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COMMUNICATION

Preparation and Evaluation of a Sustained-Release Formulation of Nifedipine HPMC Tablets

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ABSTRACT

A nifedipine (NF) polyethylene glycol (PEG) solid dispersion was prepared. Using this solid dispersion, NF hydroxypropylmethylcellulose (HPMC) matrix tablets were prepared. Both the high-viscosity grade HPMC (Methocel K15M) and low-viscosity grade HPMC (Methocel K100) were applied in the tablets to form the matrix. The dissolution and absorption of NF from the tablet were evaluated as a formulation that had a sustained release over 24 hr. The Hixson-Crowell equation and Higuchi equation were used to investigate the dissolution mechanism, and the erosion and diffusion codependent mechanism was established. Adalat GITS 30 was used as a reference dosage form. Each beagle dog was also administered an intravenous injection to obtain the pharmacokinetics parameters. The Loo-Riegelman method was applied to study the in vitro/in vivo correlation of the tested tablets and Adalat GITS 30, and significant correlation was proved. Absolute bioavailability and comparative bioavailability of the tested tablet were studied. The results indicated that the NF HPMC tablet could be an ideal 24-hr sustained-release formulation.

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INTRODUCTION

Nifedipine (NF) is one of the calcium antagonists most widely used clinically, mainly as an antianginal and antihypertensive agent. However, NF has a relatively short elimination halftime, about 3.4 hr in the human body (1). Therefore, it is necessary to prolong the plasma levels to maintain the clinical effect. One method to prolong the plasma drug level is to employ the sustained-release formulation. Recently, some NF sustained-release formulations were developed; the most famous is Adalat GITS (2).

A polymer of hydroxypropylmethylcellulose (HPMC) is often used to prepare sustained-release tablets because it is nontoxic, easy to handle, and does not require any special technology for production of sustained-release tablets (3–5). However, it is seldom applied in preparing water-insoluble drug sustained-release tablets because it is hard to release the drug from the tablet. NF is practically insoluble because its dissolution in water is only 7–11 mg/L (6,7). Therefore, in the present study, we prepared a sustained-release dosage form containing NF PEG solid dispersion and HPMC. We studied the release mechanism of NF from the HPMC matrix tablet in vitro. We studied the absorption profile of the tested formulation by administering the formulation to four beagle dogs and giving an intravenous injection to the dogs. We also studied the comparative bioavailability using Adalat GITS 30 as the reference.

EXPERIMENTAL

Materials

Nifedipine was obtained from Tianjing Hebei Pharmaceutical Company (China). Hydroxypropylmethylcellulose (Methocel K15M CR, Methocel K100 CR, Colorcon) and polyethylene glycol 6000 (PEG6000; Guangzhou Pharmaceutical Co., China) were used. Methanol and *n*-hexane were high-performance liquid chromatography (HPLC) grade. All other chemicals were analysis grade.

Methods

Nifedipine is sensitive to daylight and ultraviolet (UV) light; therefore, all experiments were carried out under light.

Preparation of Tablets

The solid dispersion of NF in PEG6000 (1:6 w/w) was prepared by the melting method. A three-layer tablet was prepared. The outer layer was a mixture containing Methocel K15M and NF solid dispersion with a ratio of 1:2 (w/w), and the inner layer contained Methocel K100 and NF solid dispersion, also with a ratio of 1:2 (w/w). The weight ratio of outer layers to the inner layer was 7:3. The mixture was compressed into flat-faced tablets (11 mm diameter containing 40 mg NF) under 100 MPa pressure using an evacuable die and hydraulic press for preparing KBr tablet for infrared (IR) spectroscopy.

Dissolution Study

The USP paddle method was employed. The medium was 1000 ml of 1% (w/w) polysorbate 80 water solution at 37°C ± 0.5°C. The paddle speed was 75 rpm. At appropriate time intervals, 5 ml of the solution was withdrawn, filtered, and assayed. An equal volume of fresh dissolution medium was added into the apparatus.

The assay of NF was made by spectrometry at 334 nm. All dissolution experiments were carried out in sextuple, and mean values are reported.

