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COMMUNICATION

Effects of Cyclodextrin Derivatives on Bioavailability of Ketoprofen

Hye Jin Ahn,[1] Kyoung Mi Kim,[1] Jin-Suck Choi,[2] and Chong-Kook Kim[1,*]

[1]*College of Pharmacy, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Gu, Seoul 151-742, Korea*
[2]*Department of Pharmacy, Dan Kuuk University Hospital, Chunan 330-180, Chung Nam, Korea*

ABSTRACT

In order to develop a new oral dosage form of ketoprofen with enhanced dissolution rate and bioavailability, inclusion complexes of ketoprofen with cyclodextrin derivatives such as α-cyclodextrin, β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, and dimethyl-β-cyclodextrin were prepared using a spray dryer, and comparative studies on the in vitro dissolution and in vivo absorption of ketoprofen were carried out. Ketoprofen in the inclusion complexes was completely dissolved within 5 min. On the other hand, only about 50.1% of ketoprofen powder alone dissolved in 60 min. The initial dissolution rates of ketoprofen in the inclusion complexes markedly increased in distilled water at 37°C, which were over 5-fold higher than that of powder alone. The maximal plasma concentration of ketoprofen (C_{max}) and area under concentration–time curve ($AUC_{0\to 8h}$) after the oral administration of inclusion complexes increased about 6-fold (46.69 or 45.36 vs. 7.55 μg/ml) and 3-fold (44.41 or 50.14 vs. 17.33 μg·hr/ml) compared to those of powder alone. It was obvious that ketoprofen inclusion complex might be a useful solid dosage form in improving the dissolution rate and bioavailability of poorly water-soluble ketoprofen.

*To whom correspondence should be addressed.

INTRODUCTION

The cyclodextrins are water-soluble, nonreducing, and macrocyclic polymers which have glucose molecules joined by an α-1,4-linkage. Molecules with suitable size and shape can be held within the cavity of cyclodextrin, that is to say, they form inclusion compounds (1).

In general, the small drug molecules showed great complexing activity with cyclodextrin molecules, and those compounds with the lowest water solubility showed a percent increase in solubility as a function of cyclodextrin concentration. Therefore, cyclodextrins have been used in pharmaceutical preparations to enhance the solubility of poorly water-soluble drugs. Natural cyclodextrins have been used extensively for this purpose. However, they are characterized by a relatively low solubility in water, which limits their application. Therefore, chemically modified cyclodextrins have been paid considerable attention to improve physicochemical properties of cyclodextrins. For example, hydroxypropyl derivatives of cyclodextrins have the advantages of enhanced solubility, lower hemolytic activity, and reduced nephrotoxicity (2,3).

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic activities. It is frequently used in the therapy of rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and other pains of nonrheumatoid origin (4). However, its solubility in water is poor and the dissolution rate and bioavailability are low. The enhancement of bioavailability is generally based on an increase in aqueous solubility and dissolution rate of ketoprofen (5,6). Therefore, many solubilization methods were applied for the development of new oral delivery systems with enhanced aqueous solubility of this drug, such as solid dispersion (7), ketoprofen–dextran ester prodrugs (8), microencapsulation of ketoprofen elixir (9), and inclusion complexation with cyclodextrin (10). It is well known that cyclodextrin interacts with the NSAID, forming an inclusion complex (5).

In this study, inclusion complexes of ketoprofen with α-cyclodextrin and three different β-cyclodextrin derivatives—β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, and dimethyl-β-cyclodextrin—were prepared using a spray dryer. The effect of cyclodextrin derivatives on the solubilization of ketoprofen was investigated to enhance the bioavailability of ketoprofen.

MATERIALS AND METHODS

Materials

Ketoprofen was purchased form Rhône–Ploulenc Pharm. Co. (Seoul, Korea). α-Cyclodextrin (α-CD), β-cyclodextrin (β-CD), 2-hydroxylpropyl-β-cyclodextrin (HPCD), and dimethyl-β-cyclodextrin (DMCD) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals were of reagent grade and used without further purification.

