J Young Pharm, 2022; 14(2) : 192-197
A multifaceted peer reviewed journal in the field of Pharmacy
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Original Article

A Piroxicam Inclusion Complexation for Solubility Enhancement: Design and Development

Saravanakumar Kasimbedu[1,*], Shilpaja Chella[1], Bharathi T[1], Nagaveni Pommala[2], Durga Srinivasa Rao Mannepalli[3]
[1]Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, Sree Sainath Nagar, Tirupati, Andhra Pradesh, INDIA.
[2]Department of Pharmaceutics, S.V.U. College of Pharmaceutical Sciences, S.V. University, Tirupati, Andhra Pradesh, INDIA.
[3]Department of Pharmaceutics, Jagan's Institute of Pharmaceutical Sciences, Muthukur, SPSR Nellore, Andhra Pradesh, INDIA.

ABSTRACT

Background: Over last few years, the physical and chemical characteristics of inclusion complexes have generated a lot of attention. One of the most important reasons for this is the significance of enzyme-substrate and drug-receptor interactions in inclusion complexes. **Materials and Methods:** The aim of the study was to design Piroxicam's inclusion complexation, to improve its solubility by the reduction of particle size which leads to improve the particle surface area thereby increases the wettability of the mixture. Physical mixture, co-grinded mixture, kneading and solvent evaporation method were used to prepare the inclusion complexation of Piroxicam with β-cyclodextrin at 1:0.5, 1:1, and 1:2 w/w (Piroxicam/β-cyclodextrin) ratios. **Results:** Differential scanning calorimetry, Fourier-transform infrared and X-ray diffraction and scanning electron microscopy studies were used to investigate the interaction of Piroxicam with β-cyclodextrin. From scanning electron microscopic studies, it was observed that crystalline were formed as spherical in shape with rough surface, small piece and Pure Piroxicam in crystalline form with rough surfaces. From Scanning electron microscopic studies, it was observed that amorphous were formed as spherical in shape with smooth surface, wide piece and β-Cyclodextrine in amorphous form with rough surfaces. **Conclusion:** The inclusion complexations of Piroxicam with β-cyclodextrin exhibited higher saturation solubility and dissolution rate than that of the pure drug of Piroxicam. Formulation K2 showed more drug release rate by reducing the particle size with complexation technique like kneading technique.

Key words: Co-grinded mixture, Inclusion Complexation, Kneading, Wetting Property, Particle Shape.

Correspondence

Prof. K Saravanakumar,

Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, Sree Saianth Nagar, Tirupati-517102, Andhra Pradesh, INDIA.

Email id: saravanakumar156@gmail.com

DOI: 10.5530/jyp.2022.14.36

INTRODUCTION

Complexation is the process of association of two or more molecules to generate a non-covalent complex with a higher solubility than the drug. Biopharmaceutical Classification System II drug's solubility and stability have been improved with the application of inclusion complexes of Cyclodextrin. Cyclodextrin's have been increasingly used in the domains of food, pharmaceuticals, chemicals, agriculture, and environmental engineering in recent years.[1-2] Piroxicam is a widely recommended nonsteroidal anti-inflammatory drug with anti-inflammatory, analgesic and antipyretic properties. It is predominantly used for the treatment of rheumatic diseases due to its significant anti-inflammatory activities and long half-life (approximately 50 hr), which allows for a once-daily dose.[3-4] Piroxicam is categorized as a class II drug with low solubility, according to the Biopharmaceutical Classification System. For oral drug bioavailability, drug release is an important and rate limiting step, especially for medicines with low gastrointestinal solubility and high permeability. It is possible to increase bioavailability and reduce side effects by improving the drug release profile of these drugs.[5] Inclusion complexation, a technique for increasing the solubility of a drug that is poorly water-soluble has been widely employed. Using this process, a drug is completely disseminated in a hydrophilic polymer using suitable preparation methods. The major strategy for enhancing the drug's solubility and dissolution rate is to reduce the particle size of the drug to submicron or molecular size.[6] Increased wettability within the dispersions causes the particle size to decrease, which in turn enhances the rate of dissolution. Furthermore, the medication is converted from a crystalline state to an amorphous, which has high energy and is very soluble.[7] Finally, the hydrophilic polymer improves the wettability of drug particles. Inclusion complexation, first proposed in the early 1970s, is a multi-component system in which the drug is dispersed in and around a hydrophilic polymer. It can be made using a wide range of processes, including physical mixtures, co-grinded mixtures, kneading, and solvent evaporation.[8-9] This process differs from conventional inclusion complexation formulation procedures in that it does not require the use of a hazardous solvent, making it more environmentally friendly and cost-effective.[10-11] The aim of the study was to use the inclusion complexation technique for improving the solubility of Piroxicam.

