at pH 4.6 varied among different brands of tablets, resulting in bio-inequivalence in man.[6] Thus, diazepam was considered to be a suitable model of a poorly water-soluble drug. In this paper, employing MCT as a model lipid, the drug absorption characteristics of diazepam-MCT soft capsules were studied in human subjects and the mechanism of uniform drug absorption of diazepam-MCT solution was examined using the rat model presented previously.[3]

Experimental

Materials——Diazepam was synthesized and purified in Sumitomo Chemical Co., Ltd. As diazepam tablets, the commercial brand Serenzin® (Sumitomo Chemical Co., Ltd.) was used. MCT, employed as the model vehicle, was obtained commercially (ODO®, Toshin Chemical Co., Japan). Each soft capsule contained 250 mg of 2% diazepam-MCT solution in a gelatin capsule. The disintegration time of each tablet and capsule was within 10 minutes in the first fluid of the JP IX Disintegration Test at 37°. Other materials used in this study were of reagent grade. Preparations employed in this investigation are listed in Table I.

Table I. Composition and Dose of Diazepam Preparations employed in This Investigation

Experiment	Lipid preparation	Aqueous preparation (Solid preparation)
Human oral administration	2% MCT solution diazepam 2 g MCT 98 g Dose: 5 mg/capsule/man	5mg diazepam tablet Serenzin® Dose: 5 mg/tablet/man
Rat oral administration (with or without pylorus ligation)	4% MCT solution diazepam 1 g MCT to make 25 ml Dose: 80 μg/2 μl/rat	4% aqueous suspension diazepam 1 g arabic gum 0.25 g water to make 25 ml Dose: 80 μg/2 μl/rat
Rat gastric absorption	4% MCT solution diazepam 1 g Sudan Blue 0.25 g MCT to make 25 ml Dose: 80 μg/2 μl/rat	4% aqueous suspension diazepam 1 g sulfaguanidine 0.25 g arabic gum 0.25 g 0.1 N HCl to make 25 ml Dose: 80 μg/2 μl/rat
Rat *in vitro* everted stomach		0.4 mg% aqueous solution diazepam 4 mg JP-1[a] to make 1000 ml Dose: 40 μg/10 ml/stomach
Rat *in vitro* everted intestine		0.4 mg% aqueous solution diazepam 4 mg polysorbate 80 100 mg JP-2[b] to make 1000 ml Dose: 40 μg/10 ml/intestine

a) The first fluid of the JP IX Disintegration Test.
b) The second fluid of the JP IX Disintegration Test.

Absorption Study in Human Volunteers——Four healthy male volunteers (30—47 years old) were fasted for 12 hours prior to the experiment. After blank plasma had been drawn a diazepam tablet or a soft capsule containing 5 mg of the drug was administered with 150 ml of water and a blood specimen was drawn at the

6) H. Ogata, Y. Horii, N. Aoyagi, T. Shibazaki, M. Koibuchi, A. Ejima, and Y. Kawazu, The 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978.

designated time. The administration of the tablet or the soft capsule was conducted in a crossover manner. At least 2 weeks was allowed for wash-out of the drug before the next dosing.

Animal Experiments——Oral absorption experiments as well as gastric absorption experiments in rats were carried out as described in our preceding paper.[3] The pylorus was ligated under ether anesthesia in the case of gastric absorption experiments. To examine the degradation of diazepam in the gastrointestinal (GI) tract, the *in vitro* everted sac method was used. After fasting for 20 hours, the rat stomach and the small intestine were removed, everted and the everted small intestine was made into three sacs of equal length. The everted stomach or small intestine was incubated in 10 ml of 0.4 mg% diazepam aqueous solution at 37° under O_2/CO_2 (95 : 5) gas bubbling. After incubation for 60 minutes the everted sacs were removed and washed with 10 ml of water. The washing was added to the incubation medium and diazepam was extracted with ether. Diazepam remaining in the tissue was extracted with ether after homogenization.

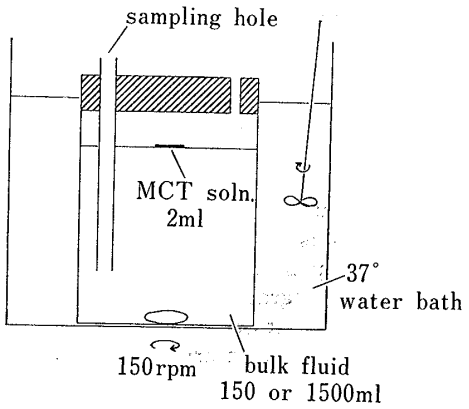

Fig. 1. Schematic Representation of the Apparatus for Dissolution Studies

Disappearance of MCT from the GI tract was measured using the *in situ* loop method. Under ether anesthesia the pylorus and ileocaecal junction were ligated, then 2 μl of MCT was ingested into the stomach or injected directly into the duodenum at a point 5 mm from the pylorus using the previously described gastric syringe[3] with a slight modification.

