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In vitro Dissolution Enhancement and Development of Pre-Programmed Pulsatile Delivery System of BCS-II Drug: Lornoxicam

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Abstract
The intension of the present investigation was to enhance the solubility and to prepare pulsatile delivery system for BCS-II drug- lornoxicam for the treatment of rheumatoid arthritis (RA).To achieve the aim, poorely soluble drug primarily converted into sild dispersion form using highly soluble hydrophilic soluble carriers (PVPVA 64, SOLUPLUS) and surfactants (LUTROL F68, LUTROL F85, LUTROL F127), then sold dispersion converted to fast dissolving tablets using super disintegrants to fasten the dissolution of drug in GIT. In order to achieve chronological release, film coated pulsatile release tablets were prepared by employing HPMC E15 as swelling agent, Konjac glucomannan triacetate as membrane former, Eudragit L100-50 as pore former and triethyl citrate as plasticizer. A 3-factor, 3-level Box-Behnken design (BBD) was utilised to optimise the formulation and to produce second order polynomial equations to predict lag time. The BBD optimization process and overlay plots has predicted the levels of independent variables A, B, and C (20% w/w, 24.72% w/w, 10.68% w/w respectively) to achieve targeted responses lag Time (6 hr) and $T_{75\%}$ (6.3 hr) and observed the same with 0.04 % relative error.

Keywords
lornoxicam, TAPS, Pulsatile tablets, Chronopharmacotherapy, Box-Behnken design, Rupturable membrane tablets.

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INTRODUCTION:
Solid Oral drug delivery is the oldest, widest and much interesting segment of the total drug delivery market. It is the convenient, fast growing and most preferred route for drug administration. [1] The ideal dosage regimen is the one which must produce

therapeutically acceptable concentration of drug at the site of action which should attained immediately and maintained constantly for the desired duration of time in the treatment. With the advancement in the present delivery technology many of the diseases like arthritis, hypercholesterolaemia, cardiovascular diseases, diabetes, neurological disorders asthma, cancer, duodenal ulcer, have a predictable cyclic rhythm, treated effectively by special type of dosage form called pulsatile drug delivery systems under the new branch of pharmaceutics called "chrono-pharmaceutics". [1-7]

Pulsatile drug delivery systems (PDDS) met the required criteria to target circadian rhythm-based diseases. Pulsatile drug delivery system can be broadly classified into 4 classes.

I.Time controlled pulsatile systems
II.Stimuli induced pulsatile systems
III.Externally regulated pulsatile systems
IV.Multi particulate pulsatile systems.

At present rupturable membrane systems gained much attention due to production simplicity and which consist of core tablet generally fast dissolving tablet, a swelling layer, and an external water insoluble, but permeable polymer coat. The basic mechanism in drug delivery from rupturable systems involves penetration of gastrointestinal (GI)-fluids through the polymer coat upon exposure, expansion of middle swelling layer, express pressure on outer polymer coat until it ruptures which releases the drug rapidly into GI fluids. Pressure exerted by the swelling layer; mechanical strength & water permeability of outer coat are the main parameters which control the lag time of pulsatile tablets [8-11].

Lornoxicam (L) (6-Chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide-1,1-dioxide) is a highly selective COX-2 inhibitor that belongs to oxicam class of non-steroidal anti-inflammatory drugs (NSAID). It has been used for a variety of acute and chronic inflammatory conditions, management of pre-operative and post-operative pain observed during gynaecological, orthopaedic, abdominal and dental surgeries. Lornoxicam being a BCS class II drug, shows limited solubility and dissolution, limits the oral absorption of drug, produces bioavailability issues which in turn needs physical treatment of drug to improve its solubility, dissolution and bioavailability [12-16]

Several techniques are available for solubility improvement which are categorized as.,

- Physical Modifications: - Micronization, nanosuspension, co-crystallization, solid dispersions, solid solutions, polymorphic forms, amorphous forms, eutectic mixtures, and cryogenic techniques.
- Chemical Modifications: - Derivatization, complexation, change of pH, use of buffer, , and salt formation.
- Miscellaneous Methods: - Supercritical fluid process, co-solvency, hydrotrophy, and use of surfactants, novel excipients solubilizers. [17-20]

Solid dispersion technique has often proved to be the most successful in improving the solubility, dissolution and bioavailability of poorly soluble drugs, as it's a simple, economical, and advantageous. It is a technique where dispersion of one or more drug substance in carrier or carrier matrix in solid state. Solid dispersions prepared by physical mixing, mixing by melting, solvent evaporation, extrusion etc. methods. [21]

Glucomannans are captured much importance in food, packing and biomedical industry. Konjac glucomannan a dietary fibre, is a water soluble, highly viscous, high-molecular weight compound extracted from root of the elephant yam, widely known as "Kojac" (Amorphophallus konjac or Amorphophallus rivieri) which is native to Asia. Because of its excellent swelling, gelling and other properties, it has several pharmaceutical and biomedical applications like treatment of obesity, preparation of biodegradable film for controlled release formulations, preparation of composite materials, edible film, packaging film, and also used as thickening agent in food and beverage industry. Due to its of hypocholesterolaemia and hypolipidemic properties, KGM gum used for weight loss treatment in USA, China. Konjac Glucomannan triacetate, fully acetylated derivative of KGM gum, maintained similar properties except water solubility. KGM Tac is water insoluble and have excellent film forming capability. [22-24]

The major objective of the present study is

- Preparation of solid dispersion, fast dissolving tablets of lornoxicam using novel carriers and super disintegrating agents.
- Preparation of pulsatile release tables using KGM Tac and HPMC E15 employing Box-Behnken Design.

MATERIALS AND METHODS:

Materials:

The materials used were as follows: Lornoxicam (LOR, gift sample from Hetero drugs, Hyderabad); PVP VA68, Lutrol F127, Microcrystalline Cellulose (MCC), spray dried Lactose, Croscarmellose Sodium, Crospovidone, Sodium starch glycolate (SSG),

Hydroxy propyl methyl cellulose (HPMC), Low-substituted Hydroxypropyl Cellulose(L-HPC), Triethyl citrate (TEC), Magnesium stearate, Eudragit L100, Konjac glucomannan triacetate (KGM Tac) (), Talc. All chemicals were of HPLC or analytical grade.

EXPERIMENTAL METHODS:

Preparation of Calibration curve: pre-weighed 50 mg of lornoxicam (LOR) was dissolved in minimum amount of methanol in a 100 mL volumetric flask, volume was adjusted up to 100 mL with the same solvent to produce stock solution. (500 µg/mL of LOR). 1, 2, 3, 4, 5, 6 mL of stock solutions were separated into different 100 mL volumetric flask, diluted with buffer pH 6.8 or distilled water up to the mark to get concentrations from 5-30 µg/mL and analysed by UV Double beam Spectrophotometer at 376 nm [25-27].

