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EFFECTS OF PARTICLE SIZE OF BULK DRUG AND FOOD ON THE BIOAVAILABILITY OF U-78875 IN DOGS

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ABSTRACT

The effects of particle size and food on the absolute bioavailability of U-78875 in dogs after oral administration of either a suspension or tablet dosage form were investigated. A reduction of particle size caused a significant increase in bioavailability along with an increase in dissolution rate. Additionally, both suspension and tablet dosage forms administered after food caused an increase in bioavailability. Thus, to accelerate drug dissolution, a reduction of U-78875 particle size from the unmilled state is important for the optimization of formulation compositions. To increase the bioavailability of U-78875, postprandial dosing should be considered.

INTRODUCTION

U-78875, 3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5-(1-methylthyl)-imidazo[1,5-α]quinoxalin-4(5H)-one, is an anxiolytic agent. Solubility of

U-78875 in water is markedly low. Sparingly soluble drugs are likely to encounter bioavailability problems after oral administration, because dissolution is the rate-limiting step in the overall absorption process. When the drug is milled or micronized to reduce its particle size (1) and to accelerate the dissolution rate, it is important to clarify the effect of particle size of bulk drug on bioavailability after oral dosing.

It has also been reported that bioavailability of sparingly soluble drugs are often influenced by food, due to the secretion of bile which acts as a solubilizing agent (2, 3). Thus, it is also important to clarify the effect of postprandial administration on bioavailability.

In the present study, we investigated the effects of particle size and of food on the bioavailability in dogs after oral administration of U-78875 in either a suspension or tablet form. We also investigated the absorption characteristics of U-78875 in rats, because it is also important in the development of oral dosage forms to clarify the intestinal absorption characteristics of drug.

MATERIALS AND METHODS

Materials: U-78875 was supplied by The Upjohn Company (MI, USA). U-78875 was milled by a conical screen mill (coarse particle), mikropulverizer (medium), and jet mill micronizer (fine) to obtain bulk drug composed of three different particle sizes, i.e., coarse, medium, and fine, respectively. Table 1 summarizes the data on mean particle sizes. The calorimetric characteristics were investigated with a differential scanning calorimeter (Perkin Elmer, USA). Other reagents used were of analytical grade.

Solubility of U-78875 in Aqueous Solution: The solubility of U-78875 was determined as follows: 100 mg of bulk drug (fine particle) was weighed and put into test tubes, each containing 10 ml of solvent solution. Distilled water, Tween 80 solution of various concentrations, and sodium CMC solution of various concentrations were used as solvents. The test

Table 1

Particle size and melting point of U-78875 bulk drug used.

particle size	mean distribution μm	specific surface area sq.m./g	melting point °C
fine	8.8	Ca. 1.65	171.8
medium	25	Ca. 0.54	172.0
coarse	100	Ca. 0.125	172.2

Melting point was measured by differential scanning calorimeter and the value was the temperature at peak.

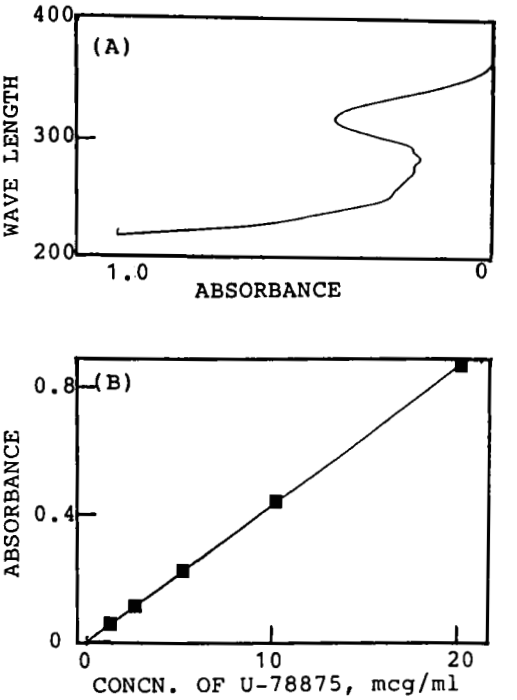

Fig. 1

(A) UV-spectrum of U-78,875 at a concentration of 10 μg/ml in water, and (B) calibration curve of U-78,875 in water at UV wave length of 316 nm: $y = 0.046x - 0.00012$ ($r=0.9999$)

tubes were shaken at 50 rpm in a water bath at 37°C for 48 hr; an aliquot was then collected after filtration through a milipore filter (pore size of 0.22 um) to determine solubility. The concentration was determined by UV absorbance at wave length of 316 nm. Fig. 1(A) shows the UV spectrum of U-78875 obtained and Fig 1(B) shows the calibration curve.

