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Abstract

This study was designed to determine the in vitro release of tegafur from a suppository and the in vivo bioavailability of tegafur in rats. Two different suppository preparations (product A-1 and product A-2) containing 750 mg of tegafur were tested for in vitro release of tegafur by the Muranishi Method (membrane diffusion method) and the partially modified paddle method (permeability through dialysis tubing). When determined by either method, the amount of tegafur released from product A-2 during the whole experimental period was significantly greater than that released from product A-1. When tested by the Muranishi method, however, the difference in the amount released during the first 10-min period was not significant. A greater bioavailability of tegafur after rectal administration was obtained by product A-2 more than product A-1. A significant correlation was observed between the in vitro release and the in vivo bioavailability. The present results indicate that there are considerable differences in physiochemical characteristics between product A-1 and product A-2.

KEYWORDS: tegafur suppository, in vitro release, in vivo bioavailability in rats

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In Vitro Release of Tegafur from a Fatty-Base Suppository and *In Vivo* Bioavailability of Tegafur

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This study was designed to determine the *in vitro* release of tegafur from a suppository and the *in vivo* bioavailability of tegafur in rats. Two different suppository preparations (product A-1 and product A-2) containing 750 mg of tegafur were tested for *in vitro* release of tegafur by the Muranishi Method (membrane diffusion method) and the partially modified paddle method (permeability through dialysis tubing). When determined by either method, the amount of tegafur released from product A-2 during the whole experimental period was significantly greater than that released from product A-1. When tested by the Muranishi method, however, the difference in the amount released during the first 10-min period was not significant. A greater bioavailability of tegafur after rectal administration was obtained by product A-2 more than product A-1. A significant correlation was observed between the *in vitro* release and the *in vivo* bioavailability. The present results indicate that there are considerable differences in physicochemical characteristics between product A-1 and product A-2.

Key words : tegafur suppository, *in vitro* release, *in vivo* bioavailability in rats

Tegafur has been widely used in the treatment of carcinomas of the digestive organs, breasts and lungs, and is administered orally or rectally. The introduction of tegafur suppository has enabled the long-term maintenance of effective levels of the active substance in the serum, the decrease of side effects and high dosage. They have been widely used for inpatients as well as outpatients.

Generally, the drug absorption from human rectum shows considerable individual variations and the *in vitro* and *in vivo* releases of

active ingredients from the suppository base are influenced by the physicochemical properties (1-4). The *in vitro* and *in vivo* releases of active ingredients are used for the pharmaceutical evaluation of these drugs.

In our previous study (5) by the Muranishi method, which is based on membrane diffusion, a considerable difference in the release of tegafur was observed between the two different suppositories. Tentatively, the different lots of the same manufacture were called product A-1 and A-2. This suggests that it is difficult to maintain the same level of the active ingredient in the serum by rectal administration of different suppository preparations.

In the present study, the relationship between the *in vitro* release of tegafur from

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product A-1 and A-2 and the *in vivo* bioavailability after rectal administration was investigated. In addition, the releases of tegafur from these two products as determined by the Muranishi method were compared with those as determined by the modified paddle method of Japanese Pharmacopeia (JP) X.

Materials and Methods

Drugs. Two tegafur suppositories of different lot number (A-1 and A-2, Futraful suppository, Taiho Pharmaceutical Co., Ltd.) were used. The suppositories containing 750 mg of tegafur were 2.2 ± 0.01 g in weight, and were prepared with the fatty vehicle, witepsol W-35. They were stored at 4-8°C in refrigerator until tests were performed. Other chemicals used were of a guaranteed grade.

***In vitro* Release Test.** The release test was carried out by the Muranishi method (6) and the paddle method of JP X modified by using dialysis tubing instead of a basket. The apparatus and the experimental conditions for both methods are shown in Fig. 1. Seamless cellulose tubing (Union Carbide Co., Ltd.) for the paddle method was cut into 8 cm lengths and soaked for at least 1 h in distilled water. When used, both ends of the tube

were closed at the length of 6 cm. The tube was hung 5 cm below the liquid surface. The concentrations of released drug in the medium were determined by ultraviolet spectrophotometry at 271.5 nm (UV method).

