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Formulation and in vivo-in vitro correlation of the dissolution property of lemildipine solid dispersions-incorporated suppositories

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Abstract

Solid dispersion-incorporated suppositories were prepared by the fusion method and pharmaceutically evaluated in vivo and in vitro. Solid dispersions of lemildipine with HPMC were manufactured by coating an organic drug-polymer solution onto the surface of crystalline lactose with a fluidized bed granulator. Lemildipine and its solid dispersions were more stable in oleaginous suppositories than in water-soluble suppositories, particularly in the molten state. The physical characteristics of the suppositories were desirable for practical use. The rectal bioavailability of lemildipine from solid dispersion-incorporated oleaginous suppository (SDIOS) in dogs was approx. 14-times higher than that from intact bulk-incorporated oleaginous suppository (IBIOS). In vivo absorption curves of IBIOS and SDIOSs were generated by deconvolution of the plasma level data. In vivo absorption proceeded at a decreasing rate and the cumulative absorption rate reached an individual or steady-state level of about 3% for IBIOS and about 42% for SDIOSs at approx. 12 h after administration. The in vivo absorption curves were meaningfully correlated with in vitro dissolution curves of the corresponding suppositories by a modified rotating dialysis cell method.

Keywords: Rectal absorption; Dissolution method; Lemildipine; Solid dispersion; Suppository; In vivo-in vitro correlation

1. Introduction

Lemildipine is a new calcium entry blocker in the dihydropyridine class developed for the treatment of hypertension. The blood level of lemildipine after oral administration of intact drug is extremely low (Product Summary, 1988). The poor bioavailability of lemildipine can be closely connected with its intrinsic low solubility (Ishimaru et al., 1991a). In order to enhance the bioavailability of lemildipine, the improvement of its dissolution characteristics is considered to be very effective. Many attempts such as chemical molec-

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ular modifications to derivatives and prodrugs (Murakami et al., 1981), physicochemical molecular modifications to salts (Ishimaru et al., 1991b) and inclusion complexes (Iwaoku et al., 1982), and physical modifications, e.g., the reduction of particle size (Rutten-Kingma et al., 1979a,b), etc., have been carried out to improve the in vivo performance of various poorly soluble drugs. Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs without molecular modification (Chow and Riegelman, 1971; Monkhouse and Lach, 1972; Yamamoto et al., 1976). Solid dispersions of lemildipine with HPMC (spray-drying solvent deposition system) were manufactured by coating an organic drug-polymer solution onto the surface of crystalline lactose with a fluidized bed granulator (Takeuchi et al., 1987). The oral bioavailability of the tablet with the solid dispersion was significantly greater than that obtained with an intact drug (Ishimaru et al., 1991a).

The present study was performed to investigate the dissolution behavior and rectal absorption characteristics of lemildipine from the solid dispersion-incorporated suppositories.

2. Experimental

2.1. Materials

Lemildipine (isopropylmethyl (±)-6-carbamoyloxymethyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2-methyl 3,5-pyridinedicarboxylate) and its methylated derivative (particle size < 74 μm), NPK-127 (as an internal standard for assay of lemildipine), were synthesized at Banyu Pharmaceutical Co., Ltd. A lemildipine solid dispersion was manufactured by a spray coating method and Table 1 shows the formula of the solid dispersion manufactured. Both lemildipine and HPMC (Shinetsu Chemical Ind., Co., Ltd) were dissolved in the mixed solvent which consisted of equivalent volumes of ethanol and dichloromethane. Sugar fatty acid ester (Mitsubishi Kasei Food Co.) was then added to the solution and dissolved with stirring. The coating solution was sprayed onto the surface of crystalline lactose (DMV 100M) with a fluidized bed granulator. The lemildipine solid dispersion was obtained by drying the spray-coated granules for overnight at 40°C. The crystal form of lemildipine in the solid dispersion layer was amorphous (by DSC analysis and powder X-ray diffractometory). Pharmasol B-115 used as an oleaginous base was purchased from Nihon Fat and Oils Co., Ltd. PEG 400 and 4000 were of JP XII grade, and their mixture (1:3, weight ratio) was used as a water-soluble base. The other chemicals used were reagent grade commercial products.

