Arch. Pharm. Res. Vol. 18, No. 1 pp. 22-26, 1995

Enhancement of Solubility and Dissolution Rate of Poorly Water-soluble Naproxen by Complexation with 2-Hydroxypropyl-β-cyclodextrin

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(Received October 14, 1994)

The solubility and dissolution rate of naproxen (NPX) complexed with 2-hydroxypropyl-β-cyclodextrin (2-HPβCD) using coprecipitation, evaporation, freeze-drying and kneading method were investigated. Solubility of NPX linearly increased (correlation coefficient, 0.995) as 2-HPβCD concentration increased, resulting in A_L type phase solubility curve. Inclusion complexes prepared by four different methods were compared by differential scanning calorimetry (DSC). The NPX showed sharp endothermic peak around 156℃ but inclusion complexes by evaporation, freeze-drying and kneading method showed very broad peak without distinct phase transition temperature. In contrast, inclusion complex prepared by coprecipitation method resulted in detectable peak around 156℃ which is similar to NPX, suggesting incomplete formation of inclusion complex. Dissolution rate of inclusion complexes prepared by evaporation, freeze-drying and kneading except coprecipitation method was largely enhanced in the simulated gastric and intestinal fluid when compared to NPX powder and commercial NAXEN® tablet. However, about 65% of NPX in gastric fluid still remained unreleased but most of NPX dissolved within 5 min in intestinal fluid. In case of inclusion complex prepared by coprecipitation method, formation of inclusion complex appeared to be incomplete, resulting in no marked enhancement of dissolution rate. From these findings, inclusion complexes of poorly water-soluble NPX with 2-HPβCD were useful to increase solubility and dissolution rate, resulting in enhancement of bioavailability and minimization of gastrointestinal toxicity of drug upon oral administration of inclusion complex.

Key words: Naproxen, 2-hydroxypropyl-β-cyclodextrin, Inclusion complex, Solubility, Thermal behavior, Dissolution rate

INTRODUCTION

Poorly water-soluble drugs have many difficulties in the development of pharmaceutical dosage forms due to low solubility, slow dissolution rate and bioavailability. Several methods such as solid dispersion, coprecipitation, spray drying and inclusion complex have been utilized for the enhancement of gastrointestinal absorption (Kedzierewicz *et al.*, 1990; Kislalioglu *et al.*, 1991; Kim *et al.*, 1994; Duchene and Wouessidjewe, 1990).

Many nonsteroidal antiinflammatory drugs (NSAIDs) with analgesic and antipyretic properties have low solubility and dissolution rate, resulting in poor bioavailability (Kim *et al.*, 1994). Gastrointestinal side effects of NSAIDs have been also widely recognized. Naproxen (NPX) selected as a model drug is a potent NSAID to treat rheumatoid arthritis, osteoarthritis and colitis (Hart and Huskisson, 1984). However, the pharmaceutical applications of NPX have been limited because of low solubility and undesirable gastrointestinal side effects such as ulceration and hemorrhage due to its acidity when given orally (Espinar *et al.*, 1991; Shanbhag *et al.*, 1992; Tammara *et al.*, 1993). Therefore, dosage forms of NPX can be modified to overcome the shortcoming. Recently, considerable attention has been given to the development of other systems such as prodrug, percutaneous delivery and inclusion complexes for the reduction of gastrointestinal side effects (Tammara *et al.*, 1992; Bonina *et al.*, 1993; Espinar *et al.*, 1991).

Cyclodextrin is an oligomer of glucose which is produced from enzymatically modified starches. Inclusion complex is formed when hydrophobic inner cavity in-

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teracts with a moiety of drug by noncovalent forces (Yoshida *et al.*, 1988). Cyclodextrin and its derivatives have been utilized by formulators to increase solubility, stability, and bioavailability of poorly water-soluble drugs, and reduce side effects and toxicity of drugs (Szejtli, 1991; Duchene and Wouessidjewe, 1990; Nambu *et al.*, 1978). The highly water-soluble 2-hydroxypropyl-β-cyclodextrin (2-HPβCD) is a commercially useful complexing agent of various compounds. Therefore, it is interesting to investigate solubility and dissolution rate of inclusion complexes containing poorly water-soluble drug to simultaneously improve bioavailability and reduce gastrointestinal toxicity when given orally. However, physicochemical properties of inclusion complex containing NPX as a function of preparation method have not been widely investigated.

