Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 280 (2004) 103–111
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Time-release compression-coated core tablet containing nifedipine for chronopharmacotherapy

Toyohiro Sawada [a,*], Hiromu Kondo [a], Hiroshi Nakashima [a], Kazuhiro Sako [a], Masahiro Hayashi [b]

[a] *DDS Research, Novel Pharmaceutical Research Laboratories, Institute for Technology Development, Yamanouchi Pharmaceutical Co., Ltd., 180 Ozumi, Yaizu-shi, Shizuoka 425-0072, Japan*
[b] *Department of Biopharmaceutics, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

Received 9 December 2003; received in revised form 7 May 2004; accepted 9 May 2004

Available online 26 June 2004

Abstract

Compression-coated time-release tablets (CC tablets) containing nifedipine, dihydropyridine Ca channel blocker, in the core tablet were prepared by dry coating with different polyethylene oxide-polyethylene glycol mixtures. Each formulation showed a clear lag period before nifedipine release initiation, followed by sustained drug release lasting up to 24 h. The lag time of nifedipine release increased as the amount of polyethylene oxide in the outer layer increased. To investigate the applicability of such CC-tablets for chronopharmacotherapy, the pharmacokinetics of CC-1 and CC-2 tablets, with different in vitro lag times before drug release, were compared with the pharmacokinetics of a sustained-release (SR) tablet in dogs. The times of first nifedipine appearance (TFA) in plasma were 0.7 ± 0.3 h for SR, 2.5 ± 1.2 h for CC-1, and 5.3 ± 1.0 h for CC-2. These data show a significant difference in in vivo lag time ($P < 0.01$) among the three formulations that correlates with the in vitro lag times. Thus, the in vivo lag time could be predicted from the in vitro lag time. Additionally, higher plasma nifedipine concentrations were observed at 8 h after administration of the CC-2 than that observed for the SR-tablet. These results indicate that a CC-tablet with a lag time before drug release is a potentially useful formulation for chronopharmacotherapy that can control the time and duration of plasma drug concentration better than existing SR technologies.

Keywords: Compression-coated tablets; Time-release formulation; Dogs; Nifedipine; Chronopharmacotherapy

1. Introduction

Oral time-controlled drug release formulations have the interesting characteristic that a drug is released from the formulation after a predetermined time before drug release begins (the lag time). Recently, such time-release formulations have been widely investigated for several possible uses. Since orally administered dosage forms move through the gastrointestinal (GI) tract and this GI transit time is fairly constant in human (Coupe et al., 1991; Wilding et al., 1993), several studies have focused on drug delivery to the ileum and the colon in the lower GI tract, where few digestive enzymes exist, in order

* Corresponding author. Tel.: +81 54 627 6752; fax: +81 54 621 0106.
E-mail address: sawada_t@yamanouchi.co.jp (T. Sawada).

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2004.05.004

to enhance absorption of drugs, such as peptides and proteins, that are degraded in the upper GI tract (Rubinstein et al., 1997). Other studies have shown that time-release formulations can be used to avoid pharmacokinetic drug–drug interactions between concomitantly administered medications, creating a time interval between their release into the gastrointestinal tract (Sawada et al., 2003a). Additionally, it is thought that time-release formulations could be an effective tool in effecting chronopharmacotherapy because their unique drug release properties could take advantage of circadian rhythms in physiologic and pathologic functions (White et al., 1998). A time-release formulation could allow drug release and a greater plasma drug concentration at the point in the circadian cycle when clinical signs develop or increase. Drugs that treat cardiovascular disease and asthma have been investigated for the chronopharmacotherapy (Lemmer, 1991) because there are circadian rhythm of the symptoms. Nifedipine is a dihydropyridine Ca channel blocker widely used in clinical practice to treat hypertension. In this study, nifedipine was used as a model drug.

Since time-controlled formulations present many intriguing treatment possibilities (Ueda et al., 1994; Krögel and Bodmeier, 1998), simple and inexpensive production methods might be effective for these formulations to gain widespread use. Compression-coated core tablet formulations are simple formulations to manufacture, and were used in this study. Compression-coated core tablets are composed of an inner core that contains an active pharmaceutical ingredient and excipients surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time.

The purpose of this study was to compare the pharmacokinetics of both sustained-release tablet and time-release tablet formulations in order to assess the applicability of each technology for chronopharmacotherpy. First, in vitro formulation studies were conducted to prepare compression-coated core tablet formulations that have lag times of drug release followed by sustained drug release. This was followed by an in vivo study on time-release formulations and a monolithic sustained release hydrogel-forming formulation conducted in dogs to compare the pharmacokinetics of these tablets.