Table 1
Formula of lemildipine solid dispersion

Ingredients	Amount (mg)
Lemildipine	100
HPMC 2910 (3cs)	300
Sugar fatty acid ester (P1670)	200
Lactose (DMV 100M)	400
Total	1000

Table 2
Formulae of suppositories tested in this study

Sample	Active ingredient		Base		Total
	Intact bulk	Solid dispersions	Oleaginous	Water-soluble	
IBIOS20	20	0	1280	0	1300
SDIOS10	0	100	1200	0	1300
SDIOS20	0	200	1100	0	1300
IBIWS20	20	0	0	1280	1300
SDIWS20	0	200	0	1100	1300

Solid dispersions contained 10% lemildipine.

2.2. Preparation of suppositories

Suppositories were prepared by the fusion method and the formulas are shown in Table 2. Intact lemildipine or its solid dispersion was added to the oleaginous base melt at 50°C and water-soluble base melt at 60°C, and then thoroughly mixed. Each mixture was cooled to 30–35°C, dispersed and promptly subdivided into plastic suppository molds. After aging for at least 12 h at 5°C, the moldings obtained were used in this study.

2.3. Physical characteristics

Physical characteristics such as the hardness, melting point and softening time of suppositories were measured. The hardness of a cylindrical sample (8 mm thickness) which was provided by cutting the middle portion of a suppository was measured in its diameter direction using a Schleuniger 2E type tablet hardness tester. Melting point was measured by the capillary method. The softening time was determined using an apparatus reported previously (Ishimaru et al., 1991c).

2.4. Stability test

Each naked suppository was kept for 2 and/or 6 weeks at 35 and 60°C/ambient. After storage, 5 ml of water was added to the sample, heated to 50°C and supersonicated for 15 min. Then, 20 ml of methanol and 2 ml of methanolic solution of internal standard were added to the sample phase and supersonicated for 15 min. The mixture was diluted with methanol and filtered through a membrane filter (pore size 0.45 μm). The concentration of unchanged lemildipine in the filtrate was determined by HPLC. A Shimadzu LC-6A type HPLC system was employed and operated according to the following conditions. HPLC conditions for in vitro tests: guard column, Spherisorb $_7C_{18}$ (3.2 mm diameter × 15 mm); analytical column, Nucleosil $_5C_{18}$ (4.6 mm diameter × 250 mm); mobile phase, water/acetonitrile = 35:65; flow rate, 1 ml/min; column temperature, 40°C; detector, UV (wavelength 250 nm); injection volume, 20 μl; sample temperature, 4°C.

2.5. Dissolution test

A modified rotating dialysis cell (MRDC) method and a rotating glass cell (RGC) method were employed for the dissolution assessment of suppositories (Schoonen et al., 1976; Dibbern and Wirbitzki, 1983; Ishimaru et al., 1991d). Cylindric Durapore™ treated with Pharmasol A-105 was used as a dialysis membrane. Each suppository was placed into a sample cell with 3 ml of 0.1 M phosphate buffer solution (pH 7.4) as an inner solution and 30 pieces of glass beads. Dissolution testing by the MRDC method was performed in 1000 ml of test medium, 0.1 M phosphate buffer solution (pH 7.4) containing 0.5% SDS, at 38°C and 25 rpm. The amount of lemildipine which passed through the dialysis membrane was measured by HPLC. The dissolution properties of lemildipine from the suppository in the sample site (in the rectum) were modelled using a glass cell (20 ml size bottle) instead of the dialysis cell for the MRDC method under similar test conditions to the MRDC method. The aliquot of the inner solution was analyzed by HPLC after filtration and dilution to determine the amount of lemildipine dissolved in the sample site.

2.6. Rectal absorption test in dogs

Male beagle dogs weighing 10.5–14.0 kg were fasted for 24 h prior to the experiment. Each suppository was administered into the rectum at a dose of 10 or 20 mg lemildipine per animal. Blood samples (2.0 ml) were collected from the foreleg vein at appropriate time intervals after administration. Plasma was separated by centrifugation for 10 min at 4°C and 3000 rpm and stored at −20°C until the measurement of lemildipine concentration. The concentration of unchanged lemildipine in the plasma was assayed by HPLC.