Solubility Test

The solubility of ketoprofen with various cyclodextrins was measured according to the method of Higuchi and Connor (11). In brief, an excess amount of ketoprofen was added to an aqueous solution containing various concentrations of cyclodextrins and was shaken at 25°C. After equilibrium was attained, the supernatant was filtered through membrane filter (0.45 μm). A portion of the filtrate was analyzed spectrophotometrically at 259 nm.

Preparation of Inclusion Complex

Solid complexes were prepared using the nozzle-type spray dryer (Model 190, Büchi, Flawil, Switzerland) as follows. Various amounts of ketoprofen and cyclodextrins were dissolved in 0.01 M phosphate buffer, pH 6.8, and stirred for 24 hr at room temperature. The resulting solutions were delivered to the nozzle at the flow rate of 5 ml/min by peristaltic pump and thereafter spray dried. The inlet and outlet temperatures were maintained at 120° and 60°C, respectively. The formation of inclusion complexes was confirmed with Fourier transform-infrared (FT-IR) spectrophotometry (Perkin-Elmer Model 1710) and differential scanning calorimetry (DSC; Netzsch 200 apparatus, Germany).

Dissolution Studies

The dissolution of ketoprofen in inclusion complex was performed using the USP XIII dissolution apparatus II (paddle method) at 37°C. The paddle was placed 2.5 cm from the bottom of the vessel. Ketoprofen powder alone or an inclusion complex or physical mixture with cyclodextrin derivatives (1:1) equivalent to 25 mg

of ketoprofen was dispersed in 900 ml of deionized water at 37° ± 0.5°C with paddle stirring speed of at 100 rpm. The samples (1 ml) were withdrawn at 5, 10, 20, 30, 40, 50, and 60 min, replaced by an equal volume of temperature-equilibrated media, and filtered through membrane filter (0.45 μm). The concentration of ketoprofen was determined using a high-performance liquid chromatography (HPLC) assay.

Analysis of Ketoprofen

Ketoprofen assay was performed as described elsewhere, with a minor modification (12). A 3.9 × 300 mm C_{18} reverse-phase chromatography column (μ Bondapak TM, 10 μm, Waters Associates, Milford, USA) was used. A mobile phase [0.01 M phosphate buffer (pH 7.0):CH_3CN = 82.5:17.5] was employed with the flow rate of 1.5 ml/min. The column eluent was monitored at 258 nm.

Animal Studies

Adult, albino, male Sprague–Dawley rats weighing range between 250 and 300 g were used. Under an anesthesia with diethyl ether, the femoral artery was cannulated with 23-gauge polyethylene cannula. All were covered with wet cotton and the cannula was flushed with 0.2 ml of heparinized normal saline (80 units/ml) to prevent blood clotting. After recovering from anesthesia, fine powder or inclusion complexes equivalent to 5 mg of ketoprofen per kg of body weight was orally administered to rats with 1 ml of 0.5% carboxymethylcellulose solution. Blood samples (150 μl) were withdrawn at designated time intervals and centrifuged at 2000 *g* for 10 min. A 50 μl plasma sample was mixed with equal volume of internal standard (10 μg/ml of naproxen) and adjusted to pH 2.0 with ammonium phosphate buffer. After addition of 1 ml of ether, the mixture was shaken slowly for 15 min and centrifuged at 2000 *g* for 5 min. The resulting ether phase was recovered and the remaining water phase was extracted with 0.5 ml of ether again. The collected ether phase was evaporated to dryness in a stream of nitrogen. The residue was redissolved in 500 μl of mobile phase and 10 μl of this solution was injected into the HPLC.

