# Studies on Dissolution Tests for Soft Gelatin Capsules. IV.[1] Dissolution Test of Nifedipine Soft Gelatin Capsule Containing Water Soluble Vehicles by the Rotating Dialysis Cell Method

Masato TAKAHASHI,* Mayumi MOCHIZUKI, Tomoka ITOH, and Mihoko OHTA

*Research & Development Division, Toyo Capsule Co., Ltd., 560, Nakazato Higashi-cho, Fujinomiya-shi, Shizuoka 418, Japan.* Received June 4, 1993; accepted September 10, 1993

**The dissolution of oval soft gelatin capsules containing 5 mg of nifedipine dissolved in a water soluble vehicle was evaluated by the rotating dialysis cell (RDC) method and the paddle (PD) method as described in the Japanese Pharmacopoeia (JP) XI. The dissolution pattern of nifedipine obtained by the PD method was linear, and almost 100% of the content was dissolved within 7 to 10 min. The dissolution pattern obtained by the RDC method corresponded to the absorption pattern *vs.* time curve obtained by the oral administration test in humans. When the RDC method was performed with the cell containing a buffered solution coupled with *n*-octanol as the dissolution medium, the *in vitro* dissolution pattern best simulated the *in vivo* absorption pattern.**

**Keywords** nifedipine; soft-gelatin capsule; dissolution test; rotating dialysis cell method; water-soluble base; *n*-octanol

The soft gelatin capsule is a suitable dosage vehicle for oily substances such as cod liver oil and vitamin E. Recently, however, soft gelatin capsules containing drugs suspended or dissolved in various base types, such as aqueous and oily matrixes, emulsions, and suspensions, have also been developed, and non-oily drugs have become available in soft gelatin capsule form. Among these, bioavailability from digoxin soft gelatin capsules differed markedly from that from digoxin tablets.[2] We have classified soft capsule preparations according to the base used, and are studying their dissolution behaviors as well as the methods used to test their dissolution rates. We previously carried out a dissolution test of soft gelatin capsules containing an oily, semi-solid matrix using the paddle (PD) method, described in the Japanese Pharmacopoeia (JP) XI, [3] but the dissolution pattern by this method was unsatisfactory. We then used the bead method of Machida *et al.*,[4] but again obtained poor results.[5] However, a good dissolution pattern corresponding to *in vivo* observations was obtained by the rotating dialysis cell (RDC) method. A drug for rhinitis, widely available in the over the counter drug (OTC) market of Japan, is a soft gelatin capsule preparation containing the above oily semi-solid matrix. We also devised a slow-release soft capsule preparation containing an oily semi-solid matrix base and a water soluble base. In the pharmaceutical evaluation of these preparations, a dissolution pattern with closer correspondence to *in vivo* dissolution was obtained by the RDC method than by the PD method.[1]

Dissolution tests of soft gelatin capsules of nifedipine in water soluble bases are reported here. Nifedipine is a widely used calcium antagonist, and the rate of its absorption is regulated by its solubility in water (about 10 $\mu$g/ml. $H_2O$).[6] The dissolution pattern of nifedipine dissolved in an aqueous organic solvent and encapsulated in soft gelatin has been studied by the PD method and RDC method, and the relation of this dissolution pattern to changes in the blood concentration of the drug was evaluated in healthy individuals.

## Experimental

**Materials and Reagents** Nifedipine was dissolved in a water soluble vehicle, and oval soft gelatin capsules (Ndcp) were produced by the rotary die process. The formulation of vehicle mixture and capsule shell is shown in Table I. Reagents of special grade or those for high performance liquid chromatography (HPLC) were used.

**Apparatus and Dissolution Tests** Dissolution tests by the PD method were performed using 1000 ml each of the buffers at pH 1.2, 4.0, and 6.8 at 37±0.5 °C and a paddle rotation speed of 100 rpm, as described by JP XI.

The RDC method was carried out by replacing the paddle shaft used in the PD method with an RDC[5] (Pharm Test, Hainburg, Germany) under the conditions shown in Table II.

De-aerated buffers (pH 1.2, 4.0, 6.8) and *n*-octanol were placed inside and outside the cell (internal phase, external phase) at 37±0.5 °C. The cell was rotated at 50 rpm. Hydrophobic and hydrophilic filters (HVHP and HVLP, Japan Millipore Ltd., Tokyo, Japan) were used.

**Determination of Dissolved Nifedipine** One Ndcp was placed in a cell filled with the buffered solution, or with mixtures of the buffered solution and *n*-octanol.

