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Development of Sustained-Release Tablets Containing Sodium Valproate: In Vitro and In Vivo Correlation

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ABSTRACT We have developed a 200 mg and 400 mg sustained-release sodium valproate tablet that allows effective blood concentration of the active drug with once-a-day dosing. The controlled dissolution or sustained release of the drug was attained by a membrane-controlled system. A single-coating system did not adequately control the dissolution rate, and therefore double-coated tablets were prepared and a human pharmacokinetic study was conducted. With the 200 mg VPA-Na tablets, the nonfasting C_{max} was only 20% higher than the fasting C_{max}. An in vitro dissolution test was conducted to predict the effects of food on drug dissolution after administration of this tablet. A relatively good correlation was observed between the absorption profiles and the dissolution profiles of the drug.

Keywords Sustained-release, Tablet, Sodium valproate, In vitro and in vivo correlation

INTRODUCTION

Repeated doses of antiepileptic drugs are necessary to maintain efficacy in long-term epileptic treatment, and routine monitoring of blood concentrations is necessary to confirm effectiveness and to prevent side effects. Sodium valproate (VPA-Na) is a widely used antiepileptic drug and is effective in bipolar disorder. Sodium Valproate (VPA-Na) is a sodium salt of a fatty acid with a simple branched chain that has a shorter elimination half-life (7–13 h) than commonly used antiepileptic drugs (Bialer et al., 1985; Perucca et al., 1978; Klotz & Antonion, 1977; Bryson et al., 1983). Due to the short biological half-life, the conventional formulation of VPA-Na must be taken orally twice or three times daily to maintain the effective blood concentration of 40 to 120 μg/mL (Davis et al., 1994; Nikken Chemicals Co., Ltd., 2002). Patients usually take antiepileptic drugs like VPA-Na for years with a high level of compliance in order to control clinical seizures. Less frequent dosing, e.g., once a day, is desirable for both therapeutic and psychological reasons. Our company previously developed and launched a once-a-day dosing product, sustained-release granules. This sustained-release granule formulation is widely used for children. However, many children prefer to use tablet from elementary school

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onward. Furthermore, adult patients have to take more than 3 g of the sustained-release granules in order for the drug to have a maximum daily dose of more than 1,200 mg so ease of use does not necessarily translate into improved compliance. Additionally, the current commercial once-a-day controlled-release tablet, Depakote® Tablets (Abbott Laboratories; containing 500 mg divalproex sodium, caplet-type, size of tablet ca. 0.9×1.9 cm, weight of tablet 1 g), is larger than the tablet we present here.

The objective in the present study was to develop an easy-to-take, small, sustained-release tablet that allows effective blood concentration to be maintained by once-a-day dosing. In order to predict the in vivo pharmacokinetic behavior of a sustained-release product, we used an in vitro evaluation system that was similar to the in vivo environment. Therefore, an in vitro dissolution test of the product was designed.

MATERIALS AND METHODS

Materials

VPA-Na was purchased from Sumitomo Chemical Co., Ltd (Tokyo, Japan). The pharmaceutical additives used were ethylcellulose (Dow Chemical, Midland, Michigan, U.S.A.), light anhydrous silicic acid (Nippon Aerosil Co., Tokyo, Japan), calcium stearate (Nitto Kasei Co., Ltd., Osaka, Japan), methacrylate copolymer L (Degussa, Dusseldorf, Germany), and triethyl citrate (Morimura Bros., Inc., Tokyo, Japan). All other chemicals used were of reagent grade.

Preparation of Tablets

First, VPA-Na and several pharmaceutical additives were mixed together by a multipurpose mixer (110DM-Qrs; Shinagawa Ind. Co., Nara, Japan). Then ethanol was added to the mixture and kneaded in the same mixer. The size of the dehydrated dry granules was reduced in a mesh-type size reducer (HRG-125V; Hata Iron Works Co., Ltd., Kyoto, Japan). Next, the resulting granules and calcium stearate, a lubricant, were combined in a W-cone mixer (W100; Tokuju Corporation, Kanagawa, Japan). These mixtures were then pressed using a tabletting machine (HT-P22; Hata Iron Works Co., Ltd.), yielding 231.6 mg (9 mmΦ) or 463.2 mg (13 mm caplet type) core tablets (containing 200 or 400 mg of VPA-Na, respectively).

A coating solution was prepared by dissolving ethylcellulose, methacrylate copolymer L, and triethyl citrate in ethanol and by dispersing light anhydrous silicic acid in the coating solution. Uncoated tablets were sprayed with the coating solution by a coating machine (New Hicoater HCT-80N; Freund Corporation, Tokyo, Japan) and dried to produce membrane-coated, sustained-release tablets.

Dissolution Test

A dissolution test was performed according to the procedure described in the JP Dissolution Test (paddle and beads method) (The Japanese Pharmacopeia, 2001). The paddle rotational speed was kept at 50 rpm, at 37 ± 0.5°C. Release test was carried out in 900 mL of pH 6.8 phosphate buffer (0.05 mol/L) using a dissolution tester (NTR6100A, TCP-61CAP, PAS-615; Toyama Sangyo Co., Ltd., Osaka, Japan). Samples of 10 mL were withdrawn at predetermined time intervals, and replaced with the same volume of fresh medium. Each sample solution was analyzed by an HPLC to determine the dissolution rate of VPA-Na.

A UV absorption spectrometer was used as the HPLC detector with a detection wavelength of 210 nm. The HPLC column was an Inertsil ODS (GL Sciences, Inc., Tokyo, Japan) with a stainless-steel column with an inside diameter of 4.0 mm and a length of 25 cm. The analysis was performed at 40°C. The mobile phase was 0.02 M phosphate buffer (pH 3.0) (The Japanese Pharmacopeia, 2001) and acetonitrile (60:40 v/v).

