



## Enhancing solubility and dissolution of piroxicam by spray drying using Pluronic F127

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### ABSTRACT

Piroxicam, an anti-inflammatory drug, exhibits poor water solubility, dissolution and flow properties. Thus, the aim of the present study was to improve the solubility and dissolution rate of Piroxicam by preparing microspheres by spray drying technique. Piroxicam microspheres containing different ratio of F127 were produced by spray drying using dichloromethane as solvent to enhance solubility and dissolution rate. The prepared formulations containing different ratio of drug and polymer were evaluated for in vitro dissolution and solubility. The prepared formulations were characterized by scanning electron microscopy, differential scanning calorimeter, X-ray diffraction and Fourier transform infrared spectroscopy. Dissolution profile of the spray dried microspheres was compared with its physical mixture and pure sample. Spray dried microspheres exhibited decreased crystallinity and the solubility and dissolution of the microspheres containing different ratio of drug and pluronic F127 were significant improved compared with its physical mixture and pure sample of piroxicam. Dissolution of microspheres containing 1:3 w/w (SD 3) showed higher % release i.e. 94 % in 60 min compare to other formulation. Consequently, Hence, From the above result it can be conclude that spray dried microspheres of Piroxicam is a useful technique to improve the solubility and dissolution of poorly water soluble drug like Piroxicam.

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### Introduction

Piroxicam is a Non-steroidal anti inflammatory, analgesic and anti-pyretic drug which is widely used in Muscular-skeletal disorder like osteoarthritis. Piroxicam has bad taste, half life of 30 hrs and poor water solubility.

According to the biopharmaceutical classification system (BCS), Piroxicam is an extreme example of a class II compound meaning that its oral bioavailability is determined by its dissolution rate in the GI tract (1-8).

Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of very poorly soluble compounds might be improved to minimize the limitations to their oral availability.

There have been numerous efforts to improve drug dissolution rates. These include (a) reducing the particle size to increase the surface area; (b) using water-soluble carriers to form inclusion complexes; (c) solubilization in surfactant systems; (d) using pro-drugs and drug derivatization; and (e) manipulation of the solid state of drug substances to improve the drug dissolution i.e. by reducing the crystallinity of drug substances through formation of solid dispersions. However, there are practical limitations to these techniques (9).

Although particle size reduction is commonly used to increase the dissolution rate, there is a practical limit to the size reduction that can be achieved by such commonly used methods as controlled crystallization and grinding.

The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wet-ability. Salt formation is not feasible for neutral compounds and

the synthesis of appropriate salt forms of drugs which are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co solvents leads to liquid formation that is usually undesirable from the viewpoints of patient acceptability and marketing (10). Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs (11-14). There are different types solid dispersion systems categorized according to the physical states of the drug and the carrier in the systems. It may be a molecular solid solution, a dispersion of amorphous or crystalline drug particles in an amorphous carrier matrix, or a combination of a solution and dispersion of solids.

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 wet-ability, and 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. 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(15,16,17). The large surface area of the resulting particle should result in an enhanced dissolution rate and, consequently, improved bioavailability. The aim of the present study was to improve the solubility and dissolution rate of Piroxicam by spray drying technique using different ratio of pluronic F127.

#### Method and material:

##### Materials

Piroxicam and Pluronic F127 were obtained as a gift sample from Ipca Pharmaceutical, Mumbai, India. All chemicals and buffers used were of analytical grade.

##### Preparation of Microspheres of Piroxicam

The spray dried microspheres (SD) were prepared by spray-drying technique. The spray drying was performed by Mini Spray Dryer LSD -48; (Jay instrument & systems Pvt. Ltd. Mumbai). The different drug-polymer ratios used for various microsphere formulations were prepared described in Table 1. The polymer solution was prepared by adding given quantity of polymer to the dichloromethane as solvent. The given quantity of Piroxicam was added to the polymer solution and the resulting mixture was spray-dried. The spray drying parameters are described in Table 2.