2. Materials and methods

2.1. Materials

Nifedipine was purchased from Sagami Chemical Industries (Tokyo, Japan). Polyethylene oxide (PEO) with an average molecular weight of 7 million was purchased from Dow Chemical (Piscataway, NJ, USA). Macrogol 6000 (PEG), a polyethylene glycol with an average molecular weight between 7300 and 9300, was purchased from Sanyo Chemical Industries (Kyoto, Japan). Other reagents used were of analytical reagent grade.

2.2. In vitro experiments

2.2.1. Preparation of tablets

2.2.1.1. Solid dispersion of nifedipine. A solid dispersion of nifedipine was prepared using the spray-drying method. Nifedipine and hydroxypropylmethylcellulose (HPMC2910) in a 10:9 mass ratio, were dissolved in methanol. The solution was spray-dried using a spray-dryer (Yamato Kagaku; Tokyo, Japan). The X-ray diffraction profiles of the solid dispersion were measured using a RINT1400 X-ray diffractometer (Rigaku Corporation, Tokyo, Japan) with Ni-filtered CuKα radiation to evaluate the crystallinity of the solid dispersion.

2.2.1.2. Sustained-release tablet (SR tablet). The solid dispersion of nifedipine, sucrose, and PEO were mixed in a 171:60:120 mass ratio, and the 351 mg of this mixture was compressed directly using a single press tableting machine fitted with concave punches that had a 9-mm diameter and a 9-mm radius of curvature to obtain SR tablets including 90 mg of nifedipine.

2.2.1.3. Time-release compression-coated core tablets (CC tablet). The solid dispersion of nifedipine, sucrose and PEO were mixed in a 171:30:60 mass ratio, and for each core, the 261 mg of this mixture was compressed directly to prepare the core tablets using a single press tableting machine fitted with a concave punches that had an 8-mm diameter and an 8-mm radius of curvature. Then, complete compression-coated tablets were prepared by placing 50% of the outer layer powder mixture in the die, manually centering the pre-

Table 1
Formulation of sustained release tablet and compression-coated tablets

	Formulation code				
	SR	CC-1	CC-2	CC-3	CC-4
Core part					
Nifedipine	90	90	90	90	90
HPMC	81	81	81	81	81
Sucrose	60	30	30	30	30
PEO	120	60	60	60	60
Subtotal (mg)	351	261	261	261	261
Diameter (mm)	9	8	8	8	8
Outer layer					
PEO	0	50	75	100	150
PEG	0	250	225	200	150
Total (mg)	351	561	561	561	561
Diameter (mm)	9	10.5	10.5	10.5	10.5
Gelation index (%)	80	–	–	–	–
Core erosion ratio (%)	–	66	67	68	69

viously prepared tablet cores on the powder in the die, and loading the remaining 50% of the outer layer powder mixture into the die. The contents were then compressed using a single press tableting machine fitted with a 10.5-mm diameter concave punches and a 10.5-mm radius of curvature to obtain CC tablets including 90 mg of nifedipine. The composition of each formulation is shown in Table 1.

2.2.2. In vitro gelation index test

Sustained-release tablets were immersed in the Japanese Pharmacopoeia XIII (JP) Disintegration Test second fluid (pH 6.8) at 37 °C for 2 h. After the tablets were removed from the medium, the gelated portion of the tablet was carefully removed to obtain the non-gelated core. The dry mass of each non-gelated core (W_{core1}) was measured after drying for 20 h at 40 °C. The initial mass of each tablet (W_{ini1}) and the mass of non-gelated core were used to calculate the gelation index as follows:

$$\text{Gelation index (\%)} = \left[1 - \left(\frac{W_{core1}}{W_{ini1}}\right)\right] \times 100 \quad (1)$$

2.2.3. In vitro core erosion test

Compression-coated tablets were separately immersed in the Japanese Pharmacopoeia XIII (JP) Disintegration Test second fluid (pH 6.8) at 37 °C for 3 h. After the tablets were removed from the medium, the gelated portion of the outer layer and the dissolved or gelated portion of each core tablet was carefully removed to obtain the non-eroded residual core. The dry mass of each non-eroded residual core (W_{core2}) was measured after drying for 20 h at 40 °C. The initial mass of each core tablet (W_{ini2}) and the mass of each non-eroded residual core were used to calculate the core erosion ratio as follows:

$$\text{Core erosion ratio (\%)} = \left[1 - \left(\frac{W_{core2}}{W_{ini2}}\right)\right] \times 100 \quad (2)$$