Phase Solubility Studies:

Phase-solubility studies were carried out by adding excess of drug (25 mg) in 25 ml of aqueous solutions of different carriers (0.5%,1%, 1.5%, 2%, 2.5% and 3%).The suspensions were continuously shaken in orbital shaker and incubated for 24hrs at 37 ± 2°C and finally centrifuged for 5 min at 2000 rpm .The supernatant liquid was filtered and analysed for drug content by UV-Visible double beam spectrophotometer at 376 nm [28-30].

Infrared Spectroscopy:

The incompatibility between drug and excipients was checked by FTIR spectra obtained on SHIMADZU 8400S, Japan. The finely grounded drug, potassium bromide was compressed to produce pellets and scanned for Infrared spectra over the wave number of 8000 to 400cm^{-1}. [31].

Preparation of lornoxicam solid dispersion: Solid dispersion was prepared by solvent evaporation method by taking 10 gm of the finely powdered drug and carrier or carrier mixture (Soluplus, PVP VA64, Lutrol F68, Lutrol F85, Lutrol F127), dissolved in 25 ml methanol with continuous stirring. The solution was slightly heated with continuous stirring to evaporate solvent, further dried in a vacuum oven at 40°C for 12 hr, milled to produce granules and analysed for drug solubility. Composition of solid dispersions were given in **table no:01** [32].

Evaluation and characterisation of solid dispersions:

Solubility studies:

LOR Solubility in different media was determined by equilibrium solubility method. An excess quantity of LOR was added to 10mL screw-capped glass vials containing 5 mL of Distilled water , 0.1N HCl pH 1.2,Phosphate buffer pH 6.8 and pH 7.4.The vials were shaken mechanically on mechanical shaker (Lab India, Mumbai, India) at 37 ± 2◦C, allowed to equilibrate in incubator for 24 h. centrifuged for 5 min at 2000 rpm .The supernatant liquid was carefully decanted, filtered and analysed for drug content at 376 nm employing UV visible spectrophotometer.[28-30].

Drug content and Yield:

Solid dispersion equivalent to 8 mg of LOR was accurately weighed and dissolved with small quantity of methanol in 100 ml volumetric flask, volume was made up to mark with phosphate buffer pH 6.8 and filtered. 1 ml of filtrate was diluted to 100 ml using phosphate buffer pH 6.8 and absorbance measured at 376 nm. Drug content was measured using standard curve, % Yield calculated from following equation.

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theotical Yield}} \times 100$$

Stability Constant and Gibb's Free Energy:

The stability constant (Ks) between each drug–carrier component was calculated from the phase-solubility profiles using below equation:(46)

$$Ks = \frac{\text{Slope}}{So(1\text{-slope})}$$

The values of Gibbs free energy of transfer, ΔGo tr for carrier and drug- carrier solutions were calculated by utilising following relationship.

$$\Delta Go_{tr} = -2.303RT.\log \frac{S_0}{S_s}$$

Where, So and Ss are solubilities of pure drug and solid dispersion in solvent respectively.

Surface morphology:

The shape and surface morphology of the solid dispersion was studied by scanning electron microscopy (SEM), JEOL JSM 6390, England. The samples were fixed on aluminium stubs with double-sided tape, gold coated sputter and examined in the microscope using an accelerating voltage of 15 kV, at a working distance of 8 mm and magnification of X500, X2000. study shows complete disappearance of crystal of drugs and confirms that drug is totally solubilized in solid dispersion system.

Preparation and Evaluation of fast dissolving core tablets:

Exact quantities of Solid dispersion (equivalent to 8 mg of pure drug LOR)and excipients i.e. Spray dried lactose (SDL), Microcrystalline Cellulose (MCC,) Croscarmellose Sodium, Crospovidone Sodium starch glycolate (SSG), were weighed, sieved through 60# separately, mixed in weight order, glidant and lubricant were added, compressed with 8mm flat and round punches. The composition of FDTs were given in **Table no:2&3** [33-37]. The FDT core tablets were tested for Weight variation, Friability,

Hardness, wetting time, disintegration time and *In-vitro* dissolution studies **[35,36,37]**.

***In-vitro* dissolution studies of solid dispersion and FDTs:**

Dissolution studies of pure drug (8mg) and solid dispersions (weight equivalent to 8 mg of pure drug) and FDTs were conducted in USP dissolution apparatus using 900 mL of pH 6.8 phosphate buffer at 37°C ± 0.5°C. At specific time intervals 5ml of aliquots were withdrawn and filtered, analysed spectrophotometrically at 376nm for drug release.

Study of Dissolution Parameters- (% DE), (MDT), T_{50}%, T_{75}%, T_{95}%:

Model independent parameters like Percent dissolution efficiency (%DE), mean dissolution time (MDT), T_{50}%, T_{75}%, T_{95}% were calculated to check the relative performance of carrier conc., in SDs. %DE, MDT values computed using below equations and PCP Disso v3 software (Pune, India). Time of Percent Drug Dissolved (T_{50}%, T_{75}%, T_{95}%) were calculated from dissolution graphs. (47)

$$DE = \frac{\int_0^t y \times dt}{y100 \times t} \times 100\%$$

Where y = amount of drug release up to specific time 't'

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}j\Delta Mj}{\sum_{j=1}^{n} \Delta Mj}$$

Where j = the sample number,
N = Number of dissolution sample times,
t^j = Time at midpoint between tj and tj−1
ΔMj = Amount of drug released between tj and tj−1.

Formulation of Lornoxicam Pulsatile tablets:

Lornoxicam Pulsatile tablets were prepared by coating core tablets with double layer of inner swelling layer and outer rupturable membrane coat. HPMC E15 used in inner coat as swelling layer and KGM Tac, Eudragit L100-50 and Triethyl citrate film former, pore former, plasticizer respectively in outer coat. Initially core tablets coated with10% HPMC E15 aqueous solution and 8% aq. solution of talc up to desired weight. Then outer coating was applied by spraying solution of KGM Tac, Eudragit L100-50, Triethyl citrate in a solvent mixture (Acetone: Isopropyl alcohol,70:30) in coating pan up to desired weight (**Table no.4**). The pan conditions were given (**Table no.5**). The Box-Behnken design (BBD) with 3 factors and 3 levels with 17 runs (**Table: 6)** was employed for the optimization study employing Design Expert software (version 10.1, Stat-Ease Inc., Minneapolis, USA). weight HPMC E15 (A), concentration of Eudragit-L100-50 (B) and membrane coating weight (C) were selected as independent variables and lag time in drug release (R1), Time for 75% drug release-$T_{75\%}$ (R2) were as selected as dependent variables. from the results, second order polynomial equations generated [38,39] and formula optimised using it.

$$R = b_0 + b_1A + b_2B + b_3C + b_4AB + b_5AC + b_6BC + b_7A^2 + b_8B^2 + b_9C^2$$

where R is the studied response, b_0–b_9 are the regression coefficients and A, B and C are the factors studied [42,43].

Dissolution studies of pulsatile tablets:

The dissolution studies for LOR pulsatile tablets were carried out using the USP dissolution apparatus II at 37 ± 0.5°C and 50 rpm for 2 h in pH 1.2 HCl (900 mL) proceeded by pH 6.8 phosphate buffer for another 7 hrs. At specific time intervals 5mL of aliquots were withdrawn and replaced with same volume of fresh medium to maintain sink conditions. The withdrawn samples were then analysed for amount of drug release at 376 nm [40,41]**.** The time taken for tablet to rupture its outer membrane was determined.