Pharmacokinetic Data Analysis

The noncompartmental pharmacokinetic parameters, including area under the drug concentration–time curve ($AUC_{0\rightarrow 8h}$) and area under the moment of the concentration–time curve ($AUMC_{0\rightarrow 8h}$) from 0 to 8 hr, were calculated using the RSTRIP II program (Salt Lake City, UT, USA). The maximal plasma concentration of drug (C_{max}) and time to reach maximum plasma concentration (T_{max}) were also obtained from plasma data. Mean residence time (*MRT*) was calculated with the standard method of Gibaldi and Perrier (13).

The data from different formulations were compared for statistical significance by one-way analysis of variance (ANOVA). The statistical significance of means among different formulations was compared by the Duncan multiple range test. All results were expressed as mean ± standard deviation (*SD*).

RESULTS AND DISCUSSION

The inclusion complexation of drug molecules with cyclodextrins has been used to increase the dissolution rate of drugs, to increase the bioavailability of sparingly soluble drugs, to increase drug stability, and to reduce gastric irritancy (14). Ketoprofen is only slightly soluble in water and frequently causes gastric irritation when administered orally. In order to improve the poor dissolution characteristics and decrease gastric irritation of ketoprofen, inclusion complexation with cyclodextrin derivatives was employed.

The solubilities of ketoprofen with α-cyclodextrin, β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, and dimethyl-β-cyclodextrin are shown in Fig. 1. The solubility of ketoprofen increased in a linear fashion as a

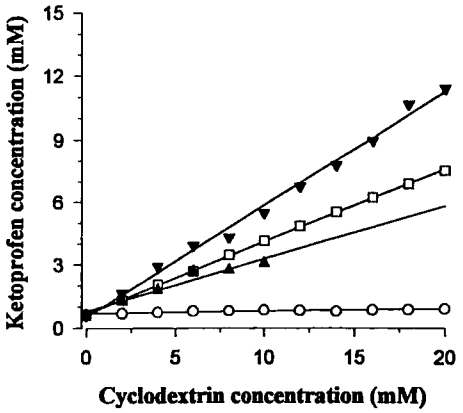

Figure 1. The solubility of ketoprofen with cyclodextrin derivatives. Key: ○, α-CD; ▲, β-CD; □, HPCD; ▼, DMCD.

function of concentration of β-cyclodextrin (β-CD) and its derivatives. The apparent complex formation constants (K) were calculated with the assumption of 1:1 stoichiometry. The inclusion complex formed with DMCD is the most stable (K = 2425 M^{-1}). The inclusion complexes with β-CD and HPCD were also stable (K = 441 M^{-1} and 842 M^{-1}, respectively). However, the value obtained from α-cyclodextrin (K = 23.5 M^{-1}) relates to the formation of complex with very low stability. This indicates that ketoprofen would have difficulty in fitting into the small cavity within α-cyclodextrin, α-Cyclodextrin was no longer used for further studies.

The dissolution profiles of ketoprofen from physical mixtures, inclusion complexes, and powder alone in distilled water at 37°C were determined. Dissolution of ketoprofen from powder alone was slow and incomplete even after 60 min. In the physical mixture, the dissolution rate was slightly enhanced, which is probably due to a slow interaction between host and guest, whereas ketoprofen inclusion complexes were immediately dispersed and completely dissolved within 5 min, as shown in Fig. 2. Initial dissolution rate of ketoprofen in the inclusion complexes within 5 min increased markedly (about 5-fold) compared to powder alone. The percentage of ketoprofen dissolved from inclusion complexes for 60 min increased approximately 2-fold compared to powder alone. Therefore, it is supposed that interaction between ketoprofen and cyclodextrins in the inclusion complex is somewhat different from that in the physical mixture.

Figure 3 shows the mean plasma concentration–time profiles of ketoprofen after the oral administration of ketoprofen inclusion complex with β-CD or HPCD (equivalent dose of 5 mg/kg as ketoprofen) to rats. DMCD was rejected for the bioavailability test, since DMCD has high cost and the property of gastric irritation induction (15).

