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Formulation of a Fast-Dissolving Ketoprofen Tablet Using Freeze-Drying in Blisters Technique

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ABSTRACT The aim of this work was to develop a ketoprofen tablet which dissolve-rapidly in the mouth, therefore, needing not be swallowed. The solubility and dissolution rate of poorly water-soluble ketoprofen was improved by preparing a lyophilized tablet (LT) of ketoprofen using freeze-drying technique. The LT was prepared by dispersing the drug in an aqueous solution of highly water-soluble carrier materials consisting of gelatin, glycine, and sorbitol. The mixture was dosed into the pockets of blister packs and then was subjected to freezing and lyophilization. The saturation solubility and dissolution characteristics of ketoprofen from the LT were investigated and compared to the plain drug and the physical mixture (PM). Results obtained showed that the increase in solubility of ketoprofen from LT matrix, nearly three times greater than the solubility of the plain drug, was due to supersaturation generated by amorphous form of the drug. Results obtained from dissolution studies showed that LT of ketoprofen significantly improved the dissolution rate of the drug compared with the PM and the plain drug. More than 95% of ketoprofen in LT dissolved within 5 min compared to only 45% of ketoprofen plain drug dissolved during 60 min. Initial dissolution rate of ketoprofen in LT was almost tenfold higher than that of ketoprofen powder alone. Crystalline state evaluation of ketoprofen in LT was conducted through differential scanning calorimetry (DCS) and x-ray powder diffraction (XRPD) to denote eventual transformation to amorphous state during the process. Scanning electron microscopic (SEM) analysis was performed and results suggest reduction in ketoprofen particle size.

INTRODUCTION

Ketoprofen (3-benzoyl-a-methylbenzene-acetic acid) is a non-steroidal anti-inflammatory (NSAID) drug with analgesic, anti-inflammatory, and antipyretic effects. It is widely used in the treatment of inflammation and pain associated with rheumatic disorders such as rheumatoid arthritis, osteoarthritis, and in

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soft tissue injury (Fossgreen, 1976; Kantor, 1986; Airaksinen, 1993). Ketoprofen is also widely used to treat postoperative pain and fever in children (Nikanne et al., 1999; Keinänen-Kiukaanniemi et al., 1980; Kokki et al., 2000). After solubilization ketoprofen is completely and rapidly absorbed from the gastrointestinal tract. However, bioavailability of ketoprofen is limited by its poor water solubility following oral administration. Ketoprofen was also reported to cause local gastrointestinal side effects which require withdrawal of treatment (Moore et al., 1996; Alarcon et al., 2002; Motola et al., 2001). Therefore, several solubilization techniques were applied and reported to enhance the aqueous solubility of ketoprofen. For improving the solubility and dissolution rate of the drug in water, formation of inclusion complexes with cyclodextrin (Lu et al., 2004) and skimmed milk (Topalogu et al., 1999) were carried out. To enhance the dissolution rate and bioavailability of ketoprofen, a novel dry elixir dosage form has been proposed (Ahn et al., 1998). The formation of ketoprofen solid dispersions (Jachowicz et al., 2000; Solanker & Jagtap, 2005) and ketoprofen-dextran ester prodrug (Larsen et al., 1991) has been reported to improve ketoprofen solubility and dissolution and to reduce its ulcerative side effects. Solid dispersions are widely used to improve the water solubility and dissolution of many drugs and are traditionally prepared using fusion or solvent techniques. Both techniques suffer from a number of disadvantages. Preparation of solid dispersions by fusion technique is not suitable for heat sensitive drugs, besides, phase separation can occur upon cooling. Preparation of solid dispersions by solvent technique requires the use of large amounts of water to dissolve the carrier and the poorly water-soluble drug making the process uneconomic and impractical. Organic solvents are often used instead but because of their toxicity their use remains impractical while the use of solvent mixtures such as ethanol–water and ethanol–methylene chloride usually results in crystallization of lipophilic drugs during drying. Preparation of solid dispersions by freeze drying on the other hand has been reported to have many advantages. The risk of crystallization and phase separation during the process is usually low. The process is suitable for thermolabile drugs and a large variety of carrier materials can be used. The physical stability of solid dispersions prepared by lyophilization is usually higher when compared to other techniques. In one study it has been shown that varying the shelf temperature, freezing temperature, freezing time, and drug content resulted in the formation of a very small fraction of crystalline drug during the process indicating that lyophilization is a very robust process (Van Drooge et al., 2004).

