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IN VITRO DISSOLUTION ENHANCEMENT STUDIES ON BINARY SOLID DISPERSIONS OF LORNOXICAM

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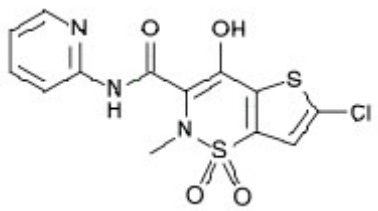
ABSTRACT
The poor solubility and wettability of a non steroidal anti-inflammatory drug, Lornoxicam leads to poor dissolution and hence, low bioavailability after oral administration. The objective of the study was to formulate solid dispersions of Lornoxicam to improve the aqueous solubility and dissolution rate to facilitate faster onset of action. Lornoxicam is a BCS class II drug having low aqueous solubility and therefore low bioavailability. In the present study, solid dispersions of Lornoxicam with three different hydrophilic polymers and one superdisintegrant in 4 drug-carrier ratios were prepared by solvent evaporation and common solvent methods. Solid dispersions were characterized by infrared spectroscopy (IR) and evaluated for drug content, dissolution rate constant, regression coefficient. The dissolution rate and dissolution efficiency of the prepared solid dispersions were evaluated in comparison to the corresponding pure drug. The *in-vitro* dissolution studied showed increased drug release rates compared to that of pure API alone. The increasing order of dissolution rate of solid dispersions Lornoxicam with various polymers was HPMC > PVP > PEG. The solid dispersions in combined carriers gave much higher rates of dissolution than superdisintegrants alone. Finally, *in-vitro* dissolution studies showed that Lornoxicam release was greatly improved by formation of solid dispersion. A 170.2 fold increase in the dissolution rate of Lornoxicam was observed with solid dispersions prepared using combined carriers such as HPMC, MCC whereas only a 15.78 fold increase was observed with solid dispersions prepared using only MCC. Thus, the solid dispersion technique can be successfully used for enhancement of dissolution rate.

Key words: *Lornoxicam; Solid dispersions; hydrophilic polymers; super disintegrants.*

INTRODUCTION

Lornoxicam (L) (6-Chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2*H*-thieno[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide) is a non steroidal anti-inflammatory drug (NSAID) that belongs to the class of oxicams. Lornoxicam is a highly selective COX-2 inhibitor used for a variety of acute and chronic inflammatory diseases[1] and in the management of preoperative and post operative pain associated with gynecological, orthopedic, abdominal and dental surgeries[2]. Its structural formula is given below:



Lornoxicam is insoluble in water and slightly soluble in simulated gastric fluid. Because of its poor aqueous solubility, Lornoxicam has limited dissolution rate[3] and thus delay in onset of action. Being a BCS class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in its solubility and bioavailability[4]. Aqueous solubility of any therapeutically active substance is a key property; it governs dissolution, absorption, and thus the *in vivo* efficacy[5]. To improve the dissolution and bioavailability of poorly water – soluble drugs, various techniques such as hot-melt extrusion[6], common solvent and solvent evaporation[7], cyclodextrin complexation[8], micronization[9], co-grinding[10], solubilization, salt formation, complexation with polymers[11], change in physical form, use of prodrug and drug derivatization, addition of surfactants have been employed. Chiou[12] and Sivert A[13] used the solid-dispersion technique for enhancing dissolution of poorly water soluble drugs. Preparation of solid dispersion is a technique that provides deposition of the drug on the surface of certain materials that can alter the dissolution characteristics of the drug. Deposition of drug on the surface of an inert carrier leads to a reduction in the particle size of the drug, thereby providing a faster dissolution rate. Various hydrophilic materials with high surface area

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can be utilized for deposition of the drug on their surfaces[14]. Surface modification and solid-dispersion formulations using hydrophilic excipients can significantly alter the dissolution behavior of hydrophobic drug materials. A number of insoluble drugs have been shown to have improved dissolution character when converted to solid dispersion. Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers[15]. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water soluble drug is increasing[16,17]. Various hydrophilic carriers such as polyethylene glycol have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs[18].

MATERIALS AND METHODS

Lornoxicam was a gift sample provided by Sun Pharmaceuticals, Vadodara, India and all other materials were of pharmacopoeial grade and procured from commercial sources.