**Table 1 Spray-Dried microspheres formulation**

Numbers	Formulation numbers	Different ratio of polymer and drug (w/w)
1	SD 1	1:1
2	SD 2	1:2
3	SD 3	1:3
4	PM 1	1:1
5	PM 2	1:2
6	PM 3	1:3

**Table 2 Spray-Drying Parameters**

Inlet temperature (°C)	Feed pump speed %	Vacuum (mm Wc)	Aspirator level (kg/cm <sup>2</sup> )
45	14	-75	2.0

##### Preparation of physical mixtures of Piroxicam

Physical mixtures (PM) were prepared by mixing Piroxicam and polymer (in the same ratio as used for spray dried) in a mortar for 5 min and then sieving (<355µm).

##### Evaluation of microspheres

##### Determination of percentage yield and Drug content

The percentage yield of each formulation was determined according to the total recoverable final weight of microspheres and the total original weight of Piroxicam.

Microspheres (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, samples were measured at 334 nm. Drug content was determined from standard plot.

##### Differential scanning calorimeter (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 transforms infrared spectroscopy (FTIR)

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.

##### Powder X-ray diffraction analysis

X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffract-meter, with Cu as anode material and graphite monochromatic, 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.

##### Mechanical Properties

Tensile strength of microspheres was determined by compressing 500 mg of crystals using hydraulic press at different ton/cm<sup>2</sup> for 1 min. The compacts stored in desiccators for overnight to allow elastic recovery.

The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester.

The tensile strength ( $\sigma$ ) of the compact (ton/cm<sup>2</sup>) was calculated using following equation.

$$\sigma = 2F/\pi Dt$$

Where, F, D and t are hardness (ton), compact diameter (cm) and thickness (cm), respectively. Each sample was determined in triplicate.

##### Determination of solubility

Drug solubility was determined by adding excess amounts of pure Piroxicam, its physical mixture and microspheres to water and pH 7.4 phosphate buffer at 37 ± 0.5°C, respectively. The solutions formed were equilibrated under continuous agitation for 24 h and passed through a 0.8 µm membrane filter to obtain a clear solution.

The absorption of then samples was measured using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 334 nm and the concentrations in µg/ml were determined. Each sample was determined in triplicate.

##### Dissolution studies of microspheres

The dissolution of Piroxicam commercial sample, microspheres and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml pH 1.2 HCL buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 334 nm. Each sample was determined in triplicate.

##### Result and discussion

The glass transition temperature (T<sub>g</sub>) is the second-order phase change temperature at which a solid glass is transformed to a liquid-like rubber. As the temperature increases above, T<sub>g</sub> various changes, such as increase of free volume, decrease of viscosity, increase of specific heat, an increase of thermal expansion, are noticed.

During spray drying, if the drying temperature exceeds the T<sub>g</sub> of the polymer, the powder becomes soft or sticky while still warm. This cause sticking of the powder to the side walls of drying chamber. The T<sub>g</sub> of Pluronic F127 as provided by the manufacturer is 56°C so dichloromethane was selected as solvent with boiling point 36°C, i.e., lower than the T<sub>g</sub> of Pluronic F127.

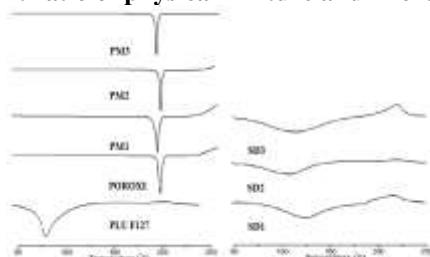
The spray dried microspheres formulations collected and they were free-flowing and white in color. The percentage yield of spray dried microspheres of different ratio of Pluronic F127 and Piroxicam was showed in Table no 3. This small yield can be increase by adding of solid substance or in large scale production as it was small scale preparation. Drug content for the spray dried microspheres of different ratio of Pluronic F127 and Piroxicam were showed in Table no 3.

