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Development and pharmacokinetic evaluation of once-daily sustained-released matrix capsules of nifedipine using solid dispersion technique

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The purpose of this study was to develop once-daily sustained-release matrix capsules of nifedipine (F1) using the combination of solid dispersion and drug controlled release techniques. F1 were prepared by the wetting granules methods using hydroxypropyl methyl cellulose (HPMC) as hydrophilic retard drug release agent and ethylcellolulose (EC) ethanol solution based on the polyvinyl pyrrolidone / stearic acid solid dispersion. *In vitro* drug release kinetic model of F1 was fitted well with the zero-order kinetic equation: Q=0.0736 t+0.0871 (R=0.993) in the range of 0-6 h, the first-order kinetic equation: Ln (1-Q) =-0.0934 t-0.1375 (R=0.999) in the range of 6-24 h, respectively. The relative bioavailability of F1 was studied in rabbits after oral administration using a commercial available controlled release tablet (F2) as a reference. The pharmacokinetic results showed no significant differences in Cmax, MRT and AUC (0-24h). The relative oral bioavailability value from F1 in comparison with F2 was 97.12 %. The results of both *in vitro* and *in vivo* studies indicated that once-daily sustained-release matrix capsules of NFD prepared by the optimized formulation exhibited excellent sustained-release effects and high relative oral bioavailability.

Key words: Once-daily sustained-release matrix capsules of nifedipine, solid dispersion, pharmacokinetic behavior.

INTRODUCTION

For the treatment of chronic diseases, such as hypertension and angina pectoris, the most suitable administration route is the oral route. Tablets and capsules are the most popular oral dosage forms available in the market and are preferred by physicians and patients. In long-term therapy of the treatment of hypertension, conven- tional formulations of the most antihypertensive drugs need to be administered twice or three times a day, which result in marked blood pressure fluctuations. However, the formulations of drug sustained (controlled) release delivery systems are preferred for such therapy because of the advantages like reduced frequency of administra- tion and fluctuation in plasma drug concentration, maintenance of stable blood pressure and improvement of patient compliance (Barakat and Almurshedi, 2011; Sousa de Silva et al., 2011).

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Successful treatment of hypertension in clinical practice means maintenance of blood pressure at a normal physiological level. Therefore, the oral drug sustained (controlled) release delivery system for the treatment of hypertension is an ideal strategy.

Nifedipine (NFD), a well known dihydropyridine type Calcium channel blocker that inhibits entry of calcium ions through membrane into cardiac and vascular smooth muscle cells, is widely used in hypertension treatment (Iwai et al., 2011). Conventional oral formulations of NFD are required to be administered in multiple doses and therefore have several disadvantages because of its short elimination half-life (Lee et al., 1999; Li et al., 2009). For example, use of short-acting nifedipine was associated with increased risk of stroke occurrence in elderly hypertensive patients (Lee et al., 2011). To increase therapeutic index and reduce side effects, more attention has been focused on the development of NFD oral sustained (controlled) release delivery system. At present, the main oral dosage forms of NFD used in the treatment of hypertension include twice-daily sustained-release preparation and once-daily controlled-released tablets. Though once-daily controlled-release tablets of NFD as oral osmotic pump tablets produced in Bayer Schering Pharma AG have many advantages, such as zero-order drug delivery rate throughout the gastrointestinal tract, reducing risk of adverse reactions, a high degree of in vitro and in vivo correlation and improving patient compliance (Liu and Xu, 2008; Mehramizi et al., 2007), many patients in developing countries like China could not accept them due to its high cost- because of complex processing technology involved in their manufacturing. Therefore, the development of once-daily sustained-release dosage form of NFD is desirable.

According to the lower solubility of NFD, the combination of solid dispersion and drug controlled release techniques were employed to develop once-daily sustained-release matrix capsules of NFD for the first time. The formulation design and *in vitro* drug release evaluation were studied. *In vivo* study in rabbits was carried out to evaluate the oral NFD pharmacokinetic behavior from once-daily sustained-released matrix capsules (F1) developed by the optimized formulation in comparison with imported NFD once-daily controlled-release tablets (F2) used in clinic as the reference after oral administration.

