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FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISPERSIBLE TABLET CONTAINING NANOPARTICLES OF PIROXICAM

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ABSTRACT
Piroxicam is a First line drug of NSAIDs used in a Rheumatoid Arthritis with low solubility, the aim of the study was to formulate and optimize Piroxicam agglomerates with improved dissolution characteristics. Drug loaded agglomerates were prepared using quasi-emulsion solvent diffusion technique, where in the agglomerates prepared with consideration to internal phase and external phase medium with using bridging liquid, dispersing agent and polymer. Process variables were evaluated and preliminary screening was carried out in concern to preparation of the agglomerates. Evaluation of the factorial batches was carried out like microscopy study, percentage yield, drug content, micrometric properties etc. The results of X-ray diffraction indicate that Piroxicam in agglomerates was disordered, suggesting that Piroxicam is highly dispersed in agglomerates, further the agglomerates was evaluated for all the parameters like FTIR, SEM, Particle Size analysis, XRD analysis, Drug content, Percentage yield and dissolution study. The prepared agglomerates was Compressed in FDT Form. Finally it was concluded that the agglomerates prepared have good dissolution characteristic as compared to that of pure drug as well as marketed formulation.

KEY WORDS: Nanoparticles, Quasi emulsion solvent technique, Crospovidone, Croscarmellose Na, Nanoparticulate FDT.

INTRODUCTION
It is estimated that more than 1/3 of the compounds being developed by the pharmaceutical industry are poorly water soluble. An important property of a drug substance is solubility, especially aqueous system solubility. The solubility/dissolution behavior of a drug is key factor to its oral bioavailability. The bioavailability of these drugs is limited by their low dissolution rates. An improvement of oral bioavailability of poor water-soluble drugs remains one of the most challenging tasks of drug development. To overcome poor solubility, many approaches have been studied. They are generally salt formation, use of surfactant, use of prodrugs and Micronization. In Micronization, the particle size of a drug powder is reduced to a Nano scale size (typically 50-100 nm), which increases the specific surface area and dissolution rates. However, many new drugs are so poorly soluble that Micronization is not sufficient, which motivated the development of nanoscale systems. By decreasing the particle size from a micron to a nanometer scale, there is a significant increase in the surface area and related dissolution rate. NanoParticles are Agglomerate by the Quasi Emulsion Solvent Diffusion Technique of pure drug particles in an inner liquid phase. NanoParticle engineering enables poorly soluble drugs to be formulated as Good Solvent, Bridging liquid and Polymer, or with a combination of pharmaceutical excipients.

QESD method presents numerous advantages, in that it is a straightforward technique, rapid and easy to perform. In this method, the drug is dissolved in an organic solvent such as Acetone, DCM and Water. The organic solvent is evaporated either by reducing the pressure or by continuous stirring. Particle size was found to be influenced by the type of stabilizer, concentrations of stabilizer, and homogenizer speed. In order to produce small particle size, often a high-speed homogenization or ultrasonication may be employed.

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID), analgesic, and antipyretic that needs rapid release from its dosage form to achieve pharmacological response in therapy, so it is considered to be an ideal drug to be made into FDT dosage form. Piroxicam is sparingly dissolves in water. To increase its solubility in water, the particle size needs to be reduced into Nano scale or nanoparticle. This is due to Nanoparticulate FDT must rapidly dissolve into saliva, so that its formulation must consist of ingredients that readily dissolve in water.

There have been some studies evaluating the effects of Crospovidone and Croscarmellose sodium as superdisintegrant on the characteristics of oral solid dosage form. However, the differences of their effects on the characteristic of FDT are still unknown. Therefore, this study is aimed to compare the characteristic of FDT formulated by using Crospovidone and Croscarmellose sodium as superdisintegrant.

METHODOLOGY

PREFORMULATION OF DRUG

The Preformulation study is widely generate dat1a useful to develop stable dosage forms that can be large produced for manufacturer.