RESULTS AND DISCUSSION:

Calibration curve:

The UV absorption values of LOR at 376 nm in distilled water, HCl, phosphate buffer pH 6.8 and pH 7.4 were plotted against its concentrations **(Fig.1).** LOR showed good linearity (R^2 Values in distil water, HCl, PB pH 6.8, PB pH 7.4 were 0.9985,0.9989,0.9996,0.9992 respectively) between 5-30 µg/mL concentrations and obeyed Beer-Lambert's law.

Phase Solubility studies:

The phase solubility studies of LOR with different carriers PVPVA 64, Soluplus and Carriers with surfactants Lutrol F68, Lutrol F85, Lutrol F127 in distilled water were studied and observed increment in LOR solubility with respect to carrier concentration **Fig.no:2**.The phase diagram was shown A_L type graph with first order dependency as per Higuchi and Connors. The calculated apparent stability constant of for all dispersions was in the range of 3.82 to 10.67. The dispersion prepared with LOR, PVPVA64, Lutrol F127 in the ratio of 1:1.6:0.4 shown highest value.

Infrared spectroscopy:

The FTIR graph of pure LOR compared with reference for specific functional groups and confirmed its identity. FTIR spectrum of LOR has been showing specific absorption peaks of –NH2- (stretch) at 3052 cm^{-1}, strong band for C=O (stretch) at 1654.64 cm^{-1}

and O=S=O (bending) at 1325.28 cm^{-1},CO-NH- stretch at 1607.4, aliphatic C-H (stretch) at 1386.13 cm^{-1}.Similary formulation also shown IR absorption peaks –NH2-(stretch) at 3053 cm^{-1}, strong band for C=O stretch at 1669.64 cm^{-1} and O=S=O (bending) at 1326.51 cm^{-1},CO-NH- stretch at 1606.8, aliphatic C-H (stretch) at 1404.13 cm^{-1}. It was observed absorption peaks in pure drug and formulation, no much difference observed therefor it could be concluded that there was no strong interaction between drug and excipients. **Fig no.3,4.**

Solubility Studies:

The solubility of pure drug LOR has been studied in distilled H_2O, 0.1N HCl, phosphate buffer pH 6.8 it has been found 0.038 mg/mL, 0.025 mg/mL, 0.172 mg/mL respectively. The dispersions LSD1 & LSD2 prepared by using PVP VA64 shown 18.53-fold,25.86 - fold solubility increment respectively, whereas dispersions LSD3, LSD4 prepared with soluplus has been showing less increment value 16.46-fold, 21.96-fold in H_2O. Dispersions LSD5-LSD11 prepared by incorporation of Lutrol surfactants further enhanced up to 39.99-fold in H_2O. LSD11 Lutrol F127 shown remarkable improvement in solubility by 39.99-fold,28.26-fold, 45.34-fold H_2O, 0.1N HCl, PB pH 6.8 respectively. **Table no:7.**

Gibb's Free Energy and Drug content:

The Gibbs free energy (ΔG tr) data in **Table no:8** shown increment in negative values from -7516.77 to -9507.32 kJ/mol clearly favouring spontaneous solubility of LOR and confirms high, faster solubility in media. The drug content of all dispersion LSD1-LSD11 was found in between 95.38% to 98.75% and indicates complete mixing of drug with carrier complex and minimum material loss. Solubility and Gibbs free energy studies of pure drug and dispersions indicated that LOR solubility increased as a function of carrier and surfactants concentrations.

Surface morphology:

SEM photographs of optimised dispersion LSD11 were given in **Picture No:5.** The surface of particles showing complete mixing of drug and excipients and little surface irregularity without smoothness.

Dissolution studies of solid dispersion:

Dissolution studies of pure LOR and solid dispersions conducted, data presented in **Table No: 9 and 10**. **Figure no:6.** Pure LOR dissolved only 28.79 % in in 60 min whereas all the solid dispersions released the drug nearly 70- 99% in the stipulated 60 min time. Dispersions (LSD1 &LSD2) prepared with PVPVA64 showed higher drug release compared dispersions (LSD3 & LSD4) prepared with Soluplus. Hence PVPVA64 better candidate to select for further solubility enhancement. PVPVA64 & Lutrol surfactants combinations used to prepare dispersions from LSD6-LSD11, observed great improvement in drug release. Among 11 Dispersion, LSD11 showed faster drug release i.e 48% in 5 min and 99.7 % in 45min.

Study of Dissolution Parameters- (% DE), (MDT), T_{50}%, T_{75}%, T_{95}%:

Model independent parameters computed using formulas and by using PCP Disso v3 software (Pune, India), results were given in **Table no:8.** By comparing all dispersions, LSD11 showing highest values $\%DE_{10}$ and $\%DE_{20}$ 41.68,62.17 respectively. Least MDT, T_{50}%, T_{75}%, T_{95}% value i.e 8.26 min,5.3 min,11.76, 26.08 min. based on this parameter's surfactant Lutrol F127 improved the drug release synergistically.

Evaluation of fast Dissolving core Tablets:

15 batches (**LC1-LC15**) of FDTs were prepared by direct compression technique and presented to *invitro* Q.C tests weight variation, hardness, friability, disintegration time, wetting time and drug content and results given in **Table no:11**. Average weight of FDTs ranges from 99.85 -102.12mg , % friability ranges from 0.283 to 0.831% and Drug content ranges from 99.77 – 100.01 % , Hardness ranges from 3.83 to 4.25 kg/cm^2 which were meets official requirements as per IP. The average wetting time of all FDTs was in the range of 31-217 seconds. Disintegration time of FDTs were shown in the range of 39 to 240 seconds and proved that the disintegration time decreases with increment in Disintegrant in tablets. Among 15 batches, LC13 batch prepared by using mixture of disintegrating agents (6%w/w Crosspovidone,1%w/w Crossmellose Sodium,1% w/w SSG) shown least disintegration time (39sec).

Dissolution studies of LOR FDTs:

Dissolution studies of FDTs carried in PB pH 6.8 and results were shown in **Figure no :7 and 8**. The results demonstrated that as disintegrant concentration increases the from 2% to 8%, the drug release was fastened. Out of 15 FDTs, it was observed that LC13 FDTs prepared with mixture of disintegrants shown rapidity in rapid release i.e 66.2% in 10 min and 99.2% in 45 min.

Statistical Optimization of pulsatile tablets:

17 batches of pulsatile tablets prepared as per design study, subjected to Rapture test and dissolution studies to determine lag Time (R1) and the $T_{75\%}$ (R2),the results were given in **Table No:6**. The multiple regression analysis was conducted using the Design Expert software (version 10.1), to find Significant model which fits data which was selected

based on highest Regression coefficient (R^2), Insignificant Lack-of-Fit Test , lesser PRESS value. The results were given in **Table No: 12 and 13**. Based on the table no:7 &8, for quadratic model shown lesser PRESS value (2.45 for R1,141 for R2) and higher adjusted R^2 value (Lag time R^2 = 0.9524, $T_{75\%}$ R^2 =0.9624) and Lack-of-Fit Test value was lowest (R1=0.5282, R2= 0.339) and insignificant. There Quadratic model selected for generation of polynomial equation as follows.

