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Design and Development of Multi-Application Lornoxicam Fast Dissolving Tablets by Novel Drug - Drug Solid Dispersion Technique with Ranitidine

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ABSTRACT:

In the present research investigation, the effect of a novel- drug-drug solid dispersion approach on the dissolution of insoluble Lornoxicam (LOR) with soluble Ranitidine (RAN) was studied. Solid dispersion of LOR with RAN (8:150) was prepared by solvent evaporation technique. Solid dispersions were characterized by FTIR study. Solid dispersions were then compressed into fast dissolving tablets (FDTs) and evaluated for quality control tests. Long-term treatment with NSAIDs may produce gastrointestinal symptoms for which histamine H₂-receptor antagonists may be prescribed. Thus, there is a need for a formulation that is not only providing improvement in solubility but at the same time reduces GI adverse effects of Lor. The solubility of Lor was increased in solid dispersion as observed from phase solubility study. Pharmacological studies on LOR FDTs were carried out in rats for establishing its gastric tolerance relative to marketed tablet (MT) containing 8 mg lornoxicam. MT caused significant gastric damage, our novel Lor FDTs at equimolar dose did not cause any GI damage. This gastric-sparing effect could be attributed to the beneficial action of RAN present in the formulation.

KEY WORDS: Lornoxicam, Ranitidine, drug-drug solid dispersion.

INTRODUCTION:

Lornoxicam (LOR), (2-[2-[2-(2,6 dihydropyridyl) amino phenyl]acetyl]oxyacetic acid), is a nonsteroidal anti-inflammatory, analgesic and antipyretic drug used in rheumatoid arthritis, post-traumatic pain, musculo-skeletal and joint disorders¹.

Lornoxicam is practically insoluble in water. For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods like micronization, complexation and solid dispersion techniques².

Ranitidine hydrochloride is histamine H₂- receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, zollinger-Ellison syndrome, gastro esophageal reflux disease and erosive esophagitis. It is freely soluble in water. The recommended adult oral dosage of Ranitidine hydrochloride is 150 mg twice daily or 300mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of Ranitidine hydrochloride four times a day³.

Long-term treatment with NSAIDs may produce gastrointestinal symptoms for which histamine H₂-receptor antagonists may be prescribed. Thus, there is a need for a formulation that is not only providing improvement in solubility but at the same time reducing the GI adverse effects of LOR. It is also important that such a formulation should involve simple technique so that it can be easily employed at a commercial level. Like other NSAIDs, LOR appears to interact with warfarin, sulphonyl ureas, digoxin and furosemide. It is not affected by the co-administration of Ranitidine, aluminium, magnesium and calcium containing antacids¹.

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The enhanced dissolution of poorly soluble drugs such as griseofulvin⁴, chloramphenicol⁵, naproxen⁶ and triamterene⁷ from solid dispersion has been well documented. Similar studies were performed on glibenelamide⁸, clofibrate⁹, zolpidem¹⁰, albendazole¹¹, allopurinol¹², and promising results were reported.

Extensive review of literature indicates that physiological inert carriers have so far been used in solid dispersions for improving dissolution of poorly soluble drugs. Panner Selvam.M et al¹³, have reported drug-drug solid dispersion approach wherein a poorly soluble drug was dispersed in a soluble drug. However, chronic use of these NSAIDs can induce severe gastrointestinal (GI) toxicity such as bleeding, ulceration and perforation and also cardio renal complications which greatly limit their therapeutic usefulness¹⁴. According to an investigative report on "Toxic and Deadly NSAIDs, conservative estimates of NSAID- related GI complications account for more than 107,000 hospitalizations and 16,500 deaths annually among arthritis patients in the united states alone. Therefore, there exists an unmet medical need for safe NSAIDs that do not cause adverse effects on GI tract. Hence in the present study was directed towards developing solid dispersion of Lornoxicam (poorly soluble drug) in Ranitidine hydrochloride (soluble drug), by solvent evaporation method.

MATERIALS AND METHODS:

Lornoxicam was obtained as gift sample from Hetero Drugs Hyderabad, India. Ranitidine was gift sample from Micro labs; Bangalore, Microcrystalline cellulose (MCC) and Crospovidone were obtained from Maple biotech pvt Ltd, Pune, India. DC Mannitol, Talc and Magnesium stearate, were purchased from S.D Fine chemicals Ltd, Mumbai, India. All other chemicals were of analytical grade.

