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RESEARCH PAPER

Evaluation of Monolithic Osmotic Tablet System for Nifedipine Delivery In Vitro and In Vivo

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ABSTRACT

The aim of this study was to evaluate the monolithic osmotic tablet system (MOTS) containing a solid dispersion with the practically water-insoluble drug nifedipine in vitro and in vivo. In the drug release study in vitro, the release profiles of this system had almost zero-order kinetics. The influences of tablet formulation variables, sizes of the delivery orifice, membrane variables, and values of pH in the dissolution medium on nifedipine release from MOTS have been investigated. The results provided evidence that the tablet core played an important role in MOTS. While orifice sizes and membrane variables affected the nifedipine release rate, MOTS was independent of the dissolution medium. The appropriate orifice size was found to be in the range of 0.5–1.0 mm. The coating membrane incorporating hydrophilic polyethylene glycol (PEG) formed a porous structure. The human pharmacokinetics and relative bioavailability of MOTS containing nifedipine were compared with a commercial Adalat® osmotic tablet system containing an equivalent dose of nifedipine following an oral single dose of 30 mg given to each of 11 healthy volunteers in an open, randomized crossover study in vivo. The relative bioavailability for MOTS was 112%. There was no statistically significant difference in the pharmacokinetic parameters between two dosage forms. It is concluded that the monolithic osmotic tablet controlled release system is feasible for a long-acting preparation as a once-daily treatment.

Key Words: Nifedipine; Monolithic osmotic tablet system; In vitro; In vivo.

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INTRODUCTION

The osmotic pump system, which has extended the utility of osmotic pressure as the driving force for the controlled release of drugs, has been under development for at least four decades. This system has many advantages, such as drug release at a constant delivery rate over an extended action period, lack of sensitivity to variation of the pH or motility of the gastrointestinal tract, thereby reducing risk of adverse reactions, and improved patient compliance. On the other hand, the in vivo predictability of release rate of this system can be based on the in vitro data. Various osmotic pumps have been reviewed in U.S. patent literature by Santus and Baker.[1] The first device using osmotic principles to deliver active ingredients was reported in the 1950s by Ross and Nelson.[2] During the past four decades, there has been a growing interest in developing osmotic pump dosage forms for the controlled delivery of drugs.[3–9] The elementary osmotic pump (EOP) dates to the 1970s.[3,10] The EOP consists of an osmotic core incorporating the drug and surrounded by a semipermeable membrane with a delivery orifice. In operation, the osmotic core imbibes water from the surrounding medium via the semipermeable membrane. Subsequently, a drug solution is generated within the device and delivered out of the device via the orifice at an approximate zero-order rate. However, the EOP is unsuitable for delivering water-insoluble drugs and is suitable only for water-soluble drugs. To overcome this problem, a two-layer osmotic tablet system had been designed for the release of water-insoluble drugs.[11,12] A sandwiched, osmotic tablet system (SOTS) was reported in the patent literature.[13] The system was based on the sandwiched tablet core consisting of a middle push layer and two attached drug layers. After coating, two orifices were simply drilled on both side surfaces. However, from the technological point of view, the manufacturing of the reproducible two-compartment systems might be more difficult than one-compartment systems. For this reason, a monolithic osmotic tablet system (MOTS) for water-insoluble drug delivery was reported in the patent literature.[14,15] This monolithic osmotic tablet system is simple in preparation, but it has a shortcoming in that its release profile slightly deviates from the straight line.

In this study, a monolithic osmotic tablet system was prepared to deliver nifedipine with the purpose of improving the linearity of the release profile of the monolithic osmotic tablet system. The aim of this research was to study the influences of tablet core variables, orifice sizes, and membrane variables as well as the pH values of the dissolution medium on drug release from the monolithic osmotic tablet system designed in our lab. Moreover, this system has been evaluated in vivo is comparisons with the commercial Adalat® osmotic tablet system. A single dose crossover study using a suitable high-performance liquid chromatography (HPLC) analytical procedure[16] was done.

