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Influence of pluronic F-68 on dissolution and bioavailability characteristics of multiple-layer pellets of nifedipine for controlled release delivery

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Abstract

A multiple-layer design of pellets for nifedipine was developed using pluronic F-68 to enhance dissolution rate. The influence of ratios of nifedipine in the inner layer to that in the outer layer, the ratios of pluronic F-68 to nifedipine in the solid dispersion, and the thickness of the control membrane on dissolution characteristics were investigated. With an increasing ratio of pluronic F-68 to nifedipine, the dissolution rate of nifedipine was gradually promoted and the extent of release was enhanced as well. DSC thermograms illustrate the gradual disappearance or broadening of the nifedipine melting peak with the presence of pluronic F-68. The decrease of the nifedipine ratio in the inner layer and the increase of the ratio of pluronic F-68 to nifedipine in the outer layer can enhance the release of nifedipine. With a fixed nifedipine ratio of 1.5 between the inner layer and the outer layer, increasing the ratio of pluronic F-68 to nifedipine in the outer layer significantly increased the initial release rate of nifedipine. By increasing the nifedipine ratio of the inner layer to the outer layer to 1:1, the increase of coating percentage referenced to the total weight decreased the release rate of nifedipine from the inner layer. The pharmacokinetic bioequivalence between the test product (Cardilate, N-6) and Coracten was found with a multiple-dose oral administration of 20 mg in 12 healthy, normal Chinese male volunteers.

Keywords: Dissolution; Multiple-layer; Controlled-release; Pellets; Pluronic F-68; Nifedipine

1. Introduction

Pellet dosage forms and their formulation design have shown many advantages and flexibility in enhancing therapeutic safety and potency [1,2]. As a result, on many occasions formulators prefer to select pellet dosage forms as the main choice during dosage form development [3]. Basically, several kinds or different release rates of drugs might be included in the same pellet. A nearly constant release rate of drug can be obtained by mixing several sets of pellets, each with their own rate limiting characteristics [4,5]. A targetable pellet dosage form is available as well by coating drug-containing pellets with enteric materials or other polymeric materials selectively degradable in the lower region of the GI tract for instance colon [6]. Optimally, the effectiveness of drug therapy can be improved by building

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loading and a maintenance doses into the pellet dosage form [7–9]. Consequently, less frequent administration and an optimal therapeutic plasma drug concentration are expected to improve patient compliance.

Nifedipine is a poorly water-soluble drug and relatively difficult to develop [10–12]. A pellet dosage form design containing loading and maintenance doses would be valuable to improve the therapeutic effectiveness of nifedipine. However, the poor solubility of nifedipine itself further complicates the optimal design of multiple layers for nifedipine. In a previous study, a one-step method of spray-coating a solid dispersion solution onto nupareil seeds was reported to form a solid dispersion of nifedipine in situ on the pellets [13]. It was concluded that it was easier to prepare a solid dispersion with this spray coating method than with the traditional solvent evaporation method, and fewer processing steps were involved. In this study, a multiple-layer design of controlled release pellets for nifedipine was developed using pluronic F-68 as solubility enhancer and its influence on dissolution was characterized. The same technology for preparing a solid dispersion for nifedipine was applied to minimize complications during the preparation of a multiple layer design of a pellet solid dosage form. The influence of ratios of nifedipine in the inner layer to that in the outer layer, the ratios of pluronic F-68 to nifedipine in the solid dispersion, and the thickness of the control membrane on drug release patterns were investigated.

2. Materials and methods

Nifedipine was obtained from Sunlite Chemical Industry Co. Ltd. (Japan). Sugar spheres (1.00–1.40 mm) were from Wei-Ming Pharmaceuticals, MFG. Co. Ltd. (Taipei, Taiwan). Tween 80 and acetone were supplied by Riedel-de Haën (Germany). Pluronic F-68 (Polyoxyethylene–Polyoxypropylene copolymer, 80:20) was purchased from BASF Wyandotte Co. (Germany). Surelease® was from Colorcorn (UK). Triethylamine, sodium hydroxide, phosphoric acid (E-Merck, Germany), acetonitrile, ethylacetate (BDH Laboratory Supplies, Poole, UK) and butamben (Sigma Chemical, Co. St. Louis, MO, USA) were purchased. All solvents were HPLC grade, and all chemicals were AR grade. Coracten Spansule 20 mg capsules (Lot no. 134252) obtained from the innovative SmithKline & Beecham Pharma (Munchen, Germany) were used for the reference product. Cardilate S.R. 20 mg capsules (Lot no. NFP2002) made by B&F Pharmaceutical and Chemical Co (Taoyuan, Taiwan) based on formulation N6 were used as the test product.