The effect of mechanical strength on the drug dissolution from tablets was evaluated using the paddle and bead method (Aoki et al., 1992). In brief, 250 g of plastic beads (spherical beads with a diameter of ca. 6 mm and specific gravity of ca. 1.02 g/cm^3) and 200 mL of 0.1 mol/L HCl (pH1.2) were added to the vessel, and the paddle was rotated at 25 rpm. The analytical procedure and conditions were the same as those used in the paddle method.

Simulation of the Dissolution Profile

Sodium Valproate (VPA-Na) is rapidly and almost completely absorbed from the entire gastrointestinal tract (Klotz & Antonion, 1977; Hosoya et al., 1994). In the sustained-release form, VPA-Na is continuously absorbed for more than 16 h without any decrease in bioavailability (BA) in healthy adults (Bialer et al.,

1985), and the proposed product design would not lead to any reduction in BA, even though the dissolution rate is controlled. Therefore, the tablet was designed under the assumption that the rate of dissolution of VPA-Na from the tablet would be equivalent to the rate of drug absorption from the gastrointestinal tract, and that the cumulative amount of the drug that dissolved at 24 h would approximate the BA. The maximum and minimum blood concentrations (C^{ss}_{max} and C^{ss}_{min}) at steady state after once-a-day, repeated administration were simulated using a linear 1-compartment model. We assumed a dose (D) of 1,200 mg of VPA-Na, a patient body weight of 70 kg (D = 17.1 mg/kg of VPA-Na), an absolute bioavailability (F) of 1.0, and a dosing interval (t) of 24 h. The apparent volume of distribution (Vd) and elimination rate constant (k_{el}) reported by Perucca et al. (1978) were used (Vd = 0.147 L/kg, k_{el} = 0.0549 h^{-1}).

Pharmacokinetic Analysis

The percent absorbed was calculated by Eq. 1 according to the Wagner-Nelson Method (Wagner & Nelson, 1964). $AUC_{0-\infty}$ was calculated using the fasting values in Table 4, k_{el} was calculated by the least-square method using either four or five points after the drug absorption was complete, and $t_{1/2}$ was determined by Eq. 2.

$$\% = (k_{el} \cdot AUC_{0-t} + C_t)/k_{el} \cdot AUC_{0-\infty} \quad (1)$$

$$t_{1/2} = 0.693/k_{el} \quad (2)$$

where AUC_{0-t} is AUC (μg h/mL) after oral administration to time t (h), and C_t is plasma concentration (μg/mL) of VPA at time t(h) after oral administration.

Human Pharmacokinetic Study

The plasma concentration of VPA-Na was measured after oral administration of test tablets to humans under fasting conditions. The tablets were also administered after consumption of a high-fat meal (nonfasting; 900 kcal, fat content at least 35%) to evaluate the effects of a high-fat meal on the time profile of plasma drug concentration. The study was conducted with a single-dose crossover design in healthy adult male volunteers (age, 20 to 30 years; body weight, 50 to 80 kg). Written informed consent was obtained from all subjects.

RESULTS AND DISCUSSION

Simulation of the Dissolution Profile

Figure 1 and Table 1 show simulated profiles of plasma concentration of VPA-Na. When a value of 1.0 h^{-1} or less was selected for the absorption rate constant (k_a), the plasma concentration was maintained within the effective range of 40 to 120 μg/mL. Additionally, the range of variation in the blood concentration ($C^{ss}_{max}/C^{ss}_{min}$) was 3.0 for 1.0 h^{-1} and 1.5 for 0.1 h^{-1} of k_a. Because a small range of variation is preferable, 0.1 h^{-1} was selected for k_a.

Table 2 shows the effect of the dissolution rate constant (k_d) on the dissolution ratio over 24 h under the assumption that k_d is close to k_a. The k_d was determined

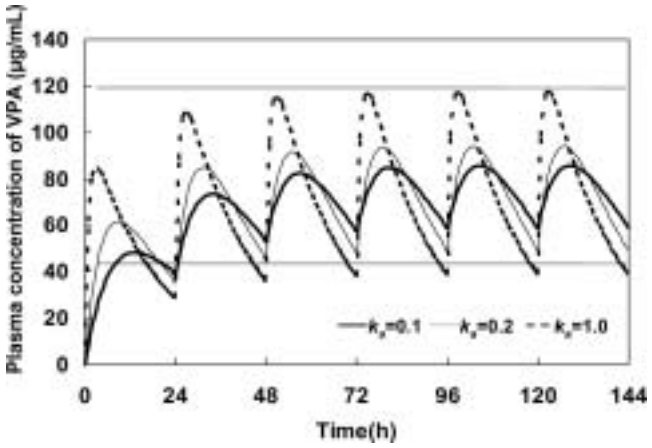

FIGURE 1 **Simulated Plasma Concentration of VPA After Oral Administration of VPA-Na (1,200 mg Day^{-1}) for 6 Days. Key: k_a = 1.0: Dashed Line, k_a = 0.2: Thin Solid Line, k_a = 0.1: Bold Solid Line.**

TABLE 1 **Pharmacokinetic Parameters Obtained by Simulation**

k_a (h^{-1})	$C^{ss}min$	$C^{ss}max$	$C^{ss}max/C^{ss}min$
1.0	39	118	3.0
0.2	49	94	2.0
0.1	59	86	1.5

$C^{ss}max$: $Cmax$ at steady state (μg/mL).
$C^{ss}min$: $Cmin$ at steady state (μg/mL).

