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Dissolution and absorption of nifedipine in polyethylene glycol solid dispersion containing phosphatidylcholine

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Summary

The in vitro dissolution and in vivo absorption of solid dispersions of nifedipine-polyethylene glycol (nifedipine-PEG) and nifedipine-phosphatidylcholine-polyethylene glycol (nifedipine-PC-PEG) were investigated. The X-ray diffraction patterns and DSC thermograms showed that up to a ratio of 5:95 of nifedipine-PEG, the nifedipine was dispersed homogeneously in an amorphous state or dissolved in the solid dispersions. The incorporation of 5% PC into the nifedipine-PEG solid dispersion demonstrated no change in the solid-state characteristics of nifedipine as in the nifedipine-PEG solid dispersion. The dissolution of nifedipine from the solid dispersions was markedly enhanced as compared with the pure drug. The incorporation of PC into the nifedipine-PEG solid dispersion resulted in a 2.6- and 2.2-fold increase in nifedipine initial dissolution rate and dissolution after 60 min, respectively. This was attributed to the formation of lipid vesicles which entrapped a certain concentration of nifedipine during dissolution. The area under the curve after oral administration of the nifedipine-PC-PEG solid dispersion was 3.4-fold greater than that of the nifedipine-PEG solid dispersion.

Introduction

Nifedipine, a calcium-channel blocking agent, is a useful drug in the treatment of a variety of cardiovascular disorders including angina pectoris and hypertension (Sorkin et al., 1985; Ferguson and Vlasses, 1986). However, it is poorly soluble in water. When administered orally the bioavailability is poor (Duhm et al., 1972; Pabst et al., 1986).

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The solid dispersion of poorly water-soluble drugs in polyethylene glycol or polyvinylpyrrolidone was found to enhance drug dissolution and consequently improve the bioavailability (Chiou and Riegelman, 1970, 1971; Stupak and Bates, 1972; Vila-Jato and Alonso, 1986). Nifedipine-polyvinylpyrrolidone has been developed into such a system to increase drug absorption (Sugimoto et al., 1980). Griseofulvin-dimyristoylphosphatidylcholine solid dispersion has also shown to improve the drug dissolution and bioavailability (Venkataram and Rogers, 1984, 1988).

In this study, an attempt was made to investigate the in vitro dissolution behavior and in vivo absorption of solid dispersion systems of nifedip-

ine-polyethylene glycol (nifedipine-PEG) and nifedipine-polyethylene glycol with the incorporation of phosphatidylcholine (nifedipine-PC-PEG). Comparison between the results obtained from both systems was also made to evaluate the effect of phosphatidylcholine on the increase of dissolution and absorption of the nifedipine from the solid dispersions.

Materials and Methods

Materials

Nifedipine (USP XXI), melting range 171–175°C, was obtained from Chung Hsin Pharmaceutical Co. Ltd (R.O.C.). Polyethylene glycol (PEG) 4000 was purchased from Wako Pure Chemical Industry (Japan). Phosphatidylcholine (PC, from fresh egg yolk, type XI-E) was obtained from Sigma Chemical Co. (U.S.A.). Pentothel (thiopentone sodium BP) was supplied by Abbott Australiasia Pty Ltd (Australia). All other chemicals were of reagent grade.

Methods

Since nifedipine is sensitive to light, all experiments were performed under subdued light (Ebel et al., 1978; Sugimoto et al., 1980).

Preparation of nifedipine-PEG and nifedipine-PC-PEG solid dispersions

Solid dispersions were prepared by the solvent method. The required amount of nifedipine and PEG 4000 was accurately weighed and dissolved in chloroform. The mixture was evaporated under a stream of nitrogen on a water bath at 45°C and further drying was performed using a vacuum desiccator for 12 h. The dried mass was powdered, uniformly mixed with a mortar and pestle and sieved. The final products were stored in an amber desiccator and placed in a dark room. The solid dispersions in the particle size range of 40–60 mesh were used in the experiment and all samples were examined within 2 days after preparation. The concentration of nifedipine in each batch of the solid dispersions was assayed by a spectrophotometric method at 237 nm.

