



## Preparation and characterization of spray dried microparticle of ketoprofen by spray drying method

Mudit Dixit\*, Parthasarathi. K. Kulkarni, Panner Selvam R and H.G Shivakumar  
Department of Pharmaceutics, J.S.S College of pharmacy, J.S.S University, Mysore-570015, India.

### ARTICLE INFO

#### Article history:

Received: 11 February 2012;

Received in revised form:

15 April 2012;

Accepted: 7 May 2012;

#### Keywords

Spray drying,  
Spray Chilling,  
Ketoprofen,  
Dissolution,  
Crystallinity.

### ABSTRACT

Ketoprofen, an anti-inflammatory drug, exhibits poor water solubility and flow properties, poor dissolution and poor wetting. Consequently, the aim of this study was to improve the dissolution of ketoprofen. Microparticles containing ketoprofen were produced by spray drying and spray chilling technology to enhance dissolution rate. The prepared formulations were evaluated for in vitro dissolution and solubility. The produced drug particles were characterized by scanning electron microscopy (SEM), differential scanning calorimeter (DSC), x-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). Dissolution profile of the spray dried microparticle was compared with chilled spray microparticle, pure sample and recrystallized sample. Spray dried microparticle exhibited decreased crystallinity, but for spray chilled particles there was evidence of polymorphic changes in the drug and improved micromeritic properties. The dissolution of the spray dried microparticle was improved compared with spray chilling microparticle, recrystallized and pure sample. Consequently, it is believed that spray drying of Ketoprofen is a useful tool to improve wettability, solubility and hence the dissolution behavior of poorly water soluble drugs, in contrast to spray chilling technique.

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### Introduction

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tableting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tableting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Spray dried [14] microparticle is one of such techniques to improve the micromeritic properties and dissolution of drug.

Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water [2, 3, 5, 6]. As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. Various techniques such as melt adsorption, supercritical fluid processes, using different composition of solvents to prepared the microparticle to improve the dissolution rate of poorly water soluble drugs. and amorphous state to improve their dissolution [1,8,20]. Manipulation of the solid state by decreasing crystallinity of drug substances through formation of solid dispersion is one of the methods used for promoting drug dissolution [6, 9]. The solid dispersion technique has often proved to be the most

successful in improving the dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients because it is simple, economic, and advantageous technique. The concept of solid dispersion covers a wide range of systems. The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability, drug precipitation as a metastable crystalline form or a decrease in substance crystallinity.

The type of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture [3, 19]. Microwaves irradiation was used recently for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug, Spray drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size. Spray chilling or spray congealing is another form of solid dispersion where the melted mass is atomized into droplets, which quickly solidify in a cool air [7]. The advantage in spray chilling is that no additional manufacturing step is needed to pulverise the solid dispersion. In pharmacy, spray chilling has been used to prepare sustained-release formulations, to improve stability [14, 18] and to mask the unpleasant taste [22]. The technique also has the advantages of being free from organic solvents compared to spray drying. The method has also been used by the food industry, for example, to encapsulate vitamins and minerals [4]. ketoprofen was chosen as a hydrophobic drug. Ketoprofen 2- (benzoyl-3-phenyl) propionic acid is one of the safest and most potent non-steroidal anti-inflammatory drugs being widely used in the market. The drug used to treat rheumatoid arthritis, osteoarthritis, and mild to moderate pain. It has low aqueous

solubility and hence poor dissolution. The present work was conducted to improve the wettability, solubility and hence the dissolution of ketoprofen using spray drying and spray chilling techniques.

## Materials and Methods

### Materials

Ketoprofen was obtained as a gift sample from Micro labs, Bangalore, India. Chloroform was procured from Merck, Mumbai, India. All chemicals and buffers used were of analytical grade.

