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Correlation between dissolution rate and bioavailability of different commercial mefenamic acid capsules

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Summary

A dissolution test was performed with five brands of 250 mg mefenamic acid capsule products available on the market. Three of them, the fast dissolving A and the slow dissolving D and E were subjected to a bioavailability study using a commercially available suspension as the reference. The products were administered orally in a cross-over design to 6 healthy men, and then parameters for the bioavailability were calculated from the plasma concentration–time curve. Analysis of variance indicated several significant differences among the products with respect to C_{max}, T_{max} and AUC. The relative availabilities of A, D and E were 86, 81 and 28%, respectively, with the AUC value (0–7 h) for the suspension as 100%.

No correlation was observed between the in vitro dissolution rate of the drug from the capsules and the in vivo data, because the dispersing behavior of the capsule exerted a marked influence on its in vitro dissolution rate. To eliminate the influence of the capsule disintegrating process, a dissolution test was done on the contents of the capsules. A good correlation was found between the bioavailability and the dissolution rate of the drug from the capsule contents.

Product E with the lowest bioavailability was passed through a 200-mesh sieve, placed in a new capsule, and tested for its bioavailability in humans. The AUC value was greater than that of the original product and the bioavailability was about equal

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to that of the suspension. The in vitro dissolution rate of the drug from the pulverized product E was also markedly increased.

Introduction

Drug products containing the same drug in the same amount may differ significantly in the quantity of drug absorbed from the dosage form following oral administration (Brice and Hammer, 1969; Schneller, 1969; Barr et al., 1972; Shargel and Yu, 1980). Several studies have documented the importance of formulation factors affecting drug bioavailability (Tyrer et al., 1970; Manninen et al., 1971; Shinkuma et al., 1979). Particularly in the case of a nearly insoluble drug, evaluation of its bioavailability is important from the aspects of effectiveness and safety.

Mefenamic acid, [N-(2,3-xylyl)]anthranilic acid, has been widely used clinically as an anti-inflammatory analgesic (Iizuka et al., 1974). Its solubility is 41 μg/ml in water and thus its bioavailability may differ among different preparations. This has not been adequately studied; there has been only one report, which indicated that the bioavailability of mefenamic acid in tablets and capsules showed no significant differences (Tall and Mistilis, 1975).

The present study examined five brands of capsule products of mefenamic acid presently available on the Japanese market. Tests were conducted on the product assay, weight variation, disintegration and dissolution. Three products were subjected to a bioavailability study and the relationship between the dissolution rate, including the method for the dissolution test, and the bioavailability were studied.

Materials and Methods

Materials

Five brands of 250 mg mefenamic acid capsule products (A–E) available on the market were tested. Stock powders of mefenamic acid and flufenamic acid were generously supplied by Sankyo-Warner Lambert. All the reagents used were commercially available and of analytical grade.

Weight variation

The Japanese Pharmacopeia X (J.P.X) hard gelatin capsule weight variation test was performed on the five brands of capsules.

Product assay

The contents of 20 capsules of each brand were carefully removed and weighed accurately. After finding the mean weight of the contents per capsule, the contents were mixed uniformly and used as the brand sample. A weighed amount of this powder, equivalent to about 150 mg of mefenamic acid, was dissolved in 200 ml of hydrochloric acid–methanol solution (0.84 ml of concentrated hydrochloric

acid/1000 ml of methanol). After filtering and appropriate dilution, the sample was assayed spectrophotometrically at 350 nm on a double-beam spectrophotometer (Type 624, Hitachi, Tokyo). The Beer-Lambert law was obeyed over the concentration range used in this work.

Disintegration test

The J.P.X disintegration test apparatus and procedure with disk were used to determine the disintegration time of the capsules in the 1st fluid (pH 1.2) of the J.P.X disintegration test fluids.