PREPARATION OF SOLID DISPERSIONS

Preparation Employing Superdisintegrants

Solid dispersions of Lornoxicam in superdisintegrants were prepared by solvent evaporation method. The required quantities of drug were dissolved in methanol to get a clear solution in a dry mortar. The superdisintegrants (passed through 120 mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 50°C for 4 hours in an oven. The product was crushed, pulverized and sifted through mesh no.100. The different preparations of Lornoxicam were shown in the Table 1.

Sl. No.	Composition		
	Drug	Carriers	SD Code
1.	Lornoxicam (2)	PEG(2), MCC (6)	L-PEG-MCC, 226
2.	Lornoxicam (2)	PVP (2), MCC(6)	L-PVP-MCC, 226
3.	Lornoxicam (2)	HPMC (2), MCC (6)	L-HPMC-MCC, 226
4.	Lornoxicam (1)	MCC(4)	L-MCC, 14

Table 1: *Lornoxicam Content of various Solid dispersions*

Estimation of Lornoxicam

A spectrophotometric method based on the measurement of absorbance at 376 nm in 0.1 N HCl, pH 1.2 was used in the present study for the estimation of Lornoxicam. The stock solution of Lornoxicam was subsequently diluted to a series of dilutions containing 2,4,6,8 and 10 mg/ml of solution, using 0.1 N HCl. The absorbance of these solutions was measured in UV-VIS spectrophotometer (ELICO SL - 159) at 376 nm against same dilution as blank[19]. The absorbances relating to different concentrations of Lornoxicam in 0.1 N HCl, .The present analytical method obeyed Beer's law in the concentration range of 2-10 mg/ml and is suitable for the estimation of Lornoxicam from different solutions.

Estimation of Lornoxicam in solid dispersions

From each batch, 4 samples of 50 mg were taken and analyzed for Lornoxicam. 50 mg of dispersion was weighed and transferred into a 100 ml volumetric flask. Methanol was added and mixed the contents thoroughly to dissolve the drug from the dispersion. The solution was then filtered and collected carefully into another 100 ml volumetric flask. The solution was made up to volume with the solvent. The solution was suitably diluted with 0.1 N HCl of pH 1.2 and assayed at 376 nm for Lornoxicam.

Fourier-transform infrared spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FT-IR) has been used to assess the interaction between Lornoxicam and polymers in the solid state. The samples were scanned over the frequency range of 4000-500 cm^{-1}. The chemical interaction between the drug and the carrier often leads to identifiable changes in the infrared (IR) profile of the solid complexes[20]. The principal peaks corresponded to the structural features of Lornoxicam are found due to O-H stretching at 3215.39 cm^{-1}, N-H stretching at 3061 cm^{-1}, Aromatic C-H stretching at 2814 cm^{-1}, secondary amide stretching at 1590 cm^{-1}, 1532 cm^{-1}, R-SO_2-R stretching at 1144 cm^{-1}, 1322 cm^{-1}, 1377 cm^{-1}, stretching at 827 cm^{-1} due to C-H aromatic ring bending and –CCl stretching at 785 cm^{-1}. Any sign of interaction would be reflected by changes in the characteristic peaks of Lornoxicam depending on the extent of interaction. In IR study solid dispersions showed combination of the peaks of Lornoxicam and carrier. The overlays of IR spectra are presented in Fig. 1. The FT-IR spectra of solid dispersions were compared to the Lornoxicam. In all the cases the characteristic bands of Lornoxicam confirm the existence of the drug in its unaltered form. The FT-IR spectra of solid dispersions of Lornoxicam showed almost all the bands of Lornoxicam, without affecting its peak position and trends, which indicated the absence of well defined interactions between Lornoxicam, HPMC and MCC.

Dissolution Rate Study

Dissolution rate of Lornoxicam solid dispersions were studied using an USP XXIII six station dissolution rate test type II apparatus (Electro Lab). The dissolution rate was studied in 900 ml of simulated gastric fluid without enzyme pH 1.2 at a paddle speed of 100 rpm and a temperature of $37^0 \pm 1^0C$ [21]. Lornoxicam or solid dispersion of Lornoxicam equivalent to 8 mg of drug was used in each dissolution rate test. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45 µ) at different time intervals, suitably diluted, and assayed for Lornoxicam. The dissolution experiments were conducted in triplicate and their results are given in Table 2. Dissolution rates of Lornoxicam and its solid dispersions followed first order kinetics. The dissolution profiles of various solid

dispersions are shown in Figure 2. Dissolution parameters such as $T_{50,}$ DE_{30} and K_1 are given in Table 3.