The noncompartmental pharmacokinetic parameters in Table 1 were calculated based on the observed plasma data. When the equivalent dose of ketoprofen (5 mg/kg) was administrated to rats, the inclusion complex with β-CD and HPCD attained peak plasma level of 46.69 and 45.36 μg/ml, which was about 6-fold higher than that of powder alone (7.55 μg/ml). The area under the plasma concentration–time curve ($AUC_{0\to 8h}$) of ketoprofen–β-CD and ketoprofen–HPCD complexes were 2.6-fold (44.41 vs. 17.33 μg·hr/ml) and 2.9-fold (50.14 vs. 17.33 μg·hr/ml) increased, respectively, when compared to powder alone. However, there was no difference in $AUC_{0\to 8h}$ values between inclusion complexes. T_{max} and MRT of inclusion complexes were significantly decreased compared to that of powder alone, which relates to the rapid dissociation of the complex following the dissolution in the GI tract. This means that ketoprofen–cyclodextrin inclusion complexes might improve the absorption characteristics of ketoprofen.

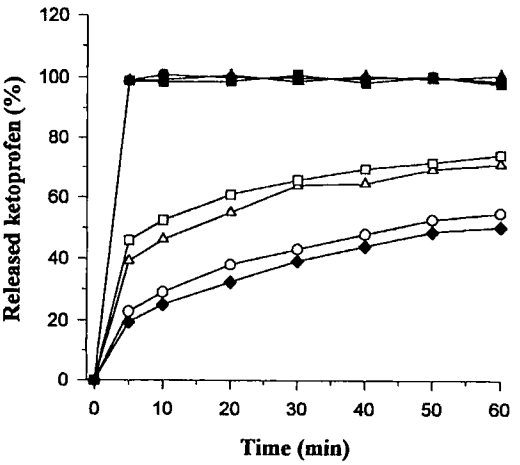

Figure 2. The dissolution profiles of ketoprofen from inclusion complexes in distilled water. Key: ◆, powder, ○, physical mixture with β-CD; ●, inclusion complex with β-CD; △, physical mixture with HPCD; ▲, inclusion complex with HPCD; □, physical mixture with DMCD; ■, inclusion complex with DMCD.

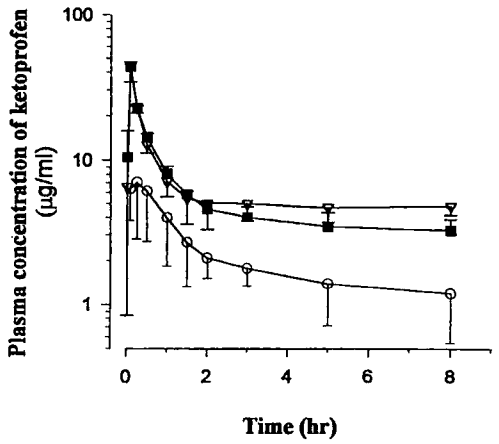

Figure 3. Plasma concentration profiles of ketoprofen after oral administration of ketoprofen inclusion complexes with β-CD and HPCD to rats. Key: ○, powder; ▽, inclusion complex with β-CD; ■, inclusion complex with HPCD.

Table 1

Pharmacokinetic Parameters of Ketoprofen After Oral Administration to Rats

Product	$AUC_{0-8\ h}$ (μg·hr/ml)	C_{max} (μg/ml)	T_{max} (hr)	*MRT* (hr)
Powder	17.33 ± 5.49	7.55 ± 4.65	0.23 ± 0.20	2.06 ± 0.90
β-CD complex	44.41 ± 5.47*	46.69 ± 4.46*	0.07 ± 0.02*	0.42 ± 0.24
HPCD complex	50.14 ± 6.47*	45.36 ± 4.89*	0.07 ± 0.02*	0.28 ± 0.01

*Significantly different at $p < 0.05$.

Therefore, ketoprofen–cyclodextrin inclusion complexes might be a useful solid dosage form to improve the dissolution rate and bioavailability of water-insoluble ketoprofen.

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