Dissolution test

A preliminary experiment for the dissolution test showed that Method 2 (paddle method: a sinker was used in this experiment to keep the sample from floating) of J.P.X was more suitable for the dissolution test with mefenamic acid capsules than Method 1 (rotating basket method). When a dissolution test was carried out by Method 1 in 900 ml of pH 7.4 phosphate buffer (0.05 M), the solution reached saturation because the drug was practically insoluble in water. The amount of the dissolution medium was increased from 900 to 3000 ml, but stirring of the medium fell off markedly. Thus, this method was considered unsuitable. When a dissolution test was carried out by Method 2 of J.P.X, moderate stirring of the dissolution medium was possible even with an increase in the amount of the dissolution medium from 900 to 3000 ml. Furthermore, using a sinker as shown in Fig. 1, enabled clear

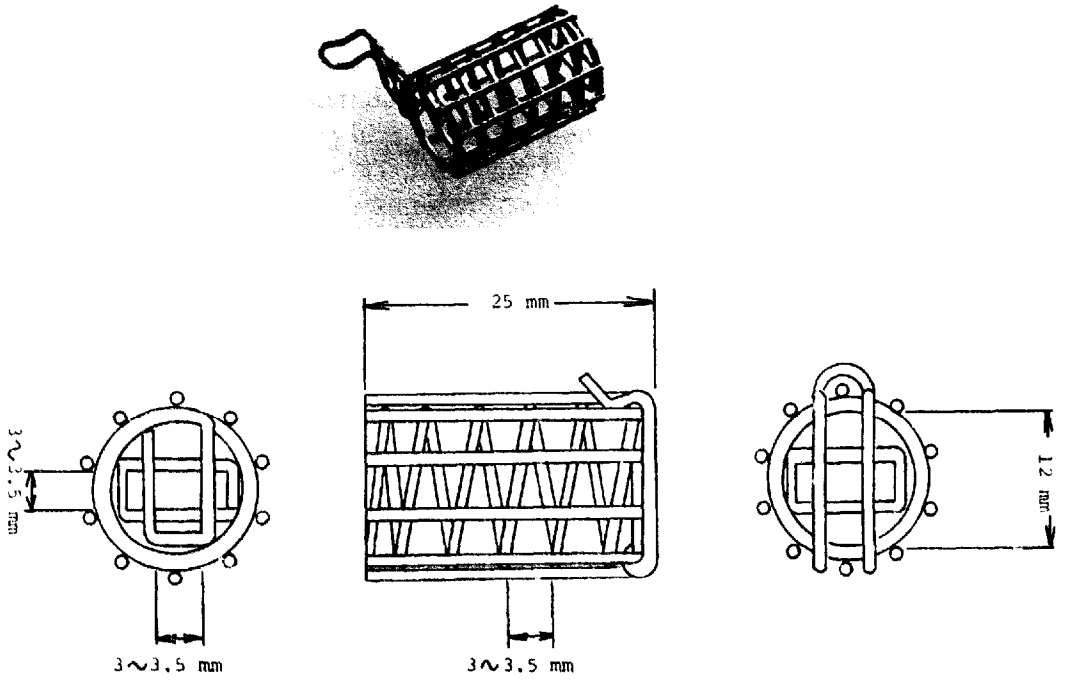

Fig. 1. Photograph and diagrams of the sinker. A, acidproof wire clasp; B, acidproof wire pole.

observations on the disintegration of the capsule and outflow of its content. Thus, the dissolution test was carried out by Method 2 of J.P.X using a 3-liter round-bottomed flask and Dissolution Apparatus Model TR-5 of Toyama Sangyo. The stirring speed was set at 150 rpm and the dissolution vessel, containing 2990 (suspension) or 3000 (capsule) ml of pH 7.4 phosphate buffer (0.05 M), was maintained at 37 ± 0.5 °C in a constant-temperature water bath.

One capsule was put in a sinker which was then sunk at the center of flask, or a weight of suspension corresponding to 250 mg of mefenamic acid was introduced carefully into the bottom of the flask using a syringe fitted with an extra-long needle (Howard et al., 1979). The dissolution samples were withdrawn periodically, filtered through a 0.45-μm millipore filter, and the drug concentration determined with a spectrophotometer at 350 nm. Fresh aliquots of phosphate buffer were added each time to maintain a constant volume.

Bioavailability studies in humans

(1) Clinical protocol

From the products tested for dissolution, A, D and E were selected for bioavailability studies. A commercially available suspension (Pontal syrup, Lot CO81, Sankyo-Warner Lambert) containing 32.5 mg of mefenamic acid/ml was employed as a reference product.