MATERIALS AND METHODS

Materials

NFD was obtained from Chongqing Kerui Pharmaceuticals Com., Ltd. (Chongqing, P.R. China). Ethylcellolulose (EC, 10cp), hydroxypropyl methyl cellulose (HPMC) were provided by Shanghai Coloron Coating Technology Com., Ltd. (Shanghai, P.R. China). Nifedipine controlled-released tablets (30mg) (batch: BJ06208) were purchased from the First Affiliated Hospital of Luzhou Medical College (Sichuan, P.R. China). Polyvinyl pyrrolidone (PVP k-29/32) was a gift sample from ISP Technologies, Inc (USA). Microcrystalline cellulose (MCC, Avicel PH101) was donated by Japan Credit Rating Agency, Ltd. (Tokyo, Japan). Stearic acid was purchased from Sinopharm Chemical Reagent Co.Ltd. (Shanghai, P.R. China). Magnesium Stearate was purchased from Luzhou Juhe Chemical Reagent Co.Ltd. (Sichuan, P.R. China). Acetonitrile and methanol (HPLC grade), Ethanol and other reagents used throughout the study (analytical grade) were purchased from Luzhou Kelong Reagent Co.Ltd. (Sichuan, P.R. China).

Preparation of sustained-release capsules

A solid dispersion of NFD was prepared by solution-evaporation method. NFD, PVP and Stearic acid with different mass ratio were dissolved in ethanol at 50°C. The organic solution was stirred using a half-moon paddle stirrer at 600 rpm to evaporate the solvent and the precipitate was dried at 40°C for 24 h to solid dispersion granules and stored in a sealed desiccators.

Sustained-release capsules of NFD were prepared by wet granulation technique. The solid dispersion granules of NFD obtained from the above procedure, HPMC and MCC were mixed well in a different mass ratio. EC ethanol solution (12% wt/vol) was chosen as bonding agent to prepare wet granulation using 24 mesh sieves. The granules were dried at 40°C for 3h, and then dry granules were mixed with magnesium stearate, which serves as lubricant, and passed through 20 mesh sieves. Based on the result of NFD content determination of semi-finished products, the sustained-release capsules of NFD (30 mg of NFD/capsule) containing granules of about 305 mg total weight were obtained by filling hard gelatin capsules (2 #).

Evaluation of granules

Angle of repose

The angle of repose of granules was measured by the funnel method. In brief, the accurately weighed granules were placed in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was determined and then the angle of repose was calculated according to equation (1).

$$\tan \theta = h/r \quad (1)$$

Where, h and r in (1) represent the height and radius of the powder cone.

Bulk density

The loose bulk density (LBD) and tapped bulk density (TBD) of granules were determined. A quantity of 3 g of powder was introduced into a 10 ml measuring cylinder followed by lightly shaking to prevent any agglomerates from forming. When the initial volume was observed, the cylinder was allowed to fall freely under its own weight onto a hard surface from the height of 2.5 cm at 2 s interval. The tapping was continued until no further change in volume was observed. LBD and TBD were calculated according to equation (2) and (3).

LBD=weight of the powder / volume of the packing (2)
TBD=weight of the powder / tapped volume of the packing (3)

Table 1. Factors and levels for orthogonal experiments.

Level	Experimental factor		
	The amount of NFD solid dispersions (g) (A)	The amount of HPMC (g) (B)	The concentration of EC (%) (C)
1	0.75	0.75	3.0
2	0.9	0.9	4.0
3	1.05	1.05	5.0

X-ray powder diffraction

Solid dispersions and corresponding physical mixtures were analyzed using an X' D/MAX-2500/PC diffract meter (Rigaku Corporation, Tokyo, Japan) with a copper anode (Cu Ka radiation, λ=0.15405 nm, 40 kV. 40 mA). The diffraction behavior was measured between 10-90 θ at room temperature.

Differential scanning calorimeter (DSC)

A differential scanning calorimeter (METTLER 1100LF RT-350, Switzerland) was used to investigate crystalline nature of the drug in the solid dispersions. About 3 mg of samples in an open aluminum standard pan was heated at a scanning rate of 10°C ℃/min from a temperature to 350°C under an argon gas (99.999%) flow.