MATERIALS AND METHODS

Materials

Piroxicam, β-cyclodextrin (Yarrow chemicals products), Acetone (Merck Life Science Private Limited), Ethanol (Changshu Hong Sheng Fine Chemical Co. Ltd.) All other chemicals and materials were analytical grade and used accordingly.

Methods

Calibration curve of Piroxicam

10 mg of Piroxicam was weighed and dissolved in a few ml of 0.1N HCl, then brought up to a volume of 10 ml with 0.1N HCl. To obtain 10 µg/ml stock solution, 1 ml of stock solution was diluted up to 100 ml with 0.1N HCl. Working dilutions were prepared from this stock solution by transferring 1, 2, 3, 4, and 5 ml of solution into 10ml volumetric flask and

diluting to the desired concentrations, yielding concentrations of 10, 20, 30, 40, and 50 µg/ml, respectively. Using a UV/visible spectrophotometer (Agilent technologies Cary 60 UV-Vis), the absorbance of these working dilutions was measured at λ_{max} (350nm).[12-15]

Fourier Transforms Infrared Spectroscopy

Fourier Transforms Infrared spectrophotometer was used to take Infrared spectrum measurements of Piroxicam and their Inclusion Complexes.[16] The method used was potassium bromide pellets. Under a hydraulic pressure of 600 psi, the Inclusion Complexation was finely ground with KBr to produce the pellets and the background spectrum was recorded under the same conditions. Each spectrum was obtained with a spectral resolution of 2 cm^{-1} in the range 4000-400 cm^{-1}.

Differential Scanning Calorimetry

The thermograms were recorded on a DSC Q200 Universal V4 7A TA instruments. Differential Scanning Calorimetry study was performed with pure drug Piroxicam. A sample of 5-10 mg was placed in the pierced DSC aluminium pan and scanned at temperatures ranging from 25 to 300°C. The heating rate was 10°C/min, nitrogen was used as a pure gas and liquid nitrogen was used to cool the system. This was accomplished with the use of a differential thermal analyzer.[17] Differential Scanning Calorimetry studies were conducted to investigate the drug's thermal behaviour.

X- ray diffraction

The sample is applied to a low-background sample holder (Amorphous silica holder) and placed on the goniometer's sample stage. The current and voltage are set 40mV and 35mV on the instrument with B-B geometry, and data has been collected.[18] The Bruker model D8 advance is an instrument make, Goniometer: D8 Theta /2 Theta.

Piroxicam inclusion complex preparation

Binary complexes of Piroxicam, β-Cyclodextrin were prepared at 1:0.5, 1:1, and 1:2 molar ratios, as described in detail below.

Physical mixture

A solid physical mixture of drug and polymer was made by homogeneously mixing for 1 hr in a glass mortar and pestle, passing through the appropriate sieve number, drying and finally storing in desiccator.

Co-grinding

Using a mortar and pestle, a solid binary inclusion compound was made by grinding and mixing the drug and polymer together.[19] The physical combination was introduced in mortar and pestle for a given duration after the drug and polymer were thoroughly combined. This methodology outperformed previous alternatives in terms of cost and environmental impact since, unlike similar procedures, it does not involve the use of harmful organic solvents.[20] This process differs from the physical mixture method, it necessitates a significant amount of combined attrition and impact on the powder blend whereas co-grinding does not.

Kneading method

The polymer was impregnated with a small amount of water or a hydro alcoholic solution and then turned into a paste using this process.[21] The drug was then mixed into the paste and kneaded for a set amount of time. The kneaded dough is then dried and, if necessary, passed through a sieve.

