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Interaction of naproxen with β-cyclodextrin in ground mixture

N. Çelebi and N. Erden

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

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Summary

The purpose of the present study was to investigate the interaction of naproxen (NAP) with β-cyclodextrin (β-CD) in ground mixtures. The effects of grinding on the physicochemical properties of NAP were studied by means of IR spectroscopy and X-ray diffraction analysis. Ground mixtures of NAP with β-CD and microcrystalline cellulose (MCC) were prepared by grinding a ceramic ball mill. The dissolution rate of NAP from the ground mixtures was significantly greater than that from physical mixtures and intact NAP powder. The ground mixture with β-CD showed the fastest dissolution profile. These results indicate that β-CD can enhance the dissolution rate of NAP.

Introduction

Grinding (co-grinding) is an important industrial process that is used for the size reduction of drugs, in order to enhance the dissolution rates. In addition to size reduction, grinding also has a striking effect on the properties of the crystals. It has been recently reported that grinding or milling not only reduces particle size but also causes changes in molecular behavior, such as the phase transition of polymorphs, crystallinity and chemical reaction rate in the solid phase (Nakai, 1986). Grinding efficiency is improved by supplementation with additives, and molecular interactions between drugs and polymer additives can occur in ground mixtures. When crystalline drugs were ground with microcrystalline cellulose (Yamamoto et al., 1976), chitin and chitosan (Sawayanagi et al., 1983a,b), cyclodextrins (Nakai et al., 1978; Nagai, 1981; El-Gendy et al., 1986; Çelebi and Nagai, 1987), gelatin, polyvinylpyrrolidone, and methyl cellulose, the poorly soluble drugs became amorphous and their dissolution rates and bioavailabilities were markedly improved. Moreover, cyclodextrins (CD) may have an advantage over the other materials as regards safety as an additive. On the basis of this viewpoint as well, CD seems to afford a promising means for pharmaceutical preparations (Nambu et al., 1978). Several papers have been published that describe the extensive application of CD complexation to enhance the solubility, dissolution rate and bioavailability of slightly soluble drugs (Seo et al., 1983; Uekama et al., 1983a,b; Debreures et al., 1985; Duchene et al., 1986).

Correspondence: N. Çelebi, Department of Pharmaceutical Technology, Faculty of Pharmacy, Gazi University, Etiler, 06330 Ankara, Turkey.

Generally, the rates of release of drugs from ground mixtures are very high and the enhanced dissolution results in the rapid absorption of the drugs (Yamamoto et al., 1976).

As part of a series of pharmaceutical studies on naproxen, in the present investigation, the rates of dissolution of drugs from ground mixtures of NAP with β-CD were determined. Since NAP is slightly soluble in water, the interaction of NAP with β-CD in the solid state was confirmed by powder X-ray diffractometry and IR spectroscopy.

Naproxen [d-2,6-(methoxy-2-naphthyl)propionic acid] is a nonsteroidal anti-inflammatory drug that also exerts analgesic and antipyretic activities (Segre et al., 1974; Mahler et al., 1976).

Materials and Methods

Materials

β-Cyclodextrin (β-CD) and naproxen (NAP) were kindly provided Chinoin Pharmaceutical and Chemical Works (Hungary) and Bilim Pharmaceutical Co. Ltd (Turkey), respectively. All other materials and solvents were of analytical reagent grade.

Methods

Preparation of ground mixtures Ground mixtures of defined compositions, composed of NAP with β-CD (1 : 1 molar ratio) and microcrystalline cellulose (MCC) (1 : 1 weight ratio) were prepared by grinding in a ceramic ball mill. The duration of grinding was 20 min for CD (GM1) and 30 min for microcrystalline cellulose (MC1) (Kawano and Ogino, 1982).

Preparation of physical mixtures Physical mixtures of NAP with β-CD (PM1) (1 : 1 molar ratio) and MCC (MH1) (1 : 1 weight ratio) were prepared by simple blending in a ceramic mortar.

IR absorption spectroscopy IR absorption spectroscopy was carried out using a Perkin-Elmer 1330 model IR infrared spectrophotometer according to the KBr disk method.

X-ray powder diffraction X-ray powder diffraction analysis was performed with a Jeol type JDX-8P diffractometer. Measurement conditions were as follows: X-ray source, Ni-filtered CuKα radiation; voltage, 40 kV; current, 20 mA; time constant, 2 s; scanning speed, 2 °/cm.

Measurement of dissolution rate The rate of dissolution was determined according to the USP XX paddle method in buffer solution at pH 1.2 and 37.0 ± 0.5 °C. A given quantity of each sample, corresponding to the amount passing through a 0.125 mm sieve, was placed in dissolution medium. After an appropriate interval, a 4 ml sample of the solution was removed and then rapidly filtered. The NAP content of each sample was assayed by recording the UV absorbance at 331 nm on an ultraviolet spectrophotometer (Perkin-Elmer Hitachi 200).