TABLE 2 **Relationship Between k_d and % of Dissolved Drug at 24 h**

k_d (h^{-1})	Dissolved (%)
1.0	100
0.2	99
0.1	91

from the slope of a sigma-minus plot of % dissolution-time curve. This simulation suggests that a lower k_d has a reducing effect on BA. Therefore, a lower limit of 0.1 h^{-1} was chosen for k_d. The tablet design was selected to permit the dissolution rate within these two lines (k_d = 0.1 to 0.2 h^{-1}), as shown in Fig. 2.

Investigation of the Tablet Formulation

The sustained-release mechanism of the tablets may involve either a matrix- or a membrane-controlled system (Lee & Robinson, 1978; Langer, 1993). However, matrix-controlled tablets require a large amount of water-insoluble pharmaceutical ingredients for highly water-soluble drugs such as VPA-Na. The membrane sustained-release mechanism was used in our Selenica® Granules for VPA-Na. Since the specific surface area of the tablets is smaller than that of granular preparations, tablet drug dissolution can be controlled using smaller amounts of coating than is required with granules. Therefore, we investigated sustained-release tablets with a membrane-controlled system.

Selection of Coating Materials for the Membrane-Controlled System

Ethylcellulose, widely used for controlled release of large, water-soluble molecules, was first selected as the controlled-release membrane for this product (Porter, 1989). We closely examined whether the ethylcellulose coating might dissolve in the oily Na-free VPA base produced by VPA-Na and gastric acids (pK_a of VPA-6.4).

A preliminary solubility study of VPA-Na was conducted. Sodium Valproate (VPA-Na) oil was prepared by adding 1 mol/mL HCl to the VPA-Na solution and by separating the oily VPA. The casting films were prepared by several kinds of copolymers and immersed in Na-free VPA oil. If the original form of the polymer was maintained for 24 h, the films were judged insoluble in Na-free VPA oil. The results of this study (Table 3) showed that a single-layer ethylcellulose film was completely dissolved in the VPA-Na oil within 1-2 h. This result suggested that controlled release of VPA-Na by the ethylcellulose film would be difficult, especially when the ethylcellulose film-tablet remained in the stomach for a long period (for example if a high-fat meal had been consumed). Therefore, a mixed film consisting of ethylcellulose with other additives was utilized to delay the dissolution rate. Finally, a film composed of ethylcellulose and methacrylate copolymer L was not dissolved in the VPA-Na oil for more than 24 h. Then, we concluded that this mixed film could be used for the controlled-release of VPA.

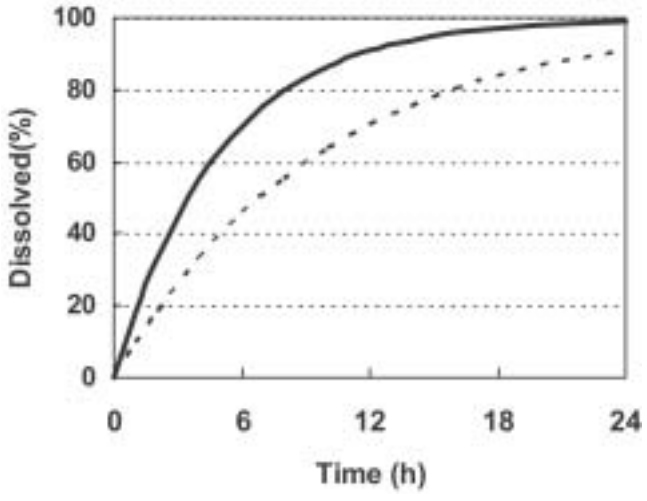

FIGURE 2 **Ideal Dissolution Profiles of VPA-Na. Key: k_d = 0.2: Solid Line, k_d = 0.1: Dashed Line.**

Investigation of Coated Tablets

Three test tablets were coated with a mixed membrane composed of ethylcellulose and methacrylate copolymer L (400 mg VPA-Na tablets). Each coating amount was from 12 mg to 33 mg. Dissolution profiles of these tablets showed a faster dissolution than the target profile (data not shown; k_d values were 0.475, 0.359, and 0.415). Moreover, an increase in the coating amount decreased the dissolution rate but increased the lag time. Thus, the target k_d value (0.1 to 0.2 h^{-1}) could not be obtained with the single-coated tablets.

TABLE 3 **Dissolution of Casting Film in VPA Oil**

Film composition	Dissolved time (h)
Ethylcellulose	1-2
Ethylcellulose HPMC[1]	2-3
Ethylcellulose Eudragit RS[2]	5-6
Ethylcellulose Eudragit L[3]	>24

[1]Hydroxyethylcellulose
[2]Aminoalkyl Methacrylate Copolymer RS
[3]Methacrylic Acid Copolymer L

Investigation of Double-Coated Tablets (1)

We then investigated double-coated tablets, which had a membrane with different characteristics, in order to control the dissolution rate. Ethylcellulose was selected as the second coating material. In the double-coated tablets, the amount of primary and secondary coating was set at 15 and 4, 6, 10, or 14 mg, respectively, for the tablets designated D0, D1, D2, and D3.

Dissolution profiles of the obtained double-coated tablets were evaluated. The slope of the dissolution profiles (n = 6) in Fig. 3 suggested a decrease in dissolution when the amount of the secondary coating was increased. This demonstrated that the dissolution rate was effectively controlled. Suitable dissolution profiles with the target k_d were obtained for tablets D1 and D2. The dissolution profiles for tablets D0 and D3 were also very good, since the k_d values obtained were close to the target k_d.