Orthogonal experimental design

According to the results of the preliminary experiments, the L9 (3^4) orthogonal array was used to optimize the formulation of sustained-release capsules of NFD. The orthogonal experiment with four factors and three levels are shown in Table 1. The *in vitro* drug release behavior was chosen as a main marker to investigate these formulations. For once-daily sustained-release dosage form of NFD, the desirable drug release percentages at 2, 12 and 24 h were 20, 70 and 90%, respectively. Q2, Q12 and Q24 were the cumulated release of sustained-release capsules of NFD developed in this study at 2, 12 and 24 h. Therefore, the equation of K=|20-Q2|+|70-Q12|+|90-Q24| was obtained. K represented comprehensive score. When smaller the value of K was, the percentages of the drug release from the experimental preparation were more similar with the desirable drug release values.

***In vitro* release test**

The basket method of the China Pharmacopoeia (2010 version) drug release test was used to study *in vitro* dissolution behavior of NFD. The release medium composed of 900 ml of 0.25% sodium dodecyl sulphate (SDS) with a stirring speed of 100 rpm was maintained at 37±0.5°C. Five milliliter (5 ml) of samples was withdrawn at regular intervals and then the samples withdrawn were filtered through a 0.45 μm hydrophilic Millipore membrane. The level of the drug release was determined by using a UV-visible spectrophotometer (UV-2102, Shanghai, P.R.,China) at 238 nm. A 5 ml of blank release medium at 37±0.5°C was added to the container after sampling to maintain a constant volume of the release medium.

Pharmacokinetic study

Pharmacokinetics studies were performed using New Zealand albino rabbits weighing 2±0.5 kg, which were purchased from the Laboratory Animal Center of Luzhou Medical College. The use of rabbits in this study was approved by the Luzhou Medical College animal ethical experimentation committee (Sichuan, P.R. China). These rabbits were fasted for at least 12 h before the experiments, but had free access to water. Both once-daily sustained-released matrix capsules of NFD (F1) developed by the optimized formulation and imported NFD controlled-release tablets (F2) as the reference were orally administered to six rabbits at a dose of 30 mg/rabbit. Two milliliter (2 ml) of blood sample was withdrawn before and after oral administration. Each blood sample was centrifuged immediately at 3000 rpm for 5 min and plasma was separated and then stored at -20°C until analysis.

HPLC analysis

The above biosamples were analyzed by HPLC method as previously described (Sawada et al., 2004). In brief, 50 μL of nicardipine solution in methanol (10μg/mL) as internal standard were introduced in 10 ml tubes and dried at 45°C under a nitrogen steam. Then, the plasma samples (1 ml), 1ml of Na_2HPO_4 (50 μM) and 5 ml of the organic solvents composed of n-hexane and ethyl acetate (1:1, v/v) were successively added and vortex-mixed for 15 min. The mixture was centrifuged at 8000 rpm for 10 min. Then, the organic solvent was collected and evaporated to dryness at 45°C under a nitrogen steam. The residues were reconstituted in 200 μL mobile phase and centrifuged at 10000 rpm for 10 min. Samples (20 μL) injected into the HPLC system consisted of Dionex ultimate 3000 series including pump (LPG- 3400SD), UV-vis detector (VWD-3100), auto injector (WPS-3000) and column oven (TCC-3000). Separation was performed on a reverse phase C18 column (Inertsil ODS-SP; 4.6×250 mm, 5um particle size, made in Japan) with a guard column (Dionex C18, 4.3 mm×10.0 mm) at 30°C and mobile phase consisted of acetonitrile - methanol - distilled water (15:55:30, v/v) at a flow rate of 1.0 ml/min. Chromatographic separation was monitored at 235 nm with UV detector. The following pharmacokinetic parameters were determined by using DAS 2.0 pharmacokinetics software: the area under the plasma drug concentration-time curve up to 24 h post-administration ($AUC_{0\text{-}24\ h}$), the time to reach the maximum plasma drug concentration (T_{max}), the maximum plasma drug concentration (C_{max}), the elimination half-life ($T_{1/2}$) and the mean residence time (MRT).