***In vivo* Bioavailability in the Rat.** Male Sprague Dawley (JCL-SD) rats weighing 250-280 g were used. The animals, fed on MF diet (Oriental Yeast Co., Ltd.) for one week prior to the experiment, were divided into groups of 3 rats. The animals were fasted for 16 h before and during the experiment. Suppositories of 4 mm in diameter were prepared. Each suppository was cut into pieces to give a rectal dose of 200 mg tegafur/kg body weight.

Blood samples were collected 30 min, 1, 2, 4 and 8 h after rectal administration from the inferior vena cava of ether-anesthetized rats. The serum was separated immediately by centrifugation at 3,000 rpm for 20 min. Tegafur concentrations in serum were determined by the UV method and high performance liquid chromatography (HPLC) with UV detection. The concentrations were calculated by a Data Module (Waters Associates). The tegafur concentrations in serum were plotted against time, and the pharmacokinetic parameters were determined according to one compartment open model. Parameters such as the maximum drug concentration (C_{max}), the time to C_{max} (T_{max}), half life ($t_{1/2}$) and the area under the serum

Fig. 1 Cross-sectional diagram of dissolution apparatus of the paddle method of JP X (A) and suppository release apparatus of Muranishi method (B). The apparatuses consist of: 1, suppository placed in membrane tubing (A-3) or chamber (B-8) containing 3 ml of artificial plasma; 2, artificial plasma (pH 7.5 ± 0.1) for the dissolution medium (900 ml in A, and 300 ml in B); 3, seamless cellophane tubing in A, and double layered membrane of Visking cellulose tubing (Shiraimatsu Co., Ltd.) and lipid membrane prepared by filling the pores of a filter (SM 70) with Barrier D1 (Sartorius) in B; 4, rotating rod (25 rpm); 5, thermometer; 6, sampling pipet; 7, stirrer (100 rpm); 8, plastic cylindrical chamber (B); 9, thermostatic bath of 37.5 ± 0.5 C.

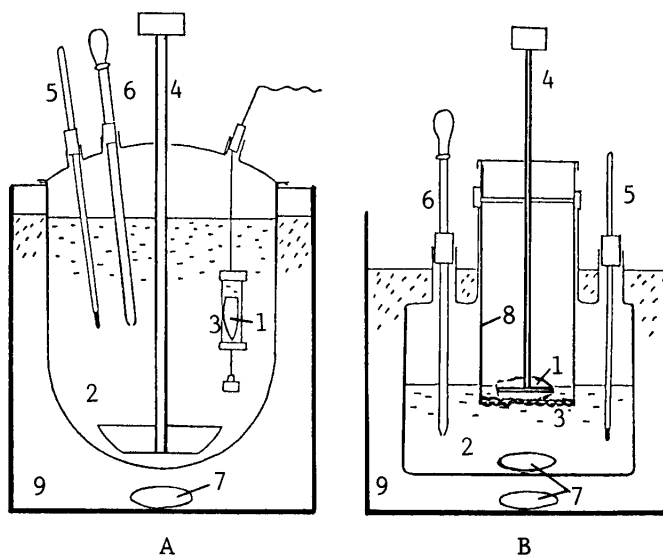
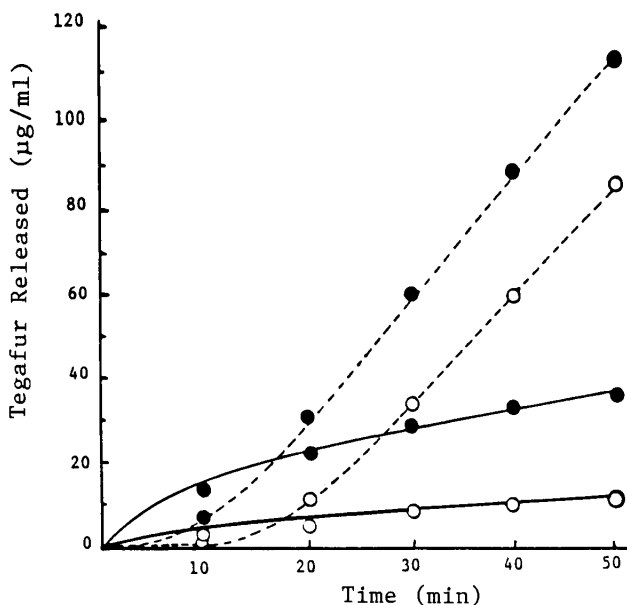


Fig. 2 Comparison of release of tegafur from product A-1 (○) and product A-2 (●) by the paddle method (solid line) and Muranishi method (broken line). Each point represents the mean of five experiments.



drug concentration-time curve (AUC) were assessed by conventional methods. The data were evaluated for statistical significance by Student's *t* test.