As the model substance nifedipine, a calcium channel blocker of the dihydropyridine type, has been used for many years to treat hypertension and angina pectoris.[17] It is practically insoluble in water with solubility less than 10 μg/mL.[8–20]

MATERIALS AND METHODS

Chemicals and Reagents

The following were used: Nifedipine powder (Sigma Chemical Co., St. Louis, MO, USA); gum arabic (GA, BP Chemicals Ltd., UK, 200 mesh, heated with C_2H_5OH to remove enzymes and dried); polyvinylpyrrolidone (PVP-K30, BASF, Germany); sodium chloride (NaCl, Qingdao chemicals Ltd., China); carboxymethyl cellulose (CMC-Na, Buckeye Scientific Co. Inc.,); film-forming polymers cellulose acetate and polyoxyethylene glycol (PEG-6000) (Shanghai Colorcon Coating Technology Ltd., China); diethyl phthalate (DEP, BP. Chemicals Ltd., UK); osmotic pump system (Adalat, Bayer, Germany); reagent grade absolute acetone was used as the coating solvent; reagents and organic solvents used were of analytical or HPLC grade. Double-distilled water was used.

Preparation of MOTS

Firstly, the solid dispersions of nifedipine-PVP-K30 (SD) were prepared. The characteristics of the solid dispersions had been systematically studied in our previous works.[21] The solid dispersion of nifedipine-PVP-K30 (1:5) was used in the present study. Based on the results of our previous work, the formulation of a tablet core was optimized. The basic formulation of MOTS core is shown in Table 1. A constant dose of 180 mg nifedipine-PVP solid dispersion (loading 30 mg nifedipine) was fixed in all formulations. The MOTS tablet core was made by directly compressing the mixture of chemicals in the formulation in a Korsch MP1 tablet-machine using a

Table 1. Formulation, cumulative release of nifedipine at 24 h (%), and their correlation coefficients.

No.	NaCl (mg)	CMC-Na (mg)	Gum arabic (mg)	Cumulative release at 24 h (%)	r^2
1	20	20	160	69.78 ± 0.039^s	0.9819
2	35	30	135	66.92 ± 0.026^s	0.9650
3	40	40	120	67.89 ± 0.013^s	0.9534
4	50	10	140	91.62 ± 0.031	0.9982
5	60	25	115	78.42 ± 0.027^s	0.9475
6	70	35	95	67.84 ± 0.035^s	0.9388
7	80	50	70	52.79 ± 0.044^s	0.9535

Data are mean ± SD of six such experiments performed. ^{s}means significant difference of cumulative release (%) to that of core No. 4 (one-way ANOVA test).

Table 2. Coating solution formulations and membrane thickness.

	5% cellulose acetate solution (CA) in acetone		
No.	Plasticizer	Level (w/w CA)	Membrane thickness (μm)
Coating 1	0	0	60–90
Coating 2	Diethyl phthalate	5	60–90
Coating 3	PEG-6000	10	60–90
Coating 4	PEG-6000	20	60–90

round punch of 6.0 mm in diameter. The formulation of the coating solution is shown in Table 2, which was sprayed onto the tablet cores utilizing a baffled pan coater (BY300, Shanghai, China). A spraying rate of 8 mL/min with an atomizing air pressure of 0.9 kg/cm^2 and the inlet air temperature of 50° was used. The deviation of membrane thickness was controlled less than 5 μm. The tablets coated with the membrane were dried at 50° for at least 24 h. One orifice for drug release was drilled on the surface of each coated tablet using a fine needle before release rate studies were conducted.