For the preparation of nifedipine-PC-PEG solid dispersion, the nifedipine and PC were dissolved in chloroform and added to the PEG 4000 chloroform solution with vigorous stirring; the subsequent procedures for drying and sieving were then conducted as described above for the preparation of nifedipine-PEG solid dispersion.

Dissolution study

Dissolution of the solid dispersions was determined according to the USP Apparatus 2 method in 500 ml of water as the test medium at a stirring speed of 150 rpm and at 37°C. Samples equivalent to 10 mg of nifedipine were subjected to the test. 5-ml volumes of sample solution were withdrawn at given intervals of time and an equal volume of water at 37°C was infused back in order to maintain a constant volume of the dissolution medium. The sample solution was filtered through a 1.2 μm membrane filter and centrifuged at $2.8 \times 10^5 \times g$ for 30 min to obtain a clear solution for analysis. To ensure that the sample solution was free from interference by drug particles or lipid vesicles, the filtrate or supernatant was examined under a microscope and scanned with the spectrophotometer from 500 to 210 nm to compare the nifedipine methanolic solution. The sample solutions were analyzed spectrophotometrically at 237 nm. Triplicate runs were carried out in each study. In order to measure the nifedipine concentration in the dissolution medium containing lipid vesicles, the sample solution was filtered through a 1.2 μm membrane filter but centrifugation was omitted. The lipid vesicles were able to pass through the filter and remained in the filtrate. Then, 1 part of the filtrate was added to 9 parts of methanol and vortexed vigorously to dissolve the lipid vesicles, yielding a clear solution for analysis.

Differential scanning calorimetry (DSC)

DSC was carried out with a Du Pont 910 DSC cell base equipped with a Du Pont 1090B Thermal Analyzer System. Samples were placed in

sealed aluminum pans and scanned at a rate of 10°C/min under a nitrogen atmosphere.

Powder X-ray diffraction study

Powder X-ray diffractometry was performed with a Rigaku X-Ray Diffractometer System Geigerflex D/MAX-IIIA by using Ni-filtered CuKα radiation.

In vivo absorption in rats

Male Sprague–Dawley rats weighing 280–350 g were used. The rats were fasted overnight prior to the experiment, but water was allowed ad libitum. After the rats had been anesthetized with Pentothel, solid dispersion (equivalent to 1 mg of nifedipine per kg of body weight) was administered orally by intubation with a metal tube. 0.5 ml of water was injected into the metal tube by a syringe after intake of the drug. At the time intervals of 20, 40, 60, 120, 180 and 240 min after dosing, heparinized blood samples were drawn from each rat by cardiac puncture. The blood samples were centrifuged, and the plasma was separated and frozen until analysis. For each determination, five rats were used.

Analysis of nifedipine in plasma

The plasma concentration of nifedipine was determined by high-performance liquid chromatography (HPLC). 1 ml of the internal standard of cimetidine hydrochloride (30 μg/ml) and 1 ml of 1 N sodium hydroxide solution were added to 2 ml of plasma in a glass-stoppered amber test tube and mixed well with a vortex mixer. The mixture was extracted with 7.5 ml of dichloromethane/*n*-hexane (3:7, v/v) and agitated for 5 min. After centrifugation for 5 min at 2000 × *g*, the organic layer was separated, transferred into an amber test tube and evaporated under nitrogen. The residue was reconstituted with 200 μl of the mobile phase before injection into the HPLC.

The HPLC system consisted of two solvent delivery pumps (Jasco, 880-PU, Japan), a solvent mixing module (Jasco, 880-30), a variable-wavelength ultraviolet and visible light detector (Jasco, 870-UV), an on-line degasser (Erma, ERC-3511, Japan), an autosampler (Jasco, 855-AS), a system controller (Jasco, 801-SC) and an integrator (SIC, Chromatocorder 12, Japan). The column employed for analysis was a reversed-phase column (25 cm × 4.6 mm) packed with Lichrosorb RP-18, 5 μm (Merck, Germany). The mobile phase was 0.01 M phosphate buffer with pH 6.1/acetonitrile (1:1, v/v). The detector was operated at a wavelength of 237 nm. The flow rate was 1 ml/min and the temperature was ambient. The retention time of the HPLC peak for nifedipine was 8.3 min and for cimetidine 3.7 min. No interference by plasma components was found in the peaks of interest during the analysis.

