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COMMUNICATION

Enhancement of Bioavailability of Ketoprofen Using Dry Elixir as a Novel Dosage Form

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ABSTRACT

To enhance the dissolution rate and bioavailability of poorly water-soluble ketoprofen, a novel oral dosage form of ketoprofen, termed ketoprofen dry elixir, was developed by the spray-drying technique. Ketoprofen, dextrin, and sodium lauryl sulfate were dissolved in an ethanol–water mixture (20:25 w/w) and thereafter spray-dried to form the ketoprofen dry elixir.

Comparative studies on the in vitro dissolution and in vivo adsorption of ketoprofen in the form of dry elixir and powder were carried out. Ketoprofen in the dry elixir completely dissolved within 5 min. On the other hand, only about 50.1% of ketoprofen powder alone dissolved during 60 min. The initial dissolution rate of ketoprofen in the dry elixir markedly increased in distilled water at 37°C, becoming fourfold higher than that of ketoprofen powder alone.

The maximal plasma concentration of ketoprofen (C_{max}) and the area under the concentration–time curve from zero to 8 hr ($AUC_{0-8\ hr}$) after the oral administration of dry elixir increased about 3.2- (24.6 versus 7.6 μg/ml) and 2.2- (38.4 versus 17.3 μg hr/ml) fold compared with powder alone. It was obvious that ketoprofen dry elixir might be a useful solid dosage form to improve the dissolution rate and bioavailability of poorly water-soluble ketoprofen.

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INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic actions. It is frequently used in the therapy of rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and other pains of nonrheumatoid origin (1,2). Solubilized ketoprofen is absorbed rapidly and completely from the gastrointestinal tract after oral administration. However, ketoprofen is poorly water soluble and its dissolution rate and bioavailability are relatively low. The enhancement of bioavailability is generally based on the increase in solubility and dissolution rate of ketoprofen (3,4). Therefore, many solubilization methods were applied for the development of a new oral delivery system with enhanced aqueous solubility of this drug, such as the formation of solid dispersions (5), ketoprofen–dextran ester prodrug (6), and inclusion complexation with various types of cyclodextrin (7,8).

Recently, we developed a new oral dosage form, a dry elixir, for increasing the dissolution rate of poorly water-soluble drugs (9,10). Dry elixir is a powder form of microcapsule containing an alcoholic drug solution. Poorly water-soluble drugs encapsulated in the dry elixir are rapidly soluble in the gastrointestinal tract after oral administration, which leads to preferable bioavailability (10).

In this study, the ketoprofen dry elixir was prepared and dissolution rate and bioavailability of ketoprofen encapsulated in the dry elixir were evaluated.

MATERIALS AND METHODS

Materials

Ketoprofen and dextrin (TK-16®) were purchased from Rhône-Poulenc Rorer Pharm. Co. (Seoul, Korea) and Matsdani Chemical Co. (Tokyo, Japan), respectively. Ethanol (94.5% v/v) and sodium lauryl sulfate were obtained from Ducksan Chemical Co. (Seoul, Korea) and Aldrich Chemical Co. (Milwaukee, WI), respectively. All other chemicals were of reagent grade and used without further purification.

Preparation of Ketoprofen Dry Elixir

Dry elixir was prepared using the nozzle-type spray-dryer (model 190, Büchi, Flawil, Switzerland) as follows: 1 g of ketoprofen was dissolved in 45 g of ethanol–water cosolvent (20:25 w/w). This solution was prewarmed to 60°C and blended with 0.2 g of sodium lauryl sulfate and 20 g of dextrin. The resulting solution was 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 95 and 60°C, respectively. The pressure of spray air was 3 kg/cm^2 and the flow rate of dry air was maintained at the aspirator setting of 10. The direction of air flow was the same as that of spray-dried product.

