International Journal of Pharmaceutics, 85 (1992) 1–6

IJP 02744

Research Papers

The effect of some natural polymers on the solubility and dissolution characteristics of nifedipine

F. Acartürk, Ö. Kışlal and N. Çelebi

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Gazi, Etiler 06330, Ankara (Turkey)

(Received 19 August 1991)
(Modified version received 11 November 1991)
(Accepted 25 November 1991)

Key words: Nifedipine; Gelatin, water-soluble; Albumin, egg; β-Cyclodextrin; Kneaded mixture; Dissolution profile

Summary

The effect of natural polymers, such as water-soluble gelatin and egg albumin, on the solubility and dissolution characteristics of nifedipine has been studied. Comparison of such polymers was carried out by complexation with β-cyclodextrin. The interaction of nifedipine with these polymers both in aqueous solution and in the solid state was examined by performing solubility analysis, powder X-ray diffractometry and differential scanning calorimetry measurements. In addition, the surface tension of the samples was evaluated. Solid mixtures of nifedipine and polymer in various ratios were prepared by the kneading technique and their dissolution was carried out according to the dispersed amount method. It was found that water-soluble gelatin and β-cyclodextrin resulted in a significant increase in the rate of dissolution of nifedipine as compared to drug alone. Further, water-soluble gelatin may be particularly useful for the enhancement of dissolution of nifedipine.

Introduction

Nifedipine (NF), a highly active Ca^{2+} channel blocker, is used in the treatment of angina pectoris and hypertension (Reynolds, 1989). However, NF is only slightly water soluble as a result of which the drug may exhibit poor absorption characteristics. A number of attempts have been made to improve the dissolution of NF; for this purpose, solid dispersions of NF in water-soluble carriers such as urea (Şumnu, 1986), polyvinylpyrrolidone (PVP) (Sugimoto et al., 1980; Şumnu, 1986), polyethylene glycol (PEG) (Şumnu, 1986; Morimoto et al., 1987), sodium benzoate, sodium salicylate (Jain et al., 1988), alone or combined in various proportions, have been reported. Complexation with cyclodextrins (Cyd) has been extensively employed to improve the solubility, dissolution and bioavailability of various drugs (Nambu et al., 1978; Seo et al., 1983; Uekama et al., 1983, 1984). On the basis of this viewpoint, inclusion compounds of NF with various CyDs were investigated in a previous report (Yamamoto et al., 1989).

The use of natural polymers as drug carriers has recently attracted considerable attention in

Correspondence: F. Acartürk, Dept of Pharmaceutical Technology, Faculty of Pharmacy, University of Gazi, Etiler 06330, Ankara, Turkey.

the pharmaceutical field due to their inert nature and safeness (Imai et al., 1989a,b, 1991).

The aim of the present study was to evaluate the effects of natural polymers such as water-soluble gelatin (WSG) and egg albumin (EGA) on the solubility and dissolution characteristics of NF and to compare the results of cyclodextrin-NF complexation with those of the natural polymers.

Materials and Methods

Materials

NF (FAKO Pharmaceuticals, Istanbul, Turkey), WSG (Nitta Gelatin Co., Ltd, Osaka, Japan), EGA (Nakarai Chemical Co., Ltd, Kyoto, Japan) and β-cyclodextrin (β-CyD) (Nihon Shokuhin Kako Co., Ltd, Tokyo, Japan) were kindly supplied and used as received. All other materials and solvents were of analytical grade. All experiments were carried out under conditions of protection from light.

Methods

Solubility Phase solubility studies were carried out according to the method of Higuchi and Connors (1965). Excess amounts of drug were added to aqueous solutions containing various concentrations of polymers and vigorously shaken at 20 ± 0.5°C for 7 days in the case of β-Cyd, but only 4 h for WSG and EGA in order to avoid polymer decomposition. After attainment of equilibrium, the samples were passed through a 0.45 μm membrane filter. The concentration of NF was determined spectrophotometrically at 342 nm.