Organoleptic Characteristics of Piroxicam

Physical examine was done to check Organoleptic Characteristics of Piroxicam like color and odor.

Determination of Melting Point of Piroxicam

Melting point of Piroxicam had been evaluated by the capillary method.

Solubility study of Piroxicam

The aqueous solubility of Piroxicam in powder form was determined by a shake-flask method. Briefly, an excess amount of Piroxicam was suspended in 10ml of water, and the suspensions were shaken at 37°C. Aliquots were withdrawn and filtered through a 0.22µm Whatmen filter. The filtered solute was diluted in suitable solvent and the Piroxicam concentration in the filtrate was analyzed by UV analysis method at 243nm (Systronic 2203, Japan).

Saturation solubility studies

Saturation solubility measurements was analyze by ultraviolet absorbance determination at 243 nm using a Shimadzu UV-Visible spectrophotometer. The saturation solubility studies was carried out for both unprocessed pure drug. 10 mg of unprocessed pure drug was weighed and introduce into 25 ml stoppered conical flask containing 10 ml distilled water. The flasks was seal and place in a rotary shaker for 24 hrs. at 37°C and equilibrate for 2 days. The samples was collect after the specific time interval, and it is filter and analyze. The dilute samples was analyzed using UV spectrophotometer at 243 nm. The results were analyzed in triplicate and standard deviations are report.

Identification and Determination of Wavelength max (λmax) of Piroxicam

A stock solution of 1 mg/ml of Piroxicam was prepared by dissolving 100 mg of drug in small quantity of Methenolic HCl and sonicated for few minutes and diluted with 100 ml of 0.1N HCl (pH 1.2). The stock solution was serially diluted to get solution in the range of 20µg/ml and λ max of the solution was found out by scanning from 200 - 400 nm.

Preparation of Calibration Curve for Piroxicam

Stock solution of Piroxicam was prepared by dissolving 100 mg of drug in small quantity of methanol and sonicated for few minutes and diluted with 100 ml of 0.1N HCl (pH 1.2). The stock solution was diluted to get solutions in the range of 2, 4, 6, 8, 10 µg/ml and λ max of the solution was found. The absorbance of the different diluted solutions was measured in a UV-Visible spectrophotometer at 243 nm. A calibration curve was plotted by taking concentration of solution in X axis and absorbance in Y axis and correlation coefficient 'r^2' was calculated.

Identification of Drug- Piroxicam by FT-IR Spectroscopy

Fourier–transform infrared (FT–IR) spectra of moisture free powdered samples of SS, its QSED nanoparticles and PVPK-30 were obtained using a spectrophotometer (FTIR-8300, Shimadzu Co., Kyoto, Japan) by potassium bromide (KBr) pellet method. The scanning range was 750–4000 cm-1 and the resolution was 1 cm.

METHOD OF PREPARATION OF PIROXICAM NANOPARTICLE

The Nanoparticles agglomerates was prepared using **Quasi-Emulsion Solvent Diffusion Technique** where in the drug was mixed with the good solvent and bridging liquid was added to the same, Acetone (good solvent), the bridging liquid Dichloromethane was added to the same with that dispersing agent was added to the same and different hydrophilic polymers were dissolved in distilled water to obtain 1% W/V concentration of solution (external phase). After preparation of both the Phases .The drug solution was added to external phase with continuous stirring at a speed of 1500rpm, 2000rpm, and 2500rpm for 120 minutes using a mechanical stirrer. The agglomerates were collected by filtration and dried at room temperature.

FORMULATION AND DEVELOPMENT OF PIROXICAM NANOPARTICLES

Formula as per the preliminary study of Piroxicam Nanoparticles

Table No. 01 Ingredients which are used.

Ingredients	Uses
Piroxicam	Drug
Acetone	Good Solvent
Dichloromethane (DCM)	Bridging liquid
PVP-K-30	Polymer
SLS	Surfactant
Water	External Phase

Table No. 02 Factorial Batches.

