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Evaluation of the correlation between in vivo and in vitro release of phenylpropanolamine HCl from controlled-release tablets

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Summary

The dissolution behavior of two controlled-release matrix tablets, formualtions A and B, containing phenylpropanolamine HCl as a model drug was studied using a paddle method and a paddle-beads procedure. The paddle-beads method involves a system in which polystyrene beads are inserted into the dissolution medium to cause mechanical destruction or frictional force. These tablets have the advantages of pH- and agitation-independent release performance in vitro using the paddle method. These matrices and solution were orally administered to six beagle dogs, and the results were analyzed by deconvolution. In vitro dissolution curves using the paddle method did not coincide with the in vivo profiles in the fasted condition, while in vitro release using the paddle-beads method was similar to the in vivo profile in the fasted condition in dogs. The paddle-beads method may be useful for investigating in vivo/in vitro correlation of controlled-release dosage forms.

Introduction

During the developmental stages of oral controlled-release dosage forms, it is essential to use dissolution methods that allow pharmacokinetic screening of the dosage forms in order to predict the interplay of biological factors, physico-chemical properties of the drug, and composition and characteristics of the dosage form. The in vitro dissolution test is performed to evaluate drug release from the systems that influence these factors. The dosage forms are then administered to humans to estimate the absorption rate and bioavailability. However, frequent use in humans is difficult and should be restricted, especially in new drug development and preformulation studies. Thus, it is necessary to establish an in vitro test method that can predict the progress of drug release and the absorption of products in humans. Several approaches to assess the in vivo/in vitro correlations, particularly for controlled release dosage form, have been used. These include plots of a dissolution parameter ($T_{50\%}$, etc.) vs a pharmacokinetic parameter (Uchida et al., 1989), and statistical moment analysis based on the cor-

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relation between the mean dissolution time in vivo ($MDT_{in\ vivo}$) and the mean dissolution time in vitro ($MDT_{in\ vitro}$) (McNamara et al., 1990). In these reported methods, the in vivo/in vitro correlations were based on mean data, rather than on individual data. Recently some methods have been applied to evaluate the in vivo/in vitro correlation individually. The rotating dialysis cell method was useful in studying the effects of food on the absorption of cotrolled-release dosage forms (El-Arini et al., 1990). The rotating basket method at 100 rpm in 400 ml pH changing media, seemed to mimic the physiological conditions in the gastrointestinal (GI) tract under fasting conditions in man (Hussein and Friedman, 1990). Although three kinds of formulations had similar in vitro release rates using the paddle method at 50 rpm, plasma drug levels were different (Dahl et al., 1990).

Liaw et al. (1990) reported that the Theo-dur® tablet surface was seen to erode in vivo and that the discharged tablets were entrapped in gastric or intestinal mucin plugs. Therefore, mechanical destruction or a frictional force appears to be needed in the in vitro dissolution test. The paddle method in which the medium contains beads therefore seemed useful in order to evaluate drug release from a tablet and to simulate the in vivo release profile in the in vitro dissolution test. This method has also been reported by Machida et al. (1991). In the present study, to correlate in vitro/in vivo dissolution profiles in dogs as for preliminary study, in vitro dissolution testing using polystyrene beads was performed.

Materials and Methods

Materials

Phenylpropanolamine HCl (PPA) was obtained from ALPS Pharmaceutical Ind. (Gifu, Japan) and chlorprenaline HCl was supplied by Eisai (Tokyo, Japan). Hydroxypropylcellulose (2320 cps viscosity grade, Nihonsoda, Tokyo, Japan) and ethylcellulose (10 cps viscosity grade, Dow Chemical, U.S.A.) were used to prepare solved mixtures of hydrogel. All other chemicals used were of analytical grade.