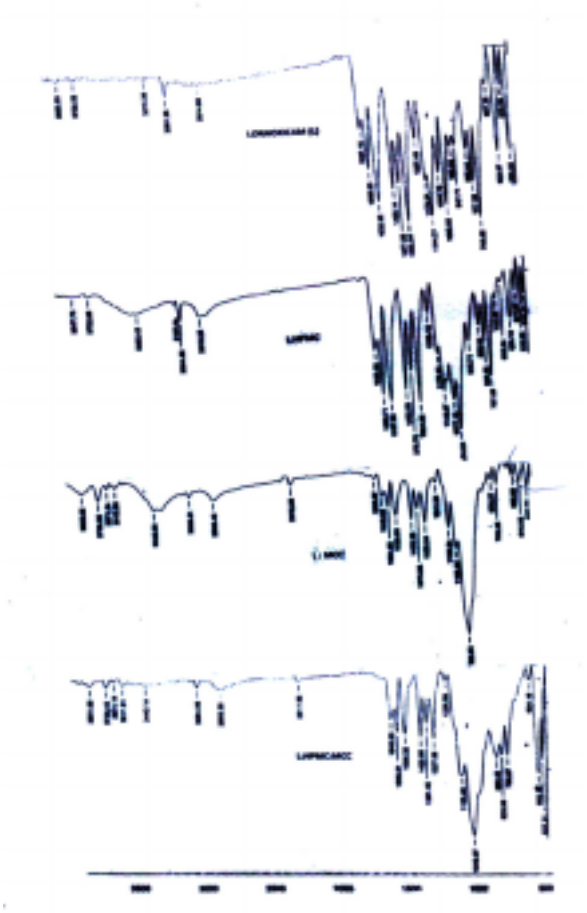

Fig. 1 : *FTIR Spectra of (i) Lornoxicam (ii) Lornoxicam : HPMC (iii) Lornoxicam : MCC (iv) Lornoxicam : HPMC : MCC*

Table 2: *Dissolution Profiles of Lornoxicam Solid Dispersions*

Time (min)	Percent Lornoxicam Dissolved ($\bar{x} \pm s.d.$,)				
	L	L-PEG-MCC 226	L-PVP-MCC 226	L-HPMC-MCC 226	L- MCC 14
5	1.32±0.3	40.9±0.5	65.3±0.67	85.9±0.88	35.9±0.67
10	1.73±0.8	42.2±0.6	68.7±0.65	88.3±0.86	37.9±0.65
20	2.12±0.6	43.3±0.46	70.1±0.89	94.5±0.87	39.5±0.67
30	2.31±0.7	55.6±0.89	70.3±0.99	95.3±0.76	40.1±0.78
45	3.14±0.3	57.6±0.77	70.6±0.76	96.4±0.76	40.2±0.75
60	5.21±0.4	60.2±0.65	70.8±0.65	97.3±0.88	40.3±0.76
90	6.13±0.5	62.3±0.86	70.8±0.49	98.5±0.48	40.6±0.76
120	8.24±0.3	63.5±0.76	70.8±0.89	99.2±0.78	40.9±0.77

RESULTS AND DISCUSSION

All the estimated dissolution parameters indicate rapid and higher dissolution of Lornoxicam from all solid dispersions when compared to Lornoxicam. pure drug. The dissolution profiles of various solid dispersions are shown in Fig 2. L-HPMC-MCC (2:2:6) solid dispersion gave rapid and higher dissolution than the pure drug. Combined carriers gave much higher enhancement in the dissolution rate of than water dispersible carriers