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Piroxicam	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg
Acetone	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml	5ml
DCM	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
PVP-K-30	0.50mg	0.50mg	0.50mg	0.75mg	0.75mg	0.75mg	0.75mg	0.75mg	0.75mg
SLS	0.50mg	0.50mg	0.50mg	0.50mg	0.50mg	0.50mg	0.50mg	0.50mg	0.50mg
Water	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml	100ml
Speed (rpm)	1500	2000	2500	1500	2000	2500	1500	2000	2500

CHARACTERIZATION OF PIROXICAM NANOPARTICLES

Particle size

Particle size was determine by using a Zetasizer 3000 (Malvern Instruments, UK). This analysis yields the mean diameter (z-average, measuring range: 50–100 nm). The data presented are the mean values of three independent samples produced under identical production conditions.

Screening electron microscopy

Particle size and morphology was examined by SEM, The particle size distribution was determine by the Marvel Analyzer System (Germany) via the obtained SEM photographs.

Drug content

The prepared Nanoparticles was analyzed for drug content by UV spectroscopic method. Different batches of Nanoparticles equivalent to 20 mg of Piroxicam weighed accurately and dissolve in 10 ml ethanol. The stock solutions was diluted with distilled water and analyze by UV spectroscopy at 243 nm.

Saturation solubility studies

Saturation solubility measurements was analyze by ultraviolet absorbance determination at 243 nm using a Shimadzu UV-Visible spectrophotometer. The saturation solubility studies was carried out for both unprocessed pure drug and different batches of QESD 10 mg of unprocessed pure drug and Nanoparticles equivalent to 10 mg of Piroxicam was weighed and separately introduce into 25 ml stoppered conical flask containing 10 ml distilled water. The flasks was seal and place in a rotary shaker for 24 hrs at 37°C and equilibrate for 2 days. The samples was collect after the specific time interval, and it is filter and analyze. The dilute samples was analyzed using UV spectrophotometer at 243nm. The results were analyzed in triplicate and standard deviations are report.

Preparation of Piroxicam Nanoparticle FDT

The tablets were prepared by using Slugging method.

Table No.03 Formula of Piroxicam nanoparticles ODT.

Ingredients	FDT 1	FDT 2	FDT 3	FDT 4	FDT 5	FDT 6
Piroxicam nanoparticles	20mg	20mg	20mg	20mg	20mg	20mg
Mannitol	100mg	100mg	100mg	100mg	100mg	100mg
Croscarmellose Na	20mg	20mg	20mg	-	-	-
Crospovidone	-	-	-	20mg	20mg	20mg
PVP-K-30	4mg	4mg	4mg	4mg	4mg	4mg
Avicel pH-102	50mg	50mg	50mg	50mg	50mg	50mg
Mg Stearate	3mg	3mg	3mg	3mg	3mg	3mg
Talc	3mg	3mg	3mg	3mg	3mg	3mg
Total	200mg	200mg	200mg	200mg	200mg	200mg

Flow characteristics

- **Angle of Repose**

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for powder was determined by the funnel method. The powder was allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of powder from the funnel mouth forms a pile of powder at the surface this was continued until the pile touches the stem tip of the funnel. A rough circle was drawn around the pile base and the radius of the granule cone was measured. Angle of repose was then calculated with the use of the following formula:

$\tan\theta = h / r$

Where,

θ= angle of repose

h= height of the pile

r = average radius of the powder cone

Table No.04 Pharmacopoeial specification of angle of repose.

Angle of Repose Flowability	Angle of Repose Flowability
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very very poor

- **Bulk density**

Bulk density of powder was determined by pouring gently 5g of powder into a 50 ml graduated cylinder. The volume occupied by the powder was recorded. The bulk density was calculated as follows:

$$\text{Bulk Density (g/ml)} = \frac{\text{Weight of powder in grams}}{\text{Volume of powder in grams}}$$

- **Tapped Density**

5g powder was poured gently into a 50ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume is obtained. Volume occupied by the powder after tapping was recorded and tapped density was calculated as follows:

$$\text{Tapped Density (g/ml)} = \frac{\text{Weight of powder in gram}}{\text{Volume occupied by powder}}$$

- **Carr's Index**

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr‘s index, which was determined by the following equation;

$$I = \frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}}$$

Table No.05 % compressibility values and its significance.