Statistical analysis

Students't'-tests were used to evaluate the significant differences between the pharmacokinetic data of F1 and F2. Values were reported as mean ±SD and a significance level of less than 5% was considered as the significant difference.

RESULTS AND DISCUSSION

Preliminary experiments

Nowadays, NFD has been widely used as a

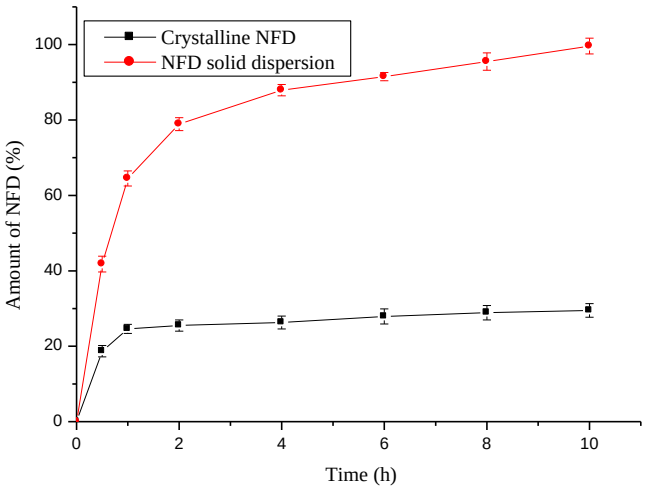

Figure 1. *In vitro* dissolution profiles of crystalline NFD and NFD-to-solid dispersion containing PVP and stearic acid (1:3 w/w) at a load of 20% in 0.25 % sodium dodecyl sulphate. (Mean±S.D., n=3).

dihydropyridine type Ca^{2+} channel blocker for the treatment of cardiovascular diseases such as hypertension and angina pectoris. However, the highly crystalline and poorly soluble characterizations of NFD result in lower oral bioavailability (Sawada et al., 2004). Application of solid dispersions composed of hydrophilic carrier in which a lipophilic drug is incorporated is a proven technique to improve the poor water solubility of drug (Huang et al., 2011; Srinarong et al., 2012). Furthermore, many studies have been reported that the solid dispersion technique was used to enhance oral bioavailability of poor water soluble drugs (Boghra et al., 2011; Tran et al., 2011). Therefore, in order to solve the poor aqueous solubility problem NFD and improve the oral bioavailability and prolong the drug release, the combination of solid dispersion and drug controlled release techniques were used to develop once-daily sustained-release matrix capsules of NFD for the first time. In the preliminary experiments, the effect of solid dispersion components with PVP and stearic acid, the amount of HPMC and concentration of EC on the dissolution rate of NFD was investigated. On the basis of a series of preliminary experiments, it was found that, when the solid dispersions was composed of NFD (0.2 g), PVP (0.2 g) and stearic acid (0.6 g), the dissolution of NFD (20% w/w) in the solid dispersion was significantly greater than that of crystalline NFD (Figure 1).

