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PREFORMULATION STUDY ON ENHANCING THE SOLUBILITY OF LORNOXICAM WITH HYDROPHILIC CARRIERS

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Abstract:
Preformulation testing is the first step in the rational development of dosage forms of a drug substance. For low aqueous solubility drugs, the challenge of making solid dispersions is in choosing the amount of carrier that would increase the aqueous solubility while keeping the overall oral dosage size small. The main objective of the present research work was to do a preformulation study of Lornoxicam (LOR), A nonsteroidal anti-inflammatory drug (NSAID). In this research, the Lornoxicam was analysed for solubility, pH effect, melting point, moisture content, powder flow properties, and compatibility with different carriers. The solubility of Lornoxicam was estimated in distilled water and pH 6.8 phosphate buffer medium; Lornoxicam showed higher solubility in pH 6.8 phosphate buffer than distilled water. The selection of polymers for the preparation of solid dispersions; hydrophilic carriers such as Poloxamer 188, Poloxamer 407, PEG 4000, PEG 6000, and PVP K-30 at different concentrations on the equilibration solubility of Lornoxicam in pH 6.8 phosphate buffer medium at room temperature was carried and found that the solubility of lornoxicam simultaneously increased with increasing carrier concentrations. The FTIR spectroscopic studies showed the stability of LOR. The DSC and XRD studies indicated that the Lornoxicam was in crystalline.

Keywords: *Lornoxicam, Solubility, Preformulation Study, Hydrophilic Carriers.*

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INTRODUCTION:

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. Preformulation testing is an analysis of the physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms. For low aqueous solubility drugs, the challenge of making solid dispersions is in choosing the amount of carrier that would increase the aqueous solubility while keeping the overall oral dosage size small[1-5]. Solubility parameters have been used to predict the solubility of the drug in a carrier which in turn determines the extent of solubility in an aqueous medium. Solubility parameters alone are not enough and other parameters such as crystallinity index can also be used to improve the drug solubility during formulation. This study used solubility parameters and crystallinity index to select carriers which increased the aqueous solubility of Lornoxicam.

Lornoxicam is an Oxicam and non-steroidal anti-inflammatory drug (NSAID), with analgesic, anti-pyretic, anti-thrombotic, and anti-inflammatory activities[6]. It belongs to Biopharmaceutical Classification System (BCS) - class II substance with low solubility and high permeability. It was reported low aqueous solubility (0.0385±0.01 mg/ml) at ambient temperature impairs its dissolution in the upper gastric fluid, which alters bioavailability and hinders its therapeutic application[7].

The main objective of the present research work was to do a preformulation study of Lornoxicam (LOR). In this research, the Lornoxicam was analyzed for solubility, pH effect, melting point, moisture content, powder flow properties, and compatibility with different carriers.

MATERIAL AND METHODS:

Materials

Lornoxicam was gifted by Shri Sai Krishna Enterprises, Kaplana Society, Chintal, Hyderabad, hydrophilic carriers such as Poloxamer 188, Poloxamer 407, PEG 4000, PEG 6000, and PVP K-30 purchased from S.D. Fine Chemicals Ltd. All other chemicals used were of analytical grade and procured from commercial sources.

Phase solubility analysis

The solubility of Lornoxicam was determined in water and pH 6.8 phosphate buffer medium. The effect of concentrations of carriers on the equilibration solubility of Lornoxicam in water and pH 6.8 phosphate buffer medium at room temperature was carried out by adding an excess quantity of drug (20 mg) into a screw-capped glass vial containing 20 ml of solvent with various concentrations of the carrier. The suspension was shaken for 24hrs on a rotary bath shaker & filtered through Whatman no.1 filter paper. The filtrate so obtained was diluted & analyzed spectrophotometrically. The free energy concept explains the process of spontaneity is associated by the free energy loss at a constant pressure & temperature. For the estimation of the spontaneity of in-vitro dissolution process, the values of Gibbs free energy (ΔGtr) were calculated for each carrier. The following equations were used for the calculation of the free energy of a system[8,9].

