International Journal of Pharmaceutics, 95 (1993) 67–75

© 1993 Elsevier Science Publishers B.V. All rights reserved 0378-5173/93/$06.00

IJP 03070

Determination of the mechanical impact force in the in vitro dissolution test and evaluation of the correlation between in vivo and in vitro release

Shigeru Aoki, Hidenobu Ando, Kimio Tatsuishi, Keizo Uesugi and Hiroshi Ozawa

Research Laboratories of Pharmaceutical Development, Eisai Co., Ltd, Takehaya-machi 1, Kawashima-cho, Hashima-gun, Gifu 501-61 (Japan)

(Received 18 June 1992)
(Modified version received 7 August 1992)
(Accepted 30 September 1992)

Key words: Phenylpropanolamine; Matrix tablet; Manometry; Impulse; Release, in vivo; Dissolution, in vitro

Summary

The mechanical impact force in the paddle-beads method was determined. A manometric catheter was passed into the dissolution vessel through a hole, and the mechanical impact force was measured. In the present study, this mechanical force was evaluated as an impulse. The impulse increased with increasing number of beads added in the medium; in particular, the impulse increased markedly with more than 2500 beads in 250 ml dissolution medium. A close relationship was observed between the drug release rate and impulse. The profile of in vitro release using the paddle-beads method with rotation at 25 rpm in 250 ml of medium containing 2500 beads was similar to that of in vivo release in the fasted condition in dogs.

Introduction

In the development of oral controlled-release dosage forms, it is essential to use dissolution methods that allow pharmacokinetic screening of the dosage form; in particular, the prediction of in vivo parameters. With respect to meaningful applications to controlled-release dosage forms, four levels of in vivo/in vitro correlation are defined (Cohen et al., 1990). The highest level of correlation represents a 1 : 1 relationship between the in vitro dissolution and the in vivo profile; namely, the in vitro dissolution and the in vivo curves are superimposable. Recently, several approaches have been applied to evaluate the in vivo/in vitro correlations individually. For example, to bring the in vitro release curve for acetaminophen close to that obtained with the in vivo data, a time-scaling factor was introduced (Van Bommel et al., 1991). Hussein and Friedman (1990) reported that the conditions of dissolution tests using the rotating basket method at 100 rpm in 400 ml of media with changing pH seemed to mimic the physiological conditions in the gastrointestinal (GI) tract under fasting con-

Correspondence to: S. Aoki, Research Laboratories of Pharmaceutical Development, Eisai Co., Ltd, Takehaya-machi 1, Kawashima-cho, Hashima-gun, Gifu 501-61, Japan.

ditions in humans, whereas the condition in dogs was more severe than this in vitro condition.

GI motility is characterized by a four-phase, cyclically recurring complex known as the interdigestive migratory myoelectric complex (IMMC: Code and Marlett, 1975). Phase III activity propels the residual stomach contents into the small intestine (Majoverian et al., 1991). The gastric emptying time of nondigestible dosage forms with a diameter greater than 5 mm is therefore determined mainly by the onset of phase III activity of the IMMC (Itoh et al., 1986). Shalaby et al. (1992) reported that hydrogels of certain sizes became compacted and partially deformed against the pyloric sphincter. Furthermore, intestinal motility is mainly governed by the propulsive efficiency of peristaltic contractions. Liaw et al. (1990) reported that the Theo-dur® tablet surface was seen to erode in vivo, and the discharged tablets were entrapped in gastric or intestinal mucin plugs. Therefore, a mechanical destruction or friction force appears to be needed in the in vitro dissolution test. In our previous paper (Aoki et al., 1992b), we proposed the paddle-beads method to introduce a mechanical impact force.

In this study, we attempted to determine the mechanical impact force in the paddle-beads method, and investigated the relationship between release rate of drug from the matrix and the mechanical impact force.

Materials and Methods

Materials

Phenylpropanolamine HCl (PPA) was obtained from ALPS Pharmaceutical Ind. (Gifu, Japan). Hydroxypropylcellulose (HPC, 2320 cps viscosity grade; viscosity was measured as the value of an aqueous solution containing 2% by weight of dry HPC at 20°C, Nihonsoda, Tokyo, Japan) and ethylcellulose (10 cps viscosity grade, Dow Chemical, U.S.A.) were used to prepare a solved mixture 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 for the controlled-release carrier. 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. The methods of preparation of SMH and the manufacturing process of tablets are described in our previous papers (Aoki et al., 1992a).