2.2.4. In vitro nifedipine release test

The second method (paddle method) of the JP Dissolution Test was used to determine the amount of nifedipine released from both the SR tablet and CC tablets, in vitro. The paddle rotation speed was set to 200 rpm. The test medium was 500 ml of the second fluid (pH 6.8) for the JP Disintegration Test to evaluate bulk nifedipine and the solid dispersion of nifedipine, or the second fluid (pH 6.8) for the JP Disintegration Test including 1% (w/w) of polyoxyethylene sorbitan monooleate to evaluate the SR tablet and the CC tablets. Samples were taken at appropriate intervals, and the amount of dissolved nifedipine was determined spectrophotometrically at 340 nm. During the dissolution test, the whole apparatus was shielded from light to prevent degradation of nifedipine. The lag time of drug release was determined from the intersection of the release profile regression line formed from data taken between 20 and 80% release with the time axis.

2.3. In vivo experiments

2.3.1. Pharmacokinetics tests

Eight male beagle dogs that weighed 10.4–15.8 kg were used in the present study. The same set of 8 dogs was used in all experiments after washout period of at least 7 days between trials. Food was withdrawn from the dogs the night before each experiment, and the animals were not fed until the final blood sample was drawn in the intravenous administration of nifedipine. However, the dogs were allowed free access to water during this period. Nifedipine was dissolved into 40% (v/v) ethanol to prepare a 3 mg/ml

nifedipine solution. The nifedipine solution was infused into the cephalic vein in a forearm of each dog at a dose of 0.5 mg/kg. In contrast, the dogs were fed 50 g of a meat-based food (HOKUETSU Dog meal; Hokuetsu Shiryo Kenkyusho; Nigata, Japan) 30 min before oral administration. After oral administration, the dogs were allowed free access to water but food was withheld until the last blood sample had been taken. Two tablets of the CC-1, CC-2, or SR tablet, containing 90 mg of nifedipine were administered orally with 30 ml of water. A heparin-coated disposable syringe was used to collect approximately 5 ml of blood from the femoral vein at each sample collection time. For the intravenous administration of nifedipine, blood samples were collected at 0.1, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 h after administration. For the oral administration of each tablet, blood samples were collected at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after administration. Plasma samples were immediately separated and stored frozen at −20 °C until assay.

All experiments using beagle dogs were approved by the animal care and use committee of Novel Pharmaceutical Laboratories, Yamanouchi Pharmaceutical Co., Ltd. and were performed in accordance with the standards listed in the "Guideline for Animal Experimentation (1987)", published by the Japanese Association for Laboratory Animal Science.

2.3.2. HPLC analysis to determine the amount of nifedipine in canine plasma

Nicardipine (4 μg/ml) dissolved in methanol as the internal standard (0.1 ml), 1 ml of 50 mM Na_2HPO_4, and 5 ml of an organic solvent composed of ethyl acetate and *n*-hexane (1:1 [v/v]) were sequentially added to 1 ml of each plasma sample contained in separate glass tubes. Each mixture was shaken for 15 min and then centrifuged for 5 min at 830 × *g* and 4 °C. Each organic layer was transferred to a separate clean glass tube and evaporated to dryness under reduced pressure. Each residue was separately dissolved in 0.2 ml of the mobile phase (description follows). For each sample, a 60-μl aliquot was loaded onto an HPLC system equipped with a reverse-phase C_{18} column (4.6 mm × 150 mm; TSK-gel ODS 80 Ts; Tosoh Corporation; Tokyo, Japan) and analyzed separately. The mobile phase consisting a of 50 mM KH_2PO_4 and acetonitrile (55:45 [v/v]) mixture was used at a flow rate of 0.6 ml/min and a temperature of 35 °C. All samples were protected from light during processing and analysis to prevent the degradation of nifedipine. Nifedipine and the internal standard were detected by UV absorbance at 237 nm, and the ratios of the peak height of nifedipine to that of the internal standard were calculated for each sample. The concentrations of nifedipine in the plasma samples were then determined from the calibration curve. The assay has been validated, and has a good linearity from 2 to 100 ng/ml with acceptable within- and between-day reproducibilities. The limit of quantitation is 2 ng/ml for nifedipine; therefore nifedipine concentrations of less than 2 ng/ml were regarded as 0 ng/ml during data analysis.