Tablets and Preparation of Oral Suspension: Oral tablets formulated with each particle size of bulk drug, with a tablet weight of 113 mg containing 10 mg of U-78875, were examined. Oral suspensions were prepared with 0.25% sodium carboxymethyl cellulose (cmc) as a vehicle, by suspending 500 mg of U-78875 in 100 ml vehicle. To avoid significant changes in the particle sizes in suspensions from the point of thermodynamic equilibrium, the suspensions were prepared 30 min before administration to dogs or use in the dissolution study.

In vitro Disintegration Study of Tablets: Disintegration of the tablets was examined by using a disintegration tester with a distoper (Toyama Sangyo, Tokyo) according to the JPXI-disintegration test.

In vitro Dissolution Study: Dissolution of U-78875 from either a suspension or tablet form was examined by the paddle method (50 rpm) according to the JPXI dissolution test. One 10 mg-tablet or 2 ml 10 mg/ml-suspension was used in this study; each formulation was tested in triplicate. At designated time points, 1 ml of medium was collected in a pipet, and 100 μl of the aliquot was diluted 10 fold with the high performance liquid chromatograph (HPLC) mobile phase which contained an internal standard (1.25 μg/ml of alprazolam).

Studies on the Location of Major Absorption Site and on the Absorption Rate in Rats (4): This study investigated whether or not absorption site specificity exists and how fast U-78875 is absorbed from the intestine. Sprague Dawley male rats, weighing between 200 g and 230 g, were fasted for 16 hr prior to the experiment; water was provided ad libitum. The in situ intestinal loop method was employed. After anesthetizing the rats intraperitoneally with sodium pentobarbital at 30 mg/kg, the middle abdomen was incised. Either about 10 cm of small

intestinal loop or about 5 cm of colonic loop was prepared, and 1 ml of drug solution was administered. The small intestine was looped as upper, middle, and lower portions. After administration, the abdomen was closed. The intestinal loop was removed at 10, 20, or 30 min after dosing, and the mucosal fluid was collected by rinsing the loop in 15 ml saline three times. The volume of combined rinse solutions was adjusted to 50 ml with saline. The concentration of the rinse solution was determined by HPLC.

Bioavailability Study in Dogs: The bioavailability study was carried out using a group of four dogs (male beagle dogs weighing between 9.5 kg and 10 kg) to evaluate three particle sizes in a tablet form and another group of four dogs to evaluate three particle sizes in a suspension form. The study was done in a 4-way cross-over design. U-78875 was given at 10 mg/dog in either a tablet or suspension form. The dogs were tested under the following two conditions: [1] In the fasted state, approximately 250 g of food (LABO D STOCK, NIHON NOUSAN) was given to the dogs at 10 a.m. of the day before dosing; the drug was administered at 9 a.m. on the following day, and the food was given at 4 hours after dosing. [2] In the fed state, approximately 250 g of food was given at 8:30 a.m., 30 min before dosing. Because the study was also to determine the absolute bioavailability, an intravenous injection was given to the dogs from the right femoral vein at 2 mg/dog (2 ml of 50% PEG 400 in saline which contained 1 mg/ml of U-78875).

After oral or intravenous administration, blood samples were collected with a heparinized syringe from the left femoral vein at designated time intervals. The blood was centrifuged at 3,000 rpm for 10 min to collect plasma, which was then frozen at -20°C prior to assay.

Assay of U-78875 with HPLC: Prior to HPLC assay, some interfering components in the sample were removed by washing the sample on a C18 mini column according to the following method: The column was washed with 6 ml methanol and then washed with 6 ml distilled water. A sample in a range of 0.5 to 1.5 ml such as plasma and a 1.0-ml internal standard solution (1.25 μg/ml of alprazolam) were loaded on the column; then the