Results

In vitro release of tegafur from product A-1 and product A-2. The results of the *in vitro* release test by the Muranishi method and the paddle method are shown in Fig. 2. When tested by the paddle method, the amounts of tegafur released from product A-1 after 10 and after 50 min were 3.6 and 11.7 µg/ml, and those released from product A-2 during the same periods were 11.7 and 35.4 µg/ml, respectively. On the other hand, when tested by the Muranishi method, the amounts of tegafur released from product A-1 and product A-2 during 10 min period were 1.7 and 8.0 µg/ml, respectively. The amounts of tegafur released from product A-2 were significantly larger ($p < 0.01$) than those released from product A-1 during the whole period, irrespective of the test methods. But the difference between the two products

in the amount released during the first 10 min was not significant when determined by the Muranishi method. Furthermore, the amounts of two drugs released in the Muranishi method were slightly smaller during the first 10 min than those in the paddle method, but significantly larger ($p < 0.01$) 30 min after or more.

Tegafur concentrations in rat serum.

Since tegafur concentrations in serum samples determined by the UV method and HPLC method were in good agreement (Fig. 3), the UV method was used for the determination of the serum concentration of the drug.

In vivo bioavailability of tegafur after rectal administration. The serum tegafur concentration after rectal administration (200 mg/kg) of product A-1 and A-2 are shown in Fig. 4. One to 4 h after rectal administration of product A-2, the serum concentration of tegafur was significantly higher ($p < 0.01$) than that after administration of product A-1. However, no significant difference was observed in the first 30 min and 8 h after administration of these products.

Fig. 3 Comparison of tegafur concentrations in rat serum determined by high performance liquid chromatography and UV methods.

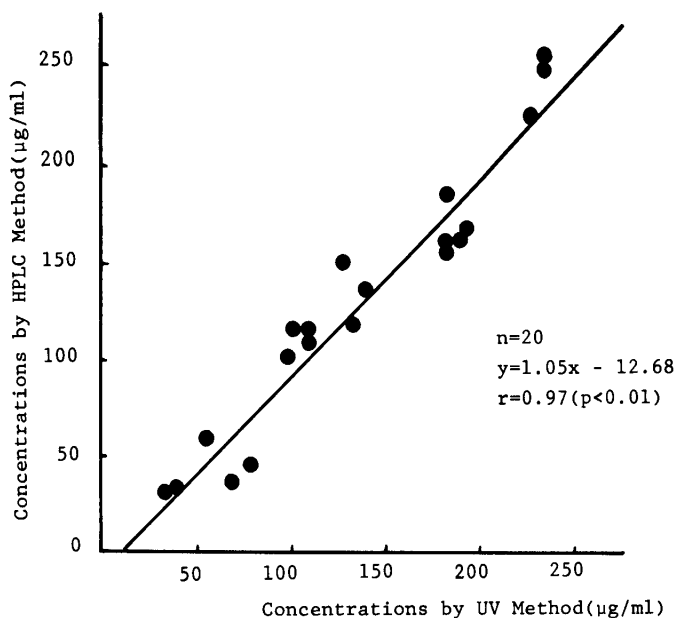
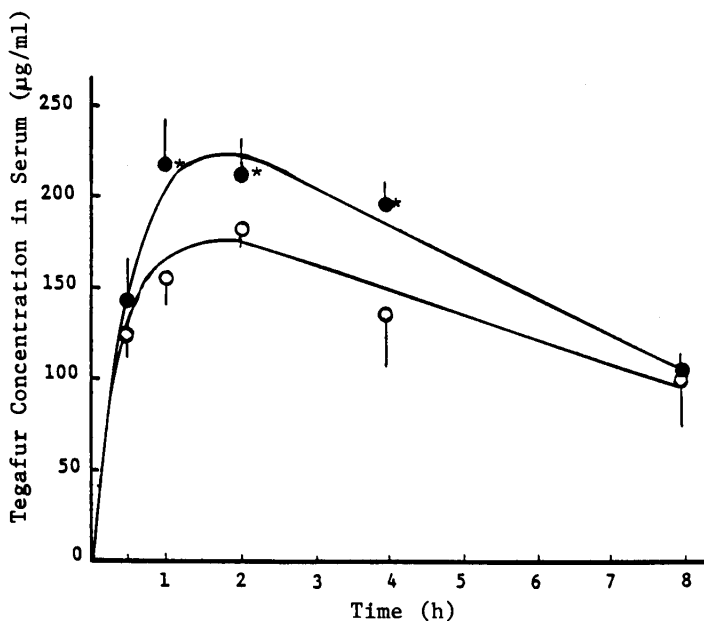