Solvent evaporation method

This approach entails dissolving the drug and polymer separately in two mutually miscible solvents, combining the two solutions to obtain molecular dispersion of the drug and complexing agents and then evaporated under vacuum, the solvent to obtain solid powdered inclusion compound.[22] In most cases, the polymer aqueous solution was simply added to the alcoholic drug solution. The resultant mixture was agitated for 24 hr before being evaporated under vacuum at 45 degrees Celsius. The dried substance was crushed before being sieved using a 60# mess sieve. This process proved efficient and cost-effective in both laboratory and large-scale manufacturing, and it provides a viable alternative to spray drying.[23]

Evaluation parameters

Flow properties

The bulk density, tapped density, angle of repose, compressibility index, and hausner's ratio can all be used to predict the flow properties of powders. The flow characteristics of Piroxicam inclusion complexation were investigated according to USP.[24]

Percentage of production yield

The percentage yield of any method was determined in order to determine the practical yield of that method, which aided in the selection of the most appropriate method of production. The prepared formulation's final weights were obtained, and the % practical yield was computed using the formula provided.

$$\% \text{ of practical yield} = (\text{practical yield} / \text{theoretical yield}) \times 100$$

Drug content

To make a stock solution, a particular amount of the produced Piroxicam inclusion complexation equivalent to 100 mg was dissolved in 100 ml of 0.1N HCl. One millilitre of the stock solution was taken out and 0.1N HCl was used to dilute it to ten millilitres. To calculate the Piroxicam content, the solution was spectrophotometrically measured at 350 nm. At this wavelength, the polymers showed no interference with the drug's absorbance.[25]

Dissolution studies

Six capsules were chosen at random from each batch (n=3). Each flask was loaded with 900 ml of 0.1N HCl in the USP-I (basket) dissolution apparatus, the basket speed was kept constant at 50 rpm, and the temperature was kept constant at 37.5°C. 5 ml of dissolving media was withdrawn, properly diluted, and examined at 350nm using a UV-Vis spectrophotometer at the indicated time intervals up to 90 min.[26]

Scanning Electron Microscopy

The sample is spread on a brass stub with a small piece of adhesive carbon tape. The sample was subsequently gold coated for 10 sec at 10mA current using a sputtering device (model: JFC1600). The gold-coated sample was placed in a Scanning Electron Microscopy chamber (Jeol, JSM 6390LA) for secondary electron/backscatter analysis. Images of scattered electrons are captured.[27]

RESULTS

The bulk density, tapped density, percentage compressibility, Hausner's ratio, angle of repose, and % practical yield of each formulation were all assessed. All the powder characteristics were represented (Table 1) and all the formulation powder characteristic data's were within the limits.

Table 1: Powder characteristics of Piroxicam inclusion complexes.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio (%)	Angle of repose (°)	% Practical yield
P1	0.28±0.021	0.31±0.005	10.0±0.024	1.10±0.004	30.11±0.024	97.9
P2	0.32±0.004	0.36±0.007	12.5±0.384	1.12±0.021	27.40±0.038	94.4
P3	0.44±0.002	0.50±0.003	13.6±0.635	1.130.0058	28.81±0.081	96.1
C1	0.3±0.007	0.33±0.004	10.1±0.087	1.1±0.0039	28.81±0.029	97.3
C2	0.31±0.012	0.37±0.024	19.3±0.0397	1.19±0.0074	27.92±0.095	96.6
C3	0.44±0.016	0.49±0.034	11.3±0.0465	1.11±0.0092	27.02±0.096	98.0
K1	0.28±0.008	0.32±0.008	14.2±0.368	1.14±0.0065	28.81±0.058	91.9
K2	0.31±0.009	0.35±0.005	12.9±0638	1.12±0.0059	27.92±0.086	92.6
K3	0.44±0.015	0.49±0.009	11.3±0.081	1.11±0.0094	29.24±0.069	90.1
S1	0.3±0.006	0.32±0.004	6.6±0.052	1.06±0.0083	30.11±0.084	93.0
S2	0.32±0.016	0.36±0.012	12.5±0.936	1.12±0.0067	26.56±0.093	93.1
S3	0.44±0.007	0.48±0.006	9.2±0.753	1.0±0.0059	30.19±0.067	92.9

*Values are represented in Mean±S.D (n = 3).