Preparation of solid mixtures The NF-WSG and NF-EGA kneaded mixtures in weight ratios of 1:1 and 1:2 and the NF-β-CyD solid complex in molar ratios of 1:1 and 1:2 were prepared by kneading. The required amounts of drug and polymer were weighed and placed in a mortar, and then the mixtures were kneaded with 1.5-times their amount of water for 1 h. The kneaded mixtures were dried under vacuum at room temperature for 48 h and then screened through a 25-mesh sieve. Physical mixtures of NF with these polymers in the same ratios were prepared by simple blending in a mortar.

Differential thermal analysis The thermal analyzer (DT-40, Shimadzu, Japan) was operated at a scanning speed of 10°C/min from 30 to 300°C.

Powder X-ray diffraction Powder X-ray diffraction patterns were recorded on an X-ray diffractometer (Jeol JDX-SP) under the following

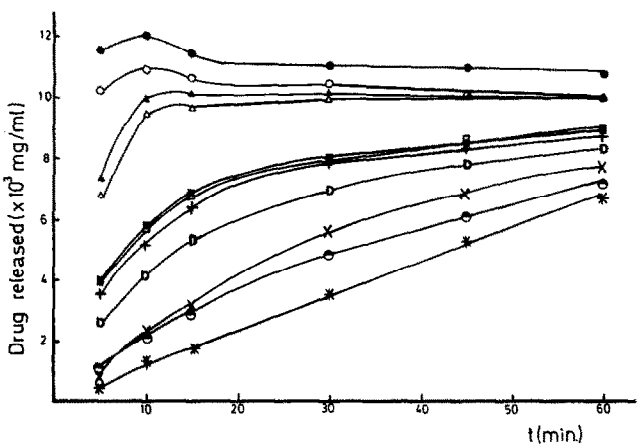

Fig. 1. Dissolution profiles of NF and its solid mixtures in pH 1.2 simulated gastric fluid at 37°C. (*) NF alone, (○) NF:WSG (1:1) kneaded mixture, (●) NF:WSG (1:2) kneaded mixture, (□) NF:WSG (1:1) physical mixture, (■) NF:WSG (1:2) physical mixture, (△) NF:β-CyD (1:1) kneaded mixture, (▲) NF:β-CyD (1:2) kneaded mixture, (◒) NF:β-CyD (1:1) physical mixture, (▷) NF:β-CyD (1:2) physical mixture, (×) NF:EGA (1:1) kneaded mixture, (+) NF:EGA (1:2) kneaded mixture.

operating conditions: X-rays, Ni-filtered Cu-K_α radiation; voltage, 40 kV; current, 20 mA; time constant, 2 s; scanning speed, 2°/cm.

Surface tension Surface tensions of samples were determined by the ring method using a Du Nouy Tensiometer (Cambridge Scientific Instruments Ltd). An amount of each sample equivalent to 10 mg NF (1:1) was weighed and dispersed in 50 ml double-distilled water. After sonication for 5 min, the samples were filtered and measured at 20°C.

Dissolution Dissolution studies were performed according to the dispersed amount procedure (Nogami et al., 1969) following the USP XXI paddle method in 500 ml of pH 1.2 simulated gastric fluid without pepsin at 37 ± 0.5°C and at 100 rpm. At appropriate intervals, 5-ml samples were withdrawn, passed through a 0.45 μm membrane filter and assayed spectrophotometrically. The volume of the mixture in the vessel was replenished with an equal amount of pure pH 1.2 solution after each sampling.

Results and Discussion

Dissolution profiles of NF alone, and kneaded and physical mixtures of NF with WSG, β-Cyd and EGA are shown in Fig. 1. The dissolution rate of NF was increased by polymer addition in the order of WSG > β-CyD > EGA as compared with that of drug alone and the physical mixtures. In particular, the incorporation of NF into WSG significantly enhanced the dissolution rate of the drug vs that with drug alone or the physical mixture. In the case of the 1:2 mixture with NF, the drug concentration after 10 min of dissolution exceeded that of drug alone as much as 9.3-, 7.7- and 4.0-fold for WSG, β-CyD and EGA, respectively. It is interesting to note that the concentration of NF following dissolution from the NF-WSG solid mixture reached supersaturation and then decreased. This behaviour may be due to dissociation of the complex after supersaturation. Although the water-soluble gelatin decomposed in solution, the solid mixtures prepared with drug and water-soluble gelatin were quite stable (Imai et al., 1990).

