Studies on Dissolution Tests for Soft Gelatin Capsules by the Rotating Dialysis Cell (RDC) Method. VI.[1] Preparation and Evaluation of Ibuprofen Soft Gelatin Capsule

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We prepared soft gelatin capsules (SC) containing ibuprofen (IB), a widely used phenylpropionic acid-derived antiphlogistic-analgesic drug. To evaluate the SC, *in vitro* dissolution tests were performed both by the paddle (PD) method described in the Japanese Pharmacopoeia (JP XII) and by the rotating dialysis cell (RDC) method which we previously developed and evaluated for application. *In vivo*, the blood IB concentration was determined after administration to beagles. Higher bioavailability was observed after administration of the SC containing IB than after administration of the bulk IB powder. A higher correlation was observed between the *in vitro* dissolution behavior and *in vivo* results by the RDC method than by the PD method, suggesting the usefulness of the RDC method in the dissolution test of SC.

Key words dissolution test; HPLC; ibuprofen; beagle dog; soft gelatin capsule

Soft gelatin capsules (SC) have conventionally been used to make solid preparations of oily liquids such as cod liver oil and vitamin E. Recently, SC containing water-soluble or slightly soluble drugs (powders) have become increasingly available on the market. SC are expected to improve the bioavailability of drugs. For example, SC containing digoxin show higher bioavailability than digoxin tablets.[2] There are SC for the sustained release of nifedipine, a slightly soluble drug.[3] The variety of available SC have been increasing.

SC can be classified according to their base into 4—5 types including an oily type, an aqueous type, and their emulsion types. Appropriate SC are selected according to the characteristics of the drug. As drugs, we used ibuprofen (IB), a phenylpropionic acid-derived antiphlogistic-analgesic drug widely used in the ethical and OTC market, and prepared their SC. To prepare a rapid-acting preparation complementary to the efficacy of IB, an oily emulsion type oily semisolid matrix (OSM), which is frequently used to obtain such preparations, was used as the base. *In vitro* dissolution tests were performed by the rotating dialysis cell (RDC) method, which we have developed and evaluated for application, and by the paddle (PD) method described in Japanese Pharmacopoeia (JP XII). The IB blood concentration *in vivo* was determined after administration to beagles. In addition, the correlation between *in vitro* and *in vivo* results were evaluated.

Experimental

Materials and Reagents After high-speed dispersion of IB, oval type SC (IBcp) were prepared as samples by the rotary die method.[4] Table 1 shows the contents of the sample.

Reagents of special grade or those for high performance liquid chromatography (HPLC) were used.

Dissolution Test In the RDC method,[5] the test solution and samples were placed in a cell covered with a filter, and the amount of drug that was transferred from the rotating cell to the test solution was measured. The RDC apparatus (Pharmatest Co., Ltd.) was applied to a dissolution test apparatus (NTR-VS3, Toyama Sangyo Co., Ltd.) that conformed to the standards of JP XII. As a dissolution test according to the JP XII, the PD method was also used. The dissolution rate at each time point was determined for IB by HPLC.

1. Conditions of the RDC Method: 1.1. Test solution: The same solution was used in the internal phase and external phase. The test solutions were the 1st (buffer solution, pH 1.2) and 2nd solution (buffer solution, pH 6.8) in the JP XII disintegration test, acetic acid buffered solution (pH 4.0) and water. The internal phase (2.5, 5.0 and 10.0 ml) and the external phase, de-aerated, (1000 ml) were prepared, and their temperature was adjusted to 37 ± 0.5 °C.

1.2. Cell: As filters for the cell, a hydrophilic filter (HVLP, Millipore Co., Ltd.) and a hydrophobic filter (HVHP, Millipore Co., Ltd.) were used. We have used these filters from the start of our study.[5] The cell rotation rates were 50, 100 and 150 rpm.

1.3. Measurement of the Dissolution Rate: A capsule of IBcp was placed in the cell containing the test solution, the amount of IB dissolved (5 ml) was obtained after 15, 30, 60, 90, 120, 180 and 240 min, and the dissolution rate was determined by HPLC.