In vitro *dissolution test*

The dissolution study was carried out using a dissolution tester (model DT-600, Freund-Jusco, Tokyo, Japan). The paddle method in JP XII was modified in order to cause a mechanical impact force in the dissolution method. Polystyrene beads (diameter 6.35 mm, specific gravity 1.05 g/cm^3) were added to the dissolution test medium. This method of dissolution testing was termed the 'paddle-beads methods' in our previous paper (Aoki et al., 1992b). Two different formulations, A and B, were used as model formulations. A volume of 250 or 500 ml of distilled water maintained at 37 ± 0.5°C was used for the dissolution medium, since this system has the advantage of pH-independent release performance in vitro (Aoki et al., 1992b). The paddle rotation speed was 25, 50 or 100 rpm. The number of beads used was 500, 1000, 1500, 2000, 2500 or 3000 for 250 ml of medium, and 500, 1000, 2000, 3000 or 4000 for 500 ml of medium. The sampling method and assay of released PPA concentration were performed as described previously (Aoki et al., 1992b).

Manometry in vitro

Three holes were made in a dissolution vessel at distances from the center of the vessel of 4.7, 4.0 and 3.0 mm; these three positions are referred as to position A–C, respectively in this paper. The catheter (pressure transducer, diameter 3 mm, area of sensor 1.75 mm × 3.0 mm, Gaeltec Ltd, U.K.) was inserted into one of the holes, and a face of the pressure sensor was attached in a direction against the flow of medium, and was sealed with a rubber stopper. The other holes were sealed with rubber stoppers. This catheter was connected via a voltage control unit (Goodman, Nagoya, Japan). A schematic diagram of the apparatus is shown in

Fig. 1. The pressure sensor was subjected to the impact force by the beads added in the medium by rotating the paddle. This force was determined with a model 72R recorder (Gasukuro Kogyo, Tokyo, Japan) and integrated with Chromatpac C-R2AX integrator (Shimadzu, Kyoto, Japan). In this study, an expression for the mechanical impact force is obtained by integration of the force vs time for 1 min, and a value is then obtained as the area under the dashed curves. That is, this value was estimated as an impulse (force multiplied by time). To measure the impulse, first, a baseline recording was made for 30 s. After rotating the paddle for 30 s, the impulse was measured for 1 min. The area of the sensor affected the impulse. Then, in this study, to normalize a value, the value was represented as the impulse given for 1 min to 1 cm^2 (N min cm^{-2}).

Determination of in vivo *drug release*

The plasma concentration-time profile of an oral solution of the drug was defined as the weighting function, and 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.

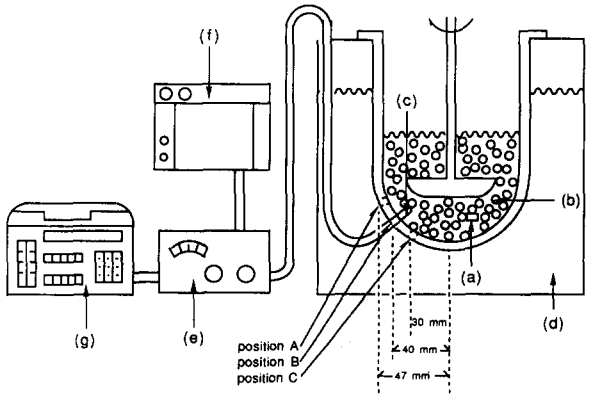

Fig. 1. Schematic diagram of the apparatus for measuring impulse. (a) Matrix tablet, (b) beads, (c) catheter, (d) water bath, (e) voltage control unit, (f) recorder, (g) integrator.

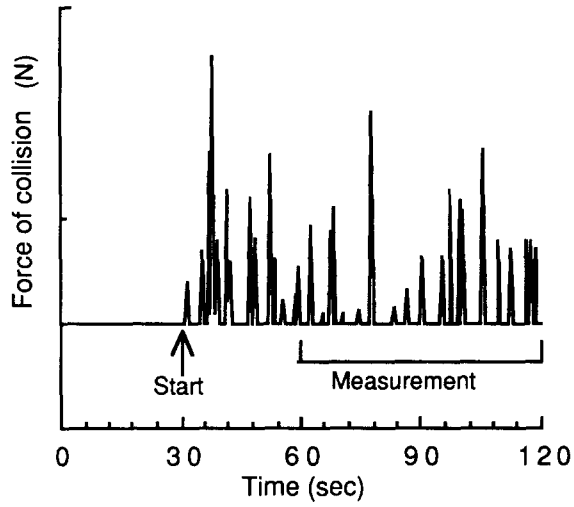

Fig. 2. A typical collision pattern in the paddle-beads method.

