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COMPARATIVE STUDIES OF LORNOXICAM SOLID DISPERSIONS WITH DIFFERENT CARRIERS AND METHOD OF PREPARATIONS

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Abstract:

The current work is focused on comparing the effect of method of preparation and the type of carrier in improving the dissolution rates of lornoxicam solid dispersions. The study was performed by preparing solid dispersions of lornoxicam with water soluble carriers like PEG 4000, PEG 6000, PVP K30, Urea and milk using methods like fusion, solvent evaporation and freeze drying. Among all, solid dispersion with PVP K30 and lornoxicam had shown up to 80% drug release at the end of 1 hour dissolution. Evaluation studies like Fourier Transform infrared spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-Ray Diffraction studies (XRD) showed change in crystallinty of lornoxicam-PVP K30 solid dispersion by freeze drying. XRD studies proved partial conversion of lornoxicam into amorphous form. Solid dispersion of lornoxicam with PVP K 30 prepared by freeze drying had shown high dissolution compared to lornoxicam and their carriers. Dissolution parameters like DP_{30}, DE_{60} were calculated for lornoxicam and lornoxicam-PVP K30 dispersion and higher DE_{60} values were observed for freeze dried preparations. Freeze drying method for preparing solid dispersion was found to be a practical and efficient method in achieving higher dissolution rates. Stability studies were conducted for a period of 3 months for the optimized dispersion and found to be stable.

***Key words**: Lornoxicam, FTIR, X-Ray Diffraction, Freeze drying*

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INTRODUCTION:

The main basic idea behind the research is to develop a novel drug delivery system for poorly soluble drugs. Poorly soluble drugs a pose general problem in pharmaceutical drug formulation [1]. Anti-inflammatory drugs categories are associated with poor solubility as a major obstacle in the development of the formulation.

Solid dispersion is one of the most promising strategies to improve the solubility and dissolution rate of poorly water-soluble drug. By reducing the drug particle size to the absolute minimum, solid dispersions improve drug wettability, bioavailability. They are usually presented as amorphous products. Recently, surfactant have been included to stabilize the formulation; thus avoiding drug recrystallization, thereby potentiating their solubility [2, 3].

The development of solid dispersions is a practically viable method to enhance bioavailability of poorly water-soluble drugs overcomes the limitations of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion [4].

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size [5-8].

The present research work is focused towards improving the rate of dissolution of anti-inflammatory drug, lornoxicam. The osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute sciatica and low back pain can be treated by lornoxicam having poor solubility which required good solubility. There have been many attempts to improve the solubility of these drugs.

MATERIALS AND METHODS:

Materials:

Lornoxicam was obtained as gift sample from Sun Pharmaceutical Ltd, Sikkim. PVP K 30, PEG 4000, PEG 6000, acetone, sodium hydroxide were obtained from SD Fines Chem Ltd, Mumbai. Water used was semi-quartz distilled. All other chemicals and reagents used were of AR grade, procured commercially and used as such without further purification.

Methods:

Preparation of Solid Dispersion [9-14]:

a) Physical mixture method: Lornoxicam and other ingredients like PVP K30, PEG 4000, PEG 6000 and Urea in molar ratio (1:2) were weighed and mixed in a mortar for 5min to obtain a homogenous powder blend, passed through sieve no. 80 and stored in desiccator over fused calcium chloride.

b) Fusion method: The first solid dispersion created for pharmaceutical application was prepared by the fusion method. The dispersion consisted of drug and carriers which were melted using a physical a physical mixture at the eutectic composition, followed by cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling.

c) Solvent evaporation method: Co evaporated products (COE) were prepared by co evaporation of equimolar drug–Carriers in methanol–Acetone (1:2 v/v) solutions on a water bath at 50 °C. Each solid product was sieved through 80# and same fraction was used for the following tests.

d) Freeze drying/ lyophilization method: Inclusion solid dispersions were prepared of Lornoxicam and other ingredients like PVP K30, PEG 4000, PEG 6000 and Urea in the ratio 1:2. Lornoxicam was dispersed at a concentration of 1.5mM in 25 ml of methanol containing 1.5 mM of solid dispersion taken in glass vials. The resulting suspension was fast frozen using liquid nitrogen and freeze dried at -40°c for 48 hrs.