Dosage forms

A solved mixture of hydrogel powder (SMH) containing 80% hydroxypropylcellulose and 20% ethylcellulose was used as the controlled-release carrier. The preparation has been described in a preceding paper (Aoki et al., 1992). Formulation A was composed of 150 mg SMH and 40 mg PPA in a tablet, and formulation B was formulated to contain 300 mg SMH and 40 mg PPA. PPA and SMH were blended using a stationary mixer (Kyouritsurikou, Tokyo, Japan), and the tablets were directly compressed with a compression instrument (Autograph IS-5000, Shimadzu, Kyoto, Japan) using 7.98 mm diameter flat-faced punches. The tablets were produced at a compression pressure of 196 MPa. An oral aqueous solution containing 20 mg PPA per ml was used as a reference formulation.

In vitro dissolution test

The in vitro dissolution rate of PPA from the controlled-release matrix tablets was determined using the methods for the JP11 paddle apparatus (DT-600 dissolution tester, Freund-Jusco, Tokyo, Japan). In this study, two methods were carried out for determination of PPA release profiles in vitro. The mean residence time in vivo ($MRT_{in\ vivo}$) was calculated by means of moment analysis (Yamaoka, 1978).

Paddle method The release of PPA from the matrix tablets was studied in distilled water, and in media of pH 1.2, 4.0 and 6.8 (ionic strengths: 0.067, 0.02 and 0.062, respectively) using 900 ml of each medium maintained at 37 ± 0.5 °C. The paddle speed was set to 100 rpm, and in distilled water, the influence of agitation was also investigated at 50 and 200 rpm. At each sampling interval, an aliquot of the dissolution medium was drawn off and assayed by high-performance liquid chromatography (HPLC). Volume losses from sample withdrawals were replaced with the dissolution medium. The components of the HPLC system were an LC-6A pump, an SLC-6B autosampler and an SPD-6A UV spectrophotometric detector set at 220 nm (all three from Shimadzu Corp., Kyoto, Japan) and a YMC-Pack FL-ODS3 column (5 cm length × 4.6 mm diameter, 3 μm; from YMC Co., Kyoto, Japan). The

mobile phase used was acetonitrile: 0.05 N potassium 2 hydrophosphate aqueous solution (5:95).

Paddle-beads method The dissolution test apparatus used was the same as that described above. The release of PPA was examined in distilled water. The medium volumes used were 250, 300, 500, and 700 ml, maintained at 37 ± 0.5 °C. A total of 1500 polystyrene beads (diameter 6.35 mm, specific gravity, 1.05 g/cm^3, Wako Pure Chemical, Osaka, Japan) were added to the medium and agitated at 100 rpm. The sampling method and assay of released PPA concentration were performed as described above.

In vivo studies

Six male beagle dogs weighing 9.0–12.0 kg were fasted overnight and used for the experiments. They were allowed free access to water and no food was given until the last blood sample had been taken. A crossover design with 1-week dosing intervals was used for three treatments; formulation A, B, and solution. Hard gelatin capsules (Kasyo, Tokyo, Japan) filled with a solution containing 40 mg of PPA in 2 ml of distilled water were orally administered with 10 ml of purified water. Formulations A and B were also administered with 10 ml of water. Blood samples were withdrawn from the cephalic vein of the forelimb up to 24 h after administration. Plasma samples were immediately separated and frozen at −20 °C until assayed.

Plasma extraction procedure

An aqueous solution of 20 μg ml^{-1} chlorprenaline HCl was prepared for use as an internal standard. Then 50 μl of the internal standard solution, 250 μl of 1 N NaOH (NaCl saturated) aqueous solution and 2 ml of methylene chloride:diethyl ether (3:7) were sequentially added to 0.5 ml plasma in a test tube. The tube was vortexed for 10 min, and centrifuged for 10 min at 3000 rpm. The upper organic layer was transferred to a clean test tube, and then dried with hydrogen gas at 40 °C. To the residual aqueous phase, 2 ml of organic solvent was added, followed by vortexing and centrifugation as before. This organic phase was transferred to the test tube, and 250 μl of 0.5% phosphoric acid aqueous solution was added. After vortexing and centrifugation as before, the organic phase was removed. The aqueous solution was injected into the HPLC.