Results and Discussion

A typical manometric recording is shown in Fig. 2. As illustrated in Fig. 2, the mechanical impact force was recorded for collisions of the beads on the sensor. The schematic diagram of the mechanical impact force resembles that of the motor complex reported by Mojaverian (1991). It was assumed the motion of the beads in the in vitro apparatus reflects the in vivo GI mobility.

The release characteristics of PPA from the matrix tablet using the paddle-beads method are shown in Fig. 3. When the drug release from a whole tablet was analyzed, linearity was not maintained because of attrition of the hydrated layer. The relationship between the drug release and square root of time was preserved during the initial drug release even though attrition occurred at that stage (Lapidus and Lordi, 1968). The release rate from the matrix without the beads was calculated by subjecting the points representing up to 80% release to least-square linear fitting. The release rate from the matrix with the beads showed good linearity only up to 60%

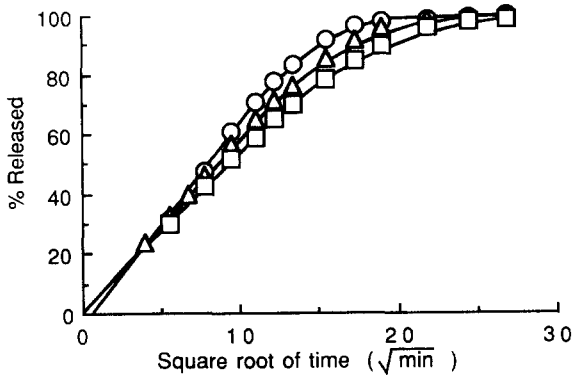

Fig. 3. In vitro release profiles of PPA from the matrix tablet using the paddle-beads method at 25 rpm in 250 ml medium. (□) 500 beads; (△) 2000 beads; (○) 3000 beads.

release, and thereafter displayed positive deviation owing to greater attrition of the hydrated layer. According to Fig. 3, the drug release follows a square root of time equation. The coefficient for the square root of time equation (CSE) was obtained by calculating the gradient of the percentage release vs root time curve up to 60% release. This CSE provides a value which characterizes the drug release rate from the matrix tablet. In this study, the drug release rate was expressed as the value of CSE.

The relationship between the number of beads and release rate of PPA from formulation A at various paddle speeds is shown in Fig. 4, which demonstrates a tendency for increase of the PPA release rate with increase in number of beads. It appears that the release rate tends to be larger with a smaller volume of dissolution medium with the same number of beads. On the other hand, the mean release rate tends to increase with increasing paddle speed, however, there was no distinct difference between the release rates at various paddle speeds in the medium with the same number of beads. It was assumed that the paddle speed influences the aqueous diffusion layer close to the outside of the matrix tablet. The fact that the paddle speed scarcely affects the PPA release rate showed that the effect of the aqueous diffusion layer on the release rate of this matrix tablet was negligible; this is because the rate-limiting step is the penetration of the medium into the matrix and the diffusion of drug from the matrix (Bamba et al., 1979).

In the paddle-beads method, it is presumed that the gelation region of the tablet is eroded by the impact (or attrition) of the beads in the medium, and the drug release rate is accelerated. In the various manometric methods, measurement of the impact force by means of a pressure measurement device in the shape of a tablet would have been appropriate, since this small device would flow freely within the medium. However, such a device with specific gravity of about 1 g/cm^2 could not be found. As a substitute, a small catheter was inserted into the dissolution vessel through a hole, and the impact force between the beads and the sensor was measured. With this method, it was anticipated that the