Then further studies were conducted to confirm the physical state of the drug incorporated in solid dispersion by using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD). The results show that the thermograms of crystalline NFD, blank solid dispersions without NFD and solid dispersions at a drug load of 20% w/w are shown in Figure 2. The melting peak of NFD was about 165.43°C while the glass transition temperature of blank solid dispersions was 60.14°C. The thermograms of PVP and stearic acid-based solid dispersion with a drug load of 20% w/w did not show a melting peak of NFD, which indicated that the solid dispersions are most likely amorphous. The X-ray diffraction behaviors of crystalline NFD, blank solid dispersions without NFD and solid dispersion at a drug load of 20% w/w are shown in Figure 3. The results show that the characteristic diffraction peaks for crystalline NFD were not observed in the solid dispersions, indicating that the NFD in the solid dispersion was amorphous form. Therefore, the solid dispersions of NFD were used as the drug source for next experiments. HPMC is the most commonly and successfully employed drug release retarding agent for the preparation of oral controlled delivery systems (Colombo, 1993). The transport mechanism involved in the drug release from hydrophilic matrices is complicated since the macrostructure and microstructure of HPMC exposed to release medium is mainly time dependent. In general, the level of HPMC used as a rate-controlling polymer in capsules or tablets to retard the release of drug from a matrix ranged from 10 to 80% (Avachat and Kotwal, 2007). When NFD sustained release capsules were prepared by using mixture of the above solid dispersion and HPMC and ethanol as granulating agent, the effect of HPMC level on the release of NFD for capsules containing 10, 20 and 30% is shown in Figure 4. The results show that, when HPMC level is increased to 30%, prolonged release of NFD was achieved up to 22 h. Therefore, it was selected for further formulation development. In order to overcome initial burst release, the above formulation was modified by using different concentration of EC in ethanol (2, 4 and 6%) as granulating agents. In the case of EC concentration (2, 4 and 6%), NFD sustained release capsules released 23.5, 14.5 and 13.8% of the drug at the end of 0.5 h; 97.4, 97.8 and 78.9% of the drug at the end of 24 h, respectively (Figure 5). When the concentration of EC was increased to 4%, the preparations could control the drug release in a better manner, which could be contributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer film, resulted in a lower diffusion rate of the drug from the matrix. However, when the concentration of EC was increased to 6%, the drug could not be completely released at the end of 24 h. Therefore, the concentration of EC (4%) as granulating agents was chosen to go for further study.

Optimization of formulation

It was found that main pharmaceutical characterizations including angle of repose, bulk density of granules and weight variation and drug content of capsules except for *in vitro* release behavior were similar among all the preliminary experimental formulation. Therefore, the drug release behavior was chosen as the estimated marker to optimize the formulation of once-daily sustained-released

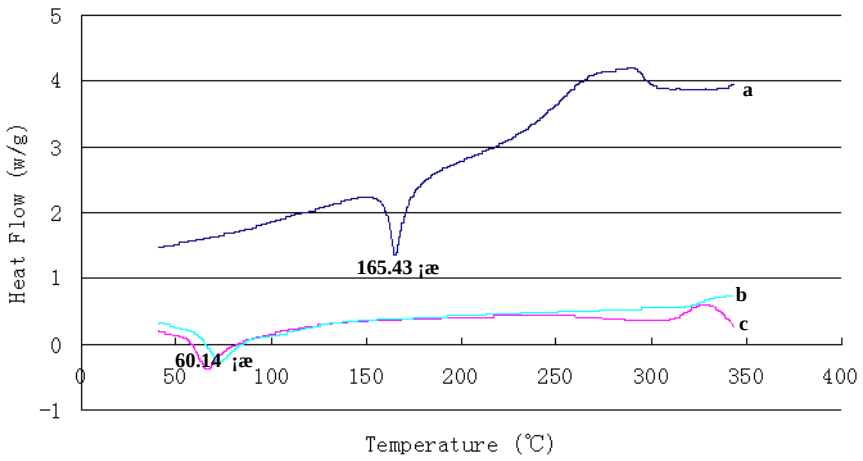

Figure 2. DSC thermograms of (a) crystalline NFD, (b) solid dispersion containing 20% w/w of NFD and (c) blank solid dispersion without NFD.

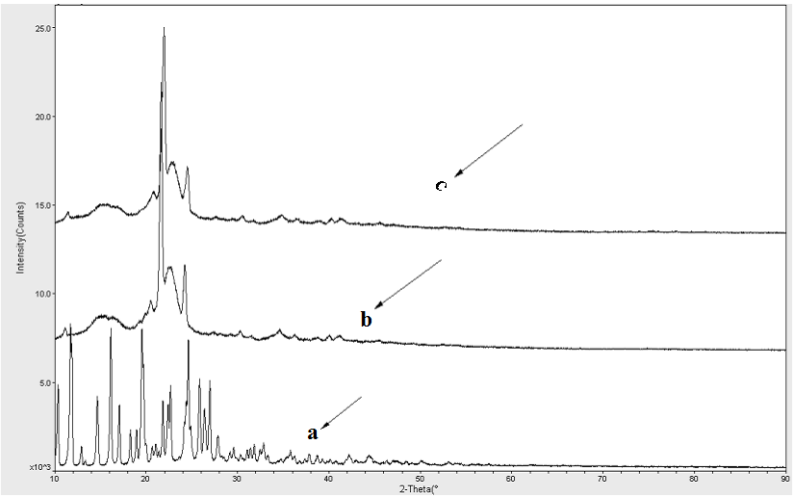

Figure 3. X-ray diffraction behaviors of crystalline NFD, blank solid dispersion without NFD and solid dispersion containing 20% w/w of NFD.