Six healthy male volunteers, ranging in age from 29 to 38 years and in body weight from 59 to 70 kg, were used in the study. General physical examination showed that they had normal hepatic and renal function. The subjects took no other medication for at least one week before and during the study. A single dose (equal to 250 mg of mefenamic acid) was administered to each subject. The subjects received each of the four treatments with products A, D, E, and the suspension, in a random crossover design. Two weeks were allowed between each treatment for complete drug elimination. The subjects were given the mefenamic acid products along with 50 ml of water on the morning following an overnight fast. They were not allowed to take any food or drink for a period from 11 h before administration of the dosage form to 5 h after it.

Venous blood samples were withdrawn at 0.5, 1, 2, 3, 5, 7 and 24 h after dosing with each product. The blood samples were centrifuged at 2500 rpm for 5 min and the plasma fraction was removed and frozen until assayed.

(2) Determination of mefenamic acid in plasma

Plasma concentrations of mefenamic acid were determined by a modified method of Lin et al. (1980). To 0.5 ml of the plasma sample were added 0.1 ml of methanol solution containing 0.9 μg of flufenamic acid as an internal standard, 0.5 ml of 6 N HCl, and 1 ml of water. After mixing, 8 ml of distilled CCl_4 was added, and the mixture was extracted by shaking for 10 min in a 15-ml glass-stoppered centrifuge tube. After centrifugation at 3000 rpm for 5 min, 7 ml of the CCl_4 layer was transferred to a 30-ml glass-stoppered centrifuge tube containing 6 ml of 1 N NaOH. The mixture was shaken for 10 min and centrifuged at 3000 rpm for 5 min. A 5 ml

portion of the aqueous layer was placed in another centrifuge tube, to which 2 ml of 6 N HCl and 5 ml of distilled CCl_4 were added. This was extracted by shaking for 10 min, and then the mixture was centrifuged at 3000 rpm for 5 min. The aqueous layer was discarded, and 4 ml of the CCl_4 layer was evaporated to dryness in a 10-ml glass-stoppered centrifuge tube. The residue was dissolved in 200 μl of methanol and 20 μl was injected into a high-pressure liquid chromatograph (HPLC). The apparatus and conditions used for HPLC were: apparatus, Shimadzu LC-3A; UV detector, SPD-2A (280 nm); column, Zorbax ODS (4.6 mm × 250 mm); column temperature, 50 °C; sensitivity, 0.04 a.u.f.s; flow rate, 0.8 ml/min; mobile phase, water–acetonitrile–acetic acid (35 : 60 : 5 v/v/v).

The linearity of the assay in the 0.1–10 μg/ml range was determined by adding known amounts of mefenamic acid to control human plasma, extracting them, and monitoring the chromatographic eluant at 280 nm. There was a linear relationship between the peak area ratio and the plasma concentration of mefenamic acid ($y = 0.5925x + 0.0284$, $r = 0.999$).

Statistical analysis

The peak plasma concentration, C_{max}, and time of peak concentration, T_{max}, were obtained from the individual plasma concentration versus time curves. The AUC (area under the plasma concentration–time curve) values were calculated according to the trapezoidal rule. The bioavailability parameters were compared among treatments by an analysis of variance using Scheffé's test or between two treatments by a paired *t*-test.

Results and Discussion

Weight variation

The results of the weight variation test are shown in Table 1. The weight of the contents of the products ranged from 277 to 403 mg. The coefficient of variation for the mean weights of all products was within the range of 1.4–4.2% and variations in weight were also small. All the products met the requirements of the J.P.X weight variation test.

Product assay

The results of the product assay test are shown in Table 1. The results are expressed as a percent of the ratio of the actual content to the labeled content. The mean content was within the range of 98–100% for all products and the difference between the mean and labeled contents was small.

Disintegration test

The results of the disintegration test in the 1st fluid (pH 1.2) are shown in Table 1. The disintegration times for 4 of the products ranged from 8 to 13 min, but that for product D was about 40 min, 3–5 times longer than that for the other products.

Dissolution test

Fig. 2 shows that the dissolution profiles differed markedly among the products. The T_{50} value, defined as the time required for 50% of the drug to dissolve in the dissolution medium, was 3, 18, 50 and 110 min for the suspension, and products A, B and C, respectively, while the amounts dissolved for products D and E after 120 min were only 30 and 5%, respectively. Observation of the dissolution behavior of the slow-dissolving products C, D and E, showed that the contents of these capsules remained as a wet powder pack long after the gelatin wall had dissolved.