In our study a fast-dissolving LT of ketoprofen was prepared by freeze-drying using several excipients. Lyophilized fast-dissolving tablets which dissolve instantaneously in the mouth has been developed to large scale production in recent years and many are approved for marketing. The increasing need for such dosage forms in the market is mainly due to the ease and the convenience of administration. This type of dosage form usually improves the overall clinical performance of drugs by reducing the incidence of noncompliance especially among pediatric and geriatric patients and those patients who find it difficult to swallow tablets and capsules. The bioavailability of some drugs, especially those suffering from a high first-pass metabolism, can be improved due to pregastric absorption and local gastro-intestinal side effects are also expected to be reduced by formulating such dosage forms (Lu et al., 2004). In this work the solubility and dissolution characteristics of ketoprofen in the prepared LT were evaluated. Differential scanning calorimetry (DSC), XRPD, and SEM analysis were performed to determine the physicochemical properties of the LT and the PM in comparison with the plain drug.

MATERIALS AND METHODS

Materials

Ketoprofen, micronized gelatine, glycine, and sorbitol were purchased from Sigma Chemical Co., St. Louis, MO. All water used was distilled de-ionized water. All other chemicals were of reagent grade and used as received.

Preparation of Ketoprofen Fast-Dissolving Lyophilized Tablets

A 2% w/v solution of gelatin in water was prepared by first soaking the gelatin in water until complete hydration. The hydrated gelatin was stirred using a magnetic stirrer until a clear solution was obtained. Equal weights of glycine (0.886% w/v) and sorbitol

(0.886% w/v) were added to the gelatin solution while stirring until completely dissolved. Glycine (used to prevent shrinkage of the tablet during manufacturing) and sorbitol (used to impart crystallinity, hardness, and elegance to the tablet) are well-known and acceptable materials used in preparing freeze-dried tablets. The percentage excipient used was optimized during the formulation process to result in a strong and elegant tablet that could be handled with ease. An accurately weighed amount of ketoprofen powder (2.5% w/v) was then dispersed in the aqueous solution of gelatin, glycine, and sorbitol. One milliliter of the resulting suspension was poured into each of the pockets of a tablet blister pack to result in a ketoprofen dose of 25 mg in each tablet. The tablet blister packs, each containing 10 tablets, were then transferred to a freezer at –22°C and kept in the freezer for 24 h. The frozen tablets were placed in a lyophilizer for 24 h using a Novalyphe-NL 500 Freeze Dryer (Savant Instruments, Holbrook, NY) with a condenser temperature of –45°C and a pressure of 7×10^{-2} mbar. The LTs were kept in a desiccator over calcium chloride (0% relative humidity) at room temperature until further used. Four blister packs containing a total of 40 tablets were produced in each run. Eight randomly selected tablets (two from each pack) were assayed for drug content uniformity. The mean % drug content was found to be 95.3% ± 1.25%.

Preparation of the Physical Mixtures

Ketoprofen was uniformly mixed with gelatin, glycine and sorbitol in the same percentage used in the LT using a mortar and pestle. The prepared mixtures were kept in a desiccator until used.

Solubility Studies

Ketoprofen (100 mg), its LTs and PMs equivalent to 100 mg ketoprofen were placed in glass stoppered flasks and 100 mL water was added to each flask. The flasks were shaken in a water bath at 25°C for 15 h (USP XIX). The solutions were filtered through a membrane filter (0.45 μm) and the dissolved drug was measured spectrophotometrically at 262 nm. This experiment was done in triplicate.

Dissolution Studies

The dissolution profiles of ketoprofen LT and PM, compared with the plain drug, were determined in a dissolution tester (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ) following the USP paddle method. All tests were conducted in 900 mL of distilled water maintained at 37 ± 0.5°C with a paddle rotation speed at 50 rpm. The amount of drug used was equivalent to 25 mg. After specified time intervals, samples of dissolution medium were withdrawn, filtered, and assayed for drug content spectrophotometrically at 262 nm after appropriate dilution with water.

Differential Scanning Calorimetry Studies

Samples weighing approximately 5 mg were sealed in aluminum pans and analyzed using a Shimadzu DSC-60 (Kyoto, Japan). The samples were heated in an atmosphere of nitrogen and thermograms were obtained by heating at a constant heating rate of 10°C/min in the range of 20–150°C. Thermograms for ketoprofen, LT, and PM were obtained.