% Compressibility	Flow Character
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

- **Hausner’s ratio**

Hausner‘s ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. Tapped density and bulk density were measured and the Hausner‘s ratio was Calculated using the equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of Nanoparticulate FDT

Weight Variation

The weight of the tablet is routinely measured to ensure that the tablet contains proper Amount of drug. 20 tablets were taken at random for the test and were weighed, individually and the average weight was calculated. The % deviation of each tablet from the average weight was calculated.

$$\% \text{ deviation} = \frac{\text{Average weight - weight of individual table} \times 100}{\text{Average weight}}$$

Table No.06 Specifications for weight variation test.

Sr. No	Avg. Wt. of Tablet	% Deviation
1.	80 mg or < 80	10
2.	> 80 but < 250 mg	7.5
3.	250 mg or more	5

Hardness

Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using a simple Monsanto hardness tester. In this, a tablet is placed between the plungers, and was tightened from one end, and pressure required to break the tablet diametrically was measured.

Friability

In this test 10 tablets was weighed and placed in a Roche Friabilator test apparatus, and then the tablets was subjected to rolling and repeated shocks, resulting from free Falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets will be removed, de-dusted and weighed again. The friability was determined as the Percentage loss in weight of the tablets.

% Friability = 1 – (wt. of tablets after test/ wt. of tablets before test) x 100

Diameter

The thickness and diameter of the tablets was determined using a Vernier caliper. Five tablets from each formulation were used and average values were calculated.

Wetting time & Water Absorption Ratio (%)

A piece of tissue paper folded twice was placed in a small petri-dish containing 6 ml of purified water. A tablet was put on the paper, and the time required for complete wetting was measured. Six trials for each batch were performed; average time for wetting with standard deviation was recorded. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

R = 100 (Wa-Wb)/ Wb

Where, Wa and Wb are the weight after and before water absorption, respectively. The average value with standard deviation was recorded.

Drug content uniformity

10 tablets were weighed and triturated. The tablet triturate equivalent to 50 mg of the drug was weighed accurately, dissolved in 0.1N HCl and suitably diluted with 0.1 N hydrochloric acid (HCl) solution of pH 1.2. The content of Piroxicam was determined spectrophotometrically at 243 nm against blank using UV-visible spectrophotometer.

In vitro disintegration time

In vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The water was maintained at a temperature of 37±0.5ºC and time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

In vitro Drug Release Study

Dissolution studies were carried out using 900 mL of **0.1N HCl** in Distilled water at 37 ± 0.5 °C at 75 rpm. The samples were withdrawn (5 ml) at specific time 60 min and sink condition was maintained. The solutions were immediately filtered through a 0.45 µm membrane filter, suitably diluted and the concentrations of Piroxicam in samples were determined spectrophotometrically at 243 nm.

Table No.07 Dissolution Profile.

Instrument	USP Dissolution apparatus
Type	Paddle method
Medium	900ml 0.1N HCl (pH-0.1N)
Temperature	37 ± 0.5 °C
RPM	50
Testing time	15min
Amount withdraw	5ml
Amax	243nm
Sample withdrawal interval	Every 2min

RESULTS AND DISCUSSION

Organoleptic Characteristics

The color of Piroxicam was visualized white with odorless having white powder.

Melting Point of Piroxicam

Melting point was carried out to determine the purity of sample. The Drug sample has melting point of 200°C-202°C which was in the range and indicate the purity of sample as Piroxicam.

Wavelength max (λmax) of Piroxicam

λmax of sample was found to be 243 nm which is approximately equal to standard value of 2 nm.

