Global Journal of Pharmacology 8 (4): 601-608, 2014
ISSN 1992-0075

DOI: 10.5829/idosi.gjp.2014.8.4.83203

Improving the Solubility and Dissolution Rate of Poorly Water Soluble Lornoxicam by Solid Dispersion Method and to Compare Effectiveness of Hydrophilic Polymers

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Abstract: The present study was an attempt to improve the solubility and dissolution rate of poorly water soluble drug Lornoxicam by solid dispersion method and to compare effectiveness of hydrophilic polymers. Resultant solid dispersions to be evaluated for drug content Infrared spectroscopy, Differential scanning colorimetry, X-Ray Diffraction and Dissolution studies. A poorly water soluble drug needs a great understanding of dissolution and absorption behaviour to successfully formulate them into bioavailable drug products. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. Lornoxicam solid dispersions were prepared by solvent evaporation method, using super disintegrants like PGS, HPMC, MCCP, DCP. A series of formulations were formulated and characterized for their in vitro drug release studies. Among all the super disintegrants used in formulated lornoxicam solid dispersions HPMC shows the highest dissolution rate of lornoxicam than MCCP, PGS, DCP. The increase in dissolution rate of drug may be due to increase in wettability, hydrophilic nature of the carrier and also due to usage of super disintegrant and also possibly due to reduction in drug crystallinity. By this it was concluded that solid dispersion technique was more suitable for increasing the solubility and dissolution rate of poorly soluble drugs like lornoxicam.

Key words: Lornoxicam · Solid dispersion · Soluble carriers · Combined carriers · Super disintegrants · content percentage drug · Infra-red spectroscopy · Rheumatoid arthrtis

INTRODUCTION

Lornoxicam is a non-steroidal anti-inflammatory drug of the oxicam class it is widely used as analgesic (Pain relieving) anti-inflammatory and antipyretic (fever reducing) Properties. It is used for the treatment of various types of pain, resulting from osteoarthritis, ankylosing spondylitis, chronic low back pain, surgery, sciatica inflammatory diseases of the joint and other inflammations [1]. It is manufactured by Optimus Pharma, under the tradename Xefo in various forms (tablets, injection etc.). It shows its effect by inhibiting the synthesis of cyclooxygenase and polymorphoneuclear (PMN) - leukocyte migration. It also inhibits the release of superoxide from human PMN-leukocytes, Inhibits release of platelet derived growth factor (PDGF) from human platelets and stimulates the synthesis of proteoglycans in cartilage but it does not inhibit the synthesis of 5-lipoxygenase [2]. Lornoxicam absorbed from gastrointestinal tract but has poor water solubility and low dissolution rate, due to this according to biopharmaceutical classification system most of the NSAIDs are place under class II. Rate of absorption and/or extent of bioavailability for such hydrophobic drugs are controlled by rate of dissolution in gastrointestinal fluids as they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. It is mostly given orally in a dose of 4mg twice or thrice a day. Its plasma concentration is found to be 280mg/l within 2.5 hours after single

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administration of 4mg [3]. Dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°), due to erratic or incomplete absorption from GIT. The bioavailability of these drugs can be improved by improving the drug wettability this can be achieved by solid dispersion method as in this method the solid particles are reduced to absolute minimum therefore it proves to be a promising strategy to improve oral bioavailability for Poorly water soluble drugs. In the present study the solubility and dissolution rate of poorly water soluble drug Lornoxicam is improved by solid dispersion method by employing soluble carriers (PVP), superdisintegrants (PEG) and (Pregelatinised starch) and by employing combined carriers and the effectiveness of hydrophilic polymers is compared. Resultant solid dispersions to be evaluated for drug content Infrared spectroscopy, Differential scanning colorimetry, X-Ray Diffraction and Dissolution studies.

MATERIALS AND METHODS

Lornoxicam- Obtained as a gift sample from Hetero drugs limited, Hyderabad, India.

Sodium hydroxide (NaOH), Potassium dihydrogen phosphate (KH2PO4)- Hydroxy propyl methyl cellulose (HPMC), Micro crystalline cellulose (MCC), Poly vinyl pyrrolidine (PVP) Poly ethylene glycol(PEG), Dicalcium phosphate (DCP), Pregelatinised starch (PGS), Methanol and All other materials used were of pharmacopoeial grade. They were procured from commercial sources.