Drug Evaluation Studies:

a) Drug content estimation: 30mg equivalent of solid dispersion was accurately weighed and transferred to 10ml volumetric flask. 5ml acetone was added to dissolve and added 1ml 0.05N NaOH. Final volume was made up to the mark with acetone. From this 1ml was taken in 100ml volumetric flask and made up to the mark with 0.1N HCl. The absorbance was measured at 381nm using 0.1N HCl as blank. The drug content was estimated using slope of calibration curve.

b) Dissolution characteristics [12,15]: Lornoxicam solid dispersion equivalent to 10mg of Lornoxicam was used for the dissolution studies. Dissolution experiments were carried out in triplicate (n =3) with an USP XXIII paddle apparatus in 0.1N HCl at 37 ◦C using at a rotation speed of 100 rpm. A 5ml amount of dissolution medium was withdrawn at intervals of 5, 10, 15, 30, 45 and 60 min. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Test samples were filtered through a 0.45 µ whattman filter and suitably diluted. The absorbance of diluted samples was estimated for amount of Lornoxicam dissolved by measuring in UV/VIS spectrophotometer at 381nm.

c) Dissolution Efficiency: Dissolution efficiency (DE) and the time to release 50% of drug ($t_{50\%}$) were used to compare the results of dissolution tests of different formulations.

$$DE_{60}\% = \frac{\int_0^t y\ dt}{y100^t} \times 100$$

DE is defined as the area under the dissolution curve

up to time t expressed as a percentage of the rectangle described by 100% dissolution in the same time where Y_t is the percentage of drug dissolved at any time t, Y_{100} denotes 100% dissolution, and the integral represents the area under dissolution curve between time zero and t. Time t in this study was 1 h.

Stability Studies:

The selected formulation was packed in vials, the stability study conducted in three different storage conditions like room temperature, refrigeration and in stability chamber at 40°C ± 2°C/75% ± 5% for three months and evaluated for their physical appearance, drug content and other parameters.

Drug-Excipients Interaction Studies

a) Fourier Transform Infrared Spectroscopy (FTIR):

A Fourier transform infrared spectrum (FTIR) was used to identify the formation of solid dispersion. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 1300) in the region between 4000-400[1]. Solid dispersion formation was evaluated by comparing the IR spectra of the solid complex with drug.

b) Differential Scanning Calorimetry:

The thermal behavior of Lornoxicam and Carriers inclusion solid dispersion was studied using Differential Scanning Calorimetry in order to confirm the formation of solid complex. The samples were heated from 0 to 350 °C at a heating rate of 10 °C/min under a nitrogen flow, flowing at a rate of 40cc/min through the DSC cell.

c) Powder X-Ray Diffraction Study:

X-Ray diffraction of inclusion solid dispersion and the pure components was performed to identify the interaction of the drug with carriers using a PW 1720 X- ray generator and a PW 1710 diffractometer control (Philips Electronic Instrument). The scanning range (2θ) was from 5° to 90°, and the scan step and scan speed were 0.04° and 0.02°/s, respectively.

d) Scanning Electron Microscopy (SEM):

The morphologic properties of the pure drug and freeze dried powders of formulations were characterized by scanning electronic microscopy (Cambridge instrument: Stereoscan 360).

RESULTS AND DISCUSSION:

The rate and extent of dissolution of the active ingredient from any solid dosage form determines the rate and extent of absorption of the drug. In the case of a poorly water soluble drug, dissolution is the rate limiting step in the process of drug absorption. Poorly soluble drug have been shown to be unpredictably and slowly absorbed as compared with drugs with higher solubility.

The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (1961). Gibbs et al. (1976) proposed an alternative solvent technique for the preparation of solid dispersions. Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin and Wilken, 1980).