Determination of In Vitro Drug Release

Dissolution in vitro was performed according to the standard US. Pharmacopeia (USP) dissolution methodology (Apparatus#2, rotating paddles, 100 rpm, 37°, 900 mL of medium). The release rates were determined in three kinds of dissolution medium of 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4). During the release studies, 1 mL of sample was pipetted out at 2, 4, 6, 8, 12, 14, 16, and 24 h and filtered through filter (0.8 μm). An equal volume of fresh dissolution medium at the same temperature was added. The dissolution test was performed in triplicate. All samples were analyzed with the HPLC method.

Pharmacokinetics In Vivo Study

According to a randomized crossover design, 11 healthy male volunteers (age 20–22 years, weight 60–70 kg) after giving informed consent participated in this study, which was approved by the local Ethics Committee, each volunteer received a single dose of two different formulations: Form A, MOTS (30 mg of nifedipine) and Form B, the marketed osmotic pump tablet Adalat (30 mg of nifedipine) with 200 mL of water. The wash-out period was 2 weeks. The plasma samples were collected into test tubes at 0, 0.5, 1, 2, 4, 8, 12, 16, 20, and 24 h after intake. 1.0 mL of plasma sample, 0.5 mL of 1 M sodium hydroxide aqueous solution, and 5.0 mL of hexane–dichloromethane (7:4, v/v) were mixed by vortexing 15 s; after centrifugation (3000 rpm, 5 min), the supernatant of organic solvent was separated and evaporated to dryness, and the residue was reconstituted with 100 μL of methanol for HPLC analysis. During the study, the plasma samples were protected

from light. The standard calibration curve was linear in the range of 20–400 ng/mL and accuracy values were < 2% at all the investigated concentrations.

HPLC Analysis

The concentrations of nifedipine in the in vitro and in vivo studies were determined by the following HPLC method: column, Zorbax ODS (150 × 4.6 mm, 5 μm, USA); mobile phase, methanol–water (70:30, v/v); flow rate, 1.0 mL/min; column temperature, ambient temperature; internal standard, diazepam; detection wavelength, 218 nm; injection volume, 20 μL. The limit of quantitation of the analytical method was 20.0 ng/mL. The accuracy values were < 5% at all the investigated concentrations.

Pharmacokinetic Analysis

Statistical Program for Scientific Studies (SPSS 10.0) package (for a Windows operating system) was used to perform statistical analysis of the data. A one-way analysis of variance (ANOVA test) was used to compare multiple groups. The pharmacokinetic parameters were determined from the plasma drug concentration-time data. C_{max} was the maximum concentration in the plasma, and T_{max} was the time taken to reach C_{max}. The area under the plasma concentration vs. time curve (AUC) from the time of drug administration up to 24 h after administration was calculated by the trapezoidal rule, and AUC from 24 h to infinity was obtained by extrapolation. The pharmacokinetic data were analyzed for significance with the Mann Whitney U test. Data were presented as mean values with the standard deviation (mean ± SD). A P-value of less than 0.05 was considered to be statistically significant.

RESULTS AND DISCUSSION

Optimal Core Formulation

The delivery rate of a drug from an osmotic pump depends to a large extent on the solubility of the drug. However, by modulating the solubility of water-insoluble drugs within the core, effective release patterns may be obtained. Various cyclodextrin derivatives have been used to solubilize poorly water-soluble drugs.[22,23] In this study, solid dispersion was designed in the core in order to increase the solubility of nifedipine. To study the influence of the amount of chemicals on nifedipine release, MOTS cores with various formulations were prepared, subsequently coated with coating solution 3 in Table 2, and drilled with a circle orifice with a diameter of 1.0 mm. The relationship between the core formulation variables and the cumulative release of nifedipine at 24 h is summarized in Table 1. The results indicate that the MOTS made from core formulation No 4 was able to deliver nifedipine not only for up to 24 h, but also at an approximately constant rate. This core formulation was chosen as the optimal one in the present study.