Bioavailability studies in human

On the basis of the in vitro data, product A with the fastest dissolution rate and products D and E with the slowest dissolution rate were selected for further study of the relationship between their dissolution rates and bioavailabilities (Aoyagi et al., 1982) and were subjected to a bioavailability test using the suspension as the reference.

Fig. 3 presents the mean plasma concentration of the mefenamic acid–time curve at each sampling time following oral administration of each dosage form to the subjects. Analysis of variance of the parameters determined for all 4 treatments is shown in Table 2. There was a statistically significant difference in the mean peak plasma concentrations (C_{max}) among the treatments. The mean peak plasma concentration ranked in the order of the suspension, and products D, A and E. The lowest peak concentration (product E) was only 23% of the highest one (suspension). There was a statistically significant difference in the time of peak plasma concentra-

TABLE 1

PRODUCT ASSAY, WEIGHT VARIATION AND DISINTEGRATION DATA FOR 5 MEFENAMIC ACID CAPSULE PRODUCTS

Manufacturing parameter	Product				
	A	B	C	D	E
Mean percent of labeled content [a]					
Mean (%)	98.46	99.85	99.77	100.33	99.27
S.D. (%)	1.33	2.76	2.32	2.06	1.99
Weight variation [b]					
Mean (mg)	337.21	402.49	276.58	344.30	314.58
S.D. (mg)	5.34	16.88	5.15	4.90	7.19
C.V. (%)	1.58	4.19	1.86	1.42	2.29
Disintegration time [a] in the 1st fluid (pH 1.2)					
Mean (min)	7.7	13.2	8.9	39.9	10.9
S.D. (min)	0.9	1.0	0.4	2.0	1.4

[a] n = 3; [b] n = 20.

S.D. = standard deviation; C.V. = coefficient of variation.

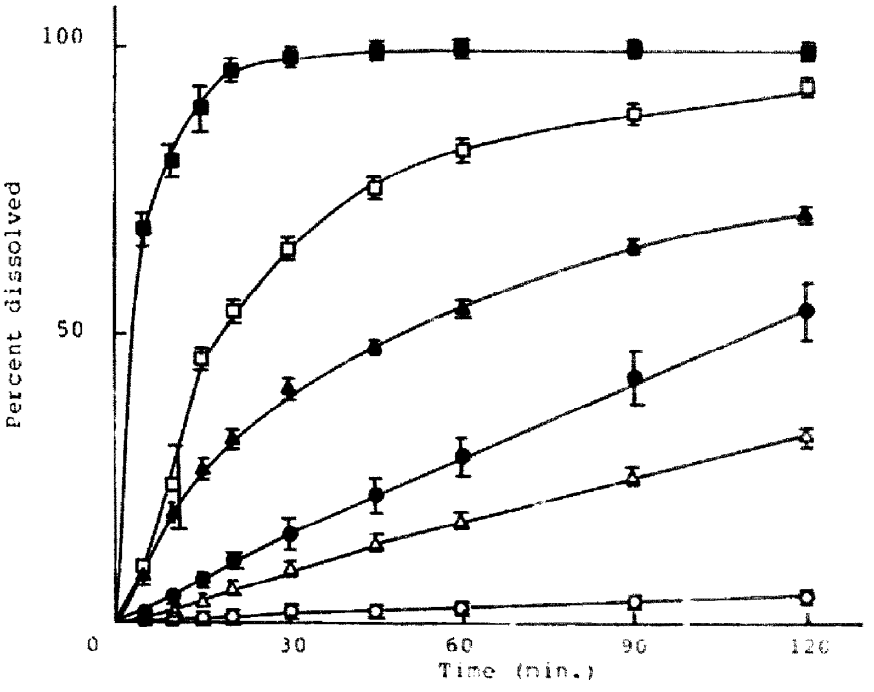

Fig. 2. Dissolution profiles of mefenamic acid capsules using the paddle method with a sinker. Dissolution medium: 3000 ml of pH 7.4 phosphate buffer (0.05 M). Each point represents the mean result ± S.D. of three determinations. Product A, □; B, ▲; C, ●; D, △; E, ○; and the suspension, ■.