Preparation of Solid Dispersions Employing Soluble Carriers (PVP): Solid Dispersions of Lornoxicam were prepared by common solvent method employing methanol as solvent for lornoxicam solid dispersions. The required quantities of drug and carrier were weighed and dissolved in the corresponding solvent in a round bottom flask to get a clear solution. The solvent was then removed by evaporation under reduced pressure (vaccum) at 60°C with constant mixing. The mass obtained was crushed pulverized and shifted through mesh no.100. In each case solid dispersions were prepared in the ratio of drug carrier namely 8:2 [4].

Preparation of Solid Dispersions Employing Superdisintegrants (PEG and Pregelatinised Starch): Solid dispersions of Lornoxicam in superdisintegrants, polyetheleneglycol (PEG), (pregelatinised starch) were prepared by solvent evaporation method [5]. The required quantity of drug was dissolved in methanol to get a clear solution in a dry mortar. The super disintegrant (passed through 120 #) 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 shifted through mesh no.100. In each case solid dispersions in the superdisintegrants were prepared at three different ratios of drug excipient namely 1:1, 1:2 and 1:4 respectively.

Preparation of Solid Dispersions Employing Combined Carriers: The required quantities of drug and water soluble carriers (PEG, PVP, HPMC) were dissolved in the solvent to get a clear solution in a dry mortar. The super disintegrant was then added to the drug solution and dispersed. The solvent was then evaporated 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 a oven [6,7]. The product was crushed, pulverized and shifted through mesh N0. 100.

Determination of Percentage Drug Content: From each batch, 4 samples of 50 mg of Lornoxicam each were taken and analysed for the drug 50 mg dispersions were weighed 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 upto volume with the solvent. The solution was suitably diluted with appropriate dissolution fluid and assayed at 376 nm for Lornoxicam.

$$\text{Percent drug content} = \frac{\text{Pradtical drug content in solid dispersions}}{\text{Theoretical drug content in solid dispersion}}$$

***In vitro* Dissolution Study [8, 9]:** Dissolution rate of Lornoxicam was studied using an USP XXIII six station dissolution rate test apparatus (Electro Lab). Drug or solid dispersion of drug equivalent to 8 mg of Lornoxicam was used in each dissolution rate test. 8 mg of pure drug and solid dispersions were weighed and transferred to the dissolution flask containing 900 ml of Phosphate buffer pH 7.4. Temperature of 37° ± 1°C was maintained for each test. Paddle stirrer was used at a speed of 50 rpm. About 5ml samples of dissolution medium were withdrawn through a filter (0.45 µ) at different time intervals and were appropriately diluted and assayed for Lornoxicam.

Drug	Dissolution Fluid Used
Lornoxicam	Phosphate buffer of pH 7.4 (900 ml)

Characterization

Infra-Red Spectroscopy: The IR spectra were recorded using an FTIR spectrophotometer (Thremo nicolate nexus 670 spectrometer).The samples were scanned over the frequency range of 4000-400/cm. KBr pellet method was employed to detect chemical interaction between drug and polymer [10-13].

X-Ray Diffractometry: The XRD was carried out for lornoxicam, HPMC and DCP by using CUkA source operated at 40kV, 20 mA, 3°/min scanning rate and 3° to 40° (2q) range (JDX 8030, Jeol, Japan). The positions and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier patterns of the solid dispersions [14].

Diffential Scanning Calorimetry (DSC): The DSC thermograms of the samples were recorded using a differential scanning calorimeter (DSC 823e, mettler toledo star system) approximately 2-5 mg of each sample was heated in a pierced aluminium pan from 25°C to 350°C at a heating rate of 10°c/min under a stream of nitrogen.the DSC thermograms of pure lornoxicam, solid dispersions prepared using HPMC and DCP [15].