$$G=E+PV-TS$$
$$G=G_0+nRTlnP$$
$$\Delta G=-2.303RT \log s_0/s$$

Where, S_0=the solubility in presence of polymer,
S= Solubility without polymer
n = No. of moles and G = Free Energy.
R = Universal Gas Constant,

Melting point determination

The physical properties of a compound, such as melting point and boiling point can provide useful information which can help in the identification of a sample or establish its purity. The temperature at which a solid melts and becomes a liquid is the melting point. Since this requires that the intermolecular forces that hold the solid together have to be overcome, the temperature at which melting occurs will depend on the structure of the molecule involved - an example of the relationship between structure and properties. Hence, different compounds tend to have different melting points. The melting temperature of Lornoxicam was confirmed by differential scanning calorimetry (DSC).

Determination of moisture content

The moisture content of Lornoxicam was determined by Sartorius MA35 digital moisture analyzer. The analyzer warmed up for 30 minutes after initial connection to the power supply. The samples were placed in the sample pan in a thin, even layer. The moisture content of samples was determined at a temperature of 105° C[10].

Powder flow properties

The tapped density[11-13] and bulk density[14-17] of Lornoxicam was determined by using bulk density apparatus. Hausner's ratio and Carr's index were

determined by utilizing the acquired values of bulk density and tapped density. The angle of repose parameter of the drug was estimated by fixed funnel technique[18,19]

Compatibility studies

Compatibility studies between model drug and excipients were done by keeping the ingredients in a small USP type glass vial (10ml) relative humidity at 75± 5% and at temperature 40± 2ºC using a stability chamber (Thermo lab, India) for one month. Compatibility studies were completed with all the excipients[20-22].

Fourier transform infrared spectroscopy (FT-IR)

The FT-IR spectra were obtained using FT-IR spectrometer (Shimadzu). The sample was previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix in 1:5 (sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty-five scans were obtained at a resolution of 4 cm^{-1} from 4500 to 400 cm^{-1} [23-25].

Differential Scanning Calorimetry

The DSC measurements were performed on a Pyris Diamond TG/DTA differential scanning calorimeter with the thermal analyzer. Accurately weighed samples (about 5 mg) were placed in sealed aluminum pans. An empty aluminum pan was used as a reference[26-28].

X-ray diffraction

The X-ray powder diffraction (XRD) pattern of Lornoxicam was acquired by utilizing "Philips Holland PW 1710" with Cu Kα radiation and a crystal monochromator. The diffraction patterns keep running at 2^0/min in terms of 2θ angle[29].

RESULTS AND DISCUSSION:

Phase solubility study

The phase solubility studies of Lornoxicam was carried out in water and pH 6.8 phosphate buffer medium in presence of hydrophilic polymers at 25 ºC. The apparent solubility of Lornoxicam was found 0.071mg/mL and 0.068 mg/mL in pH 6.8 phosphate buffer and water respectively. For the selection of polymers for the preparation of solid dispersions; different polymers like PVP K30, PEG 4000, PEG 6000, Poloxamer 188 and Poloxamer 407 at different concentrations on the equilibration solubility of Lornoxicam in distilled water and pH 6.8 phosphate buffer medium at room temperature was carried and found that the solubility of Lornoxicam simultaneously increased with increasing carrier concentrations. Among all the hydrophilic carriers, poloxamer 407 and poloxamer 188 had shown the highest increase in solubility of Lornoxicam because poloxamer molecules exhibited an amphiphilic character in aqueous solution on the basis of the polyethylene oxide (PEO) solubility in water. The order of increased solubility for different hydrophilic carriers was found as poloxamer 188> poloxamer 407> PEG 6000> PEG 4000 > PVP K30. Using poloxamer 407 at highest concentration, the solubility increased about 8.26-fold in phosphate buffer pH 6.8 and 8.14 fold in distilled water as compared to pure Lornoxicam. So Poloxamer 188 and Poloxamer 407 were selected as hydrophilic carriers for the preparation of solid dispersions and further studies. The free energy concept explains the process of spontaneity is associated by the free energy loss at a constant pressure & temperature. The values of Gibbs free energy (ΔGtr_o) associated with the aqueous solubility of Lornoxicam in presence of hydrophilic carriers at various concentrations were all negative; indicating the spontaneous nature of Lornoxicam solubilization. The values decreased with increasing the hydrophilic carrier concentration. From the free energy curve, it was asserted that the increase in negativity of free energy values; solubility of Lornoxicam simultaneously increased. The phase solubility curve and free energy curve of Lornoxicam with various concentrations of hydrophilic polymers in pH 6.8 phosphate buffer medium are shown in figure 1 and 2 respectively.