Saturation solubility studies

Study reveals that Piroxicam is very slightly soluble in water, acetate buffer, phosphate buffer, 0.1 N HCl but freely soluble in Acetone, alcohol such as methanol.

Table No.08 Saturated Solubility Study in Different Solvent.

Name of Solvent	Piroxicam solubility (mg/ml)			Solubility mean±SD) (mg/ml)
Water	0.03369	0.02218	0.02833	0.028067 ± 0.004703
Methanol	0.06837	0.06587	0.6587	0.06698 ± 0.00104
Acetone	0.070148	0.07074	0.06781	0.07001 ± 0.001585

Table No.09 Data for calibration curve of Piroxicam in 0.1N HCl.

Conc. µg/ml	Abs.
5	0.201
10	0.400
15	0.618
20	0.757
25	0.969

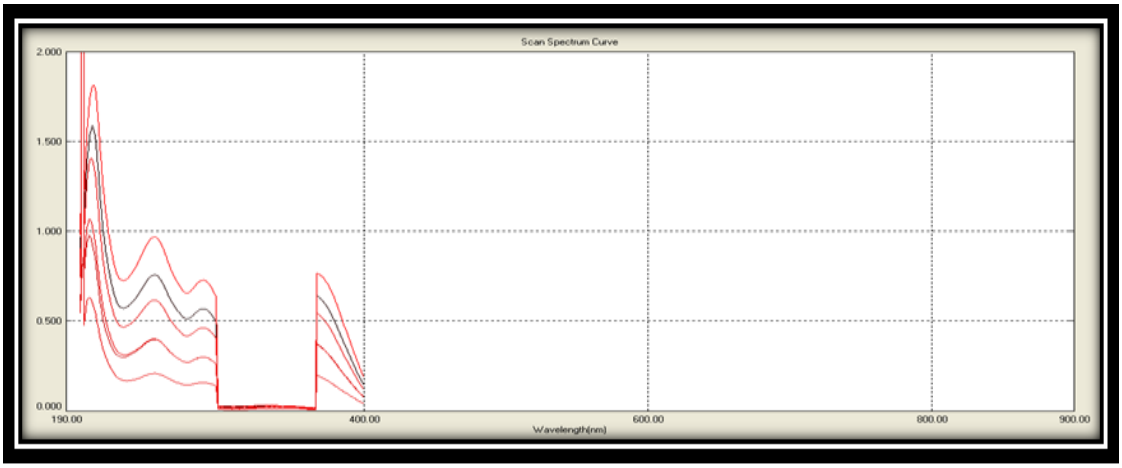

Figure.01 Calibration Curve of Piroxicam 0.1N HCl.