Different formulations containing polymer: Drug ratio(w/w)	Concentration of Piroxicam microspheres in water ( $\mu\text{g/ml}$ ) $\text{SD}\pm 3$	Concentration of Piroxicam microspheres in pH 7.4 $\mu\text{g/ml}$ $\text{SD}\pm 3$	Percentage yield%	Drug content $\text{SD}\pm 3$	Particle size determination ( $\mu\text{m}$ ) $\text{SD}\pm 3$
Pure drug	0.055	1.4			
SD 1	11.23	26.73	57.23	96.21 $\pm$ 0.01	6-8
SD 2	17.57	31.64	58.80	97.39 $\pm$ 0.04	6-9
SD 3	25.07	41.54	64.38	98.98 $\pm$ 0.01	5-8
PM 1	5.32	11.86	-	97.29 $\pm$ 0.02	-
PM 2	9.22	16.26	-	98.38 $\pm$ 0.01	-
PM 3	12.52	20.18	-	97.37 $\pm$ 0.03	-

**Table 3 Solubility of Piroxicam microspheres at different ratios of Pluronic F127 in water and pH 7.4 phosphate buffer.**

DSC curves obtained for pure material, physical mixtures and microspheres are showed Fig. 1. In DSC curve, pure Piroxicam had a sharp endothermic peak at 202°C that corresponded to the melting point of Piroxicam. In the thermogram of Pluronic F127, a sharp peak (56°C) was observed, which was associated with the endothermic melting of Pluronic F127. In DSC study, as the amount of Pluronic F127 increased in microspheres, the size of the Piroxicam endothermic peak was reduced. In formulations number Physical mixture 1, 2 and 3, showed no change in Piroxicam endothermic peak was observed. In case of microspheres, the two melting transitions in the system made up of Piroxicam and Pluronic F127 indicated that both materials formed a separate phase. It was found that Piroxicam was in a crystalline state in the microspheres. The position of the melting peak of Pluronic F127 remained largely unchanged, while that of Piroxicam shifted depending on the concentration. In formulation of microspheres SD 1, 2 and 3, the endothermic peak of Piroxicam was no longer observed. This could be because Piroxicam was molecularly or amorphously dispersed in the phases. Suggesting absence of crystallinity and presence of amorphous state of the drug. On the other hand, the physical mixtures of Piroxicam and Pluronic F127 showed an apparent endothermic peak for Piroxicam at 200.43 - 202°C.

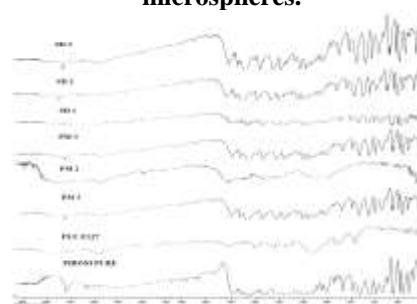
**Fig 1 Shows DSC Spectrum of pure Piroxicam, pluronic 127 & its different ratio of physical mixture and microspheres.**



FTIR is a very powerful technique in detecting presence of interaction in drug-carrier microspheres. The appearance or disappearance of peaks and/or the shift of their positions are often an indication of interactions such as hydrogen bonding. Piroxicam contains one hydrogen donor (-OH and -NH) whose characteristic absorption bands are O-H at 3339  $\text{cm}^{-1}$  for form I and 3381  $\text{cm}^{-1}$  for form II (Fig. 2). Also, a broad well defined band was observed in the spectrum of pluronic F127 in 1600–1700  $\text{cm}^{-1}$  assigned to the carbonyl stretching vibration. The carbonyl group is more favorable in hydrogen bonding over the tertiary amine because of the steric hindrance of the latter group. The spectrum of physical mixture shown in Figure 2 was simple summation of pure drug and pluronic F 127, revealing no perceptible interaction between the two components. Little evidence could be deduced from the carbonyl band region, probably due to the strong absorption of the carbonyl group of the polymer. In contrast, FTIR spectra of piroxicam, physical

mixture and spray-dried microspheres sample display different absorption bands in 3200–3600  $\text{cm}^{-1}$ , with the N-H or O-H stretching vibration completely lost (Fig. 2). This observation, combined with the XRD result, can be attributed to the formation of hydrogen bonding between OH or NH group of piroxicam with the carbonyl group of pluronic F127. The prepared microspheres containing Piroxicam with Pluronic F127 showed the characteristic peaks of the drug and the polymers. This suggests the absence of any interaction between the drug and the polymers.