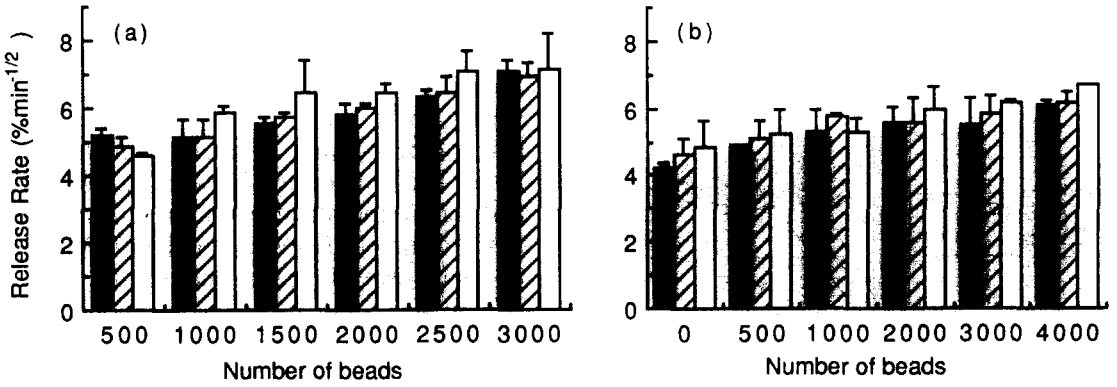

Fig. 4. Effect of the number of beads on release rate of PPA in 250 ml medium (a) and 500 ml medium (b). Vertical bars indicate S.D. (■) 25 rpm; (▨) 50 rpm; (□) 1000 rpm.

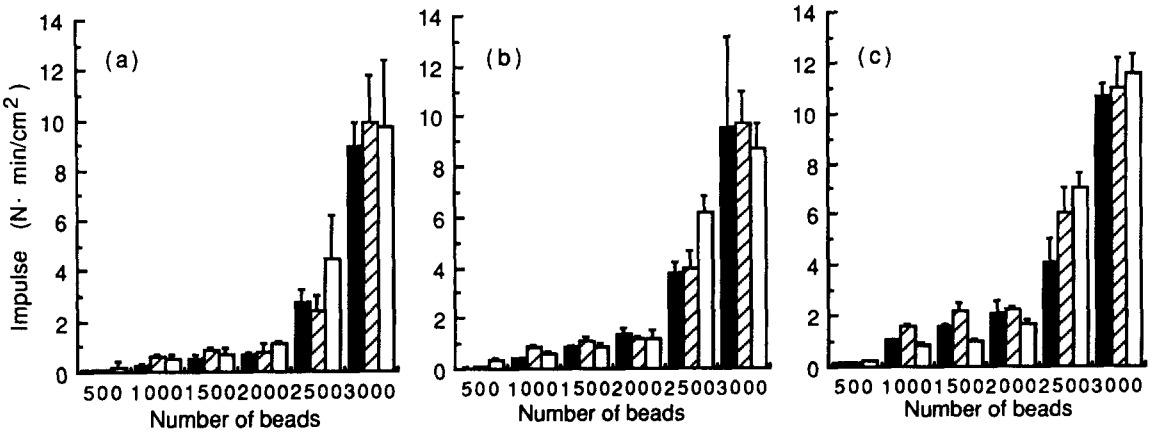

Fig. 5. Effect of the number of beads on the impulse at various paddle speeds and sensor positions in 250 ml medium. (a) 25 rpm, (b) 50 rpm, (c) 100 rpm. (■) Position A; (▨) position B; (□) position C.

value of the impulse might differ depending on the location of the catheter, consequently the impulse was measured at positions A–C in 250 ml of medium. The influence of the paddle speed on the impulse was also investigated (Fig. 5). With respect to the impulse, the number of beads had a greater effect than the position of the sensor. For all paddle speeds, an increase in the number of beads increased the impulse at each position of the sensor; in particular, the impulse markedly increased with more than 2500 beads. The theoretical void volume of beads consisting of uniform spheres with closest packing is 26%, and for loosest packing, 48% (Martin et al., 1970). It was assumed that the void volume of the beads filled was about 40% in this study; thus, the void volume of about 2300 beads was equal to the volume of the medium (250 ml). The void volume of 2500 beads was greater than 250 ml of medium, and this medium was present between the beads. Thus, at a number of beads ≤ 2000, floating beads in the medium collided with the sensor. In comparison, at a number of beads ≥ 2500, the beads were agitated by the rotating paddle, the agitated beads then colliding with the sensor. It was considered that the impact force given from the agitated beads was greater than that from the floating beads. It was assumed that the impact