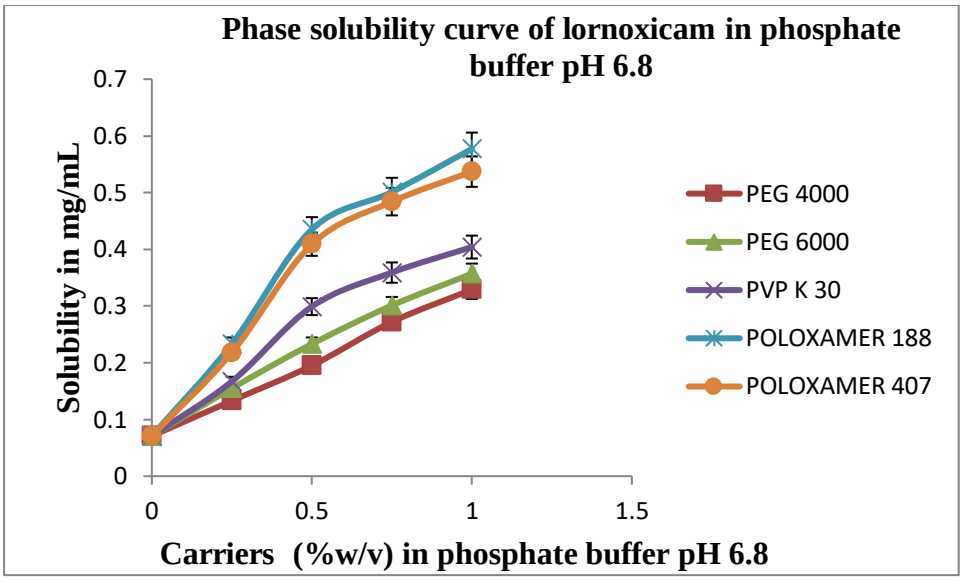

Figure 1: Phase solubility curve of Lornoxicam in phosphate buffer pH 6.8

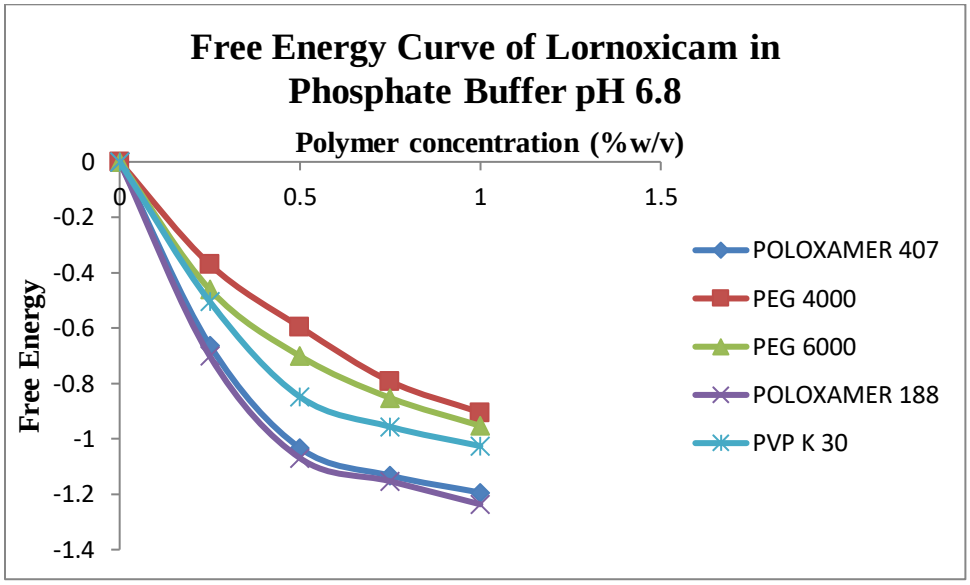

Figure 2: Free energy curve of Lornoxicam in phosphate buffer pH 6.8

Melting point determination: The melting temperature of Lornoxicam was confirmed by differential scanning calorimetry (DSC). A sharp endothermic peak was seen at 221.46ºC, which corresponded to the Lornoxicam melting point and is presented in **figure 4.** The melting point asserted that the Lornoxicam is thermally stable and appropriate for preparation of solid dispersions by fusion techniques.

Determination of moisture content: The moisture content of Lornoxicam was determined by Sartorius MA35 digital moisture analyzer and found to be 0.74 %. The result found in the moisture analysis of Lornoxicam asserted that the drug is non-hygroscopic in nature.

Powder flow properties: The parameters like Carr's index, Hausner's ratio, tapped density; bulk density and angle of repose were determined to observe the flow properties of Lornoxicam for simple in manufacturing of tablets by direct compression technique. The parameters of Lornoxicam were determined and are shown in **table 1**. The results of precompression parameter studies indicated that Lornoxicam showed excellent flow properties which support manufacturing of of Lornoxicam by direct compression technique.

Table 1: Powder flow properties of Lornoxicam

Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
0.496±0.08	0.583±0.14	23.34±0.17	14.92	1.17