matrix capsules of NFD. The results of orthogonal experiments are shown in Table 2. According to the R-values, the order of the influence of above three main factors on *in vitro* release of NFD from the preparation was as follows: B>C>A. On the basis of the results of orthogonal experiments, the optimal formulation (F1) was composed of the amount of NFD solid dispersions (1.05 g) containing PVP / stearic acid weight ratio (1:3) at a drug load of 20%, HPMC (0.75 g) and the concentration of EC (4%).

In order to validate the optimal formulation and investigate reproduction, three batches (110506, 110507, and 110508) of once-daily sustained-release matrix capsules of NFD (30 mg) were prepared using the optimized formulation. The angle of repose of granules was 23.24±0.02, 22.99±0.03 and 23.18±0.02, respectively. The LBD and TBD values of granules were 0.77±0.02 and 0.84±0.03, 0.75±0.02 and 0.83±0.02, 0.77±0.02 and 0.84±0.03, respectively. The content of these preparations was 10.03, 9.94 and 10.02%, respectively. Drug release profiles from the three batches developed in this study and NFD controlled release tablets (30mg) (batch: BJ06208) purchased from the First Affiliated Hospital of Luzhou Medical College are shown in Figure 6. The similar results of *in vitro* release rate of NFD from the three batches of once-daily sustained-release matrix capsules were observed. The above results showed excellent reproduction and validation for the optimized formulation. The mean release amount of NFD of the three batches at the end of 2, 12 and 24 h was 25.5, 72.2 and 90.5%, respectively. In the case of NFD controlled-release tablets, the release rate was

Table 2. The results of L9 (3^4) orthogonal experiments.

S/N	The amount of NFD solid dispersions (g) (A)	The amount of HPMC(g) (B)	The concentration of EC (%) (C)	K
1	1 (0.75)	1 (0.75)	1 (3)	17.75
2	1 (0.75)	2 (0.9)	2 (4)	19.53
3	1 (0.75)	3 (1.05)	3 (5)	20.77
4	2 (0.9)	1 (0.75)	2 (4)	36.48
5	2 (0.9)	2 (0.9)	3 (5)	15.89
6	2 (0.9)	3 (1.05)	1 (3)	13.29
7	3 (1.05)	1 (0.75)	3 (5)	31.48
8	3 (1.05)	2 (0.9)	1 (3)	20.57
9	3 (1.05)	3 (1.05)	2 (4)	24.43
K1	19.35	29.16	17.20	
K2	21.89	18.67	26.81	
K3	25.49	19.50	22.71	
R	6.24	10.49	9.61	

Table 3. Pharmacokinetic parameters of NFD after after oral administration of once-daily sustained-release matrix capsules of NFD (F1) developed in this study (closed squares) and once-daily NFD controlled releases tablets (F2) as reference (closed circles) to rabbits at a dose of 30 mg/ rabbit. (n=6).

Parameter	Tmax (h)	Cmax μg/L	T1/2 (h)	MRT (h)	AUC(0-24h) μg/L*h
F1	4±0.8	38.7±3.2	13.3±1.7	9.7±0.8	572.6±57.8
F2	6±0.6	35.7±2.9	16.7±2.0	10.7±1.2	589.6±38.4