Analysis of the In Vitro Data

The Hixson-Crowell equation (Eq. 1) (8), zero-order release equation (Eq. 2), and Higuchi equation (Eq. 3) were applied to process the in vitro data to find the equation with the best fit.

$$Q_d/A = 1 - (1 - k_1 t)^3 \quad (1)$$

$$Q_d/A = a + k_2 t \quad (2)$$

$$Q_d/A = b + k_3 k^{1/2} \quad (3)$$

where Q_d is the amount of drug dissolved, A is the total amount of the drug, t is the dissolution time, and k_1, k_2, and k_3 are constants. The Hixson-Crowell equation indicates an erosion-dependent release mechanism (8). On the other hand, the Higuchi equation expresses a diffuse release mechanism.

Bioavailability Study

The sustained-release tablet or Adalat GITS 30 was administered to four male beagle dogs after they were kept in the fasting state for 12 hr with 30 ml water. To obtain the pharmacokinetics parameters, an intravenous injection (6 mg NF per dog) was administered to each dog via the crural vein. The drug samples were adminis-

tered according to a randomized crossover design with a 2-week washout period between dosing. At appropriate intervals, a 4-ml blood sample was withdrawn into the syringes from the forefoot vein of each beagle dog; the blood samples were then centrifuged for 15 min at 3000 rpm to obtain a plasma sample. For the measurement of NF in the plasma, 1 ml of plasma was used. During the experimental period, food was not allowed in the first 4 hr, but water was available all the time.

The plasma concentration of NF was determined by HPLC. To 1 ml of plasma was added 100 μl of 2 M NaOH and 5 ml of a solution (*n*-hexane and dichloromethane 70:30, v/v); the mixture was agitated with a vortex mixer for 10 min. The mixture was centrifuged at 3000 rpm for 10 min, and 4 ml of the upper organic phase was withdrawn and evaporated to dryness in a centrifugal evaporator (model RD-21, Yamato Scientific, Tokyo, Japan). The residue was dissolved in 100 μl of the mobile phase containing butaperazine (600 ng/ml) as an internal standard, and 20 μl of the solution were put into the HPLC system. The HPLC conditions were as follows: LC-9A pump (Shimadzu, Japan); reversed-phase column (Hyper ODS2 C18, 5 μm, 200 mm × 4.6 mm, Dalian Elite Scientific Instruments Co.); mobile phase 0.15 M acetate acid–sodium acetate buffer (pH 3.5)–methanol (1:1); flow rate 1 ml/min; column oven (CTO-6A, Shimadzu); temperature, 50°C. The pressure was approximately 9.3 MPa. An ultraviolet-visible (UV-Vis) spectrophotometric detector (SPD-6AV, Shimadzu) was set at 236 nm, 0.005 AUFS.

Pharmacokinetics Analysis

The intravenous injection data were analyzed through pharmacokinetics models and were described well by a two-compartment model. Each dog's pharmacokinetics parameters were obtained through this model. Based on these parameters, we computed absorption profiles of the tested tablets and the Adalat GITS 30 for each dog using the Loo-Riegelman method (9), described by the following:

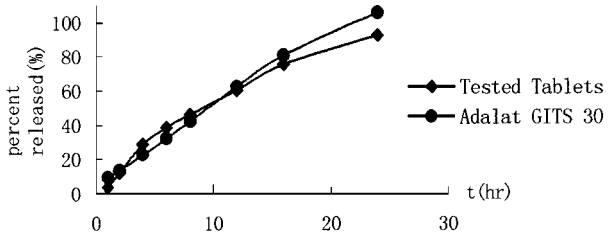

Figure 1. The release profiles of the tested tablets and Adalat GITS 30.

$$A_{abs}(t_i) = V_c C(t_i) + V_c C_2(t_i) + CL \int_0^{t_i} C(T)dT \quad (4)$$

where

$$C_2(t_i) = C_2(t_{i-1})e^{-k_{21}\Delta t_i} + \frac{k_{12}}{k_{21}} C(t_{i-1})(1 - e^{-k_{21}\Delta t_{i-1}}) + \frac{k_{12}}{(k_{21})^2} \frac{[C(t_i) - C(t_{i-1})]}{\Delta t_i} (e^{-k_{21}\Delta t_i} + k_{21}\Delta t_i - 1) \quad (5)$$

Equation 4 expresses the cumulative amount absorbed in terms of the measured concentration $C(t)$, the parameters of the two-compartment disposition model (V_c, K_{12}, K_{21}), and the clearance CL.