RESULTS AND DISCUSSION

A total of twelve formulations were formulated and characterized for their in vitro drug release studies. Table 1 shows the list of solid dispersion and their composition. Among these twelve formulation maximum yield was found to be 86.07% from tablets prepared from L-13 and of 70.40% from L-3. Table 2 shows the content of lornoxicam in each solid dispersion the percentage drug content was found to be 20% in L-06, L-04, L-05, L-13, L-14, L-16, L-17, L-19, L-20 and L-21. Table 3, 4, 5 and 6 shows the percentage lornoxaicam dissolved. Among all formulations solid dispersions prepared by combined carriers showed better dissolution profile of 95 ±5 %, compared to the formulation using using a PVP and PEG alone. From the results obtained it is clear that the dissolution of lornoxicam has improved considerably from DCP and PGS solid dispersions as compared to PVP and PEG-4000 solid dispersions. The reason for the poor dissolution of pure drug could be poor wettability and/or agglomeration of particles. Invitro release studies reveals that there is marked increase in the dissolution rate of lornoxicam from all the solid dispersions when compared to pure loraxicam itself Figure 1, 2, 3, 4 and Table 7 shows dissolution Profiles of lornoxicam and its Solid Dispersions in Comparison to lornoxicam Pure Drug. The increase in dissolution rate of drug may be due to increase in wettability, hydrophilic nature of the carrier and also due to usage of super disintegrant and also possibly due to reduction in drug crystallinity.

Table 1: List of Lornoxicam Solid Dispersions Prepared and their Composition

S.No	Drug	Carriers	SD Code
1.	Lornoxicam	MCC(6)	L-01
2.	Lornoxicam	DCP(6)	L-03
3.	Lornoxicam	MCC(4)	L-04
4.	Lornoxicam	PGS(4)	L-05
5.	Lornoxicam	DCP(4)	L-06
6.	Lornoxicam	HPMC(1)	L-09
7.	Lornoxicam	PEG(2) MCC(6)	L-13
8.	Lornoxicam	PVP(2) MCC (6)	L-14
9.	Lornoxicam	PEG(2)DCP(6)	L-15
10.	Lornoxicam	PVP(2) DCP6)	L-16
11.	Lornoxicam	PEG (2) PGS(6)	L-17
12.	Lornoxicam	PVP(2)PGS(6)	L-18
13.	Lornoxicam	HPMC(2) DCP(6)	L-19
14.	Lornoxicam	HPMC(2) PGS(6)	L-20
15.	Lornoxicam	HPMC(2) MCC(6)	L-21
16.	Lornoxicam	PEG(2)MCC(10)	L-22
17	Lornoxicam	PVP(2) MCC(10)	L-27
18	Lornoxicam	HPMC(2) PGS(10)	L-29
19	Lornoxicam	HPMC(2) MCC(10)	L-30

Table 2: Lornoxicam Content in Various Solid Dispersions Prepared

S.No.	SD Code	Percent Lornoxicam Content
1.	L-01	14.28
2.	L-03	14.28
3.	L-04	20.00
4	L-05	20.00
5.	L-06	20.00
6.	L-09	18.33
7.	L-13	20.00
9.	L-15	20.00
10.	L-16	20.00
11.	L-17	20.00
12.	L-18	20.00
13.	L-19	20.00
14.	L-20	20.00
15.	L-21	20.00
16	L-22	20.00
17.	L-27	14.28
18.	L-29	14.28
19.	L-30	14.28

Table 3: Dissolution Profiles of Lornoxicam Solid Dispersions

	Percent Lornoxicam Dissolved				
Time (min)	L	L-01 L:MCC 1:4	L-13 L:PEG:MCC 2:2:6	L-14 L:PVP:MCC 2:2:6	L-21 L:HPMC:MCC 2:2:6
5	5.3	35.99	65.28	34.91	85.96
10	13.4	38.95	68.76	40.29	94.55
20	21.49	39.48	70.11	40.30	95.32
30	21.56	40.02	70.12	40.32	96.43
45	26.86	40.06	70.21	40.43	98.54
60	29.54	40.08	70.32	40.54	99.89