Table 2: Piroxicam drug content in different formulation.

Sl. No	Formulation codes	Drug content (%)
1	P1	37.21±0.032
2	P2	77.95±0.065
3	P3	80.25±0.061
4	C1	37.59±0.081
5	C2	80.27±0.052
6	C3	85.90±0.032
7	K1	38.12±0.026
8	K2	91.59±0.072
9	K3	86.32±0.089
10	S1	32.88±0.054
11	S2	76.16±0.073
12	S3	86.16±0.093

Values are represented in Mean±S.D (n = 3).

The drug content from the Inclusion complexes of Piroxicam were assessed by dissolving them in 0.1N HCl, The % drug content was in the range of 38-91%, K_2 formulation shows a maximum drug content than the other formulation (Table 2).

Piroxicam's standard calibration curve was prepared in 0.1N HCl and in the concentration range of 10-50 µg/ml, Piroxicam followed Beer Lambert's law. The equation was discovered as y=0.015x+-0.0157 (R^2=0.9921) (Figure 1). The linear association between concentration and absorbance was revealed by the correlation coefficient values. The drug content and *in-vitro* drug release estimations are based on the corresponding standard curves.

The Infrared spectra of pure Piroxicam is characterized by 1636 cm^{-1} (Keto C=O stretching), 1434 cm^{-1} (Aromatic –CH_3 stretching), 1025 cm^{-1} (=SO_2 bending) (Figure 2). The Infrared bands of pure drug: polymer shows no significant shifts or reduction in intensity of the Infrared bands. Hence there was no incompatibility problem between the drug and polymers used in the study.

The thermogram of the inclusion complexes involving Piroxicam showed an endothermic peak at 198.75°C, corresponding to its melting point. This peak indicates the crystallinity of Piroxicam. Only one sharp peak

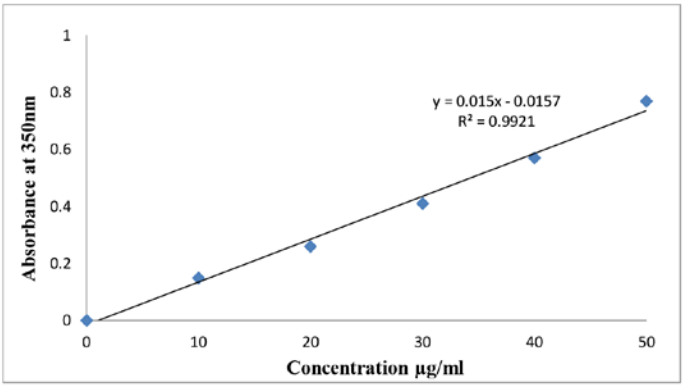

Figure 1: Standard calibration curve in 0.1N HCl.

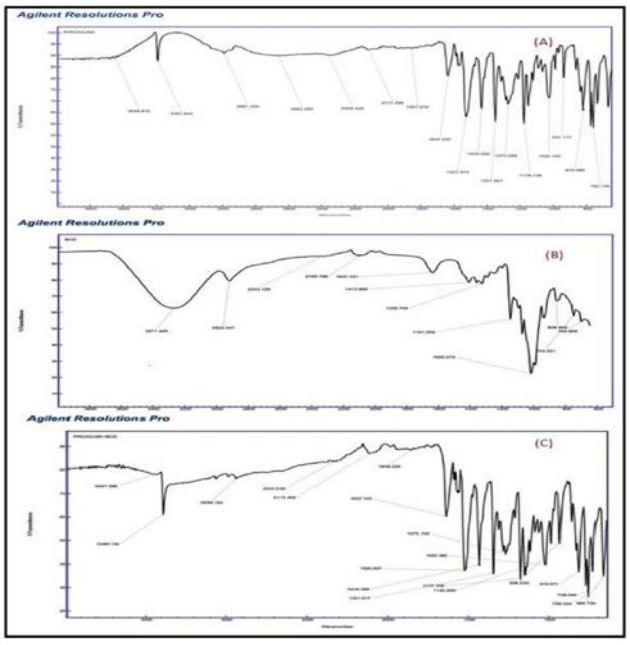

Figure 2: FT-IR Spectrum of (A) Piroxicam (B) β-cyclodextrin (C) Piroxicam and β-cyclodextrin.