Results and Discussion

It was determined that β-CD increased the solubility of NAP approx. 3.5-fold and resulted in an A_L-type solubility diagram (Erden, 1988). Using data from the solubility diagram, an inclusion complex of NAP and β-CD (molar ratio, 1 : 1), as opposed to the ground mixture, was prepared by performing freeze-drying and neutralization. Solid-state interactions and dissolution rates of thus prepared complexes have been reported previously (Erden and Çelebi, 1988). In the present article, the solid-state interaction of NAP with β-CD, as followed using the method for ground mixtures, which is routinely employed as a preparative procedure in the case of cyclodextrin inclusion compounds, was investigated by IR spectroscopy and X-ray diffraction analysis. In addition, the profiles for the rates of NAP dissolution from the ground mixture were simultaneously determined.

The IR spectra are depicted in Fig. 1, in which NAP shows a hydroxyl stretch band at 3500–2500 cm^{-1} and a carbonyl band at 1725–1685 cm^{-1}. No shifts were observed in the peaks of the IR spectra for the physical mixtures of NAP and β-CD. For ground mixtures, although a shift in the hydroxyl peak did occur, we found no difference in the case of the carbonyl band. The above-mentioned shift in the hydroxyl peak is indicative of an interaction between NAP and

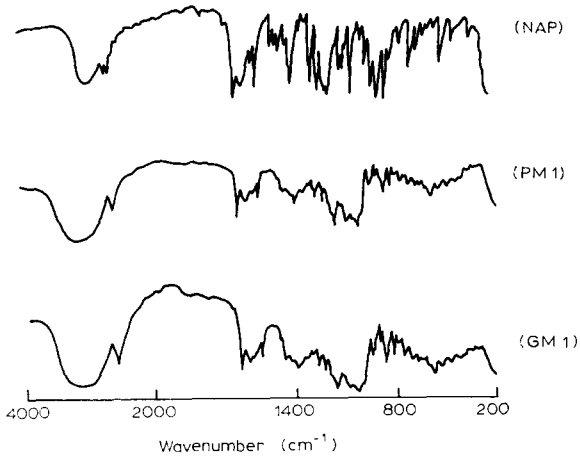

Fig. 1. IR spectra of: (NAP) intact naproxen; (PM1) physical mixture of NAP and β-CD; (GM1) ground mixture of NAP and β-CD.

β-CD. An NAP-β-CD ground mixture of molar ratio 1:2 displayed a shift in the peak at 1685 cm^{-1} which demonstrates the occurrence of a stronger interaction as compared to the case for a 1:1 molar ratio (Erden, 1988).

The X-ray powder diffraction patterns are shown in Fig. 2: although no evidence of an amorphous structure is found for the ground mixture, the peak heights are clearly seen to change (Erden and Çelebi, 1988). The NAP peak located at a 2θ angle of 8.6° is observed to increase only in the case of the physical mixture. β-CD also exhibits a peak at 8.6°, which is, however, of greater intensity than that of NAP. This peak is evident in both types of mixture. In the ground mixtures, the peaks of both NAP and β-CD are readily distinguishable. These observations suggest that an inclusion complex between the two was incompletely formed; nevertheless, this does not exclude the possibility of their undergoing an interaction.

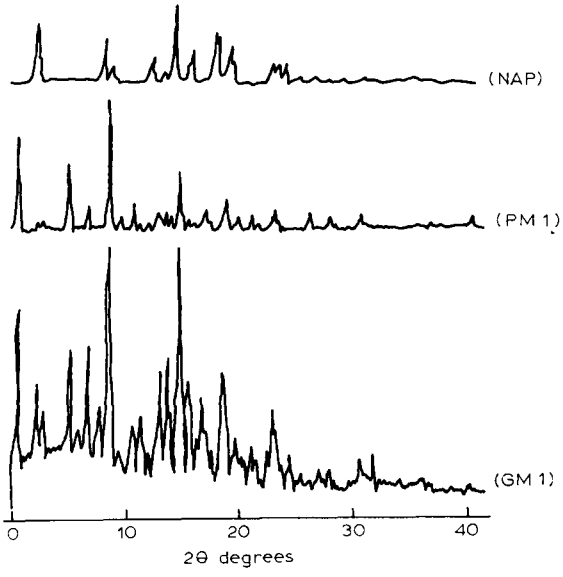

Fig. 2. X-ray powder diffraction patterns of: (NAP) intact naproxen; (PM1) physical mixture of NAP and β-CD; (GM1) ground mixture of NAP and β-CD.