Scanning Electron Microscope of the Free Membrane

The water is imbibed into the core through the semipermeable coating, so the release kinetics are limited by the membrane formulation variables. The permeability of the coating to water can be adjusted by controlling the membrane structure in order to control nifedipine release kinetics. Variables are the membrane thickness and the size of delivery orifice. To assess the importance of the membrane structure, several free membranes of cellulose acetate were prepared by pouring the coating solution listed in Table 2 into an aluminum-evaporating pan covered with an inverted funnel to prevent solvent removal by convection. After drying, the free membranes (60–90 μm in thickness) were lifted off the pan and the surface morphology was examined by a scanning electron microscope (Amray-1000B). Scanning electron micrographs of the membranes indicated that the surface porosity varied by varying the plasticizer contents in the cellulose acetate (CA) solution. The morphology of the coating 2 (Fig. 1A) showed a homogenous surface structure. Instead of having a continuous surface appearance, micropores formed through the membrane with PEG-6000 as the plasticizer. As the PEG concentration increased, the number and size of the micropores increased (as shown in Fig. 1B, C). Coating 3 was used in the present study because of the CA membrane with hydrophilic PEG forming a porous structure and thereby increasing the permeability of the CA membrane and the drug release rate from MOTS.

Influences of the Membrane Thickness

To study the effect of membrane thickness on the kinetics of drug release from the system, tablets were coated with a membrane made of cellulose

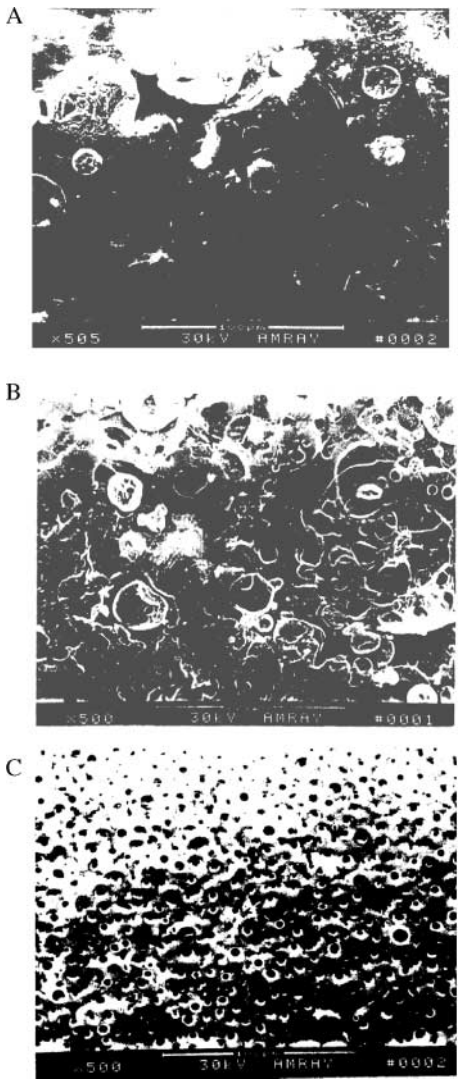

Figure 1. Scanning electron micrographs of the CA membrane: (A) Coating 2, (B) Coating 3, (C) Coating 4.

acetate and PEG 6000 (10%) of $60 \pm 5\,\mu m$, $75 \pm 5\,\mu m$, and $90 \pm 5\,\mu m$ in thickness. The orifice diameter was 1.0 mm. The release rate constants and mean amounts of released nifedipine are shown in Table 3. The results show that nifedipine was released from the MOTS at zero-order kinetics with a membrane thickness in the range of 60–90 μm. No significant difference occurred in the release rate of nifedipine from the MOTS with membrane thickness of 60–90 μm (one-way ANOVA test).