HPLC assay of plasma samples

Plasma samples were assayed for PPA by a method using HPLC with UV detection. Separation on the octadecylsilane column (Nucleosil, 250 mm length × 4.6 mm diameter, 10 μm) was achieved at ambient temperature at a flow rate of 2 ml min^{-1}. The mobile phase contained 0.01 M SDS-0.2% phosphoric acid aqueous solution:acetonitrile (6:4). UV detection was at 210 nm.

Pharmacokinetic studies

Plasma PPA levels after oral administration were fitted to a one-compartment pharmacokinetic model using the nonlinear least-squares regression program, MULTI (Yamaoka, 1984). Other model-independent parameters including maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were determined according to a standard procedure. The area under the concentration time curve (AUC) and mean residence time for p.o. from zero time to infinity (MRT_{po}) were calculated by a linear trapezoidal method. AUC_{0-24} was calculated from zero time to 24 h, and $AUC_{0-\infty}$ by extrapolation using the expression C_t/k, where C_t is the last estimated plasma concentration, and k denotes the elimination rate constant. The mean dissolution time in vivo ($MDT_{in\ vivo}$) was evaluated by subtracting $MRT_{solution}$ from MRT_{tablet} (Yamaoka and Tanigawara, 1983). The relative bioavailabilities, F^R, of the two controlled-release formulations were calculated as the ratio of the AUC for these formulations to that of solution. The Wagner-Nelson method was used to determine the fractional oral absaorption at each sampling time:

$$\%\ \text{absorbed} = \frac{C_{p,t} + AUC_{0-t}k}{AUC_{0-\infty}k} \times 100$$

where $C_{p,t}$ is the plasma concentration of PPA at time t, and AUC_{0-t} and $AUC_{0-\infty}$ denote the

areas under the PPA plasma concentration-time profile from zero time to t and from zero time to infinity, respectively, following oral administration of solution.

Numerical deconvolution

The unit input impulse to the GI tract is considered to be the response to a unit dose of an oral solution of the drug. Polyexponential expressions are fitted to the real plasma concentration-time course and simulated data employing the MULTI system, and defined as the weighing function. The plasma concentration-time function obtained following administration of a solid oral dosage form of the same drug is defined as the response function of the system. The in vivo release rate from that dosage form can then be calculated by combining the weighting and response functions by means of deconvolution. An expression for the cumulative percent of dose, D, input at time t is obtained by integration of the release rate from that dosage form and multiplied by $100/D$, and the cumulative percent of the dose released into the GI tract is thus obtained.

Results and Discussion

PPA was used as the model drug for a controlled-release dosage form. PPA is a chemically stable, freely soluble compound which is rapidly absorbed in dogs when administered in an immediate release dosage form (Hussein, 1987).

SMH was examined as a controlled-release carrier in a tablet containing PPA. The in vitro dissolution results using the paddle method (Figs 1 and 2) demonstrate very consistent behavior of formulations A and B under various experimental conditions. The paddle method produced similar results irrespective of the agitation or pH conditions.

Fig. 3 shows the mean plasma concentration vs time curves in dogs for solution and formulations A and B. Table 1 lists some of the pharmacokinetic data. Relatively large intraindividual variations in C_{max} were observed following the administration of solution compared with that of controlled-release tablets. These results are consistent with the data reported by Ellar and Della (1990). However, the variations in AUC were somewhat larger with controlled-release tablets than with solution.

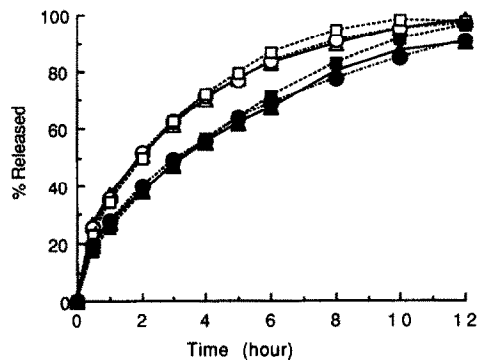

Fig. 1. In vitro dissolution profiles for formulations A and B using the paddle method at various speeds of rotation in 900 ml distilled water: (open symbols) PPA release for formulation A; (solid symbols) PPA release for formulation B. Circles, 50 rpm; triangles, 100 rpm; squares, 200 rpm.