2.1. Preparation of multiple-layer pellets

Formulation of nifedipine controlled-release pellet for multiple-layer design is listed in Table 1. The inner layer of multiple-layer pellets contained nifedipine with the addition of pluronic F68 to enhance hydrophilicity. Nifedipine with a fixed ratio (10:1) of pluronic F68 was dissolved in a solvent

Table 1
Multiple-layered design and formulation of nifedipine controlled-release pellets

Rx	N-1	N-2	N-3	N-4	N-5	N-6	N-7	N-8
			Inner	layer				
Nifedipine	1.5[a]	1.5	1.5	1.5	1.5	1.0	1.0	1.0
			Middle	layer				
EC (%)[b]	5.0	5.0	5.0	5.0	5.0	5.0	7.5	10.0
			Outer	layer				
Nifedipine	0.5[a]	1.0	1.0	1.0	1.0	1.0	1.0	1.0
N:P Ratio[c]	2/1	2/1	1/2	1/3	1/1	1/1	1/1	1/1

[a] Ratio of nifedipine in the inner layer to that in the outer layer.
[b] Percent of ethylcellulose relative to nifedipine in the inner layer.
[c] Ratio of nifedipine in the outer layer to pluronic F68.

mixture of acetone/alcohol/water (2:1:1, v/v). One kilogram of sugar spheres was charged into the product container of a fluidized-bed granulator and coater (Glatt Air Techniques, model GPCG-1) with a rotor insert. After appropriate machine adjustments and when the outlet temperature reached 35°C, the acetone/alcohol/water solution containing both nifedipine and pluronic F68 was tangentially sprayed onto the tumbling pellets from an atomizing nozzle (1 mm) attached to a peristaltic pump. During processing, the spray rate and inlet air temperature were adjusted to maintain the outlet temperature between 25 and 27°C. When the spraying was finished, the pellets were dried at 40°C for 30 min. These pellets were kept in the container until further processing.

The middle layer of the multiple-layer pellets was a rate-controlling membrane, which made use of 25% w/w ethylcellulose (surelease) as an aqueous dispersion form. During processing, the coating solution was tangentially sprayed onto the tumbling pellets at a spray rate of about 6–7 g/min. The outlet temperature was maintained in the range from 27 to 29°C by adjusting the inlet temperature and spray rate. When the spraying was finished, coated pellets were dried at 40°C for 5–10 min and then discharged for further drying into a hot air oven at 60°C for 12 h.

The outer layer of the multiple-layer pellets was an immediate-release portion of nifedipine solubilized with various ratios of pluronic F68. As above, nifedipine and various ratios of pluronic F68 were dissolved in a solvent mixture containing acetone, alcohol, and water. The operation conditions were the same as those described for the preparation of the inner layer. Finally, pellet products were discharged and dried at 40–45°C until the moisture content of the pellets reached an appropriate level (less than 1%). All operations were protected from light exposure.

2.2. Dissolution studies

The dissolution profiles of nifedipine from pellet samples (an amount equivalent to 20 mg of nifedipine) were determined at a temperature of 37±0.5°C and a stirring rate of 50 rpm using the paddle method (USP XXIII) in 900 ml of simulated gastric fluid (pH 1.2, without enzyme) containing 1% Tween 80. Under dark conditions, samples were automatically measured at predetermined intervals to measure the UV (Jasco model 7800, Japan) absorbance at a wavelength of 350 nm. An average of five replicates was reported for each time point.