R1: Lag Time = 4.73 - 0.7342 A - 0.4622 B + 1.18 C - 0.2550 AB - 0.5375 AC + 0.0055BC
+ 0.3600 A^2 + 0.4365 B^2 - 0.3559 C^2

R2: $T_{75\%}$ = 5.19 - 0.6891 A - 0.4994 B + 1.20 C - 0.2530 AB - 0.6258 AC + 0.0087 BC
+ 0.3298A^2 + 0.4508 B^2 - 0.4154 C^2

Response surface Analysis conducted on data, generated 2-D contour plot and 3-D response surface plots to check the effect of independent factors on responses variables2-D contour plot and 3-D response surface plots. (**Fig No:9,10)** and showed linearity between the independent factors and response. Further it was observed that factor C: Membrane Coating weight shown highest influence on responses when comparing other factors.

Optimization of pulsatile Tablets:

BBD was used for optimisation of formulation, overlay plots were also generated for given responses with Constraints (lag time: 6hr, T75% 6.3 hr). **Fig No:11** suggested optimized formulation with 20 % w/w, 24.72 w/w and 10.69 % w/w of A, B and C, it was prepared, evaluated for responses and given in **Table No:14**. The optimised formulation shown responses with an acceptable relative error 0.0495 - 0.0483.

Fig no.1: Lornoxicam calibration curve in phosphate buffer pH 6.8.