2.7. Analytical procedure of lemildipine in plasma

1 ml of saline and 10 μl of NPK-127 methanolic solution (2.5 μg/ml) as an internal standard were added to 1.0 ml of the plasma in order. This solution was mixed and retained in a Bond Elute™ ODS. 4 ml of water and 3 ml of 40% methanol were applied as washings. Lemildipine retained was eluted with 2.0 ml of methanol. The eluate was dried at around 25°C under reduced pressure and the residue was dissolved in 120 μl of methanol. The solution was filtered with a 0.45 μm pore size membrane filter. Aliquots of the filtrate were applied to HPLC analysis. The operating conditions for HPLC were as follows. *HPLC conditions*: guard column, Spherisorb $_5C_{18}$ (4.6 mm diameter × 30 mm); analytical column, Nucleosil $_5C_{18}$ (4.6 mm diameter × 250 mm); mobile phase, water/acetonitrile = 35:65; flow rate, 1

ml/min; column temperature, 40°C; detector, UV (wavelength; 350 nm); injection volume, 30 μl; sample temperature, 4°C.

3. Results and discussion

3.1. Physicochemical characteristics

Five suppositories were prepared, and the physical characteristics and chemical stability were measured according to the methods described above. The results are listed in Table 3. The hardness values of the solid dispersion incorporated suppositories were larger than those of the intact bulk incorporated suppositories. A difference in the melting points between IBIOS and SDIOSs was not observed, nor between IBIWS and SDIWS. Except for the hardness of IBIWS20, the physical characteristics of all suppositories were satisfactory for practical use.

No decomposition of lemildipine in the oleaginous systems (IBIOS20, SDIOS10 and SDIOS20) and water-soluble systems (IBIWS20 and SDIWS20) was observed when the sample was kept in the solid state (5 and 35°C/ambient) for up to 6 weeks. However, the amounts of lemildipine remaining in the oleaginous systems were considerably higher than that in the water-soluble systems when the sample was kept in the molten state (60°C/ambient). In general, an increase of 10°C in storage temperature brings about a 2–3-fold increase in the reaction rate (Amirjahed, 1977). The rapid degradation rate of lemildipine at 60°C when the solid dispersion form of the drug was used, however, cannot be explained only by the increase in storage temperature, since severe degradation was not observed when the bulk drug was used in the oleaginous system. The oleaginous suppositories remained in the solid state under the storage condition at 35°C, although this temperature was almost equal to their melting points. The increase of 30°C from 5 to 35°C in storage temperature brought about no change in the decomposition rate of suppositories, while the increase of 25°C from 35 to 60°C strongly affected the rate. This may suggest that the degradation rate is greatly accelerated by the phase transformation from the solid to molten state. Although the suppositories are predicted to be stable at temperatures below the melting point of the formulation, the oleaginous system was selected for subsequent experiments due to its increased stability at higher temperature.

3.2. Dissolution profile

The dissolution profiles of lemildipine from oleaginous suppositories selected using a modified rotating dialysis cell (MRDC) method are shown in Fig. 1. The dissolution rates of lemildipine from its solid dispersion incorporated oleaginous suppositories (SDIOSs) were significantly improved compared to that obtained when the intact bulk drug was incorporated into the oleaginous suppository (IBIOS). We already reported that the MRDC method was useful to predict the bioavailability of a drug after rectal administration of an oleaginous suppository (Ishimaru et al., 1991d). In this method, suppositories are dis-

Table 3
Physicochemical characteristics of lemildipine suppositories

Sample	HD	MP	ST	SW	PR (%)		
	(kg)	(°C)	(min)		35°C/2W	35°C/6W	60°C/2W
IBIOS20	2.9	34.8	3.8	IS	102.4 ± 0.9	102.1 ± 0.4	99.5 ± 0.2
SDIOS10	4.8	34.8	5.3	IS	97.9 ± 2.1	100.1 ± 0.8	95.1 ± 0.2
SDIOS20	5.8	35.0	6.8	IS	101.3 ± 0.6	101.1 ± 0.6	91.3 ± 1.0
IBIWS20	1.0	51.3	NS	SO	100.5 ± 0.4	99.9 ± 2.6	63.7 ± 7.7
SDIWS20	3.4	52.0	NS	SO	99.9 ± 1.4	101.3 ± 0.9	27.5 ± 18.7

HD, hardness ($n = 5$); MP, melting point ($n = 3$); ST, softening time ($n = 5$); SW, solubility; PR, % remaining of lemildipine at 2 and/or 6 weeks after storage at 35 and 60°C ($n = 4$–5); NS, not softened; SO, soluble; IS, insoluble.