$MDT_{in\ vivo}$ was obtained from subtracting MRT_{tablet} from $MRT_{solution}$ (Tanigawara et al., 1982). The $MDT_{in\ vivo}$ values of formulations A and B were 3.0 ± 0.9 and 7.6 ± 2.2 h (mean $\pm$ S.E.), respectively. $MDT_{in\ vitro}$ obtained by means of the paddle method was approx. 3.45 ± 0.35 and 5.11 ± 0.89 h (average $\pm$ S.D.) for formulations A and B, respectively. It appears that

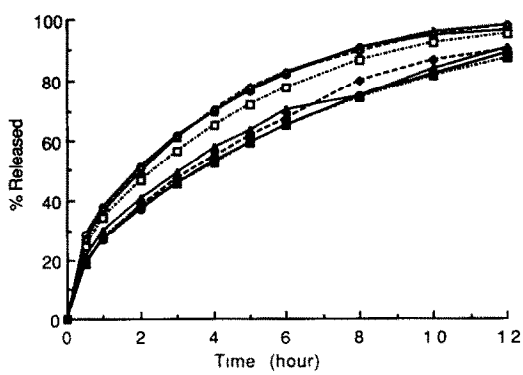

Fig. 2. In vitro dissolution profiles for formulations A and B using the paddle method with rotation at 100 rpm in 900 ml medium: (open symbols) PPA release for formulation A; (closed symbols) PPA release for formulation B. Circles, pH 1.2; triangles, pH 4.0; squares, pH 6.8; lozenges, distilled water.

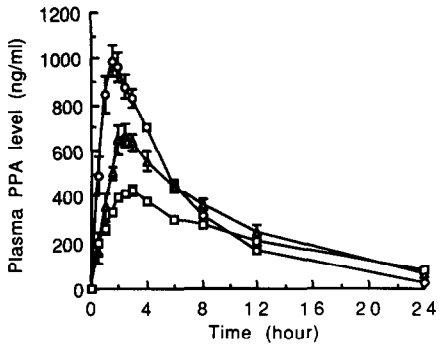

Fig. 3. Mean plasma level of PPA obtained after oral adminsitration in dogs. Each point represents mean ± S.E. ($n = 6$). Circles, solution; triangles, formulation A; squares, formulation B.

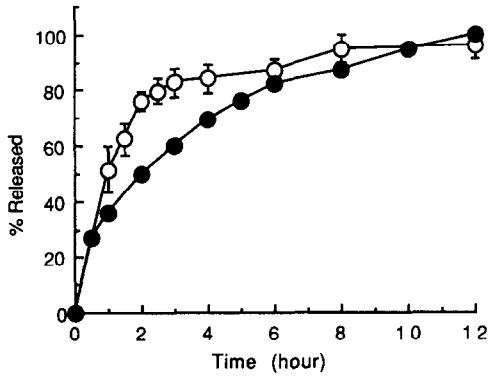

Fig. 4. Comparison of dissolution for in vivo curve (open circles, mean ± S.E.) obtained by deconvolution and in vitro curve (filled circles) by means of the paddle method with rotation at 100 rpm in 900 ml distilled water.

$MDT_{in\ vivo}$ is roughly related to $MDT_{in\ vitro}$ determined from the paddle method. Fig. 4 shows an in vivo mean dissolution profile from formulation A plotted via deconvolution and in vitro mean dissolution curves obtained using the paddle method. A discrepancy between the in vivo profile and the in vitro curves was observed. This indicates that the in vivo release rate in dogs was faster than that in vitro. MRT provides significant information with respect to the kinetic features of the process which a drug undergoes in the GI tract and body, and $MDT_{in\ vivo}$ was defined as the magnitude of the in vivo dissolution rate, although the drug absorption at the later stage appreciably influenced MRT and $MDT_{in\ vivo}$. It is considered that if a close correlation between $MDT_{in\ vivo}$ and $MDT_{in\ vitro}$ is observed, a discrepancy between in vivo and in vitro release profiles may occur. VRT expresses the width of distribution and provides an index of the length of time over which drug action is maintained (Yamaoka, 1984). A statistical difference in VRT values between solutoin and formulation A was recorded ($p < 0.1$), although efficient sustained drug release in vivo was not achieved.