was observed which confirmed that Piroxicam is free from impurities. (B) Thermogram of the inclusion complexes involving β-Cyclodextrin showed an endothermic peak at 116.94°C, corresponding to its melting point. This peak indicates the crystallinity of β-Cyclodextrin. Only one sharp peak was observed which confirmed that β-Cyclodextrin is free from impurities. (C) Thermogram of the inclusion complexes involving drug+polymer showed an endothermic peak at 197.99°C, corresponding to its melting point (Figure 3). This peak indicates the crystallinity of Piroxicam and β-Cyclodextrin. Only one sharp peak was observed which confirmed that Piroxicam, β-Cyclodextrin is free from impurities. Hence drug is in pure form.

The inclusion complexes filled in capsule were introduced into USP type–I (basket), the conditions were maintained in same conditions as mentioned. The dissolution characteristics of the Piroxicam, β-cyclodextrin was observed (Figure 4). It is clear that the Kneading (K_2) approach significantly increased the drug's dissolution rate. The results demonstrate that K_2 had the highest dissolving rate (98.7% of the drug dissolved in 90 min).

Characteristics of 2-theta values are 15.357, 15.427, 16.033, 16.514, 26.135, 27.05 in Piroxicam Powder X-Ray Diffraction has been observed in the Kneaded complex mixture. The Piroxicam Powder X-Ray

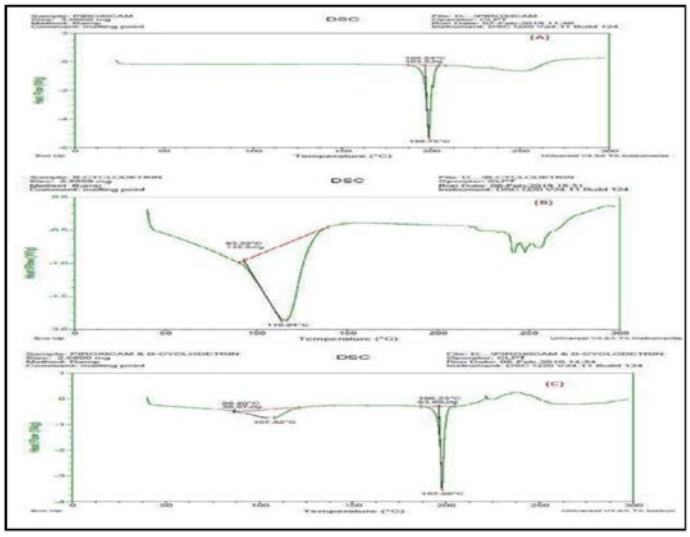

Figure 3: DSC Spectrum of Piroxicam, β-cyclodextrin and Piroxicam and β-cyclodextrin.

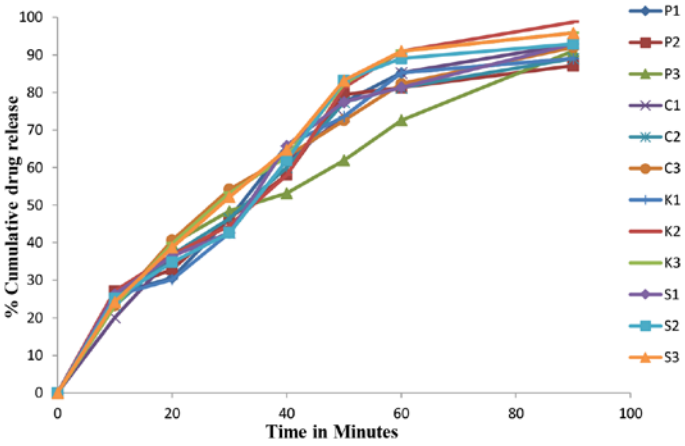

Figure 4: *In-vitro* drug release profile of inclusion Piroxicam in 0.1N HCl.

