

Formulation and Development of Lornoxicam Fast Dissolving Tablets: Influence of Different Excipients on Property and Performance of Patient Friendly Dosage Form

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ABSTRACT

Lornoxicam is a Non-steroidal anti-inflammatory drug with analgesic properties and belongs to the class oxicams. In the present research invention, study the influence of various excipients on disintegration behavior of LOR. The fast dissolving tablets have advantages of solid dosage forms such as good stability, accurate dosing, easy handling and those of liquid formulations such as easy administration and minimal risk of suffocation. All the formulations were evaluated for hardness, friability, wetting time, disintegration time and drug release study. Formulation containing microcrystalline cellulose (MCC) shows less disintegration time compared to others. It was also concluded that MCC was found to be better excipient as compared to spray dried lactose and DC-Mannitol. The drug compatibility with excipients were checked by FTIR and DSC studies and results reveals that there were no drug excipients interactions.

Keywords: Fast Dissolving Tablets, Lornoxicam, Excipients.

INTRODUCTION

Many patients have difficulty in swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy¹. The demand for solid dosage forms that can be dissolved and suspended in water, chewed, or rapidly dissolved in the mouth is particularly strong in the pediatric and geriatric markets, with further application to other patients who prefer the convenience of a rapidly administered dosage form.

Because of the increase in the average human life span and the decline, with age, in swallowing ability, oral tablet administration to patients is a significant problem and has become the object of public attention²⁻³. The problem can be resolved by the creation of fast dissolving

tablets, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, then are swallowed in the normal way. Less frequently, they are designed to be absorbed through the buccal and esophageal mucosa as the saliva passes into the stomach. In the latter case, the bioavailability of a drug from fast dissolving formulations may be even greater than that observed for standard dosage forms. Furthermore, side effects may be reduced if they are caused by first-pass metabolism⁴.

Fast dissolving formulations, commonly called fast melting tablets, also offer advantages over other dosage forms such as effervescent tablets, extemporaneous suspensions, chewing gum, or chewable tablets, which are commonly used to enhance patient compliance. Effervescent tablets and extemporaneous suspensions

require preparatory steps before administration of the drug. The advantages of fast dissolving tablets increasingly are being recognized in both industry and academia. Their growing importance was underlined recently when the European Pharmacopoeia adopted the term fast dissolving tablets as a 'tablet to be placed in the mouth where it disperses rapidly before swallowing'⁵.

Lornoxicam, a congener of tenoxicam, is a new NSAID belonging to the oxicam class. It is a strong analgesic and anti-inflammatory NSAID as compared to other NSAIDs. Its analgesic activity is comparable to that of opioids. Studies have shown that it is more effective than 10 mg morphine when used at doses \geq 8mg to control pain after oral surgery. Lornoxicam combines the high therapeutic potency of oxicams with an improved gastrointestinal toxicity profile as compared to naproxen which is probably due to the short half-life of lornoxicam as compared to the other oxicams⁶.

Polacrillin Potassium (KYRON T-314) is 2-methyl-2-propenoic acid polymer with divinylbenzene, potassium salt. It is a cation exchange resin used in oral pharmaceutical formulation as a tablet superdisintegrant. It appears as a cream colored, odorless and tasteless, free flowing powder⁷.

Hence in the present research investigation an attempt was made to develop Lornoxicam fast dissolving tablets using different excipients by direct compression method.

MATERIALS AND METHODS

Lornoxicam was obtained as gift sample Hetero Drugs Hyderabad, India. Polacrillin potassium (KYRON T-314) obtained as gift sample from Corel pharma Ahmedabad, Microcrystalline cellulose (MCC) obtained from Maple biotech pvt ltd, Pune, India. DC-Mannitol, Spray Dried Lactose, Talc and Magnesium stearate, were purchased from

S.D Fine chemicals ltd, Mumbai, India. All other chemicals were of analytical grade.

Preparation of Lornoxicam fast dissolving Tablets

Drug and all other ingredients pass through the sieve no. 60. Drug, excipient and superdisintegrant were mixed in mortar and mixed well by pestle. To the above mixture talc and magnesium stearate were mixed. The tablets were prepared by direct compression on rotary press (Model Rimek-II. Karnavati Engg. Ahmedabad), fitted with concave punches of 8mm diameter.

