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# In Vivo Evaluation of Two Novel Controlled-Release Nitrendipine Formulations

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**ABSTRACT** The objective of this work is to assess two novel controlled-release nitrendipine formulations, i.e., sustained-release nitrendipine microspheres having solid dispersion structure and a novel pH-dependent gradient-release delivery system for nitrendipine in healthy male volunteers, which were prepared by current authors. Domestic commercial nitrendipine tablets and Baypress™ nitrendipine tablets were employed as reference formulations. In a randomized, single-dose, fasting-state, crossover study design with a 1-week washout period, each subject received a 40-mg nitrendipine formulation. Plasma samples were collected over a 25-hour period after oral administration and were analyzed by a validated method using high performance liquid chromatography with ultraviolet detection. Pharmacokinetic parameters were determined using a noncompartmental analysis. The results provided evidence that the time to maximum plasma concentration of two novel controlled-release nitrendipine formulations were statistically significant prolonged in comparison with that of Baypress™ nitrendipine tablets. The relative bioavailabilities of test formulations were intensively improved compared with the domestic nitrendipine tablets, while the ratio is in a range of 80–120% in comparison with Baypress™ nitrendipine tablets. It is concluded that the two types of controlled-release systems are feasible for improving the dissolution rate of nitrendipine and obtaining a long-acting in vivo as well.

**KEYWORDS** Nitrendipine, Pharmacokinetics, Relative bioavailability, Controlled-release formulation

## INTRODUCTION

One of the main goals in the pharmaceutical technological field is to improve the dissolution rate of poorly water-soluble drugs, which directly affects the in vivo uptake, and to prolong the therapeutic period of active drug. In our previous research, two types of controlled-release formulations of nitrendipine, a dihydropyridines calcium channel antagonist used as a poorly water-soluble model drug, were manufactured using different polymers by a combination of solid dispersion technique and quasi-emulsion solvent

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**TABLE 1** Synoptic Description of the Compositions of Two Test Formulations

| Formulations | Compositions | Amount (g) |
|---|---|---|
| C | Nitrendipine | 1.0 |
| | Aerosil | 4.0 |
| | Hydroxypropylmethylcellulose phthalate | 2.5 |
| | Eudragit RS PO | 0.75 |
| | Ethylcellulose | 0.3 |
| D | Nitrendipine | 1.5 |
| | Eudragit E-100 | 1.5 |
| | Aerosil | 1.5 |
| | Hydroxypropylmethylcellulose phthalate | 1.5 |
| | Hydroxypropylmethylcellulose acetate succinate | 2.0 |

diffusion method. The manufacturing process, in vitro evaluation, and relative bioavailability test in healthy dogs have been reported elsewhere (Cui et al., 2003; Yang et al., 2004a, 2004b). The results of the pharmacokinetic studies in healthy dogs indicate that nitrendipine in these two preparations have a relatively high absorption rate.

However, due to the fact that the formulations will be ultimately administered in human beings, pharmacokinetic studies and clinical trials in humans are the most reliable and essential methods for evaluating the products instead of the test in animals. In addition, because of many differences between humans and animals in anatomy, physiology, and other relational parameters such as pharmacokinetics and metabolizing, it is hard to obtain reliable estimates of the pharmacokinetic behaviors of the drug in humans using only test results from animals. So, a guideline developed by the American Association of Pharmaceutical Scientists in 1987 suggests that bioavailability tests of products in humans is necessary in the evaluation of controlled-release pharmaceutical dosage forms, unless the drug is highly toxic or the testee would be in danger during the test (Skelly et al., 1987). Until now, many pharmacokinetic studies relevant for nitrendipine in humans have been reported, which verified the safety and low toxicity of the drug in human beings (Baksi & Edwards, 1989; Lobo et al., 1987; Mikus et al., 1991). As a pilot study for future clinical trials, the pharmacokinetic behaviors of two types of self-manufactured controlled-release nitrendipine formulations were investigated in four healthy male volunteers in this paper. The pharmacokinetic parameters as well as relative bioavailability were analyzed in comparison with domestic commercial nitrendipine tablets and Baypress™ nitrendipine tablets as reference formulations.