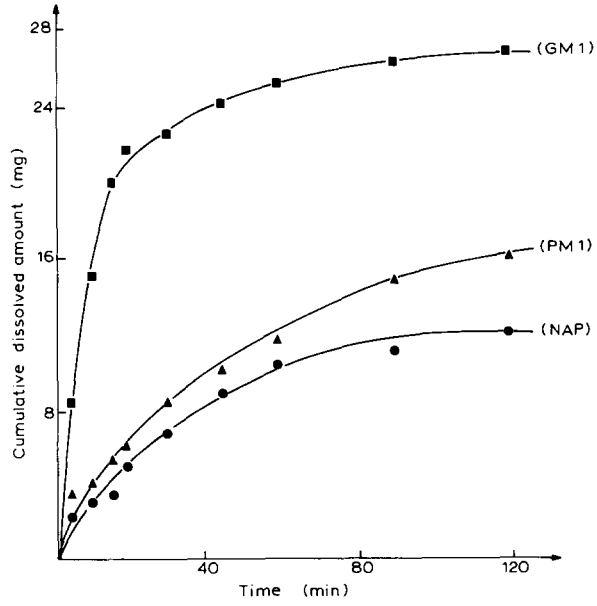

Fig. 3. Dissolution profiles of NAP from ground mixture of NAP and β-CD in pH 1.2 buffer solution at 37 °C: (NAP) intact NAP; (PM1) physical mixture of NAP and MCC; (GM1) ground mixture of NAP and β-CD.

Drugs that are rapidly released from the ground mixture, irrespective of the solubility and dissolution mechanism, have been discussed on the basis of their molecular behavior (Nakai, 1986); NAP release takes place at a faster rate from ground mixtures than from physical mixtures, especially during the initial stages.

This is amply demonstrated in Fig. 3: 15% of the intact NAP content is dissolved within 15 min, whereas the values measured for the ground and physical mixtures were 81 and 21%, respec-

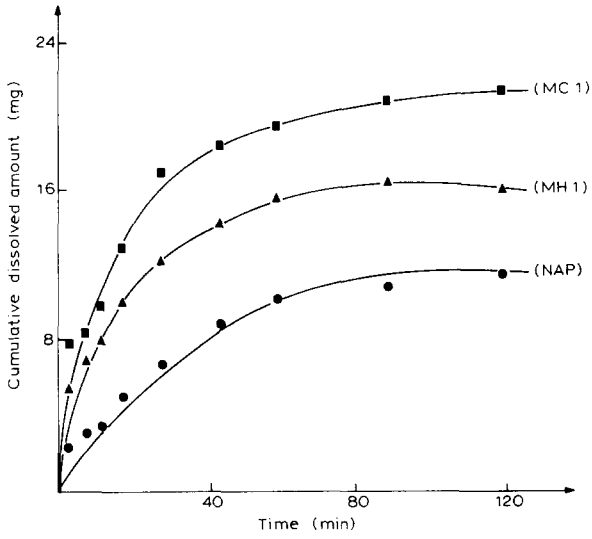

Fig. 4. Dissolution profiles of NAP from ground mixture of NAP and MCC in pH 1.2 buffer solution at 37 °C: (NAP) intact naproxen; (MH1) physical mixture of NAP and β-CD; (MC1) ground mixture of NAP and β-CD.

tively. The ground mixture released 100% of the NAP within 60 min. The solubility and rate of dissolution of NAP are enhanced by the action of β-CD as a solubilizing agent. Additionally, since NAP is surrounded by β-CD, the possibility of aggregation and agglomeration taking place is virtually non-existent, whilst the dispersion and wetting ability of NAP increase. It is for the afore-mentioned reasons that the rate of dissolution of NAP increases. Furthermore, the average size of the drug particles diminishes on grinding, and thus is another factor contributing to the faster dissolution rate.

In an earlier study (Yamamoto et al., 1976), microcrystalline cellulose (MCC) was used to enhance the dissolution of sparingly soluble drugs during the process of preparing ground mixtures. Therefore, we also examined MCC in the current paper in order to evaluate its effect, if any, on the dissolution rate of NAP when present in ground and physical mixtures. The ground mixture gave rise to the faster release of NAP among the two types (Fig. 4). It clearly seen that grinding is effective at increasing the rate of dissolution. It has been reported elsewhere (Nakai, 1986) that the degree of crystallinity varies inversely with respect to the duration of grinding and that an amorphous form results. Also, ground mixtures prepared with MCC, on being placed in an aqueous medium, were reported to lead to the immediate penetration of water molecules into the inter-particle spaces, as MCC only forms a weak network (Nakai et al., 1977a,b). Identical results have been published by others (Sawayanagi et al., 1983a,b) concerning ground mixtures of various combinations of drugs and polymer additives.

In conclusion, co-grinding with β-CD reduced the size of NAP crystals and greatly enhanced its rate of dissolution.

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