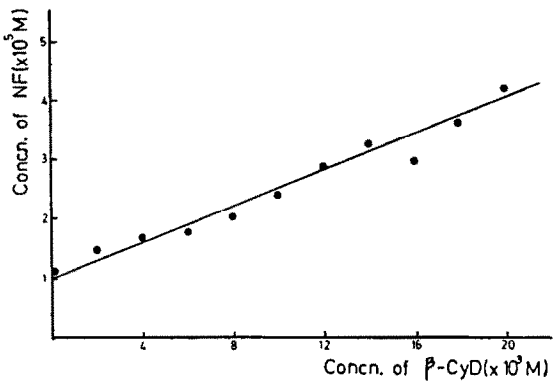

Fig. 2. Phase solubility diagram of the NF-β-CyD system in water at 20°C.

The enhancement in the rate of dissolution of NF may be explained on the basis of an increase in solubility and a decrease in crystallinity of the drug due to the addition of polymers. Therefore, drug solubilities were evaluated in the presence of polymers. Phase solubility diagrams of NF with β-CyD and WSG are presented in Figs 2 and 3, respectively. The solubility of the drug increased linearly as a function of the β-CyD concentration and the solubility curve can be generally classified as type A_L (Higuchi and Connors, 1965). Assuming that a 1:1 (guest:host) complex was initially formed, the apparent stability constant of the NF-β-CyD complex, as calculated from the linear portion of the solubility plot, amounted to 140 M^{-1}. In the case of WSG and EGA, no appreciable increase in solubility of NF was found. Therefore, the rapid rate of dissolution of the drug

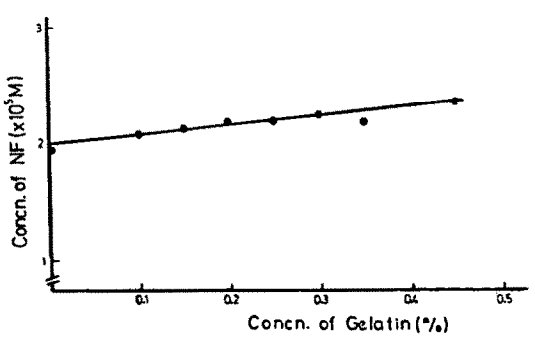

Fig. 3. Phase solubility diagram of the NF-WSG system in water at 20°C.

from NF-WSG and NF-EGA solid mixtures is difficult to explain in terms of increased solubility.

The interaction of NF with the polymers in the solid state was investigated by DTA and X-ray diffractometry measurements. Fig. 4 depicts the DTA thermograms of the kneaded and physical mixtures (1 : 1). NF exhibited a sharp endothermic peak at 172°C due to melting. The intensity of the endothermic peak of NF decreased in the kneaded mixtures as compared with the physical mixtures and NF alone, however, the peak did not disappear completely. This may be due to the energy level of the kneaded mixtures being near to that of the physical mixtures.

Next, the crystallinity of drug in the kneaded mixtures with WSG, β-CyD and EGA was compared with that of drug alone and in the physical mixture by means of powder X-ray diffractometry. The diffraction patterns of NF alone and NF-polymer (1 : 1) kneaded and physical mixtures are illustrated in Fig. 5. The intensities of the diffraction peaks of the kneaded and physical mixtures of NF with WSG and β-CyD are reduced vs that of NF alone. Nevertheless, the diffraction peaks of the drug in the kneaded mixture are identical to those in the physical mixtures with WSG and β-CyD. However, the reduction in the intensity of the sharp peaks and the broadening of all peaks in the pattern of the NF-EGA solid mixture suggest that NF has interacted with EGA. However, a weak interaction does occur between drug and WSG and β-CyD and the drug powder is dispersed as separate crystals in the kneaded mixtures. Therefore, in order to explain the rapid dissolution of the kneaded mixture of drug with WSG, further investigation was necessary. Since WSG has surface activity, it may improve the wettability of drug particles by water through dispersion of the drug particles in WSG. Hence, surface tension measurements were carried out of the mixtures. Table 1 summarizes the values determined for the surface tension of the kneaded and physical mixtures and drug powder as measured by the ring method.