Table 4: Dissolution Profiles of Lornoxicam Solid Dispersions

Time (min)	L	L-6 L:DCP 1:4	L-15 L:PEG:DCP 2:2:6	L-16 L:PVP:DCP 2:2:6	L-19 L:HPMC:DCP 2:2:6
5	5.3	30.89	69.15	58.02	80.96
10	13.4	30.62	79.78	97.76	96.92
20	21.49	33.84	79.98	97.78	96.99
30	21.56	37.07	80.0	98.89	97.99
45	26.86	37.06	80.12	98.9	99.0
60	29.54	38.68	80.23	99.99	99.98

Table 5: Dissolution Profiles of Lornoxicam Solid Dispersions

	Percent Lornoxicam Dissolved				
Time (min)	L	L-05 L:PGS 1:4	L-17 L:PEG:PGS 2:2:6	L-18 L:PVP:PGS 2:2:6	L-20 L:HPMC:PGS 2:2:6
5	5.3	21.75	39.75	56.02	82.12
10	13.4	21.78	47.50	65.82	91.32
20	21.49	21.85	55.00	72.63	99.80
30	21.56	21.90	58.25	77.65	99.82
45	26.86	21.92	59.00	80.32	99.89
60	29.54	22.00	59.02	82.31	100.00

Table 6: Dissolution Profiles of Lornoxicam Solid Dispersions

	Percent Lornoxicam Dissolved				
Time (min)	L	L-01 L:MCC 1:6	L-22 L:PEG:MCC 2:2:10	L-27 L:PVP:MCC 2:2:10	L-30 L:HPMC:MCC 2:2:10
5	5.3	68.49	48.73	96.87	72.71
10	13.4	67.69	63.72	97.87	80.97
20	21.49	68.69	64.85	97.98	82.91
30	21.86	69.50	68.83	98.85	85.92
45	26.86	72.37	71.63	99.00	92.97
60	29.54	77.34	73.54	100.00	97.00

Table 7: Dissolution Parameters of Lornoxicam and its Solid Dispersions in Superdisintegrants

		Dissolution Parameter			
Sl. No.	Solid Dispersion	T_{50} (min)	% Dissolved in 10 min	DE_{30} (%)	K_1 (min^{-1})
1.	L-01	> 60 min	-	67.15	-
2.	L-02	<120	36.30	20.14	0.031
3.	L-03	<5	66.87	61.26	0.110
4.	L-04	<120	38.95	35.56	0.102
5.	L-05	>120	21.75	46.54	0.025
6.	L-09	>120	27.66	27.06	0.030
7.	L-13	<5	68.76	63.12	0.117
8.	L-14	<120	40.26	36.21	0.052
9.	L-16	<5	97.70	88.05	0.382
10	L-17	<10	47.50	35.27	0.064
11	L-19	<5	96.92	87.72	0.350
12.	L-20	<5	91.32	86.51	0.246
13.	L-21	<5	94.55	88.09	0.290
14	L-27	> 60		90.94	

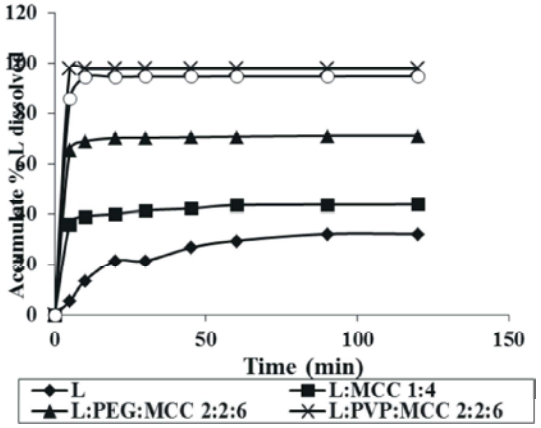

Fig. 1: Dissolution Profiles of Lornoxicam and its Solid Dispersions in Comparison to Lornoxicam Pure Drug