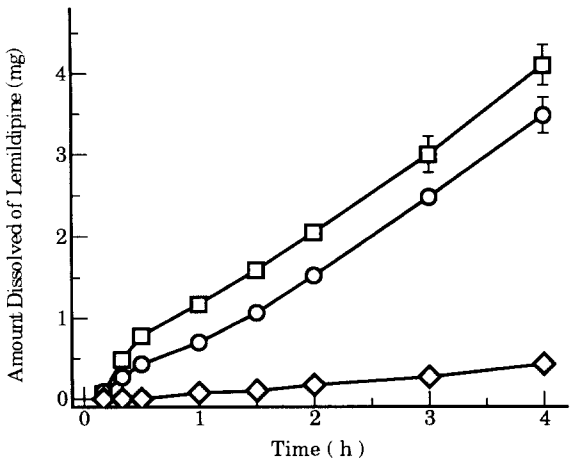

Fig. 1. Dissolution profiles of lemildipine from suppositories by modified rotating dialysis cell method. Each point represents the mean ±S.D. of three determinations. (□) SDIOS20, (○) SDIOS10, (◇) IBIOS20.

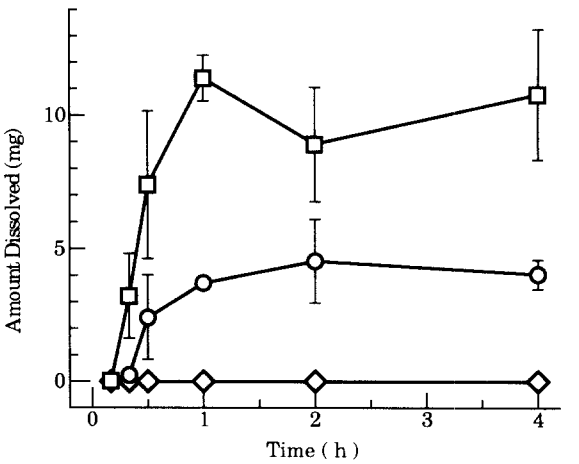

Fig. 2. Dissolution profiles of lemildipine from suppositories by rotating glass cell method. Each point represents the mean ±S.D. of three determinations. (□) SDIOS20, (○) SDIOS10, (◇) IBIOS20.

solved in the inner phase, the drug passing through the membrane from the inner phase to the outer phase. The inner phase is composed of 3 ml of pH 7.4 buffer solution, and the outer phase is 1000 ml of pH 7.4 phosphate buffer containing 0.5% SDS as a solubilizer for lemildipine. Thus, the inner phase is considered to be a non-sink, while the sink condition is maintained in the outer phase. A sequence of in vitro dissolution processes by the MRDC method is similar to that observed in in vivo absorption processes after the administration of the suppository.

Then, dissolution assessment by the RGC method was performed to reproduce the dissolution behavior in the inner solution of the MRDC method. In contrast to the solid dispersion alone, the SDIOSs resulted in dissolution behavior accompanied by extended supersaturation in the non-sink inner phase as shown in Fig. 2 and 3. The supersaturated phenomena of SDIOS persisted for more than 4 h. On the other hand, supersaturation was not observed in the IBIOS. The areas under the dissolution curves (AUDCs) of the IBIOS20, SDIOS10 and SDIOS20 in the inner solution were 0.002, 4.835 and 11.915 mg h ml^{-1}, respectively. The maximum concentrations (in vitro C_{max}) of the IBIOS20, SDIOS10 and SDIOS20 were 0.001, 1.515 and 3.803 mg/ml, respectively. Thus, the dissolution rate of lemildipine from the oleaginous suppository in the inner phase of the MRDC method was greatly improved by incorporating a solid dispersion into the suppository. The permeation rate of lemildipine through a fat-treated membrane into the outer