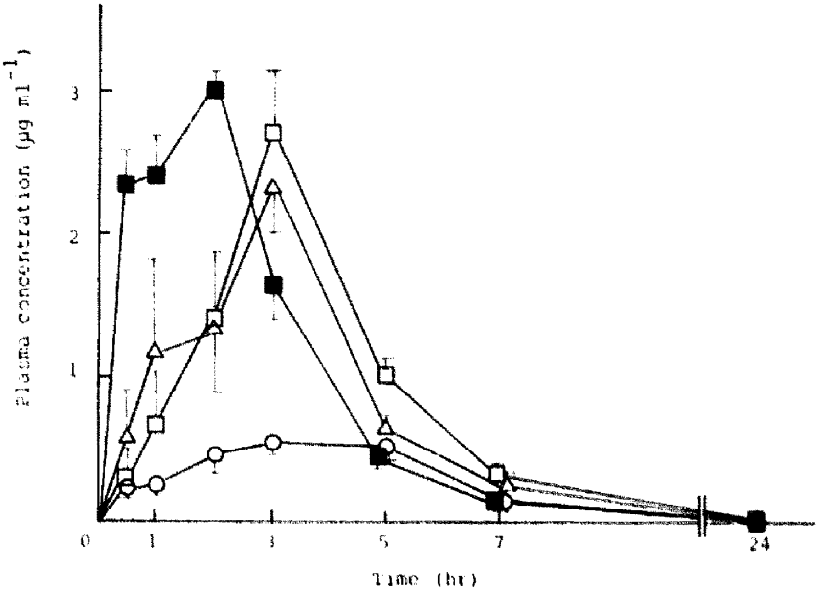

Fig. 3. Mean plasma concentrations of mefenamic acid following oral administration of mefenamic acid capsules or a suspension. Each point represents the mean result ± S.E. of six subjects. Product A, □; D, △; E, ○; and the suspension, ■.

tion (T_{max}) among the treatments. The T_{max} ranked in the order of the suspension, and products D, A and E. The mean data show that product E took 2.7 times as long as the suspension to reach peak plasma concentration. There have been some reports that the absorption rate is faster for a suspension than a solid dosage form for nearly insoluble drugs (Sjögren et al., 1965; Langlois et al., 1972). We too obtained similar results, that is, the absorption rate of the suspension was faster than that of the other capsules, probably because the dissolution rate of the suspension was faster than that of others. There was a statistically significant difference in the area under the plasma concentration–time curve (AUC) up to 7 h after oral administration among the treatments. With the AUC of a suspension as 100%, the relative availabilities after oral administration of products A, D and E were 86, 81 and 28%, respectively.

Correlation between bioavailability and in vitro dissolution rate

Since there was no correlation between the results of the dissolution test (Fig. 2) and the results of the bioavailability study (Fig. 3, Table 2) and since disintegration of product D took about 40 min (Table 1), a dissolution test was conducted for the contents of the capsules.

The mean weight of the content per capsule of each product was determined and an accurately weighed amount equivalent to 250 mg of mefenamic acid was used as the test sample. After carefully dispersing each sample on the surface of the dissolution medium, mefenamic acid release from the capsule contents was monitored as described in Materials and Methods but without using the sinker. The dissolution profiles of mefenamic acid from capsule contents are shown in Fig. 4.

TABLE 2

ANALYSIS OF VARIANCE FOR 4 TREATMENTS (RANDOMIZED BLOCK DESIGN WITH SUBJECTS AS BLOCKS, TWO-WAY ANALYSIS OF VARIANCE) [a]

Parameter	Mean [b]				df [c]	SS [d]	MS [e]	F-ratio
	Suspension	A	D	E				
$AUC_{0\to7}$ (μg·h/ml)	9.88	8.50	8.04	2.72	3	177.686	59.229	19.53 *
Subject					5	27.561	5.512	1.82 NS
Error					15	45.480	3.032	
Total					23	250.727		
C_{max} (μg/ml)	3.32	2.92	3.30	0.77	3	26.818	8.939	20.24 *
Subject					5	2.816	0.563	1.28 NS
Error					15	6.623	0.44[illegible]	
Total					23	36.257		
T_{max} (h)	1.42	2.83	2.33	3.83	3	17.865	5.95[illegible]	7.88 *
Subject					5	4.052	0.810	1.07 NS
Error					15	11.322	0.75[illegible]	
Total					23	33.239		

[a] NS = not significant at 0.05 level, * = significant at 0.01 level. [b] Underlined values are not significantly different from each other according to Scheffé's test ($P < 0.05$). [c] Degrees of freedom. [d] Sums of squares. [e] Means squares.