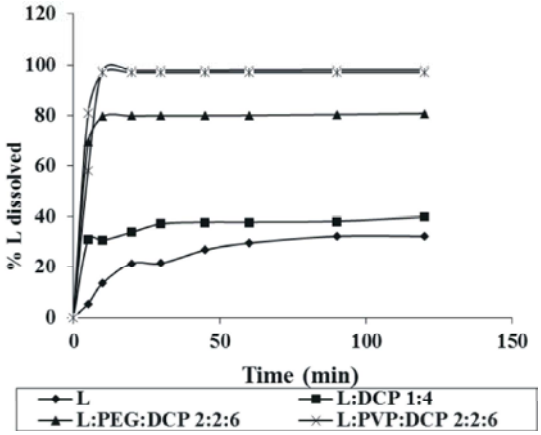

Fig. 2: Dissolution Profiles of Lornnoxicam and its Solid Dispersions in Comparison to Lornoxicam Pure Drug

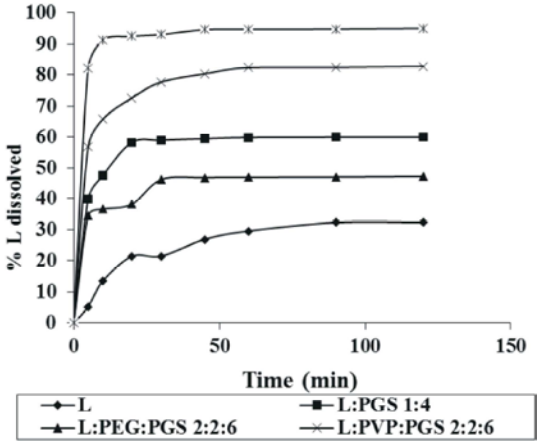

Fig. 3: Dissolution Profiles of Lornoxicam and its Solid Dispersions in Comparison to Lornoxicam Pure Drug

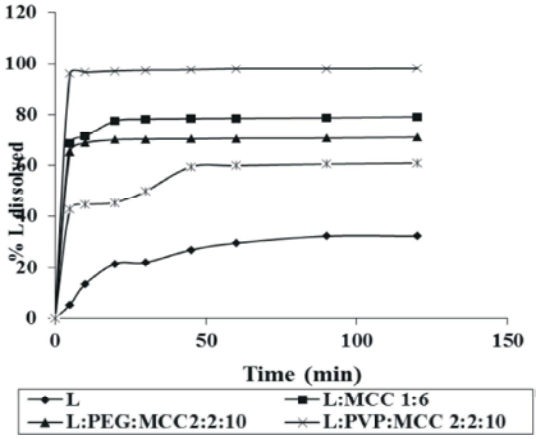

Fig. 4: Dissolution Profiles of Lornoxicam and its Solid Dispersions in Comparison to Lornoxicam Pure Drug