2.3. Bioavailability studies

2.3.1. Instrumentation

A high-performance liquid chromatographic system equipped with a pump (Model PU-975, Jasco), an 851-AS auto-sampler system, and a CHEMLAB DATA STATION (Scientific Information Service Corporation, Taipei, Taiwan). A 25 cm×4.6 mm (I.D.) reversed-phase Microsorb-MV C_{18} column (Rainin Instrument Company, Inc., USA) with a particle size of 5 μm was employed. The isocratic mobile phase consisted of water, methanol, acetic acid, and triethylamine in the proportion of 40:60:1:0.03 (v/v). The flow rate was set at 1.0 ml/min. The eluent was detected with a Jasco UV detector at a wavelength of 340 nm. The peak height ratio (PHR) of nifedipine to the internal standard (i.e. butamben) was used to calculate the calibration curve and the nifedipine concentration in plasma.

2.3.2. Internal standard solution and sample preparation

Internal standard, butamben, was freshly prepared at 80.0 μg/ml in methanol. All frozen plasma samples and blanks were thawed at room temperature in the dark prior to analysis. The calibration curves were prepared for each assay days run by transferring 100 ul of the calibration solutions containing 5.0–500 ng of nifedipine in a tube containing 1 ml of blank plasma. Similarly, 1 ml of plasma was taken from the thawed plasma sampled from human subjects that had received nifedipine. The sample plasma or standard plasma was mixed with 50 μl of the butamben solution and vortexed for several seconds. The pH of the mixture was adjusted to 12 with 0.1 N NaOH and vortexed thoroughly. Six milliliters of a solvent mixture of MTBE and isooctane (75:25 v/v) was added for extraction. After being vortexed, it was centrifuged (Universal 16R,

Zentrifugen, Hettich, Germany) at speed of 3000 rpm for 5 min. The supernatant (the organic phase) was transferred to another clean glass tube and was evaporated with nitrogen gas at room temperature until dryness. The extract was reconstituted with 200 μl of the mobile phase, and it was vortexed again for several seconds until completely dissolved. The mixture was then centrifuged at 10 000 rpm for 15 min, and 100 μl was injected onto HPLC for analysis.

2.3.3. Volunteers

The protocol of the bioavailability study was approved by the Institutional Review Board of Taipei Medical College Hospital. Twelve healthy Chinese adult males (age: 21–26 years, average 22.7±2.2 years; mean body weight 69.1±9.4 kg) participated in this study after medical screening through a series of examinations including a physical examination, biochemistry (blood and urine) tests and chest X-ray (as necessary). Each volunteer was informed by a doctor who explained of the entire study, the reported possible side effects of nifedipine, and volunteers' privileges which were presented in a consent form. Consent forms were obtained from all volunteers when they decided to participate in this study. During the study, volunteers were advised not to take any medication (for at least 1 week) or caffeine-containing beverages or food (24 h before the study). The circumstances leading to the withdrawal were recorded and documented. All adverse reactions were recorded in the 'Case Report'. Any serious effect resulting in withdrawal from the study was documented and the investigators were notified immediately.

2.3.4. Study design

A randomized, multiple-dose, two-treatment, two-period, two-sequence crossover study design was conducted. A total of 12 healthy subjects was arranged to receive, on separate occasions, multiple oral doses of Coracten (reference product) or Cardilate SR (test product) in 20 mg pellet capsules according to a randomized plan. The reference or test product was orally administered to each volunteer in a fasting state on the first day, and followed meals on dosing days 2 through 4 of each treatment period. Dosage on the fifth day was given in a fasting state as well. The drug was administered with 200 ml water. On the study day, volunteers were under fasting status 12 h before oral administration of study drugs and 4 h after medication. Water was freely supplied during the study. The washout period between the two treatments exceeded 10 times the drug's elimination half-life.

Heparinized venous blood samples, 5–10 ml, were collected by means of an indwelling venous cannula of the cubital vein on profile days according to the predetermined time schedule. The schedule included a blank sample just prior to dosing and then at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 h after the first day and the fifth days dosing. On dosing days 2 through 4 of each treatment, blood samples were collected at 12 and 24 h. Any deviation from the stated sampling time was recorded on the form. Plasma was separated immediately by centrifugation at 3000 rpm in 10 min, and then was transferred to suitably labeled tubes and stored at −20°C until assay.