Product E markedly differed from products A and D, with the dissolution rate being slowest for product E. T_{50} values for products A, D and E were 9, 11 and 94 min, respectively. The dissolution behaviors for products A and D were similar.

In order to find a correlation between the in vitro dissolution rate and bioavailability, T_{50} values were plotted along the abscissa and the AUC values up to 7 h were plotted along the ordinate. A good correlation was observed between the T_{50} and AUC values ($Y = -0.0798x + 11.5939$, $r = 0.993$).

Finholt (1974) has stated that the rate of dissolution of drugs from capsules is a complex function of the rates of different processes, such as solution of the gelatin shell, penetration of water into the powder mass, deaggregation of the powder mass and dissolution of the powder particles. Despite these complex processes, however, the drug from a well-formulated product may be released in 5–10 min after oral administration of a capsule to man (Feinblatt and Ferguson, 1956; Eckert, 1967). The deaggregation rate and solubility (Aguiar et al., 1968; Samyn and Jung, 1970) of the drug released into digestive fluid after disintegration of a capsule have been reported to exert an influence on the absorption of the drug concerned.

The dissolution test was done on the contents of the capsules. The results reflect very well the results obtained in vivo, thus showing that the bioavailability can be estimated by this procedure. Evaluating the deaggregation and dissolution rates of the drug from the capsule content in vitro may be an effective means for estimating the dissolution rate of a capsule in the digestive fluid.

To study whether or not disintegration of the capsule influences the in vitro

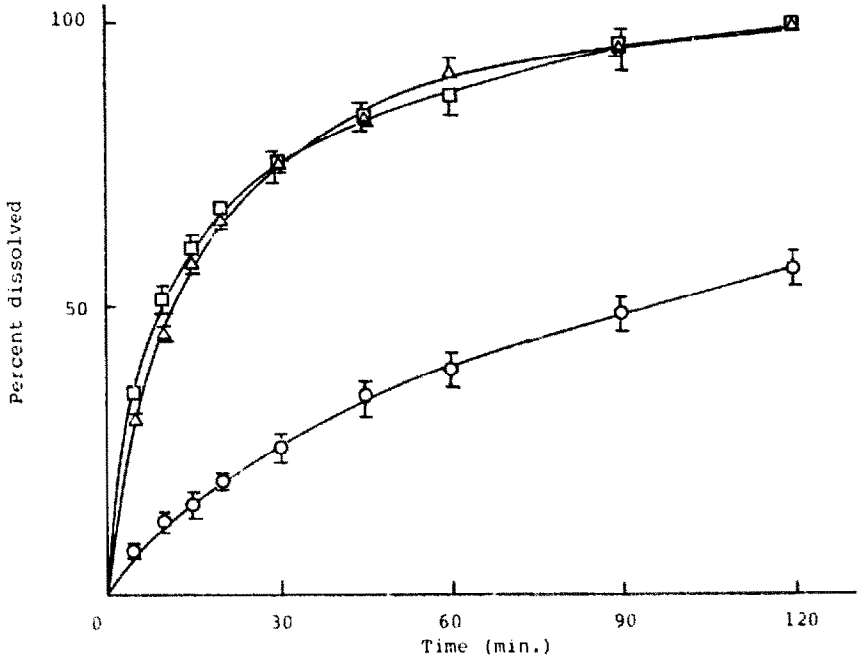

Fig. 4. Dissolution profiles of mefenamic acid from capsule contents using the paddle method. Dissolution medium: 3000 ml of pH 7.4 phosphate buffer (0.05 M). Each point represents the mean result ± S.D. of three determinations. Product A, □; D, △; E, ○.

dissolution rate of the drug from a capsule, the disintegration time for each product was examined further. The disintegration test was conducted by the procedure described in Materials and Methods using pH 7.4 phosphate buffer (0.05 M). The emptied capsules of these products were also subjected to the disintegration test. Table 3 shows the results of the disintegration test in pH 7.4 phosphate buffer (0.05 M).

Since there were no significant differences in the disintegration time among the emptied capsules, the capsule shell apparently had no direct influence on disintegration of the filled capsules. Results of the disintegration test with filled capsules showed that their behavior differed markedly with the pH of the test fluid and the results obtained with pH 7.4 phosphate buffer tended to be closer to those of the dissolution test (Tables 1 and 3). That is, the time required for disintegration of products D and E was about double that of product A. The delay in capsule disintegration and outflow of the contents is considered to result in a slower dissolution rate of the drug from the capsules.

