

## A NOVEL TECHNIQUE TO ENHANCING THE SOLUBILITY AND DISSOLUTION OF KETOPROFEN USING FREEZE DRYING

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### ABSTRACT

The aim of the present work was to develop a ketoprofen freeze dried tablet (FDT). Which dissolve instantaneously in the mouth. The solubility and dissolution rate of poorly water-soluble ketoprofen was improved by preparing a FDT of ketoprofen using freeze-drying technique. The FDT was prepared by dispersing the drug in an aqueous solution of highly water-soluble carrier materials consisting of gelatin, lysine, and sorbitol. The mixture was poured in to the pockets of blister packs and then was subjected to freezing and lyophilization. The FDT was characterized by DSC, XRD and SEM and was evaluated for saturation solubility and dissolution and compared with physical mixture (PM) and pure drug. The samples were stored in stability chamber to investigate their physical stability for 90 days. Result obtained by DSC and X-ray studied showed that Crystalline state of ketoprofen in FDT transformation to amorphous state during the formation of FDT. SEM result suggests reduction in ketoprofen particle size. The solubility of ketoprofen from the FDT showed six and half times greater than pure drug was due to super-saturation generated by amorphous form of the drug. Dissolution studies showed that dissolution rate of FDT of ketoprofen significantly improved compared with the PM and the pure drug. More than 90% of ketoprofen in FDT dissolved within 5 min. compared to only 29.21% of ketoprofen pure drug dissolved during 60 min. In stability test, the dissolution release profile of the ketoprofen in FDT was almost unchanged as compared with the freshly prepared FDT.

**Key words:** Freeze drying, freeze dried tablet, ketoprofen, solubility and dissolution.

### INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug, scarcely soluble in water, which is widely used as analgesic and for the acute and long-term treatment of rheumatoid arthritis and osteoarthritis. Its short elimination half-life and adverse effects, like gastrointestinal mucosa ulceration, restrict its oral use and make it a good candidate for transdermal administration<sup>1, 2</sup>. However, due to the excellent barrier function of the skin, the need to use safe and effective enhancers for improving transdermal absorption of drugs is well recognized<sup>3, 4</sup>.

Most of the NSAIDs belong to class II category under Biopharmaceutical classification system (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. Rate of absorption and / or extent of bioavailability for such insoluble hydrophobic drug are controlled by rate of dissolution in gastro-intestinal fluids. However, its oral bioavailability is very low, probably due to poor solubility in water and insufficient dissolution rate<sup>5, 6</sup>.

Currently, several approaches are widely used to fabricate Rapid Dissolving tablet (RDT) including lyophilisation, solid dispersion, mucoadhesive micro-particulate, direct compression and moulding. Therefore, several solubilization techniques were applied and reported to enhance the aqueous solubility of poorly water soluble drugs like ketoprofen, formation of fast dissolving ketoprofen with gelatin, sorbitol and amino acid like glycine<sup>7</sup>. mefenamic acid, formation of Solid Dispersions of mefenamic acid with crospovidone<sup>8</sup>, formation of mefenamic acid capsule with sodium lauryl sulphate<sup>9</sup>, The Fast-dissolving mucoadhesive micro-particulate containing piroxicam<sup>10</sup>. The formation fast dissolving tablet of piroxicam acid has been proposed<sup>10, 11</sup>. However, in terms of sales value, sales volume and number of products available on the market, freeze drying (lyophilisation) method has been the most successful<sup>12</sup>. The fabrication of , freeze drying RDTs is based on creating a porous matrix by subliming the water from pre-frozen aqueous formulation of the drug containing matrix forming agents and other excipients such as preservatives, flavors and lyoprotectants<sup>13</sup>. The matrix of the freeze drying RDT consists of two components that work together to ensure the development of a successful formulation. The first component is water soluble polymers such as gelatin, dextrin, alginate<sup>14</sup> and maltodextrin<sup>15</sup>. This