Dissolution Studies

The dissolution test of ketoprofen encapsulated in the dry elixir was performed using the USP 22 dissolution apparatus II (paddle method) at 37°C. The paddle was placed 2.5 cm from the bottom of the vessel. Powder or dry elixir equivalent to 25 mg of ketoprofen was dispersed in 900 ml of deionized water at 37 ± 0.5°C with paddle stirring speed at 100 rpm. The samples (1 ml) were withdrawn at 5, 10, 20, 30, 40, 50, and 60 min with replacement by an equal volume of temperature-equilibrated medium and then filtered through a membrane filter (0.45 μm). The concentration of ketoprofen was determined using an HPLC assay.

Animal Studies

Adult, albino, male Sprague–Dawley rats weighing between 250 and 300 g were used. Under an anesthesia with diethyl ether, the femoral artery was cannulated with 23-gauge polyethylene cannula. All incisions 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 the rats recovered from anesthesia, fine powder alone or dry elixir equivalent to 5 mg of ketoprofen per kg of body weight was orally administered to rats using an oral needle. Ketoprofen powder alone or dry elixir (equivalent to 5 mg of ketoprofen) was dispersed in 1 ml of 0.5% carboxymethylcellulose solution prior to dosing. 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 phosphate buffer. After the 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 remaining water phase was extracted with 0.5 ml of ether again. 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.

Analysis of Ketoprofen

Ketoprofen assay was performed as described elsewhere with a minor modification (11,12). A reversed-phase chromatography column (3.9 × 300 mm C_{18}, μBondapakTM, 10 μm, Waters Associates, Milford, MA) was used. A mobile phase composed of 0.01 M phosphate buffer (pH 7.0) CH_3CN = 82.5:17.5 was employed with a flow rate of 1.5 ml/min. The column eluent was monitored at 258 nm.

Pharmacokinetic Data Analysis

The noncompartmetal pharmacokinetic parameters including area under the drug concentration–time curve (AUC) and area under the moment of the concentration–time curve (AUMC) from zero to 8 hr were calculated using the RSTRIP II program (Salt Lake City, UT). The maximal plasma concentration of drug (C_{max}) and time to reach maximum plasma concentration (T_{max}) were also obtained from plasma data. The following standard methods were used to calculate mean residence time (MRT) (13).

$$AUC = \int_0^t C_p dt$$

$$AUMC = \int_0^t C_p t dt$$

$$MRT = AUMC/AUC$$

where C_p is the plasma concentration of drug at time t. The data among formulations were compared for statistical significance by the analysis of variance (ANOVA) test. All results were expressed as mean ± standard deviation (SD).

RESULTS AND DISCUSSION

It was previously reported that microcapsules containing ethanol in dextrin shell can be prepared by spray-drying the solution of dextrin dissolved in an ethanol–water cosolvent system (14,15). By employing this technique, we previously reported that microcapsules containing NSAID and ethanol in dextrin membrane had enhanced the dissolution rate of poorly water-soluble NSAID compared with drug fine powder alone (9). In order to evaluate the bioavailability of ketoprofen encapsulated in the dry elixir, dry elixir containing ketoprofen (3% w/w) and ethanol (35% w/w) was prepared and comparative studies on the in vitro dissolution and in vivo absorption characteristics were compared with those of ketoprofen powder alone.

The dissolution profiles of ketoprofen in the dry elixir and ketoprofen powder alone in distilled water at 37°C are shown in Fig. 1. Ketoprofen dry elixir was immediately dispersed and completely dissolved within 5 min. Initial dissolution rate of ketoprofen encapsulated in the dry elixir increased markedly (about fourfold) compared to ketoprofen powder alone. The percentage of ketoprofen dissolved from dry elixir for 60 min increased approximately twofold compared to ketoprofen powder alone. Ketoprofen elixir encapsulated in the dextrin microcapsules dispersed immediately into dissolution medium following the dissolution of dextrin shell. The increased dissolution rate of ketoprofen suggested that the ketoprofen dry elixir might have a good oral bioavailability.