### Preparation of microparticles

#### Microparticles prepared by spray drying

##### Preparation of spray dried crystals of Ketoprofen (SD)

Ketoprofen (4 g) was dissolved in 25 ml of IPA heated at 45°C until a clear solution was obtained. The drug solution was poured into chloroform (15ml) maintained at room temperature. The resulted solution was spray dried using Mini Spray Dryer LSD -48; (Jay instrument & systems Pvt. Ltd. Mumbai) at a Feed rate of 10%, an vacuum in the system -65 MM WC, Atomization pressure rate 1 kg/cm<sup>2</sup>, Aspirator level at 35%, inlet temperature at 85±2°C and outlet temperature at 40 ±1°C. The formed crystals were separated using cyclone separator, collected and stored in a desiccator at ambient temperature until use. In spray dried water is used as ketoprofen melting point is lower than the water.

##### Preparation of recrystallization sample of Ketoprofen (RS)

Ketoprofen (4 g) was dissolved in 25 ml of IPA heating at 45°C and 15 ml of chloroform were added. The drug solution was poured quickly into 60 ml of water maintained at 20°C with occasional stirring. The crystals of Ketoprofen were collected by filtration and were dried at 45°C for 12 hours.

Determination of residual solvents in different crystals by gas chromatography

GC studies were carried out on SHIMADZU model 2014 (Shimadzu Technologies, Japan) coupled with a split/split less injector, operated in a split-mode and FID. The computer with GC solutions software has been used to control the gas chromatograph. Rtx-5 capillary column (cross bond 5% di-phenyl/95% di-methyl-polysiloxane) with a length of 30 meters coil and an internal diameter of 0.25 mm was used throughout the study.

### Evaluation of microparticles

#### Determination of percentage yield and Drug content

The percentage yield of each formulation was determined according to the total recoverable final weight of microparticles (prepared by spray drying and spray chilling) and the total original weight of ketoprofen.

Microparticles (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, measured at 260 nm. Drug content was determined from standard plot.

#### 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.

#### Fourier transform infrared (FTIR) spectroscopy

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Samples were dispersed in KBr powder and the pellets were made by

applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

### X-ray 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 spherical nature and Surface topography of the crystals.

### Solubility studies

The solubility [12] of ketoprofen microparticle (prepared by spray drying and spray chilling) in water was determined by taking excess quantity of microparticles in 50 ml to screw-capped glass vials filled with water. The vials were shaken for two hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and drug concentration was determined at 260 nm.

### Dissolution studies of microparticle

The dissolution of ketoprofen pure sample, microparticle (prepared by spray drying and spray chilling) and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 260 nm.

### Determination of the physical stability

To determine the physical stability of SA, SD and FD. They were placed in a climate chamber of 40°C and 75% relative humidity (RH). After 90 days, the % drug release of Ketoprofen in the prepared crystals was determined by dissolution study and compared with freshly prepared crystals.

### Result and discussion:

The solvents chosen for the spray drying were Iso propyl alcohol (IPA) with water and chloroform. These both the solvent were miscible in any proportion with each other.

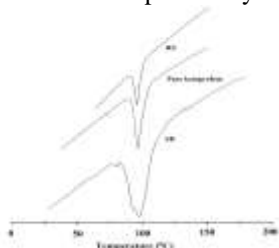
Recrystallization of Ketoprofen was done to find out the changes in crystal lattice, being induced by solvents that can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of all crystals were compared with pure sample and recrystallized sample. Recrystallization of Ketoprofen was carried out using same solvent composition as was used for all crystallization technique [15].

The spray dried formulations collected and powders were free-flowing and white. The percentage yield of spray dried ketoprofen was found to be 67%. Drug content for the spray dried formulation was found to be 98±0.002. The percentage yield for spray chilled ketoprofen particles was found to be 83%. Such yields are higher compared to spray dried products. Drug content for spray chilled ketoprofen partical was found to be 96±0.001.