The purpose of this study was to investigate solubility of poorly water-soluble drug as a function of 2-HPβCD concentration and to compare dissolution rate varying preparation methods of inclusion complexes with 2-HPβCD.

MATERIALS AND METHODS

Materials

Naproxen (NPX) powder and commercial NPX (NAXEN®) tablet were kindly provided by the courtesy of Chong-Kun Dang Co. (Seoul, Korea). 2-Hydroxypropyl-β-cyclodextrin (2-HPβCD) was provided by Aldrich Chemical Co. (Milwaukee, WI). The average molecular weight and molar substitution of 2-HPβCD were 1500 and 0.8, respectively. Ammonium hydroxide (NH_4OH) was obtained from Duksan Pharmaceutical Co. (Seoul, Korea). All other chemicals were of reagent grade and used without further purification.

Solubility studies

Solubility studies were carried out according to the method of Higuchi and Connors with minor modification (1965). Excess amounts of drug were added to distilled water containing various concentrations of 2-HPβCD. The resulting suspension was sonicated and vortexed, and then placed in a constant temperature water bath at 25± 1℃ for six days. The parafilm was used to cover the top to prevent evaporation. Samples were collected and filtered through a membrane filter (0.45 μm). The concentration of NPX was determined using an UV-VIS spectrophotometry (Pharmacia LKB Ultrospec, Cambridge, England) at the wavelength of 271 nm with a proper dilution.

Thermal analysis

Thermal behavior of inclusion complexes was examined using a Shimadzu differential scanning calorimetry (Kyoto, Japan). The shape and phase transition temperature of NPX, physical mixture and four inclusion complexes with different preparation methods were compared.

Preparation of simulated gastric and intestinal fluid

The simulated gastric fluid was prepared by dissolving NaCl (6 g) in about 2900 ml of deionized water and then diluted HCl (7.4%) was added to adjust pH 1.4± 0.1. The final volume was adjusted to 3000 ml using deionized water. The simulated intestinal fluid was also prepared as follows. Potassium phosphate monobasic (20.4 g, KH_2PO_4) was dissolved in about 2800 ml of deionized water and then NaOH (1 N) was added to adjust pH 7.4± 0.1. The final volume was adjusted to 3000 ml using deionized water.

Preparation of inclusion complex

Four different methods, coprecipitation, evaporation, freeze-drying and kneading were used for the preparation of NPX-inclusion complexes. In evaporation method, drug (0.60 g) was dissolved in 5% ammonia water (15 ml) and then 3.91 g of 2-HPβCD (1 : 1 molar ratio) was added. The resulting solution was evaporated at 40℃ under the reduced pressure. The rotating speed was 40 rpm. In freeze-drying method, drug (0.60 g) was dissolved in 15 ml of 5% ammonia water and then 3.91 g of 2-HPβCD (1:1 molar ratio) was added. The resulting solution was freezed and dried using a freeze dryer over 48 h. In kneading method, drug (0.60 g) and 2-HPβCD (3.91 g) at an equimolar ratio were mixed in a pestle to form the paste by adding ethanol (10 ml) drop by drop. The paste was dried at 50℃ over 24 h in an oven. In coprecipitation method, drug (0.60 g) was dissolved in 5 ml of ethanol. 2-HPβCD (3.91 g) at an equimolar ratio was added and then adjusted into 50 ml using deionized water. The solution was then shaked at 25℃ over 24 h. The coprecipitate was then filtered through a membrane filter (0.45 μm). All inclusion complexes formed were further dried in a desiccator until use. The contents of drug in inclusion complex prepared by coprecipitation, freeze-drying, evaporation and kneading method were 56, 9.0, 9.8 and 9.9% (w/w), respectivley.

Dissolution studies

In vitro dissolution test of drug was performed in triplicate using dissolution apparatus II (Fine Scientific DST600A, Seoul, Korea). The standard paddle method was used at 37± 0.5℃ with the stirring speed of 50 rpm. Inclusion complexes equivalent to 100 mg of drug were applied in the 500 ml of enzyme free simulated gastric (pH 1.4± 0.1) and intestinal (pH 7.4± 0.1)

fluid. Dissolution samples (3 ml) were collected at a given time interval with the replacement of equal volume of temperature-equilibriated media and filtered through a 0.45 μm membrane filter. The drug dissolved was measured using an UV-VIS spectrophotometer at the wavelength of 271 nm with a proper dilution.

