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Design and In-vitro Evaluation of a Modified-release Oral Dosage Form of Nifedipine by Hybridization of Hydroxypropyl-β-cyclodextrin and Hydroxypropylcellulose

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Abstract—To modify the release rate of nifedipine, a potent calcium channel antagonist, a double-layer tablet was designed, anticipating a more balanced oral bioavailability and a prolonged efficacy than the simple plain tablet. Amorphous nifedipine powders prepared by spray-drying with 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD) and nonionic surfactant HCO-60 were employed as a fast-release portion to attain an initial rapid dissolution of nifedipine. Hydroxypropylcelluloses (HPCs) with different viscosity grades (type L, M, and H) were used for a slow-release portion to provide an appropriate sustained-release. Taking into account the physiological conditions of the gastrointestinal tract (pH and motility), an optimal formulation of the double-layer tablet was obtained by changing the mixing ratios of each component. For example, the tablet consisting of HP-β-CyD with 3% HCO-60/(HPC-L:HPC-M) in the weight ratio 1/2(1:1) provided a sufficient slow release of the drug over a wide pH region following an initial rapid dissolution. The release of nifedipine from the double-layer tablets was little affected by pH of the medium and rotation speed of paddle after accelerated storage conditions (60°C, 75% r.h.). The present results suggest that a combination of HP-β-CyD, HCO-60 and HPCs can serve as a modified-release carrier for poorly water-soluble nifedipine.

Nifedipine, a calcium channel antagonist, in conventional formulations is known to have a short-elimination half-life with significant fluctuations in plasma drug concentrations (Foster et al 1983; Kleinbloesem et al 1984). To attain a prolonged therapeutic effect and a reduced incidence of side-effects, many attempts have been made to maintain a suitable plasma level of nifedipine for a long period of time with minimal frequency of administration (Sugimoto et al 1982; Pabst et al 1986; Kleinbloesem et al 1987). For this purpose, rationally designed drug carrier materials have been used to control drug release at the desired level. The multi-functional characteristics of cyclodextrins (CyDs) have been widely applied to improve pharmaceutical properties of drug molecules; this may make them candidates for novel drug carriers (Uekama & Otagiri 1987; Szejtli 1988; Duchêne 1991). We have recently reported that 2-hydroxypropyl-β-cyclodextrin (HP-β-CyD) is particularly useful to improve the dissolution rate of nifedipine, solving the bioavailability problems encountered by storage of amorphous nifedipine in solid dosage forms (Uekama et al 1992). From the practical point of view, HP-β-CyD is useful because of its superior properties (a highly water-soluble, amorphous powder with no detectable oral toxicity) as a pharmaceutical additive (Müller & Brauns 1985; Pitha 1988; Uekama et al 1991). The release of theophylline, which has a narrow therapeutic range, has been controlled by hybridizing its hydrophilic and hydrophobic CyD complexes (Horiuchi et al 1991). These led us to design a double-layer tablet formulation of nifedipine consisting of a slow-release matrix together with a fast-release portion, because the initial release in a certain amount of drug will give more balanced oral bioavailability, reducing the first-pass metabolism in intestine and liver (Foster et al 1983; Kleinbloesem et al 1984). In the present study, therefore, a combination of highly hydrophilic HP-β-CyD and nonionic surfactant was used for the fast-release portion to improve the low solubility and wettability of nifedipine in water, and three viscosity grades of hydroxypropylcelluloses (HPCs) were used for the slow-release portion to elicit an appropriate sustained-release of nifedipine from the viscous matrices.