component maintains the shape and provides mechanical strength to the tablets (binder). The second constituent is matrix supporting/disintegration enhancing agents such as sucrose and mannitol, which acts by cementing the porous frame work, provided by the water soluble polymer and accelerates the disintegration of the RDT<sup>16, 17, 18</sup>. Although there is wide availability of literature describing the preparation of RDTs by freeze drying, the number of matrix supporting/disintegration enhancing agents used has been limited to saccharides and polyols with majority of the work dedicated to the inclusion of mannitol<sup>15, 17, 18</sup>. This is primarily because the incorporation of these matrix forming agents requires fulfillment of stringent characteristics such as reasonable drying time, stability during freeze-drying process, as well as formation of elegant tablets with short disintegration time and adequate mechanical properties. However, high concentration of saccharides and polyols is required to achieve these quality features<sup>15, 17, 18</sup>, thus restrains their application in delivering drugs for the treatment of long-term chronic conditions especially for children, diabetic and obese patients, due to limited intake requirement. Therefore, this present study aim to develop novel excipients by investigating the feasibility of using amino acids as matrix supporting agents (second component) in the fabrication of rapid dissolving tablets prepared by freeze drying in order to produce tablets with enhanced properties and wider application to pediatric and geriatric patient population.

Amino acids are the basic structural units (monomer) of proteins. An alpha amino acid consists of an amino group, a carboxyl group, a hydrogen atom and a distinctive side chain bonded to a carbon atom (alpha carbon). Basically, the side chains of amino acids are responsible for the variation in their physicochemical properties. Naturally occurring amino acids can exist in both the L (laevo) and the D (dextro) forms, which are mirror images of each other. However, incorporation of the D form of the amino acid has been limited for pharmaceutical applications due to their potential pharmacological activity, microbiological concerns and toxicity<sup>19</sup>. On the other hand, the L form of the amino acids has been used extensively in pharmaceutical and cosmetic formulations such as pH-sensitive drug carrier<sup>20</sup>, cicatrization topical dermatological preparations<sup>21</sup>, salt conjugate of poorly soluble drug<sup>22</sup>, oral tablets, as lubricant<sup>23</sup> and disintegration enhancer<sup>19</sup>, inhalable delivery

systems<sup>24</sup> and freeze-dried product, as cryoprotectants<sup>25</sup> and bulking agent<sup>26</sup>.

In this present study to prepare Ketoprofen FDT and were evaluated for DSC, XRD, and SEM analysis were performed to determine the physicochemical properties of the FDT and compare with its physical mixture and pure drug and determined the saturated solubility and dissolution characteristics of the Ketoprofen in the prepared FDT.

## MATERIALS AND METHODS

### Materials

Ketoprofen, micronized gelatin, lysine, and sorbitol were gifted by IPCA pharmaceutical Ltd. Mumbai, India. All water used distilled de-ionized water. All other materials used are analytical grade.

### Preparation of Ketoprofen Freeze dried 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 clear solution was obtained. Equal weights of lysine (0.886% w/v) and sorbitol (0.886% w/v) were added to the gelatin solution while stirring until completely dissolved. An accurately weighed amount of Ketoprofen powder (2.5% w/v) was dispersed. 1 ml of the resulting suspension was poured into each of the pockets of a tablet blister to contain ketoprofen dose of 25 mg. The tablet blister packs, each packs containing 8 tablets were then transferred to a ultra low freezer at -40 °C and kept in the freezer for 24 hr. the frozen tablets were placed in a lyophilizer for 24 h using a Freeze Dryer (IISHIN Lab. Co. Ltd. Korea) with a condenser temperature of -40°C and a pressure of 40 mbar followed by a secondary drying at 25 °C for 12h. The FDTs were kept in a desiccator's room temperature until further experiment. Five blister packs containing a total of 40 tablets were produced in each batch. Eight tablets randomly selected for drug content uniformity. The mean percentage drug content of ketoprofen was found to be 99.38% ± 0.014%.

### Preparation of the Physical Mixtures

Ketoprofen was uniformly mixed with gelatin, lysine and sorbitol in the same percentage used in the FDT using a mortar and pestle. The prepared mixtures were kept in desiccators until used (11).

### Differential scanning calorimetry (DSC)

A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

### X-ray Diffraction analysis

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV. The process parameters used were set as scan step size of 0.0170 (2θ).

### Scanning electron microscopy (SEM)

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm morphological nature and Surface topography of the crystals.