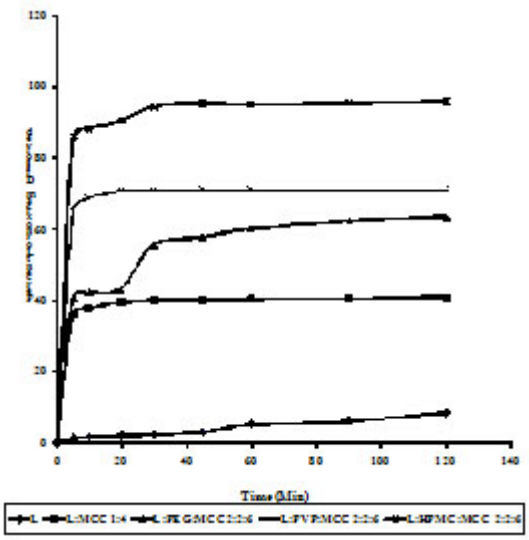

Fig. 2 : *Dissolution Profiles of Lornoxicam and its solid dispersions*

Table 3: *Dissolution Parameters of Lornoxicam and its Solid Dispersions in Superdisintegrants*

Sl. No.	Solid Dispersion	Dissolution Parameter			
		T_{50} (min)	DE_{30} (%)	K_1 (min^{-1})	No. of folds increase in K_1
1.	Lornoxicam	>120	1.74	0.00076	-
2.	L-PEG-MCC, 226	25	41.06	0.021	27.63
3.	L-PVP-MCC, 226	4.3	63.14	0.051	67.53
4.	L-HPMC-MCC, 226	03	83.77	0.129	170.2
5.	L-MCC, 14	>120	35.31	0.012	15.78

alone. Solid dispersions of superdisintegrants and combined carriers gave rapid and higher dissolution of Lornoxicam. when compared to pure drug. In each case, the K_1 and DE_{30} values were increased. All the solid dispersions in combined carriers gave much higher rates of dissolution, several times higher than the dissolution rate of pure drug. L-HPMC-MCC 226 solid dispersion gave a 170.2 fold increase in the dissolution rate of Lornoxicam whereas solid dispersion of Lornoxicam in MCC alone (L-MCC 14 solid dispersion) gave only 15.78 fold increase. Thus combination of superdisintegrants with water soluble carriers PEG, PVP, HPMC resulted in a greater enhancement in the dissolution rate of Lornoxicam.

The dissolution data were fitted into zero order, first order, and Hixson-crowell models to assess the kinetics and mechanism of dissolution. The kinetic model that best fits the dissolution data was evaluated by comparing the correlation coefficient (r) values obtained in various models. The model that gave higher 'r' value is considered as the best fit model. The correlation coefficient (r) values obtained in the analysis of dissolution data as per different models are given in Table 4. The 'r' values were higher in the first order model than those in the zero order models with all the solid dispersions of Lornoxicam, indicating that the dissolution of Lornoxicam from all the solid dispersions

followed first order kinetics. Dissolution of Lornoxicam from all the solid dispersions followed first order kinetics with correlation coefficient 'r' above 0.8 (Table 4).

The first order dissolution plots of various solid dispersions are shown in Fig. 3. The dissolution parameters (K_1, DE_{30} and T_{50}) indicated rapid and higher dissolution of Lornoxicam from solid dispersions when compared to plain drug. The increasing order of dissolution rate of Lornoxicam from solid dispersions observed with various hydrophilic polymers was HPMC>PVP>PEG. The dissolution data of Lornoxicam

Table 4: *The Correlation Coefficient (r) values in the Analysis of Dissolution Data of Lornoxicam Solid Dispersions as per Zero order, First Order and Hixson-Crowell Cube Root Models*

Sl. No.	Solid Dispersion	Correlation coeffcient (r) value		
		Zero order	First order	Hixson-Crowell
1.	Lornoxicam	0.935	0.988	0.987
2.	L-PEG-MCC, 226	0.778	0.837	0.885
3.	L-PVP-MCC, 226	0.721	0.755	0.741
4.	L-HPMC-MCC, 226	0.739	0.862	0.825
5.	L-MCC, 14	0.465	0.691	0.892

and their solid dispersions were also analyzed as per Hixson-Crowell's[22] cube root equation. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the cube-root law to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell plots of the dissolution data were found to be linear (Fig. 4) with all solid dispersions. The increasing order of dissolution rates of solid dispersions of Lornoxicam are comparable with solid dispersions of raloxifene-crospovidone[23] atorvastatin-beta cyclodextrin[24] complexation curcumin-cellulose acetate solid dispersion[25] Etodolac solid dispersion with cyclodextrin[26] Etodolac-PEG solid dispersion[27]. The solid dispersions of Lornoxicam