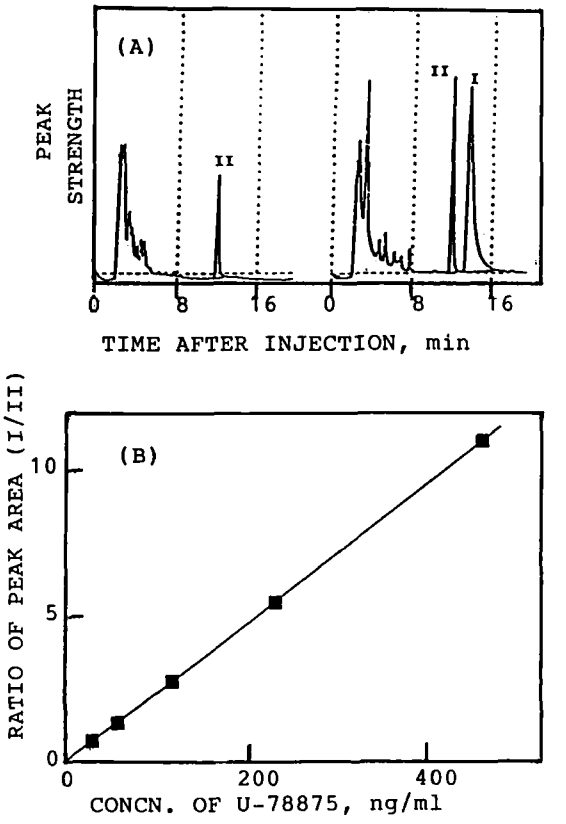

Fig. 2

(A) Typical chromatogram of U-78,875 (I) with alprazolam (II) in HPLC: A-a and A-b were the spectrum after injection of sample from plasma which were collected before and after drug administration, respectively.
(B) Calibration curve of U-78,875 in sample from plasma:
Y = 0.0266x - 0.031 (r=0.9988).

column was washed with 6 ml of distilled water. Finally, the drug and internal standard were eluted with 3 ml of methanol. The methanol solution was dried under nitrogen gas flow. The residue was dissolved with 250 μl of mobile phase for HPLC assay.

U-78875 was assayed by HPLC as follows: A liquid chromatograph (Model LC-6A, Shimadzu), equipped with a UV detector (SPD-6A,

Shimadzu), autoinjector (SIL-6B, Shimadzu), system controller (SCL-6B), and chromatopac (CR-4A, Shimadzu), was used. The separation column was 4.6 mm i.d. x 125 mm long and contained a reverse-phase column material (Nucleosil C18, Wako Pure Chemicals, Osaka). The mobile phase was a mixture of 0.05 M ammonium acetate buffer (pH 5.3), acetonitrile, and tetrahydrofulan in volumes of 650, 350, and 20 ml, respectively. The flow rate was 0.6 ml/min. U-78875 was detected at 316 nm. Assay limitation of U-78875 was 5 ng/ml. Fig. 2(A) shows a typical chromatogram of U-78875; Fig. 2(B) shows the calibration curve.

Statistical Analyses: Statistical analyses were performed by ANOVA method.

RESULTS AND DISCUSSION

Solubility of U-78875 in Aqueous Solution

The melting point of U-78875 did not change during the milling process or micronizing process as shown in Table 1. These results indicate that U-78875 exhibits sufficient physical stability to withstand the forces of particle size reduction.

The solubility of U-78875 in distilled water at 37°C is 77.4 μg/ml ± 1.8 (n=3). This result indicates that U-78875 is poorly soluble in water. Because the dissolution process of poorly water-soluble drugs is often the rate limiting step in the apparent absorption after oral administration, it is extremely important to understand the effect of particle size on bioavailability.

As there was a concern that additives used to prepare the suspension dosage form may influence the solubility of U-78875 in water, the effect of sodium CMC was investigated. When sodium CMC was added at concentrations of 0.25 to 0.5 %w/v, the solubility of U-78875 did not change. However, at 1 %w/v it increased the solubility slightly. Thus, the concentration of 0.25 %w/v sodium CMC was chosen to prepare the suspension of U-78875.

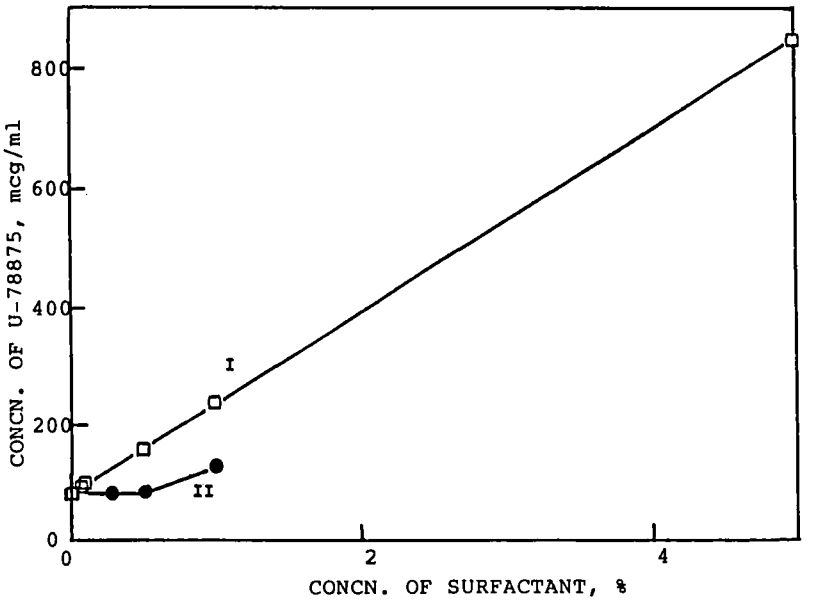

Fig. 3

Effect of polysorbate 80 (I) and sodium CMC (II) on the solubility of U-78,875 in distilled water. Regarding to the effect of polysorbate 80: y = 152.3x + 80.1 (r=0.999).