**Fig 2 Shows FT-IR Spectrum of pure Piroxicam, pluronic F127, its different ratio of physical mixture and microspheres.**



X-Ray diffraction was used to analyze potential changes in the inner structure of Piroxicam nanocrystal during the formulation. 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 unprocessed Piroxicam and Pluronic F127, their different physical mixture and microspheres formed by spray drying showed in Fig. 3.

The characteristic peak of the Piroxicam appeared in the  $2\theta$  range of 10–30°, indicating that the unprocessed Piroxicam was a crystalline material. In XRD thermograph of pure Piroxicam powder, physical mixture and prepared microspheres showed that crystallinity of Piroxicam in the formulations was not affected significantly.

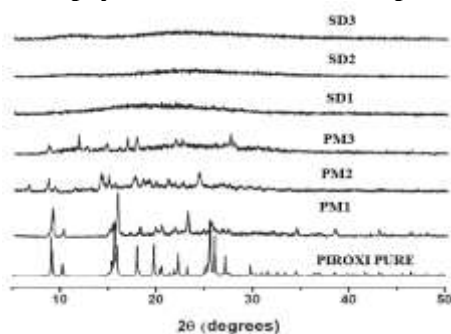
The x-ray diffraction pattern of the pure drug exhibit its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity.

The diffraction study of the different physical mixture of drug and pluronic F127 showed the peak corresponding to the crystalline drug molecules present in the mixture, although their intensity was lower than pure drug may be due to the high percentage of pluronic F127 & drug ratio employed.

The diffraction pattern of the different spray dried microspheres of drug showed absence, broadening, and reduction of major piroxicam diffraction peaks indicating that mostly an amorphous form (disordered state) existed in the microspheres.

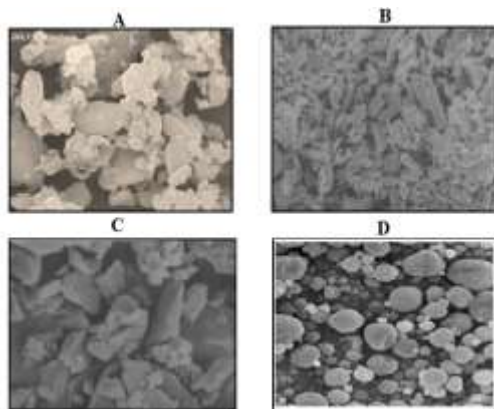


**Fig 3 shows XRD Spectrum of pure Piroxicam & different ratio of physical mixture and microspheres.**



The SEM image of the A) Piroxicam, B) pluronic F127, C) their physical mixture and D) microspheres are shown in Fig. 4. The Piroxicam particles in the physical mixture were broken into much smaller ones, irregular size and result show that piroxicam particles could be seen in the physical mixture and on the other hand, the shape of microspheres were spherical in shape with small in size and micrograph of microspheres shows a matrix formation in which no crystals of piroxicam could be seen. The spherical shape of microspheres has advantage of not to form cake because of less point of contact during the time of storage compare to other shape. So it has better physical stability then other shape.

**Fig 4 Shows SEM photographs of A) pure Piroxicam, B) Pluronic F127, C) Physical mixture D) Microspheres.**

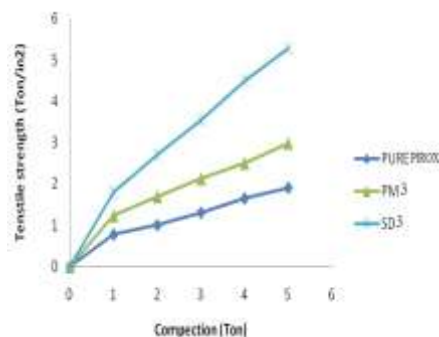


Microspheres exhibited superior compressibility characteristics compared to Physical mixture and pure sample of Piroxicam drug crystals (fig. 5). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the microspheres under plastic deformation compared to that of single crystal. Tensile strength of the same ratio of microspheres and physical mixture (1:3%) showed that tensile strength of microspheres higher than physical mixture.. But tensile strength of microspheres ratio of 1:3 % (SD 3) show much higher than any ratio of microspheres, physical mixture (PM 3) and pure sample this may be due to the increasing in the plastic inter particle bonding of microspheres.