2.3.3. Analysis of pharmacokinetics data

The maximum plasma level (C_{max}) was determined according to a standard procedure. The linear trapezoidal method was used to calculate the area under the plasma concentration versus time curve (AUC). The time of first appearance (TFA) of nifedipine in plasma was defined as the blood sample collection time when nifedipine was first detected in plasma. Nifedipine absorption after oral administration of SR tablet and CC tablets was calculated from intravenous administration of solution and of the tablets by the point-area deconvolution method (Iga et al., 1986). The paired Student's *t*-test was used to test for differences between the formulations at a 5% significance level except for TFA values, which were compared by signed rank test; again, a 5% significance level was chosen. The statistical software package SAS (version 8.2; SAS Institute Inc.; Cary, NC, USA) was used to analyze the data.

3. Results and discussion

3.1. Dissolution of nifedipine

The oral bioavailability of crystalline nifedipine is low because of its poor water solubility (Sugimoto et al., 1981). Its oral bioavailability increases when it is in the amorphous form (Uekama et al., 1992). Therefore, solid dispersion of nifedipine with hydroxypropylmethylcellulose (HPMC) was prepared by spray-drying to generate an amorphous form of nifedipine. The X-ray diffraction patterns of nifedip-

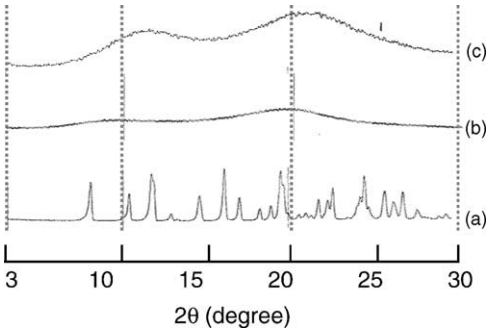

Fig. 1. X-ray diffraction spectra of (a) crystalline nifedipine bulk, (b) HPMC, and (c) the nifedipine-HPMC solid dispersion with a mass ratio of 10:9.

ine, HPMC, and the nifedipine-HPMC solid dispersion are shown in Fig. 1. The characteristic diffraction peaks for crystalline nifedipine (Fig. 1a) were not observed in the solid dispersion (Fig. 1c), which indicate that the nifedipine in this solid dispersion was amorphous form. Fig. 2 shows dissolution profiles of nifedipine from bulk crystalline and the solid dispersion in aqueous solutions. The dissolution of nifedipine in the solid dispersion was markedly greater than

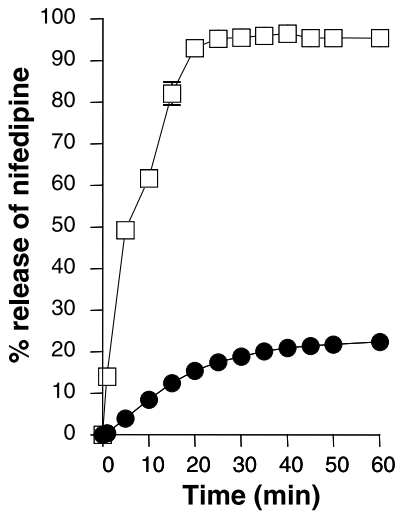

Fig. 2. In vitro dissolution profiles of crystalline nifedipine (closed circles) and the nifedipine-HPMC solid dispersion (open squares) using the paddle method at a rotation speed of 200 rpm in the 2nd fluid (pH 6.8) for the JP Disintegration Test. Each point represents the mean ± S.D. of three experiments. Loading amount of nifedipine is 20 mg.

the dissolution of crystalline nifedipine. Therefore, the solid dispersion of nifedipine was used as the drug source for subsequent experiments.