The area under the plasma concentration-time curve (AUC) was determined using the trapezoidal rule and extrapolated to infinity.

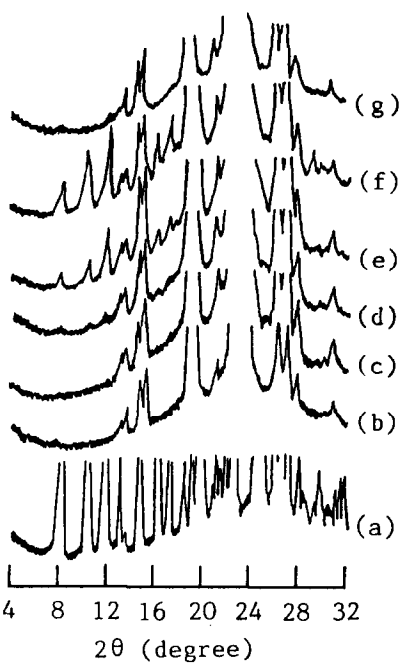

Fig. 1. X-ray diffraction spectra of nifedipine (a), PEG 4000 (b), nifedipine-PEG solid dispersion with weight ratio of 1:99 (c), 5:95 (d), 8:92 (e) and 10:90 (f) and nifedipine-PC-PEG solid dispersion with weight ratio of 5:5:90 (g).

Results and Discussion

Solid-state analysis

X-ray diffraction patterns of nifedipine, PEG 4000, nifedipine-PEG solid dispersions with various contents of nifedipine and nifedipine-PC-PEG solid dispersion are shown in Fig. 1. The characteristic diffraction peaks for nifedipine in the patterns gradually increase with nifedipine content. In the solid dispersions with nifedipine content in the range 1–5%, the diffraction peaks of nifedipine were not observed but peaks due to PEG 4000 were noted. This indicated that the crystalline characteristics of nifedipine disappeared in these solid dispersions. The diffraction pattern of the nifedipine-PC-PEG (5:5:90) solid dispersion showed a similar result to that of the nifedipine-PEG (5:95) solid dispersion. It is likely that the incorporation of PC into the solid dispersion would not alter the amorphous state or solubility of the nifedipine in the solid dispersion.

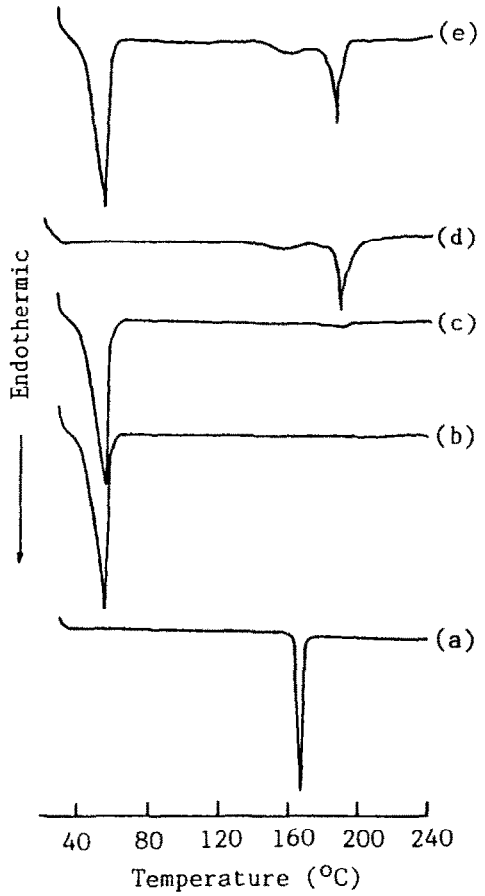

Fig. 2. DSC thermograms of nifedipine (a), PEG 4000 (b), nifedipine-PEG (5:95) solid dispersion (c), PC (d) and nifedipine-PC-PEG (5:5:90) solid dispersion (e).