***In Vitro* Dissolution Study**——The dissolution characteristics of diazepam from MCT solution were investigated using the apparatus shown in Fig. 1. An aliquot of 2.0 ml of 2% (w/v) diazepam-MCT solution was placed on 150 or 1500 ml of the bulk fluid, and stirred with a magnetic stirrer at a speed of 150 rpm. At the designated time, 2 ml of bulk fluid was drawn up through a glass tubing. The first fluid of the JP IX Disintegration Test (pH 1.2) and distilled water were used as bulk fluids. An adequate volume of ethanol was added to the specimen and the dissolution rate was determined by measuring the optical density at 240 nm.

Assay Procedure for Diazepam——At the designated time after administration to a rat, the stomach and the whole small intestine of the rat were removed and homogenized, and diazepam remaining there was extracted with ether. To the ether extract of diazepam from the human plasma or samples in rat experiments, SL-512 was added as an internal standard and unchanged diazepam was analyzed by gas chromatography. A gas chromatograph (GC-5A, Shimadzu Seisakusho, Japan) equipped with a ^{63}Ni-electron capture detector was used. A glass column of 1.5 m × 0.3 cm was packed with 10% SE-30 on Chromosorb W 80/100 AW-DMCS. The temperatures were adjusted to 260°, 290° and 310°, for the column, the injection port and the detector block, respectively. The flow rate of the carrier gas (99.999% N_2) was set at 60 ml/min.

Assay Procedure for Sulfaguanidine and Sudan Blue——The markers of gastric emptying, sulfaguanidine and Sudan Blue, in the washings or in tissue were analyzed by a method identical to that described in our previous papers.[3,4]

Assay Procedure for MCT——At 30 minutes after administration, the stomach or the small intestinal loop was washed out with ether and the remaining MCT was analyzed by gas chromatography under the conditions described in our preceding paper.[3]

Results and Discussion

Plasma Diazepam Level after Oral Administration of Soft Capsules in Human Volunteers

Drug products of incomplete bioavailability tend to be associated with large inter- and intrapatient variability in drug absorption rate, which is especially undesirable for a drug with a narrow safety margin. The results of *in vitro* experiments suggest that soft encapsulation of a lipid solution of such a drug could overcome the problems of content uniformity and dissolution characteristics.[7] Furthermore, as shown in our preceding paper,[3] the gastric emptying rate of the lipid-soluble drug SL-512 in the rat, administered as MCT solution, was less variable than that of the same drug administered as an aqueous suspension. Since the gastric emptying process of SL-512 is the rate-determining step of drug absorption from

7) F. Hom and J. Miskel, *J. Pharm. Sci.*, **59**, 827 (1970).

lipid preparations,[4] the above results suggest that a soft capsule is the preferable dosage form for a lipid-soluble drug in view of the low variability in the drug absorption rate. To investigate the uniformity in the bioavailability of diazepam soft capsules, the plasma level of diazepam was measured after administration to human subjects. Soft capsules or tablets of diazepam were administered to four fasted healthy volunteers by a crossover method and the time course of the plasma diazepam level observed is shown in Fig. 2. Although inter-

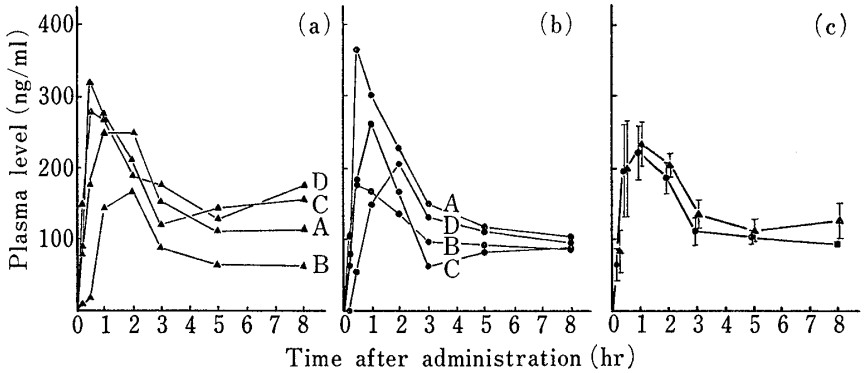

Fig 2. Plasma Level of Diazepam after Oral Administration of Tablets or Soft Capsules in Human Volunteers—Crossover Study