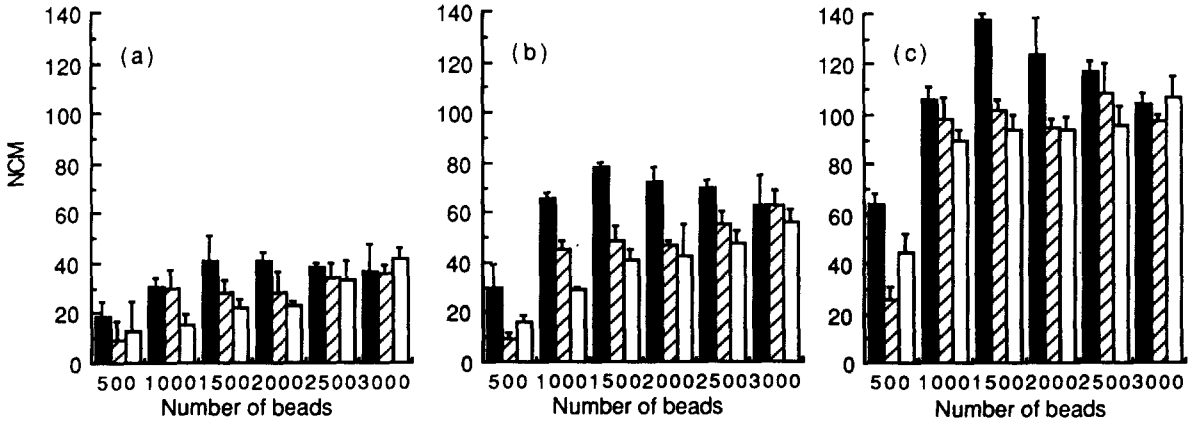

Fig. 6. Effect of the number of beads on the NCM at various paddle speeds and sensor positions in 250 ml medium. (a) 25 rpm, (b) 50 rpm, (c) 100 rpm. (■) Position A; (▨) position B; (□) position C.

force on the beads was markedly increased when the number of beads was more than 2500.

The influence of the sensor position on the impulse seemed to be negligible, except under the conditions of 2500 beads at a paddle speed of 25, 50, and 100 rpm. It appeared that the sensor position slightly affected the impulse. To investigate the relationship between the impulse and the number of beads in detail the number of collisions per min (NCM) an the mean impulse obtained at one collision (MIC) were determined. The MIC was calculated by dividing the impulse obtained for 1 min, by the NCM. NCM increased with increasing paddle speed regardless of the sensor position, and NCM increased with increasing number of beads up to 1000 beads for all sensor positions (Fig. 6).

However, NCM tended to decrease with increase in the number of beads above 1500 beads at position A, while NCM tended to increase as the number of beads increased at position C. It was assumed that this resulted from the motion of the beads around the paddle. The motion of the beads is dependent on the shape of the vessel (hemispherical bottom of vessel) and the location of the paddle wing for stirring. At position A, the inside diameter was greater and the distance between the paddle wing and the sensor was smaller than at position C. The motion of the beads at position A was greater than that at position C, and NCM at position A was greater than at position C with up to 1500 beads. It appears that with increase in the number of beads, NCM at each position of the sensor tended to be equal; the velocity of the beads tended to be the same owing to the close packing of the beads. On the other hand, MIC at position A was less than that at position C (Fig. 7), due to the shorter collision time. Furthermore, the beads in the lower part of the vessel were subjected to greater gravity than those in the upper part of the vessel. It was therefore presumed that the impact force of collision of beads at position C was greater than that at position A. Then with a bead number of 2500 at a paddle speed of 25 or 50 rpm, the difference in NCM between the paddle speeds was small, however, the values of MIC at positions A and C were different, and thus the impulse at positions A and C differed. On the other hand, the values of MIC at positions A and C were almost the same up to 2000 beads at 100 rpm; however, the values of NCM were different. It thus appears that the sensor position affected the impulse at 100 rpm.