Influences of the Delivery Orifice Size

The size of the delivery orifice has been reported to have an appropriate range for the EOP. The size of the delivery orifice must be smaller than the maximal size to minimize the solute diffusion through the orifice. Also, it must be sufficiently large, above a minimal size to minimize hydrostatic pressure inside the system which would affect the zero-order release rate.[10,24,25] The coated tablets were drilled on the surface with a round orifice of various sizes. The release data of nifedipine from the MOTS as a func-

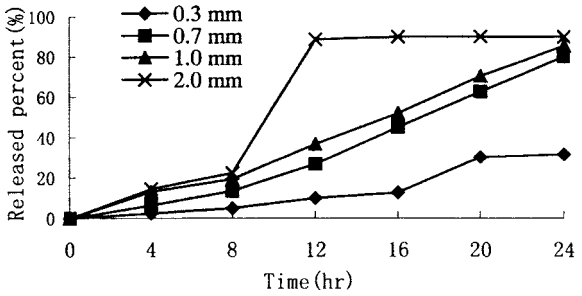

Figure 2. Release profiles of nifedipine from osmotic pump systems with different sizes of delivery orifice, $n = 6$.

Table 3. Released amounts and rate constants (K) of nifedipine from MOTS in the dissolution medium of various pH values.

Time (h)	$60 \pm 5\,\mu m$		$75 \pm 5\,\mu m$		$90 \pm 5\,\mu m$	
	Amounts (mg)	K (mg/h)	Amounts (mg)	K (mg/h)	Amounts (mg)	K (mg/h)
4	6.93 ± 0.034	1.73	6.54 ± 0.040	1.63	6.190 ± 0.022	1.54
8	12.01 ± 0.023	1.29	10.82 ± 0.020	1.07	10.21 ± 0.031	1.00
12	18.62 ± 0.033	1.65	17.57 ± 0.035	1.69	16.02 ± 0.026	1.45
16	23.16 ± 0.030	1.14	21.89 ± 0.029	1.08	21.18 ± 0.021	1.29
20	26.37 ± 0.041	0.82	24.79 ± 0.032	0.73	24.16 ± 0.035	0.73
24	28.50 ± 0.037	0.53	26.45 ± 0.016	0.41	25.97 ± 0.023	0.45
Mean		1.19 ± 0.46		1.10 ± 0.49^{n}		1.07 ± 0.43^{n}

Data are mean ± SD of six such experiments performed. [n]means no significant difference of release rate to that of $60 \pm 5\,\mu m$ (one-way ANOVA test).

Table 4. Released amounts and rate constants (K) of nifedipine from MOTS with the different membrane thickness.

	pH 1.2		pH 6.8		pH 7.4	
Time (h)	Amounts (mg)	K (mg/h)	Amounts (mg)	K (mg/h)	Amounts (mg)	K (mg/h)
4	6.74 ± 0.021	1.68	6.53 ± 0.029	1.63	6.64 ± 0.031	1.66
8	11.61 ± 0.025	1.21	11.43 ± 0.020	1.22	11.76 ± 0.026	1.28
12	18.57 ± 0.017	1.74	18.21 ± 0.025	1.69	18.16 ± 0.021	1.60
16	22.60 ± 0.023	1.00	22.37 ± 0.022	1.04	22.85 ± 0.030	1.17
20	25.96 ± 0.030	0.84	25.38 ± 0.023	0.75	25.66 ± 0.033	0.95
24	28.26 ± 0.031	0.57	27.93 ± 0.019	0.63	28.11 ± 0.025	0.61
Mean		1.17 ± 0.47		1.16 ± 0.44^{n}		1.21 ± 0.40^{n}

Data are mean $\pm$ SD of six such experiments performed. ^{n}means no significant difference of release rate to that in pH 1.2 (one-way ANOVA test).