Compatibility studies: No change was found in vials except in the vial (V6) contained PVP K30. More yellowish color was developed after 15 days. Hence PVP K30 vial was subjected to autoclaving for 15 minutes at 121^0C and 15ψ pressure. Performing autoclaving was to get relevance (high temperature and humidity) with compatibility study in a short interval. The resultant product after autoclaving was yellowish. So it was concluded that PVP K30 itself was changing color at high temperatures and humidity. No sign of incompatibility with Lornoxicam was found, hence selected. The observations are shown in **Table 2**.

Table 2: Data after storage at 40^0C and 75% relative humidity

Sl No	Content	1st day	3rd day	7th day	15th day	1 month
V1	Lornoxicam (LOR)	Slightly yellow	No change	No change	No change	No change
V2	LOR+ Poloxamer 188	Slightly yellow	No change	No change	No change	No change
V3	LOR+ Poloxamer 407	Slightly yellow	No change	No change	No change	No change
V4	LOR+PEG 4000	Slightly yellow	No change	No change	No change	No change
V5	LOR+PEG 4000	Slightly yellow	No change	No change	No change	No change
V6	LOR + PVP K30	Slightly yellow	No change	No change	**More Yellowish**	**More Yellowish**

Fourier transform infrared spectroscopy (FT-IR)

The characteristic peaks of Lornoxicam were at Aromatic-CH: 3100 cm -1, –NH: 3066 cm -1, -C=O: 1647 cm -1, -CONH-: 1594 cm -1, -SO2: 1327 cm -1,C-Cl: 790 cm -1. The observed peaks of Lornoxicam matched the reference. The observed peak is shown in **figure 3**.