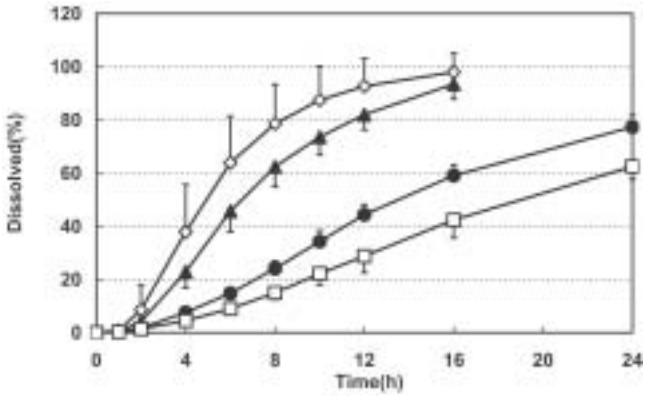

FIGURE 3 **Dissolution Profiles of Tablets D0-D3 with Rotation at 100 rpm in pH 6.8 (n = 6, mean ± S.D.). Key: Open Diamond Represents Tablet D0, Closed Triangle Represents Tablet D1, Closed Circle Represents Tablet D2, Open Square Represents Tablet D3.**

Since the obtained dissolution profile was ideal or almost ideal, human pharmacokinetic study was conducted using these four tablets. The study had a single-dose (400 mg of VPA-Na) design, and was conducted under fasting conditions in healthy volunteers. The results are shown in Fig. 4. The percent absorption from tablets D0, D1, D2, and D3 was evaluated using the Wagner-Nelson method. Figure 5 shows the dissolution rate in pH 6.8 against the absorption rate under fasting conditions for each tablet. The slopes in the figure were 0.8896–1.4978 (correlation coefficient, r = 0.9856–0.9975). Three of four, excluding D1, showed almost a 1:1 relationship between percent absorbed and percent dissolved. Hence, the assumption that the dissolution rate of VPA-Na from the tablets was equivalent to the absorption rate from the gastrointestinal tract was validated, showing that this in vitro evaluation method closely reflects the in vivo environment. However, the dissolution test was conducted at a paddle rotational speed of 100 rpm, even though distinguishing differences between formulations at a slower stirring speed is easier. Because several reports citing strong correlation was found between the in vivo and in vitro results at 50 rpm (Kaniwa et al.,

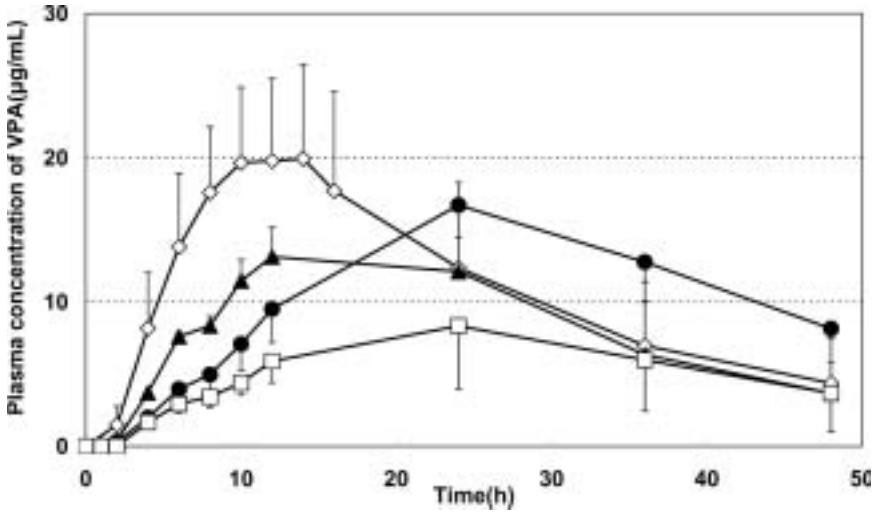

FIGURE 4 **Plasma Concentration of VPA After Oral Administration of Tablets D0-D3. Each Point Represents the Mean Plasma Concentration of VPA for six Healthy Volunteers. Key: Open Diamond Represents Tablet D0, Closed Triangle Represents Tablet D1, Closed Circle Represents Tablet D2, Open Square Represents Tablet D3.**

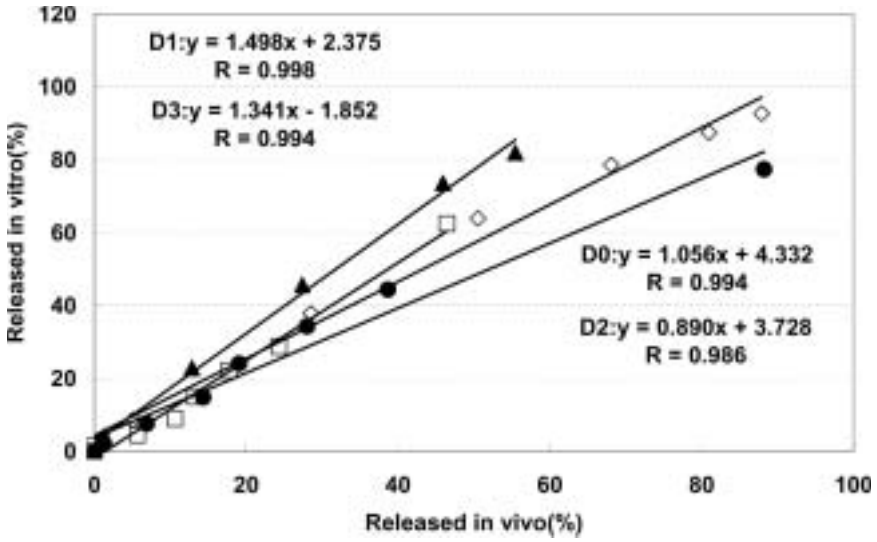

FIGURE 5 **Relationship Between In Vivo Absorption and In Vitro Dissolution of VPA from Different Formulations (D0-D3). In Vitro Data Use the Paddle Method with Rotation at 100 rpm in pH 6.8. Key: Open Diamond Represents Tablet D0, Closed Triangle Represents Tablet D1, Closed Circle Represents Tablet D2, Open Square Represents Tablet D3.**

1989; Shah et al., 1992), subsequent dissolution tests were performed at a paddle rotational speed of 50 rpm.