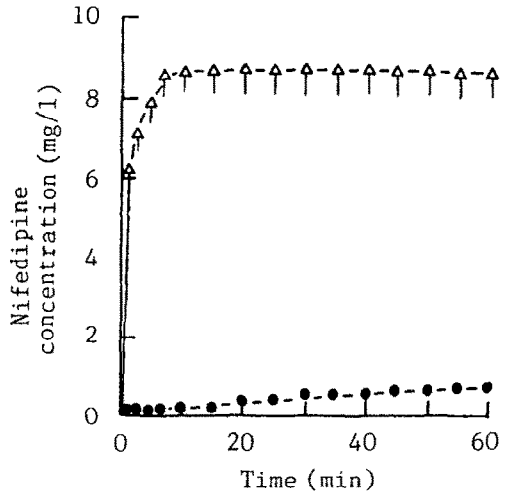

Fig. 3. Dissolution profiles of nifedipine (●) and nifedipine-PEG (5:95) solid dispersion (△).

The DSC thermograms of nifedipine, PEG 4000, PC, nifedipine-PEG solid dispersion and nifedipine-PC-PEG solid dispersion are shown in Fig. 2. Nifedipine, PEG 4000 and PC demonstrated an endothermic peak at 174, 58 and 185°C, respectively. The thermogram of the solid dispersion of nifedipine-PEG (5:95) showed no nifedipine peak but did exhibit a peak for PEG at 58°C. In the case of the solid dispersion of nifedipine-PC-PEG (5:5:90), the thermogram also showed no nifedipine peak but peaks for PEG and PC were evident at 58 and 185°C, respectively. The DSC results confirmed the data from X-ray diffraction demonstrating that the nifedipine could be dispersed homogeneously in an amorphous state or dissolved in the PEG in the concentration range from 1 to 5% nifedipine, and that the presence of PC in the solid dispersion would not affect the amorphous or solution state of the nifedipine in the solid dispersion.

Dissolution study

The dissolution profiles of nifedipine and nifedipine from the nifedipine-PEG solid disper-

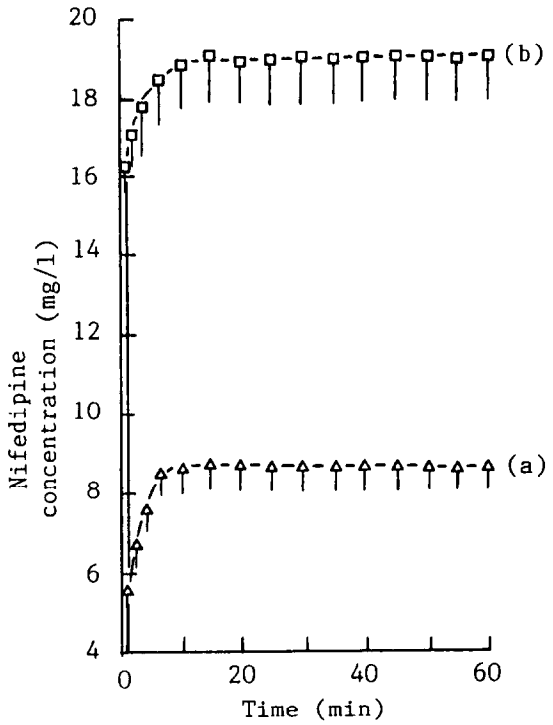

Fig. 4. Dissolution profiles of nifedipine-PC-PEG (5:5:90) solid dispersions. Nifedipine concentrations determined from: (a) the clear supernatant of the sample solution after centrifugation and (b) the sample solution where the lipid vesicle entrapped nifedipine concentration was taken into account.

sion are shown in Fig. 3. The dissolution of nifedipine was markedly enhanced in the solid dispersion.