Preparation Of LOR solid dispersion with Ranitidine:

Solid dispersion of Lor (8mg) with Ranitidine (150mg) was prepared by solvent evaporation method. Accurately required quantity of LOR and Ranitidine were dissolved in methanol with magnetic stirring. Solvent was evaporated at reduced pressure at 40 °c in a rotary evaporating apparatus. The prepared solid dispersion was stored over silica gel for 12 hrs at room temperature. The dried dispersion was passed through a 250 µm sieve, then stored in a desicator and used for further investigation.

Drug content of solid Dispersion¹⁵:

158 mg of SD was weighed and transferred to 250 ml volumetric flask and dissolved in 0.1 N Hcl (Ph 1.2) and the volume were made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically (PG instrument T₈₀ model UV/VIS spectrophotometer) at 376 nm.

Phase solubility study¹⁵.

Phase solubility study was performed to prove that the

Table1: Depicts the composition of Lornoxicam FDTs

Ingredients mg/tab	Formulation L
SD equivalent to 8mg of LOR	158
Mannitol	90
crospovidone	10
MCC	30
Aspartame	6
Mg.Stearate	3
Talc	3
Total wt	300

solubility of the drug increases with the solid dispersion by dissolving it in 0.1 n Hcl (PH 1.2) at 37±0.5°c was carried out by adding an excess of SD into a screw capped glass vial. The vial was placed on a water bath shaker and agitated at 37±0.5°c for 72 hrs. An aliquot of each solution was withdrawn and filtered through whatman filter. The assay of LOR was determined spectrophotometrically at 376nm, a wavelength at which Ranitidine does not interfere.

Preparation of tablets containing SD of LOR:

The SD equivalent to 8 mg of LOR was taken and mixed with directly compressible diluents and superdisintegrant in a plastic container. Magnesium stearate and Talc were passed through sieve # 60, mixed and blended with initial mixture and followed by the compression of the blend.

Evaluation of powder blends¹⁶⁻¹⁷:

Angle of repose:

Angle of repose (θ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

$$\theta = \tan^{-1} h/r$$

Compressibility index:

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility that is calculated as follows:

$$C = (pt - pb) / pt \times 100$$

pt - Tapped density, pb - Untapped bulk density

Hausner's ratio:

Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

$$\text{Hausner's ratio} = pt / pb$$

pt - Tapped density, pb -Untapped bulk density

Table 2: Pre and Post Compressional parameters of Lornoxicam tablets

Parameters	L
Angle of repose (θ) (\pm SD),	21.65(0.28)
Compressibility (%) (\pm SD), n=3	14.42(0.17)
Housners ratio (%) \pm SD), n=3	1.31(0.03)
Hardness (kg/cm ²) \pm SD, n=3	3.55(0.2 1)
Friability (% w/w) \pm SD, n=3	0.30(0.04)
Thickness (mm) \pm SD, n=6	4.65(0.05)
Diameter(mm)	8.00(0.07)
Weight variation \pm SD, n=10	158(0.24)
Wetting time (Sec) \pm SD, n=6	52.00 \pm 0.40
Disintegration time (Sec) \pm SD, n=6	18.42 \pm 0.90
Drug content (%) \pm SD, n=6	100.30(0.50)

Evaluation of lornoxicam Tablets¹⁸⁻²²:

All prepared tablets were evaluated for hardness, thickness, friability, disintegration time, wetting time, drug content. Pfizer hardness tester was used for the determination of the hardness of the tablets. The tablet was placed in contact between the plungers and the handle was pressed, the force of the fracture was recorded .The thickness of tablets were recorded during the process of compression using calipers (Mitotoyo; Japan) .The friability of the tablets was determined using a Roche Friabilator (Electrolab,EF-2 Friabilator) by taking two tablets from each batch and accurately weighed and placed in the Friabilator then operated for 100 revolutions .Then the tablets were dedusted and reweighed .Percentage friability was calculated using the formula= $(1-w_0/w) * 100$.

In the disintegration time study, the tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1 liter beaker containing 900ml of 0.1 N HCl pH 1.2 and time of disintegration was recorded at $37\pm 2^{\circ}\text{C}$. In the wetting time study, a piece of tissue paper folded twice was placed in a petridish (with internal diameter 6.5cm) containing 5ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For drug content analysis a total 10 tablets were weighed and powdered .The powder equivalent to 8 mg of Lornoxicam was taken and dissolved in 0.1 N HCl pH 1.2 .After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (a PG instrument T₈₀ model UV/VIS spectrophotometer) at 376 nm.