Figure 2 shows the mean plasma concentration–time profiles of ketoprofen dry elixir (equivalent dose of 5 mg/kg as ketoprofen) to rats. The noncompartmental pharmacokinetic parameters in Table 1 were calculated based on the observed plasma data. Ketoprofen dry elixir attained peak plasma level of 24.6 μg/ml at 0.08 hr, which was 3.2-fold higher than that of ketoprofen powder alone (24.6 versus 7.6 μg/ml). The $AUC_{0-8\ hr}$ of ketoprofen dry elixir increased 2.2-fold when compared to ketoprofen dry elixir, but decreased compared to that of ketoprofen powder alone (38.4 versus 17.3 μg·hr/ml). T_{max} and MRT values of ketoprofen dry elixir were decreased compared to those of ketoprofen powder alone (0.23 versus 0.08 hr and 2.06 versus 0.28 hr, respec-

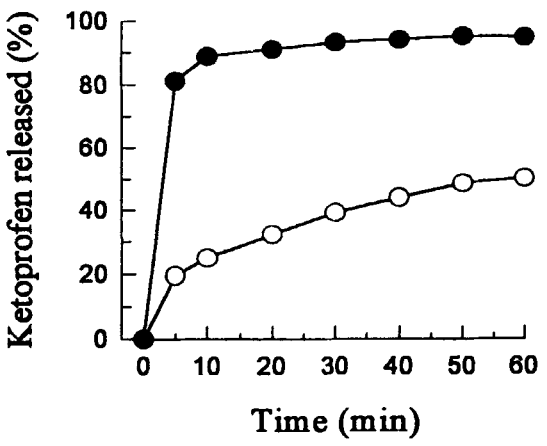

Figure 1. The dissolution profiles of ketoprofen in distilled water. Key: ○, powder; ●, dry elixir.

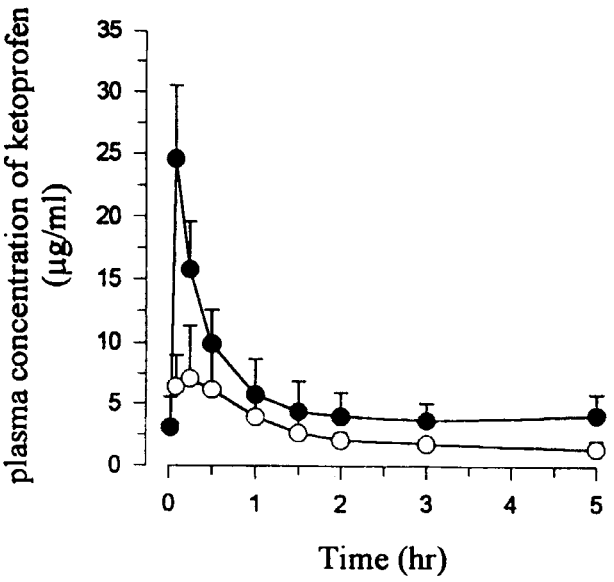

Figure 2. Plasma concentration profiles of ketoprofen after oral administration. Key: ○, powder; ●, dry elixir.

tively), which relates to a more transient effect on physiological function because of a rapid onset of action.

CONCLUSION

Comparative studies on the in vitro dissolution and in vivo absorption of ketoprofen in the form of dry elixir and powder alone were carried out. Ketoprofen in the dry elixir was completely dissolved within 5 min. On the other hand, only about 50% of ketoprofen fine powder dissolved in 60 min. The initial dissolution rate of ketoprofen in the dry elixir markedly increased in distilled water at 37°C, which was more than fourfold higher than that of ketoprofen powder alone. The C_{max} and $AUC_{0-8\ hr}$ of ketoprofen after the oral administration of ketoprofen dry elixir were almost 3.2- and 2.2-fold increased, respectively, when compared to ketoprofen powder alone.

Therefore, ketoprofen dry elixir might be a useful solid dosage form to enhance the bioavailability of ketoprofen. It should also be noted that ketoprofen dry elixir might facilitate the pharmaceutical preparation because of an improvement of content uniformity and simplification of the manufacturing process.

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Table 1

Pharmacokinetic Parameters of Ketoprofen After Oral Administration to Rats

Products	$AUC_{0-8\ hr}$ (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
Dry elixir	38.39 ± 15.56[a]	24.55 ± 5.99[a]	0.08 ± 0.00	0.28 ± 0.01

[a]Significantly different at $p < 0.05$ by the Student's *t*-test when compared with ketoprofen powder alone.

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