At appropriate time intervals, samples (5 ml) were withdrawn from the cells or vessel, and the amount of nifedipine dissolved was determined by HPLC. The dissolution test was continued for 240 min. The HPLC conditions were as follows: pump, JASCO TRI ROTAR-V; data processor, Shimadzu C-R3A; column, 4.6 i.d. × 250 mm packed with Nucleosil $5C_{18}$; mobile phase, a mixture of methanol–water (7:3); flow rate,

TABLE I. Contents of Sample for Testing

| Ingredients and quantities | |
|---|---|
| Contains: | |
| Nifedipine | 5.0 mg |
| Polyethylene glycol | 150.0 mg |
| Propylene glycol | 19.0 mg |
| Purified water | 25.0 mg |
| Mentha oil | 0.5 mg |
| Dipotassium glycyrrhizinate | 0.5 mg |
| Fill weight | 200.0 mg |
| Capsule film: | |
| Gelatin | 105.1 mg |
| Concentrated glycerin | 28.4 mg |
| D-Sorbitol (70%) | 5.2 mg |
| Ethyl *p*-hydroxybenzoate | 0.2 mg |
| Propyl *p*-hydroxybenzoate | 0.3 mg |
| Titanium oxide | 0.8 mg |
| Coloring agent | q.s. |
| Total weight | 340.0 mg |

Table II. Testing Conditions for RDC Method

| Condition No. | Internal phase: Buffer solution | Internal phase: Buffer volume (ml) | External phase | Rotation speed (rpm) | Filter type |
|---|---|---|---|---|---|
| 1 | pH 1.2 | 2.5 | pH 1.2 | 50 | HVLP |
| 2 | pH 1.2 | 5.0 | pH 1.2 | 50 | HVLP |
| 3 | pH 1.2 | 10.0 | pH 1.2 | 50 | HVLP |
| 4 | pH 1.2 | 2.5 | pH 1.2 | 50 | HVHP |
| 5 | pH 1.2 | 5.0 | pH 1.2 | 50 | HVHP |
| 6 | pH 1.2 | 10.0 | pH 1.2 | 50 | HVHP |
| 7 | pH 1.2 | 2.5 | *n*-Octanol | 50 | HVHP |
| 8 | pH 1.2 | 5.0 | *n*-Octanol | 50 | HVHP |
| 9 | pH 1.2 | 5.0 | *n*-Octanol | 50 | HVLP |
| 10 | pH 4.0 | 5.0 | *n*-Octanol | 50 | HVLP |
| 11 | pH 6.8 | 5.0 | *n*-Octanol | 50 | HVLP |
| 12 | pH 4.0 | 5.0 | *n*-Octanol | 50 | HVHP |
| 13 | pH 6.8 | 5.0 | *n*-Octanol | 50 | HVHP |
| 14 | pH 1.2/*n*-octanol | 5.0/5.0 | pH 1.2 | 50 | HVLP |
| 15 | pH 4.0/*n*-octanol | 5.0/5.0 | pH 4.0 | 50 | HVLP |
| 16 | pH 6.8/*n*-octanol | 5.0/5.0 | pH 6.8 | 50 | HVLP |
| 17 | pH 1.2/*n*-octanol | 5.0/5.0 | pH 1.2 | 50 | HVHP |
| 18 | pH 4.0/*n*-octanol | 5.0/5.0 | pH 4.0 | 50 | HVHP |
| 19 | pH 6.8/*n*-octanol | 5.0/5.0 | pH 6.8 | 50 | HVHP |
| 20 | pH 1.2 | 1.0 | *n*-Octanol | 50 | HVHP |
| 21 | pH 1.2 | 1.2 | *n*-Octanol | 50 | HVHP |
| 22 | pH 1.2 | 1.4 | *n*-Octanol | 50 | HVHP |
| 23 | pH 1.2 | 1.6 | *n*-Octanol | 50 | HVHP |

1 ml/min; detection, UV 240 nm.

**Bioavailability** Blood concentrations of nifedipine were determined by HPLC[7] in 6 healthy subjects who had orally or sublingually received one Ndcp using the methods described by Ooka *et al.*[8]

## Results and Discussion

**PD Method** With the PD method, approximately 100% of the nifedipine contained in Ndcp was dissolved within 7—10 min, irrespective of the pH of the external phase (Fig. 1). The dissolution occurred after the disintegration of the capsule shell. Therefore, nifedipine is considered to have dispersed and diffused into the external phase with the water soluble vehicle, which freely mixes with aqueous solutions, immediately after the rupture of the shell.