2.3.5. Pharmacokinetic data analysis

The following parameters were assessed for the period of 0–12 h for all treatments: The area under the plasma concentration curves from time zero to the last measurable nifedipine sample time and to infinity ($AUC_{0-last,ss}$ and $AUC_{0-\infty,ss}$) at steady state; percent peak-trough fluctuation of plasma concentration (%PTF(τ); maximum concentration at steady state ($C_{max,ss}$); minimum plasma concentration at steady state ($C_{min,ss}$); time to maximum concentration ($T_{max,ss}$) after steady state; and relative bioavailability and relative total clearance for the 12 h profile period (CL/F).

All pharmacokinetic variables were calculated by non-compartmental methods. C_{max}, C_{min}, $C_{max,ss}$, and $C_{min,ss}$ were read directly from the data, while T_{peak} and $T_{peak,ss}$ were determined at the respective blood-sampling times corresponding to C_{max} and $C_{max,ss}$. AUC_{0-last} and $AUC_{0-last,ss}$ were calculated according to the linear trapezoidal rule, and $CL/F = Dose/(K^{*}_{el}AUC_{0-last,ss})$. The variable %PTF($\tau$) was calculated as $100^{*}[C_{max,ss} - C_{min,ss}]/C_{av}$, where $C_{av} = AUC_{0-last,ss/\tau}$, and τ is the dosing interval in question.

2.3.6. Statistical analysis

Two-way ANOVA was performed with the SAS General Linear Models Procedure at a significance level of 0.05. The test and reference treatments of each study were compared with respect to relevant pharmacokinetic variables using an analysis of variance of the subject, treatment, and period effects with raw data or after a logarithmic transformation of the data. Point estimates and 90% confidence intervals for the ''test/reference'' mean ratios of these raw data or ''log(test)−log(reference)'' mean difference of logarithmically-transformed variables were calculated. Whenever there was no statistically significant difference, statistical power to detect at least a 20% difference between products was checked using the following equation where n is the number of subjects, MSE is the mean square error of the error term with the degrees of freedom, df. MSE and df were obtained from ANOVA table of SAS output. The d is 20% of the least square mean from the reference. Bioequivalence of the test treatment to the reference treatment was assessed on the basis of the confidence intervals for the ''test/reference'' mean ratios of these raw variables or ''log(test)−log(reference)'' mean difference of logarithmically-transformed variables in relation to the bioequivalence range of 80%–120% for the raw data and 80%–125% for the logarithmically transformed data.

$$t_{\beta,\mathrm{df}} = \frac{\delta}{\sqrt{\mathrm{MSE}\cdot\frac{2}{n}}} - t_{0.975,\mathrm{df}}$$

$$\text{Power} = 1 - \beta$$

3. Results and discussion

The use of a nonionic surfactant to improve the solubility of nifedipine in simulated gastric acid medium is demonstrated in Fig. 1. With an increasing ratio of pluronic F-68 to nifedipine, the dissolution rate of nifedipine was gradually promoted and the extent of release was enhanced as well. DSC thermograms shown in Fig. 2 illustrate the gradual disappearance or broadening of the nifedipine melting peak with the presence of pluronic F-68. This implies that, depending on the ratio of pluronic F-68 to nifedipine, partial or complete solution of nifedipine in the pluronic F-68 melt during melting is possible. This explains the fact that the dissolution of nifedipine in the presence of pluronic F-68 gradually increased with an increasing ratio of pluronic F-68 to nifedipine. Enhancement of hydrophilicity of

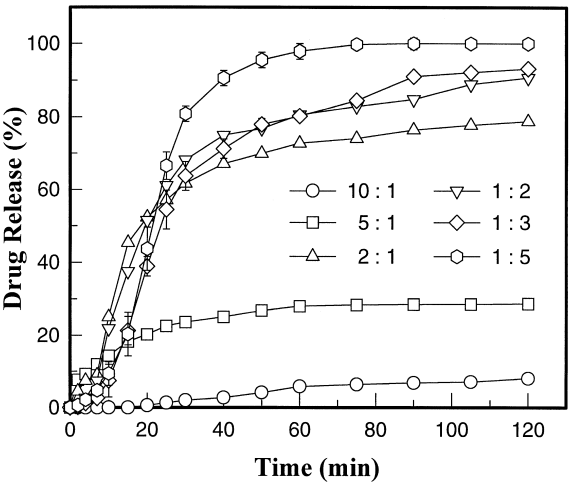

Fig. 1. Dissolution profiles of nifedipine solubilized with various amount of pluronic F-68 from pellets. (10:1 represent nifedipine/pluronic F-68 ratio).