### Solubility studies

Ketoprofen (100mg), its FDTs and PMs Equivalent to 100 mg Ketoprofen were placed in glass stopper flasks were shaken in a water bath at 37°C for 24 hr. The solutions were filtered through a membrane filter (0.45µg) and the dissolved drug was measured spectrophotometrically at 285 nm. Each sample was done in triplicate.

### Dissolution studies

The dissolution profile of pure Ketoprofen compared with the PM and FDT, were determined by using USP dissolution apparatus

XXIV-Type II (Electro Lab, Mumbai). All tests were conducted in 900 ml of distilled water maintained at 37 ± 0.2°C with a paddle rotation speed at 100 rpm. After specified time intervals, samples of dissolution medium were withdrawn and replaced by equal amount of fresh medium and then filtered and the amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 285 nm. Each sample was done in triplicate.

### Determination the physical stability

To determine the physical stability of FDT was placed in a climate chamber of 20°C and 45% relative humidity (RH). After 90 days, the % drug release of Ketoprofen in the FDTs sample was determined by dissolution study and compare with freshly prepared FDT.

## RESULTS

DSC curves obtained for pure Ketoprofen, physical mixtures and FDT shown in Fig. 1. DSC studied carried out to evaluate the crystalline properties of Ketoprofen in FDT, PM and pure drug, X-Ray diffraction was used to analyze potential changes in the inner structure of Ketoprofen nanocrystal during the formulation of FDT. The extent of such changes depends on the chemical nature and physical hardness of the active ingredient. The powder X-ray diffraction patterns of the pure drug, physical mixture and FDT showed in Fig. 2. The results of DSC were further conformed by X-ray diffraction studies (Fig 2).

SEM micrographs of Pure Ketoprofen, PM, and FDT are shown in Fig. 3. The result showed that Ketoprofen crystals could be seen in the PM while the micrograph of FDT shows a matrix in which no crystals of Ketoprofen could be seen.

The solubility of Ketoprofen increase from FDT (0.143 mg/ml), nearly six and half times higher when compared to the solubility of the pure drug (0.023 mg/ml), suggesting the presence of high amount of amorphous form of the Ketoprofen drug in FDT, that indicates the super-saturation obtained from the FDT. Increase in solubility of Ketoprofen from the PM (0.045 mg/ml), almost two times higher than the pure drug. The results of Solubility's of different formulation shown in Table 1.

The dissolution curves of Ketoprofen in distilled water shown in Fig. 4. The dissolution rate profiles were plotted as the % release from the FDT, physical mixture and pure Ketoprofen versus time in minute. The rate of dissolution of pure Ketoprofen was slow Compared with physical mixtures and FDT. Ketoprofen in the FDT was immediately dispersed and almost completely dissolved (93.32%) in 5 min. initial dissolution rate of Ketoprofen in the FDT increased markedly about thirty two fold compared to pure Ketoprofen in 5 min. The dissolution rate was also higher and faster in FDT than in PM. The percentage of Ketoprofen dissolved from its PM for 60 min (80.45%) increased approximately two and half fold compared to Ketoprofen pure alone (29.21%).

The dissolution behavior of Ketoprofen FDT must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of amorphous FDT, the molecular mobility should be as low as possible. However, FDT, partially or fully amorphous, are thermodynamically unstable and will have a natural tendency to crystallize, because the crystalline state has a lower energy compared to amorphous material. However, amorphous material can be kinetically stable, which implies that the equilibrium state, i.e. crystalline, is not reached within the timeframe of the experiment or shelf life of the product. Therefore, the physical state should be monitored because changes therein are likely to alter the drug release. The results of the stability study of FDT stored at 20 °C and 45% relative humidity for 90 days were shown in Fig. 5.

## DISCUSSION

In the Preparation of ketoprofen FDT different fast dissolving carrier materials were used. Among them lysine is used to prevent