**RDC Method 1) Tests Using *n*-Octanol as the External Phase** With the RDC method, soft capsules containing an oily semi-solid matrix showed satisfactory dissolution when the external phase was the buffer at pH 1.2, and 2.5—10 ml of the same buffer was used as the internal phase. However, as shown in Fig. 2, all soft capsules containing water soluble vehicles showed poor dissolution under these conditions (Table II, Nos. 1—6), probably because of the low solubility of nifedipine in the buffer used as the external phase. Fine crystals of nifedipine remained in the cell after the experiment. In the RDC method simulating the transfer of drugs from the intestinal lumen (inside the cell) to tissues (outside the cell), the internal phase is preferably the buffer, whereas the external phase need not be. Therefore, we changed the external phase to *n*-octanol, which is frequently used to calculate the partition coeficients of drugs, and is considered to be suitable for the RDC method simulating *in vivo* pharmacokinetics. As a result, the dissolution pattern was

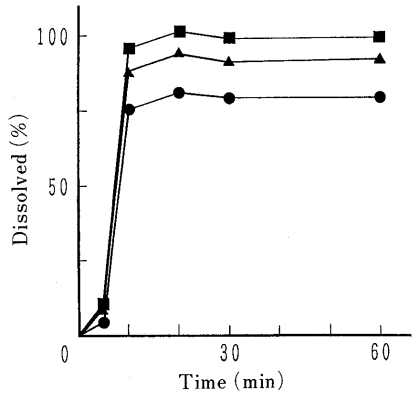


Fig. 1. Dissolution Profiles of Ndcp Using PD Method (JPXI, 100 rpm)
●, pH 1.2; ■, pH 4.0; ▲, pH 6.8.

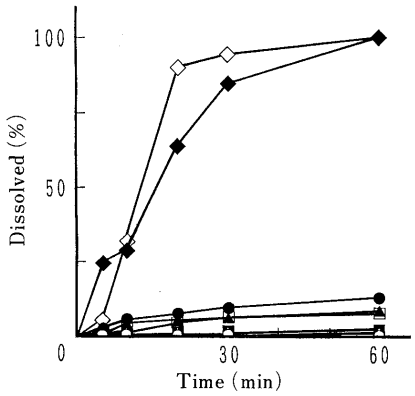


Fig. 2. Effect of External Phase Type (Buffer or *n*-Octanol) on Dissolution of Ndcp
●, condition 1; ■, condition 2; ▲, condition 3; ○, condition 4; □, condition 5; △, condition 6; ◆, condition 7; ◇, condition 8.

clearly improved by using *n*-octanol (Fig. 2).

**2) Effects of Filters** First, 0.5% (w/v) nifedipine solution in *n*-octanol was filtered to confirm its adsorption onto filters. Neither HVLP nor HVHP filters significantly absorbed nifedipine.

Secondly, the partition coefficient of water or buffered solutions with *n*-octanol for nifedipine, measured by shaking for 24 h, was 52.3. This indicated that nifedipine could be transferred from the cell to the external phase if the dissolution test was performed using *n*-octanol as the external phase.

Figure 3 shows the dissolution patterns observed when the two filters were used in various combinations with internal phases different in pH (Table II, Nos. 8—13). The dissolution pattern testing with the HVHP filter was better than that with the HVLP filter. That is, the dissolution rate with the latter was lower than that with the former. This depended on whether or not the filter was wetted with *n*-octanol. The penetration of nifedipine was suppressed because the HVLP filter was wetted with a buffered solution and not with *n*-octanol. However, when the HVHP filter was wetted with *n*-octanol, drug penetration increased.

**3) Tests Using *n*-Octanol as the Internal Phase** Dissolution tests were carried out using *n*-octanol as the internal phase and various buffers as the external phase (Table II,

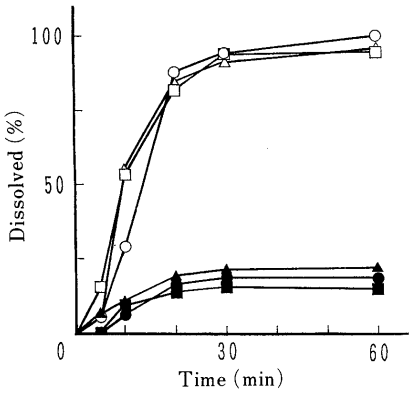


Fig. 3. Effect of Filter Type on Disslution of Ndcp

●, condition 9; ■, condition 10; ▲, condition 11; ○, condition 8; □, condition 12; △, condition 13.