In vitro dissolution of nearly insoluble drugs from hard gelatin capsules is reported to be affected markedly by various factors such as the particle size and packing of the drugs (Newton and Rowley, 1970), the deaggregation rate of the capsule contents (Arnold et al., 1970), additives (Samyn and Jung, 1970; Newton and Razzo, 1976), and manufacturing methods (Wagner et al., 1966; Aguiar et al., 1968). Thus, bioavailability also could be affected by the same factors. In this study too, disintegration of products D and E and outflow of the capsule contents were delayed due to some of these factors. As a result, the dissolution rates of the drug from capsules of products D and E were markedly slower than that of product A (Fig. 2). The dissolution rate was slower for product E than product D probably because dissolution of the drug from the capsule contents was slower for product E (Figs. 2 and 4, Table 3).

Accordingly, the differences in the bioavailabilities among the products in the in vivo study may be due to differences in the dissolution rate of the drug into digestive fluid from the capsule contents.

TABLE 3

DISINTEGRATION DATA FOR 5 MEFENAMIC ACID CAPSULE PRODUCTS IN pH 7.4 PHOSPHATE BUFFER (0.05 M)

Product	Disintegration time (min)	
	Filled capsule	Emptied capsule
A	11.5 ± 1.2	12.7 ± 1.4
B	13.9 ± 1.2	15.6 ± 1.7
C	14.7 ± 1.6	12.3 ± 1.2
D	24.7 ± 1.5	11.9 ± 1.0
E	23.2 ± 3.6	14.0 ± 3.8

Each value represents the mean result ± S.D. of 3 determinations.

Dissolution rate of product E and improvement in absorption by the digestive tract

Since the dissolution rate of a drug exerts a great influence on its absorption by the digestive tract, various methods to increase the dissolution rate of nearly insoluble drugs have been reported (Atkinson et al., 1962; Simonelli et al., 1969; Doluisio et al., 1973; Shinkuma et al., 1981). The low bioavailability of product E may be due to its poor dissolution in digestive fluid. Thus, ways to increase the dissolution rate of the drugs were studied. The contents of product E were ground in a mortar and fine powders passed through a sieve of 200-mesh were used as the sample. The sample equivalent to 250 mg mefenamic acid was placed in a new capsule and administered orally to 6 healthy volunteers, after which the mean plasma concentration–time profile of mefenamic acid was determined. The other procedures were the same as those described for the bioavailability test. Table 4 shows their mean values for in vivo parameters. The pulverized product E improved bioavailability leading to about a 3.5-fold increase in AUC, a 4.5-fold increase in C_{max} and a 2.6-fold decrease in T_{max} over the original product E-values which are about equal to those of the reference suspension.

The dissolution test in pH 7.4 phosphate buffer (0.05 M) was performed on the pulverized product E. It dissolved slower than the original powder and 35% less had dissolved after 120 min. There was no correlation between the dissolution test and bioavailability. Micronization sometimes dramatically increases the tendency of a drug powder to aggregate, which may lead to a decrease in effective surface area. Because of air adsorption on its surface, pulverized fine powder remains partly floating on the dissolution medium during the test and a wetting agent is sometimes added to the medium to wet the powder surface (Finholt, 1974). Fig. 5 shows the dissolution profiles of two formulations (the original and the pulverized product E) in pH 7.4 phosphate buffer (0.05 M) with 0.05% Tween 80 added. The dissolution

TABLE 4

PLASMA LEVELS, C_{max}, T_{max} AND AUC AFTER ORAL ADMINISTRATION OF PULVERIZED PRODUCT E AND PRODUCT E

Parameter	Time (h)	Formulation		Paired *t*-test [a]
		Pulverized product E	Original product E	
Plasma level (μg/ml)	0.5	0.60 ± 0.26 [b]	0.23 ± 0.05	NS
	1.0	2.00 ± 0.49	0.24 ± 0.06	$P < 0.02$
	2.0	3.06 ± 0.69	0.46 ± 0.13	$P < 0.05$
	3.0	1.76 ± 0.35	0.55 ± 0.09	$P < 0.05$
	5.0	0.68 ± 0.08	0.52 ± 0.10	NS
	7.0	0.18 ± 0.03	0.13 ± 0.03	NS
	24.0	0.07 ± 0.04	0.01 ± 0.04	NS
C_{max} (μg/ml)		3.57 ± 0.57	0.77 ± 0.06	$P < 0.01$
T_{max} (h)		1.50 ± 0.20	3.83 ± 0.49	$P < 0.01$
$AUC_{0\rightarrow 7}$ (μg·h/ml)		9.36 ± 1.09	2.72 ± 0.24	$P < 0.01$