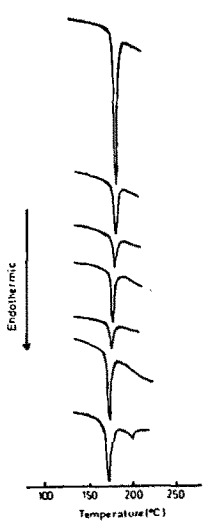

Fig. 4. DTA thermograms of NF-solid mixtures: (A) NF alone, (B) physical mixture of NF and WSG, (C) kneaded mixture of NF with WSG, (D) physical mixture of NF and β-CyD, (E) kneaded mixture of NF with β-CyD, (F) physical mixture of NF and EGA, (G) kneaded mixture of NF with EGA.

TABLE 1

Surface tension of samples measured by the ring method

Compound	Surface tension (dyn/cm)		
	Alone	Kneaded mixture	Physical mixture
Nifedipine	65		
Water-soluble gelatin	49	49	60
β-Cyclodextrin	69	59	67
Egg albumin	58	56	56

As shown in Table 1, the surface tension of the NF-WSG kneaded mixture was lower than that of drug alone and of the physical mixture. However, the surface activity was not significantly changed by β-CyD and EGA.

The above results may be explained on the basis that the kneaded mixture of NF with WSG improved the wettability of the drug powder, and consequently enhanced the dissolution rate of the drug. The enhanced dissolution rate of NF from NF-β-CyD complexes may be due to the increase in solubility of NF, however, on taking the X-ray and DTA data into account, we considered that the inclusion complex of NF and β-CyD had not been completely formed in the solid state. In the case of EGA, the enhancement in dissolution

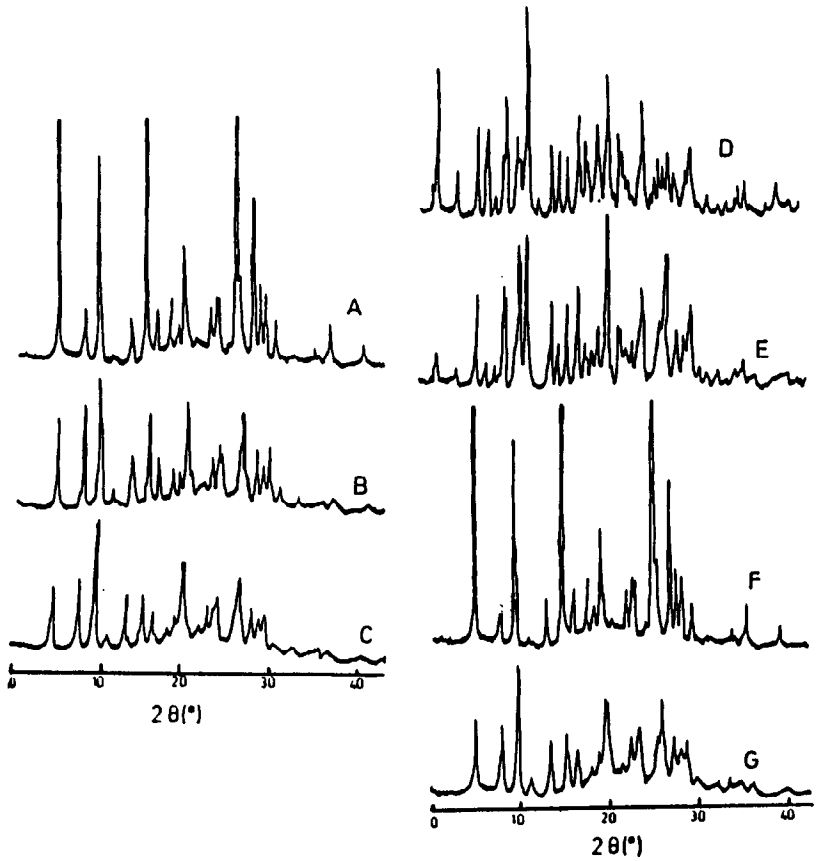

Fig. 5. Powder X-ray diffraction patterns of NF solid mixtures: (A) NF alone, (B) physical mixture of NF and WSG, (C) kneaded mixture of NF with WSG, (D) physical mixture of NF and β-CyD, (E) kneaded mixture of NF with β-CyD, (F) physical mixture of NF and EGA, (G) kneaded mixture of NF with EGA.

rate of NF may be explained by the decrease in crystallinity of NF as a result of dispersion.