Evaluation of powder blends⁸⁻⁹

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

Evaluation of Lornoxicam Tablets¹⁰⁻¹⁴

All prepared tablets were evaluated for hardness, thickness, friability, disintegration time, water absorption, 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 = $(1 - w_o/w) * 100$. In Water absorption ratio, a piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

$$R = 100 (W_a - W_b) / W_b \quad \text{----- (g)}$$

Where, W_b – weight of tablet before absorption

W_a – weight of tablet after absorption

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 phosphate buffer pH 6.8 and time of disintegration was recorded at $37 \pm 2^\circ$ 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 4mg of Lornoxicam was taken and dissolved in phosphate buffer pH 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV 1700 Shimadzu Corporation, Japan) 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 (Phosphate buffer pH 6.8) was taken in vessel and the temperature was maintained at $37 \pm 0.5^\circ$ 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 Phosphate buffer pH 6.8 prior to analysis in the UV Spectrophotometer (a PG instrument T₈₀ model UV/VIS spectrophotometer) at 376 nm.

Drug-polymer interaction study by Fourier-transformation infrared (FTIR) spectroscopy and DSC studies

FTIR Studies

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.

DSC Studies

Subtraction of the heat capacity of the buffer sample from the biomolecule sample results in the heat capacity contribution of the

biomolecule alone (this is the “differential” part of the DSC) DSC cells are either capillary or “lollipop” in shape, and there are always two of them. Both cells are loaded with buffer the instrument is setup for multiple (20) data collection runs (heating/cooling cycles). “Buffer/buffer” data is collected (≥ 3 runs). When the instrument is cooling down, prior to a heating cycle, the protein is introduced at 25 °C. A “protein/buffer” data run is collected. Similar lornoxicam loading is repeated two more times to obtain 3 “Lor/buffer” scans

RESULTS AND DISCUSSIONS

The values of pre-compression parameters evaluated were within prescribed limits and indicated a good free flowing property. The post compression parameters such as hardness, friability, thickness, disintegration time, wetting time, drug content results are shown in Table 2.

In all the formulations, the hardness test indicates good mechanical strength. Friability of all formulations was less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high ($\geq 100\%$) and uniform in all the formulations. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than $\pm 7.5\%$, which provides good uniformity. It was observed that disintegration time decreased from 22 to 18 sec as observed from LT1 to LT3. It may be due to the nature of the excipient. Of course Mannitol and Lactose are hydrophilic in nature while MCC is hydrophobic. Even though the formulation LT3 prepared with MCC was disintegrated within 18 sec. It is because of disintegration property of MCC. While using combination of different excipients (Batches LT4 to LT6), it was observed that there was no change in disintegration time when combining the Lactose with Mannitol (LT4), but there is decrease in disintegration time when MCC was combined with Mannitol and Lactose. It

may be due to increased hydrophilic nature of formulations LT5 and LT6.

The influence of various excipients on dissolution profile of Lornoxicam was also studied. It was observed that formulation LT3 was taken only 12 min to release 99% of drug where as formulation LT1 and LT 2 were taken 20 to 22 min to release 99% drug release respectively. There is no significant change in time was observed to release the drug with formulation LT4 (combination of Mannitol and Lactose), it took 22 min to release 99% drug. When combining MCC with Mannitol (LT5) and with Lactose (LT6) decrease in time was observed.

The FTIR spectrum of lornoxicam showed (Figure 2) a characteristic peak at 3396, 3354 and 2924 cm^{-1} corresponding to $-\text{NH}$ stretches vibration. Intense absorption peak was found at 1,642 cm^{-1} due to the stretching vibration of the $\text{C}=\text{O}$ 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 $\text{N}-\text{H}$ group in the secondary amide. The stretching vibrations of the $\text{O}=\text{S}=\text{O}$ group appeared at 1332, 1337 and 1309 and cm^{-1} . Other prominent peaks appeared at 831.94 cm^{-1} corresponding to $-\text{CH}$ aromatic ring bending and heteroaromatics and at 781.20 cm^{-1} due to the $\text{C}-\text{Cl}$ bending vibration. All these prominent peaks of Lor were present in mix of Lor with DC-Mannitol (figure 3), with Spray Dried Lactose (figure 4) and with MCC (figure 5) It clearly indicates that the drug has retained its purity without losing its characteristics.

Our experimental results were assessed on the basis of physical data obtained for drug and polymers as well as formulations.

The drug taken lornoxicam which was a hydroxy thio molecule this drug gave rise to the $-\text{OH}$ group of absorption of 3400 cm^{-1} which was in the tetameric condition. The $\text{N}-\text{H}$ functionality present in molecule were indicated by presence of indicate peak 3100 cm^{-1} . The peak due to the $\text{C}-\text{H}$ of the aromatic was noticed at 3067 cm^{-1}

supporting at molecule contain in pyridin residue and thiosol residue. The aliphatic C-H peaks were noticed that 2925 and 2875 cm^{-1} the peak due to the so which was part of ring system noticed that 1733 cm^{-1} suggested that given molecule . The drug has given this three charectristic of absorption peak. DSC thermo gram (Fig 6) of pure drug of Lornoxicam shows an endothermic peak at melting point 233.4 C, which is slightly decreased to 223.07 C for formulation LT1 containing Lornoxicam and Dc-Mannitol. Formulation LT2 which was formulated by using Spray Dried Lactose shows the endothermic peak at 222.43 C and Formulation LT3 which was formulated by using MCC shows the endothermic peak at 224.44 C, indicating negligibile change in melting point of all formulation shows all most nearer to melting point of the pure drug which clearly indicating that there is no inter action between drug and polymer.