3.2. In vitro characteristics of sustained-release tablet and compression-coated tablets

Oral controlled-release formulations are designed to modify drug release to optimize the drug therapy and to improve patients compliance. It is important that controlled-release formulations release a drug not just in the small intestine but also in the lower gastrointestinal (GI) to provide sustained release. For gel-forming matrix tablets, it has been reported that rapid gelation provides continuous drug release (Sako et al., 1996). It has also been reported that compression-coated tablets with a greater core erosion ratio steadily release their drug after the lag time until they have completely dissolved (Sawada et al., 2003b). To compare the performance of these formulations, an SR tablet was prepared by adding sucrose, a highly water soluble excipient, to the gel-forming polymer polyethylene oxide (PEO) to enhance water penetration into the tablet (Table 1). As a result, the gelation index of this modified SR tablet was 80%, showing that the tablet would be able to release a drug even in the lower GI tract where little water exists. Time-release tablets, CC-1, CC-2, CC-3, and CC-4, were prepared using the dry-coating method (Table 1). To increase the core erosion ratio, sucrose was added to the core tablet formulation and polyethylene glycol (PEG) was added to the outer layer. The core erosion ratio of all CC tablets are greater than 60%. We previously reported that a CC tablet with a large core erosion ratio can significantly increase in vivo drug release from compression-coated tablets, leading to increased drug absorption from the lower GI tract (Sawada et al., 2003b). Thus, it was expected that the CC tablets sufficiently released nifedipine in the GI tract. Fig. 3 shows nifedipine dissolution profiles from the SR tablet and the CC tablets. The nifedipine release from CC tablets showed a clear lag time before nifedipine dissolution began, indicating the compression-coated tablets function as time-release formulations. The lag time before nifedipine release from each compression-coated tablets was 2.2 h for CC-1, 3.5 h for CC-2, 6.1 h for CC-3, and 8.5 h for CC-4. These lag times increased as the amount of

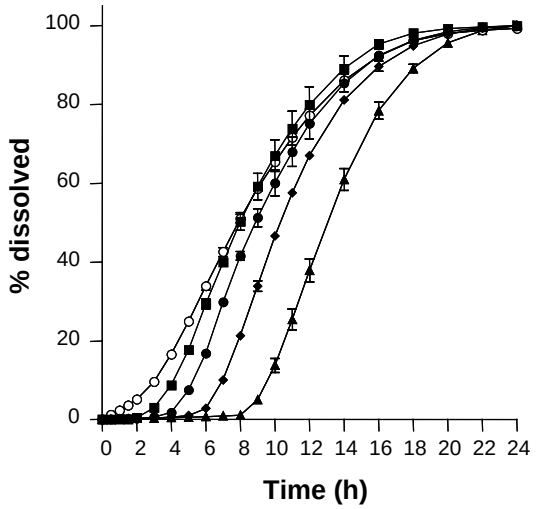

Fig. 3. In vitro dissolution profiles of nifedipine from SR tablet (open circles), CC-1 (closed squares), CC-2 (closed circles), CC-3 (closed diamonds), and CC-4 (closed triangles) using the paddle method at a rotation speed of 200 rpm in the 2nd fluid (pH 6.8) for the JP Disintegration Test including 1% (w/w) of polyoxyethylene sorbitan monooleate. Each point represents the mean ± range of two experiments except for points of SR tablet, which represent mean ± S.D. of three experiments.

PEO in the outer layer increased. It might be caused by delaying the erosion rate of the outer layer with high content of PEO because of its high viscosity and gel-forming ability. Fig. 4 shows the correlation between the amount of PEO in the outer layer and the in vitro lag time. The coefficient of determination (r^2) was 0.976. These results demonstrate that the lag time of drug release from the CC tablets can be controlled by changing the amount of PEO in the outer layer.

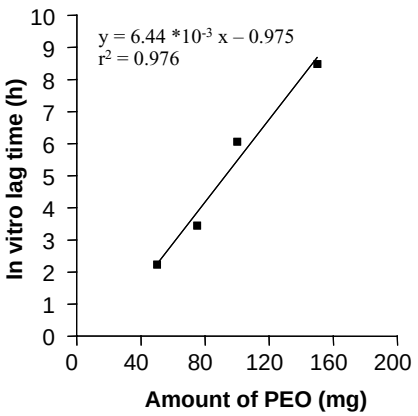

Fig. 4. Relationship between the amount of PEO in the outer layer of compression-coated tablets and the in vitro lag time before drug release.

3.3. In vivo performance of sustained-release tablet and compression-coated tablets

In order to investigate the in vivo performance of these formulations and what predictive value the in vitro lag time of drug release has on in vivo release performance, the SR tablet and two kinds of compression-coated time-release tablet formulations with different in vitro dissolution profiles, CC-1 and CC-2 (Table 1), were separately administered to eight dogs. Fig. 5 shows the mean plasma concentration profiles of nifedipine after oral administration of these tablets to dogs. The resulting pharmacokinetic parameters of these formulations are shown in Table 2. When the SR tablet was administered to eight dogs, the time of first appearance (TFA) of nifedipine in plasma was 0.7 ± 0.3 h. In five of eight dogs, nifedipine was first detected in plasma at 0.5 h, the first sampling period after administration. The plasma concentration increased steadily and lasted until 24 h after administration. It is thought that this plasma nifedipine concentration profile is typical for a standard once-daily formulation. In the beagle dogs after intravenous administration, mean plasma nifedipine concentrations declined with a mean terminal half-life of 2.1 h (Fig. 6). Therefore, the long lasting plasma concentration is likely caused by nifedipine release from the gelated SR tablet throughout the GI tract which is responsible for continuous drug absorption. Similarly, for the CC tablets, lag times of the plasma