It was concluded that both WSG and β-CyD significantly increased the dissolution profile of NF as compared with that of drug alone. WSG may be particularly useful for the enhancement of dissolution of NF.

Acknowledgements

The authors would like to thank FAKO Pharmaceuticals (Turkey) for supplying nifedipine. We are also grateful to Pharm. P. Bulut for performing the DTA analyses.

References

Higuchi, T. and Connors, K.A., Phase solubility techniques. *Adv. Anal. Chem. Instrum.*, 4 (1965) 117–212.

Imai, T., Nishiyama, T., Ueno, M. and Otagiri, M., Enhancement of the dissolution rates of poorly water-soluble drugs by water-soluble gelatin. *Chem. Pharm. Bull.*, 37 (1989a) 2251–2252.

Imai, T., Saito, Y., Matsumoto, H., Satoh, T. and Otagiri, M., Influence of egg-albumin on dissolution of several drugs. *Int. J. Pharm.*, 53 (1989b) 7–12.

Imai, T., Kimura, S., Iijima, T., Miyoshi, T., Ueno, M. and Otagiri, M., Rapidly absorbed solid oral formulations of Ibuprofen using water-soluble gelatin. *J. Pharm. Pharmacol.*, 42 (1990) 615–619.

Imai, T., Nohdomi, K., Acartürk, F. and Otagiri, M., Enhancement of dissolution and absorption of mefenamic acid by egg-albumin. *J. Pharm. Sci.*, 80 (1991) 484–487.

Jain, N.K., Patel, V.V. and Taneja, L.N., Hydrotropic solubilization of nifedipine. *Pharmazie*, 43 (1988) 194–196.

Morimoto, K., Tabata, H. and Morisaka, K., Nasal absorption of nifedipine from gel preparations in rats. *Chem. Pharm. Bull.*, 35 (1987) 3041–3044.

Nambu, N., Shimoda, M., Takahashi, Y., Ueada, H. and Nagai, T., Bioavailability of powdered inclusion compounds of nonsteroidal antiinflammatory drugs with β-cyclodextrin in rabbits and dogs. *Chem. Pharm. Bull.* 26 (1978) 2952–2956.

Nogami, H., Nagai, T. and Yotsunayagi, T., Dissolution phenomena of organic medicinals involving simultaneous phase changes. *Chem. Pharm. Bull.*, 17 (1969) 499–509.

Reynolds, J.E.F. (Ed.), Nifedipine, *Martindale, The Extra Pharmacopoeia,* 29th Edn, Pharmaceutical Press London, 1989, p. 1509.

Seo, H., Tsuroka, M., Hashimoto, T., Fujinaga, T., Otagiri, M. and Uekama, K., Enhancement of oral biavailability of spironolactone by β- and γ-cyclodextrin complexations. *Chem. Pharm. Bull.*, 31 (1983) 286–291.

Sugimoto, I., Kuchiki, A., Nakagawa, H., Tohgo, K., Kondo, S., Iwane, I. and Takahashi, K., Dissolution and absorption of nifedipine from nifedipine-polyvinylpyrrolidone coprecipitates. *Drug. Dev. Ind. Pharm.*, 6 (1980) 137–160.

Şumnu, M., Increasing dissolution rate and gastrointestinal absorption of nifedipine via solid dispersion. *STP Pharma,* 2 (1986) 214–220.

Uekama, K., Narisawa, S., Hirayama, F. and Otagiri, M., Improvement of dissolution and absorption characteristics of benzodiazepines by cyclodextrin complexation. *Int. J. Pharm.*, 16 (1983) 327–338.

Uekama, K., Hirayama, F., Fujise, A., Otagiri, M., Inaba, K. and Saito, H., Inclusion complexation of prostaglandin F_2 with γ-cyclodextrin in solution and solid phases. *J. Pharm. Sci.*, 73 (1984) 382–384.

Yamamoto, M., Yoshida, A., Hirayama, F. and Uekama, K.., Some physicochemical properties of branched β-cyclodextrin and their inclusion characteristics. *Int. J. Pharm.*, 49 (1989) 163–171.