Hussein and Friedman (1990) reported that the conditions for performing dissolution tests, i.e., the rotating basket method at 100 rpm in 400 ml of media with changing pH, appeared to mimic the physiological conditions in the GI tract in the fasting state in man, while the conditions in dogs were more severe than this in vitro situation. The

TABLE 1

Pharmacokinetic parameters of PPA in dog plasma following oral administration of solution, and formulations A and B

Parameters	Solution	Formulation A	Formulation B
C_{max} (ng ml^{-1})	1022.0 (68.1)	692.2 (59.6)	439.3 (18.9)
T_{max} (h)	1.67 (0.17)	2.50 (0.18)	2.83 (0.11)
AUC_{0-24} (ng h ml^{-1})	7105.3 (217.4)	6760.1 (397.2)	5200.8 (257.9)
F^{R}_{0-24} (%) [a]		95.1	73.2
$AUC_{0-\infty}$ (ng h ml^{-1})	7410.2 (141.5)	7371.8 (561.8)	6487.4 (694.7)
$F^{R}_{0-\infty}$ (%) [b]		99.5	87.5
$MRT_{in\ vivo}$	6.68 (0.34)	9.68 (1.13)	14.29 (2.34)
$MDT_{in\ vivo}$		3.00 (0.90)	7.60 (2.16)
VRT	37.02 (3.49)	76.95 (19.50)	214.94 (74.88)

Values in parentheses represent S.E.

[a] Relative bioavailability calculated from zero time to 24 h.

[b] Relative bioavailability calculated from zero time to infinity.

motility pattern in the GI tract and mucus should play a significant role in the dissolution of an administered tablet. Formulation A had the advantages of pH- and agitation-independent release performance in vitro using the paddle method. It appears that the physiological conditions in the GI tract of dogs differed from those of the dissolution test using the paddle method. Therefore, a mechanical impact or fractional force was necessary for the in vitro dissolution test. The paddle method involves scarcely any mechanical destruction, impact or frictional force. The paddle-beads method was therefore introduced in order to evaluate drug release from a tablet and to simulate the in vivo release profile in the in vitro dissolution test.

Fig. 5 depicts the apparatus for application of the paddle-beads method. The paddle and container of the dissolution fluid were the same as those specified in the JP11 dissolution test. Polystyrene beads were selected, since their specific gravity is about 1.05 g/cm^3 (almost equal to the density of water), and they can move freely at low agitation speeds (e.g., 10 rpm). Since the surface of polystyrene is hydrophobic, drug adsorption onto the surface of polystyrene beads should be examined when utilizing this method. On insertion of the polystyrene beads into PPA solution of known concentration, the extent of adsorption onto the surface was less than 0.3%;

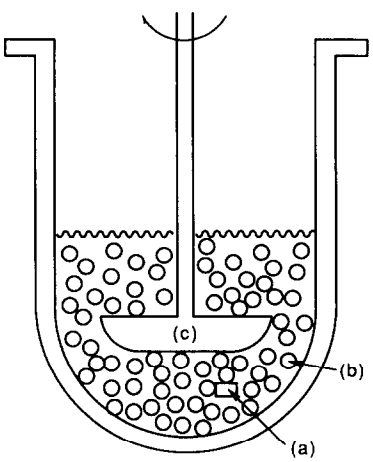

Fig. 5. Dissolution apparatus: (a) matrix tablet; (b) polystyrene beads; (c) paddle.