The mean of the cumulative amount absorbed was reported. The in vitro/in vivo correlation was examined through correlating the mean of the cumulative amount dissolved and the mean of the cumulative amount absorbed.

The area under the plasma NF concentration time curve (AUC) of each dog was calculated by the trapezoidal method. Mean residence time (MRT) was calculated using statistical moment analysis. The mean value was

Table 1

Mechanism of Nifedipine Release from the Test Tablets and Adalat GITS 30

	Tested Tablets	Adalat GITS 30
Hixson-Crowell equation	$(1 - Q_d/A)^{1/3} = 1.004 - 0.0239t$	$(1 - Q_d/A)^{1/3} = 1.165 - 0.0529t$
	$R = .9984$	$R = .9177$
Zero-order equation	$Q_d/A = 0.1019 + 0.0379t$	$Q_d/A = 0.0638 + 0.0435t$
	$R = .9738$	$R = .9957$
Higuchi equation	$Q_d/A = 0.2308t^{1/2} - 0.189$	$Q_d/A = 0.2568t^{1/2} - 0.2469$
	$R = .9990$	$R = .9879$

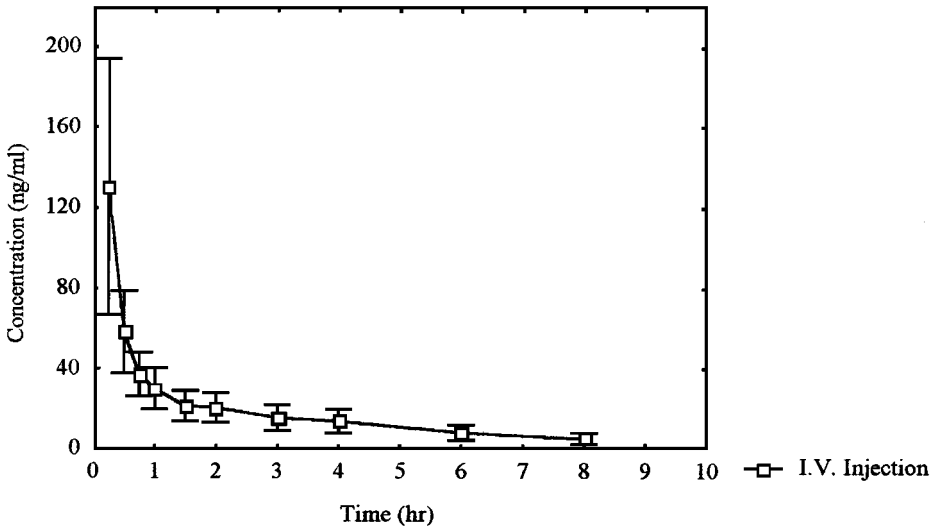

Figure 2. The mean value (±SD) of plasma NF concentration after intravenous injection.

reported. The absolute bioavailability and comparative bioavailability of the tested formulations were calculated.

RESULTS AND DISCUSSION

In Vitro Release of Nifedipine from the Tested Tablets and Adalat GITS 30

The release of NF from the tested tablets and Adalat GITS 30 is shown in Fig. 1. It shows that the tested tablets and GITS 30 have similar in vitro release profiles. Three release mechanisms (Hixson-Crowell equation, zero-order release equation, and Higuchi equation) were applied to study the dissolution data of the tested tablets and Adalat GITS 30. The fitted equation and correlation coefficient of each equation is shown in Table 1. The dissolution data of the tested tablets best fits the Hixson-Crowell equation and the Higuchi equation. Therefore, this indicates that the dissolution is both erosion and diffusion dependent. However, the dissolution data of Adalat GITS 30 fit the zero-order release model best, as advertised by its manufacturer.

Pharmacokinetics Parameters of Nifedipine in Beagle Dogs

The NF plasma concentration value for four beagle dogs after intravenous injection are shown in Fig. 2. The data for the plasma NF value for each dog were processed through software 3P87. The pharmacokinetics parameters for each dog were obtained, and the mean value of each parameter is reported in Table 2. The clearance of NF is very high, which indicates elimination is very fast and proves the necessity of development of NF sustained-release products.