# MATERIALS AND METHODS

## Chemicals and Reagents

Nitrendipine was obtained form Nanjing Pharmaceutical Factory (China); nimodipine was obtained from Shangdong Xinhua Pharmaceutical Factory (China); Domestic nitrendipine conventional tablets (Formulation A, Tianjin the Pacific Pharmaceutical Factory, China) and Baypress™ nitrendipine tablets (Formulation B, Bayer Pharm. Co., Germany) were employed as the reference formulations in this pharmacokinetic test. The test formulations, i.e., sustained-release nitrendipine microspheres having solid dispersion structure (Formulation C) (Cui et al., 2003) and a novel pH-dependent gradient-release delivery system for nitrendipine (Formulation D) (Yang et al., 2004a, 2004b) were prepared in the Department of Pharmaceutics, Shenyang Pharmaceutical University, China. A synoptic description of the compositions of two test formulations are listed in Table 1. Methanol, tetrahydrofuran, ethyl ether, and hexane were of chromatographic grade and other chemicals were of analytical grade.

## Subjects

Four healthy male volunteers ($21 \pm 2.2$) with a mean body weight of $63.9 \pm 6.5$ kg were enrolled in the study after providing written informed consent. Subjects were free to leave the experiment at any time. They were found to be in good health by physical

**TABLE 2** Plasma Concentration of Nitrendipine After a Single Oral Administration of Formulations A and B to Four Volunteers ($ng \cdot mL^{-1}$)

| | Formulation A | | | | Formulation B | | | |
|---|---|---|---|---|---|---|---|---|
| Time/h | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.3 | 2.0 | 1.9 | 3.8 | 4.4 | 4.9 | 3.1 | n.d. | 2.9 |
| 0.7 | 3.5 | 2.7 | 4.6 | 12.5 | 8.0 | 5.9 | 2.4 | 8.6 |
| 1.0 | 3.4 | 3.9 | 16.3 | 19.1 | 14.3 | 7.6 | 3.9 | 10.6 |
| 1.5 | 3.6 | 5.3 | 20.0 | 19.9 | 20.6 | 7.5 | 6.4 | 9.9 |
| 2.0 | 5.8 | 4.0 | 24.7 | 14.1 | — | 7.3 | 9.1 | 30.7 |
| 3.0 | 6.1 | 5.4 | 22.7 | — | 18.1 | 6.0 | 70.4 | 30.1 |
| 4.0 | 4.9 | 20.7 | 35.1 | 13.5 | 11.9 | 4.6 | 59.9 | 25.7 |
| 6.0 | 1.8 | 3.0 | 12.7 | 7.6 | 5.0 | 3.1 | 25.3 | 16.6 |
| 8.0 | n.d. | 1.1 | 12.3 | 6.0 | 3.9 | 1.4 | 14.4 | 12.8 |
| 10.0 | n.d. | n.d. | 6.6 | 4.9 | 2.7 | 1.1 | 10.1 | 6.9 |
| 12.0 | n.d. | n.d. | 6.2 | 2.4 | 2.9 | n.d. | 7.0 | 4.7 |
| 15.0 | n.d. | n.d. | 4.1 | 1.8 | n.d. | n.d. | 5.1 | 2.1 |
| 25.0 | n.d. | n.d. | 2.3 | 1.1 | n.d. | n.d. | n.d. | n.d. |

Note: n.d., Not determined; —, Sample failed.

examination. They received no drug other than the trial medication 4-week prior, during, and 1 week after the study period. All of them stated they drank no alcohol, drank only nonstimulant drinks, and did not consume tobacco; and alcohol intake was prohibited from 1 week before to 1 week after the trial period. The protocol was approved by the Hospital's Ethical Committee and the study conducted according to the recommendations of the World Medical Association Declaration of Helsinki.

## Study Design and Procedures

The four subjects included in the trial received conventional domestic nitrendipine tablets, Baypress™ nitrendipine tablets, and two types of self-manufactured, controlled-release formulations of nitrendipine according to a randomized four-way crossover design. The dose of nitrendipine administered to the subjects was 40 mg. A washout period of 1 week separated each treatment. Following an overnight fast, subjects received the medication at 8:00 a.m. They were given a standard meal 4 hours later. Heparinized blood samples (5 mL) were obtained from a forearm vein before oral administration and at intervals after oral administration. The plasma was separated by centrifugation and frozen at −20°C until the time of assay.