The solubility of Piroxicam, their physical mixture and microspheres in water and in pH 7.4 phosphate buffer is shown in Table 3. The solubility of Piroxicam at 37°C was found to be 0.055µg/ml and 1.4µg/ml in water & pH 7.4 phosphate buffer, respectively. These results show that the solubility of Piroxicam increased on increasing the concentration of Pluronic F127 in microspheres. The solubility of Piroxicam from the

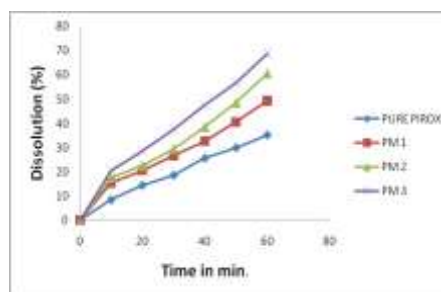
microspheres was significantly higher than from it is physical mixture, when the microspheres and physical mixture contained the same weight ratio of Piroxicam i.e. 1:3% (SD 3 & PM 3). It was found that the solubility of Piroxicam from microspheres much higher than physical mixture of same % in pH 7.4 phosphate buffer as well as in water. The higher solubility of Piroxicam from microspheres may be due to the increased in surface area, wet-ability of microspheres and solubilizing effect of the Pluronic F127 as carrier to micro spheres.

**Fig 5 Shows Tensile strength of pure Piroxicam, physical mixture and microspheres**



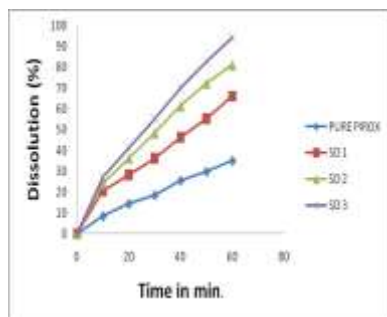
The dissolution curves of Piroxicam in pH 7.4 phosphate buffer shown in Fig. 6. The dissolution rate profiles were plotted as the % release from the different microspheres, physical mixture and pure Piroxicam versus time in minute. The rate of dissolution of pure Piroxicam was slow Compared with Piroxicam from its physical mixtures and different microspheres in 60 min. The % release of microspheres containing ratio of 1:3(SD 3) showed high release compare to other microspheres containing different ratio, its physical mixture and pure Piroxicam. There was a significant difference in the drug release between the microspheres, physical mixture and pure sample. The increase in dissolution from the physical mixtures was probably due to the wetting and solubilizing effect of the Pluronic F127, which could reduce the interfacial tension between the Piroxicam and the dissolution medium, thus leading to a higher dissolution rate. The large surface area of the resulting microspheres should result in an enhanced dissolution rate and thereby improve the bioavailability.

**Figure 6 Shows Dissolution of pure Piroxicam and its different ratio of Physical mixture**



Spray dried microspheres exhibited decreased crystallinity compare to its physical mixture and pure Piroxicam. DSC and XRD studies showed that there is no change in the crystal structure of Piroxicam during the spray drying process i.e., polymorphism has not occurred. The solubility and dissolution of the spray dried microspheres was improved significantly compared with its physical mixture and pure sample. The drug dissolution rate from microspheres was highest at the polymer-drug ratio of 1:1 w/w% (SD3).

**Figure 6 Shows Dissolution of pure Piroxicam and its different ratio of microspheres**



#### Conclusion:

In this present study, an increased solubility and dissolution rate of Piroxicam were achieved by spray dried microspheres using different ratio of Pluronic F127. Hence this spray drying technique was very simple method & can be used for formulation of tablets of Piroxicam by direct compression without further process like (mixing, granulation) with directly compressible tablet excipients.

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