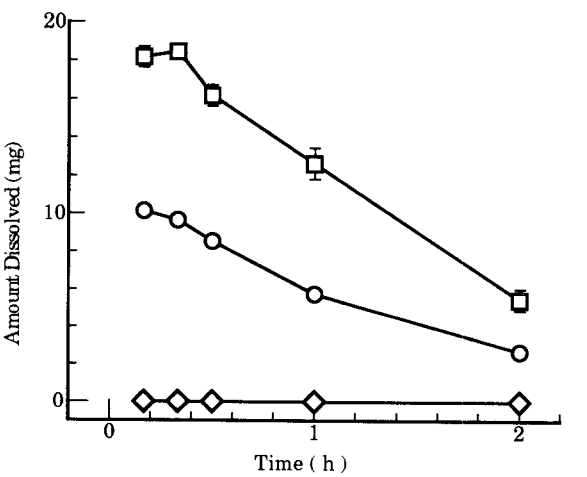

Fig. 3. Dissolution profiles of lemildipine from solid dispersion granules or intact bulk by rotating glass cell method. Each point represents the mean ±S.D. of three determinations. (□) Solid dispersion granule (equivalent to 20 mg of lemildipine); (○) solid dispersion granule (equivalent to 10 mg of lemildipine); (◇) intact bulk (20 mg).

phase depended upon the solute concentration in the inner phase, as shown in Fig. 1 and 2. This suggests that membrane permeation is controlled by a simple diffusion mechanism and that the driving force of permeation is a concentration gradient of solute between the inner and outer phases. The dissolution rate of lemildipine was enhanced by the use of solid dispersions, however, the amount dissolved at the plateau region (at 1–4 h in Fig. 2) in the inner phase was approx. 60% of the loading dose. A somewhat low cumulative amount of dissolution is considered to be due to the duration of the supersaturated state in the inner phase.

3.3. Absorption profile

Fig. 4 shows the rectal absorption profiles of lemildipine from oleaginous suppositories in beagle dogs. The plasma concentration of lemildipine after rectal administration of the IBIOS20 was extremely low. By incorporating solid dispersion particles instead of intact drug into an oleaginous base, the rectal bioavailability of lemildipine was significantly enhanced. As summarized in Table 4, maximal plasma concentrations (in vivo C_{max}) and area under the plasma concentration curves (AUC) for the SDIOS20 were 184.1 ng/ml and 3093.6 ng h ml^{-1}, respectively. These values were 15.7- and 14.0-fold greater than the corresponding values for the IBIOS20. The time required to reach the maximum peak (T_{max}), mean residence time (MRT) and plasma half-life ($T_{1/2}$) of lemildipine for the

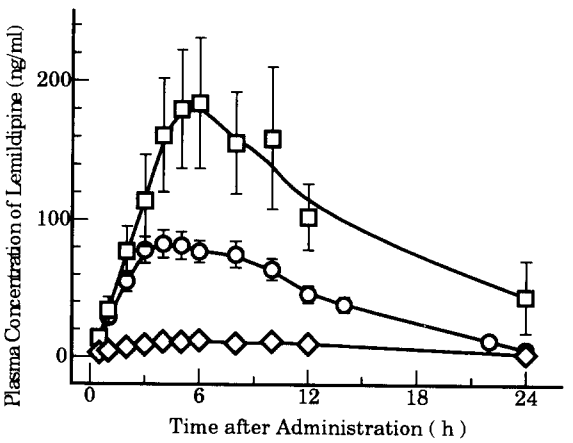

Fig. 4. Plasma concentration-time curves of lemildipine after rectal administration of suppositories in dogs. Each point represents the mean ±S.E. of four or eight determinations. (□) SDIOS20, (○) SDIOS10, (◇) IBIOS20.

SDIOS10 or 20 were almost the same as those from the IBIOS20. No change in these pharmacokinetic parameters suggests that the increase in the absorbable drug fraction is obtained by incorporating the solid dispersion and is not due to the marked changes in membrane permeability in the rectum and metabolic fate of the drug. Enhanced bioavailability may be closely related to the supersaturation of lemildipine in the rectum in a similar manner to that observed in the dialysis cell in vitro.