shrinkage of the tablet during manufacturing and was possibly due to the plasticizing effect of the lysine. This is in line with previously reported research, which has shown that freeze-dried systems upon inclusion of solutes within the formulation result in lowering of the glass transition temperature and is dependent on the interactions between the added excipient and unfrozen water<sup>22</sup>. Addition of plasticizing agents potentially reduces the intermolecular forces between binder molecules and increases polymer chain mobility, thereby providing a cushioning effect. However, the degree of plasticizing varied between the amino acids, which can be attributed to the differences in their physicochemical properties<sup>23</sup> and total number of moles added. sorbitol used to impart crystallinity, hardness, and elegance to the tablet is well-known and acceptable materials used in preparing of freeze-dried tablets. Previous research has shown that the two common methods to enhance the mechanical strength of the lyophilized FDTs are the inclusion of higher concentration of the binder and addition of excipients such as matrix supporting agents (saccharides and polyols)<sup>8</sup>. In this study, the use of 5% (w/w) gelatin stock solution as a binder proved to give the RDTs high resistant to friability. The percentage excipients used was optimized during the formulation process to result in a strong and elegant tablet that could be handled with ease. Generally, the mechanical properties of tablets are mainly influenced by the intermolecular bonding force and contact points between the excipients<sup>27</sup>.

In DSC curve, pure Ketoprofen had a sharp endothermic peak at 96°C that corresponded to the melting point of Ketoprofen and that was in accordance with a previous report in literature<sup>4,6</sup>. The thermogram of the PM showed the endothermic peak of Ketoprofen, although broader, spitted, and slightly shifted to the left, indicating that the crystalline state is maintained but decreased in the PM and shown sharp endothermic peak at 95.4°C. However, the melting endotherm was absent on the DSC thermogram of the FDT, suggesting absence of crystalline or amorphous form of the drug. This could be because of Ketoprofen was molecularly dispersed in the freeze dried tablet (FDT).

The XRD spectra of the Ketoprofen appeared in the  $2\theta$  range of 10–30° indicating that the unprocessed Ketoprofen was a crystalline material. The pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The X-ray diffraction study of the PM of drug and excipients showed the peak 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 FDT of drug showed absence, broadening and reduction of major Ketoprofen diffraction peaks indicating that mostly an amorphous form (disordered state) or drug exists an molecular dispersion in FDT. These results could explain the observed enhancement of solubility and rapid dissolution of Ketoprofen in FDT.

The SEM micrograph of FDT suggests that the particles of drug might have been reduced during dissolution in the gelatin-lysine-sorbitol solution. This could therefore indicate that Ketoprofen particle size has been reduced which also accelerates solubility and dissolution.

Solubility result showed that increase in solubility of Ketoprofen from FDT could be due to the solubilizing effect of highly water soluble carrier materials used in the formulation such as lysine and sorbitol. The higher solubility of Ketoprofen from FDT may be due to the increased in surface area, wettability and solubilizing effect of highly water soluble carrier materials used in the formulations.

The increased dissolution rate of Ketoprofen from its FDT suggesting that Ketoprofen FDT 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. The enhancement in solubility and dissolution rate of Ketoprofen in its FDT may be attributed to the formation of amorphous state in the FDT of the fast dissolving carrier materials.

The influence of FDT on the physical stability of Ketoprofen was investigated. The % of drug release from FDT almost same i.e. (99.68%) after 90 days of storing when compare with the freshly prepared FDT i.e. (99.76 %) after 60 min. Above result showed that FDT of Ketoprofen was stable after 90 days storing at 20 °C and 45% relative humidity.

## CONCLUSION

From the present study it could be suggested that successful formulation of Freeze dried tablet of Ketoprofen can be developed that is safe, water-soluble excipient and is feasible for enhancing the solubility and dissolution rate of Ketoprofen. Since, the results obtains were attributed to the formation of an amorphous state of the Ketoprofen freeze dried tablet and probability to reduction of Ketoprofen particle size. The physical stability of FDT result showed that FDT was stable and release from FDT almost unchanged after 90 days. Based on these results, it can be concluded that the freeze dried Ketoprofen tablet could be a suitable in terms of solubility and dissolution in water. This technique provides a promising manufacturing procedure for formulation of tablets of Ketoprofen by direct compression with directly compressible tablet excipients without mixing or formulation steps. Moreover, the properties of the tablet are suitable for enhancing the bioavailability.