Table 2
Pharmacokinetic parameters obtained from oral administration of SR, CC-1, or CC-2 tablets to fed dogs

Formulation code	AUC (ng h/ml)	C_{max} (ng/ml)	TFA[a] (h)
SR	328.5 ± 75.8	31.0 ± 4.8	0.7 ± 0.3
CC-1	339.5 ± 115.7	38.7 ± 6.0*	2.5 ± 1.2**
CC-2	379.3 ± 154.0	40.0 ± 8.0*	5.3 ± 1.0**

Data represent the mean ± S.D. from eight dogs.
[a] TFA, time of first appearance in plasma.
* Significantly different from SR ($P < 0.05$).
** Significantly different from SR ($P < 0.01$).

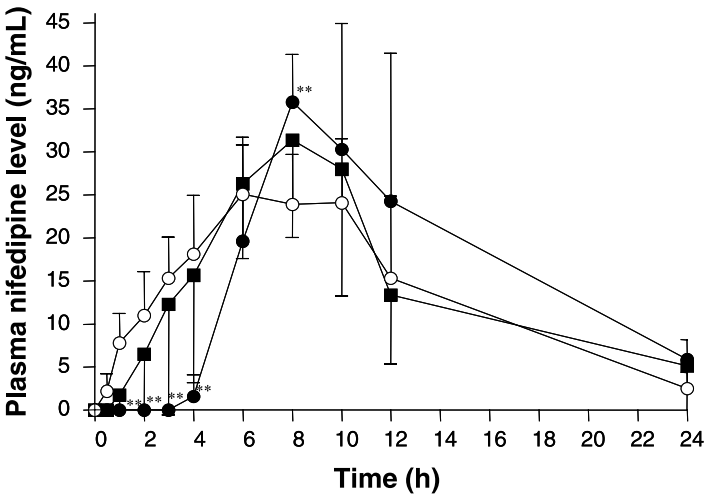

Fig. 5. Mean plasma levels of nifedipine after oral administration of the SR tablet (open circles), the CC-1 tablet (closed squares), and the CC-2 tablet (closed circles) at a dose of 180 mg nifedipine to fed beagle dogs. Each point represents the mean ± S.D. from eight dogs. **Significant difference at $P < 0.01$ between SR tablet and CC-2 tablet.

concentration profile of nifedipine were clearly observed for both CC-1 and CC-2. The TFA values of nifedipine in plasma, which are indicators of the in vivo lag time, were 2.5 ± 1.2 h for CC-1, and 5.3 ± 1.0 h for CC-2. These values demonstrate that compression-coated tablets with a lag time before drug release in vitro function as time-release formulations in vivo, especially for the CC-2 formulation; in three of eight dogs, the formulation had a 4-h TFA and the rest showed a 6-h TFA. The inter-individual variation in TFA was small and caused by only one sampling chance. As shown in Fig. 7, there is a significant correlation between the in vitro lag time before drug release and the TFA, which represents the in vivo lag time of drug absorption ($r^2 = 0.824$). From the results shown in Figs. 4 and 6, the in vivo lag time before drug absorption for compression-coated time-release formulations can be predicted from the in vitro dissolution property and is controlled by the amount of PEO in the outer layer.

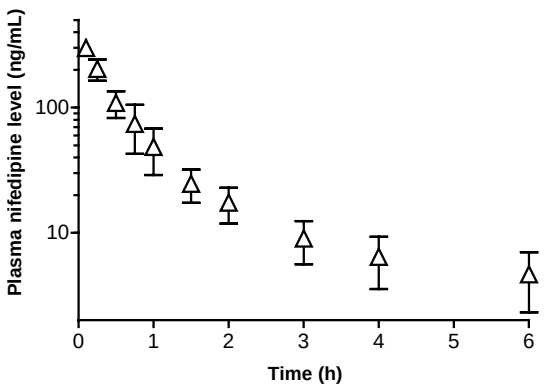

Fig. 6. Mean plasma levels of nifedipine after intravenous administration at a dose of 0.5 mg/kg to fasted beagle dogs. Each point represents the mean ± S.D. from eight dogs.