Piroxicam by FT-IR Spectroscopy

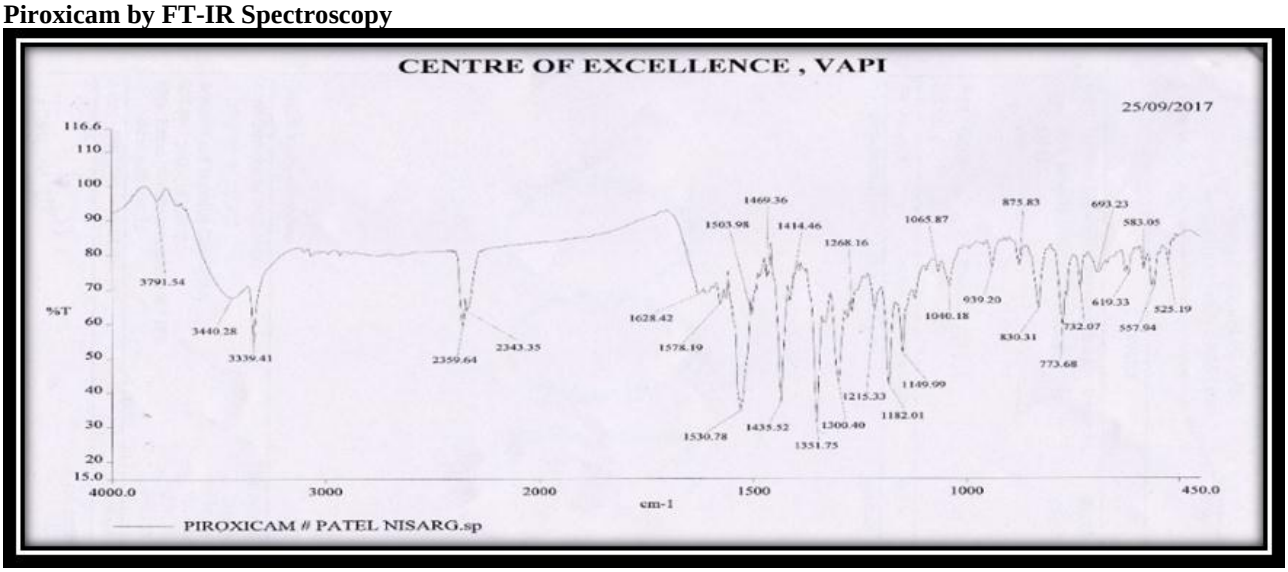

Figure.02 FTIR for Pure Drug Piroxicam.

Table No.10 IR Interpretation Date.

Std. Absorption range (cm-1)	Observed value (cm-1)	Bond type
1680-1630	1628.42	C=O amide stretching
1640-1550	1530.78	N-H bending
1450	1435.52	C-H asymmetrical bending
1375	1351.75	Symmetrical bending
1375-1300	1300.40	S=O asymmetrical stretching
1350-1140	1182.10	S=O symmetric stretching
939.20	1040.18	C-N stretching