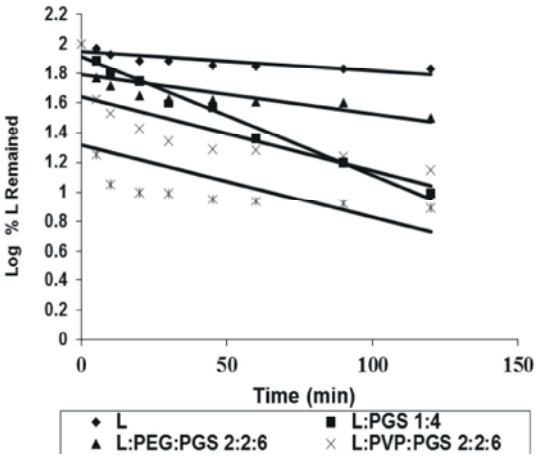

Fig. 5: First Order Dissolution Plots of Lornoxicam and its Solid Dispersions

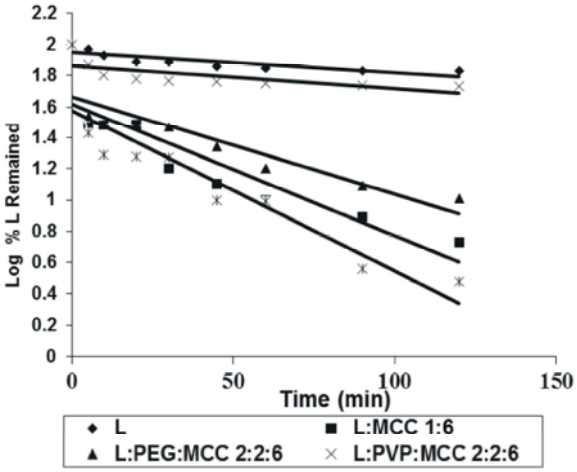

Fig. 6: First Order Dissolution Plots of Lornoxicam and its Solid Dispersions

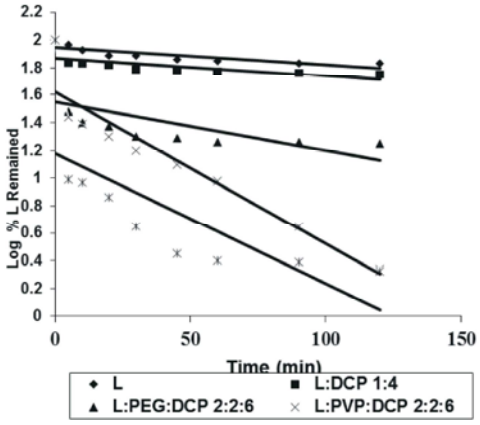

Fig. 7: First Order Dissolution Plots of Lornoxicam and its Solid Dispersion

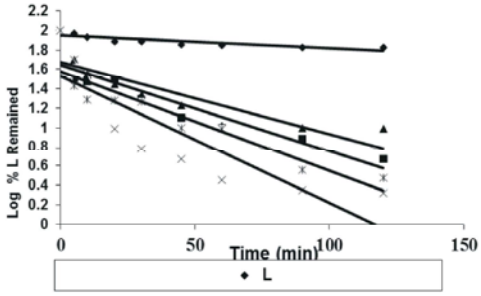

Fig. 8: First Order Dissolution Plots of Lornoxicam and its Solid Dispersions

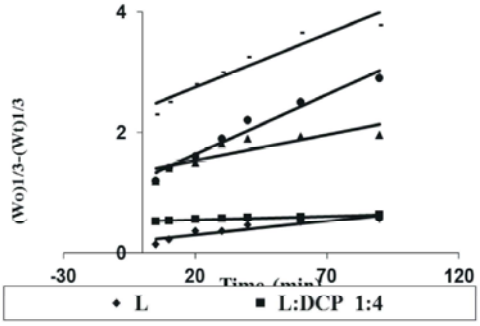

Fig. 9: Hixson-Crowell Dissolution Plots of Lornoxicam and its Solid Dispersions

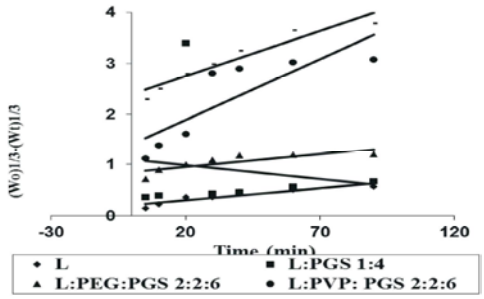

Fig. 10: Hixson-Crowell Dissolution Plots of Lornoxicam and its Solid Dispersions

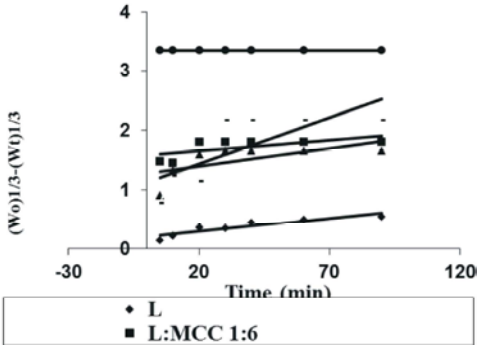

Fig. 11: Hixson-Crowell Dissolution Plots of Lornoxicam and its Solid Dispersions