The relationships between (a) the release rate of PPA for formulation A shown in Fig. 4 and (b) the impulse obtained under various condition, the volume of the medium, the paddle speed, and the number of beads, are plotted in Fig. 8. The values of the impulse in Fig. 8 were utilized as the values at position B, since the latter were intermediate between the values at the three posi-

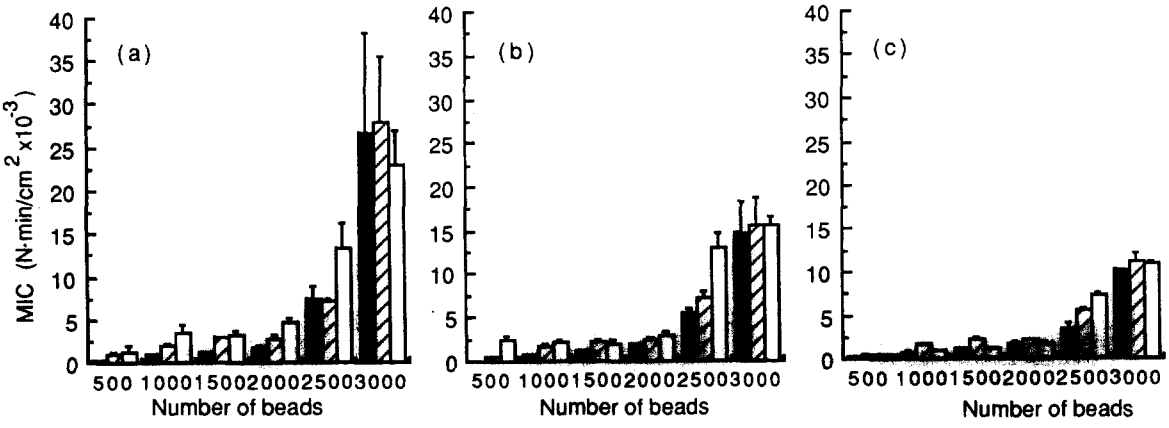

Fig. 7. Effect of the number of beads on the MIC at various paddle speeds and sensor positions in 250 ml medium. (a) 25 rpm, (b) 50 rpm, (c) 100 rpm. (■) Position A; (▨) position B; (□) position C.

tions. A close relationship was observed between release rate and impulse. The impulse abruptly increased with increase in release rate above 6% $min^{-1/2}$. It was considered that when the void volume of the beads was greater than the medium volume, the impulse radically increased, although the release rate did not increase markedly. From the result shown in Fig. 8, a close relationship between the impulse and drug release rate was achieved by attaching the sensor to the vessel. It was concluded that the release rate was identical with the same impulse, even though conditions such as medium volume, paddle speed, and number of beads in the paddle-beads method varied.

Aoyagi (1992) reported that the agitation strength in the GI tract of beagle dogs was equal to that of an in vitro paddle speed of 25 rpm. Therefore, in order to examine the correlation between in vivo and in vitro release, the conditions of the paddle-beads method were set at 25 rpm in 250 ml of medium with 2500 beads (Fig. 7). The relationship between the in vitro release data obtained from the paddle-beads method and the in vivo profile reported in our previous study (Aoki et al., 1992b) is shown in Fig. 9. A solid line represents unit slope and zero intercept. The in vivo drug release from formulation A was similar to the in vitro drug release under the conditions

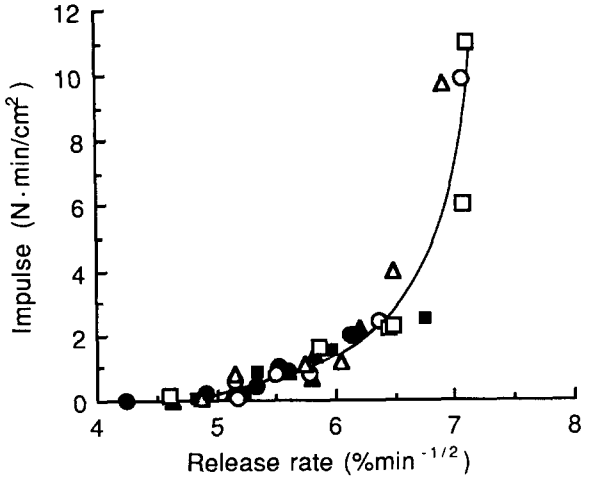

Fig. 8. Relationship between release rate of PPA and the impulse at position B. Open symbols indicate 250 ml medium; closed symbols correspond to 500 ml medium. (○) 25 rpm; (△) 50 rpm; (□) 1000 rpm.