In this work, an attempt was made to study the effectiveness of method of preparation and type of carrier in improving solubility and dissolution rate of poorly soluble drug, Lornoxicam. Polyethylene glycol (PEG) 4000, PEG 6000, PVP K30, Urea, Milk individually were used as carriers in this study. Fusion method, solvent method and freeze drying methods were used to prepare solid dispersions of lornoxicam.

Solubility Studies: Solubility studies were performed for pure lornoxicam and solid dispersion in 0.1N HCL It was observed that solid dispersions had shown good solubility compared to pure lornoxicam. Among all dispersion lornoxicam:PEG and lornoxicam:PVP K30 had shown higher solubilities than lornoxicam alone.

Dissolution Studies:

The dissolution rate of lornoxicam from all the physical mixture was significantly higher than lornoxicam alone. This demonstrates the solubilizing effect of the Urea, PVP K30, and PEG 4000, PEG 6000 carriers. The dissolution profile of solid dispersion prepared using all these carriers exhibited significant increase in rate of dissolution in 0.1N HCL. Dissolution for all the dispersions was significantly greater than those for lornoxicam alone. Rate of dissolution was higher with the dispersion prepared by the freeze drying method. An attempt was made to check out the enhancement of dissolution with milk powder as carrier due to it's surface active agent and amino acids contents which are proposed against gastric disturbances caused by NSAIDs with anti inflammatory action [16-18]. But significant increase in dissolution was not observed. Solid dispersion prepared with PVP K30 (Drug:carrier-1:2 ratio) by freeze drying method showed 80% drug release (Table 1) which was almost 8 times that of pure lornoxicam and significantly greater than other dispersions and other method of preparation (Fig 1).

The solid dispersion prepared with PEG 4000 also showed up to 60% drug release prepared by freeze drying and 52% drug release for solvent evaporation.The dissolution profile showed 6 times higher release for freeze dried dispersion compared to pure drug. The dispersion prepared with PEG 6000 showed second highest release up to 68% after with PVP K30, and 6.5 times more release compared to pure drug lornoxicam.

The solid dispersions prepared by Milk and Urea didn't show higher drug release. With Urea, drug release was found to be 30.9% and with milk 19.9% respectively.

The faster dissolution rate of physical mixtures compared to pure drug was observed and could be attributed to the improvement of wettability of lornoxicam particles due to the presence of hydrophilic polymers. Dissolution rates for solid dispersions were greater than those for physical mixtures and lornoxicam alone. This may be due to many factors such as decreased particles size of drug, specific form

of drug in these solid dispersions, in addition to the increase in drug wettability and preventing of drug aggregation by each polymer.

Comparative study with the marketed lornoxicam tablet (brand name: Lofecam 8) and with the optimized formula i.e.,lornoxicam-PVP K30 solid dispersion prepared by freeze drying was performed. Marketed formulation showed only 27.17% drug release after a period of 1 hr (Fig 2).

Dissolution Efficiency: Dissolution efficiency of pure drug and lornoxicam-PVP K30 dispersion were calculated. It was observed that higher dissolution efficiency, almost 50 times more than of pure lornoxicam was observed for lornoxicam-PVP K30 dispersion by freeze drying method (Table 2). All lornoxicam-PVP K30 showed greater dissolution efficiency compared to Lornoxicam alone.

Table 1: Dissolution studies of Lornoxicam-PVP K 30 solid dispersion in 0.1N HCl

Time		Percentage Drug Release*± SD			
	Lornoxicam	Physical mixture	Solvent evaporation	Fusion	Freeze drying
5	2.20±0.18	12±0.07	30.7±0.16	20.1±0.32	36.0±0.09
10	3.93±0.34	17±0.12	35.9±0.15	33.8±0.34	42.6±0.11
15	5.51±0.32	20.5±0.32	45.0±0.24	45.7±0.71	49.1±0.18
30	7.20±0.54	29.2±0.14	58.3±0.76	54.0±0.09	57.2±0.14
45	9.20±0.19	38.7±0.54	60.5±0.81	60.5±0.19	68.9±0.12
60	9.70±0.45	48.5±0.21	62.8±0.34	62.6±0.18	80.0±0.15