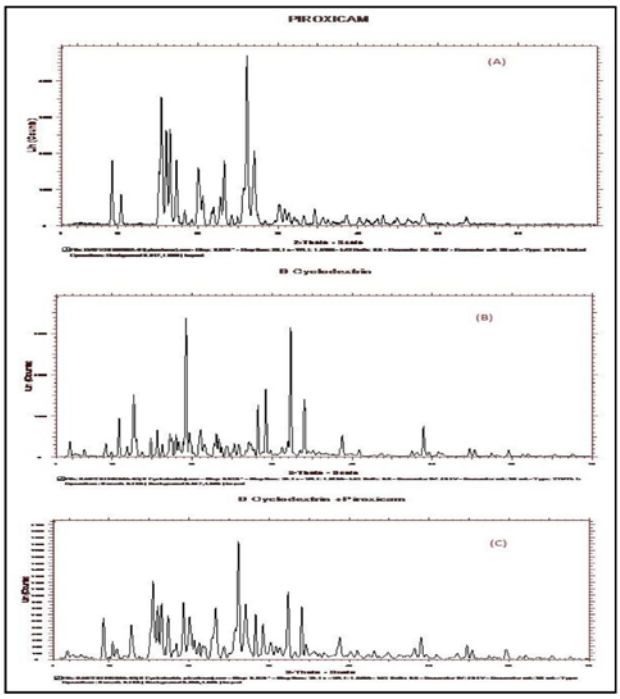

Figure 5: XRD Spectrum of Piroxicam, β-cyclodextrin, Kneaded inclusion complex.

Diffraction of inclusion complexes % intensity of the peaks were found to be decreased. The degree of crystallinity was found to be decrease in Kneaded complex mixture compare to Piroxicam (Figure 5).

Scanning Electron Microscopy Spectrum of Piroxicam, β-cyclodextrin, kneaded complexes exhibit their different shapes which includes crystalline, amorphous and partial crystalline and represented (Figure 6). Individual Active Pharmaceutical Ingredient, Piroxicam shows their shape in the form of crystalline manner whereas beta cyclodextrin shows smooth surface.

DISCUSSION

A spectrophotometric method for estimation of Piroxicam, based on the measurement of absorbance at 350nm in 0.1N HCl, gives a straight line; y=0.015x+-0.0157 with a regression coefficient (R^2=0.9921). The physical observation of Piroxicam and mixtures showed no change in their physical properties.[4] This revealed that there was no significant reaction between the Piroxicam and mixtures. Drug-excipients compatibility study was performed by Fourier Transforms Infrared Spectrophotometer (Figure 2) and Differential Scanning Colorometry (Figure 3). From the infrared spectral study, it was observed that there was no significant change in the peaks of drug, polymer and drug-polymer mixtures and from the Differential Scanning Colorometry, there was no change in the melting point. Hence, no specific interaction was observed between the drug and the polymers used in the formulations.[7] The thermogram for the complexes showed the persistence of the endothermic peak of Piroxicam for the physical mixture and did not affect their solid state properties.[20] Pre compression studies of all formulations reveals that the angle of repose was found between 27°.02'±0.096 to 30°.19'±0.067, Carr's index between 6.6 to 14.2% and hausner's ratio from 1.0 to 1.19. Flow properties of all the formulations were carried out in triplicate (n=3), the consolidated results (mean±SD) were tabulated in (Table 1), Carr's index and

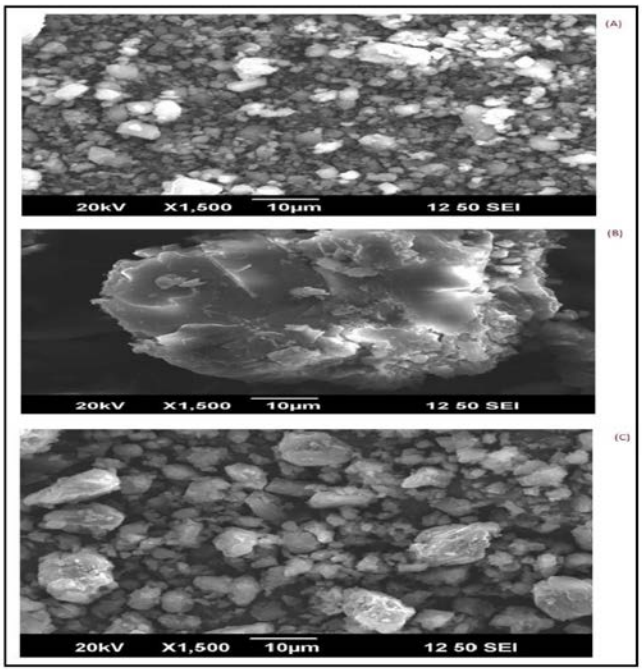

Figure 6: SEM Spectrum of Piroxicam, β-cyclodextrin and Inclusion Kneaded complex.