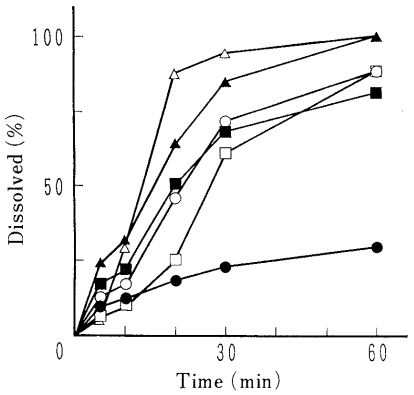


Fig. 5. Effect of Internal Phase Volume on Dissolution of Ndcp

●, condition 20; ○, condition 21; ■, condition 22; □, condition 23; ▲, condition 7; △, condition 8.

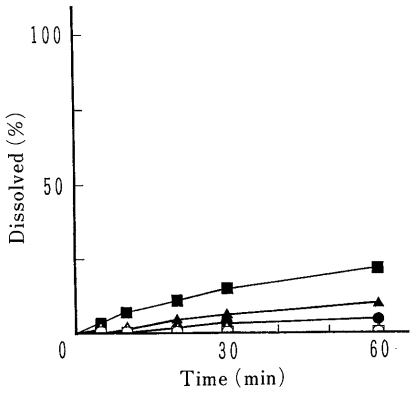


Fig. 4. Effect of *n*-Octanol of Internal Phase on Dissolution of Ndcp

●, condition 14; ■, condition 15; ▲, condition 16; ○, condition 17; □, condition 18; △, condition 19.

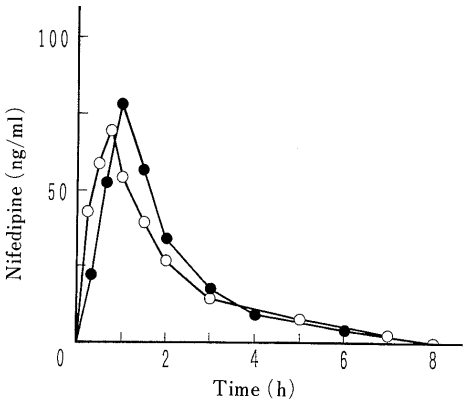


Fig. 6. Plasma Concentration of Ndcp in Men

●, oral administration; ○, sublingual administration.

Nos. 14—19). However, *n*-octanol was used as a 1 : 1 mixture with a buffer to facilitate the disintegration of the capsules. All capsules showed poor dissolution, regardless of the filter or the buffer (Fig. 4). This may be ascribed to the fact that the concentration gradient of nifedipine was limited to the cell. After disintegration of the capsule by the buffer in the cell, concentration gradients of nifedipine developed against both the *n*-octanol inside the cell and the buffer outside the cell. Actually, however, the transfer of nifedipine was comparable to that in the test using buffers as both the internal and external phases (Fig. 2). The pH had no effect on dissolution. To confirm this dissolution pattern, dissolution tests were performed either by placing a solution of nifedipine in *n*-octanol in the cell (the external phase was a buffer) or by placing nifedipine and a buffer in the cell (the external phase was *n*-octanol). Dissolution was low under the former condition but was high under the latter condition. From these findings, the dissolution of nifedipine in this method is considered to be dependent on the concentration gradient of the drug toward *n*-octanol and not by the pH of the buffer.

**4) Effects of the Volume of the Internal Phase** The effects of the volume of the internal phase were evaluated using *n*-octanol as the external phase, by which high dissolution rates were observed (Table II, Nos. 7, 8, 20–23). When the volume of the internal phase was 1.0 ml or less, disintegration of the capsule was insufficient, and dissolution was not satisfactory. This suggested that the volume of the internal phase should be greater than 1 ml (Fig. 5).

**5) Correlation between *in Vivo* Results** Nifedipine is mainly given orally. If immediate responses are necessary, the patient is instructed to crush the soft gelatin capsule with the teeth and hold the contents under the tongue. This method can be used only when soft gelatin capsules are given. In the present study, Ndcp were administered orally with or without crushing with the teeth, and the blood concentrations of nifedipine *vs.* time curves were compared in humans. As shown in Fig. 6 and Table III, the blood concentrations of nifedipine rose more rapidly when it was administered sublingually after crushing. The observed values were analyzed by the non-linear least squares method (algorism: Simplex method) to calculate kinetic parameters in the two-compartment model. With the calculated values, deconvolution was made by the method of Loo–Riegelman.[9] The *in vitro* dissolution patterns obtained by the PD method and the RDC method (Table II, No. 8) were compared (Fig. 7).

The absorbed ratio of nifedipine is considered to be 56%,[10] and a time lag of 19 min was added to the *in vitro* data to adjust for the time required to raise *in vivo* blood concentrations.