Fig. 4 Comparison of the time course of serum tegafur levels after rectal administration (200 mg tegafur/kg) of product A-1 (○) and product A-2 (●) in the rat. Each point represents the mean of five rats; vertical lines represent the SEM. * $p<0.01$ in product A-2 as compared to product A-1.



Pharmacokinetic parameters determined after rectal administration of these products are shown in Table 1. C_{max} for product A-2 was significantly higher ($p<0.01$) than that for product A-1. The AUC for product A-2

was greater than that of product A-1, but the difference was not statistically significant. There was no difference among other pharmacokinetic parameters for the two products.

Table 1 Pharmacokinetic parameters determined according to a one-compartment open model from the serum tegafur concentration curve after rectal administration in rats^a

Parameters ^b	Product A-1	Product A-2
AUC (0-8) ($\mu\text{g}\cdot\text{h}/\text{ml}$)	1915.6 \pm 431.6	2079.9 \pm 156.6
Cmax ($\mu\text{g}/\text{ml}$)	178.6 \pm 12.6	230.0 \pm 9.1 ^c
Tmax (h)	1.7 \pm 0.1	1.6 \pm 0.2
t _{1/2} (h)	6.0 \pm 1.3	5.0 \pm 0.4
Ccl (ml/min)	1.4 \pm 0.3	1.2 \pm 0.1
Vd (l/kg)	0.7 \pm 0.1	0.5 \pm 0
Ka (h ⁻¹)	0.12 \pm 0.02	0.14 \pm 0.01

a: Each value represents the mean \pm SEM of three rats.

b: AUC, area under the serum drug concentration-time curve; Cmax, maximum drug concentration; Tmax, time to Cmax; t_{1/2}, half life; Ccl, total body clearance; Vd, apparent volume of distribution; Ka, absorption rate constant.

c: p < 0.01 as compared to product A-1.

Discussion

There are several reports that physicochemical alterations of fatty suppository bases can occur when they are stored over 25°C. For instance, the decrease of bioavailability of paracetamol suppository in fatty base and the diminution of aminophylline release from the fatty suppository base were recognized when they were stored at 30°C (1, 2). Furthermore, Yoshino *et al.* (3) reported that a rise in melting point, prolongation of softening time and diminution of release were commonly observed in some fatty vehicles by storing over 25°C. In the present study, the amounts of tegafur released from product A-2 in the Muranishi's and paddle methods were significantly greater than those released from product A-1, even when they were stored at 4-8°C. This result indicates that marked differences in the physicochemical characteristics of fatty suppository preparation between product A-1 and A-2 are produced even by storing in cool place. Further, the *in vitro* releases from the two products by the Muranishi's and paddle methods were similar. Therefore, the paddle method of JP X can be applied to the pharmaceutical evaluation of fatty suppositories.

There are few studies on the relationship between the *in vitro* release of active ingre-

dients from suppositories and the *in vivo* bioavailability. Vidras *et al.* (4) reported that the *in vitro* release of indomethacin suppository correlated well with the *in vivo* bioavailability for the first 45 min. In the present study, the bioavailability of tegafur after rectal administration of product A-2 is greater than that after the administration of product A-1. Significant correlation was also observed between the *in vitro* release and *in vivo* bioavailability. In addition, not only by the Muranishi method but also the paddle method, the good correlation between the *in vitro* and *in vivo* data was recognized. Therefore, it is evident that these methods are rather simple but useful in evaluating the quality of fatty suppositories.

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