## Analysis of Nitrendipine in Plasma

Plasma samples were analyzed for nitrendipine concentration using high performance liquid chromatography (HPLC) with UV detection at a wavelength of 238 nm (Janis et al., 1983). The internal standard nimodipine (40 ng, in 20 μL methanol) was mixed with plasma sample (1 mL) and 0.4 mL 1.0 N NaOH solution. The mixture was extracted with 5 mL hexane ethyl ether (1:1 v/v) and centrifuged 3000 rpm for 5 minutes. The hexane ethyl ether phase was separated and evaporated to dryness under nitrogen. The residue on the internal wall of the tube was washed with 0.5 mL hexane ethyl ether (1:1 v/v) and evaporated to dryness under nitrogen again. The resultant residue was dissolved in a 40-μL mobile phase of HPLC. The HPLC mobile phase was a mixture of methanol-tetrahydrofuran-water (47:15:38 v/v). An aliquot (20 μL) of the reconstituted residue was injected on the 5-μm Spherosorb ODS (200 mm × 4.6 mm) column (Beijing Dikma Co., China). The flow rate and the temperature of the column were fixed at 0.5 mL/min and 35°C, respectively.

In the current experimental conditions the lowest limit of quantitation of nitrendipine in plasma was 1.0 ng/mL. Standard curves were linear from 1 to 80 ng/mL of nitrendipine. Accuracy was verified with values of interassay coefficients of variation and

**TABLE 3** Plasma Concentration of Nitrendipine After a Single Oral Administration of Formulations C and D to Four Volunteers ($ng \cdot mL^{-1}$)

| | Formulation C | | | | | Formulation D | | | |
|---|---|---|---|---|---|---|---|---|---|
| Time/h | 1 | 2 | 3 | 4 | Time/h | 1 | 2 | 3 | 4 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | n.d. | n.d. | 1.5 | 22.9 | 0.3 | 1.0 | 1.5 | 3.9 | n.d. |
| 1.0 | 9.3 | n.d. | 3.5 | — | 0.7 | 4.0 | 3.0 | 5.8 | 8.8 |
| 1.5 | 4.5 | 4.0 | 10.9 | 13.4 | 1.0 | 2.1 | 4.7 | 7.6 | 9.4 |
| 2.0 | 8.5 | 1.7 | 17.4 | 1.7 | 1.5 | 3.9 | 6.9 | 11.1 | 7.0 |
| 3.0 | — | 4.2 | 18.9 | 4.5 | 2.0 | 10.2 | 8.4 | 35.8 | 6.5 |
| 4.0 | 25.4 | 4.9 | 17.6 | 4.9 | 3.0 | 15.8 | 7.7 | 42.0 | 6.1 |
| 5.0 | 14.5 | 7.4 | 13.1 | 12.4 | 4.0 | 19.4 | 7.3 | 49.3 | 17.5 |
| 6.0 | 10.0 | 5.5 | 9.7 | 5.1 | 5.0 | 12.8 | 3.7 | 32.2 | 34.9 |
| 8.0 | 2.8 | 4.1 | 5.8 | 25.5 | 6.0 | 7.1 | 2.9 | 26.5 | 25.7 |
| 10.0 | n.d. | 2.2 | 4.6 | 14.8 | 8.0 | 4.2 | 1.6 | 10.0 | 20.9 |
| 12.0 | n.d. | 2.2 | 2.5 | 7.7 | 10.0 | 2.8 | 1.4 | 9.1 | 9.0 |
| 15.0 | n.d. | 1.3 | 2.7 | 1.3 | 12.0 | 2.4 | n.d. | 5.4 | 5.6 |
| 25.0 | n.d. | n.d. | n.d. | n.d. | 15.0 | 1.3 | n.d. | 3.9 | 4.6 |
| | | | | | 25.0 | 1.4 | n.d. | 2.8 | 2.1 |

Note: n.d., Not determined; —, Sample failed.

relative errors between 2.87% and 9.50% for whole range of concentrations assayed.

## Pharmacokinetic Analysis

A noncompartmental pharmacokinetic method was employed to determine the pharmacokinetic parameters of nitrendipine. The area under the plasma concentration-time curve (AUC) from the time of drug administration up to 25 h after administration was calculated by the trapezoidal rule, and AUC from 25 h to infinity was obtained by extrapolation. The maximum plasma concentration ($C_{max}$) and time of $C_{max}$ ($T_{max}$) were observed directly from the plasma concentration-time curve. Elimination rate constants ($k_e$) and half-life of elimination ($t_{1/2}$) were calculated from the slope of a linear regression equation, which was derived from the regression of the last four points of plasma concentration-time curve. The relative bioavailability of test and reference formulations was evaluated by a comparison of the $AUC_{0-25}$ of the respective formulation.