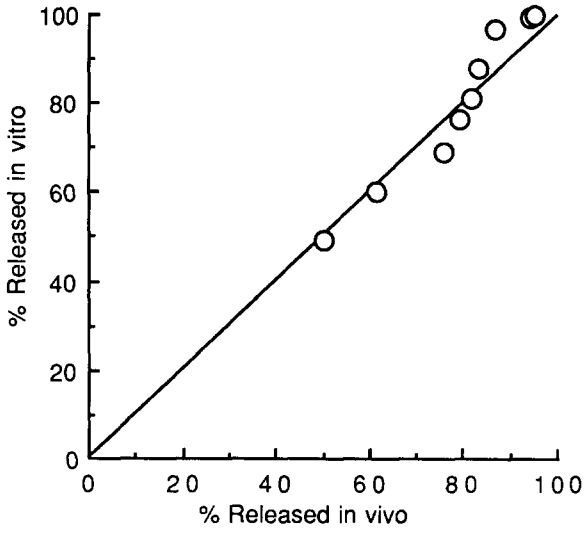

Fig. 9. Relationship between in vivo dissolution and in vitro dissolution of PPA from formulation A. The solid line represents a 1:1 in vivo/in vitro correlation. In vitro release test conditions; rotation at 25 rpm in 250 ml medium with 2500 beads.

of 25 rpm in 250 ml of medium with 2500 beads. According to Fig. 3, approx. 6.5 h are required to achieve 90% dissolution and this 90% in vitro dissolution is in good agreement with the in vivo release. In this case, the relative bioavailability from 0 to 24 h for formulation A was 95.1% (Aoki et al., 1992b), whereas in vitro percent release after the 12 h dissolution test was 100%. Then the in vivo release data almost coincided with those for in vitro release.

The paddle-beads method under the above conditions was also applied to formulation B, and the in vivo/in vitro correlation was investigated (Fig. 10). A 1:1 relationship between in vitro dissolution and in the in vivo profiles was demonstrated up to 60% release in vitro. In the previous report (Aoki et al., 1992b) a discrepancy between the in vitro release rate of PPA from formulation B and the in vivo release rate was observed after 3 h of oral administration. Mizuta et al. (1990) reported a mean oro-colonic transit time of 2.9 h in the fasted condition in dogs. It was assumed that a discrepancy between in vivo and in vitro results was due to the slow release of PPA in the ileum.

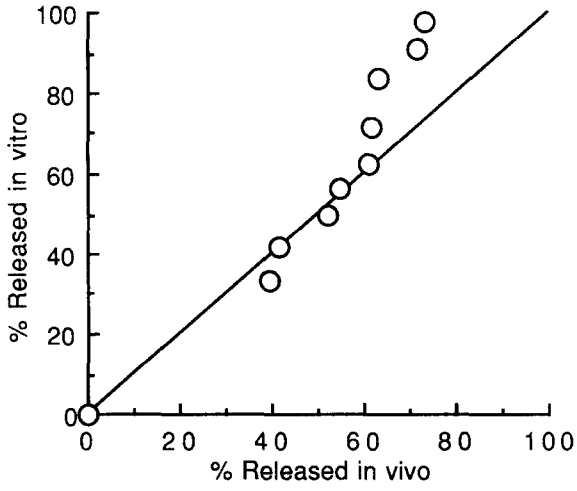

Fig. 10. Relationship between in vivo dissolution and in vitro dissolution of PPA from formulation B. The solid line represents a 1:1 in vivo/in vitro correlation. In vitro release test conditions; rotation at 25 rpm in 250 ml medium with 2500 beads.

Itoh et al. (1986) reported that after oral administration of a Heidelberg capsule attached to a surgical suture, a strong pulling force (> 10 g) was noted at the suture tied to the capsule during the IMMC activity. Furthermore, Liaw et al. (1990) reported that the Theo-dur® tablet surface was eroded and the discharged tablets were entrapped in gastric or intestinal mucin plugs. From these facts, the impulse in the stomach or the small intestine was roughly calculated as more than 1 N min cm^{-2}. The in vivo release rate for formulation A was calculated as 6.3% $min^{-1/2}$ using the data obtained previously (Aoki et al., 1992b). Therefore, the impulse measured by the sensor attached to the ves sel was about 2.2 N min cm^{-2} from the result in Fig. 7. A difference between the values of the in vivo and in vitro impulses was observed. It was assumed that this difference was attributed to the in vitro measurement method; the impact force was measured between beads and the sensor attached to the vessel. The drug release was affected by the impact force between the moving matrix tablet and beads, and it was presumed that this impact force relates to the in vivo impulse. It is considered that the impact force between the moving matrix tablet and beads is less than that between the fixed sensor and the beads, since the tablet and beads are moving with each other. Then the in vitro impulse achieved between the sensor and beads was greater than the in vitro impulse. However, the relative relationship between the in vitro impulse and in vitro release rate should be determined in this study.