(a) tablet, (b) 2% MCT capsule, (c) mean±S.E. of the 4 subjects; ▲ tablet, ● 2% MCT capsule.
Dose level: diazepam 5 mg/man.
The ages (y) and body weights (kg) of the subjects were A (30, 55), B (35, 51), C (40, 63) and D (47, 60), respectively.

individual variation was found in both formulations (Fig. 2-(a), (b)), the mean plasma level-time curves were in good accordance for the two dosage forms (Fig. 2-(c)). It is known that the plasma level of diazepam after tablet dosage shows great interindividual variation.[8] It was therefore considered on the basis of these results that an ordinal crossover administration study using a limited number of subjects was insufficient to clarify the properties of diazepam soft capsules due to the large interindividual variation.

In clinical practice, however, the drug absorption characteristics of a dosage form in an individual patient would be no less important than that in a group of patients. In the case of oral drug administration, the plasma level of the drug is considered to be controlled by many factors, such as the gastric emptying rate, the metabolic rate and the distribution volume of the drug. Since the metabolic rate and the distribution volume seem to be specific to individual subjects, the intraindividual variation of the plasma level of the drug would be small if the drug absorption rate was invariable. In fact, the results of repeated administration studies in subjects A, B and D (not repeated in subject C) suggested that in comparison with the case of tablets (Fig. 3-(a), 4-(a), 5-(a)), MCT soft capsules of diazepam represented an

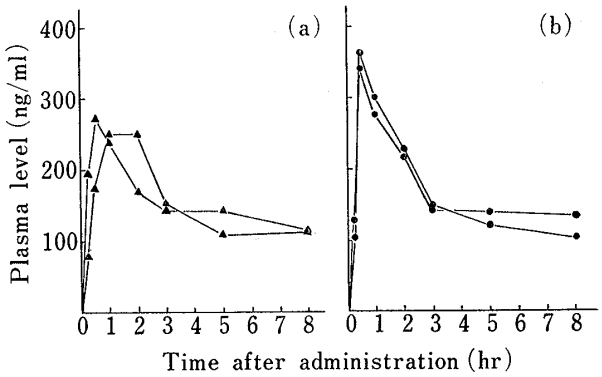

Fig. 3. Intraindividual Variation of Plasma Diazepam Appearance after Oral Administration in Subject A—Crossover Study

(a) tablet, (b) 2% MCT capsule.
Dose level: diazepam 5 mg/man.

8) M. Mandelli, G. Tognoni, and S. Garattini, *Clin. Pharmacokin.*, 3, 72 (1978).

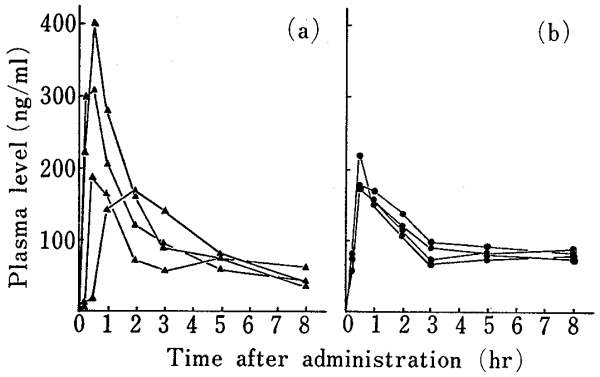

Fig. 4. Intraindividual Variation of Plasma Diazepam Appearance after Oral Administration in Subject B—Crossover Study

(a) tablet, (b) 2% MCT capsule.
Dose level: diazepam 5 mg/man.