As mentioned earlier, it is important to understand the effect of food on the bioavailability of U-78875 as the drug is poorly water-soluble. Acting as a surface active agent, bile is secreted into the small intestine after a meal, and the increased secretion of bile often enhances the solubility of drug in the intestinal fluid after meal. In the present study, polysorbate 80 (Tween 80) was used as a model surface active agent instead of bile. Tween 80 increased the solubility of U-78875 in a linear manner along with the increase in the concentration of Tween 80 (Fig. 3). As it has been reported that Tween 80 at low concentrations produces micelles in water (5), the concentration of U-78875 in the medium containing Tween 80 is composed of the sum of the amount of drug in solution (aqueous) and of the amount of drug entrapped in the Tween 80

TABLE 2

The disappearance rate constant, $k_{disappearance}$, of U-78,875 from the in situ rat intestinal loops after administration of 1.0 ml solution containing 6.25 μg of U-78,875. The $k_{disappearance}$ was calculated by first order kinetics.

site of intestine	$k_{disappearance}$, $x10^{-2}$	$t_{1/2}$, min
(1) drug solution prepared with saline.		
small intestine		
upper	8.85 ± 0.76	7.92 ± 0.68
middle	6.64 ± 0.81	10.40 ± 1.26
lower	6.20 ± 0.57	11.18 ± 1.03
colon	6.15 ± 0.81	11.27 ± 1.48
(2) drug solution prepared with 1 %w/v tween 80 in saline.		
upper small intestine	9.41 ± 0.96	7.40 ± 0.75

Each value represents the mean ± S.D. (n=3).

micelles, i.e., the increase in the solubility of the drug showed a linear relationship as a function of the concentration of Tween 80 in the medium.

Intestinal Absorption of U-78875 in Rats

When developing an oral dosage form, it is important to understand the absorption characteristics of drug in the intestine; i.e., how fast the drug undergoes uptake and whether specific absorption sites or specific absorption mechanisms are involved. To characterize the intestinal absorption of U-78875, the absorption rate after administration of U-78875 solution was investigated using the in situ rat intestinal loop method (Table 2). The absorption rate occurred by first kinetics for each intestinal loop examined (data not shown), with a half life of about 10 min. These results indicate that U-78875 is absorbed by the passive transport mechanism from the intestine. A specific absorption site for U-78875 was not observed across the entire intestine. The somewhat greater absorption rate observed at the upper small intestine may be due to the greater surface area of upper small intestinal mucosa in the prepared loop. Rapid

TABLE 3

Parameter, k in equation 2, of in vitro dissolution of U-78,875 from suspension or tablets.

formulation	particle size	k, x 10^{-3}, in each medium	
		water	1% tween 80
Suspension	fine	28.9 ± 1.2	38.2 ± 2.6
	medium	7.5 ± 0.5	9.9 ± 1.1
	coarse	1.4 ± 0.1	2.1 ± 0.6
		time for 50% dissolution min	Disintegration min
Tablets	fine	6.1 ± 0.8	less than 5
	medium	11.4 ± 0.9	less than 5
	coarse	51.7 ± 3.6	less than 5

Each value represents the mean ± S.D. (n=3).

absorption of U-78875 observed in this study (half life; about 10 min) indicates that dissolving drug is taken up from the intestine rapidly and that the absorption process may not be the rate limiting step after oral administration.

As the high partition of U-78875 to Tween 80 increased the solubility in water, the high partition of drug to the micelles may influence the intestinal absorption of drug. It is also important to investigate the effect of Tween 80 on the intestinal absorption of U-78875 in the solution form. The addition of 1% w/v Tween 80 to the solution did not cause a significant change in absorption rate.