In vitro release studies:

The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (0.1 N HCl pH 1.2) was taken in vessel and the temperature

was maintained at $37 \pm 0.5^{\circ}\text{C}$. The speed of the paddle was set at 50 rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with 0.1 N HCl pH 1.2 prior to analysis in the UV Spectrophotometer (a PG instrument T₈₀ model UV/VIS spectrophotometer) and drug concentration were calculated by simultaneous equation method as below²³⁻²⁴.

This method of analysis is based on the absorption of drugs (X and Y) at the wavelength maximum of the other. The quantification analyses of Lor and Ran in a mixture were performed with the following equations.

$$C_R = (A_2 a y_1 - A_1 a y_2) / a x_2 a y_1 - a x_1 a y_2$$

$$C_L = (A_1 a x_2 - A_2 a x_1) / a x_2 a y_1 - a x_1 a y_2$$

C_R = concentration of Ran and C_L = concentration of Lor, $a x_1$ and $a x_2$ = Absorptivities of Ran at λ_1 (313.5nm, λ_{\max} of Rani) and λ_2 (376nm, λ_{\max} of Lor), $a y_1$ and $a y_2$ = Absorptivities of Lor at λ_1 (313.5nm, λ_{\max} of Rani) and λ_2 (376nm, λ_{\max} of Lor). A_1 = Absorbance of sample at 313.5 nm and A_2 = Absorbance of sample at 376 nm

Drug-polymer interaction study by Fourier-transformation infrared (FTIR) spectroscopy:

The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer, Perkin-Elmer (spectrum-100) Japan. Two percent (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem Ltd., Mumbai, India) disc, was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. Each KBr disc was scanned 16 times at 2-mm/ sec at a resolution of 4 cm⁻¹ using cosine apodization. The characteristic peaks were recorded.

Scanning Electron Microscopy (SEM) study:

The SEM study of pure drug and its solid dispersion were studied to know the physical nature of drug and its solid dispersion.

In-vivo studies:

wistar albino rats of either sex weighing around 150-250g were taken from inbreed colony animals, which were housed in polypropylene cages at $24\pm 2^{\circ}\text{C}$ in the animal house and fed with commercial pellet diet supplied by Kamadhenu Agencies Bangalore and water ad libitum. The food was withdrawn 18 hours before the experiment but allowed free access of water. To avoid coprophagy and fighting, the rats were fasted in wire bottomed cages. All animals' experiments were carried out in accordance with the guidelines of CPCSEA.

Experimental procedure:

The animals were divided in 3 groups of each. The first group

Table 3: Effect of pure drug and formulation on pH and ulcer score in rats.

S. N O	TREATME NT	U_N	U_S	U_P	U_I	pH
1	Group I (Normal)	0	0	0	0	2.75 ± 0.05
2	Group II(MT)	1.5 ± 0.01***	2.5 ± 0.866***	75	11.5	2.30 ± 0.01
3	Group III (Lornoxicam FDTs)	0.75 ± 0.01***	1.01 ± 0.01***	25	4.26	5.75 ± 0.06

P < 0.001 when compared to Normal

*** P < 0.001 when compared to Pure Lornoxicam, MT=Marketed Tablet

served as standard control, the second group was administered with Market tablet containing Lornoxicam equivalent to 0.40 mg/kg/day for 30 days p.o. the third group was administered with Lor FDTs prepared by Ran solid dispersion equivalent to 0.40 mg/kg/day.

The following groups of animals were used.

Group I: Control

Group II: Marketed Tablet containing lornoxicam equivalent to 0.40mg/kg/day po.

Group III: Lor FDTs equivalent to 0.40mg/kg/day. Po.

At the end of the 30 days experimental observations, the animals were scarified with an overdose of chloroform and the stomachs were opened along the greater curvature, rinsed with saline to remove gastric contents and blood clots and examined by a magnifier lens ($\times 5$) to assess the formation of ulcer. The number of erosions formed on glandular portion of stomach was counted and each was registered using the following scores.

Condition Score

No ulcers 0

Superficial ulcers 1

Deep ulcers 2

Perforations 3

Ulcer index was calculated as:

$$U_I = U_N + U_S + U_P * 10^{-1}$$

U_I = Ulcer index

U_N = Average number of ulcers

U_S = Average severity score

U_P = Percentage of animals with ulcers

Stomach was then dissected out and contents were drained into tubes and were centrifuged at 1000 rpm for 10 minutes. The pH of gastric juice was recorded using a pH meter.