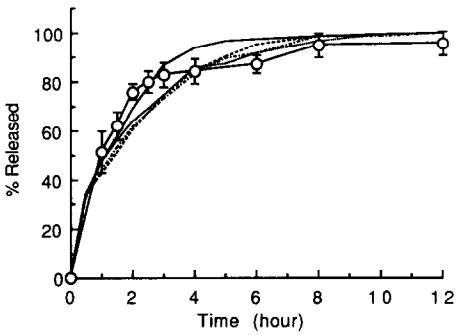

Fig. 6. Comparison of dissolution profiles from formulation A for in vivo curve (open circles, mean ± S.E.) obtained by deconvolution and in vitro curves using the paddle-beads method with rotation at 100 rpm in various volumes of distilled water containing 1500 polystyrene beads. (———) 250 ml; (- - - - -) 300 ml; (— — —) 500 ml; (– · – · –) 700 ml.

thus, it is assumed that PPA is not adsorbed onto the surface of polystyrene. Hydrophobic drugs are considered to present a problem due to adsorption onto the surface of polystyrene beads. In the case where this phenomenon was observed, to prevent drug adsorption onto the beads, the polystyrene beads were either coated with EC using a fluidized bed technique, or the surface of the polystyrene was preadsorbed with HPC (Law and Kayes, 1983) added to the dissolution medium. Using such procedures, drug adsorption on the surface of polystyrene can be avoided.

Fig. 6 shows the in vivo release profiles resulting from deconvolution, and in vitro curves obtained by means of the paddle-beads method in which the volume of the medium was changed from 250 to 700 ml. In vitro release using the paddle-beads method mimicked that in vivo, especially at a volume of medium of 250 ml. The volume of medium needed is at least 3-fold that required for a saturated solution to provide sink conditions (Cohen et al., 1990). PPA dissolves freely in water (1 g dissolves in not more than 10 ml water), and therefore to dissolve 40 mg PPA, a 250 ml volume of aqueous medium is sufficient to maintain sink conditions. The speed of rotation of the paddle was set at 100 rpm, since discrepancies between the in vivo results on humans and dogs were observed (Hussein and Friedman, 1990), which appear to be due to the more pow-

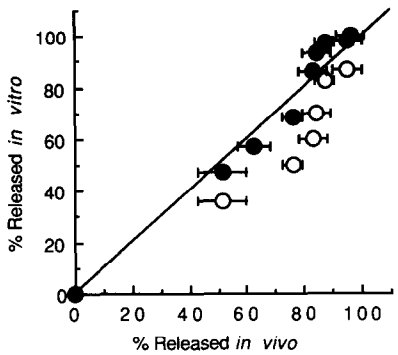

Fig. 7. Relationship between in vitro dissolution and in vivo release of PPA from formulation A. (Open circles) In vitro data using the paddle method vs in vivo data. (Closed circles) In vitro data using the paddle-beads method with rotation at 100 rpm in 250 ml distilled water vs in vivo data.

erful force of disintegration in the digestive tract of the dog (Aoyagi et al., 1985) compared with that of man. Polystyrene beads were observed to collide with a tablet in the medium, and appeared to result in a mechanical or frictional force on the tablet.

If the in vivo release plot is strictly in agreement with the in vitro profile, a plot of one vs the other should be linear with unit slope and zero intercept. The release data obtained using the paddle and paddle-beads methods are plotted in this fashion for formulation A in Fig. 7. The solid line in Fig. 7 represents the linear regression with a slope of unity and zero intercept. Drug release was found to be faster in vivo than in vitro when using the paddle method, whereas both patterns of drug release were observed to be similar in the case of the paddle-beads method. This difference can be partly ascribed to mechanical forces such as impaction and friction between the matrix tablet and the polystyrene beads. Using the paddle-beads method, we were able to demonstrate a close correlation between the percentage release in vivo (x) and that in vitro (y). At greater than 80% in vivo drug release for formulation A, the rate of in vivo drug release was found to become lower than that in vitro (Fig. 6). In addition, at above 80% in vivo release, the slope of the plot was observed to deviate from unity (Fig. 8). Although F^{R}_{0-24} for formulation A amounted 95.1%, in vitro drug release using the paddle-beads method reached 100% after a 12 h dissolution testing. The plot of this relationship approached unit slope. It appears that the paddle-beads method with rotation at 100 rpm in 250 ml medium containing 1500 polystyrene beads reflects the in vivo force between the tablet and the GI tract.