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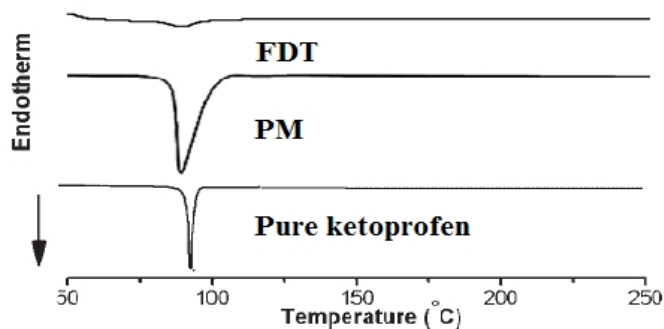
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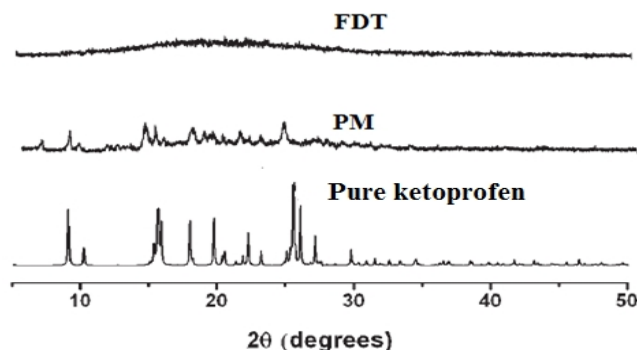
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**Table 1** Solubility of ketoprofen Pure Drug, PM and FDT in Distilled water at 37°C

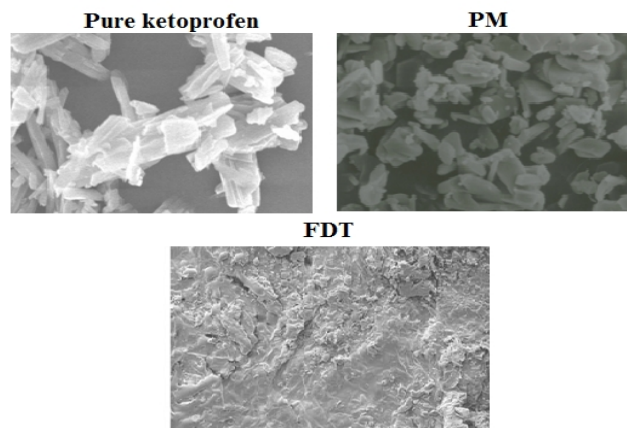
ketoprofen samples ( mg/ml)	Solubility mg/ml (± SD, n=3)
Pure ketoprofen	0.023 ±0.011
PM	0.045 ±0.016
FDT	0.143 ±0.013



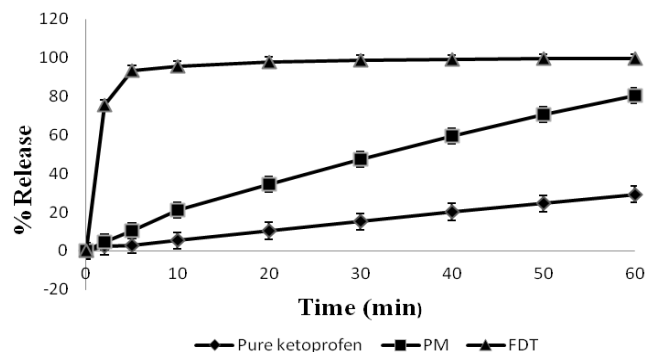
**Figure 1** DSC spectrum of Ketoprofen samples



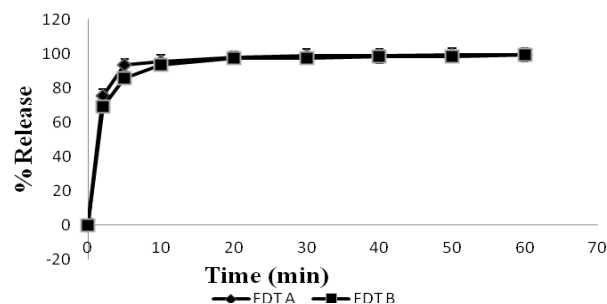
**Figure 2** X-ray powder diffraction spectrums of Ketoprofen samples



**Figure 3** Scanning electron micrographs of Ketoprofen samples



**Figure 4** Dissolution Profiles of Ketoprofen pure drug, PM and FDT in Distilled Water at 37°C



**Figure 5** Stability Dissolution Profiles of ketoprofen samples FDT A). Freshly FDT, FDT B). FDT after 90 days of storing.

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