The dissolution pattern measured by the method of

TABLE III. Pharmacokinetic Parameters of Nifedipine after Oral Administration and Sublingual Administration of Ndcp in Men ($n=6$, mean±S.D.)

| | $C_{max}$ [a] (ng/ml) | $T_{max}$ [b] (h) | $T_{1/2}$ [c] (h) | $AUC$ $(0-\infty)$ [d] (ng/ml·h) | $MRT$ [e] (h) | $VRT$ [f] |
|---|---|---|---|---|---|---|
| Oral administration | 87.25± 7.99 | 0.83±0.28 | 0.84±0.20 | 150.57±25.38 | 1.93±0.34 | 1.79±0.80 |
| Sublingual administration | 74.87±15.63 | 0.79±0.37 | 1.17±0.76 | 142.66±43.01 | 1.82±0.65 | 2.06±1.02 |

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

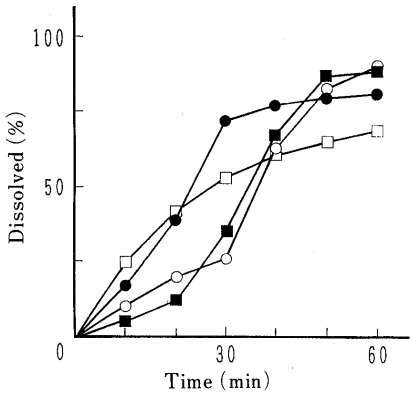


Fig. 7. Relationships between Dissolution Behavior (Time Lag Model) and Absorption Pattern

●, JP XI PD method (pH 1.2/1000 ml, 100 rpm); ○, RDC method (condition 8); ■, Loo–Riegelman (oral administration); □, Loo–Riegelman (sublingual administration).

JP XI was linear, and different from that obtained by other methods. The dissolution pattern measured by the RDC method was almost paralleled the absorption pattern obtained after the oral administration of one Ndcp. The curve after sublingual administration showed no time lag, indicating a difference in the route of absorption.

Since nifedipine soft gelatin capsules are produced with a water soluble base, their dissolution patterns measured by the RDC method resemble their *in vivo* behaviors. Thus, the results presented above suggest that the RDC method closely reflects the *in vivo* absorption pattern.

## Conclusions

Dissolution tests of nifedipine soft capsules as examples of soft capsules containing water soluble vehicles were carried out by the PD method and RDC method. Dissolution patterns similar to *in vivo* patterns were observed by the RDC method. *n*-Octanol was used in this study as the external phase, but further evaluation of possible substitutes for *n*-octanol, such as vegetable oils and aqueous solutions supplemented with surfactants, is considered to be needed to obtain test solutions more suitable for routine work.

The RDC method appears to be useful as a dissolution test simulating *in vivo* pharmacokinetics if its applicability is widened to dosage forms other than soft gelatin capsules, especially since finding substitutes for animal experiments is a subject of global concern.

**Acknowledgement** The authors would like to thank Dr. Mitsuru Uchiyama for his helpful suggestions. This study was performed as part of the International Joint Research Program organized by the Human Science Foundation.

**References and Notes**

1) Part III: M. Takahashi, T. Itoh, M. Ohta, *Yakuzaigaku*, **53**, 1 (1993).
2) J. A. Bustrak, J. D. Katz, J. H. Hull, J. R. Foster, J. E. Hammond, R. H. Christenson, *J. Pharm. Sci.*, **73**, 1397 (1984).
3) Part I: M. Takahashi, T. Fukasawa, M. Negishi, K. Serizawa, T. Shida, M. Goto, *Yakuzaigaku*, **50**, 125 (1990).
4) Y. Machida, T. Tokumura, S. Komuro, Y. Tsushima, K. Tatsuishi, M. Kayano, T. Nagai, *Chem. Pharm. Bull.*, **34**, 6 (1986).
5) Part II: M. Takahashi, T. Fukasawa, M. Negishi, K. Serizawa, T. Shida, M. Goto, *Yakuzaigaku*, **50**, 133 (1990).
6) B. Duhm, W. Maul, H. Medenwald, K. Patzschke, L. A. Wegner, *Arzneim.-Forsh.*, **22**, 42 (1972).
7) K. Miyazaki, N. Kohri, T. Arita, *J. Chromatogr.*, **310**, 219 (1984).
8) S. Ooka, S. Kawamura, *Rinsyo To Kenkyu*, **62**, 308 (1985).
9) J. C. K. Loo, S. Riegelman, *J. Pharm. Sci.*, **57**, 918 (1968).
10) C. H. Kleinbloesem, P. van Brummelen, J. A. van de Linde, P. J. Voogd, D. D. Breimer, *Clin. Pharmacol. Ther.*, **35**, 942 (1984).