X-ray Powder Diffraction Analysis

X-ray diffraction experiments were performed in a Scintag x-ray diffractometer (USA) using Cu K α radiation with a nickel filter, a voltage of 45 kV, and a current of 40 mA. Diffraction patterns for ketoprofen, LT, and PM were obtained.

Scanning Electron Microscopic Analysis

Surface morphology of ketoprofen, its LT as well as its PM, was examined by SEM (Jeol JSM-6400, Tokyo, Japan). Cross-sections of the LT were made to study their inner structure. Photographs were taken at magnification of 1000.

RESULTS AND DISCUSSION

The increase in solubility of ketoprofen from LT matrix (0.058% w/v), nearly three times higher when compared to the solubility of the plain drug (0.021% w/v), indicates that the superstaturation obtained from the LT is generated by the amorphous form of

the drug in the LT. The increase in solubility of ketoprofen from the PM (0.031% w/v), nearly one and half times higher than the plain drug, could be due to the solubilizing effect of highly water soluble carrier materials used in the formulation such as glycine and sorbitol. Solubilities are presented in Table 1.

The dissolution profiles of ketoprofen in the LT, in the PM, and ketoprofen powder alone in distilled water at 37°C are shown in Fig. 1. Ketoprofen in the LT was immediately dispersed and almost completely dissolved in 5 min. Initial dissolution rate of ketoprofen in the LT increased markedly (about tenfold) compared to ketoprofen powder alone. The dissolution rate was also higher and faster in LT than in PM. The percentage of ketoprofen dissolved from its PM for 60 min (80%) increased approximately twofold compared to ketoprofen powder alone (43%).

The increased dissolution rate of ketoprofen from its LT suggests that ketoprofen LT might have a rapid oral absorption following disintegration in the mouth and dissolution in the saliva since solubilized ketoprofen is absorbed rapidly and completely from the gastrointestinal tract after oral administration.

TABLE 1 **Solubility of Ketoprofen as a Plain Drug, in LT, and PM in Distilled Water at 25°C**

Ketoprofen (% w/v)	Form of drug	Solubility (% w/v ± SD)
0.1	LT	0.058% ± 0.018
0.1	PM	0.031% ± 0.012
0.1	plain drug	0.021% ± 0.006

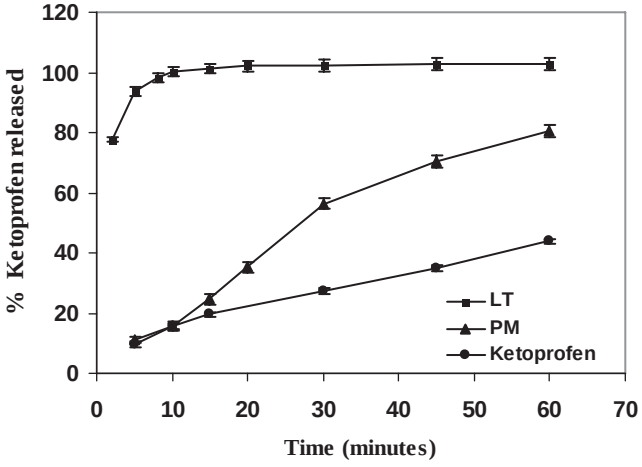

FIGURE 1 **Dissolution Profiles of LT, PM, and Ketoprofen Powder in Distilled Water at 37°C. *N* = 3 with SD.**

The enhancement in solubility and dissolution rate of ketoprofen in its LT may be attributed to the formation of amorphous state in the porous lyophilized matrix of the fast dissolving carrier materials.

To evaluate the crystalline state of ketoprofen in LT and PM, DSC studies were performed on ketoprofen powder, its LT, and PM (Fig. 2). The DSC curve of ketoprofen showed a sharp endothermic peak at nearly 90°C, corresponding to its melting transition point. The thermogram of the PM showed the endothermic peak of ketoprofen, although broader, splitted, and slightly shifted to the right, indicating that the crystalline state is maintained in the PM. However, the melting endotherm was absent on the DSC thermogram of the LT, suggesting absence of crystallinity and presence of amorphous state of the drug.