The dissolution medium of the nifedipine-PC-PEG solid dispersion formed a turbid solution after dissolution. Under the microscope, lipid vesicles were observed from the turbid dissolution medium. This was attributed to the PC in the solid dispersion that formed lipid vesicles while dissolution took place.

The turbid dissolution medium of the nifedipine-PC-PEG solid dispersion demonstrated a clear supernatant after ultracentrifugation. The dissolution profile shown in Fig. 4 (curve a) for the nifedipine-PC-PEG solid dispersion was constructed according to the drug concentration remaining in the clear supernatant. The dissolution medium for the nifedipine-PEG solid dispersion after dissolution was clear and no particle interference was detected. The concentration in the medium showed no difference before and after ultracentrifugation. The dissolution profile for the nifedipine-PEG solid dispersion (Fig. 3) is similar to that for the nifedipine-PC-PEG solid dispersion (Fig. 4a).

Fig. 4 (curve b) depicts the dissolution profile for nifedipine-PC-PEG solid dispersion constructed from the nifedipine concentrations in the dissolution medium in which the concentration of the lipid vesicle entrapped nifedipine was taken into account. This profile showed a significant increase in dissolution of nifedipine. The initial dissolution rate was 16.3 mg/l per min for nifedipine-PC-PEG solid dispersion and 6.2 mg/l per min for nifedipine-PEG solid dispersion. The concentration for nifedipine after 60 min of dissolution was 19.1 and 8.7 mg/l for the solid dispersion with and without the incorporation of PC, respectively. There was a 2.6-fold increase in initial dissolution rate and a 2.2-fold enhancement of dissolution after 60 min for the solid dispersion with the incorporation of PC. During dissolution, PC as well as nifedipine molecules would dissociate from the solid dispersion. PC molecules could form vesicles which entrap some dissociated nifedipine molecules; also, the lipid-soluble nifedipine molecules could be accommo-

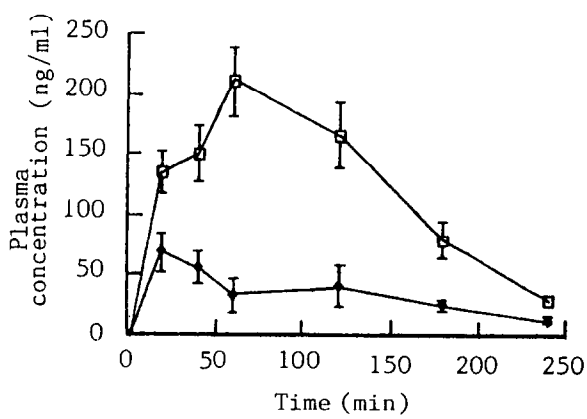

Fig. 5. Plasma concentration-time profiles of nifedipine after oral administration of nifedipine-PEG (5:95) solid dispersion (◆) and nifedipine-PC-PEG (5:5:90) solid dispersion (□) in rats.

dated in the bilayer structure of the PC vesicles. Obviously, the increase in dissolution for the nifedipine-PC-PEG solid dispersion was due to the formation of lipid vesicles which entrapped a certain concentration of nifedipine. Moreover, The enhancement of the dissolution behavior of the solid dispersion in the presence of PC may be due to the extraction of nifedipine in solution by lipid vesicles formed from the dissolution of the PC in the solid dispersion leading to an increase in the apparent solubility of nifedipine (Venkataram and Rogers, 1988).

In vivo absorption in rats

The profiles of the plasma concentration of nifedipine vs time after oral administration of nifedipine-PEG and nifedipine-PC-PEG solid dispersions are shown in Fig. 5. The plasma concentrations of nifedipine in the presence of PC were significantly higher than those in its absence. The AUC value determined for the nifedipine-PEG solid dispersion was 9375 μg min per ml and for nifedipine-PC-PEG solid dispersion 31676 μg min per ml. This indicated a 3.4-fold increase in absorption of nifedipine for nifedipine-PC-PEG solid dispersion.

In conclusion, it is clear that the incorporation of PC into the nifedipine-PEG solid dispersion showed an enhancement of the in vitro dissolution characteristics of nifedipine and this was comparable with the result on the increase in in vivo absorption.

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