In Vivo Bioavailability of the Tested Tablets and GITS 30

The mean values of plasma NF levels after administration of the tested tablets and Adalat GITS 30 are shown

Table 2

Mean Value of the Pharmacokinetics Parameters Obtained from Intravenous Injection

AUC (ng · hr/ml)	CL (L/hr)	V_C (L)	K_{10} (L/hr)	K_{12} (L/hr)	K_{21} (L/hr)
240.4 ± 35.5	25.3 ± 3.9	14.9 ± 6.3	3.3 ± 2.1	4.5 ± 2.8	0.58 ± 0.23

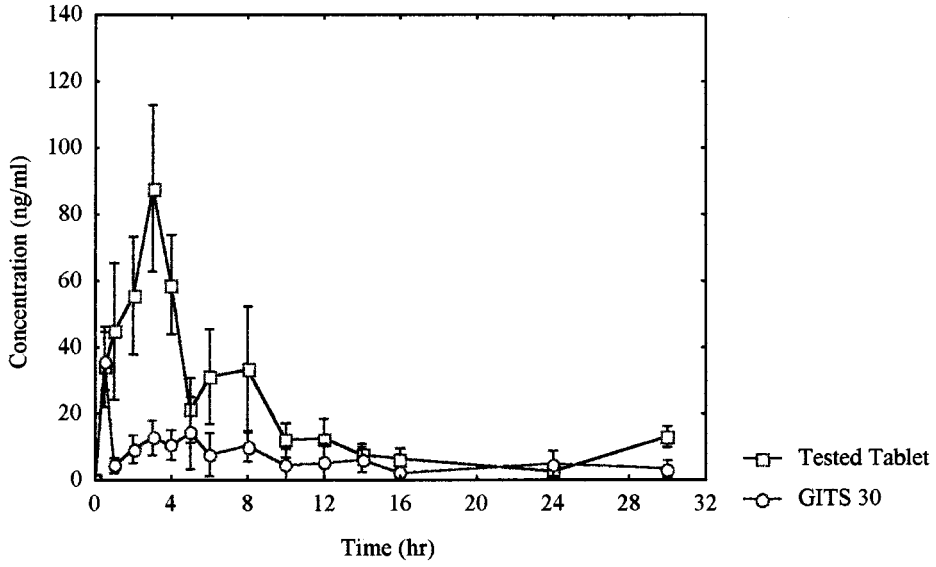

Figure 3. The mean value (±SD) of plasma NF concentration of four beagle dogs after administration of tested tablet or GITS 30.

in Fig. 3. The plasma NF level of the tested tablets is much higher than that of the Adalat GITS 30. However, if we consider minimal effective plasma NF level (10–15 ng/ml), the tested tablets could maintain above this level for 24 hr; on the other hand, the Adalat GITS 30 could hardly maintain it for 12 hr. The peak of the plasma NF level of the tested tablets is a little higher, but it is still lower than the minimal toxic level (100 ng/ml). Therefore, the tested tablet is an ideal sustained-release dosage form for 24 hr use.

The mean pharmacokinetics parameters of the tested tablets and Adalat GITS 30 are shown in Table 3. The difference of bioavailability between the tested tablet and Adalat GITS 30 was very significant. This is the result of incorporation of NF PEG solid dispersion into the tested tablet, which significantly promoted the dissolution rate from the tablet. However, the differences of MRT, MAT, and MDT were not statistically significant ($P > .1$) between the tested tablet and Adalat GITS 30. In addition, we found that the difference between the MAT and MDT of the tested tablets was very small. Therefore, it is concluded that the in vivo/in vitro correlation is very significant.

