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Formulation and Evaluation of Lornoxicam Fast dissolving tablets

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ABSTRACT

Lornoxicam, is a widely prescribed Non-steroidal anti-inflammatory drug belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. It needs enhancement in the dissolution rate in its formulation development. The main objective was to formulate and evaluate Lornoxicam FDT by incorporating the Lornoxicam solid dispersion to enhance dissolution rate and solubility rate with the aid of novel polymers by adopting design of experiment CCD software technology. Nine SD formulations prepared with varying concentrations of PEG 4000, Labrasol, Soluplus, Kolliphor EL, Kolliwax GMS II, HPMC, Colloidal Silicone dioxide (Aerosil 200), and PVPK25 in three different drugs : polymer : surfactant (SLS) ratios of1:1:1,1:2:1 and 1:3:1 by solvent evaporation method and were evaluated for drug content,% practical yield and dissolution rate and solubility studies. The solubility study indicates that formulation (SD9) containing drug: Soluplus (1:3) and SLS has superior solubility of 0.68±0.10µg/ml, which is 75-fold higher than pure drug. The formulations SD9 maximum percentage yield and drug content. The optimized Lornoxicam solid dispersion (SD9) was further used to prepare FDT by direct compression method using 3^3 Response surface method (3variables and 3 levels of super disintegrants) by using Design of experiments of tware with super disintegrants like locust bean gum, gum karaya, plantago ovate and diluents such as mannitol, Avicel PH101 and aspartame as sweating agent and aerosol as anti adherent. Total 27 Lornoxicam FDTs formulated using natural super disintegrants locust bean gum, gum karaya, plantago ovate mucilage with varying concentrations by design of experiment tool. All the formulations evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, disintegration time, *in vitro* drug release studies. The formulation LF24 showed highest drug release of 99.21±1.87 % at 10mins. LF24 was found to be optimized formulation which contains different concentrations of locust bean gum, gum karaya, plantago ovate mucilage the results were analysed by ANOVA and FTIR studies which shows no interaction between the ingredients. The % CDR of Lornoxicam FDT (LF24) was much higher than that of Lornoxicam marketed formulation. Thus, Lornoxicam FDTs using natural super disintegrants like locust bean gum, gum karaya, plantago ovate mucilage were suitable combinations for formulating Lornoxicam FDTs.

Keywords: Lornoxicam fast dissolving tablets, central composite design(CCD), Locust bean gum, gum karaya, plantago ovate mucilage super disintegrants, mannitol, AvicelPH101 aspartame, FTIR studies.

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INTRODUCTION

About 95% of all new potential therapeutic drugs (APIs) exhibit low and variable oral bioavailability due to their poor aqueous solubility at physiological pH and consequent low dissolution rate. These drugs are classified as class II drugs under BCS with low solubility and high permeability characters. These BCS class II drugs process challenging problems in their pharmaceutical product development process. Lornoxicam, a widely prescribed Non-steroidal anti-inflammatory drug (NSAID) belongs to class II under BCS classification and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Because of poor aqueous solubility and dissolution rate it poses challenging problems in its tablet formulation development. It needs enhancement in the dissolution rate in its formulation development. Fast disintegration drug delivery system is intended at enhancing efficacy and drug bioavailability of presented drugs, reduction in drug dosing frequency, minimizes side effect and enhances patient compliance. Fast disintegration dosage forms are disintegrated by saliva. The formulations with lower solubility are a challenge for formulation researchers; solubility enhancement is major issue for ideal bioavailability. Solid dispersions (SDs) are traditional techniques used for enhancing dissolution properties and bioavailability of sparingly soluble drugs. The current study is aimed at formulation SD of selected drugs and incorporating into fast dissolution tablets for enhanced bioavailability. In the present work an attempt has been made to improve the solubility of Lornoxicam by solid dispersions using solvent evaporation method along with the aid of novel polymers and further incorporating into fast disintegrating tablets by adopting design of experiment.

MATERIALS AND METHOD

Lornoxicam, the API was procured from aurobindo pharma lab, Hyderabad. Super disintegrants such as locust bean gum, gum karaya, plantago ovate are obtained from yarrow chemicals, Mumbai. All the fine chemicals such as Avicel PH101, mannitol, aspartame, aerosil, talc and magnesium stearate are obtained from commercial sources. All other materials used were pharmacopoeial grade.

METHODS

Estimation of Lornoxicam

An UV Spectrophotometric method by using (ElicoSL164Doublebeam Spectrophotometer) based on the measurement of absorbance at 376nm in Phosphate buffer of pH 6.8 was used for the estimation of Lornoxicam. The method was validated for linearity, Accuracy and precision. The method obeyed Beer's law in the concentration range of 1 – 10µg/ ml.