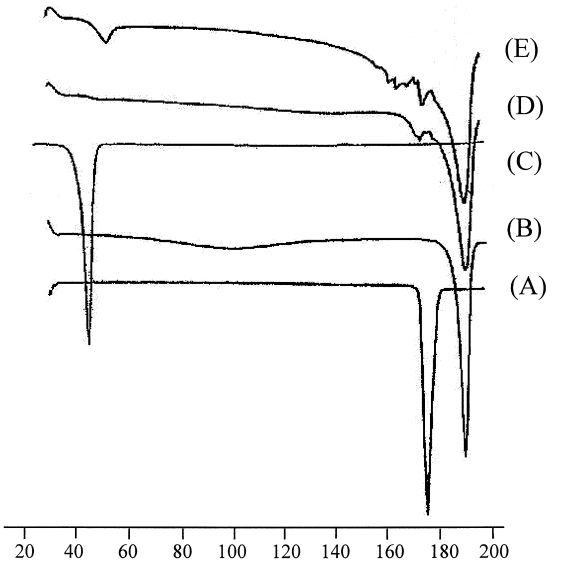

Fig. 2. DSC thermograms for nifedipine without or with the presence of pluronic F-68. (A) nifedipine; (B) sugar spheres; (C) pluronic F-68; (D) nifedipine/pluronic F-68=10:1; (E) nifedipine/pluronic F-68=2:1.

nifedipine with the help of pluronic F-68 is another possible reason for the enhancement of the drug dissolution rate.

Pluronic F-68, therefore, was selected for use in improving nifedipine dissolution in this multiple-layer design. The release profile of nifedipine from a commercial product, Coracten, was examined for reference. Fig. 3 displays the release of nifedipine from three formulations with different nifedipine ratios of the inner layer to the outer layer, with a fixed ratio of pluronic F-68 to nifedipine in both layers. A comparison between N1 and N2 demonstrates that the decrease of the nifedipine ratio in the inner layer enhances the initial rate of drug release. A comparison between N2 and N5 illustrates that the increase of the ratio of pluronic F-68 to nifedipine in the outer layer was further able to promote the initial release of nifedipine. The latter shows a release profile close to that for Coracten.

With a fixed nifedipine ratio of 1.5 between the inner layer and the outer layer, the influence of the ratio of pluronic F-68 to nifedipine in the outer layer on the initial release of nifedipine was examined, and the results are displayed in Fig. 4. As expected, increasing the ratio of pluronic F-68 to nifedipine in the outer layer significantly increased the initial release rate of nifedipine. This is due to the enhancement of hydrophilicity or solubility of nifedipine in the presence of pluronic F-68. However, with this nifedipine ratio of 1.5, the initial release rate was faster but the latter release rate was slower compared to those for the release of nifedipine from Coracten.

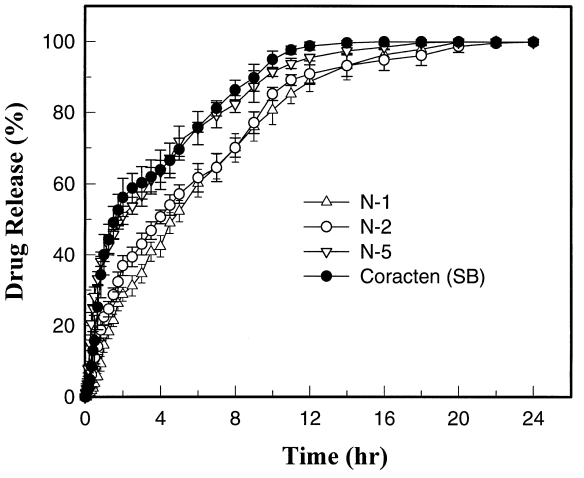

Fig. 3. Release profiles of nifedipine from multiple-layer pellets coated with various ratios of nifedipine in the inner and the outer layers using paddle method at a stirring rate of 50 rpm in simulated gastric fluid (pH 1.2). △, N-1 (3:1); ○, N-2 (1.5:1); ▽, N-5 (1:1); ●, Coracten (SB) ($n=5$).