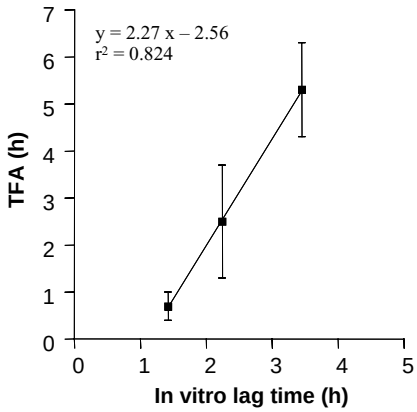

Fig. 7. Relationship between the in vitro lag time before drug release and the time of first appearance in plasma in vivo (TFA). Each point represents the mean ± S.D. from eight dogs.

Additionally, there is no significant difference in the area under the plasma concentration-time curves between the SR tablet and the CC-1 or CC-2 tablets. Therefore, it is thought that both SR and CC tablets released sufficient drug in the GI tract.

3.4. Possible applications for chronopharmacotherapy

Blood pressure and heart rate have distinct circadian rhythms in both normotensive and hypertensive persons (Pickering and James, 1993; White and Morganroth, 1989). In a person who is awake during the daytime and asleep during the nighttime, blood pressure rises in the early morning upon awakening, reaches a plateau at the highest values of the day during work or physical activity, and declines to its lowest value around midnight (Bevan et al., 1969). The lower concentrations of anti-hypertensive drugs during sleep are recommended for such patients. Because it has been reported that an excessive reduction in blood pressure during sleep might predispose elderly hypertensive patients to ischemic cerebrovascular disease (Kario et al., 1996; Nakamura et al., 1995). A compression-coated core tablet tested in this study might effectively control the concentrations of such drugs by regulating the drug release. Table 3 shows the nifedipine absorption of the SR tablet and two CC tablet formulations calculated using deconvolution method. In the first 6 h after oral administration of the SR tablet, approximately 38% of dose was absorbed. In contrast, only 11% of the dose was absorbed after oral administration of the CC-2 tablet. Therefore, by delaying drug release from the formulation, a CC-2-like formulation taken at bedtime might reduce the excessive reduction in blood pressure during the nighttime.

Conversely, it has also been reported that a steep elevation in blood pressure occurs in the early morning (White, 2001), and that regulating this morning surge in blood pressure might be an effective way to prevent both target organ damage and subsequent cardiovascular events such as myocardial infarction and stroke in hypertensive patients (Kario et al., 2003). It is thought that clinically effective plasma drug concentrations in the early morning would maximize an anti-hypertensive drug's effect on blood pressure during that period. Paradoxically, waking to take such a drug in the early morning might induce the morning surge in blood pressure that the drug is designed to prevent. Thus, a formulation with a lag time before drug release might achieve the desired drug concentration profiles. Results from the present study show promise; the CC-2 tablet formulation produced larger plasma nifedipine concentrations during 8–12 h after administration than did the SR tablet, especially there was a significant difference at 8 h ($P < 0.01$). In contrast, lower plasma nifedipine concentrations of the CC-2 tablet than those of the SR tablet were observed up to 6 h after administration, especially there were significant differences up to 4 h ($P < 0.05$) (Fig. 5). These results suggest that if a CC-2-like formulation is taken prior to sleep, the plasma nifedipine concentration would reach clinically effective levels in the early morning that might effectively regulate the morning surge in blood pressure.

Table 3
Fraction of in vivo absorption of nifedipine from SR, CC-1, or CC-2 tablets after oral administration to fed dogs

Formulation code	0–6 h (%)	6–12 h (%)	12–24 h (%)
SR	38.4 (1.00)	45.2 (1.00)	16.3 (1.00)
CC-1	31.5[a] (0.82)	49.0[a] (1.08)	19.5[a] (1.19)
CC-2	11.1* (0.29)	55.3* (1.22)	33.7* (2.06)

Each value represents the mean of eight dogs and the ratio to the value for the SR tablet is shown in parentheses.
[a] Not significantly different from SR.
* Significantly different from SR ($P < 0.05$).

4. Conclusion

In conclusion, the results of both in vitro dissolution tests and in vivo pharmacokinetics measurements indicate that compression-coated core tablets whose outer layer consists of a PEO and PEG mixture act as time-release formulations. These results also show that the in vitro lag time before drug release can be used to predict the in vivo lag time of drug release. Additionally, the plasma nifedipine profiles after oral administration of CC-2 tablet suggest that a formulation that achieves clinically appropriate plasma nifedipine concentration in the early morning might effectively regulate the morning surge in blood pressure responsible for myocardial infarction and stroke in hypertensive

patients. Thus, compression-coated time-release formulations that control the plasma drug concentrations by design show promise as drug delivery systems for chronopharmacotherapy.