Investigation of Double-Coated Tablets (2)

Up to this point, our investigation focused on tablets containing 400 mg of VPA-Na. However, we also thought it would be useful to prepare 200 mg tablets of VPA-Na. Based on our investigation of the 400 mg tablets, the following values were chosen for the combined amount of coating (the primary and secondary membrane) for the 200 mg tablets: 11 mg (tablet E), 15 mg (tablet F), 18 mg (tablet G), and 19 mg (tablet H). The thickness of the coating membrane was approximately 200 μm. Dissolution tests (paddle method) were performed for these tablets using 900 mL of pH 6.8 and a paddle rotational speed of 50 rpm. The results of these tests (n = 6) are shown in Fig. 6. The lag time of ideal dissolution profiles was set to 3 h based on the results in the figure. Most dissolution behaviors from the test tablets were contained between two ideal curves (k_d = 0.1 to 0.2 h^{-1}). Next, human pharmacokinetic studies were conducted for these tablets.

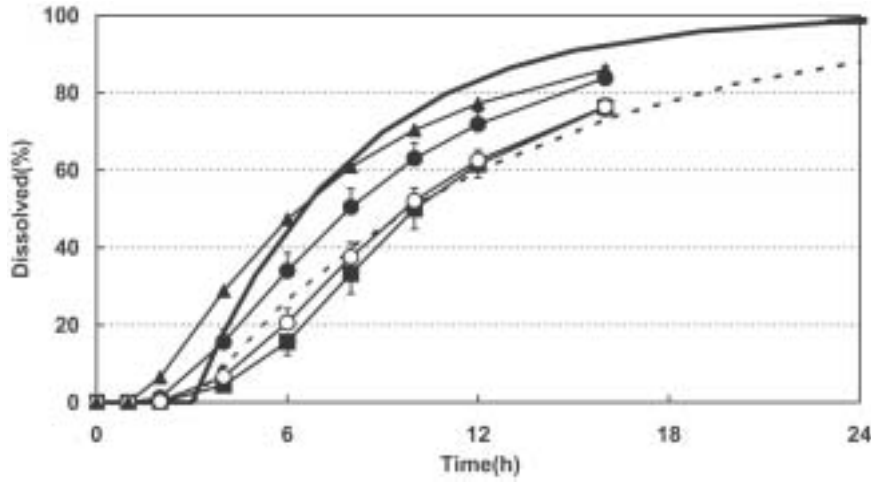

FIGURE 6 **Dissolution Profiles of Tablets E–H with Rotation at 50 rpm in pH 6.8 (900 mL) (n = 6, mean ± S.D.). Key: Closed Triangle Represents Tablet E, Closed Circle Represents Tablet F, Closed Square Represents Tablet G, Open Circle Represents Tablet H, Solid Line Represents k_d = 0.2, Dashed Line Represents k_d = 0.1.**

Pharmacokinetic Study in Humans

The drug concentration in the plasma was measured after administration of one tablet containing 200 mg VPA-Na. Figure 7 shows the time profile of plasma drug concentration. The obtained pharmacokinetic parameters are summarized in Table 4. Nonfasting C_{max} was higher than fasting C_{max}, with the following average ratio (range) of nonfasting C_{max} to fasting C_{max}: tablet E, approximately 1.5 (1.14 to 2.30), tablet F, approximately 1.36 (0.94 to 1.96), and tablet G, approximately 1.2 (0.40 to 1.68). Under nonfasting conditions, increases in plasma drug concentration were found immediately after administration in 13 of 19 subjects receiving tablet E, 1 of 5 subjects receiving tablet F, and 2 of 6 subjects receiving tablet G, suggesting that the tablets had lost their sustained-release characteristics shortly after entering the stomach (the burst phenomenon). In contrast, tablet H showed similar plasma concentration-time profiles under both fasting and nonfasting conditions.

Evaluation of the Absorption Rate

The percent absorption from tablets E, F, G, and H was evaluated using the Wagner-Nelson method. The in vitro release in pH 6.8 against the in vivo release