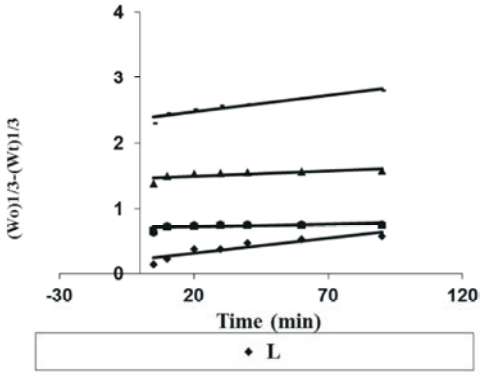

Fig. 12: Hixson-Crowell Dissolution Plots of Lornoxicam and its Solid Dispersions

The data obtained from x-ray diffraction study revel that the solid dispersions have reduced crystallinity when compared to pure lornoxicam. The mechanism and kinetics of lornoxicam from lornoxicam solid dispersion were evaluated using various mathematical models like zero order, first order, Hixson-Crowell model.

Among all the super disintegrants used in formulated lornoxicam solid dispersions HPMC shows the highest dissolution rate of lornoxicam than MCCP, PGS, DCP.

From the above results, it was concluded that solid dispersion technique was more suitable for increasing the solubility and dissolution rate of poorly soluble drugs like lornoxicam.

Zero-order model: @@ = @@0@@, where @@ represents the fraction of drug released in time @@ and @@0 is the apparent release rate constant or zero-order release constant.

First-order model: l n (1 - @@) = - @@ 1s t@@, where @@ represents the fraction of drug released in time @@ and @@ 1 is the first-order release constant. The graphs is plotted against time and log percentage loroxicam remained and are represented in Figure 5, 6, 7 and 8.

Hixson-Crowell model: @@ 0 1 / 3- @@@@ 1 / 3= @@ @@, where @@ 0 and @@@@ represent initial mass and mass remained at time @@, respectively; @@ H C is the rate constant. Table 8 show the results of the curve fitting into these above-mentioned mathematical models indicate the release behaviour of lornoxicam from these newly prepared solid dispersions. When the correlation coefficients of these mathematical models for lornoxicam release were compared, it was found to follow Hixson-Crowell model with the best-fit correlation coefficient value (R^2 = 0.9839 to 0.9958). Again, a plot of @@ 0 1 / 3- @@@@ 1 / 3 versus time using dissolution data was drawn and it was found linear graphs are represented in Figure 9, 10, 11, 12 with all lornoxicam solid dispersions. This observation indicates that the dissolution of lornoxicam from these newly prepared solid dispersions occurred from discretely suspended or deposited (monodispersed) particles. This might have also contributed to the enhanced dissolution rate of lornoxicam from solid dispersions using sugars as hydrophilic carriers.

Table 8: 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

		Correlation coefficient (r) value		
S:no	Solid dispersion	Zero order	Zero order	Zero order
1.	Pure Drug	0.849	0.996	0.930
2.	L-01	0.469	0.857	0.758
3.	L-03	0.586	0.892	0.905
4.	L-04	0.423	0.864	0.956
5.	L-05	0.543	0.907	0.983
6.	L-06	0.584	0.890	0.952
7.	L-09	0.457	0.892	0.967
8.	L-13	0.418	0.755	0.913
9.	L-14	0.430	0.767	0.612
10.	L-15	0.568	0.933	0.807
11.	L-16	0.493	0.982	0.808
12.	L-17	0.577	0.937	0.901
13.	L-18	0.904	0.992	0.991
14.	L-19	0.466	0.999	0.856
15.	L-20	0.481	0.974	0.944
16.	L-21	O.363	0.980	0.937
17.	L-22	0.840	0.937	0.929
18.	L-27	0.403	0.866	0.950
19.	L-29	0.401	0.980	0.957
20.	L-30	0.330	0.953	0.925

CONCLUSION

Lornoxicam is a non-steroidal anti-inflammatory drug and need to be rapidly absorbed for immediate pain relief but as the drug has poor water solubility, it causes poor bioavailability of the drug. Solid dispersion of lornoxicam prepared by using different polymers (carriers) enhanced the solubility and dissolution of the drug leading to enhanced bioavailability and rapid action. The solid dispersions prepared by combined polymers showed better dissolution rate than the pure drug.

ACKNOWLEDGEMENT

The authors are very thankful to Hetero drugs limited, Hyderabad, India for providing with the gift sample of Lornoxicam.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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