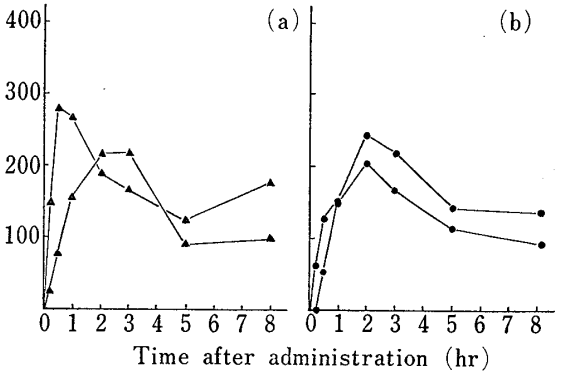

Fig. 5. Intraindividual Variation of Plasma Diazepam Appearance after Oral Administration in Subject D—Crossover Study

(a) tablet, (b) 2% MCT capsule.
Dose level: diazepam 5 mg/man.

improved preparation as regards intraindividual variation (Fig. 3-(b), 4-(b), 5-(b)). Statistically significant differences ($p<0.05$) were observed between the two dosage forms at 0.25, 0.5, 1 and 2 hour in subject B by variation analysis. This result was in good accordance with a recent report that intrasubject variation of the absorption of digoxin from a soft capsule was smaller than that from a tablet.[9] Although the available data were limited, a tendency was noted in subject A and B that the time required to reach peak plasma level was shorter for the soft capsule than the tablet, suggesting faster drug absorption from the soft capsule. This is consistent with the results of a recent report wherein soft capsules of temazepam showed a significantly faster plasma peak time than hard capsules in man.[10]

Evaluation of Diazepam-MCT Solution using Rats

In our preceding paper[3] the utility of an *in vivo* evaluation method using rats for lipid-containing oral dosage forms was presented employing SL-512 as a model drug. Using the same method, MCT solution of diazepam was compared with an aqueous suspension, a model of solid formulations, to investigate the mechanism of the apparently faster and uniform absorption of diazepam from MCT soft capsules.

The gastric retention of diazepam at 30 and 60 minutes after oral administration was estimated preliminarily to be 55.8±4.0 and 27.8±2.6% of dose for MCT solution, and 65.7 ±8.3 and 38.9±6.8% of dose for the aqueous suspension (mean±S.E. of 3 animals), respectively. The observed gastric disappearance rate of diazepam seemed to follow a first-order process for both preparations. Both SL-512 and Sudan Blue retained in 2 μl of MCT emptied from the stomach following an apparent first-order process for more than 120 minutes after

Table II. *In Vitro* Degradation of Diazepam by an Everted Sac of Rat Stomach or Small Intestine

Site of GI tract	Diazepam remaining (% of initial)		
	In the medium	In the tissue	Overall
Stomach	34.4±1.4	66.5±4.0	100.9±4.8
Small intestine	97.3±1.9	3.8±1.2	101.2±0.7

Data are expressed as the means±S.E. of at least 4 experiments.

9) R. Stoll, *Clin. Pharmacol. Ther.*, **23**, 131 (1978).
10) L. Fuccella, G. Bolcioni, V. Tamassia, L. Ferrario, and G. Tognoni, *Europ. J. Clin. Pharmacol.*, **12**, 383 (1977).

oral administration to rats.[3] Using our rat model of dosing 2 mcl of test preparations, the amount of diazepam remaining in the GI tract at 30 minutes after oral administration was measured in this report and the extent of absorption was calculated by subtracting the remaining part from the initial dose.

Before this experiment, the absence of degradation of diazepam in the GI tract during the experiments was ascertained by the *in vitro* everted sac method. As shown in Table II, 100% of diazepam added to the initial incubation medium was recovered from both the stomach and the small intestine after incubation for 60 minutes. In this study, 67% of diazepam was retained in the gastric tissue after washing, suggesting a large gastric absorption capacity for diazepam.

Table III. Gastrointestinal Retention of Diazepam after Oral Administration to Rats

Preparation	% of dose remaining at 30 min		% of dose absorbed
	Stomach	Small intestine	
MCT soln.	59.5± 4.1 [a)]	1.1±0.6	39.4±4.1
Aq. susp.	72.0±10.6 [a)]	2.3±0.7	25.7±8.2

Dose level: diazepam 4% (w/v), 2 μl/rat.
Data are expressed as the means±S.E. of 5 animals.
a) $F=6.70, p<0.05$.

The gastric disappearance rate of orally dosed diazepam was apparently faster from MCT solution than from an aqueous suspension (Table III). As was the case for SL-512,[3] the intestinal retention of diazepam was so small that the absorption rate of the drug was mainly dependent on its gastric disappearance rate. It was noteworthy that the gastric disappearance of diazepam was less variable in the case of MCT solution than in that of the aqueous suspension ($p<0.05$ by variation analysis). This was in good accordance with the case of SL-512 reported in our preceding paper[3] and with the results of human studies of diazepam described above. Considering the absence of gastric degradation and the slight intestinal retention of diazepam, these results suggest that the observed uniform drug absorption rate of diazepam-MCT preparation is attributable to low variability in the gastric disappearance rate of diazepam administered as MCT solution.