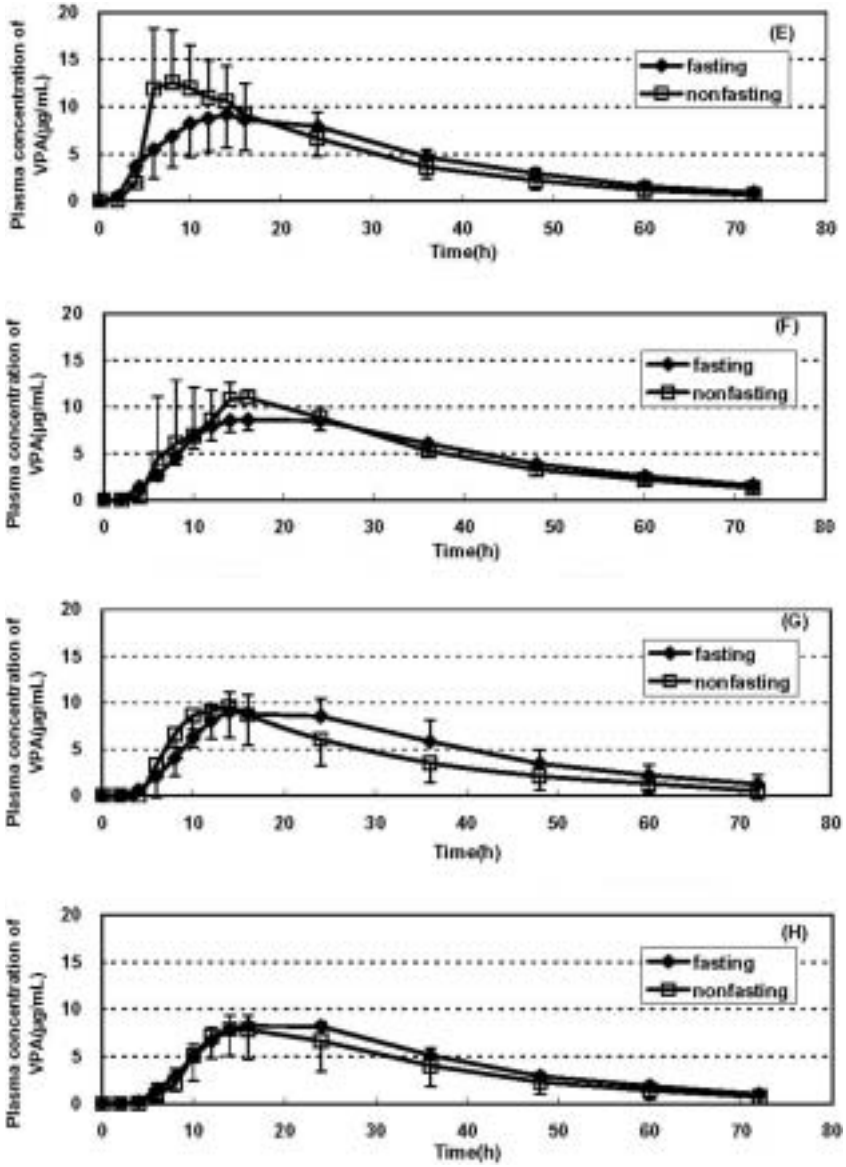

FIGURE 7 **Comparison of Plasma Concentration of VPA Between Fasting and Nonfasting Conditions. Each Point Represents the Mean ± S.D. Key: Closed Symbols and Open Symbols Represent Fasting Conditions and Nonfasting Conditions, Respectively.**

TABLE 4 **Pharmacokinetic Parameters of VPA-Na After Single Oral Administration of E, F, G, and H Tablets**

	E (n = 19)		F (n = 5)		G (n = 6)		H (n = 6)	
Parameter	Fasting	Nonfasting	Fasting	Nonfasting	Fasting	Nonfasting	Fasting	Nonfasting
	324.26	320.42	350.88	353.81	336.09	266.42	296.29	249.91
AUC_{0-72}	99.45	89.83	55.48	52.24	92.64	107.49	23.93	117.76
	348.32	336.70	394.67	388.34	371.24	287.56	320.52	270.72
AUC_{0-8}	114.40	107.40	76.30	65.21	118.96	123.07	31.24	128.19
	9.54	14.18	9.19	12.46	9.48	10.93	8.82	8.13
Cmax	2.19	3.22	0.98	3.24	2.15	3.46	0.52	2.78
	12.93	12.06	18.36	17.57	16.19	15.75	15.72	15.63
t1/2	3.45	3.59	2.41	2.57	3.34	2.91	1.78	1.82

Upper row: mean; Lower row: S.D.
AUC_{0-72} (μg h/mL): Zero to 72 h area under the plasma concentration-time curve.
AUC_{0-8} (μg h/mL): Zero to infinite area under the plasma concentration-time curve.
Cmax (μg /mL): The maximum plasma concentration.
*t*1/2 (h): Half-life period.

under fasting conditions for each tablet showed 1.0 for the slope of the line in each case. In addition, the line for each tablet passed close to the origin, indicating that the in vitro release and the in vivo release were well correlated (Fig. 8). These results demonstrated that the present in vitro evaluation method adequately reflects the in vivo pharmacokinetic profile.

Evaluation of Mechanical Strength of the Membrane

The in vitro dissolution test conditions were investigated to predict the effects of food. The typical gastric residence time has been determined to be about 2 to 6 h (Davis et al., 1987), and this time increases to 8 h after consumption of a high-fat meal. Dissolution medium with pH 1.2 was selected to reproduce in the stomach. In order to reproduce the postprandial gastric environment, solid matter (plastic beads) was added to the vessel and the mixture was stirred with a paddle, placing the tablet constantly under stress conditions. After the test, the tablets were removed and inspected. The effect of a high-fat meal was established based on whether the original shape of the tablet was maintained or not.

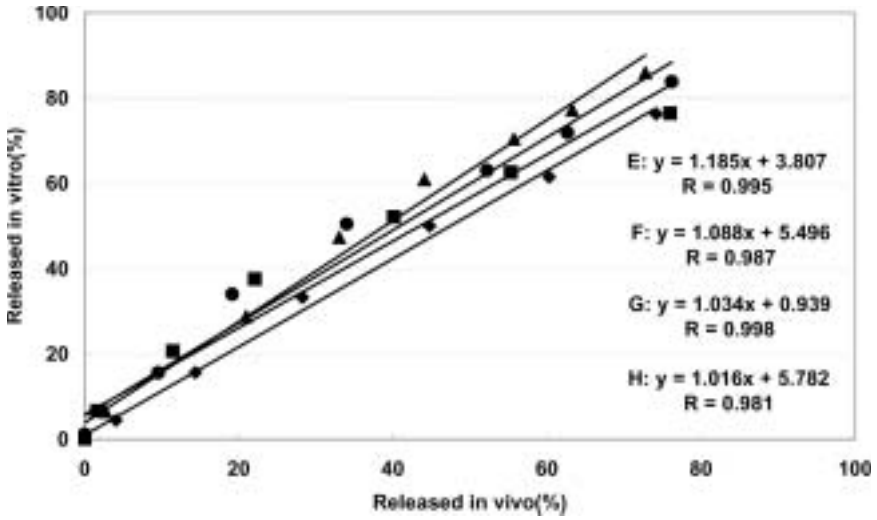

FIGURE 8 **Relationship Between In Vivo Absorption and In Vitro Dissolution of VPA from Different Formulations (E–H). In Vitro Data Use Paddle Method with Rotation at 50 rpm in 900 mL (pH 6.8). Key: Triangles Represent Tablet E, Circles Represent Tablet F, Squares Represent Tablet G, and Diamonds Represent Tablet H.**