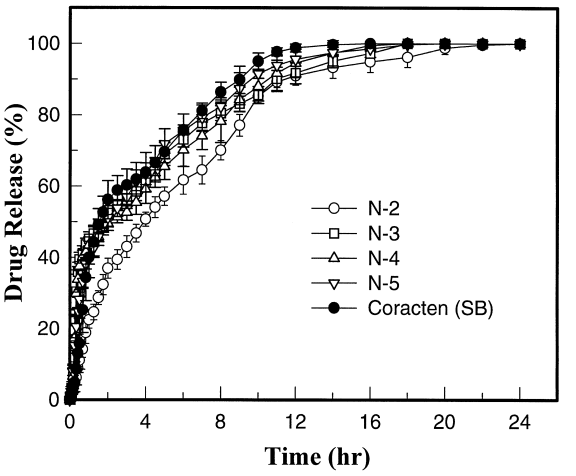

Fig. 4. Release profiles of nifedipine from multiple-layer pellets coated with various ratios (N:P) of nifedipine and pluronic F68 at the outer layer using paddle method at a stirring rate of 50 rpm in simulated gastric fluid (pH 1.2). ○, N-2 (2:1); □, N-3 (1:2); △, N-4 (1:3); ▽, N-5 (1:1); ●, Coracten (SB) ($n=5$).

By increasing the nifedipine ratio of the inner layer to the outer layer to 1:1, the influence of the thickness of the controlling membrane was investigated. The thickness of the controlling membrane was manipulated by coating with different amounts of Surelease. Fig. 5 illustrates that increasing the coating percentage of the total weight decreases the release rate of nifedipine from the inner layer. Fick's first law indicates that the thickness of the controlling membrane decreases the concentration gradient between both sides of the controlling membrane. Because of this, the decrease of the release rate across the membrane with increasing thickness of the controlling membrane is expected. The closeness of the initial portion of the release profiles to that of Coracten was further demonstrated by these formulations with a nifedipine ratio of 1:1 between the inner layer and the outer layer.

The assay method was validated before implementation. The retention time for nifedipine and

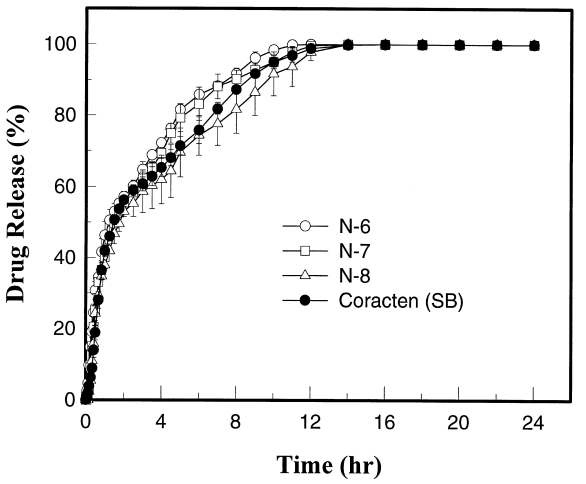

Fig. 5. Release profiles of nifedipine from multiple-layer pellets coated with different concentrations (%) of ethylcellulose using paddle method at a stirring rate of 50 rpm in simulated gastric fluid (pH 1.2). ○, N-6 (5.0%); □, N-7 (7.5%); △, N-8 (10%); ●, Coracten (SB) ($n=5$).

butamben (internal standard) ranged from 8 to 9 min and from 10 to 12 min, respectively. A good linearity ($r^2=0.999$) within the concentration range of 5.0 to 500 ng/ml was found. The limit of quantitation was 5.0 ng/ml. The coefficients of variation for accuracy and precision of the intraday assay ($n=3$) for the calibration curve in the concentration range examined (5.0, 10.0, 20.0, 40.0, 60.0, 80.0, 100, 200, and 500 ng/ml) ranged from 0.99 to 11.45% and 1.41 to 7.04%, respectively, whereas those for interday assays ($n=5$) ranged from 0.22 to 11.467% and from 0.57 to 10.53%, respectively. The accuracies for the intraday and interday assays were found to be acceptable with mean relative errors of less than 15% for the nominal concentrations.