In Vitro Dissolution of U-78875 from Suspension

The dissolution of U-78875 from the suspension prepared with 0.25% w/v of sodium CMC was influenced significantly by the particle size of the bulk drug, i.e., it took longer to dissolve as the particle size increased (Table 3 and Fig. 4). Ninety percent of the fine particle suspension

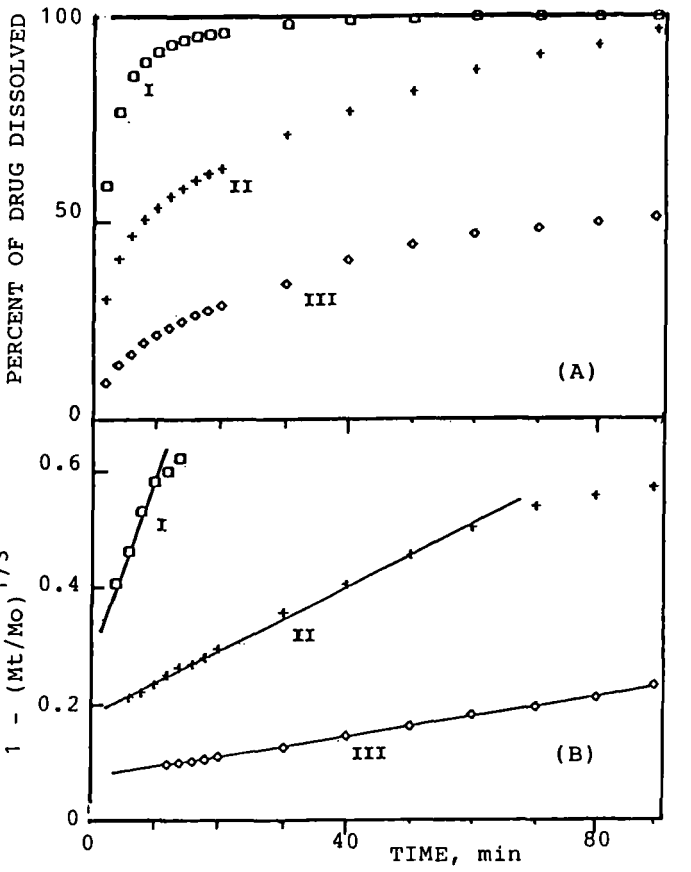

FIG 4.

(A) Dissolution profiles of U-78,875 from suspension at a paddle rotation of 50 rpm: (I) fine particles; (II) medium particles; and (III) coarse particles. (B) The cube root plot of dissolution profiles of U-78,875 from suspension: (I) y=0.0298x + 0.291 (r=0.997); (II) y=0.00751x + 0.183 (r=0.997); and (III) y=0.00141x + 0.0745 (r=0.999).

dissolved within 10 min, 90% of the medium particle suspension dissolved within 75 min. However, complete dissolution of the coarse particle suspension was not achieved within 3 hr. In general, the dissolution of drug may be characterized by the cube root law which is represented in equation [1] (6).

$$1 - (Mt/Mo)^{1/3} = kt \quad [1]$$

$$k = S(DCs/3h) \quad [2]$$

where Mt and Mo are the mass of drug undissolved at time t and time zero, respectively. S is the total surface area, Cs is the solubility of drug in medium, D is the diffusion coefficient of drug in medium, and h is the thickness of diffusion layer during dissolution process. k represents the cube root dissolution rate constant from each particle size. The dissolution of drug from particle of each size followed the cube root law at the early stage of dissolution (Fig. 4). Table 3 summarizes the k values. The k value is dependent on the total surface area of each particle size in the U-78875 suspension, as described in equation [2]. These results indicate that the reduction of particle size accelerates the dissolution rate of U-78875 markedly.

Bioavailability of U-78875 in Dogs after Oral Administration in Suspension

After intravenous administration of U-78875 at a dose of 2 mg/dog, disappearance of U-78875 in plasma apparently followed one-compartment model kinetics under either a fasting condition or a postprandial condition (Fig. 5). To estimate the absolute bioavailability (BA), the area under the curve (AUC) of plasma U-78875 concentration after oral administration was compared to that after intravenous administration, as described in the equation [3]. Thus, the AUC of U-78875 was determined according to the method of Yamaoka et al (7) and was summarized in Table 4.

$$BA = (AUC)oral(Dose)iv/(AUC)iv(Dose)oral \quad [3]$$

To characterize the kinetics of U-78875, we used a model-independent method (7), which was based on the moment analysis, where behavior of drug in plasma was defined by mean in vivo residence time (MRT) in equation [4].