TABLE 5 **The Result of the Paddle and Beads Dissolution Method, 25 rpm, pH1.2**

Sample	Rate of the burst tablet (X/6)
E	6/6
F	5/6
G	6/6
H	0/6

Table 5 presents the results obtained for tablets E, F, G, and H individually, and Fig. 9 presents the dissolution profiles with the paddle and beads method. Because a high percent of the E, F, and G tablets burst, these tablets were determined to be weak under mechanical stress, as might be expected. H tablets did not tend to burst. Figure 9 demonstrates that the strength of the membrane is almost completely dependent on the amount of coating. No membrane destruction was observed when tested at pH 6.8 under the same conditions (data not shown), whereas the membrane was destroyed using the paddle method (at 50 rpm and pH 1.2) shown in Fig. 9.

The percent absorption from tablets E, F, G, and H under nonfasting conditions was evaluated using the Wagner-Nelson method. Figure 10 shows the percent dissolution at pH 1.2 using the paddle and beads method against the percent absorption under nonfasting conditions for each tablet. The in vivo lag time was 2 h longer than in vitro. As shown in Fig. 10, a 1:1 linear relationship was obtained with each tablet between percent absorbed and percent dissolved, except for F tablets (correlation coefficient r = 0.9553–0.9981). From this correlation, we conclude that a tablet that was not affected in the paddle and beads dissolution test would have a low potential for efficacy in humans, and that it would be possible to predict the percent absorption from such a tablet in nonfasting conditions (especially having a high-fat meal) release occurring in humans. Since the in vivo–in vitro correlation was not always obtained for the tablets, further improvement of this evaluation is required.

Numerous studies have been published on the correlation between in vivo and in vitro systems, and in vitro evaluation systems that reflect the effects of mechanical strength of food consumption on tablets have also been investigated. Katori and colleagues (1995, 1996) suggested that the paddle method and the flow-through cell method reflect in vivo systems for single units as does the rotating dialysis method for multiple units. Using their self-developed dissolution testing system, Aoki et al. (1992, 1993) investigated the conditions required for a dissolution test for matrix-type sustained-release tablets, in which beads were added to the vessel, describing a method that reflected the mechanical strength of the in vivo gastrointestinal tract in fasting dogs. Additionally, Qiu and colleagues (2003a, 2003b) investigated an in vitro dissolution test (paddle method) that reflected the in vivo environment in matrix-type sustained-release tablets containing divalproex sodium, the sodium salt of a dual coordination compound of VPA-Na. These reports addressed the fasting in vivo/in vitro correlation

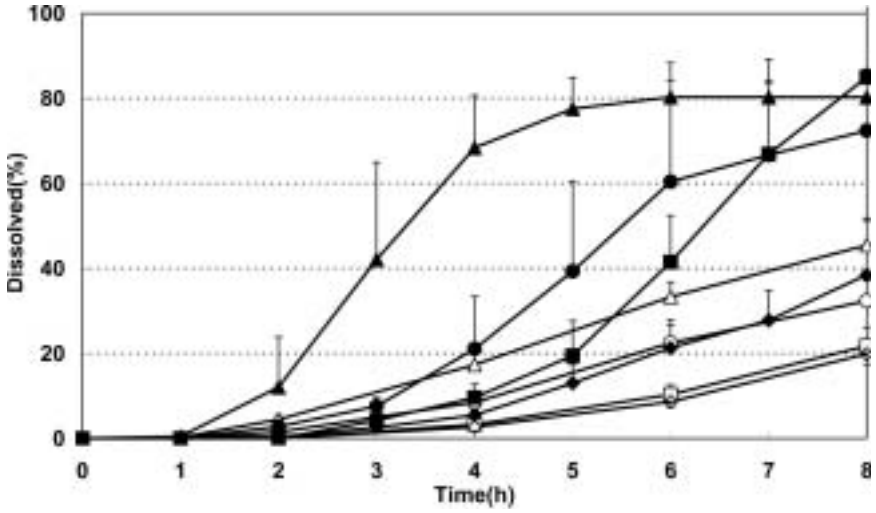

FIGURE 9 **Dissolution Profiles of Test Tablets (E–H). Key: Open Symbols Represent in 900 mL (pH 1.2), Paddle Method with Rotation at 50 rpm (Mean ± S.D., n = 6). Closed Symbols Represent the Paddle and Beads Method with Paddle Rotational Speed at 25 rpm in 250 mL (pH 1.2). Triangles Represent Tablet E, Circles Represent Tablet F, Squares Represent Tablet G, and Diamonds Represent Tablet H.**