The paddle-beads method with rotation at 25 rpm in 250 ml of medium with 2500 beads could be applied to predict the in vivo dissolution of the two formulations. This method may be of great value in the development of oral controlled-release dosage forms to screen the dosage form such as a hydrogel matrix tablet or to predict the in vivo dissolution profile.

Acknowledgment

This work was supported in part by a grant from the Japan Health Sciences Foundation.

References

Aoki, S., Ohwaki, T., Uesugi, K., Tatsuishi, K., Ozawa, H. and Kayano, M., Preparation of a new type of controlled-release carrier and evaluation of drug release from the matrix tablet and its physical properties. *Int. J. Pharm.*, 85 (1992a) 29–38.

Aoki, S., Uesugi, K., Tatsuishi, K., Ozawa, H. and Kayano, M., Evaluation of the correlation between in vivo and in vitro release of phenylpropanolamine HCl from controlled-release tablets. *Int. J. Pharm.*, 85 (1992b) 65–73.

Aoyagi, N., The biopharmaceutical evaluation of orally administered sustained release doage form. *Pharm Tech Jap.*, 8 (1992) 41–46.

Bamba, M., Puisieux, F., Marty, J.P. and Carrstensen, J.T., Release mechanisms in gel-forming sustained release preparations. *Int. J. Pharm.*, 2 (1979) 307–315.

Code, C. and Marlett, J. The interdigestive myo-electric complex of the stomach and small bowel of dogs. *J. Physiol.*, 246 (1975) 289–309.

Cohen, J.L., Hubert, B.B., Leeson, L.J., Rhodes, C.T., Robinson, J.R., Roseman, T.J. and Shefter, E., The development of USP dissolution and drug release standards. *Pharm. Res.*, 7 (1990) 983–987.

Hussein, Z. and Friedman, M., Release and absorption characteristics of novel theophylline sustained-release formulations: in vitro-in vivo correlation. *Pharm. Res.*, 7 (1990) 1167–1171.

Itoh, T., Higuchi, T., Gardner, C.R. and Caldwell, L., Effect of particle size and food on gastric residence time of

nondisintegrating solids in beagle dogs. *J. Pharm. Pharmacol.*, 38 (1986) 801–806.

Liaw, J., Rubinstein, A. and Robinson, J.R., Bioavailability study of Theo-dur tablets in the fasted cannulated dog. *Int. J. Pharm.*, 59 (1990) 105–114.

Lapidus, H. and Lordi, N.G., Drug release from compressed hydrophilic matrices. *J. Pharm. Sci.*, 57 (1968) 1292–1301.

Martin, A.N., Swarbrick, J. and Cammarata, A., *Physical Pharmacy*, 2nd Edn, Lea and Febiger, Philadelphia, 1970, pp. 485–491.

Mizuta, H., Kawazoe, Y. and Ogawa, K., Gastrointestinal absorption of chlorothiazide: Evaluation of a method using salicylazosulfapyridine and acetaminophen as the marker compounds for determination of the gastrointestinal transit time. *Chem. Pharm. Bull.*, 38 (1990) 2810–2813.

Mojaverian, P., Reynolds, J.C., Ouyang, A., Wirth, F., Kellner, P.E. and Vlasses, P.H., Mechanism of gastric emptying of a nondisintegrating radiotelemetry capsule in man. *Pharm. Res.*, 8 (1991) 97–100.

Shalaby, W.S.W., Blevins, W.E. and Park, K., In vitro and in vivo studies of enzyme-digestible hydrogels for oral drug delivery. *J. Controlled Release*, 19 (1992) 131–144.

Van Bommel, E.M.G., Raghoebar, M. and Tukker, J.J., Comparison of in vitro and in vivo release characteristics of acetaminophen from gradient matrix systems. *Biopharm. Drug. Dispos.*, 12 (1991) 367–373.