2. Conditions of the PD Method: Conditions were determined according to the second method (PD method) of the JP XII dissolution test methods. In addition to the 1st (pH 1.2) and 2nd (pH 6.8) solutions in the JP XII disintegration test, acetic acid buffered solution (pH 4.0) and water were used as test solutions. The paddle rotation rate was 50 rpm. IB-dissolved solution (5ml) was obtained after 15, 30, 60, 90, 120, 180 and 240 min. The amount of IB was determined by HPLC, and the dissolution rate was calculated.

Bioavailability 1. Administration to Beagles: A capsule of IBcp was orally administered, together with water, to six healthy male beagles between 26 and 27 months old (body weight, 8—12 kg). The beagles were fasted from 12 h before administration to the termination of blood collection 36 h after administration. (Water was given *ad libitum*.)

Table 1. Contents of Sample for Testing

Ingredients and quantities	(mg)
Contains	
Ibuprofen	75.0
Oily semi-solid matrix	190.0
Fill weight	265.0
Capsule film	
Gelatin	153.8
Concentrated glycerin	43.8
Ethyl *p*-hydroxybenzoate	0.6
Propyl *p*-hydroxybenzoate	0.5
Titanium oxide	1.3
Total weight	465.0

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2. Blood Sampling Method and Preparation of Blood Specimens: Blood (10 ml) was taken using a syringe and a needle *via* the forefoot vein, immediately before as well as 0.5, 1, 1.5, 2, 3, 5, 8, 12, 24 and 36 h after drug administration. Blood samples were immediately placed in a heparinized Spitz glass and centrifuged at 3000 rpm for 10 min. Plasma was obtained and stored at −20 °C until the experiment.

3. Assay of IB in Plasma: To plasma (0.5 ml) was added the internal standard solution (1 ml), the mixture was agitated, and 1 ml was applied to C_{18} Sep-Pak cartridges (Waters Co., Ltd.), washed with 10 ml of 10 mM phosphate buffer (pH 2.6), eluted with 4 ml of ethanol, and used as a sample solution.

Measurement was done in 100 μl of the sample solution by HPLC according to the JP XII General Test Methods. The ratio of the peak area of IB to that of the internal standard was calculated, and the IB concentration in each sample was determined using a calibration curve. The following conditions were used for the measurement. Internal standard solution: Clofibrate (0.25 g) was accurately measured and mixed with acetonitrile to obtain 100 ml. This solution (1 ml) was mixed with a mixture of acetonitrile–10 mM phosphate buffered solution (pH 2.6) (3 : 7) to obtain 100 ml. Detector: Ultraviolet absorptiometer. Detection: UV240 nm. Column: 4.6 × 150 mm Inertsil ODS-2. Column temperature: a constant temperature about 40 °C. Mobile phase: mixture of acetonitrile–10 mM phosphate buffered solution (pH 2.6) (1 : 1). Flow rate: adjusted so that the IB retention time was about 7 min.

Results and Discussion

Selection of OSM As described above, SC have conventionally been used only for oily drugs such as fat-soluble vitamins. However, recently SC have been increasingly used for antihistamine drugs and drugs acting on the central nervous system. Immediate action is often expected in these SC. We previously developed an antiallergic SC and administered it 5 d to 66 patients with allergic rhinitis. This SC was effective in 74.2% of the patients with perennial allergic rhinitis and 95.5% of those with seasonal allergic rhinitis, and the effects appeared early after administration.[6] The base in this SC was OSM, which was also used in this study. In this study, IB, a widely used antiphlogistic-analgesic drug, was dispersed over OSM, and SC containing IB were prepared to improve the bioavailability of the IB powder. OSM is frequently used in commercially available SC at present. Therefore, it may be important to evaluate the dissolution behavior and bioavailability of SC of this type.

Dissolution Behavior of IBcp To clarify the dissolution behavior of the SC using OSM, we previously carried out a dissolution test described in the JP XII. OSM, which is oily, did not uniformly disperse in an aqueous test solution: and its dissolution varied and was poor. Using beads, good dissolution was observed, but with low reproducibility.[7] Subsequently, we solved these problems by the RDC method,[5] and have performed studies on the dissolution behavior of SC by this method. In this study, the dissolution behavior of IBcp was evaluated primarily by this method.