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Materials and Methods

Materials

HP-β-CyD with an average degree of substitution of 5·8 and nifedipine were donated by Nihon Shyokuhin Kako Co. Ltd (Tokyo, Japan), and Bayer Yakuhin Ltd (Osaka, Japan), respectively. Three HPCs, HPC-L, HPC-M, and HPC-H with different viscosity grades (viscosity ranges of 2% aqueous solutions at 20°C of 6–10, 150–400 and 1000–4000 cP s, respectively), were supplied from Nippon Soda Co. (Tokyo, Japan). Nonionic surfactant, HCO-60, was purchased from Nikko Chemicals Co. (Tokyo, Japan). Other chemicals and solvents were of analytical reagent grade, and deionized double-distilled water was used throughout the study. All experiments were carried out under light-protected conditions to prevent the photodecomposition of nifedipine.

Preparation of nifedipine powders

Sample powders containing nifedipine were prepared according to the spray-drying method described previously (Uekama et al 1992). Nifedipine and HP-β-CyD or HPC with or without HCO-60 were dissolved in dichloromethane ethanol in various weight ratios, before spray-drying, using a Pulvis GA32 Yamato spray-drier (Tokyo, Japan). The

drying conditions were as follows: air flow rate, 0·45 m^3 min^{-1}; air pressure, 1·0 kg cm^{-2}; inlet and outlet temperatures, 85 and 55°C, respectively. Powder X-ray diffraction patterns of the spray-dried products thus obtained were measured, using a Rigaku Denki RAD-1C diffractometer (Tokyo, Japan) with Ni-filtered Cu-Kα radiation.

Ageing studies

The test powders (150 mg, < 100 mesh) were placed in glass containers, in desiccators at constant relative humidity (75% r.h.), and then stored in incubators at constant temperature (60°C), as described previously (Uekama et al 1992). At appropriate time intervals the samples were withdrawn and dried under reduced pressure at room temperature (25°C) for 24 h in phosphorous pentoxide desiccators before preparation of tablets. Amorphous nifedipine in the HP-β-CyD complex was completely converted to the crystalline form after about 30 days, when stored under the above conditions.

Preparation of nifedipine tablets

Flat-faced plain tablets of 4 mm diameter were prepared by compressing sample powder (content of nifedipine, 5 mg) under a pressure of 1000 kg cm^{-2} for 1 min in a hydraulic press (Model R-303, Riken Seiki, Tokyo, Japan). For double-layer tablets, the slow-release portion was initially placed in the die and lightly compressed, and then the fast-release portion was directly added onto the tablet, and then compressed to combine them in the same manner as the plain tablets. To examine the effect of compression pressure on drug release, pressures of 50, 500 and 1000 kg cm^{-2} were applied to the double-layer tablet for 1 min. The total mass of the double-layer tablet was adjusted to give a net content of 5 mg nifedipine on the basis of the fractional amount of the drug in each constituent. Water penetration rate into the tablets was measured by using the same apparatus described previously (Horiuchi et al 1990), i.e. the water uptake rate was read from a calibrated capillary tube (Wan & Heng 1985).

Release studies

The release of drug from the compressed tablets was measured, using an automatic dissolution testing apparatus described recently (Uekama et al 1990) at 37°C and stirring speed of 100 rev min^{-1}, unless otherwise stated. The tablet was placed in the bottom of the reservoir, and the medium (900 mL water) was continuously pumped through a glass filter stick (G3; $\phi = 20$–30 μm) at a flow rate of 3 mL min^{-1} to the flow cell in the UV detector and then back to the reservoir. The time-lag from the reservoir to the UV monitor was 0·5 min. The amount of nifedipine dissolved in the medium was automatically measured at a wavelength of 254 nm. The sink condition was maintained, since the amount of nifedipine dissolved in the medium was lower than its solubility. The pH-dependency of the release rate of nifedipine from the tablets was measured using an improved version of pH-variable dissolution testing apparatus, equipped with a pH controlling system (Horikawa et al 1992). The medium employed was a mixed buffer solution (900 mL) of 0·05 M hydrochloric acid, 0·05 M acetic acid and 0·05 M phosphoric acid, which was initially adjusted to pH 1·2 and maintained at 37°C. At the prescribed intervals, the pH of the dissolution medium was increased from 1·2 to 6·8 by addition of 2 M NaOH through an autoburret (Hiranuma UCB 900 RS, Tokyo, Japan). The release rates of the drug as a function of pH was computed with a personal computer. Three replicate values agreed to within less than 3% of the mean.