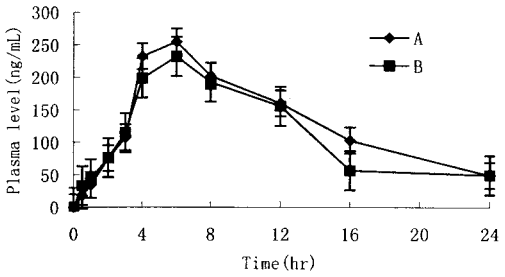

Figure 3. Plasma drug concentration-time curve of nifedipine in human following oral administration of a single dose MOTS (A) and Adalat (B) , $n = 11$.

tion of the diameter of the delivery orifice is shown in Fig. 2. The results were accordant to the EOP. Figure 2 shows that the size of the delivery orifice in the range of 0.7–1.0 mm does not significantly affect the amount of nifedipine released from the system. At a 2.0 mm orifice diameter, the drug is released more rapidly and in a noncontrolled manner. This may be due to the influence of diffusion from the bigger orifice. On the other hand, systems with an orifice diameter of 0.3 mm deliver lower amounts of nifedipine due to the hampered flow of suspension through the small orifice.

Influences of the Dissolution Medium

The release tests of the MOTS were studied in 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), as well as phosphate buffer (pH 7.4), respectively. The amounts of nifedipine released from the MOTS are shown in Table 4. The results of different pH dissolution tests clearly indicate that nifedipine release from the MOTS is independent of the pH value of the release medium. The reason may be that tablets were made of gum arabic. Water coming into the system dissolves these substances and form aqueous solutions of appropriate viscosity. The viscosity of the gum arabic solution is independent of the various pH of the dissolution medium when the proportion of gum arabic in the core is above 50% (data not shown). These observations predict that the monolithic osmotic tablet system containing a water-insoluble nifedipine will not be affected by gastrointestinal fluid.

Evaluation of MOTS In Vivo

The pharmacokinetic parameters of nifedipine following administration of the two dosage forms in 11 healthy volunteers are presented in Fig. 3. After oral administration of a single dose of the MOTS and Adalat, peak levels of plasma averaged 255 ng/mL 232 mg/mL, and AUCs were 3.7 mg·h/mL and 3.3 mg·h/mL, respectively. The relative bioavailability of nifedipine was 112%. It is concluded that nifedipine from the MOTS is bioequivalent to that of Adalat.

CONCLUSIONS

It is known that the release of water-insoluble drugs from a controlled release system is limited by drug solubility. In the present study, the MOTS was successfully prepared using tablet cores made from a nifedipine-PVP solid dispersion. The results indicate that the solid dispersion was capable of solubilizing and increasing the release of water-insoluble drugs such as nifedipine from the MOTS. Hydrophilic plas-

ticizer PEG increases the permeability due to forming micropores structure. An orifice with diameters ranging from 0.7–1.0 mm is suitable for the MOTS at a nearly constant rate up to 24 h and independent of the release medium. The in vivo study shows that the pharmacokinetic parameters of nifedipine from the MOTS are statistically equal to those of a marketed osmotic pump system. In conclusion, the monolithic osmotic tablet controlled release system, which is feasible for a long-acting preparation as a once-daily treatment, may be more beneficial in preparation process than the currently marketed osmotic pump tablet system.