**= average cumulative drug release of triplicate samples (n=3).*

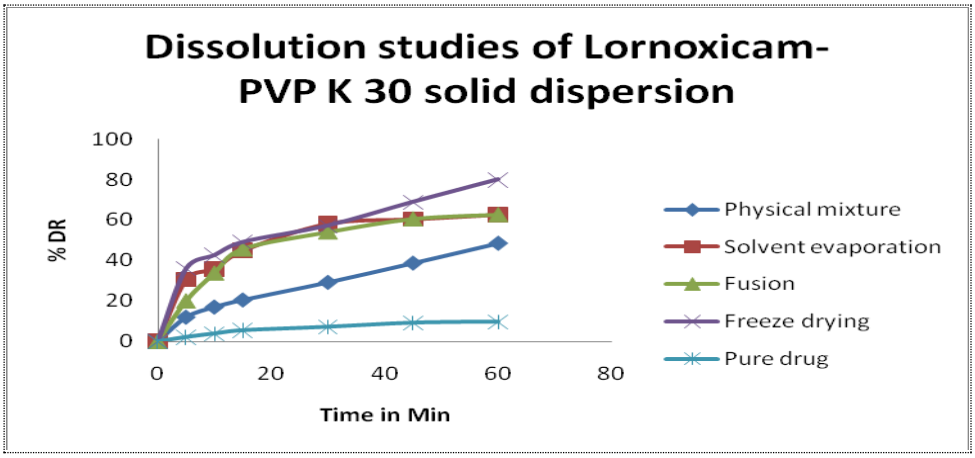

Fig 1: Dissolution profile of Lornoxicam-PVP K30 solid dispersion in 0.1N HCl

Table 2 : Dissolution Efficiency of Lornoxicam with PVP K30

Name	Methods	DP_{30}	DE_{60}
Lornoxicam		7.20	6.74
Lornoxicam + PVP K30	Physical Mixture	29.20	28.86
	Solvent Evaporation	58.30	50.60
	Freeze Drying	57.20	56.25
	Fusion	54.0	48.55

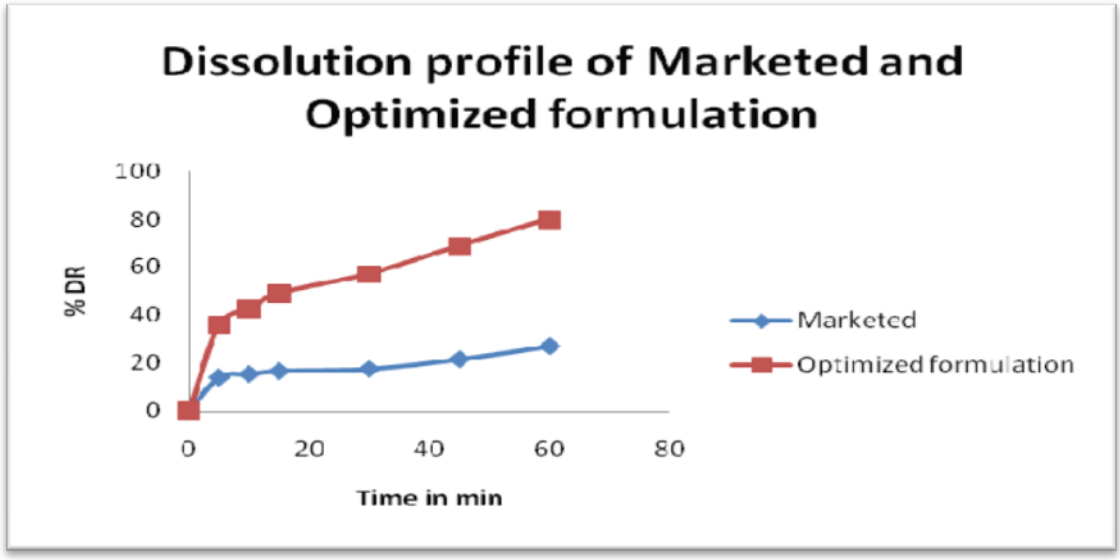

Fig 2: Dissolution profile of Optimized and Marketed Formulations

Characterization Studies of the Formulated Complexes:

Fourier Transform Infrared Spectroscopy: The IR spectrum of lornoxicam exhibit characteristic peaks for amide group at 3135.91 cm^{-1} and 3436.72 cm^{-1} for OH group, 1425.46 cm^{-1}, 1327.69 cm^{-1} due to C-S and S=O groups respectively. IR spectrum of PVP K 30 showed 2954.79 cm^{-1}, 1683.39 cm^{-1} and 1318 cm^{-1} due to C-H aliphatic, C=O and C-N stretching respectively. IR spectrum of lornoxicam-PVP K30 physical mixture (Fig 3) showed less intense peak at 3065.72 cm^{-1} and a broad, less intense peak with a shift from 3436.72 cm^{-1} to 3450.91 cm^{-1} was observed for OH group. In solid dispersion with lonoxicam-PVP K30 by freeze drying (Fig 4)showed a broad peak at 3431.76 cm^{-1} amide peak at 3101.37 cm^{-1} and C=O stretching shifted from 1734.27cm^{-1} to 1892.84 cm^{-1} . Less intense peaks were observed at other regions at 1453.28 cm^{-1} also. This suggests the possibility of intermolecular interaction between lornoxicam and PVP K30 but overall symmetry of the molecule is not significantly affected.

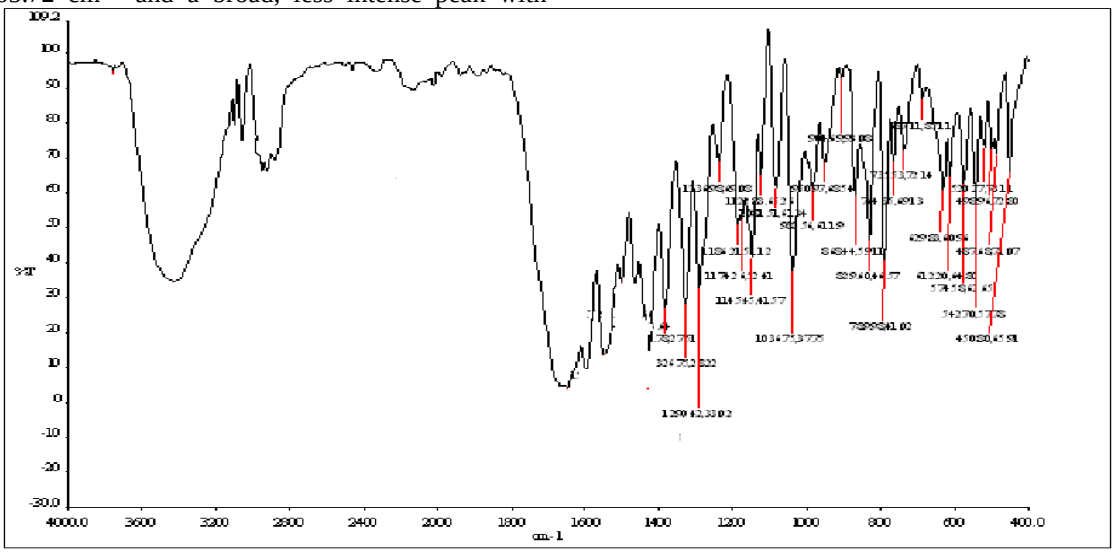

Fig 3: FT-IR spectrum of Lornoxicam-PVP K 30 by Freeze drying

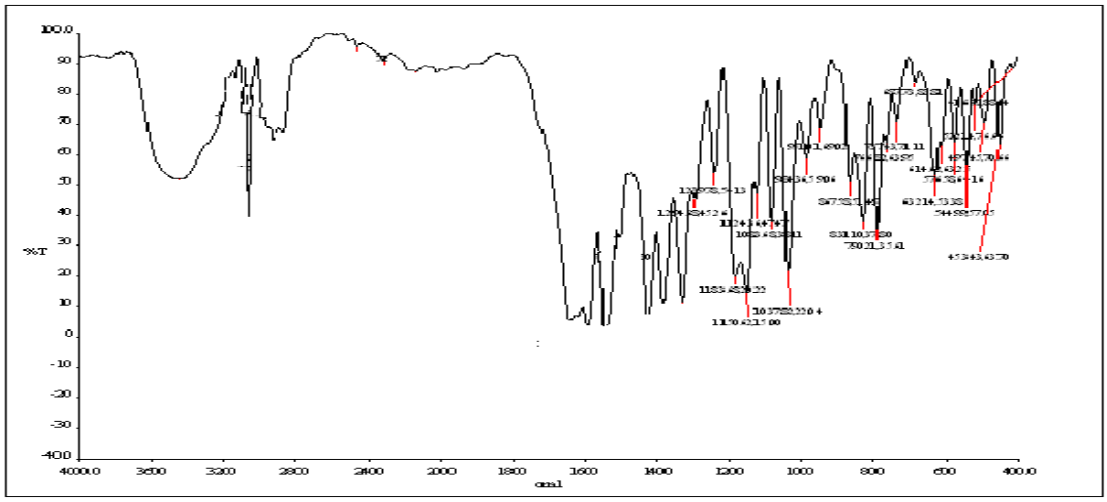

Fig 4: FT-IR spectrum of Lornoxicam-PVP K 30 by Physical Mixture.

Differential Scanning Calorimetry (DSC):

Lornoxicam displayed exothermic peak at 225^0C corresponding to its melting point with heat of fusion 556.34mJ PVP showed endothermic peak at 81.34^0C due to its melting point with heat of fusion 689.56 mJ. The thermal behavior of both physical mixture and solid dispersion of the drug-PVP were different. In case of physical mixture peak of lornoxicam shifted slightly at 222^0C with heat of fusion 87.2 mJ while it became shifted to 200^0C with heat of fusion 53.55 mJ and intensity of peak was reduced(Fig 5 and 6). Since the melting energy can be used to detect the amount of crystalline material, the significant change in heat flow indicated (from 556.34 mJ to 53.55 mJ) change in crystallinity of drug.