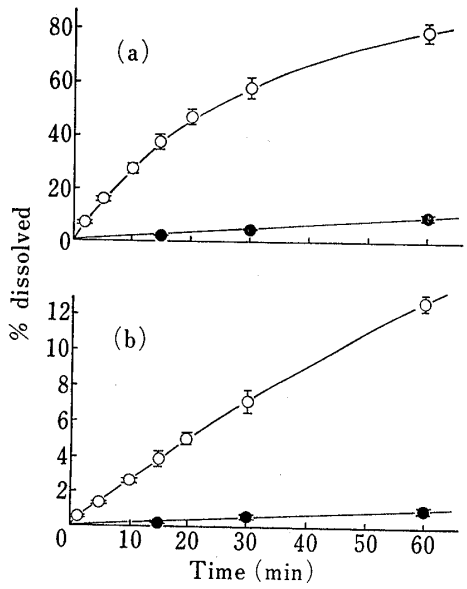

Fig. 6. *In Vitro* Dissolution Curve of Diazepam from MCT Solution

(a) MCT 2 ml, bulk fluid 1500 ml, (b) MCT 2 ml, bulk fluid 150 ml. Bulk fluids employed were distilled water (●) and the first fluid of the JP IX Disintegration Test (○). The vertical bar represents±S.D. of 3 experiments.

Significance of Dissolution of Diazepam from MCT into the Gastric Fluid in Rats

Since diazepam is a weak base, its partition into the aqueous phase could not be neglected in fluid of

Table IV. Disappearance of Diazepam from the Pylorus Ligated Stomach in Rats

% of dose lost in 30 min	
MCT soln.	Aq. susp.
13.1±5.1	21.2±4.0

Dose level: diazepam 4% (w/v), 2 μl/rat.
Data are expressed as the means±S.E. of at least 4 animals.

acidic pH. Figure 6 shows the results of an *in vitro* dissolution study. When the volume of the bulk fluid was 750 times the lipid volume (Fig. 6-(a)), 60% of diazepam was dissolved in 30 minutes into the first fluid of the JP IX Disintegration Test (pH 1.2), while the rate of dissolution into distilled water (pH 6.5) was very small.

The volume of water in the rat gastric lumen, measured by weight, was 0.15±0.01 ml (mean±S.E. of 5 rats), which was only 75 times that of the lipid administered. A similar dissolution experiment was therefore performed using bulk fluid with a volume of 75 times that of the lipid (Fig. 6-(b)). In this case, the release rate of diazepam into aqueous phase of pH 1.2 fell to one-ninth of the previous value, that is, only 7% in 30 minutes.

The disappearance of diazepam from the stomach was then compared in rats with a ligated pylorus; the results are shown in Table IV. Since gastric emptying was not involved in this experiment, the disappearance, in this case drug absorption, was apparently smaller from MCT solution than from the aqueous suspension (though the difference was not statistically significant by the t-test). This suggests that the major part of diazepam might be retained in the MCT in the stomach and thus prevented from being taken up by the gastric mucosa.

To investigate the contribution of the gastric absorption of diazepam from aqueous suspension under normal conditions, an aqueous suspension of the drug was administered into the rat stomach with sulfaguanidine. Sulfaguanidine is practically unabsorbable in the rat stomach[11] and has been used as a marker of gastric emptying. Since diazepam is not degraded in the rat stomach (Table II), the difference between the gastric disappearance of diazepam and that of sulfaguanidine essentially corresponds to the gastric absorption of diazepam. As shown in Table V, the estimated gastric absorption of diazepam was about

Table V. The Role of Gastric Absorption in the Gastric Disappearance of Diazepam from Aqueous Suspension in Rats

% of dose lost from the stomach in 30 min		Diazepam absorbed (% of dose)	$\frac{X-Y}{X}$
Diazepam (X)	Sulfaguanidine (Y)	($X-Y$)	
30.4±4.1	22.8±4.2	7.6±1.0	0.261±0.041

Two mcl of 0.1 N HCl aqueous preparation containing 4% (w/v) of diazepam and 1% (w/v) of sulfaguanidine was orally administered to a rat. Data are expressed as the means±S.E. of 4 animals.