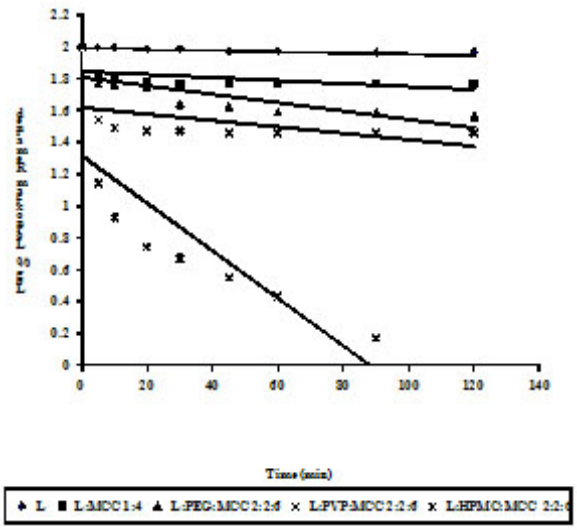

Fig. 3 *: First Order dissolution plots of Lornoxicam and its solid dispersions*

provide rapid dissolution rate by one or more of the following mechanisms :

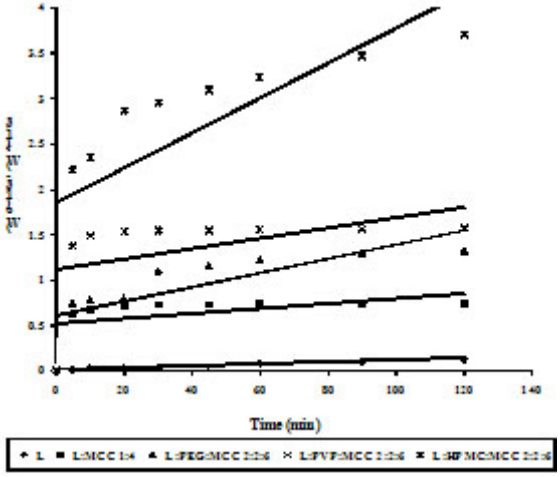

Fig. 4 : *Hixson-Crowell Dissolution Plots of Lornoxicam and its Solid Dispersions*

(i) **Particle size reduction**: Solid dispersions achieve faster dissolution rates as the drug undergoes micronization while depositing over the surface of the excipient. As Lornoxicam and carriers (MCC) are dispersed at molecular level in a solid dispersion it releases very fine particles of the drug when the carrier molecules readily dissolve in the aqueous fluids.

(ii) **Improving the wettability of the particles**: Wetting of powders is the primary condition for them to disperse and dissolve in body fluids [28]. The presence of water soluble carriers (HPMC, PVP, PEG) improves the wettability of hydrophobic drug particles.

(iii) **Conversion of crystalline drugs into amorphous form**: Solid dispersions of Lornoxicam may convert a crystalline drug into amorphous form. Since the amorphous form is the highest energy form of a pure compound it produces faster dissolution.

(iv) **Solubilizing effect** of the carriers (PVP, HPMC, PEG, DCP) by promoting wetting through increase in effective surface area.

CONCLUSION

The dissolution rate and dissolution efficiency of Lornoxicam could be enhanced several times by their solid dispersion in superdisintegrants alone and in combination with hydrophilic polymers such as PEG, PVP and HPMC. Superdisintegrants particularly microcrystalline cellulose (MCC) was found to be good carrier giving solid dispersions with enhanced dissolution rate and efficiency, several times higher than those of pure drug. Thus, solid dispersion in

superdisintegrants is recommended as an effective and efficient technique for enhancing the dissolution rate, dissolution efficiency of Lornoxicam. Super-disintegrants are inert, safe and non-toxic excipients that are currently used in compressed tablet formulations as disintegrants. These can be used as efficient carriers in solid dispersion techniques to enhance the dissolution rate of insoluble and poorly soluble drugs.

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