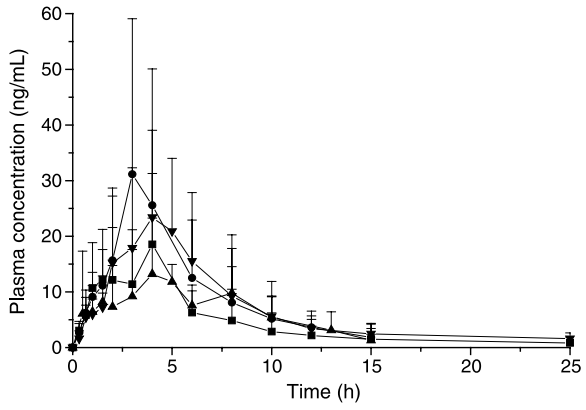


**FIGURE 1** Mean Plasma Concentration-Time Curves of Nitrendipine After Oral Administration of Reference and Test Formulations to Four Healthy Volunteers. Formulation A (■); B (●); C (▲); D (▼).

## RESULTS AND DISCUSSION

Nitrendipine was well tolerated by the four healthy volunteers. No volunteer withdrew and no obviously adverse event was found during the test. The plasma concentration data of nitrendipine after oral administration of four formulations to four healthy volunteers are listed in Tables 2 and 3. Mean plasma concentration-time curves of four nitrendipine formulations are shown in Fig. 1. Pharmacokinetic parameters of nitrendipine are summarized in Table 4. The pharmacokinetic parameters derived from volunteers showed a relatively good correlation with that of healthy dogs (Cui et al., 2003; Yang et al., 2004a). The statistically significant prolonged $t_{max}$ of test formulations are shown in Table 4 compared with that of Baypress™ nitrendipine tablets (Formulation B). In Formulation C, even though nitrendipine was molecularly dispersed by HP-55, the release rate of drug was still effectively controlled due to the retardation function

**TABLE 4** Pharmacokinetic Parameters of Nitrendipine After Oral Administration of Four Formulations to Four Healthy Volunteers

| Pharmacokinetic parameters | Formulation A | Formulation B | Formulation C | Formulation D |
|---|---|---|---|---|
| $k_e$ ($h^{-1}$) | 0.38±0.27 | 0.30±0.11 | 0.29±0.18 | 0.18±0.06 |
| $t_{1/2}$ (h) | 2.65±1.74 | 2.53±0.73 | 3.33±2.09 | 4.40±2.33 |
| $C_{max}$ ($ng \cdot mL^{-1}$) | 20.4±11.8 | 32.3±27.1 | 19.3±8.5 | 28.0±17.9 |
| $T_{max}$ (h) | 3.1±1.2 | 1.9±0.7 | 5.0±2.2[a,b] | 3.8±1.2[a,b] |
| $AUC_{0-t}$ ($ng \cdot h \cdot mL^{-1}$) | 107.74±90.70 | 165.25±129.24 | 103.58±46.86 | 166.46±114.49 |
| $AUC_{0-\infty}$ ($ng \cdot h \cdot mL^{-1}$) | 114.27±96.39 | 173.78±132.18 | 113.87±51.02 | 178.98±120.14 |

[a]Compared with formulation B.
[b]$p \leq 0.05$.

of ethyl cellulose and Eudragit RS formulated. Figure 2 shows the drug dissolution rate from Formulation C in different pH dissolution mediums. The dissolution test condition was the same as described previously (Cui et al., 2003), except that Tween-80 was added in different dissolution mediums to maintain the sink condition for the drug. Because HP-55 is a pH-sensitive polymer, and dissolves in solution of pH above 5.5, the dissolution rate of drug from Formulation C increased with an increase in pH of dissolution medium. However, all the dissolution curves showed evident sustained-release characteristics due to the function of retardant agents in formulations.

Formulation D was made up of three kinds of pH-dependent microspheres, and the polymers employed were acrylic resins Eudragit E-100 (EuE-100), hydroxypropylmethylcellulose phthalate (HP-55), and hydroxypropylmethylcellulose acetate succinate (AS-H). These polymers dissolve under acid conditions, pH values of $\geq 5.5$ and $\geq 6.5$, respectively, and nitrendipine was correspondingly released in the stomach, duodenum, and lower segment of the small intestine. The dissolution curves of drug from Formulation D have been described in detail in our previous publications (Yang et al., 2004a, 2004b), in which the dissolution behaviors of Formulation D showed obvious gradient-release characteristics under simulated gastrointestinal pH conditions. Since drug release persists throughout the whole gastrointestinal tract, this results in sustained transport of the drug and a prolonging $t_{max}$ in vivo. At the same time, because part of the drug was released rapidly with the dissolution of EuE-100 microspheres in the stomach, time to $C_{max}$ of Formulation D was shorter than that of Formulation C. However, conventional domestic nitrendipine tablets (Formulation A) also showed a lagged $t_{max}$ in comparison with Formulation B. This could be attributed to their different dissolution rates of drug from the formulations (Yang et al., 2004a; Zhu et al., 1990).