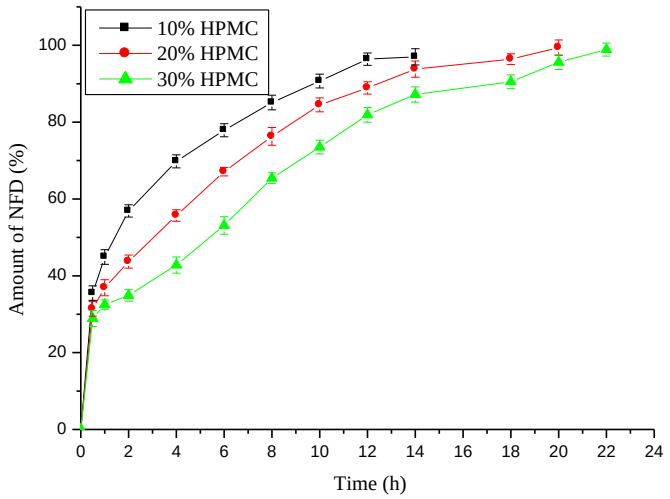

Figure 4. *In vitro* dissolution profiles of NFD sustained release capsules prepared by using mixture of above solid dispersion and HPMC (10%, 20% and 30% w/w) and ethanol as granulating agent in 0.25 % sodium dodecyl sulphate. (Mean±S.D., n=3).

observed in a steadier constant way without bust release behavior. On the other hand, it was found that *in vitro* drug release kinetic model of once-daily sustained-release matrix capsules of NFD was fitted well with the zero-order kinetic equation: Q=0.0736t+0.0871 (R=0.993) in the range of 0-6 h, the first-order kinetic equation: Ln(1-Q)=-0.0934t-0.1375 (R=0.999) in the range of 6-24 h, respectively. For NFD controlled-release tablets, the release rate during 24 h showed a zero-order kinetic model and could be expressed by the following equation: Q=5.1562t-0.3561 (R=0.996), indicating difference in the underlying drug release mechanism.

In vivo pharmacokinetic characterization

The aim of *in vivo* study in rabbits was to evaluate the oral NFD pharmacokinetic behavior from once-daily sustained-release matrix capsules (F1) developed by the optimized formulation and once-daily NFD controlled-release tablets (F2) used in clinic as a reference after oral administration. The mean plasma drug concentration – time curve after a single oral dosage is shown in Figure 7. The pharmacokinetic parameters are summarized in Table 3. After oral administration of F1 and F2 to rabbits, no sharp peak of the plasma drug concentration was observed throughout the experiments, that is, the plasma drug concentration was maintained within a narrow range for a long period of time with the mean residence time

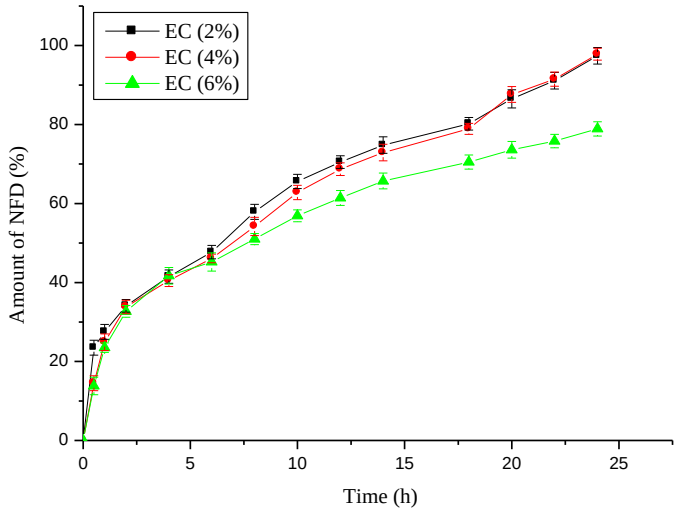

Figure 5. *In vitro* dissolution profiles of NFD sustained release capsules prepared by using mixture of above solid dispersion and HPMC (30% w/w) and EC ethanol solution (2%, 4% and 6% w/v) as granulating agent in 0.25 % sodium dodecyl sulphate. (Mean±S.D., n=3).