hausner's ratio are calculated from the mean values of bulk density and tapped density of respective batches.[9]

The micromertic studies indicate better flow properties. The enhancement in dissolution profile has been attributed due to the formation of inclusion complexes in the solid state and reduction in the crystallinity of the product, as conformed by powder X-ray diffraction study.[20] Standard deviation of all powdered characteristics were calculated by using Microsoft Excel only. For kneaded complexes, there is reduction in peaks intensity, this can be explained on the basis of major interaction between the drug and β-cyclodextrin. The effect of complexation with β-cyclodextrin on the solubility of Piroxicam can be explained in terms of the reduction in the crystallinity of the drug caused by the physical mixture, kneaded and solvent evaporation process and the inclusion into the hydrophobic cavity of the β-cyclodextrin.

Morphology of kneaded complexes was examined by scanning electron microscopy. Scanning Electron Microscopy was performed and the particle size was analyzed as 10micro meters, with formation of inclusion complexes the crystalline structure was transformed to partial smooth so that the solubility of Piroxicam was enhanced by the formation of β-cyclodextrin inclusion complexes.[21] The outer surface of kneaded complexes was smooth and dense. The distribution of drug particles, porosity or defects on the particle matrix can be provide by the particle surface microscopic analysis.

When Piroxicam and beta-cyclodextrin mixed thoroughly, the resultant spectrum shows partial smooth in nature (Figure 6). The *in-vitro* dissolution profiles was conducted on Piroxicam inclusion complexation (n=3) and the dissolution profiles of all prepared formulation are represented graphically in (Figure 4) indicates that the release rate increased as the concentration of the β-cyclodextrin increased.[15] This indicates that drug and polymer ratio is important factor affecting the rate of drug release from the inclusion complexation. Factors that may contribute to differences in drug dissolution profile include differences in water penetration rate, water absorption capacity and polymer swelling. When the size of the prepared inclusion complexation decresed which may leads to improve the surface area and decreases the contact angle between solute and solvent thereby enhance the wettability.[26] The dissolution rate increase for the physical mixture, cogrinding, kneaded and solvent evaporation mixtures is due to the wetting effect of the β-cyclodextrin, this effect is more evident for the kneaded product, where the mixing process between the two components is more intensive.

CONCLUSION

It was resolved that physical mixing, co-grinding, kneading, and solvent evaporation methods were found to be effective in increasing the solubility of the poorly water-soluble drug Piroxicam with a faster dissolution rate. Furthermore, it is possible that the conversion of crystalline solids to amorphous powder will enhance solubility and dissolution rate. As a result, we can conclude that among all the formulations, the inclusion complex of piroxicam prepared with the water soluble polymer β-cyclodextrin in the ratio 1: 1 prepared by kneading method provides the best drug release (98.7% released in 90 min.) and that this ratio can be used to improve the solubility and dissolution rate of poorly water soluble drug Piroxicam.

ACKNOWLEDGEMENT

The authors are thankful to Padma Shree. Dr. M. Mohan Babu Garu, Chairman and Visionary, Sree Vidyanikethan Educational Trust, Tirupati and Dr. Anna Balaji, Principal, Sree Vidyanikethan College of Pharmacy, Tirupati for providing us the required facilities and being a constant support to carry out this research work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PXRD: Powdered X-ray Diffraction; **P:** Physical Mixture; **C:** Cogrinding; **K:** Kneading; **S:** Solvent Evaporation; **DSC:** Differential Scanning Colorometry; **SEM:** Scanning Electron Microscopy.

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Article History: Received: 14-12-2021; Revised: 05-03-2022; Accepted: 26-04-2022.
Cite this article: Saravanakumar K, Shilpaja C, Bharathi T, Nagaveni P, Rao DSM. A Piroxicam Inclusion Complexation for Solubility Enhancement: Design and Development. J Young Pharm. 2022;14(2):192-7.