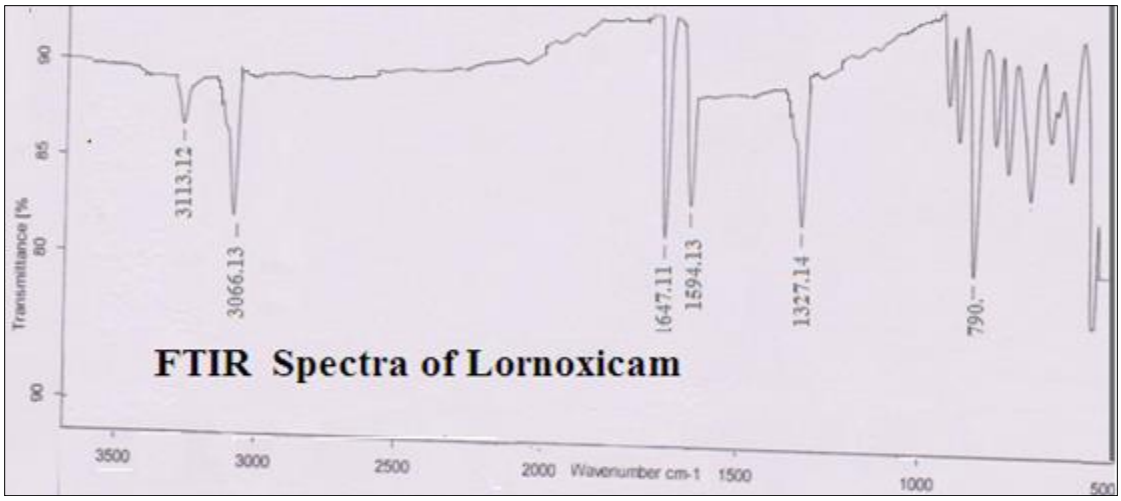

Figure 3: Fourier transform infrared spectroscopy (FT-IR)

Differential Scanning Calorimetry

DSC analysis was done for pure Lornoxicam is shown in **Figure 4**. The DSC thermogram of pure Lornoxicam showed a sharp endothermic peak at 221.46◦C, corresponding to its melting point.

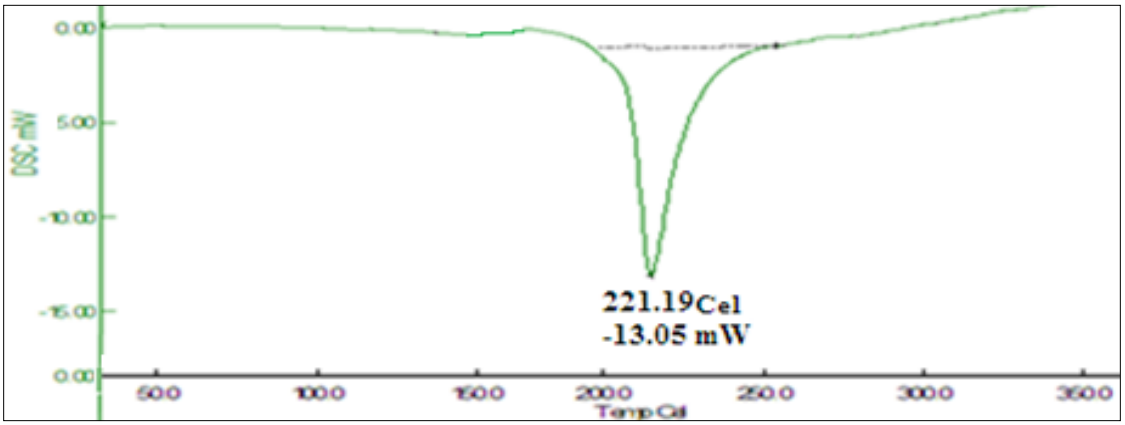

Figure 4: DSC thermogram of Lornoxicam

X-ray diffraction

The X-Ray diffraction pattern of pure Lornoxicam showed various diffraction peaks that were intense and sharp, indicating it crystalline nature. The diffraction pattern of Lornoxicam powder revealed several sharp high intensity peaks at diffraction angles 2θ of 7.9°, 12.3°, 14.5°, 18.2°, 22.2°, and 24.5°, 29.1°, 31.5° suggesting that it existed as a crystalline material. The X-Ray diffraction pattern of pure Lornoxicam is shown in **figure 5**.