In the RDC method, many experimental conditions can be set using the internal phase volume, cell rotation speed, test solution pH, and the filter as variables. Based on our experience, four test solutions were selected, three conditions were used for the internal phase volume and cell rotation speed and two for the filter. A total of 72 combinations of conditions were set. As a result, a wide dissolution rate was obtained; the dissolution rate of IB 4 h after the initiation of the test varied from about 4% (conditions: hydrophilic filter (HVLP), 10.0 ml, 50 rpm, pH 1.2) to about 100% (hydrophobic filter (HVHP), 10.0 ml, 50 rpm, pH 6.8). The effects of each variable on the dissolution rate are as follows (figures show representative results);

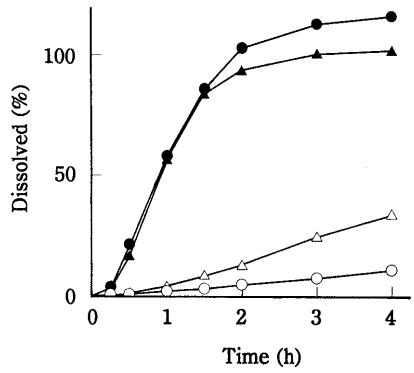

Fig. 1. Effect of Filter on Dissolution of Ibuprofen

Internal phase volume, 10.0 ml; cell rotation speed, 150 rpm. Test solution were ○, HVLP, pH 4.0; ●, HVLP, pH 6.8; △, HVHP, pH 4.0; ▲, HVHP, pH 6.8.

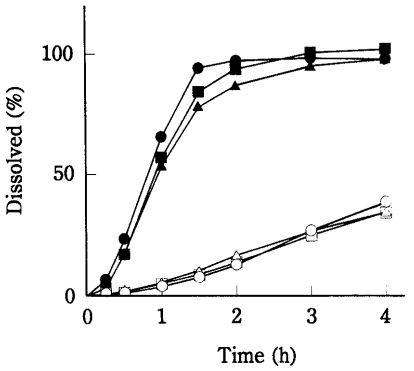

Fig. 2. Effect of Internal Phase Volume on Dissolution of Ibuprofen

Filter, HVHP; cell rotation speed; 150 rpm. Internal phase volume and test solution were ○, 2.5 ml, pH 4.0; ●, 2.5 ml, pH 6.8; △, 5.0 ml, pH 4.0; ▲, 5.0 ml, pH 6.8; □, 10.0 ml, pH 4.0; ■, 10.0 ml, pH 6.8.

1. RDC Method: 1.1. Effects of the Filter on Dissolution Behavior (Fig. 1): We have used a HVLP and HVHP that can also be used for aqueous solution and organic solvents. A slightly higher dissolution rate was observed using the HVHP. This may be due to the following difference between the two filters. HVLP absorbs water, narrowing the pore. On the other hand, HVHP does not absorb water, and therefore IB readily passes through it. This tendency was slight using the test solution with pH 6.8, but was marked using the other test solutions.

1.2. Effects of the Internal Phase Volume on Dissolution Behavior (Fig. 2): From our experience, the dissolution rate is higher with a lower internal phase volume. This may be because the concentration gradient of the drug (solute) from the inside to the outside of the cell increases, resulting in an increase in the dissolution rate. The maximum inside volume of the cell is about 20 ml as an aqueous solution. However, a volume of 10 ml or more often causes no increase in the dissolution rate. Therefore, the dissolution behavior of a preparation can be evaluated using an internal phase volume of 10 ml or less, especially 2.5, 5 and 10.0 ml. In this study, those 3

volumes were used. The internal phase volume did not affect the dissolution behavior. The dissolution rate was high at pH 6.8.