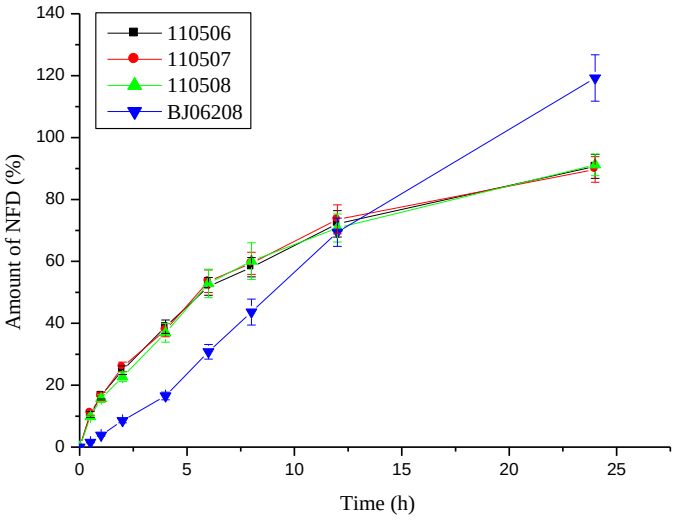

Figure 6. Cumulative release of NFD from once-daily sustained-release matrix capsules (110506, 110507, 110508) developed in this study and once-daily controlled released tablets (BJ06208) as reference in 0.25 % sodium dodecyl sulphate (Mean±S.D.,n=3).

(MRT) values of 9.7±0.8 and 10.7±1.2 h, and the maximum plasma drug concentration (C_{max}) values were 38.7±3.2 and 35.7±2.9 ng/L, respectively. The time to reach the maximum plasma drug concentration (T_{max}) and elimination half-life ($T_{1/2}$) of F1 and F was 2, 4±0.8 h and 6±0.6 h, 13.3±1.7 and 16.7±2.0 h, respectively. All the results confirmed the sustained-release characterization of NFD sustained release capsules developed in this study in the rabbit model. The AUC (0-24h) value for NFD formulations F1 and F2 was 572.6±57.8 and

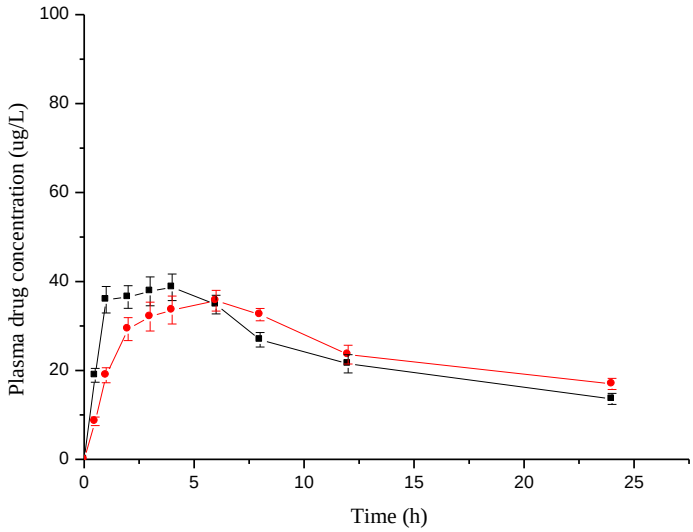

Figure 7. NFD plasma concentration-time curve after oral administration of once-daily sustained- release matrix capsules of NFD (F1) developed in this study (closed squares) and once-daily NFD controlled releases tablets (F2) as reference (closed circles) to rabbits at a dose of 30 mg/ rabbit. Each point represents the mean±S.D., n=6.

589.6±38.4μg/L*h, respectively. When student's t-tests were used to analyze the two pharmacokinetic data, no significant differences in Cmax, MRT and AUC (0-24h) were found ($P>0.05$). The relative oral bioavailability value from F1 in comparison with F2 was 97.12%, indicating bioequivalence that means the rate and extent of absorption of F1 prepared in this study do not show a significant difference from the rate and extent of absorption of the reference drug F2 when administered at the same drug dose under similar experimental conditions (Toal et al., 2012).

CONCLUSION

Once-daily sustained-release matrix capsules of NFD were successfully developed by the wetting granules methods using HPMC as hydrophilic retard drug release agent and EC ethanol solution as a bond agent based on the polyvinyl pyrrolidone / stearic acid solid dispersion. The results of both *in vitro* drug release test and *in vivo* pharmacokinetic investigation showed that once-daily sustained-release matrix capsules of NFD prepared by the optimized formulation exhibited excellent sustained-release effects and high relative oral bioavailability.

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DECLARATION OF INTEREST

The authors participate in this study report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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