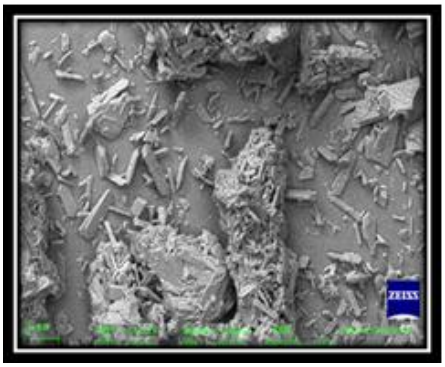

Figure.03 Pure Drug

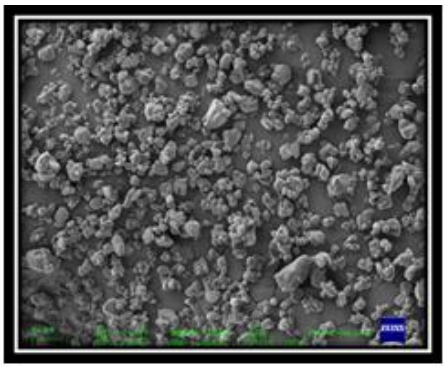

Figure.04 NanoParticles of Piroxicam

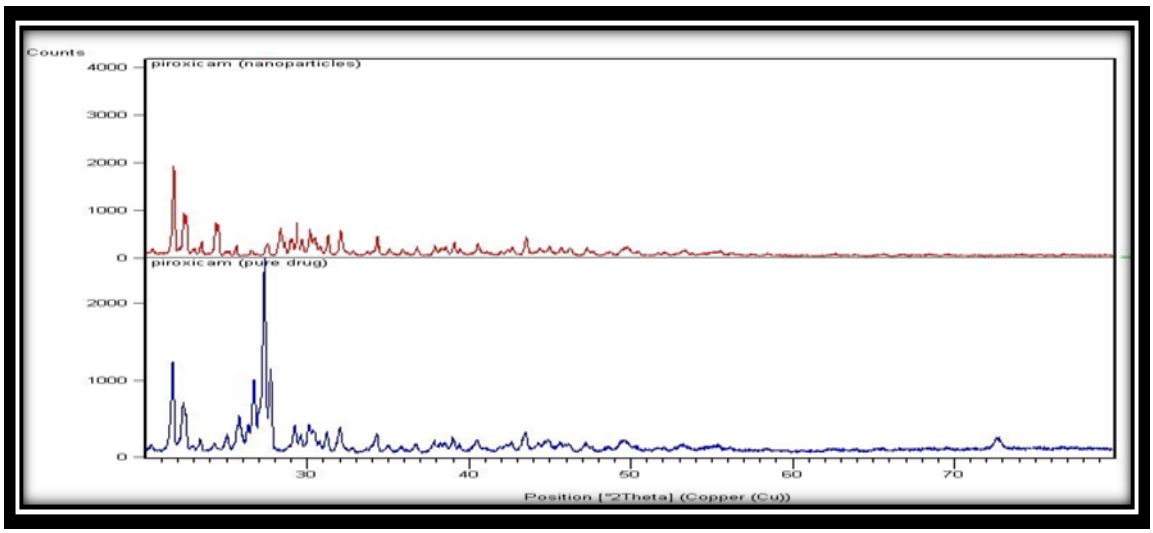

Figure.05 XRD for Pure Drug and NanoParticles.

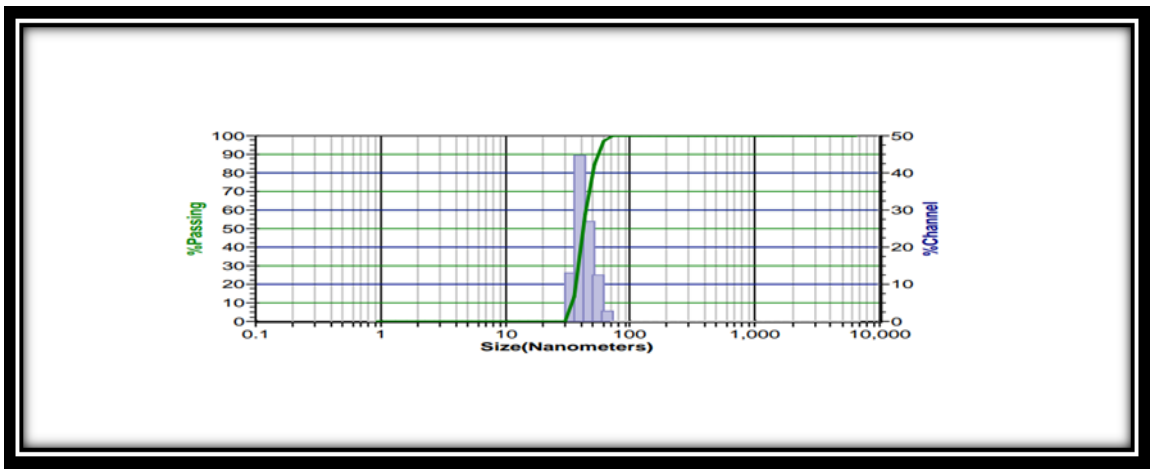

Figure.06 Particle Size Analysis.

Evaluation of Nanoparticulate FDT

Table No.11 Pre-Compression Parameters.

Formulation	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Hausner's Ratio	% Compressibility	Angle of Repose (Ɵ)
T1	0.37±0.04	0.35±0.04	1.16±0.02	13.95±0.32	22.78±1.38
T2	0.33±0.02	0.39±0.06	1.18±0.05	15.38±0.22	24.70±1.45
T3	0.35±0.04	0.41±0.07	1.17±0.11	14.63±0.13	25.64±1.47
T4	0.35±0.05	0.42±0.03	1.14±0.07	16.67±0.45	23.27±1.24
T5	0.36±0.02	0.41±0.03	1.14±0.07	12.20±0.14	23.59±1.56
T6	0.35±0.04	0.41±0.04	1.17±0.05	14.63±0.24	23.75±1.48

All values are expressed as mean ± standard deviation, n=3

All these results indicate that, the granules possess satisfactory flow and compressibility properties

Table No.12 Post-Compression Parameters.