Results and Discussion

Fast- and slow-release portions

Because of the poor solubility and wettability of nifedipine in water, a combination of highly water-soluble HP-β-CyD and nonionic surfactant HCO-60 was employed as an immediate-release carrier, in the expectation of an enhanced release rate of nifedipine. Wax-type matrices or water-insoluble cellulose derivatives have been widely used as slow-release carriers for water-soluble drugs. In the case of poorly water-soluble drugs, however, a relatively hydrophilic polymer was thought to be suitable as a slow-release carrier. Therefore, HPC, a typical hydrophilic cellulose derivative with different viscosity grades, was used as a carrier material of nifedipine in the slow-release portion, since it has exhibited release patterns suitable for a sustained-release preparation (Nakano et al 1983).

Table 1 summarizes the release data of nifedipine from the plain tablets containing spray-dried products of HP-β-CyD or three HPCs. The release of nifedipine from the HP-β-CyD tablets was faster than that of intact nifedipine. This can be ascribed to the decrease in crystallinity and particle size of nifedipine during the spray-drying process, as expected from the powder X-ray diffraction patterns (Uekama et al 1992). Although the magnitude of the stability constant of nifedipine-HP-β-CyD complex (370 M^{-1} in water at 25°C) was relatively small (Uekama et al 1992), the formation of a water-soluble complex of nifedipine with HP-β-CyD may also be responsible for the increase in dissolution rate. We have recently found that the nonionic surfactant HCO-60 significantly improves the dissolution characteristics of the nifedipine-HP-β-CyD complex, preventing the crystal-growth of nifedipine encountered on storage. The drug release from the spray-dried products containing HCO-60 was much faster than that of nifedipine-HP-β-CyD alone (see Table 1). Fig. 1 shows the effect of HCO-60 content on the water uptake rate of the plain tablets containing

Table 1. Release parameters[a] of nifedipine for fast- and slow-release formulations[b].

Fast-release formulation	Time to 50% released (min)	Release at 1 h (%)
Nifedipine alone[c]	—[d]	22·6 ± 0·6
Nifedipine + HP-β-CyD	9·1 ± 0·2	92·9 ± 1·3
Nifedipine + HP-β-CyD + 3% HCO-60	4·1 ± 0·1	100·1 ± 0·7
Slow-release formulation	**Time to 50% released (h)**	**Release at 8 h (%)**
Nifedipine + HPC-L	1·1 ± 0·0	100·0 ± 0·7
Nifedipine + HPC-M	4·3 ± 0·1	85·3 ± 0·9
Nifedipine + HPC-H	8·1 ± 0·1	48·3 ± 0·9

[a] In water at 37°C; [b] tablets containing equivalent amounts of 5 mg nifedipine; [c] diluent: starch; [d] > 10 h.

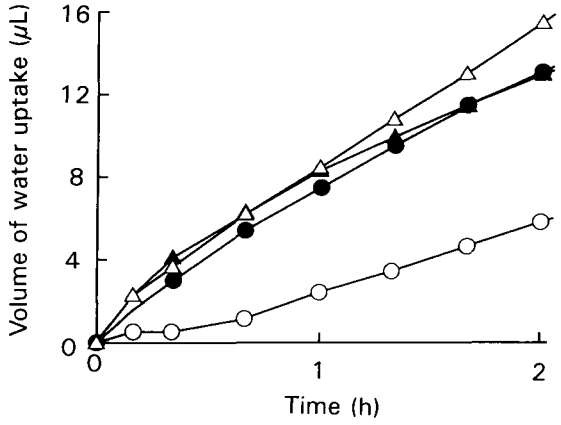

FIG. 1. Penetration of water into plain tablets containing nifedipine (5 mg) at 25°C. ○ HP-β-CyD, ● HP-β-CyD with 1% HCO-60, △ HP-β-CyD with 3% HCO-60, ▲ HP-β-CyD with 5% HCO-60.