$$MRT = tCpdt/ Cpdt \quad [4]$$

where Cp is the drug concentration in plasma at time t. MRT was

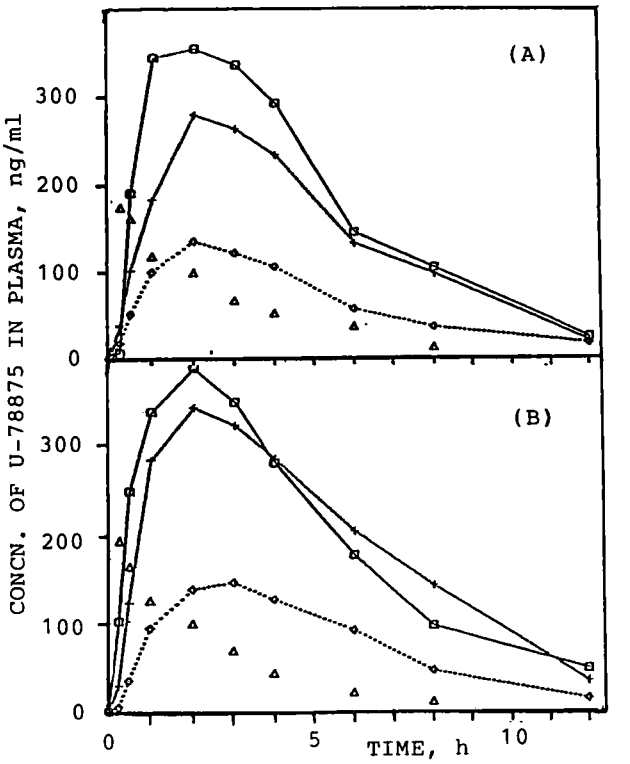

FIG. 5

Profiles of U-78875 concentration in dog plasma after oral administration in 2.0 ml suspension (drug content of 10 mg) or after intravenous administration of 2.0 ml solution (drug content of 2 mg, △). Regarding oral suspension, particle size of U-78875 used are as follows: ◇, coarse; + , medium; and □ , fine.
Each value represents the mean ± S.D. (n=4).

calculated in equation [4] by using a personal computer according to the method reported (7) and is summarized in Table 4.

There was no significant difference in AUC or MRT between the fasting condition and the postprandial condition after intravenous administration (Table 4).

TABLE 4

Pharmacokinetics parameters of U-78,875 after oral administration of suspension or intravenous administration of solution in dogs (study was carried out in cross-over with four dogs).

parameter	oral administration particle size			i.v.
	fine	medium	coarse	
(1) Under the fasting condition				
dose, mg/dog	10	10	10	2
AUC, ng h/ml	2248±196	2286±590	767±159[b]	629±128
BA[a], %	81±9	74±10	24±1[b]	100
MRT, h	4.6±0.7	4.6±0.7	5.0±0.5	3.2±0.5
MAT, h	1.4±0.2	1.4±0.3	1.8±0.2	--
Cmax, ng/ml	381±25	377±64	126±28[b]	---
Tmax, ng/ml	1.8±0.8	2.5±0.5	2.5±0.5	---
ka x 10, h^{-1}	6.7±1.1	7.2±1.5	5.0±1.3	---
ke x 10, h^{-1}	3.5±0.8	3.5±0.6	3.6±0.8	3.7±0.5
Vd, l	9.8±1.6	10.0±1.1	9.4±1.6	9.8±0.9
(2) Under the post-prandial condition				
dose, mg/dog	10	10	10	2
AUC, ng h/ml	3156±530[c]	2878±418[c]	1109±193b	655±77
BA[a], %	96±7	87±10[c]	34±3[b]	100
MRT, h	6.9±1.8[c]	6.9±0.5[c]	7.0±1.2[c]	3.3±0.5
MAT, h	3.6±2.0[c]	3.6±0.9[c]	3.7±0.8[c]	---
Cmax, ng/ml	395±116	320±47	129±7.4[b]	---
Tmax, ng/ml	3.5±0.5[c]	3.8±1.8	4.3±1.1[c]	---
ka x 10, h^{-1}	4.8±1.4	3.9±0.1	4.1±0.5	---
ke x 10, h^{-1}	3.3±0.4	3.5±0.2	3.5±0.5	3.6±0.6
Vd, l	10.1±1.5	10.1±0.9	9.8±1.8	9.6±0.2

Each value represents the mean ± S.D. (n=4). [a]BA represents the absolute bioavailability; [b]$p<0.05$ versus the results with either fine or medium particle; [c]$p<0.05$ versus the results of each particle size, respectively under the fasting condition.