Formulation 6 (N6) was selected to test for bioequivalence to Coracten. Twelve volunteers (mean body weight: 61±4 kg and mean age: 25±5 years) participated in this study. The result of comparisons between the test and the reference products revealed that there was no significant difference ($P>0.05$) in bioavailability as indicated by pharmacokinetic parameters using the multiplicative model (i.e., natural log-transformed model). The 90% confidence intervals of the mean difference for steady state ranged from 96.31 to 100.06%, 96.14 to 100.83%, 98.38 to 115.33%, 78.29 to 101.07%, 88.53 to 102.48%, and 103.66 to 116.83% for $AUC_{0-last,ss}$, $AUC_{0-\infty,ss}$, $C_{max,ss}$, $C_{min,ss}$, $C_{ave,ss}$, and fluctuation, respectively. The 90% confidence intervals of the mean difference for the initial dose ranged from 95.87 to 98.06%, 95.66 to 97.61%, 98.81 to 109.53%, 56.35 to 78.62%, 86.32 to 92.47%, and 107.67 to 116.76% for AUC_{0-last}, $AUC_{0-\infty}$, C_{max}, C_{min}, C_{ave}, and fluctuation respectively. All 90% confidence intervals of mean ratios fell within the range of 80–125%, except that C_{min} fell outside the range, and the lower limit of $C_{min,ss}$, was a little smaller. The same results of statistical analysis were obtained using the two one-sided *t*-test methods. The values of statistical power to compare mean ratios of all pharmacokinetic parameters between the two products were either equal to or close to unity, which complies with the specification that the power has to be more than 0.8. No statistical difference was found for K_{el}, $T_{1/2}$, V_d/F, or T_{peak}.

The mean $[(1-AUC_{0-last})/AUC_{0-\infty})]*100$ was less than 20% for both products, which indicates that multiple-dose administration resulted in some extent of accumulation of nifedipine. But at the last sampling time, nifedipine plasma concentrations for most volunteers appeared to be below or close to the limit of quantitation. Fig. 6 displays the similar bioavailability with the mean and one standard deviation of

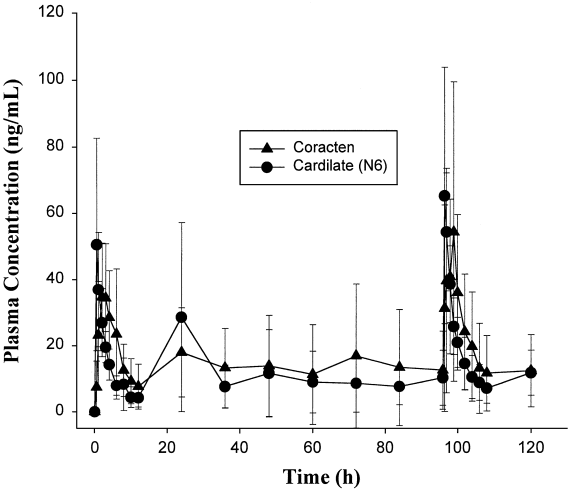

Fig. 6. Nifedipine plasma concentration–time profiles in twelve volunteers for the test and reference products.

nifedipine plasma concentration–time profile in 12 volunteers for the test and the reference products.

4. Conclusion

In conclusion, the use of pluronic F-68 to enhance nifedipine dissolution is applicable to a multiple-layer design of controlled release pellets. Proper adjustment of the nifedipine ratio between the inner layer and the outer layer and the ratio of pluronic F-68 to nifedipine in the outer layer can produce a release profile comparable with clinical needs. The pharmacokinetic bioequivalence between the test product and Coracten was found with a multiple-dose oral administration of 20 mg in 12 healthy, normal Chinese male volunteers.

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