Formulation	Weight variation (mg) ±SD n=20	Hardness (Kg/cm2)	Thickness (mm) ±SD	Water Absorption ratio % ±SD	Friability % ±SD	Drug content (%)± SD
T1	201.09±1.7	3.4±0.10	2.45±0.02	87.70 ±0.838	0.75±0.005	99.21±1.12
T2	198.76±2.8	3.4±0.15	2.46±0.01	85.40 ±1.189	0.61±0.009	98.56±1.43
T3	201.23±2.1	3.3±0.20	2.44±0.02	89.60 ±1.638	0.75±0.005	98.53±1.39
T4	198.56±2.4	3.3±0.29	2.47±0.02	89.30 ±1.177	0.78±0.005	98.32±1.56
T5	199.12±1.7	3.3±0.17	2.46±0.02	93.40 ±0.630	0.63±0.010	99.78±1.32
T6	198.89±1.5	3.3±0.12	2.43±0.02	92.50 ±2.650	0.85±0.010	98.23±1.67

All values are expressed as mean ± standard deviation, n=3

From the above result it had been concluded that cross povidone is giving better result than Croscarmellose sodium. Hence these superdisintegrant were subjected for further investigation.

Dissolution Rate of Drug from FDT of Nanoparticulate Tablet

The FDT of Nanoparticulate tablet was subjected to dissolution studies in 0.1 N HCl using USP type II apparatus at 100 rpm and 37 ± 0.5 °C. The Figure shows that drug release was more than 98% within 15 min.

Table No.13 Dissolution Rate.

Time	F1	F2	F3
0	0	0	0
2	26.04 ± 0.54	40.2 ± 0.56	44.5 ± 1.24
4	36.56 ± 0.23	50.30 ± 1.26	52.24 ± 0.45
6	58.04 ± 1.23	74.34 ± 1.25	77.34 ± 1.23
8	77.21 ± 1.22	90.20 ± 0.80	92.20 ± 0.43
10	88.52 ± 0.42	93.26 ± 0.52	95.20 ± 0.45

Time	F4	F5	F6
0	0	0	0
2	33.64 ± 0.40	50.20 ± 0.054	38.3 ± 0.56
4	42.79 ± 1.34	64.40 ± 0.34	49.1 ± 1.23
6	65.38 ± 1.23	77.40 ± 1.22	70.1 ±0.84
8	80.81 ± 0.54	89.28 ± 1.22	85.6 ± 0.67
10	90.1 ± 0.44	98.50 ± 0.82	91.8 ± 0.53

SUMMARY

The spherical crystallization is the technique where in particle size enlargement is achieved. The technique involves modification of Nanoparticles characteristics and dissolution property.

Particle size enlargement leads to show agglomeration of the crystalline drug with that of polymer and that finally leads to show improved the dissolution.

The present work was designed to develop Fast Dispersible Tablet Containing Nanoparticle of Piroxicam by Quasi Emulsion Solvent Diffusion Technique to enhance the solubility and dissolution rate.

Piroxicam higher solubility which was selected for formulation of Fast Dispersible Tablet Containing Nanoparticle tablet by Slugging Method using different

superdisintegrant i.e. Crospovidone (CP), Croscarmellose sodium (CCS).

Tablets prepared with Croscarmellose and Crosspovidone. It showed less disintegration time compared to CCS.

From all F1- F6 batches, F5 batch has Proper Spherical in shape & Size is selected. Disintegration time and Wetting time of the check point batch is 21±1.00 and 27±0.57 sec. The results are as expected thus, we can conclude that the statistical model is mathematically valid.

CONCLUSION

- The agglomerates are prepared using quasi emulsion solvent diffusion technique; the agglomerates showed improved solubility, micrometric properties as well as dissolution.
- The improved dissolution was achieved using the polymer that leads to convert the crystalline nature of the drug, finally the optimized batch is prepared with consideration to all of the factors and applying experimental design.
- The Nanoparticulate tablets are prepared, evaluated and found out observed change in the Disintegration time as well as the dissolution data.

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