The fine particle suspension prolonged slightly higher plasma drug concentration (Fig. 5) in the fasted dogs. The absolute bioavailability, which was calculated by Eq. [3], was about 80% with the fine particle, 75% with the medium particle, and about 25% with the coarse particle (Table 4). The MRT and MAT, which were calculated by Eq. [4] and [5], respectively, were not significantly different among the three suspensions.

$$MAT_{oral} = MRT_{oral} - MRT_{iv} \quad [5]$$

The oral suspensions administered 30 min after feeding resulted in the delayed Tmax and the prolonged MAT and MRT, in comparison to those in the fasted dogs. On the other hand, the bioavailability (as assumed by AUC) under the postprandial condition increased markedly in comparison to the fasted condition when using either the fine particle or medium particle suspension (Table 4). However, the postprandial bioavailability was not markedly improved when using the coarse particle suspension.

When the suspensions were administered postprandially, the bioavailability increased, probably due to the increased solubility of U-78875 caused by the increased bile after meal ingestion. It seems that the prolongation of MAT after meal relates to an increase in bioavailability. MAT seems to represent the transit time of drug in the small intestine. Because the absorption of U-78875 after dissolution occurs rapidly, the bioavailability is influenced by the amount of drug dissolved before reaching the end of small intestine. The prolongation of transit time in the small intestine results in the increased dissolution in the mucosal fluid, thus resulting in increased bioavailability. It is hypothesized that food increases the bioavailability of U-78875 in dogs due to the increase in drug dissolution in the small intestinal mucosal fluid as well as the secretion of bile which solubilize U-78875.

The somewhat short period of MAT in either fasting or fed conditions of the dogs may indicate that absorption occurs primarily in the small intestine in dogs and little absorption occurs in the large intestine, in spite of the observation that U-78875 in solution is absorbed rapidly even from

the colon in the rats. The reason for the discrepancy is possibly due to water uptake that occurs principally in the large intestine. Therefore, the fluid available to dissolve U-78875 is very small; thus little absorption of U-78875 occurs in the large intestine. Although the large intestine has a capability of absorbing U-78875 when dissolved, the small volume of mucosal fluid in large intestine apparently causes little absorption of U-78875.

The pharmacokinetics parameters, including absorption rate constant (ka), elimination rate constant (ke), and distribution volume (Vd), were calculated assuming a one-compartment model and are summarized in Table 4. These kinetic parameters were not significantly different among the particle sizes in either tablet or suspension. These results indicate that the reduction of particle size of U-78875 is an important factor in increasing the bioavailability for this formulation.

In vitro Disintegration of Tablets and in vitro Dissolution of U-78875 from Tablets

Table 3 summarizes the in vitro disintegration time of three tablet lots used in this study. Complete disintegration occurred rapidly, within 1.5 min for fine and coarse particle tablets and within 5 min for medium particle tablets.

Table 3 also shows that 50% dissolution was observed at about 7 min for fine particle tablets, about 12 min for medium particle tablets, and about 30 min for coarse particle tablets. The fact that it took longer to reach 50% dissolution in the tablets than the suspensions seems to be due to both the disintegration time and wetting of drug particle after disintegration of tablets.

Bioavailability of U-78875 in Dogs after Oral Administration in Tablets

The plasma drug concentration was highest in the dog given a fine particle tablet, followed by the one given a medium particle tablet and a

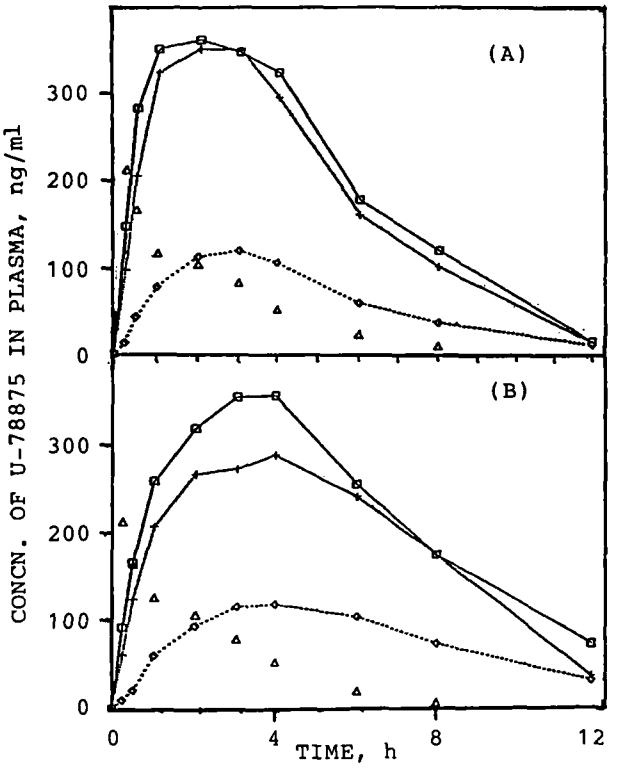

FIG. 6

Profiles of U-78875 concentration in dog plasma after oral administration of a tablet (drug content of 10 mg) or after intravenous administration of 2.0 ml solution (drug content of 2 mg, △). Regarding oral tablets, particle size of U-78875 used are as follows: ◇ , coarse; +, medium; and □, fine. Each value represents the mean ± S.D. (n=4).