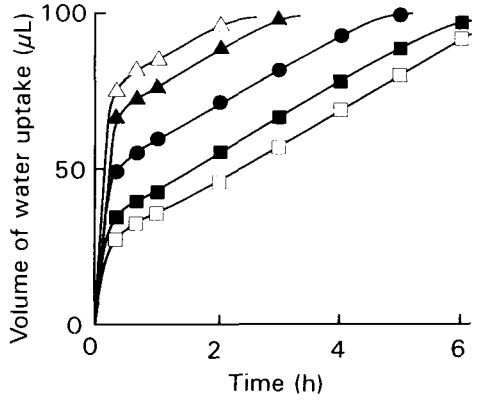

FIG. 2. Release profiles of nifedipine from double-layer tablets (total nifedipine 5 mg) consisting of nifedipine-HP-β-CyD with 3% HCO-60 as the fast-release portion (FRP) and nifedipine-HPC-M as the slow-release portion (SRP) in various weight ratios in water at 37°C. FRP:SRP, △ 3:1, ▲ 2:1, ● 1:1, ■ 1:2, □ 1:3.

nifedipine-HP-β-CyD. The penetration of water into the tablets was significantly enhanced by an increase in amount of HCO-60, probably due to the improvement of wettability. Therefore, the combination of HP-β-CyD and 3% HCO-60 was used for the fast-release portion of the double-layer tablets in the following survey. In the case of the slow-release formulation, the release rate of nifedipine was found to decrease with increasing viscosity of HPC, where an apparent zero-order release was obtained for the HPC-M and HPC-H systems. Therefore, the release rate of the drug can be modified by changing the mixing ratio of polymers with different viscosity grades depending on the required sustained period.

Design of double-layer tablets

For the design of modified-release formulation of nifedipine, the following desirable attributes were sought: a release rate should be at least 90% within 6–8 h, which may be the average passage time of a tablet in the gastrointestinal tract of subjects after oral administration (Davis et al 1984); an appropriate release of nifedipine in the early stage is necessary to reduce the significant first-pass metabolism in intestine and liver (Foster et al 1983; Kleinbloesem et al 1984), which may offer a more balanced bioavailability; nifedipine should be released according to zero-order kinetics for a long period of time, because of such therapeutic advantages as duration of pharmacological effect and lowering of side-effects (Kleinbloesem et al 1987). On the basis of these goals, a suitable formulation of nifedipine was examined by changing the mixing ratio of each component in the double-layer tablet.

Fig. 2 shows a typical example of the release profiles of nifedipine from the double-layer tablets consisting of nifedipine-HP-β-CyD with 3% HCO-60 as the fast-release portion and a nifedipine-HPC-M matrix as the slow-release portion in various weight ratios. It is apparent that the initial release rate of the drug increased with increasing amount of the fast-release portions (1:3 < 1:2 < 1:1 < 2:1 < 3:1). Fig. 3 shows another variation of the release profiles of nifedipine from the double-layer tablets. In this system, the slow-release portion was hybridized with HPC-L and HPC-M by changing the mixing ratio of two polymers, while a constant amount of the fast-release portion was used. It is obvious that the decrease in rate was proportional to the HPC-M content, eliciting an apparent zero-order release for a long period of time. From inspection of the release profiles in Figs 2 and 3, the double-layer tablet consisting of HP-β-CyD with 3% HCO-60:HPC-M in the weight ratio of 1:2 or 1:3 attained almost 90% of drug release after about 6 h, following an initial rapid dissolution (about 30%). These formulations seemed to be appropriate for our purpose with regard to the release pattern and time. On the other hand, the formulation of HP-β-CyD with 3% HCO-60/(HPC-L:HPC-M) in the weight ratio 1/2(1:1) may be appropriate for dog models, since the average passage time of tablets in the gastrointestinal tract of dog is 3–4 h (Mizuta et al 1990). Although the combination of HPC-L with HPC-M can substitute for that of HPC-L with HPC-H as the slow-release carrier, the former may be suitable for modifying the release rate of poorly water-soluble nifedipine, because the release of the drug from the HPC-H tablet seemed to be so slow that it would be subject to considerable first-pass metabolism.