Table VI. The Role of Gastric Absorption in the Gastric Disappearance of Diazepam from MCT Solution in Rats

% of dose lost from the stomach in 30 min		($A-B$)	$\frac{A-B}{A}$
Diazepam (A)	Sudan Blue (B)		
40.8±1.2	27.9±1.2	12.9±1.8	0.312±0.040

Two mcl of MCT solution containing 4% (w/v) of diazepam and 1% (w/v) of Sudan Blue was orally administered to a rat. Data are expressed as the means ±S.E. of 5 animals.

11) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.* (Tokyo), **12**, 413 (1964).

26% of the gastric disappearance of the drug after oral administration of an aqueous suspension.

A similar experiment was done with MCT preparation employing Sudan Blue as a marker of the gastric emptying of MCT. Sudan Blue was shown to be practically unabsorbable from the rat stomach.[3] As shown in Table VI, in the case of MCT solution, the difference between the gastric disappearance of diazepam (A) and that of Sudan Blue (B) was about 31% of A. It was considered that the gastric disappearance of Sudan Blue (B) essentially corresponded to the gastric emptying of diazepam retained in MCT, because the dissolution of the drug from MCT in the rat stomach seemed limited during the experiment due to the small volume of water in the gastric lumen (Fig. 6-(b)). The value $(A—B)/A$ then corresponds to the sum of the ratios of gastric absorption of diazepam and the gastric emptying of the drug free from MCT dissolved in the gastric fluid.

Assuming the gastric emptying ratio of diazepam administered with MCT by using the results of Tables IV and V, that is $0.26 \times 13/21 = 0.16$, the gastric emptying ratio of diazepam released into the aqueous medium was estimated from the data of Table VI as $(A—B)/A - 0.16 = 0.15$, which is less than a quarter of the gastric emptying ratio of diazepam retained in MCT, that is $B/A = 0.69$.

It was considered, therefore, that in the stomach a part of diazepam was released from MCT to the aqueous phase, some part of which was taken up by the gastric mucosal cells and was absorbed there, and that most of the administered diazepam moved into the duodenum while retained in MCT, together with unabsorbed diazepam in the aqueous phase, and was then absorbed from the small intestine. This was in contrast to the case of SL-512[3-5] where the dissolution of the drug from lipids into the GI fluid was practically negligible.

Disappearance of MCT in the GI Tract of Rats

Since most of the diazepam was transported into the duodenum retained in MCT, the uniform gastric emptying rate and rapid absorption of the drug in the small intestine might have been due to the rapid dispersion and rapid metabolism of MCT. Rapid digestion and absorption of MCT in the small intestine has been reported elsewhere.[12] The disappearance of MCT from the GI loop was therefore measured in the rat. As shown in Table VII, MCT

Table VII. Disappearance of MCT from Rat Gastrointestinal Loop

% of dose remaining at 30 min	
Stomach	Small intestine
75.7±1.6	5.8±3.3

Dose level: MCT 2 μl/loop.
Data are expressed as the means±S.E. of at least 4 animals.

disappeared almost completely from the small intestine and a little disappeared from the stomach in 30 minutes. This property of MCT should affect the absorption characteristics of the drug in the GI tract. Though few data have been reported on the metabolism of MCT in the stomach so far, it has been reported that lingual lipase having lipolytic activity towards the long chain triglyceride is present in the rat stomach.[13] If the observed disappearance of MCT in the stomach was caused by partial metabolism, the resulting more

12) V. Valdivieso and A. Schwabe, *Gastroent.*, **48**, 336 (1965); M. Playoust and K. Isselbacher, *J. Clin. Invest.*, **43**, 878 (1964); N. Greenberger and T. Skillman, *New Eng. J. Med.*, **280**, 1045 (1969); V. Valdivieso, *Dig. Dis.*, **17**, 129 (1972); V. Sallee and J. Dietschy, *J. Lipid Res.*, **14**, 475 (1973).
13) M. Hamosh and R. Scow, *J. Clin. Invest.*, **52**, 88 (1973).

hydrophilic metabolite would have accelerated the rapid dispersion of MCT, and thus contributed to the uniformity of gastric emptying rate of the lipid mixture holding the drug. The significance of metabolism of MCT in the stomach is now under investigation.

It was concluded that MCT soft capsules of diazepam were effective as a dosage form, producing a more uniform drug absorption rate compared with solid dosage forms for individual patients. It was further suggested by experiments in rats that this uniform absorption rate of diazepam was attributable to the low variability of the gastric drug disappearance rate, which would have been affected by the movement of MCT in the GI tract, because most of the diazepam was emptied from the stomach while retained in the lipid.