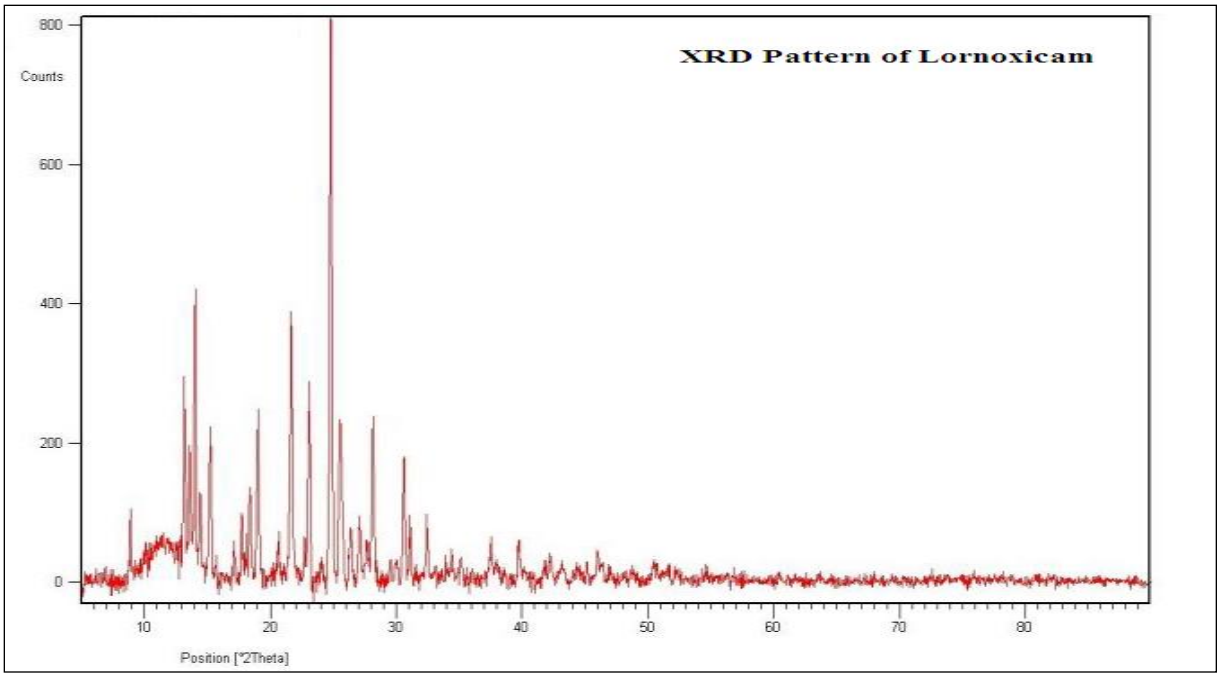

Figure 5: X-Ray diffraction pattern of pure Lornoxicam

CONCLUSION:

Preformulation testing is an analysis of the physical and chemical properties of a drug substance alone and when combined with excipients. In this research, the Lornoxicam was analysed for solubility, pH effect, melting point, moisture content, powder flow properties and compatibility with different carriers. The solubility of Lornoxicam was estimated in distilled water and pH 6.8 phosphate buffer medium; Lornoxicam showed better solubility in pH 6.8 phosphate buffer than distilled water. Among all the hydrophilic carriers, poloxamer 407 and poloxamer 188 had shown the highest increase in solubility of Lornoxicam. So Poloxamer 188 and Poloxamer 407 were selected as hydrophilic carriers for the preparation of solid dispersions and further studies. No sign of physical incompatibility was observed at relative humidity 75± 5% and temperature 40± 2ºC using stability chamber for one month. The FTIR spectroscopic studies showed the stability of LOR. The DSC and XRD studies indicated that the Lornoxicam was in crystalline form. Therefore, there is a strong need of enhancement of solubility Lornoxicam by solid dispersion technique by using hydrophilic carriers.

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