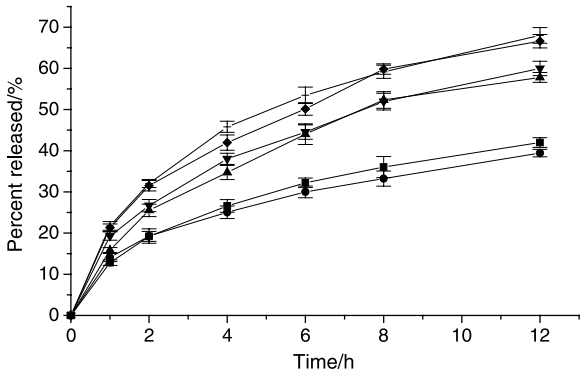


**FIGURE 2** Release Profiles of Sustained-Release Microspheres in Different pH Dissolution Mediums. Each Contain 3% Tween-80. (■) pH=1.2; (●) pH=4.0; (▲) pH=5.0; (▼) pH=5.5; (◆) pH=6.0; (+) pH=6.8.

With regard to $C_{max}$, Formulation B shows the highest value and is followed by Formulations D, A, and C. Even though nitrendipine has a practically poor solubility, the Baypress™ nitrendipine tablets show a characteristic of immediate release formulation, which possesses the shortest $t_{max}$ and highest $C_{max}$ compared with other formulations. In the pH-dependent gradient-release delivery system, the dissolution rate of the poorly soluble active drug was improved after nitrendipine was molecularly dispersed in three types of pH-dependent polymers as a solid dispersion state. It probably led to a relatively high $C_{max}$ in vivo compared with Formulations A and C. As for Formulation C, due to the restraint of retardant polymers, i.e., ethyl cellulose and Eudragit RS, the $C_{max}$ was lowered even although nitrendipine was also highly dispersed by a solid dispersion polymer HP-55 in microspheres. In addition, the low $C_{max}$ of Formulation A indicated a slow dissolution rate of nitrendipine from conventional tablets in vivo.

**TABLE 5** Relative Bioavailability of Test and Reference Formulations in Four Volunteers

| | Compared with formulation A (%) | | Compared with formulation B (%) | |
|---|---|---|---|---|
| Volunteer | Formulation C | Formulation D | Formulation C | Formulation D |
| 1 | 367.2 | 436.3 | 91.6 | 108.9 |
| 2 | 92.1 | 77.1 | 127.0 | 106.3 |
| 3 | 51.6 | 129.4 | 35.1 | 87.9 |
| 4 | 125.6 | 177.4 | 83.4 | 117.9 |
| Mean | 159.1 | 205.0 | 84.3 | 105.2 |
| S.D. | 142.0 | 159.5 | 37.9 | 12.6 |

The relative bioavailabilities of test and reference formulations in four volunteers are listed in Table 5. In comparison with Formulation A, two types of self-manufactured, controlled-release nitrendipine formulations have a correspondingly higher relative bioavailability. The ratios exceed 150%. Additionally, the relative bioavailabilities of two test formulations are located in the range of 80–120% while Baypress™ nitrendipine tablets are used as a reference formulation. It suggests that the dissolution rate of nitrendipine could be improved after it was formulated into current two types of controlled-release formulations. Meanwhile, it should be noted that nitrendipine exhibits a great individual difference in vivo, which was also pointed out in other literature (Lobo et al., 1987; Ramsch et al., 1986). The number of subjects used in this manuscript is too small to obtain statistical significance between the $\ln AUC_{0-25}$ of various formulations. Further investigation on the pharmacokinetic behaviors of these formulations should be carried out with an increase in test numbers. The current research performed as a pilot study could provide some suggestions for future relative bioavailability tests as well as clinical trials.

## CONCLUSION

The $t_{max}$ of two novel, self-manufactured controlled-release nitrendipine formulations were statistically and significantly prolonged in comparison with that of Baypress™ nitrendipine tablets. The relative bioavailabilities of test formulations greatly improved compared with domestic nitrendipine conventional tablets, while the ratio is around 100% compared with Baypress™ nitrendipine tablets. The pharmacokinetic behaviors of two self-manufactured nitrendipine formulations in four volunteers further verified the conclusions derived from the healthy dogs, which were reported in our previous research. It suggested that the two novel controlled-release formulations could improve the dissolution rate of a poorly water-soluble drug and extend the therapeutic period in vivo.

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