1.3. Effects of Cell Rotation Speed on Dissolution Behavior (Fig. 3): The dissolution rate often increases with a higher cell rotation speed. This may be because the degree of destruction of the preparation increases, promoting drug dissolution. From our experience, the dissolution behavior can be adequately clarified using 3 rotation speeds (50, 100 and 150 rpm). In this study, those 3 rotation speeds were used. The rotation speed did not affect the dissolution rate of IB. The dissolution rate was high at pH 6.8.

1.4. Effects of the Test Solution on Dissolution Behavior (Fig. 4): The selection of the test solution in the cell is especially important because it affects the destruction of the preparation and drug dissolution. The preparation should be destroyed first and transferred out of the cell.

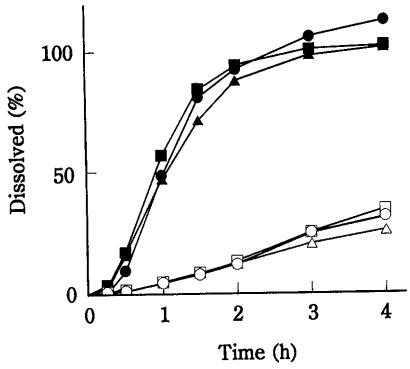

Fig. 3. Effect of Cell Rotation Speed on Dissolution of Ibuprofen

Filter, HVHP; internal phase volume, 10.0 ml.
Cell rotation speed and test solution were ○, 50 rpm, pH 4.0; ●, 50 rpm, pH 6.8; △, 100 rpm, pH 4.0; ▲, 100 rpm, pH 6.8; □, 150 rpm, pH 4.0; ■, 150 rpm, pH 6.8.

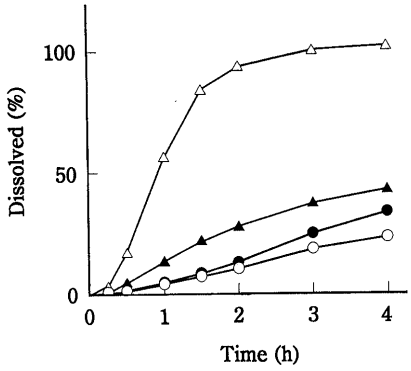

Fig. 4. Effect of Test Solution pH on Dissolution of Ibuprofen

Filter, HVHP; internal phase volume, 10.0 ml; cell rotation speed, 150 rpm. Test solution was ○, pH 1.2; ●, pH 4.0; △, pH 6.8; ▲, H_2O.

Many drugs are affected by pH, causing marked changes in dissolution behavior. In this study, water and solutions with pH 1.2, 4.0 and 6.8 were used. The dissolution rate was less than 50% with water and at pH 1.2 and 4.0 but nearly 100% at pH 6.8. These differences were only negligibly affected by the filter, the internal phase volume, and the cell rotation speed. As water, distilled water was used. Since its pH was between 4.0 and 6.8, the dissolution rate was expected to be higher than that at pH 4.0. However, the dissolution behavior at distilled water was similar to that at pH 4.0. This may be due to the acid base in IB (Fig. 5).

2. PD Method: Dissolution behavior dependent on pH was observed in the PD method as well as the RDC method. The dissolution rate was high at pH 6.8 and low at the other pHs. The difference from the RDC method was the variation in data. This is because of the sampling of clusters of contents that were unevenly dispersed after capsule disintegration and were floating in the upper area of the flask. The IB concentration may differ according to whether these clusters were sampled or not.

Bioavailability Table 2 and Fig. 6 show the results after administration of the IB powder and IBcp to beagles. Bioavailability was higher after IBcp administration than after IB powder administration. This shows that the effects appear earlier and last longer following IBcp administration than after IB powder administration. These factors are important for drugs with antiphlogistic, analgesic and antipyretic actions.