These results were further confirmed by x-ray diffraction studies (Fig. 3). The x-ray diffraction pattern of the pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The diffraction study of the PM

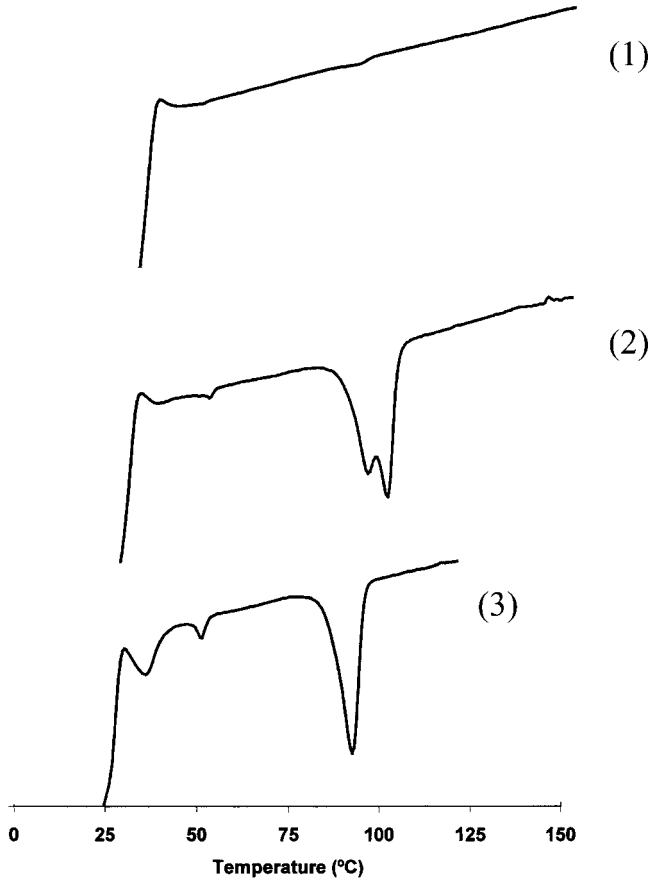

FIGURE 2 **DSC Thermograms of LT (1), PM (2), and Ketoprofen (3).**

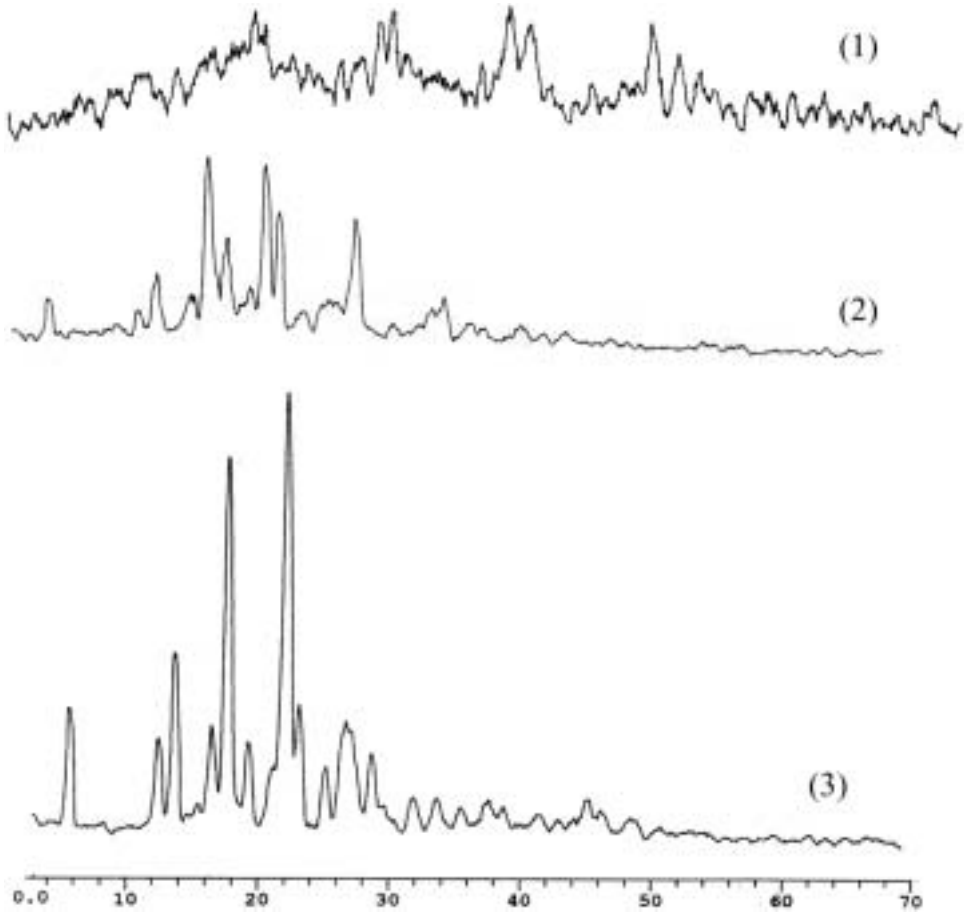

FIGURE 3 Powder X-ray Diffraction Spectra of LT (1), PM (2), and Ketoprofen (3).

of drug and excipients showed the peaks corresponding to the crystalline drug molecules present in the mixture, although their intensity was lower due to the high excipients–drug ratio employed. The diffraction pattern of the LT of drug showed absence, broadening, and reduction of major ketoprofen diffraction peaks indicating that mostly an amorphous form (disordered state) existed in the LT. These results could explain the observed enhancement of solubility and rapid dissolution of ketoprofen in LT.

SEM micrographs of ketoprofen, PM, and LT are shown in Fig. 4. The results show that ketoprofen

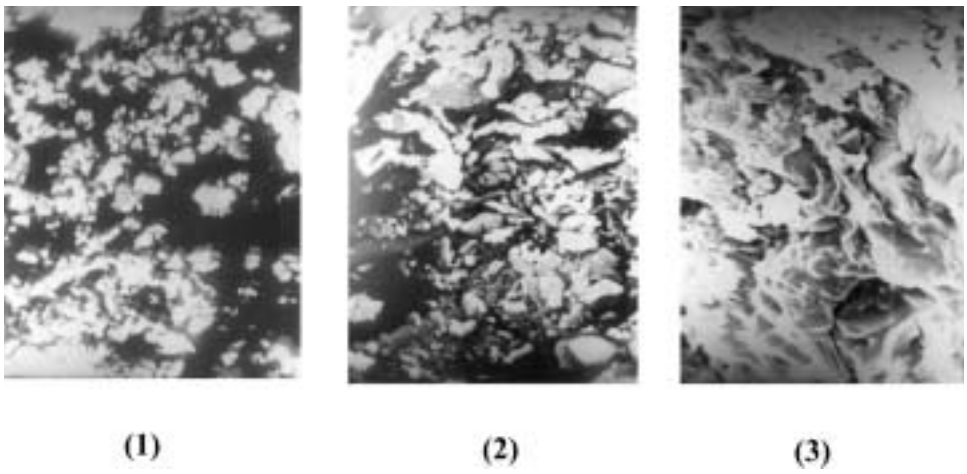

FIGURE 4 SEM Micrographs of Ketoprofen (1), PM (2), and LT (3).

particles could be seen in the PM while the micrograph of LT shows a matrix in which no crystals of ketoprofen could be seen. The SEM micrograph of LT suggests that the particles of drug might have been reduced during dissolution in the gelatin–glycine–sorbitol solution. This could therefore indicate that ketoprofen particle size has been reduced which also accelerates dissolution.

Based on these results, it can be concluded that the freeze dried ketoprofen tablet could be a suitable form of ketoprofen in terms of solubility and dissolution in water. This technique provides a promising manufacturing procedure directly resulting in sublingual tablets without any other mixing or formulation steps. Moreover, the properties of the tablet are suitable.

CONCLUSION

We demonstrated that a lyophilized ketoprofen tablet made of widely used, safe, water-soluble excipients is feasible for enhancing the solubility and increasing the dissolution rate of ketoprofen. Since the technology to the production scale of manufacture is now available, we think that the formulation we developed in this work is feasible for easy industrialization, up-scaling, and manufacturing. The results obtained were attributed to the formation of an amorphous state of the drug in the porous lyophilized matrix and probably to reduction of drug particle size. Future work will be focused on investigating the physical stability of the tablets and determining the absorption rate and bioavailability of ketoprofen from LT in human volunteers. We suggest that the prepared ketoprofen LT might have a higher oral bioavailability due to expected rapid dissolution in the saliva than standard dosage forms; therefore, it would be possible to formulate ketoprofen in LT having an eventual decreased therapeutic dose resulting in reduced side-effects encountered with ketoprofen therapy such as gastrointestinal disturbance.

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