CONCLUSION

The results of disintegration time, wetting time and dissolution rate revealed that the proposed research work is novel and can be successfully employed for the formulation of fast dissolving tablets. This novel technique is more effective in comparison with the all other exciting techniques. From this research work it can also concluded that, the proposed technique is very simple and effective to decrease the lag time to conversion into solution form for better absorption of the dosage form.

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Table1: Depicts the composition of Lornoxicam FDTs

Ingredients mg/tab	LT1	LT2	LT3	LT4	LT5	LT6
Lornoxicam	4	4	4	4	4	4
Polacrillin potassium	7.5	7.5	7.5	7.5	7.5	7.5
DC-Mannitol	130	-	-	65	65	-
Spray Dried Lactose	-	130	-	65	-	65
MCC	-	-	130	-	65	65
Aspartame	5.5	5.5	5.5	5.5	5.5	5.5
Mg.Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Total wt	150	150	150	150	150	150

Table 2: Pre and Post Compressional parameters of Lornoxicam tablets

Parameters	LT1	LT2	LT3	LT4	LT5	LT6
Angle of repose (θ) (\pm SD),	22.18(2.22)	24.27(0.95)	23.28(1.32)	24.81(1.15)	22.22(0.90)	23.50(1.70)
Compressibility (%) (\pm SD), n=3n=3	19.18(2.12)	18.55(2.14)	20.47(0.74)	22.48(2.17)	21.30(3.40)	22.59(2.37)
Housners ratio (%) \pm SD), n=3	1.25(0.02)	1.22(0.04)	1.28(0.06)	1.29(0.05)	1.24(0.06)	1.23(0.04)
Hardness (kg/cm ²) \pm SD, n=3	4.12(0.51)	4.14(0.12)	4.50(0.20)	4.18(0.31)	4.00(0.37)	4.28(0.22)
Friability (% w/w) \pm SD, n=3	0.14(0.02)	0.13(0.03)	0.25(0.07)	0.40(0.08)	0.30(0.05)	0.32(0.04)
Thickness (mm) \pm SD, n=6	3.84(0.04)	3.75(0.08)	3.88(0.05)	3.77(0.04)	3.72(0.05)	3.73(0.06)
Weight variation \pm SD, n=10	150 \pm 0.74	151 \pm 0.28	149 \pm 0.22	151 \pm 0.24	149 \pm 0.22	150 \pm 0.27
Wetting time (Sec) \pm SD, n=6	56 \pm 0.92	59 \pm 0.90	50 \pm 1.00	57 \pm 1.00	51 \pm 0.56	60 \pm 1.00
Water Absorption Ratio(%) \pm SD, n=3	79.43 \pm 0.25	75.30 \pm 0.12	80.00 \pm 0.23	84.59 \pm 0.34	80.22 \pm 0.14	85.65 \pm 0.54
Disintegration time (Sec) \pm SD, n=6	22 \pm 1.00	24 \pm 1.25	18 \pm 1.00	22 \pm 2.00	18 \pm 2.00	24 \pm 1.00
Drug content (%) \pm SD, n=6	98.00(2)	99.15(1.95)	97.50(2.20)	100.46(1.50)	102.00(2.25)	99.30(1.50)