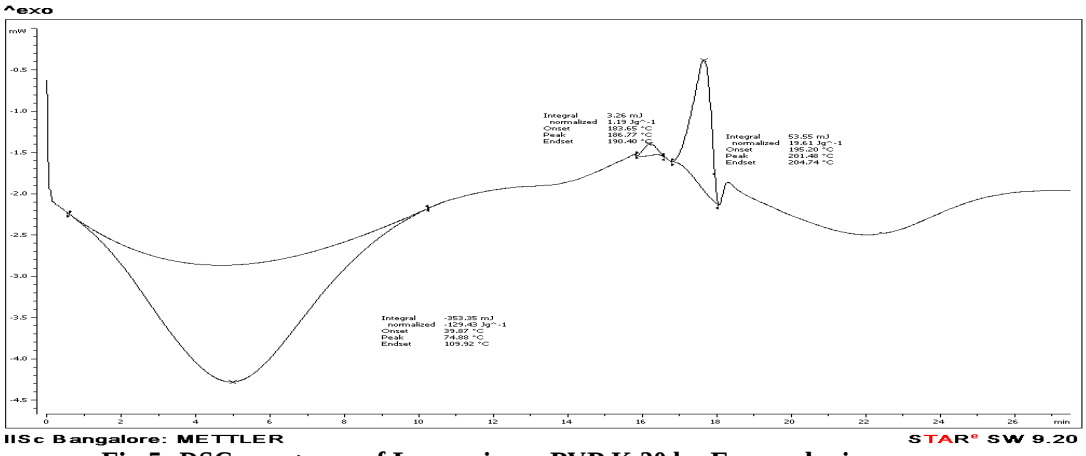

Fig 5: DSC spectrum of Lornoxicam-PVP K 30 by Freeze drying

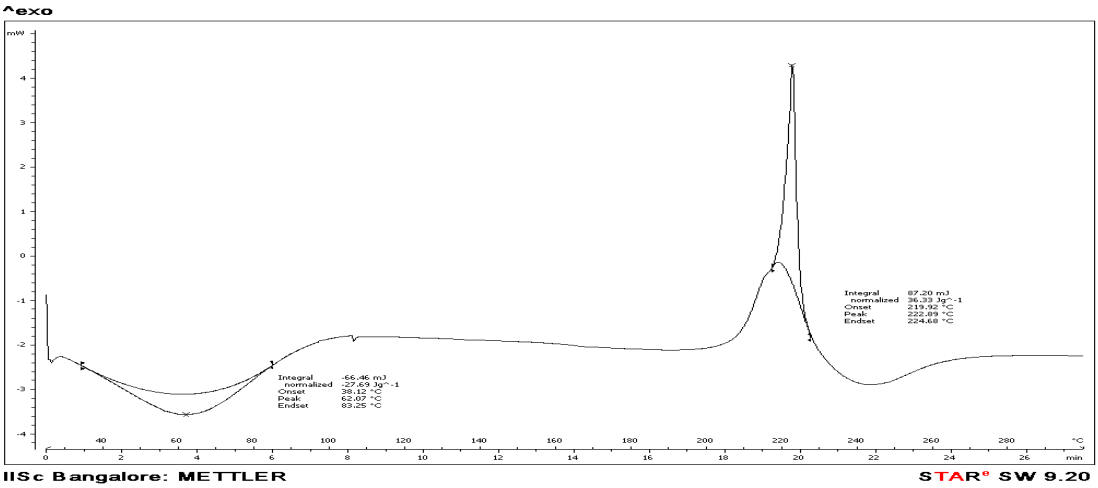

Fig 6: DSC spectrum of Lornoxicam-PVP K 30 by Physical mixture

Scanning Electron Microscopy (SEM):

The drug crystals seemed to be irregular in shape and size. Lornoxicam crystals were much smaller than PVP K30 particles (Fig 7 and 8). In case of solid