RESULTS AND DISCUSSION

Inclusion complexes of poorly water-soluble naproxen (NPX) with 2-HPβCD were prepared to enhance solubility and dissolution rate. It was known that utilization of NPX was limited because of poor bioavailability and undesirable gastrointestinal toxicity. Inclusion complexes of drugs with cyclodextrin derivatives have been useful to enhance dissolution rate and reduce gastrointestinal side effect when given orally by screening hydrophobic moiety of drug inside inner cavity of glucose ring closure (Yoshida *et al.*, 1988). It was known that NPX complexed with β-cyclodextrin has little chance to touch the stomach directly, making less irritation and injury upon oral administration of inclusion complex (Nambu *et al.*, 1978; Espinar *et al.*, 1991).

The phase solubility diagram of NPX as a function of 2-HPβCD concentration is given in Fig. 1. Solubility of NPX linearly increased (correlation coefficient, 0.995) as 2-HPβCD concentration increased, resulting in A_L type phase solubility curve according to Higuchi and Connors (1965). An apparent stability constant (K, M^{-1}) was then calculated from the initial linear portion of phase solubility diagram as follows assuming that a 1:1 complex was initially formed.

$$K = \frac{\text{slope}}{\text{intercept } (1 - \text{slope})}$$

The intercept in the equation indicates solubility of drug without 2-HPβCD. The calculated slope and stability constant were 0.2533 and 2776 M^{-1}, respectively, which was similar to another study (Frijlink *et al.*, 1991). It was obvious that 2-HPβCD was useful to improve solubility of poorly water-soluble drug.

The inclusion complexes were prepared by four different methods and then thermal behavior was examined by differential scanning calorimetry (DSC). Fig. 2 shows thermogram of NPX, physical mixtures and inclusion complexes prepared by four different methods. The NPX showed sharp endothermic peak around 156 ℃. However, inclusion complexes prepared by evaporation, freeze-drying and kneading method showed very broad peak without distinct phase transition around this temperature. These results suggested that inclusion complexes could be produced by these methods. In contrast, inclusion complex by coprecipita-

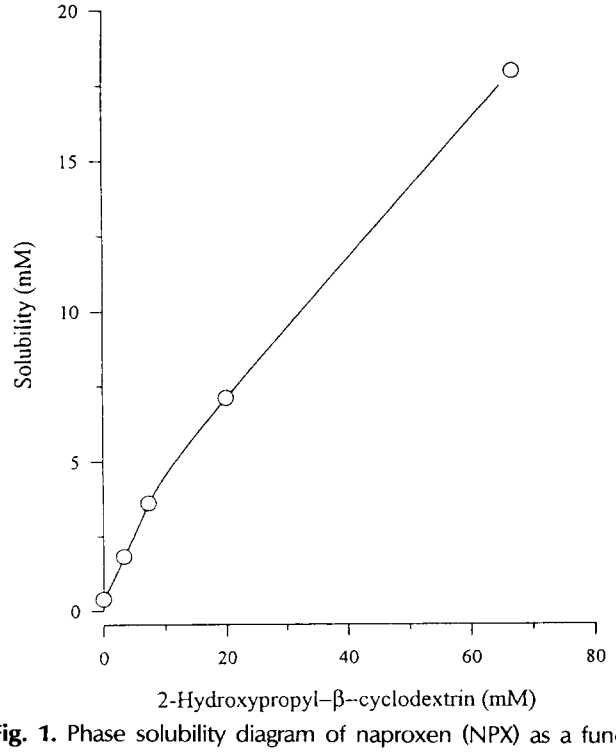

Fig. 1. Phase solubility diagram of naproxen (NPX) as a function of 2-HPβCD concentration