Based upon high solubility of Ketoprofen in IPA, high viscosity and crystal morphology, IPA determined to be suitable as all crystals medium for Ketoprofen because of its high solubility in IPA (2g/12.5ml). The controlling of residual IPA was needed all though. IPA is a toxic organic solvent based on its concentration it has little detriment to human body [16, 17].

Gas chromatography results confirmed that there were only 3.8 & 5.7 and 1.62-2.57 ppm residual of IPA and chloroform present in the prepared crystals respectively, which was much lower than the toxic level 400 & 60 ppm respectively [16, 17].

The DSC thermograms (fig. 1) show a sharp endothermic peak for all the ketoprofen crystals.

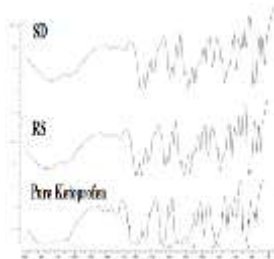


**Figure 1- DSC of Dissolution: Of Ketoprofen Samples**

This one step melt is due to only one crystal form (Triclinic) of the ketoprofen formed during the crystallization process, thus indicating that ketoprofen did not undergo any crystal modification. The temperature range of the endothermic peak of all the ketoprofen crystals lies in the range of 94°C to 96°C. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for pure ketoprofen sample was 96.58° with enthalpy of (181.01 J/g) [4]. Whereas in the case of freeze dried crystals melting endotherm was 95.24° with decreased enthalpy of (177.82 J/g) indicating decreased crystallinity.

The DSC thermogram of super cooling crystals of Ketoprofen showed melting endotherm at the characteristic endothermic peak for the drug at 95.19°C with enthalpy of 18.21 J/g indicating decreased crystallinity then compare to pure drug crystals. These results of DSC showed that decreased in crystallinity of Ketoprofen in all the crystals then pre drug crystals. The decreased in crystallinity as follow: pure sample > recrystallized sample > spray dried.

All the prepared crystals has exhibited general characteristic peaks at 2983-2930  $\text{cm}^{-1}$  (Aromatic C-H stretch carboxylic acid O-H stretch), 1695-1649  $\text{cm}^{-1}$  (C=O stretch), 1595  $\text{cm}^{-1}$  (Aromatic C=C stretch), 1437  $\text{cm}^{-1}$  (CH-CH<sub>3</sub> deformation), 2891  $\text{cm}^{-1}$  ((C-H) stretch plus O-H deformation), 1690  $\text{cm}^{-1}$  (Carboxylic O-H out of plane deformation), 860-640  $\text{cm}^{-1}$  (C-H out of plane deformation for substituted aromatic) (fig. 2) [9].



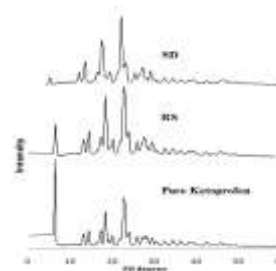
**Figure 2- FT-IR of Dissolution: Of Ketoprofen Samples**

Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of a solvent of crystallization. Infrared spectra of pure Ketoprofen recrystallized and spray dried crystals showed characteristic peaks in same position.

X-Ray diffraction was used to analyze potential changes in the inner structure of Ketoprofen crystal during the formulation of different crystals. The characteristic peak of the Ketoprofen appeared in the  $2\theta$  range of 0–50°, indicating that the

unprocessed Ketoprofen was a crystalline material. All the samples showed similar peak positions (2 $\theta$ ) in X-ray diffraction, that is, formation of different polymorphs of Ketoprofen was ruled out.

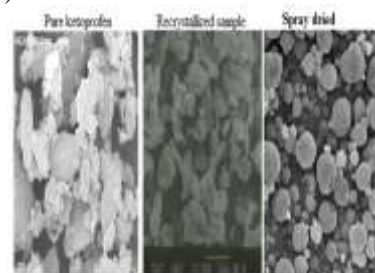
However relative intensities of XRD peaks were modified (Fig. 3).