In vivo dissolution curves of three suppositories were estimated by deconvolution of the plasma level data shown in Fig. 4 using pharmacokinetic parameters after intravenous and oral

Table 4
Pharmacokinetic parameters of lemildipine after rectal administration of oleaginous suppositories in beagle dogs at a dose of 10 or 20 mg/animal

Parameter	Intact bulk (IBIOS20)	Solid dispersion (SDIOS10)	(SDIOS20)
n	4	8	4
Dose (mg)	20.0	10.0	20.0
T_{max} (h)	6.0	4.0	6.0
C_{max} (ng/ml)	11.9	82.5	184.1
$MRT_{(infinity)}$ (h)	13.8	9.9	15.5
$T_{1/2}$ (h)	5.1	3.9	5.0
$AUC_{(0-24)}$ (ng h ml^{-1})	186.6	1069.1	2474.5
$AUC_{(infinity)}$ (ng h ml^{-1})	220.2	1129.1	3093.6
Relative bioavailability $_{(infinity)}$	1.0	5.1	14.0

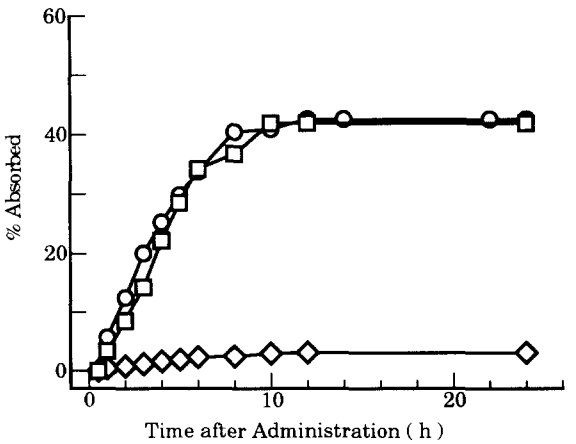

Fig. 5. In vivo absorption profiles generated by deconvolution of the plasma concentration data of lemildipine after rectal administration of suppositories in dogs. (○) SDIOS20, (□) SDIOS10, (◇) IBIOS20.

administration of the PEG400 solution of lemildipine, according to the report of Rescigno and Segre (1966). The results are shown in Fig. 5. In vivo dissolution proceeded at a decreasing rate, and in vivo dissolution reached individual steady-state levels at approx. 12 h after administration. The levels of IBIOS20, SDIOS10 and SDIOS20 were about 3, 42 and 42% of dose, respectively.

3.4. *In vivo / in vitro correlation*

In order to assess the correlation between the in vivo absorption parameters and in vitro dissolution parameters, the maximum concentration in the dissolution curve (in vitro C_{max}) and area under the dissolution curve (AUDC) were compared to the maximum plasma concentration (in vivo C_{max}) and area under the plasma concentration curve (AUC), respectively. As shown in Fig. 6, both the in vitro C_{max} and AUDC determined by the RGC method were strongly correlated to the in vivo C_{max} and the AUC. Thus, the RGC method allowed good correlations between in vivo absorption parameters and in vitro dissolution parameters at level ⟨C⟩ on the report from the AAPS/FDA/FIP/USP (Skelly et al., 1990). However, the RGC method did not permit meaningful correlations between the in vitro dissolution curves and in vivo absorption curves generated by deconvolution of the plasma level data (level ⟨A⟩ correlation) as shown in Fig. 7. Namely, the relative in vivo/in vitro correlation was evident in the RGC method, but the absolute correlation was not observed.

On the other hand, in vitro dissolution curves by the MRDC method substantially correlated to in vivo absorption curves for the corresponding suppositories as shown in Fig. 7. Dissolution testing with the MRDC apparatus is the method which can assess the permeation rate through a fat-treated membrane following dissolution into a