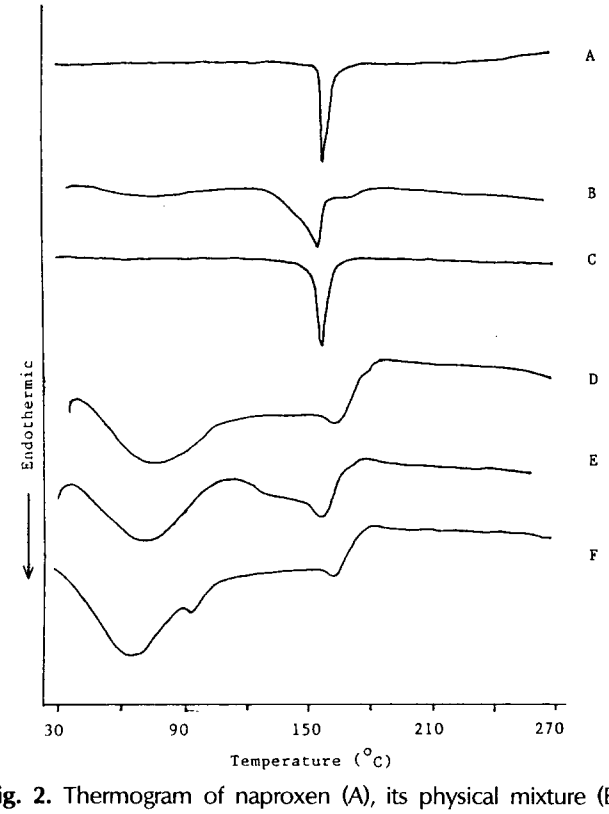

Fig. 2. Thermogram of naproxen (A), its physical mixture (B) and inclusion complexes with 2-HPβCD prepared by coprecipitation (C), evaporation (D), kneading (E) and freeze-drying method (F)

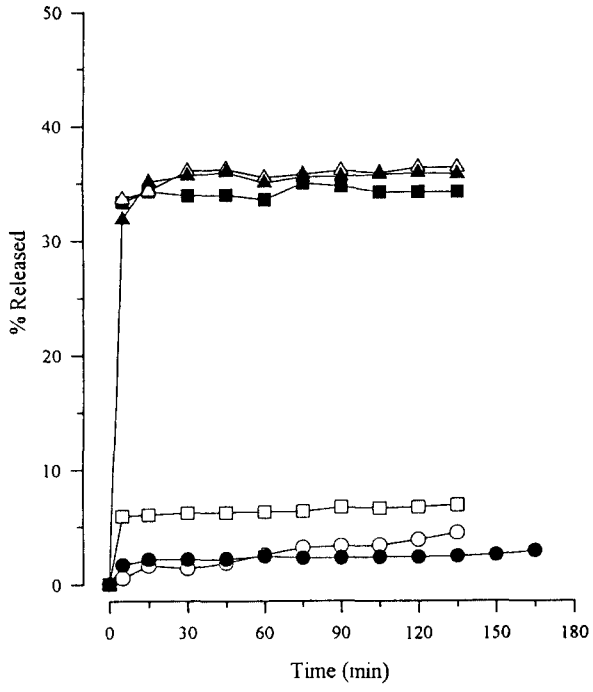

Fig. 3. Comparison of dissolution profiles of naproxen (○), commercial NAXEN® tablet (●) and inclusion complexes with 2-HPβCD prepared by coprecipitation (□), freeze-drying (■), evaporation (△) and kneading method (▲) in the simulated gastric fluid. Standard deviation is too small to show (n=3).

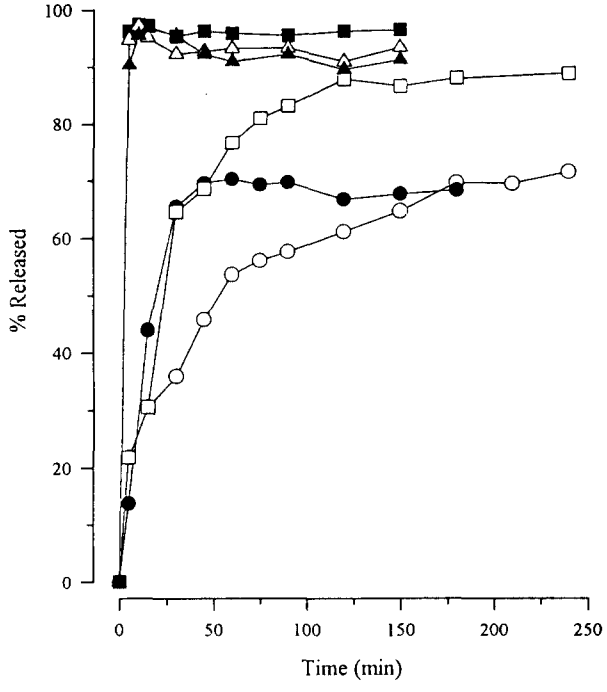

Fig. 4. Comparison of dissolution profiles of naproxen (○), commercial NAXEN® tablet (●) and inclusion complexes with 2-HPβCD prepared by coprecipitation (□, freeze-drying (■), evaporation (△) and kneading method (▲) in the simulated intestinal fluid. Standard deviation is too small to show (n=3).