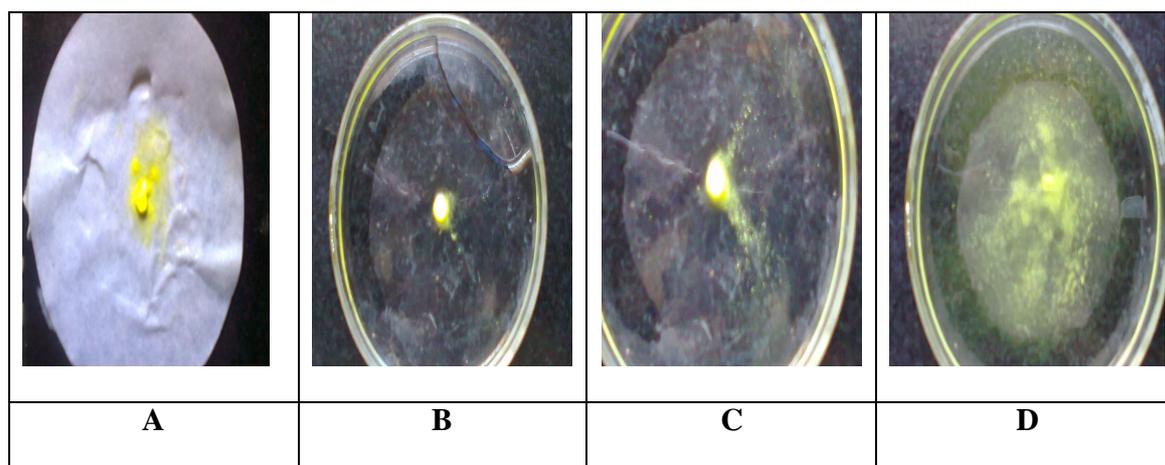


Fig. 1: Water Absorption of LT3 Formulation (A), Dispersion of LT3 Formulation at 0 Sec (B), at 5 Sec (C) and at 10 Sec (D)

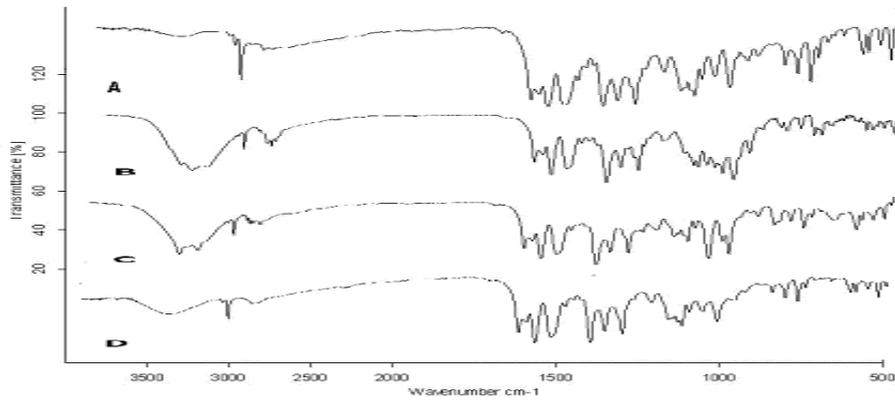


Fig. 2: FTIR spectra of Lor pure drug (A), drug with Spray Dried Lactose (B), + with DC-Mannitol(C), with MCC (D)

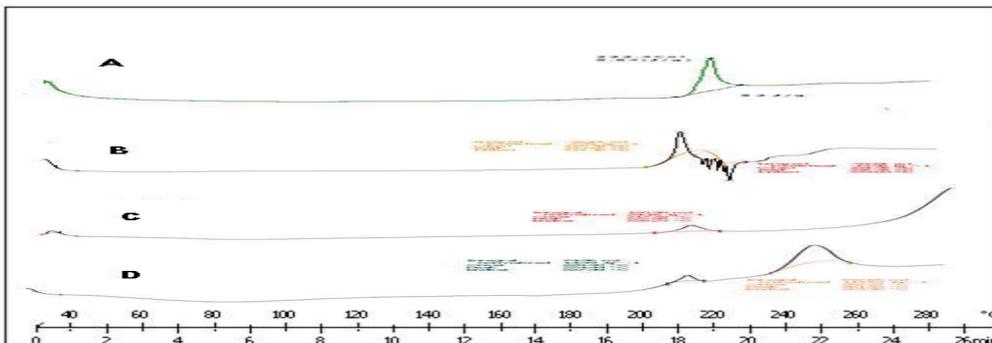


Fig. 3: DSC of of Lor pure drug (A), + with DC-Mannitol (B), drug with Spray Dried Lactose (C), with MCC

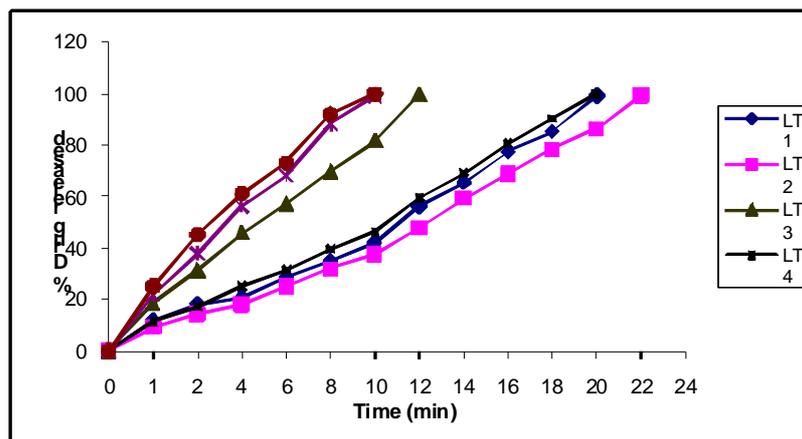


Fig. 4: Dissolution profile of Lornoxicam FDTs

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