[a] NS = not significant at 0.05 level. [b] Mean ± standard error.

rate of the pulverized product E was markedly more rapid and the T_{50} value also decreased from 63 to 14 min, which closely resembled the dissolution behavior for the capsule contents of products A and D.

Thus, the poor bioavailability of product E may be due to the deaggregation rate of the capsule content after disintegration of the capsule, the slow dissolution rate of the drug from the capsule content, and/or polymorphism of mefenamic acid. No attempt has been made to study polymorphism for this report.

Conclusions

The in vitro dissolution rate from the capsules differed markedly from one product to another (Fig. 2). With the AUC value for the reference suspension considered as 100%, the relative availabilities of products A, D and E were 86, 81 and 28%, respectively, with the differences being significant (Fig. 3, Table 2). Comparison of the bioavailabilities of products A and D showed no significant difference, but the in vitro dissolution rate was markedly slower for product D. This is probably due to a delay in capsule disintegration and outflow of its contents with subsequent slowdown of the dissolution rate of the drug from the capsule (Fig. 4, Table 3).

The bioavailability of product E was the lowest among the products examined

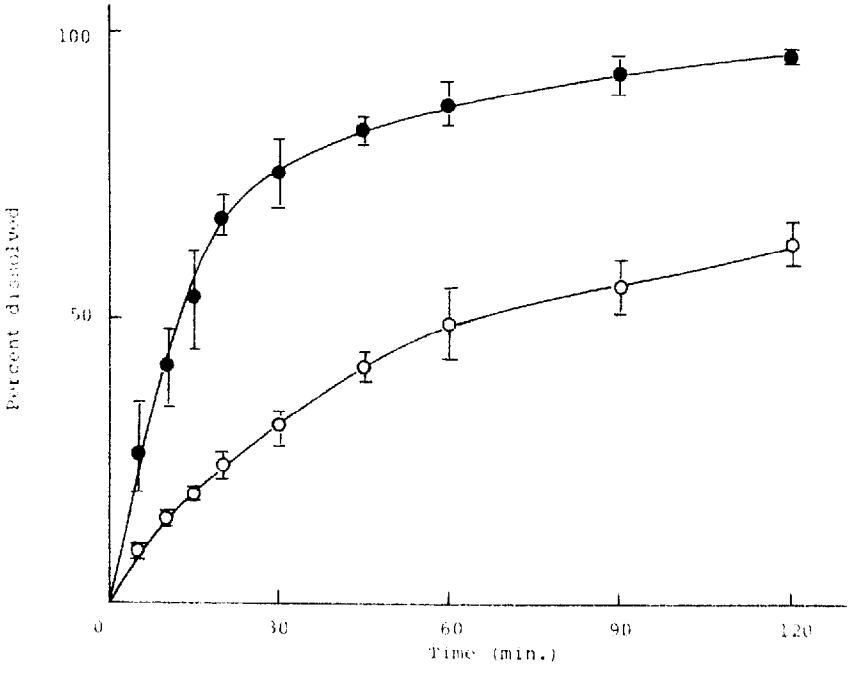

Fig. 5. Dissolution profiles of mefenamic acid from the contents of the original product E and the pulverized product E using the paddle method. Dissolution medium: 3000 ml of pH 7.4 phosphate buffer (0.05 M) containing 0.05% of Tween 80. Each point represents the mean result ± S.D. of 3 determinations. Original product E, ○; pulverized product E, ●.

(Fig. 3, Table 2) due to poor dissolution of the drug from the capsule contents (Fig. 5). When product E was pulverized, the in vitro dissolution rate increased. When this was administered orally to man, the bioavailability was about equal to that of suspension, with the AUC increasing by 3.5-fold of that of the original product (Fig. 5, Table 4).

The correlation between the bioavailability and the in vitro dissolution rate was also studied. The dissolution test results for the drug from the capsule contents reflected the in vivo data and correlation was found between the T_{50} and AUC values.

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