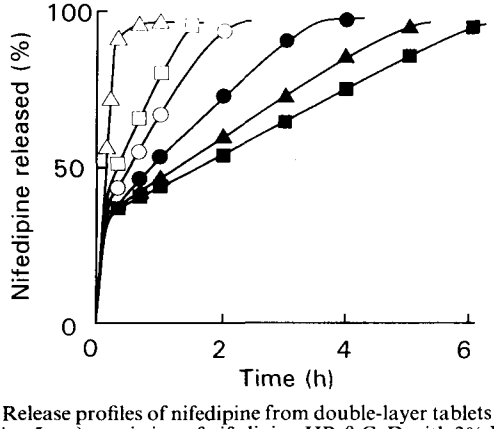

FIG. 3. Release profiles of nifedipine from double-layer tablets (total nifedipine 5 mg) consisting of nifedipine-HP-β-CyD with 3% HCO-60 as the fast-release portion (FRP) and nifedipine in HPC-L/HPC-M matrix as the slow-release portion (SRP) in various weight ratios in water at 37°C. FRP:HPC-L/HPC-M, △ 3:0/0, □ 1:2/0, ○ 1:1·5/0·5, ● 1:1/1, ▲ 1:0·5/1·5, ■ 1:0/2.

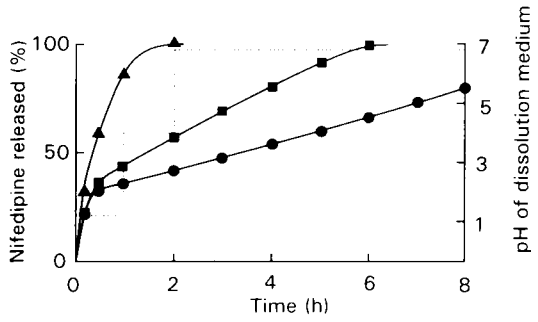

FIG. 4. Release profiles of nifedipine from double-layer tablets (total nifedipine 5 mg) consisting of nifedipine-HP-β-CyD with 3% HCO-60 as the fast-release portion (FRP) and nifedipine-HPCs as the slow-release portion (SRP) in a 1:2 weight ratio at 37°C, as a function of the pH of the medium. ▲ FRP/HPC-L, ■ FRP/HPC-M, ● FRP/HPC-H. The dotted line shows the pH of the medium.

In-vitro characteristics of the double-layer tablet

Fig. 4 shows the release profiles of nifedipine from the double-layer tablets as a function of pH of the medium. Taking into account the gastrointestinal transit of a tablet (Davis et al 1984), the pH of the medium was shifted from 1·2 to 4·0 and then fixed at 6·8 at specified time points (see dotted lines in Fig. 4). It is apparent that the drug was released independently of pH from the tablets showing an apparent zero-order rate over the wide pH range. The release of drug from the gelled matrices could have been influenced by the rotation speed of the paddle due to the change in convective movement of solvent around the hydration sheath of the gelled polymers (Lapidus & Lordi 1968). However, the release rate of nifedipine from the double-layer tablets containing HPCs was little affected by the rotation speeds. For example, the times to 50 and 100% release for the fast release portion/HPC-M tablet were $1{\cdot}57 \pm 0{\cdot}037$ and $6{\cdot}59 \pm 0{\cdot}173$ min at 50 rev min^{-1}, $1{\cdot}47 \pm 0{\cdot}031$ and $6{\cdot}39 \pm 0{\cdot}184$ min at 100 rev min^{-1}, and $1{\cdot}06 \pm 0{\cdot}025$ and $6{\cdot}02 \pm 0{\cdot}153$ min at 150 rev min^{-1}, respectively. These results suggest no significant effect of gastrointestinal motility. In the examination of the effect of compression pressure on release rate, the pressure levels covering a twentyfold change in pressure (50–1000 kg cm^{-2}) was applied to the double-layer tablet. The release patterns of nifedipine from tablets thus prepared were practically superimposable (not shown here). This indicates that compression pressure is not an important factor in changing the release pattern of the drug. As shown in Fig. 5, it is also noteworthy that no appreciable ageing effect was observed for the release rate of nifedipine from the double-layer tablets or from the plain tablets containing each component, even after 28 days at accelerated storage conditions (60°C and 75% r.h.). This may be due to the inhibition of crystal-growth and the reduction of crystal size of nifedipine in the fast-release portion consisting of HP-β-CyD and HCO-60 together within the viscous matrices of the slow-release portion.