Correlation between *in Vitro* and *in Vivo* Results The *in vivo* data on IBcp were analyzed by the Loo–Riegelman method[8] using a two-compartment open model[9] involving the primary absorption process. The correlation between the *in vitro* release rate of IB and the *in vivo*

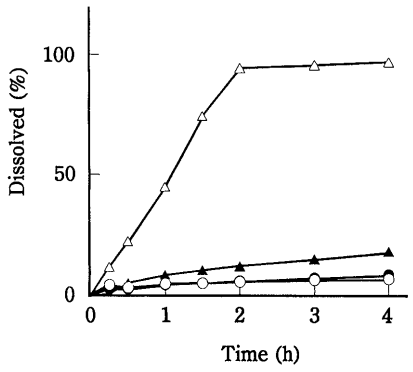

Fig. 5. Effect of Test Solution pH on Dissolution of Ibuprofen Using JP XII Paddle Method

Rotation speed, 50 rpm; test solution volume, 1000 ml.
Test solution was ○, pH 1.2; ●, pH 4.0; △, pH 6.8; ▲, H_2O.

Table 2. Pharmacokinetic Parameters of Ibuprofen after Oral Administration in Dogs ($n=6$, Mean ± S.E.)

	C_{max}[a] (μg/ml)	T_{max}[b] (h)	$T_{1/2}$[c] (h)	$AUC(0—36)$[d] (μg/ml·h)	MRT[e] (h)	VRT[f] (h^2)
Ibuprofen powder	34.23±2.19	1.58±0.15	2.07±0.38	174.21±12.05	5.11±0.54	18.47±4.58
Ibuprofen soft capsule	51.41±3.01	1.17±0.11	1.73±0.26	206.56±17.31	4.58±0.33	21.17±1.55

a) Maximum plasma concentration. *b*) Time of maximum plasma concentration. *c*) Biological half life. *d*) Area under the plasma concentration–time curve (0—36 h). *e*) Mean residence time. *f*) Variance of residence time.

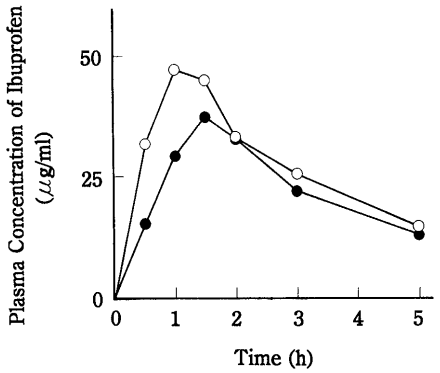

Fig. 6. Plasma Concentration of Ibuprofen after Oral Administration to Dogs

○, IBcp; ●, ibuprofen powder alone.

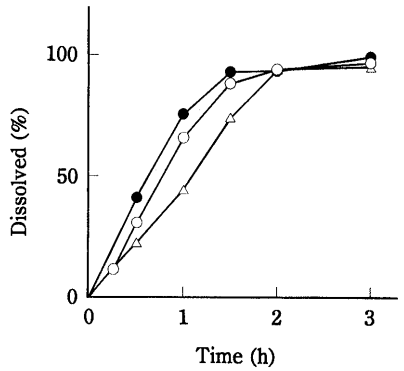

Fig. 7. *In Vitro* Release and *in Vivo* Absorption Profiles of Ibuprofen Soft Capsule

○, filter was HVLP, internal phase volume was 2.5 ml, cell rotation speed was 50 rpm, test solution was 1000 ml; ●, *in vivo*; △, JP XII paddle method (50 rpm, pH 6.8, 1000 ml).

absorption rate was evaluated (Fig. 7). The release rate observed by the RDC method showed a curve similar to the *in vivo* curve, while that observed by the PD method was linear.

Conclusion

In the IBcp prepared in this study, pK_a (4.25) affected the test results. Since IB was well dissolved in the test solution at pH 6.8, good dissolution behavior was also observed by the PD method. In our previous dissolution tests of SC using OSM, the RDC method was definitely superior to the PD method when the drug was slightly soluble or insoluble in water. For drugs relatively soluble in the test solution, such as IB in this study, the RDC method also appears to be superior to the PD method in terms of reproducibility and correlation with *in vivo* results. As was observed with IBcp in this study, the SC drug form can change the bioavailability in comparison to the drug alone. In the future, SC that aim to improve bioavailability, whether quick acting or sustained release SC, will undoubtedly increase in the market. For their development and quality control, dissolution tests of SC preparations may become more important. In the future, the RDC method will be more useful as a dissolution test method since it better reflects *in vivo* behavior.

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