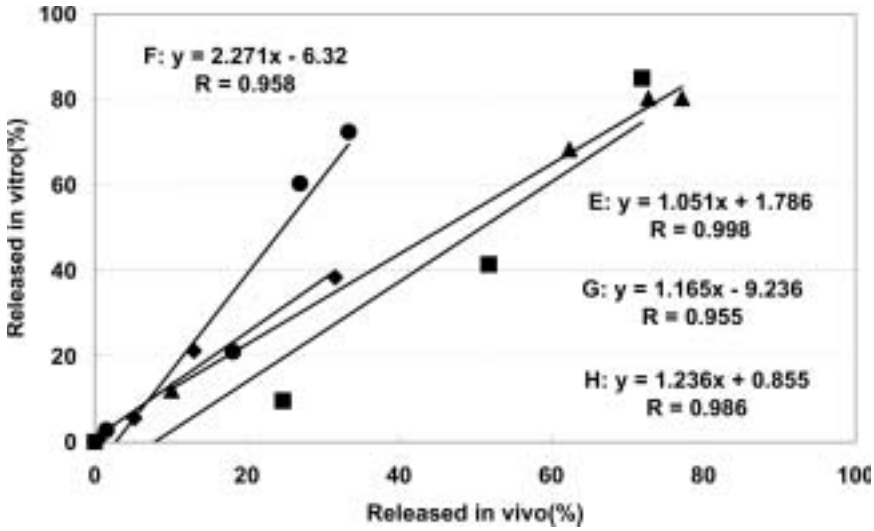

FIGURE 10 **Relationship Between In Vivo Absorption and In Vitro Dissolution of VPA from Different Formulations (E–H). In Vitro Data Use Paddle and Beads Method with Rotation at 25 rpm in 250 mL (pH 1.2). Key: Triangles Represent Tablet E, Circles Represent Tablet F, Squares Represent Tablet G, and Diamonds Represent Tablet H.**

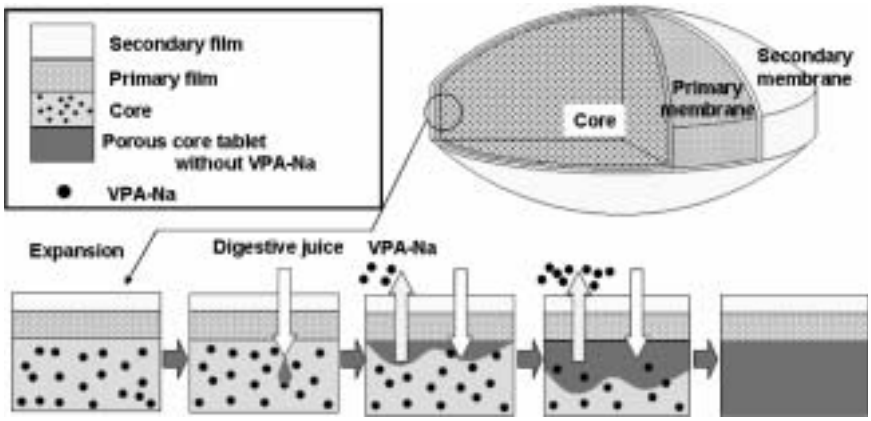

FIGURE 11 **Mechanism of Sustained-release of VPA-Na from the Tablet.**

in detail, but little data exists for nonfasting conditions (in particular, after a high-fat meal). In vitro evaluation systems in our study, especially for tablets that are readily affected by foods, reflect the in vivo dynamics in humans after a high-fat meal. Since we were able to obtain a good correlation between the percent dissolution with the paddle and beads method and the percent absorption ascertained from a human pharmacokinetic study, it was possible to predict the effects of food on a pharmaceutical product in the in vivo environment.

The Mechanism of Sustained-Release Tablets

After the dissolution test (duration 24 h), the tablets maintained the original shape. Moreover, the tablets administered to humans were eliminated in the feces in the original shape. The mechanism of VPA-Na release from the tablets in this study is illustrated in Fig. 11 and is described as follows. First, digestive juices penetrated the secondary and primary membrane to reach the core tablet, then VPA-Na dissolved in the digestive juices, after which VPA-Na was released through the primary and secondary membrane. After the drug was released from the tablet, the empty tablet was eliminated in the feces. We speculated that the drug was released by the above-mentioned mechanism.

CONCLUSION

We have developed a small, sustained-release tablet containing 200 mg VPA-Na that allows an effective

blood concentration to be maintained using once-a-day dosing. A membrane-controlled system was selected for the sustained-release mechanism because it allows the tablet size to be minimized. In order to avoid the effects of food, a number of release-control membranes in which VPA-Na would be unlikely to dissolve were explored. This led to the discovery of a mixed membrane composed of ethylcellulose and methacrylate copolymer-L. It was not possible to obtain the target k_d value with this membrane alone. Therefore, double-membrane tablets were developed, in which a different membrane (ethylcellulose as its main ingredient) was applied externally to the mixed membrane.

Human pharmacokinetic study was then conducted for tablets with different coating amounts (named tablets E, F, G, and H) showing that in most subjects receiving tablet E under nonfasting conditions (i.e., a high-fat meal), and in some subjects receiving tablets F and G, the C_{max} increased to 1.6–2.4 times higher than the corresponding value under fasting conditions. For these tablets, the consumption of a high-fat meal may have led to a situation in which the control of drug release could not be maintained. In contrast, for tablet H, the food-induced increase in C_{max} was inhibited and the drug release-control mechanism was maintained.

We also investigated the in vitro dissolution test conditions to allow the effects of food to be predicted. This involved investigation of an in vitro evaluation system for predicting in vivo pharmacokinetics under nonfasting conditions (in particular, a high-fat meal), as well as under fasting conditions. With this evaluation system, the strength of the membrane could be predicted, the percent absorption in humans could also be predicted after consumption of a high-fat meal from the percent dissolution, and furthermore, the effects of food on the in vivo kinetics of the tablets could be predicted to some extent.

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