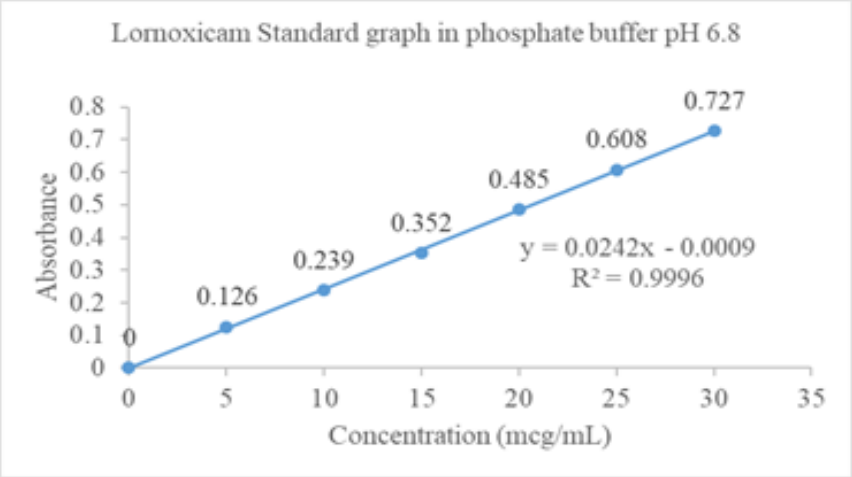

Fig No.2: Results of lornoxicam phase solubility studies

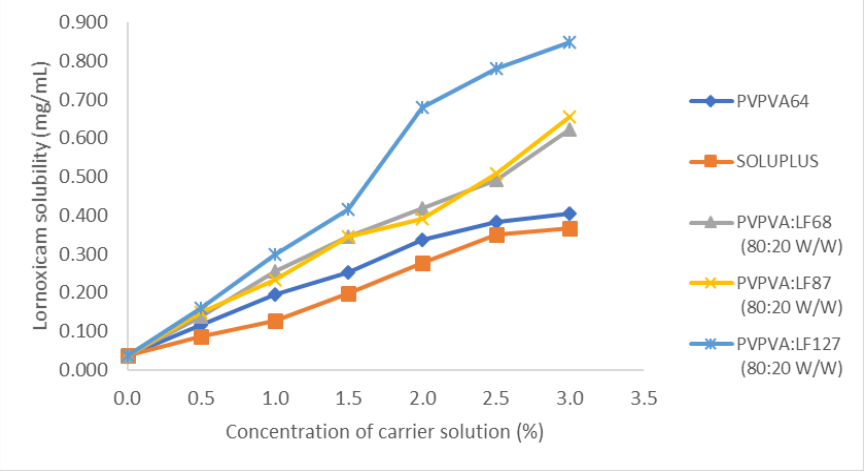

Fig. No. 3: FTIR Graph of lornoxicam

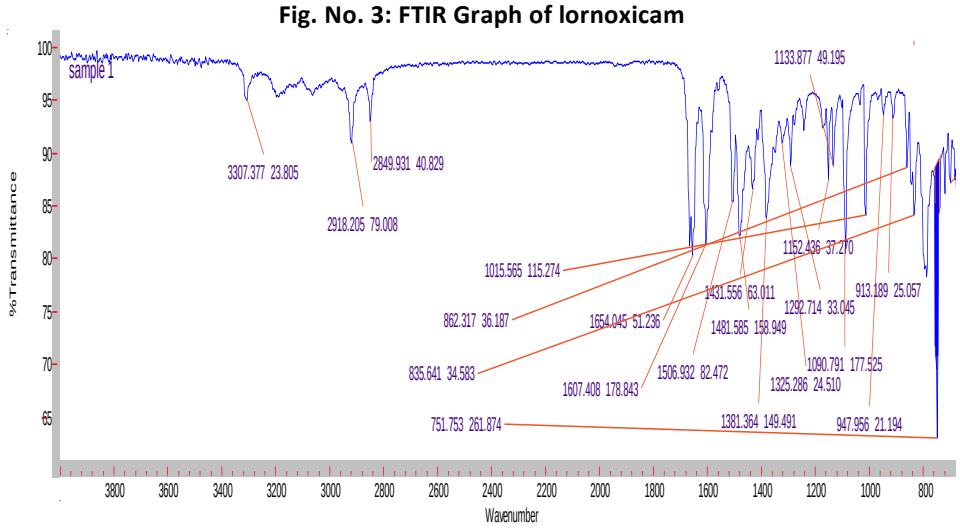

Fig No.4. FTIR graph of Final formulation

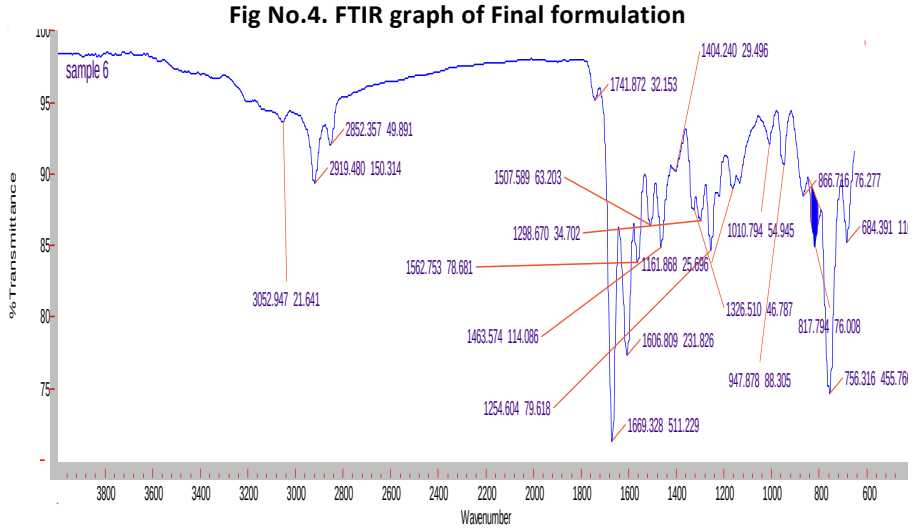

Fig.No.5: SEM photographs of LSD11 solid dispersion

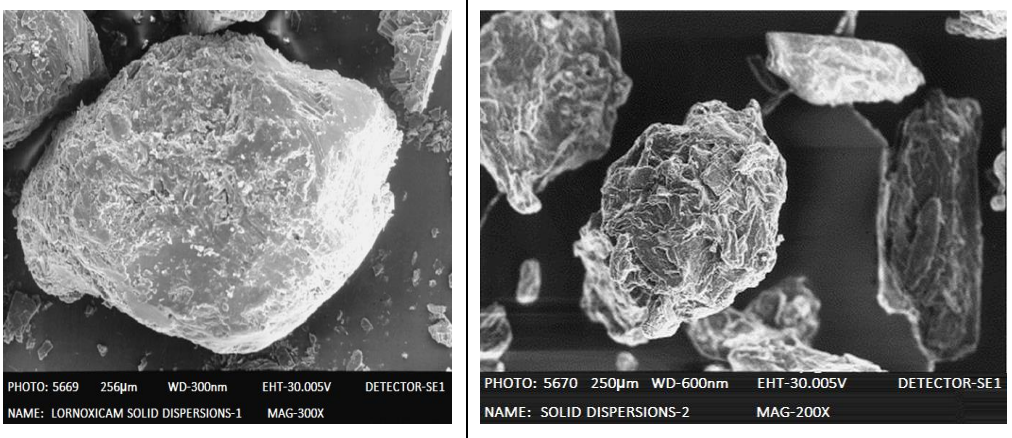

Fig.No.6: Comparison of *invitro* dissolution profiles of lornoxicam pure drug and solid dispersions (LD1-LSD11)

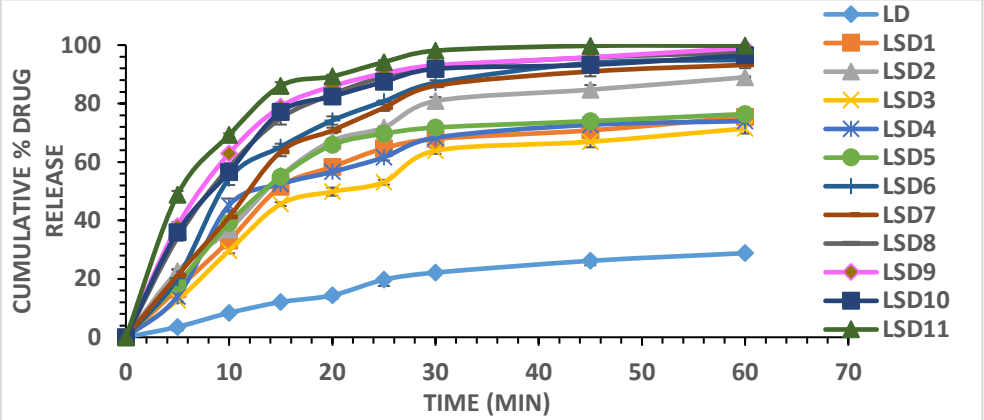

Fig.No.7: Comparison of *invitro* dissolution profiles of lornoxicam fast dissolving tablets (LC1-LC8)

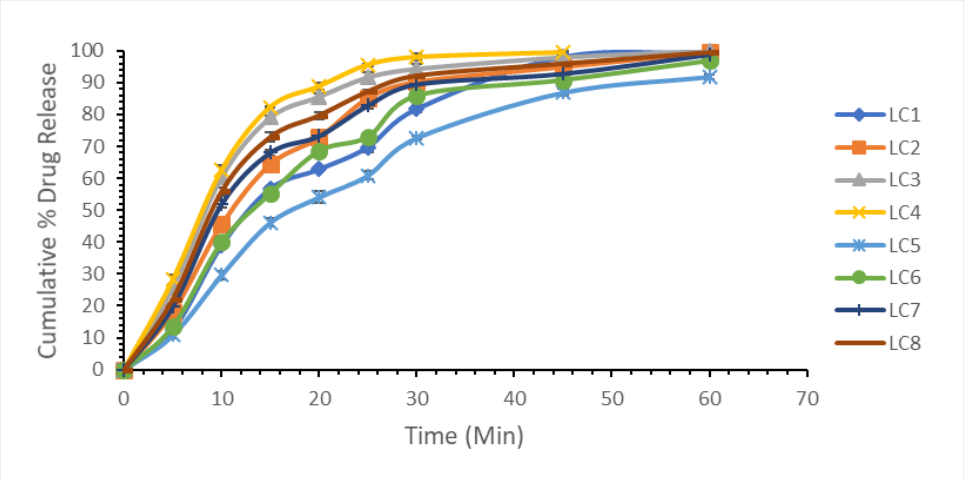

Fig.No.8: Comparison of *invitro* dissolution profiles of lornoxicam fast dissolving tablets (LC9-LC15)

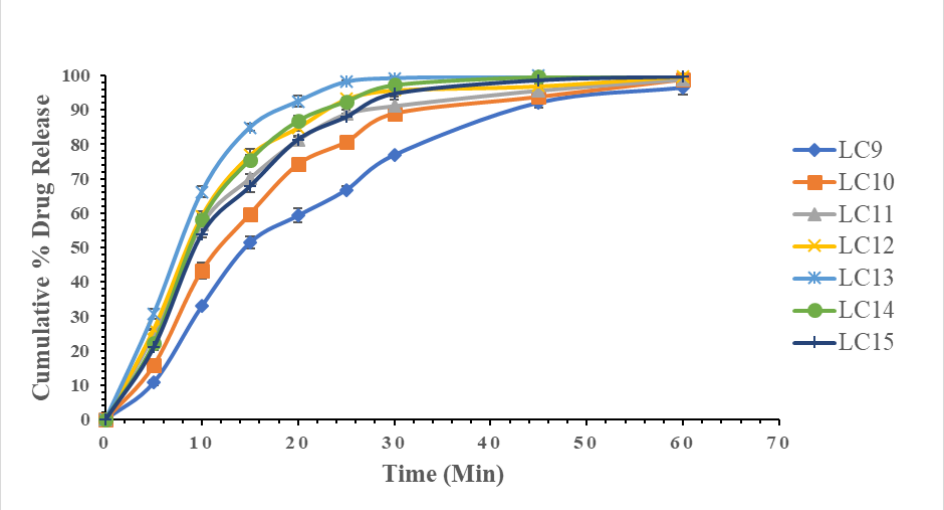

Fig.No.9:72-D Counter plot showing the effect HPMC E15 and membrane coat weight on Lag Time at medium level of membrane coat weight