In Vivo Absorption of Nifedipine from the Tested Tablets and Adalat GITS 30

Based on the pharmacokinetics parameters for each dog obtained from intravenous injection, we calculated the cumulative amount of absorbed NF from the tested tablet or Adalat GITS 30 in vivo of each dog. The mean value of the cumulative absorbed drug in vivo is shown in Fig. 4. The cumulative amount of NF absorbed in vivo at each time was correlated with the dissolution data in

Table 3

Mean Pharmacokinetics Parameters of the Tested Tablets and Adalat GITS 30

	AUC (ng · hr/ml)	Absolute Bioavailability	Comparative Bioavailability	MRT (hr)	MAT[a] (hr)	MDT[b] (hr)
Tested tablet	580 ± 189	0.375 ± 0.098	2.62 ± 0.91	11.5 ± 1.8	10.1 ± 1.1	12.7
Adalat GITS	217 ± 27	0.185 ± 0.052	—	16.5 ± 5.5	14.9 ± 4.9	13.1

[a] MAT refers to the mean absorption time in vivo.
[b] MDT refers to the mean dissolution time in vitro.

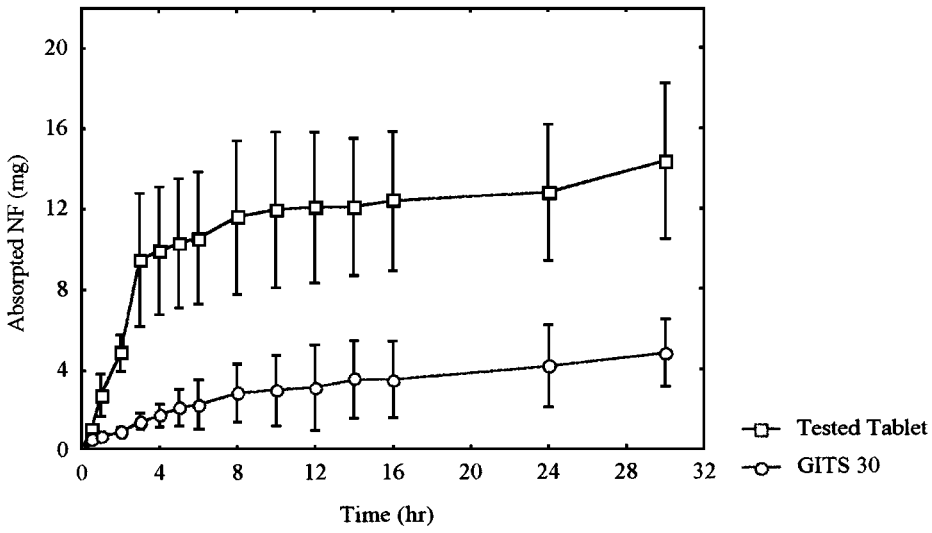

Figure 4. The mean cumulative amount of NF absorbed (±SD) in vivo from the tested tablet or Adalat GITS 30 at each time.

vitro of the same time. The in vitro/in vivo correlation coefficient of the tested tablet is .8635, and that of the Adalat GITS 30 is .9773. The correlation of both formulations is very significant ($r > r_{0.01}$). Therefore, the dissolution method discussed could be used to control qualities of these two formulations.

CONCLUSION

The self-prepared NF HPMC tablet is an idea formulation for its ability to sustain release over 24 hr. The dissolution method used in this study demonstrated good in vitro/in vivo correlation for both the tested tablet and Adalat GITS 30. The Loo-Riegelman method is very suitable for estimation of the cumulative drug absorbed in vivo.

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REFERENCES

1. T. S. Foster, S. R. Hamann, et al., J. Clin. Pharmacol., 23, 161–170 (1983).
2. J. S. Grundy and R. T. Foster, Clin. Pharmacokinet., 30(10), 28–51 (1996).
3. T. Nishiata, Int. J. Pharm., 40, 125–128 (1987).
4. T. Nishiata, Y. Hirotani, et al., Int. J. Pharm., 42, 257–260 (1988).
5. A. C. Shah, N. J. Britten, et al., J. Controlled Release, 9, 169–174 (1989).
6. N. Kohri, K. Miyazaki, et al., Chem. Pharm. Bull., 35(6), 2504–2509 (1987).
7. J. Tu, P. Wang, et al., Zhongguo Yiyao Gongye Zazhi, 27(12), 539–542 (1996).
8. K. Tahara, K. Yamamoto, et al., J. Controlled Release, 35, 59–66 (1995).
9. M. Rowaland and G. Tucker, *Pharmacokinetics: Theory and Methodology*, pp. 390–391.
10. C. H. Kleinbloesem, J. Van Harten, et al., Clin. Pharmacol. Ther., 35, 742–749 (1984).