Fig. 8 shows a similar relationship for formulation B. A 1:1 relationship between the in vitro and in vivo dissolution profiles is demonstrated at in vitro release rates up to 60%. In the range from 0 to 60%, using the paddle-beads method, the in vitro and in vivo dissolution curves are almost superimposable ($y = 0.991\ x - 0.26$, $r = 0.9960$, $p < 0.01$). At above 60% in vivo drug release for formulation B, the rate of in vivo drug release became slower than that in vitro. The reason for this will be described later.

Oral absorption data were further evaluated using the Wagner-Nelson approach. The elimination constant calculated based on the oral administration of solution (0.229 h^{-1}) was used to determine the percentage absorbed. The above value was found to be consistent with data from i.v. administration (Hussein et al., 1987), i.e., 0.20 $\pm$ 0.03 (mean $\pm$ S.D.).

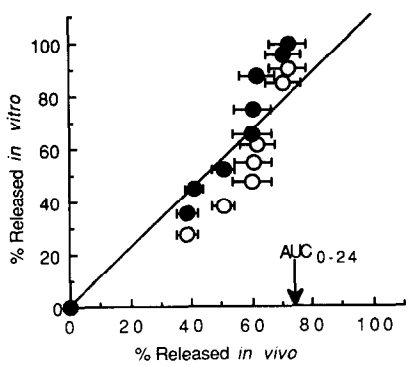

Fig. 8. Relationship between in vitro dissolution and in vivo release of PPA from formulation B. (Open circles) In vitro data using the paddle method vs in vivo data. (Closed circles) In vitro data using the paddle-beads method with rotation at 100 rpm in 250 ml distilled water vs in vivo data.

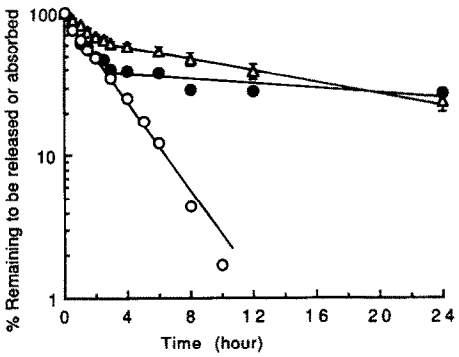

Fig. 9. Mean percentage of dose remaining to be absorbed (open triangles, mean ± S.E.) or released (closed circles) in vivo vs time after oral administration of formulation B. For comparison, the in vitro profile of the drug remaining to be released (open circles) is included.

The percentage remaining to be released or absorbed in vivo and in vitro vs time after oral administration of formulation B is plotted in Fig. 9. The rate of release of PPA in vitro behaved according to first-order kinetics. The in vivo dissolution and absorption profiles from the controlled-release tablet are clearly diphasic. The in vivo rate of release of PPA from the matrix tablet and the in vivo absorption rate were delayed to 4 h after oral administration. This was also observed for formulation A. Liaw et al. (1990) reported that the transit time from the mouth to the ileum in the fasted state was 2.5–3.6 h in dogs, and it was therefore assumed that PPA was released at a slower rate in the large intestine than in the small intestine. In Fig. 8, a discrepancy is evident between the in vivo and in vitro results at in vitro release rates greater than 60%, which appears to result from the slow release of PPA in the ileum. Moreover, F^{R}_{0-24} amounted to 73.2% for formulation B, whereas in vitro percentage release after 12 h dissolution testing attained 99.5%. This may also be related to the discrepancy between the in vivo and in vitro release rates.

The paddle-beads method may be useful for investigation of the in vivo/in vitro correlation of controlled-release dosage forms, especially when drug release from dosage forms is affected by mechanical destruction or frictional force.

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