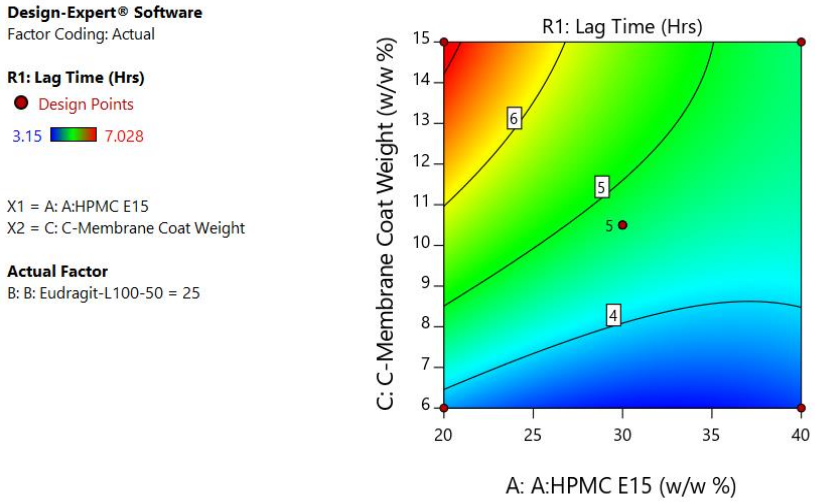

Fig.no.10: 3-D Response surface plots showing the effect HPMC E15 and membrane coat weight on Lag Time at medium level of membrane coat weight.

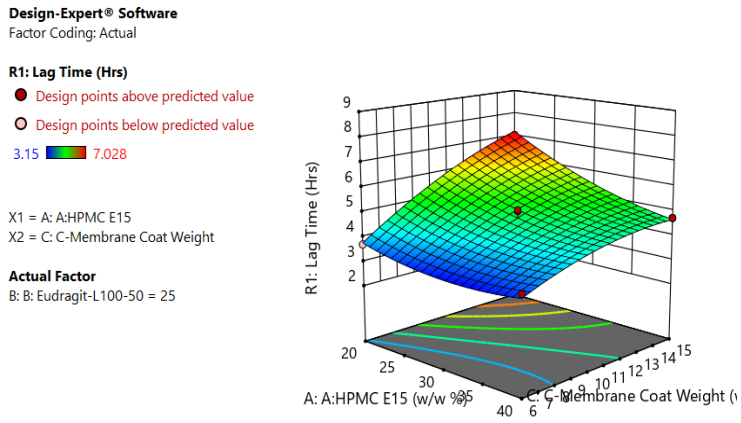

Fig.no.11: Overlay Plot showing predicted independent and dependant variables for optimised pulsatile tablets.

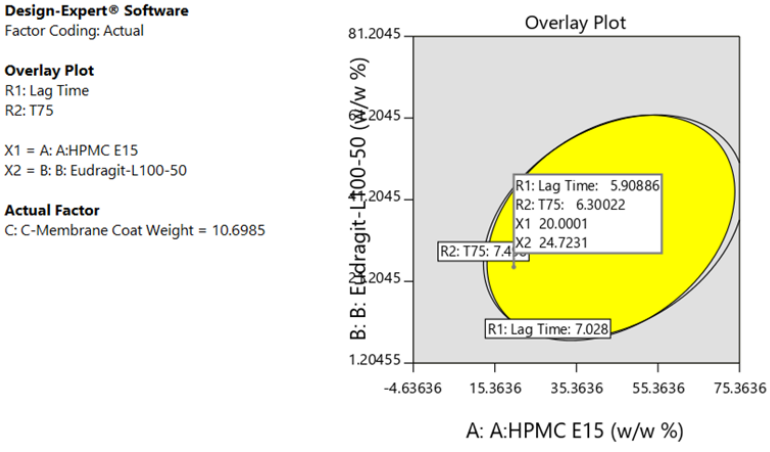

Table No.1: Composition of lornoxicam solid dispersions

S.No	Formulation Code	Drug: Carrier (or) Carrier Mixture	Drug: Carrier Ratio
1	LD	Lornoxicam (LOR)	--
2	LSD1	LOR: PVPVA 64	01:01
3	LSD2	LOR: PVPVA 64	01:02
4	LSD3	LOR: SOLUPLUS	01:01
5	LSD4	LOR: SOLUPLUS	01:02
6	LSD5	LOR: PVPVA 64: SOLUPLUS	01:01:01
7	LSD6	LOR: PVPVA 64: LUTROL F68	1:1.8:0.2
8	LSD7	LOR: PVPVA 64: LUTROL F87	1:1.8:0.2
9	LSD8	LOR: PVPVA 64: LUTROL F127	1:1.8:0.2
10	LSD9	LOR: PVPVA 64: LUTROL F68	1:1.6:0.4
11	LSD10	LOR: PVPVA 64: LUTROL F87	1:1.6:0.4
12	LSD11	LOR: PVPVA 64: LUTROL F127	1:1.6:0.4

Table No.2: Composition of lornoxicam fast dissolving core tablets (LC1 –LC8)

S.No	Ingredient	Composition of FDTs							
		LC1	LC2	LC3	LC4	LC5	LC6	LC7	LC8
1	S.D* (≈8 mg of Lornoxicam)	24.33	24.33	24.33	24.33	24.33	24.33	24.33	24.33
2	Crospovidone sodium	2	4	6	8				
3	sodium starch glycolate					2	4	6	8
4	Croscarmellose sodium								
5	Spray dried lactose	51.67	49.67	47.67	45.67	51.67	49.67	47.67	45.67
6	Micro crystalline Cellulose	20	20	20	20	20	20	20	20
7	Talc	1	1	1	1	1	1	1	1
8	Magnesium Stearate	1	1	1	1	1	1	1	1
Total weight of tablet (mg)		**100**	100	100	100	100	100	100	100

Table No.3: Composition of lornoxicam fast dissolving core tablet (LC9-LC15)

S.No	Ingredient	Composition of FDTs						
		LC9	LC10	LC11	LC12	LC13	LC14	LC14
1	S.D* (≈8 mg of Lornoxicam)	24.33	24.33	24.33	24.33	24.33	24.33	24.33
2	Crospovidone sodium					6	4	2
3	sodium starch glycolate					1	2	3
4	Croscarmellose sodium	2	4	6	8	1	2	3
5	Spray dried lactose	51.67	49.67	47.67	45.67	45.67	45.67	45.67
6	Micro crystalline Cellulose	20	20	20	20	20	20	20
7	Talc	1	1	1	1	1	1	1
8	Megnesium Stearate	1	1	1	1	1	1	1
Total weight of tablet (mg)			100	100	100	100	100	100

Table No.4: Composition of different parts of the pulsatile tablet.