**Figure 3- XRD of Dissolution: Of Ketoprofen Samples**

The relative intensities of all prepared crystals reduced than pure Ketoprofen. This could be attributed to the markedly different crystal habits of the samples. Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in crystal sizes [10, 11]. The pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The X-ray diffraction pattern of the recrystallized and spray dried crystals showed that Ketoprofen peak intensity was much lower than the pure Ketoprofen. This could be due to the increasing the wettability of all the different crystals. These results could explain the observed enhancement of solubility and dissolution of Ketoprofen from recrystallized and spray dried crystals.

SEM study showed that crystals of pure sample are of the smallest size (6-17  $\mu\text{m}$ ) and they have irregular shapes. Recrystallization leads to crystals with intermediate size (13-26  $\mu\text{m}$ ) which had rod like shapes (Fig. 4). The shape of prepared spray dried crystals is uniform and spherical in shape with small in size (5-10  $\mu\text{m}$ ).

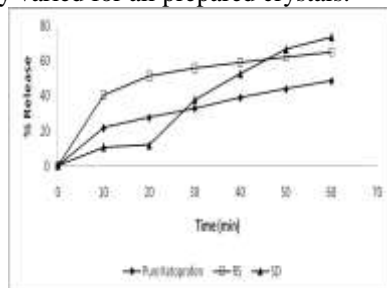


**Figure 4- SEM of Dissolution: Of Ketoprofen Samples**

All the prepared crystals showed increased solubility than the pure sample in water as well as in pH 7.4 Phosphate buffer, the spray dried crystals shows highest solubility and increased nearly threefold higher (0.0536 mg/ml) than pure Ketoprofen (0.0172 mg/ml) in water and nearly fourfold higher (8.32 mg/ml) than pure ketoprofen (2.11 mg/ml) in pH 7.4 phosphate buffer. The solubility of recrystallized crystals shows less solubility (0.0233 mg/ml & 3.73 mg/ml) than spray dried in water as well as in pH 7.4 phosphate buffer but much higher than pure drug. The reason behind enhancing the solubility may be due to the increasing the wettability of the prepared crystals or reduction in particle size.

The dissolution profiles of Ketoprofen (fig. 5) exhibited improved dissolution behavior for prepared crystals than pure sample. The reason for this faster dissolution could be linked to the better wettability of the prepared crystals or reduction in

particle size of prepared crystals. The amount of drug dissolved in 60 min greatly varied for all prepared crystals.



**Figure 5- Dissolution: of Ketoprofen Samples**

The dissolution behavior of all the prepared crystals must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. Therefore, the physical state should be monitored because changes therein are likely to alter the drug release. With respect to the influence of prepared crystals on the physical stability of Ketoprofen it follows that the % of drug release from prepared crystals remain same after 90 days of storing when compare with the freshly prepared crystals. Release analysis of all the prepared crystals formulations were significantly differ in terms of drug release ( $p < 0.05$ ) except the pure ketoprofen which is used as standard. Stability result shows that prepared crystals of Ketoprofen were stable after 90 days at 40<sup>0</sup> and 75% relative humidity.

#### Conclusion:

Spray dried microparticle of Ketoprofen were prepared by spray drying technique to improve the dissolution rate. Spray dried microparticle exhibited decreased crystallinity and improved micromeritic properties. DSC and XRD studies showed that there is no change in the crystal structure of ketoprofen during the spray drying process i.e., polymorphism has not occurred. The dissolution of the spray dried microparticle was improved compared with pure sample, Recrystallized sample. Hence this spray drying technique can be used for formulation of tablets of ketoprofen by direct compression with directly compressible tablet excipients.

#### Acknowledgements

The authors are thankful to Micro Labs, Bangalore, India for the gift sample of Ketoprofen and to Dr. H.G. Shivakumar, Principal, J.S.S.College of Pharmacy, Mysore for providing facilities to carry out this work.

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