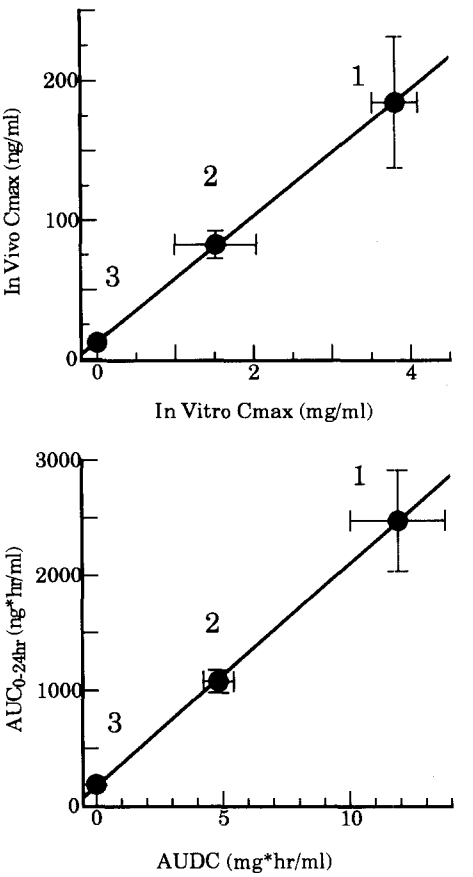

Fig. 6. Correlation between in vivo absorption parameters and in vitro dissolution parameters by rotating glass cell method. Each point represents the mean ±S.D. of 3–8 determinations. (Top) In vitro C_{max} vs in vivo C_{max}; (bottom) AUDC vs AUC. (1) SDIOS20, (2) SDIOS10, (3) IBIOS20.

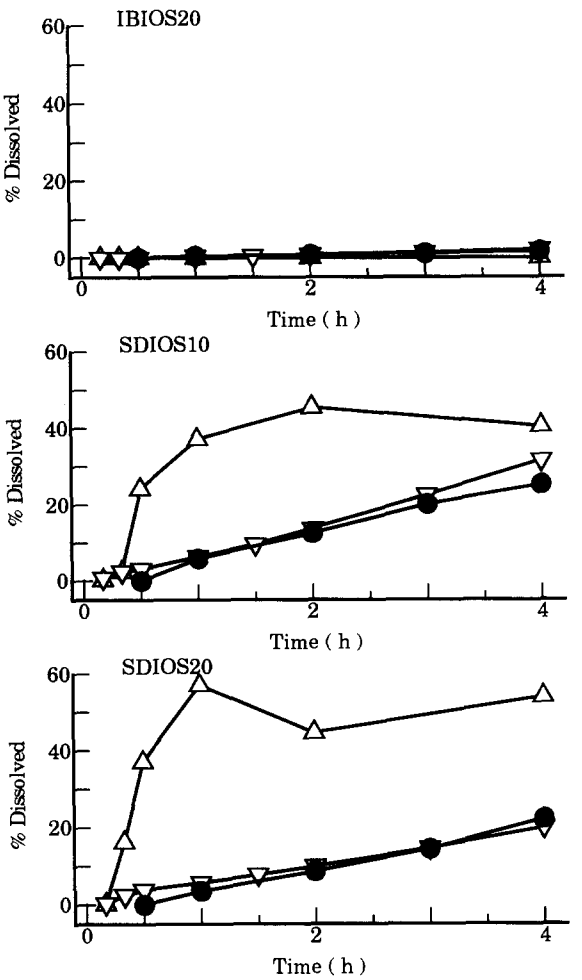

Fig. 7. Correlation between in vivo absorption (●) and in vitro dissolution by rotating glass cell method (△) and modified rotating dialysis cell method (▽).

small amount of medium. The in vitro dissolution rate of lemildipine from SDIOS into the medium (inner solution) obtained by the RGC method was more rapid than the in vivo absorption rate, as mentioned above. Steady-state drug concentrations in the inner solution increased in the order of IBIOS20, SDIOS10 and SDIOS20. The in vitro dissolution profile of lemildipine from the inner solution through a fat-treated membrane into the test medium agreed well with the in vivo absorption profiles. These results strongly suggest the usefulness of such two compartment type dissolution tests as the MRDC method in order to assess in vivo/in vitro correlation for suppositories.

4. Conclusion

Lemildipine was stable in an oleaginous suppository when incorporated as a solid dispersion form, and such physical characteristics as hardness, melting point and softening time of the suppository were satisfactory for practical use.

The in vitro dissolution and in vivo absorption of lemildipine solid dispersion incorporated oleaginous suppositories were greatly improved compared with those of intact lemildipine incorporated oleaginous suppositories.

The in vivo absorption curves were in close agreement with the in vitro dissolution curves of the corresponding suppositories generated by the modified rotating dialysis cell method equipped with a fat-treated dialysis membrane.

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