coarse particle tablet (Fig. 6). Absolute bioavailability after oral administration of tablets was about 75% with fine particles, about 60% with medium particles, and about 30% with coarse particles (Table 5). Because the group of dogs used for the bioavailability study with tablets was different from that for the study with suspensions, it may be difficult to compare the absolute bioavailability directly between the two groups. In the present study, no significant differences in pharmacokinetics parameters were observed (Tables 4 and 5) between the two groups. From

TABLE 5

Pharmacokinetics parameters of U-78,875 after oral administration of tablets or intravenous administration of solution in dogs (study was carried out in cross-over with four dogs).

parameter	oral administration particle size fine	medium	coarse	i.v.
(1) Under the fasting condition				
dose, mg/dog	10	10	10	2
AUC, ng h/ml	2201±372	1731±379	802±206[b]	585±68
BA[a], %	75±7	59±8[c]	27±4[b]	100
MRT, h	4.5±0.6	5.9±0.8	4.9±0.7	3.1±0.2
MAT, h	1.4±0.5	1.6±0.2	1.7±0.5	---
Cmax, ng/ml	432±84	288±82[c]	138±43[b]	---
Tmax, ng/ml	1.5±0.5	2.3±0.4	2.3±0.4	---
ka x 10, h^{-1}	6.9±1.5	5.4±2.5	5.9±2.3	---
ke x 10, h^{-1}	3.3±0.4	3.3±0.4	3.4±0.3	3.2±0.3
Vd, l	11.2±2.8	10.4±0.8	10.8±2.3	11.1±1.1
(2) Under the post-prandial condition				
dose, mg/dog	10	10	10	2
AUC, ng h/ml	2677±417[d]	2521±266[d]	1044±142[b]	593±66
BA[a], %	90±4[d]	85±6[d]	35±3[b]	100
MRT, h	6.1±1.2[d]	5.6±0.5	5.7±0.5	3.0±0.4
MAT, h	3.1±1.0[d]	2.6±0.4[d]	2.7±0.2[d]	---
Cmax, ng/ml	414±44	373±47[b]	152±13.3[b]	---
Tmax, ng/ml	2.8±0.4	2.5±0.5	3.0±0.7	---
ka x 10, h^{-1}	7.0±4.2	4.7±0.6	4.1±0.8	---
ke x 10, h^{-1}	3.7±0.7	3.4±0.3	3.5±0.6	3.5±0.5
Vd, l	10.5±2.5	10.0±1.0	9.8±2.4	10.8±1.1

Each value represents the mean ± S.D. (n=4).
[a]BA represents the absolute bioavailability; [b]$p<0.05$ versus the results obtained in either fine or medium particles; [c]$p<0.05$ versus the results obtained in fine particles; [d]$p<0.05$ versus the results obtained under the fasting condition.

the results with fine or medium particle tablets in the fasted state, one can draw a conclusion that the delay in dissolution time, as compared to the suspension, may result in a significant decrease in bioavailability. It seems that no significant difference in bioavailability was observed between the tablets and suspensions, because the in vitro dissolution time was not significantly different between the tablets and suspensions.

When the tablets were administered 30 min after a meal, a significant increase in bioavailability was demonstrated for both fine and medium particle tablets (Fig. 6 and Table 5). Food prolonged the MAT significantly as observed in the suspension study. Thus, a significant increase in bioavailability in dogs under the postprandial condition may be due to the prolonged gastrointestinal transit time as well as the acceleration of dissolution caused by the increased secretion of such a surface active agent as bile.

It is clear that the micronized bulk drug with fine particles achieved the most rapid dissolution and highest bioavailability of the particle sizes tested. However, the drug described as medium particle in this study is equivalent in specific surface area to the bulk drug described as "coarse" in the subsequent bioavailability study in man. The tablets prepared with medium particles in this study also gave good bioavailability in dogs under the postprandial condition. Because the medium particle used in this study had a wide range in size, it may be difficult to reproduce the particles with the same specification.

It may also be hypothesized that food increase the bioavailability of U-78875 in dogs due to the increase in drug dissolution in the small intestinal mucosal fluid as well as the secretion of bile which solubilize U-78875.

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