tion method resulted in detectable peak around 156℃ which is similar to NPX, suggesting incomplete formation of inclusion complex. These qualitative properties were further recognized by the dissolution studies.

Dissolution profiles of NPX powder, commercial NAXEN® tablet and inclusion complexes with 2-HPβCD by coprecipitation, freeze-drying, evaporation and kneading method were compared in simulated gastric fluid (Fig. 3). Dissolution rate of inclusion complexes prepared by evaporation, freeze-drying and kneading except coprecipitation method was enhanced in the simulated gastric fluid over 3 h when compared to NPX powder and commercial NAXEN® tablet. No significant difference between NPX powder and commercial NAXEN® tablet was observed. However, about 65% of drug from inclusion complexes remained unreleased. In case of inclusion complex prepared by coprecipitation method, dissolution rate was slightly increased when compared to NPX powder and commercial NAXEN® tablet but most of drug (>90%) still remained unreleased. This result was consistent with DSC thermal behavior. Formation of inclusion complex prepared by coprecipitation method appeared to be incomplete, resulting in no marked enhancement of dissolution rate. These results suggested that although coprecipitate appeared to be formed during experimental procedure, most of the coprecipitate was not the inclusion complex but drug itself. Most of 2-HPβCD was washed out during filtration process without forming complexation. This result might be true because the high contents of drug (about 56 w/w%) in the product prepared by coprecipitation method were observed when compared to freeze-drying (9.0 w/w%), evaporation (9.8 w/w%) and kneading method (9.9 w/w%), respectively. The detailed mechanism why inclusion complex prepared by coprecipitation method was incomplete is under consideration.

Dissolution profiles of NPX powder, commercial NAXEN® tablet and inclusion complexes with 2-HPβCD by coprecipitation, freeze-drying, evaporation and kneading method in the simulated intestinal fluid are compared in Fig. 4. Dissolution rate of NPX itself gradually increased because it was soluble in medium and basic condition. About 70% of NPX from powder and commerical NAXEN® tablet was dissolved in simulated intestinal fluid over 3 h. Initial dissolution rate of commercial NAXEN® tablet was slightly higher than NPX powder. However, dissolution rate of inclusion complexes prepared by evaporation, freeze-drying and kneading methods was greatly enhanced when compared to NPX powder and commercial NAXEN® tablet. Most of drug from inclusion complexes was dissolved within 5 min in simulated intestinal fluid. Dissolution rate of NPX from inclusion complex prepared by cop-

recipitation method was also increased when compared to NPX. However, the extent of dissolution rate was still lower when compared to other inclusion complexes prepared by evaporation, freeze-drying and kneading method due to incomplete formation of inclusion complex as mentioned previously.

From these findings, inclusion complexes of poorly water-soluble NPX with 2-HPβCD were useful to increase solubility and dissolution rate when compared to NPX powder and commercial NAXEN® tablet, resulting in enhancement of bioavailability. Although no toxicological examination of NPX complexed with 2-HPβCD is carried out, side effect of drug on gastrointestinal tract may be minimized because there is little chance to touch the stomach directly, making less irritation and injury upon oral administration of inclusion complex (Nambu *et al.*, 1978). Espinar *et al.* (1991) also observed significantly less gastric irritation of NPX complexed with β-cyclodextrin. Inclusion complex of poorly water-soluble NSAIDs with cyclodextrin and its derivatives may be useful as an advanced delivery system to simultaneously enhance dissolution rate and bioavailability, and reduce undesirable gastrointestinal toxicity. In the future, detailed information on *in vivo* effect of NPX-2-HPβCD inclusion complexes prepared by various methods on the bioavailability and gastrointestinal toxicity will be investigated.

ACKNOWLEDGMENT

This work was supported in part by the research grants from Korea Science and Engineering Foundation (KOSEF 941-0700-015-2).

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