S.No	Tablet portion	Ingredients	Quantity
1	Core Tablet	Solid Dispersion + Others	100 mg
2	**First Layer -** Swellable Layer	HPMC E15	20- 40 % w/w
		Talc	Q. S
		Water	Q. S
3	**Second Layer** -Membrane coat	KGM Triacetate	45 – 75 %
		Eudragit L100-50	15-35 %w/w
		Triethyl citrate	10%

	Talc	Q. S
	Acetone + IPA (70:30)	Q. S

Table No.5: Formulation of TAPS: Process or Pan parameters for application of inner and outer coatings on core tablet.

S. No	Process or Pan parameter	Set Value
1	Bed temperature	40^{o} C
2	spray rate	5mL / min
3	spray time	Up to weight gain
4	Spray nozzle aperture size	1 mm
5	Spray pressure	1.2 bars
6	Pan speed	20 rpm
7	Drying in equipment	10 min

Table No.6: Box-Behnken Design for preparation of pulsatile tablets.

Run	Batch code	Independent variable			Dependent variable	
		Actual values			R1:(Hr))	R2:(hrs)
		A (%w/w)	B (%w/w)	C (%w/w)		
1	LM1	20	25	15	7.028	7.498
2	LM2	40	35	10.5	3.939	4.467
3	LM3	30	15	6	4.028	4.484
4	LM4	40	15	10.5	5.431	5.974
5	LM5	30	35	15	5.611	5.993
6	LM6	20	15	10.5	6.611	6.977
7	LM7	30	35	6	3.15	3.47
8	LM8	40	25	6	3.522	3.971
9	LM9	40	25	15	4.706	4.999
10	LM10	30	15	15	6.467	6.972
11	LM11	30	25	10.5	4.556	5.029
12	LM12	30	25	10.5	4.569	4.967
13	LM13	20	35	10.5	6.139	6.482
14	LM14	30	25	10.5	5.006	5.507
15	LM15	30	25	10.5	5.064	5.471
16	LM16	30	25	10.5	4.472	4.998
17	LM17	20	25	6	3.694	3.967

Table no.7: solubility data of lornoxicam in different media.

S.D. CODE	SOLUBILITY (mg/mL) (Mean±SD, n=3)					
	Distill water (mg/mL) (Mean ± SD)	No of fold Solubility Increased 'n'	0.1N Hcl (mg/mL) (Mean ± SD)	No of fold Solubility Increased 'n'	Phosphate Buffer 6.8 (mg/mL) (Mean ± SD)	No of fold Solubility Increased 'n'
LD	0.038±0.001	--	0.025±0.001	--	0.172±0.002	--
LSD1	0.702±0.007	18.53	0.338±0.003	13.52	2.693±0.004	15.66
LSD2	0.987±0.004	25.86	0.456±0.004	18.25	3.821±0.004	22.21
LSD3	0.625±0.002	16.46	0.328±0.006	13.10	2.810±0.004	16.34
LSD4	0.835±0.003	21.96	0.396±0.003	15.83	3.878±0.006	22.55
LSD5	0.865±0.005	22.63	0.432±0.003	17.30	3.289±0.003	19.12
LSD6	1.112±0.006	29.35	0.513±0.005	20.51	6.251±0.006	36.34
LSD7	1.139±0.004	29.95	0.484±0.002	19.37	5.953±0.007	34.61
LSD8	1.458±0.004	38.37	0.687±0.004	27.49	7.192±0.003	41.81
LSD9	1.326±0.005	34.95	0.613±0.010	24.53	6.468±0.030	37.60

LSD10	1.290±0.005	34.11	0.595±0.010	23.8	6.181±0.015	35.94
LSD11	1.519±0.003	39.99	0.706±0.004	28.26	7.798±0.006	45.34

Table no.8: Evaluation parameters of solid dispersion

S.D Code	Gibbs Free Energy ΔG tr (kJ/mol)	Drug content (% w/w) (Mean ± SD)	% Yield (Mean ± SD)	$T_{50\%}$	$T_{75\%}$	$T_{95\%}$	$\%DE_{10}$	$\%DE_{20}$	MDT
LD	--	--	--	152.89	263.85	352.62	3.87	7.78	21.12
LSD1	-7516.77	95.38±0.219	93.3±0.432	14.58	58.69	124.01	16.52	32.57	14.54
LSD2	-8395.81	98.02±0.056	92.8±0.368	13.58	26.78	82.52	20.49	37.06	14.87
LSD3	-7217.44	96.95±0.32	94.1±0.665	20.26	74.70	152.86	13.76	28.21	16.15
LSD4	-7963.59	96.62±0.513	95.9±0.668	13.30	61.00	157.13	18.29	34.99	12.99
LSD5	-8056.86	95.33±0.288	93.2±0.624	13.44	51.15	180.83	18.92	36.31	12.36
LSD6	-8703.03	98.62±0.586	95.6±0.531	9.36	20.62	54.92	23.69	42.2	12.98
LSD7	-8765.31	96.39±0.813	96±0.249	11.98	22.71	71.88	20.91	40.32	13.86
LSD8	-9401.32	98.75±0.714	96.5±1.042	8.30	15.03	43.50	31.59	52.21	10.86
LSD9	-9157.88	96.45±0.236	96.3±0.694	7.40	13.78	40.57	34.77	55.7	10.61
LSD10	-9085.61	98.27±0.176	94.1±0.694	8.41	14.47	53.08	32.1	52.72	10.91
LSD11	-9507.33	98.65±0.504	94.3±0.499	5.30	11.72	26.08	41.68	62.17	8.26

Table No.9: Dissolution data of solid dispersion batches LD-LSD5

Time (Min)	% Cumulative Drug Release (Mean ± SD, n=6)					
	LD	LSD1	LSD2	LSD3	LSD4	LSD5
0	0±0	0±0	0±0	0±0	0±0	0±0
5	3.57±1.3	16.48±1.37	22.56±0.79	12.71±0.9	13.97±1.64	18.31±0.64
10	8.33±0.77	33.09±0.85	36.86±1.14	29.64±0.91	45.20±2.26	39.08±1.34
15	12.05±0.56	51.56±1.54	55.19±0.24	45.58±0.65	52.47±1.74	54.96±1.01
20	14.35±1.26	58.30±0.78	67.23±0.63	49.83±1.38	56.61±0.65	65.81±0.54
25	19.71±2.16	64.68±0.55	71.77±0.37	53.06±0.83	61.58±1.08	69.67±0.42
30	22.13±0.95	67.93±1.16	80.86±1.31	63.85±1.06	68.32±1.44	71.78±0.55
45	26.15±1.51	70.81±2.21	84.73±1.59	66.91±1.90	72.71±0.36	73.98±0.92
60	28.79±0.49	75.40±0.94	88.97±0.33	71.43±1.70	73.98±0.54	76.40±0.39