dispersion, it was difficult to distinguish the presence of lornoxicam crystals. Lornoxicam crystals appeared to be incorporated into the particles of polymer.

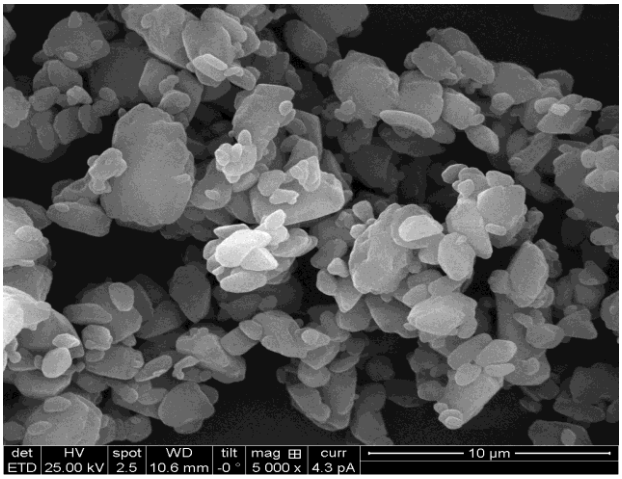

Fig 7: SEM images of Lornoxicam Pure drug at 10µm

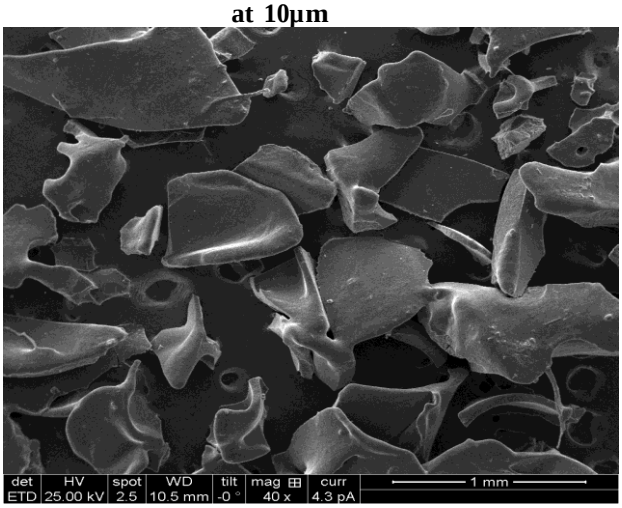

Fig 8: SEM images of Lrnoxicam – PVP K30 Solid dispersion prepared by Freeze drying method at 1 mm