RESULTS AND DISCUSSIONS:

Phase solubility study: The solubility of Lornoxicam solid dispersion with Ranitidine was increased in comparison to pure drug Lornoxicam. The pure drug solubility was 0.200µg/ml where as its solubility was increased to 0.660µg/ml in solid dispersion. The values of pre-compression parameters evaluated were within prescribed limits and indicated a good free flowing property. Angle of repose of tablets prepared by Ran solid dispersion was 21.65, compressibility index value was 14.42 and Hausners ratio was 1.31.

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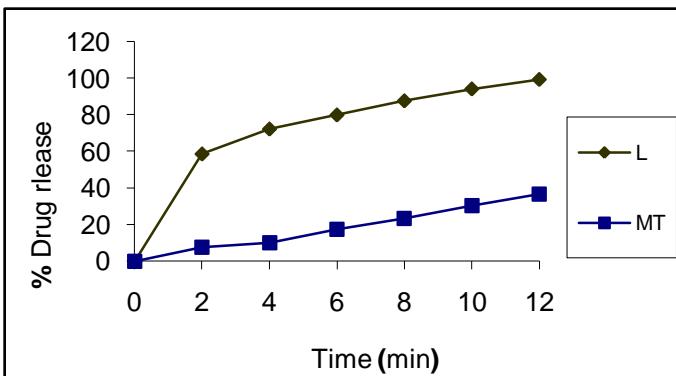
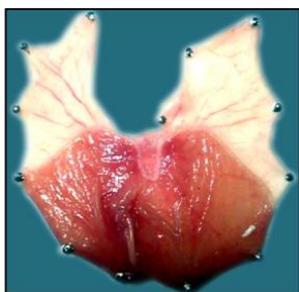


Figure - 1: Dissolution profile of Lornoxicam FDTs

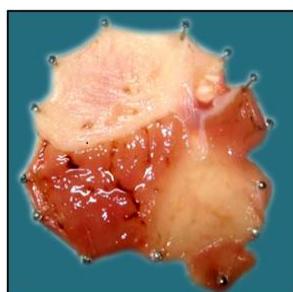
In the formulation, the hardness test indicates good mechanical strength. Friability was less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high ($\geq 100\%$). The weight variation results revealed that average percentage deviation of 20 tablets was less than $\pm 7.5\%$, which provides good uniformity. It was observed that disintegration time was 18.42 sec. It may be due to the nature of the excipient. It is also because of disintegration nature of MCC and it is white, odorless, tasteless crystalline powder containing porous microfibres of cellulose. As the length of cellulose polymer increases, the tensile strength of the tablet also increases. It is an inert insoluble powder with good flowability. It is used as a diluent, disintegrant and lubricating agent. The static and dynamic coefficient of friction of MCC is very less; hence it is used as lubricating agent.

The influence of solubility enhancement on dissolution profile of Lor was also studied. It was observed that formulation L was taken only 12 min to release 99% of drug where as Marketed tablet was released 36.68% at the end of 12th min. It maybe due to the entrapment of drug with solid dispersion in the formulation.

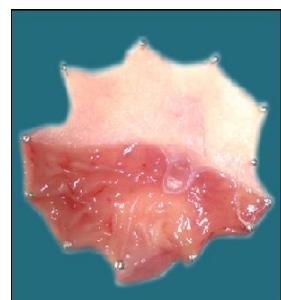
The FTIR spectrum of lornoxicam showed (Figure 1) a characteristic peak at 3396, 3354 and 2924 cm⁻¹ corresponding to –NH stretches vibration. Intense absorption peak was found at 1,642 cm⁻¹ due to the stretching vibration of the C=O group in the primary amide. Other peaks were observed at 1639 1465, 1440 and 1422 cm⁻¹ and were assigned to bending vibrations of the N–H group in the secondary amide. The stretching vibrations of the O=S=O group appeared at 1332, 1337 and 1309 cm⁻¹. Other prominent peaks appeared at 831.94 cm⁻¹ corresponding to –



A



B



C

Figure 2: Microscopical view of normal mucosal layer (A, GroupI), severe damage of mucosal layer (B, GroupII), protected mucosal layer(C, GroupIII)

CH aromatic ring bending and heteroaromatics and at 781.20 cm⁻¹ due to the C–Cl bending vibration. All these prominent peaks of Lor were present in mix of Lor with Ranitidine in formulation. It clearly indicates that the drug has retained its purity without loosing its characteristics.