References

Bevan, A.T., Honour, A.J., Stott, F.H., 1969. Direct arterial pressure recording in unrestricted man. Clin. Sci. 36, 329–344.

Coupe, A.J., Davis, S.S., Wilding, I.R., 1991. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. Pharm. Res. 8, 360–364.

Iga, K., Ogawa, Y., Yashiki, T., Shimamoto, T., 1986. Estimation of drug absorption rates using a deconvolution method with non-equal sampling time. J. Pharmacokinet. Biopharm. 14, 213–225.

Kario, K., Matsuo, T., Kobayashi, H., Imiya, M., Matsuo, M., Shimada, K., 1996. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Hypertension 27, 130–135.

Kario, K., Pickering, T.G., Umeda, Y., Hoshide, S., Hoshide, Y., Morinari, M., Murata, M., Kuroda, T., Schwartz, J.E., Shimada, K., 2003. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives. Circulation 107, 1401–1406.

Krögel, I., Bodmeier, R., 1998. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharm. Res. 15, 474–481.

Lemmer, B., 1991. Circadian rhythms and drug delivery. J. Control. Release 16, 63–74.

Nakamura, K., Oita, J., Yamaguchi, T., 1995. Nocturnal blood pressure dip in stroke survivors. Stroke 26, 1373–1378.

Pickering, T.G., James, G.D., 1993. Determinants and consequences of the diurnal rhythm of blood pressure. Am. J. Hypertens. 6, 166S–169S.

Rubinstein, A., Tirosh, B., Baluom, M., Nassar, T., David, A., Radai, R., Gliko-Kabir, I., Friedman, M., 1997. The rationale for peptide drug delivery to the colon and the potential of polymeric carriers as effective tools. J. Control. Release 46, 59–73.

Sako, K., Nakashima, H., Sawada, T., Fukui, M., 1996. Relationship between gelation rate of controlled-release acetaminophen tablets containing polyethylene oxide and colonic drug release in dogs. Pharm. Res. 13, 594–598.

Sawada, T., Sako, K., Yoshihara, K., Nakamura, K., Yokohama, S., Hayashi, M., 2003a. Timed-release formulation to avoid drug–drug interaction between diltiazem and midazolam. J. Pharm. Sci. 92, 790–797.

Sawada, T., Sako, K., Fukui, M., Yokohama, S., Hayashi, M., 2003b. A new index, the core erosion ratio, of compression-coated timed-release tablets predicts the bioavailability of acetaminophen. Int. J. Pharm. 265, 55–63.

Sugimoto, I., Kuchiki, A., Nakagawa, H., 1981. Stability of nifedipine-polyvinylpyrrolidone coprecipitate. Chem. Pharm. Bull. 29, 1715–1723.

Ueda, Y., Hata, T., Yamaguchi, H., Kotani, M., Ueda, S., 1994. Development of a novel drug release system, time-controlled explosion system (TES). I. Concept and design. J. Drug Target. 2, 35–44.

Uekama, K., Ikegami, K., Wang, Z., Horiuchi, Y., Hirayama, F., 1992. Inhibitory effect of 2-hydroxypropyl-β-cyclodextrin on crystal-growth of nifedipine during storage: superior dissolution and oral bioavailability compared with polyvinylpyrrolidone K-30. J. Pharm. Pharmacol. 44, 73–78.

White, W.B., 2001. Cardiovascular risk and therapeutic intervention for the early morning surge in blood pressure and heart rate. Blood Press. Monit. 6, 63–72.

White, W.B., Morganroth, J., 1989. Usefulness of ambulatory monitoring of blood pressure in assessing antihypertensive therapy. Am. J. Cardiol. 63, 94–98.

White, W.B., Black, H.R., Weber, M.A., Elliott, W.J., Bryzinski, B., Fakouhi, T.D., 1998. Comparison of effects of controlled onset extended release verapamil at bedtime and nifedipine gastrointestinal therapeutic system on arising on early morning blood pressure, heart rate, and the heart rate-blood pressure product. Am. J. Cardiol. 81, 424–431.

Wilding, I.R., Davis, S.S., Sparrow, R.A., Smith, K.J., Sinclair, K.A., Smith, A.T., 1993. The evaluation of an enteric-coated naproxen tablet formulation using gamma scintigraphy. Eur. J. Pharm. Biopharm. 39, 144–147.