X-Ray Diffraction Study:

The X-Ray diffraction pattern of pure lornoxicam showed various diffraction peaks that were intense and sharp, indicating it crystalline nature. The spectrum of lornoxicam-PVP K30 physical mixture was almost similar to the spectrum of the pure drug. For the diffraction pattern of freeze dried dispersion of lornoxicam-PVP K30 at 1:2 ratio, decrease in the intensity of peaks was observed, indicating partial conversion of crystalline form of lornoxicam to amorphousform, evidenced by marked reduction in the number as well as the intensity of peaks (Fig 9 and 10). The carrier at 1:2 ratio may not be sufficient for complete conversion of lornoxicam to amorphous form.

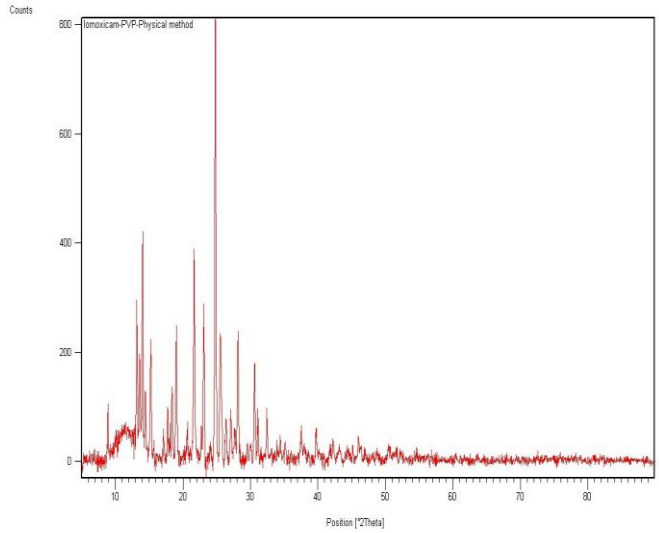

Fig 9: XRD spectrum of Lornoxicam-PVP K 30 by Physical mixture

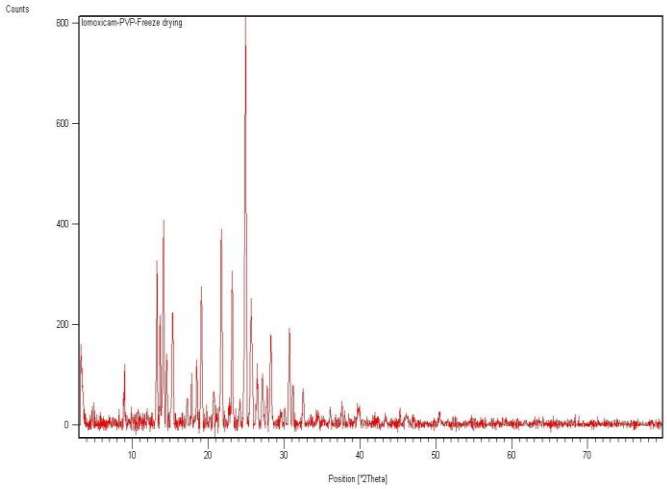

Fig 10: XRD spectrum of Lornoxicam-PVP K 30 by Freeze drying

Stability Studies:

Stability studies of lornoxicam-PVP K30 dispersion by freeze drying method was conducted for a period of 3 months no physical changes were observed. Drug content and drug release was not altered. The dispersion had shown good stability.

CONCLUSION:

Solid dispersions of Lornoxicam were prepared with different carriers employing four different methods of preparations. Among them, solid dispersions prepared with PVP k 30 by freeze drying method showed highest drug release. Many factor contributed to faster release rate such as decrease in particle size, decrease in agglomeration of particles, increase in wettability and decrease in crystallinity of drug. Freeze drying method for preparing solid dispersion was found to be a practical and efficient method to obtain a homogenous dispersion.

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