REFERENCES

1. Santus, G.; Baker, R.W. Osmotic drug delivery: a review of the patent literature. J. Contr. Rel. **1995**, *35*, 1–21.
2. Ross, S.; Nelson, J.F. A continuous long-term injector. J. Exp. Biol. **1995**, *33*, 415–420.
3. Theeuwes, F.; Higuchi, T. Osmotic Dispensing Device for Releasing Beneficial Agent. US Patent 3,845,770, 1972.
4. Higuchi, T.; Leeper, H.M. Osmotic Dispenser with Means for Dispensing Active Agent Responsive to Osmotic Gradient. US Patent 3,995,631, 1976.
5. Baker, R.W. Controlled Release Delivery System by an Osmotic Bursting Mechanism. US Patent 3,952,741, 1976.
6. Theeuwes, F. Oral dosage forms design status and goals of oral osmotic system technology. Pharm. Int. **1984**, *5*, 293–296.
7. Amidon, G.L.; Higuchi, T.; Dressman, J.B. Lipid Osmotic Pump. US Patent 4,685,918, 1987.
8. Zentner, G.M.; Rork, G.S.; Himmelstein, K.J. The controlled porosity osmotic pump. J. Contr. Rel. **1985**, *1*, 269–282.
9. Haslam, J.L.; Merfeld, A.E.; Rork, G.S. Surface wetting effects in the lipid osmotic pump. Int. J. Pharm. **1989**, *56*, 227–233.
10. Theeuwes, F. Elementary osmotic pump. J. Pharm. Sci. **1975**, *64*, 1987–1991.
11. Higuchi, T. Osmotic Dispenser with Collapsible Supply Container. US Patent 3,760,805, 1973.
12. Swanson, D.R.; Barclay, B.L.; Wong, P.S.L.; Theeuwes, F. Nifedipine gastrointestinal therapeutic system. Am. J. Med. (Suppl. 68) **1987**, *83*, 3–9.
13. Cortese, R.; Barclay, B.; Theeuwes, F. Simultaneous Delivery of Two Drugs from Unit Delivery Device. US Patent 4,449,983, 1984.
14. Chen, C.M.; Lee, D.T.; Xie, J. Controlled Release Formulation for Water Insoluble Drug in Which a Passageway is Formed In Situ. US Patent 5,736,159, 1998.
15. Chen, C.M.; Chou, J.C.H. Once Daily Pharmaceutical Tablet Having a Unitary Core. US Patent 5,837,39, 1998.
16. Horvath, V.; Hrabeczy-Pall, A; Niegreisz, Z.; Kocsi, E.; Horvai, G. Sensitive high-performance liquid chromatographic determination of nifedipine in dog plasma using an automated sample preparation system with laboratory robot. J. Chromatogr. B **1996**, *686*, 2211–2219.
17. Gibaldi, M.; Perrier, P. *Pharmacokinetics*; Marcel Dekker, Inc.: New York, 1982.
18. Ali, S.L. Nifedipine. In *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, 1989; Vol. 18, 221–288.
19. Grundy, J.S.; Foster, R.T. The nifedipine gastrointestinal therapeutic system (GITS): evaluation of pharmaceutical, pharmacokinetic and pharmacological properities. Clin. Pharmacokinet. **1996**, *30*, 28–51.
20. Takahashi, M.; Mochizuki, M.; Itoh, T.; Ohta, M. Studies on dissolution test for soft gelatin capsule containing water-soluble vehicles by the rotating dialysis cell method. Chem. Pharm. Bull. **1994**, *42*, 333–336.
21. Chen, D.W.; Liu, X.; Fu, W.Y. Studies on preparation and dissolution of the solid dispersions of nifedipine-polyvinylpyrroli-done. Chinese Pharmaceutical J. **2000**, *35*, 598–600.
22. Okimoto, K.; Miyake, M.; Ohnishi, N.; Rajewske, R.A.; Stella, V.J.; Irie, T.; Uekama, K. Design and evaluation of an osmotic pump tablet (OPT) for prednisolone, a poorly water soluble drug, using (SBE) β-cyclodextrin. Pharm. Res. **1998**, *15*, 1562–1568.
23. Okimoto, K.; Rajewski, R.A.; Stella, V.J. Release of testosterone from an osomtic pump tablet utilizing (SEB) β-cyclodextrin as both a solubilizing and an osmotic pump agent. J. Contr. Rel. **1999**, *58*, 29–38.
24. Theeuwes, F.; Higuchi, T. Osmotic Dispensing Device with Maximum and Minimum Size for the Passageway. US Patent 3,916,899, 1975.
25. Janicki, S.; Cichon, R.; Jedras, Z.; Sawichi, W. Gastrointestinal therapeutic system delivering of a water insoluble drug: isosorbide dinitrate (ISDN). Pharmazie. **1987**, *42*, 95–96.