The present results clearly demonstrate that HP-β-CyD with HCO-60 can serve as an immediate-release carrier of nifedipine, and the release rate can be modified by hybridizing with different viscosity grades of HPCs. The double-layer tablet formulation may have advantages in providing more balanced oral bioavailability than the simple plain tablet, for

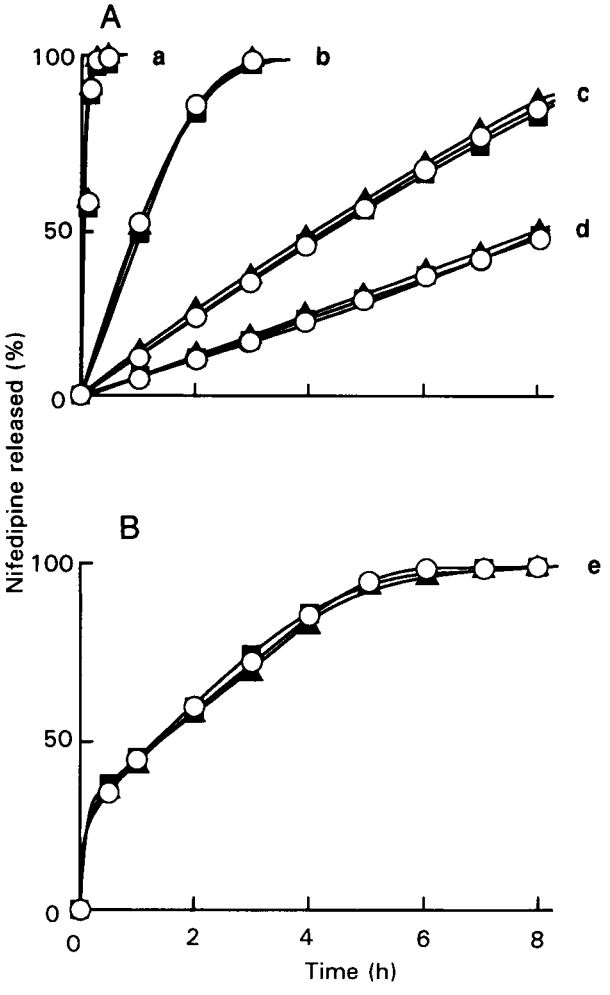

FIG. 5. Effect of storage (60°C, 75% r.h.) on the release rates of nifedipine (total nifedipine 5 mg) from plain tablets (A) and double-layer tablets (B). a. Nifedipine-HP-β-CyD with 3% HCO-60; b. nifedipine-HPC-L; c. nifedipine-HPC-M; d. nifedipine-HPC-H; e. double-layer tablet of a and c in a 1:2 weight ratio in water at 37°C. ○ Initial, ▲ after 7 days, ■ after 28 days.

poorly water-soluble drugs. However, in-vivo evaluation for the double-layer tablet of nifedipine, particularly the slow-release formulation, should be further studied, because the subsequent slow-release following an initial burst is expected to be subject to a first-pass effect.

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