The physical nature of the drug Lornoxicam and Ranitidine were studied by the SEM analysis. Lornoxicam and Ranitidine both are available in the form of crystalline. The drug was changed to amorphous nature from crystalline due to solid dispersion and can be observed as flakes in SEM image. It is necessary for the insoluble drug to increase the solubility followed by the dissolution.

The juice collected from Group II showed the pH as that of control group where as the Group III showed elevation in pH indicating its capacity to reduce the acidity. The severity of the Gastric ulceration was assessed on the basis of mean ulcer index. Group II rats exhibited mean ulcer index of 11.5, which was almost three times of Group III rats with mean ulcer index value of 4.26, proved formulation effect against ulcer formation due to regular usage of pure Lornoxicam.

CONCLUSION

The novel drug-drug solid dispersion approach is promising to improve dissolution and bioavailability of poorly soluble drug. The biological study results of our novel FDTs of Lor prepared by solid dispersion with Ran clearly indicates, these FDTs are indeed acting as potentially gastric sparing safe formulation containing NSAID.

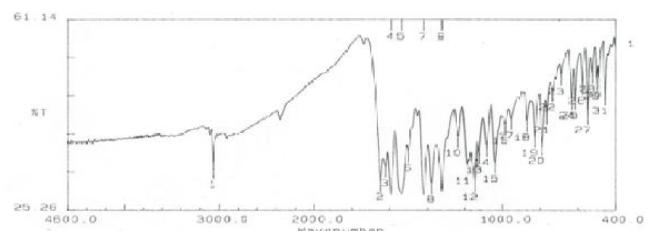


Figure 3: IR spectrum of Lornoxicam

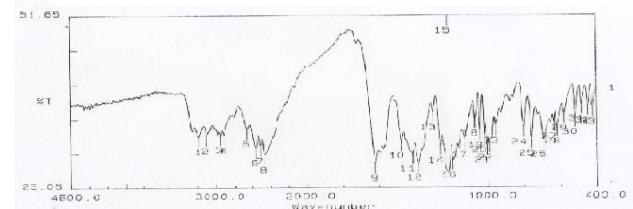


Figure 4: IR spectrum of Ranitidine

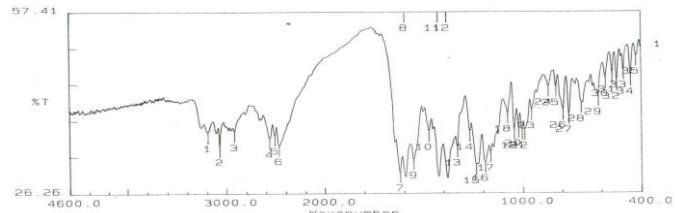


Figure 5: IR spectrum of Lornoxicam solid dispersion with Ranitidine

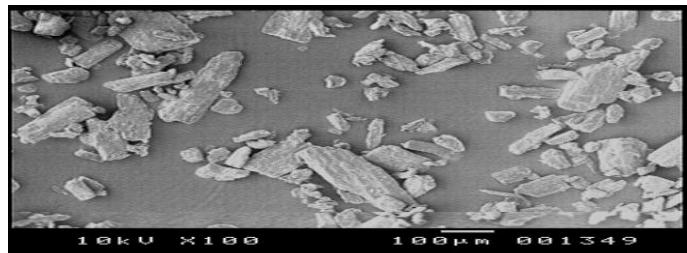


Figure 6: SEM image of pure Lornoxicam.

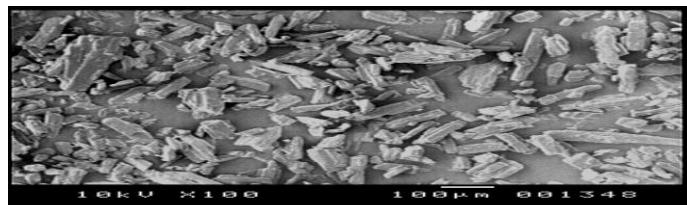


Figure 7: SEM Image of pure Ranitidine

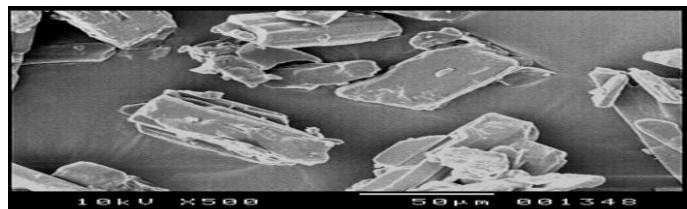


Figure 8: SEM Image of Lornoxicam solid dispersion with Ranitidine.

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