Table no.10: Dissolution data of solid dispersion batches LSD6-LSD11

Time (Min)	% Cumulative Drug Release (Mean ± SD, n=6)					
	LSD6	LSD7	LSD8	LSD9	LSD10	LSD11
0	0±0	0±0	0±0	0±0	0±0	0±0
5	20.21±1.34	21.22±1.84	34.08±1.01	38.09±1.75	35.91±1.12	48.75±1.33
10	54.35±2.24	41.19±2.30	58.21±1.39	62.88±0.49	56.57±1.06	69.22±0.55
15	65.16±1.08	63.47±1.52	74.95±2.15	78.90±1.78	77.19±1.81	86.04±1.25
20	74.19±1.41	70.79±0.96	83.17±2.16	85.86±1.21	82.39±0.71	89.29±0.60
25	80.74±0.34	78.56±1.09	89.20±0.91	90.27±1.14	87.44±1.35	94.15±0.64
30	87.05±0.90	86.08±0.45	92.56±1.13	93.05±1.61	91.87±1.25	98.08±0.16
45	93.84±0.63	90.96±1.65	95.72±0.30	95.82±1.04	93.23±1.30	99.74±0.09
60	94.92±1.32	93.21±1.12	97.48±0.62	99.01±0.39	96.52±1.18	99.79±0.04

Table no.11: Post compression test results of LOR fast dissolving tablets.

Batch	Avg.weight (Mean±SD) (mg)(n=20)	Thickness (Mean±SD) (mm)(n=6)	Hardness (Mean±SD) (Kg/cm^2)(n=3)	Friability (Mean±SD) (%)(n=3)	Disint.Time (Mean±SD) (Sec)(n=6)	Wet.Time (Mean±SD) (Sec)(n=6)
LC1	100.50±1.443	2.29±0.052	3.83±0.25	0.78±0.362	221±7.44	198±5.177
LC2	100.12±0.942	2.32±0.033	3.92±0.20	0.697±0.148	131±5.132	119±4.643
LC3	99.85±1.173	2.27±0.025	4.08±0.32	0.581±0.027	74±2.915	64±3.512
LC4	101.31±2.325	2.31±0.120	4.17±0.51	0.616±0.153	58±2.156	45±4.15
LC5	100.66±2.577	2.25±0.099	3.92±0.20	0.666±0.224	240±8.616	217±4.163
LC6	100.36±1.281	2.33±0.073	3.83±0.25	0.672±0.204	155±4.115	139±6.938
LC7	101.15±1.267	2.21±0.085	3.92±0.20	0.789±0.351	104±3.391	90±3.625
LC8	100.77±1.485	2.17±0.034	4.17±0.51	0.818±0.107	83±3.935	73±5.375
LC9	100.15±0.940	2.28±0.081	4.00±0.32	0.831±0.048	226±4.665	194±4.375
LC10	102.12±2.489	2.25±0.025	3.83±0.25	0.728±0.056	119±3.36	107±4.45
LC11	100.81±1.305	2.39±0.046	4.00±0.32	0.283±0.059	87±3.391	76±2.631
LC12	101.37±2.626	2.30±0.076	4.17±0.24	0.696±0.164	72±3.293	55±3.197
LC13	100.50±1.822	2.35±0.028	3.92±0.20	0.627±0.269	39±3.250	33±3.902
LC14	100.29±1.513	2.16±0.016	4.25±0.40	0.360±0.124	64±3.878	57±5.538
LC15	101.01±1.665	2.2±0.085	3.83±0.26	0.614±0.240	72±2.993	63±3.287

Table no.12: Model Summery statistics and lack of fit tests:

Source	R^2		Adjusted R^2		PRESS		F-value		p-value	
	R1	R2	R1	R2	R1	R2	R1	R2	R1	R2
Linear	0.8229	0.8062	0.7820	0.7615	7.20	8.25	4.83	6.64	0.072	0.042
2FI	0.891	0.8915	0.8256	0.8263	9.54	10.16	4.2	5.22	0.093	0.0658
Quadratic	**0.9792**	**0.9836**	**0.9524**	**0.9624**	**2.45**	**1.41**	**0.5282**	**0.339**	**0.6865**	**0.7996**
Cubic	0.9851	0.9864	0.9403	0.9454	Cubic model aliased - **Quadratic-suggested**					

Table no.13: ANOVA results for Quadratic model:

Source	Sum of Squares		df	Mean Square		F-value		p-value	
	R1	R2		R1	R2	R1	R2	R1	R2
Model	20.36	21.03	9	2.26	2.34	36.53	46.53	< 0.0001	< 0.0001
A	4.31	3.8	1	4.31	3.8	69.66	75.64	< 0.0001	< 0.0001
B	1.71	2	1	1.71	2	27.61	39.72	0.0012	0.0004
C	11.09	11.45	1	11.09	11.45	179.07	227.92	< 0.0001	< 0.0001
AB	0.2601	0.256	1	0.2601	0.256	4.2	5.1	0.0796	0.0585
AC	1.16	1.57	1	1.16	1.57	18.66	31.18	0.0035	0.0008
BC	0.0001	0.0003	1	0.0001	0.0003	0.002	0.0061	0.966	0.9399
A^2	0.5458	0.458	1	0.5458	0.458	8.82	9.12	0.0208	0.0194
B^2	0.8024	0.8557	1	0.8024	0.8557	12.96	17.04	0.0087	0.0044
C^2	0.5335	0.7267	1	0.5335	0.7267	8.62	14.47	0.0219	0.0067
Residual	0.4334	0.3516	7	0.0619	0.0502				
Lack of Fit	0.123	0.0597	3	0.041	0.0199	0.5282	0.2729	0.6865	0.8428
Pure Error	0.3104	0.2919	4	0.0776	0.073				
Total	20.79	21.39	16						

Table No.14: *Invitro* evaluation of optimised formulation. Comparison of results.

Dependent variable	Predicted Value	Observed Value	Relative error
R1: Lag Time (Hrs)	5.909	5.70	0.0495
R2: $T_{75\%}$ (Hrs)	6.30	5.993	0.04873

CONCLUSION:

Lornoxicam is an oxicam derivative belongs to non-steroidal anti-inflammatory drugs (NSAID) used to treat acute and chronic pain. Lornoxicam is poorly soluble BCS-II drug. For better bioavailability it is was very essential to improve its Solubility and dissolution. Solubility of LOR has been enhanced by preparing solid dispersion by solvent evaporation technique using PVP VA64 soluplus and Lutrol surfactants as carriers and found solubility of lornoxicam was increased by 39.99-fold,28.26-fold, 45.34-fold in distilled water, 0.1N HCl, PB pH 6.8 respectively in LSD11 dispersions. 15 batches of FDTs prepared to improve the dissolution and dissolution rate of the drug different super disintegrants alone and mixture. 15 FDTs batches prepared, subjected to QC tests and found LC13 batch shown rapid disintegration time (39 sec) and 90% of drug release in 20min. By using LC13 batch tablets pulsatile tablets were prepared to treat pain in rheumatoid arthritis observed at early morning. pulsatile tablets were prepared by utilising HPMC E15, KGM Triacetate, EudragitL100-50 and triethyl citrate. Box-Behnken design employed for optimisation of formula. The optimised tablets were produced predicted lag time when subjected to *in vitro* studies.

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