Preparation of Lornoxicam SD

The Lornoxicam SD prepared in varying concentrations of Soluplus, Kolliwax GMS II, HPMC and SLS (1:1:1, 1:2:1 and 1:3:1) (table 8.3). Nine Lornoxicam SD formulations prepared as per the procedure described in formula table 1

Formulation of Lornoxicam FDT Tablets

Lornoxicam FDT prepared by direct compression technique. Twenty-seven formulations (LF1-LF27) for active layer were prepared using 3^3 RSM using super disintegrants like locust bean gum, gum karaya and plantago ovata. The formulations prepared with varying concentration of super disintegrants, and magnesium stearate. The contents sieved via #60 and mixed manually. The final mixture compressed with 8mm flat punches using eight station rotary tablet press. (Table 3.4).The FDTs are prepared as per formula given in table 2. The prepared tablets analyzed for drug dissolution.

Design of Experiment

Central composite designs (CCD) are frequently used optimization designs that employs 5 level of each input factor with a reduced experiment number compared to three-level full factorial design. Twenty-seven formulations (LF1-LF27) were prepared by direct compression method using3^3 Response surface method where indicates variables and 3 levels of super disintegrants like locust bean gum, gum karaya, Plantago ovate mucilage (low, middle and high concentrations) by using Design of experiment software.

Statistical analysis

Data were analyzed using Stat-Ease Design Expert ® software V8.0.1 to obtain analysis of variance (ANOVA), regression coefficients and regression equation. Mathematical relationships were generated by multiple linear regression analysis for the mentioned variables that demonstrates. The effects of amount of gellan gum(A), amount of fenugreek seed mucilage (B) and amount of L-HPC(C) and their interaction on % CDR and DT.

Evaluation of Lornoxicam FDTs

All the Lornoxicam FD tablets prepared were evaluated for pre compression and post compression evaluation tests such as angle of repose, bulk and tapped density, Hausner's ratio and compressibility ratio, drug content, weight variation, hardness, friability, disintegration time and dissolution rate as follows:

Angle of repose

Angle of repose signifies highest angle achievable between tablet surface and the horizontal plane. A rough and irregular surface exhibit larger angle of repose. Weight accurately 100 gm of the blend and are cautiously poured through funnel with tip placed 2.5 cm height over the graph paper

that is positioned on a horizontal surface. The powder is poured till apex of pile just reaches funnel tip.

Angle of repose is calculated by the following formula

$$\Theta = \text{Tan}^{-1}(h/r)$$

Where Θ = angle of repose, r = radius, pf pile, h = height of the pile

Bulk density

Bulk density is powder mass divided by the bulk volume. It is analyzed by pouring the powder blend into graduated cylinder to determine volume (V*) and powder (M). The bulk volume calculated as

$$b = M/V^*$$

Tapped density

This is calculated by tapping a cylinder containing accurately weighed powder blend for about 250 times. Tapped density is calculated as

V_t– minimum volume occupied M-mass of the blend.

$$^*t = M/V_t$$

Compressibility Index (Carr's Index)

Carr's index (CI) signifies the easiness with which a material can be encouraged to flow. CI value <10 indicates excellent powder flow while value between 26-31 indicates power flow

The CI calculated as follows

$$\text{C.I (\%)} = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density}}$$

Hausner's Ratio

Hausner's ratio is an indicator of easiness of powder flow calculated as follows

Hausner's ratio=*dt/*db.

Where*dt =tapped density, *db =bulk density

Post compression evaluation tests

Weight variations

20 random FDTs weighed and average weight determined. Then individual tablet weighed separately to obtain %deviation from the average. The accepted deviation for tablets with average weight ≤ 130mg is 10%, for ≥130 mg is 7.5%.

Thickness

Thickness of tablet is crucial for patient acceptance and packaging hence to be controlled at ±5% deviation from standard value. Vernier Calipers used for measurement of thickness of 10 FDTs.

The average and SD values recorded (Anroop N et al., 2007).

Hardness

Monsanto hardness tester was used for determination of hardness of randomly picked 10 tablets and average of measured values reported (Nerurkar J et al., 2005).

Friability

20 tablets randomly picked were weighed and subjected to friability test in Roche friabilator that Rotated at 25 rpm for duration of 4min. Tablets were then reweighed after de-dusting(Ismat U, 2011) and following equation was used to calculate percent loss in weight due to impact and abrasion, %Friability=(Loss in weight / Initial weight)X100.

Content uniformity

Randomly picked 20 tablets were powdered in a glass mortar after calculating the average weight and amount equal to 10 mg was dissolved in 100ml of phosphate buffer pH 6.8 and filtered followed by spectrometric determination of drug content at 369 nm (Nerurkar J et al., 2005).

In-vitro disintegration time (DT)

The DT of FDTs analyzed in USP device with six glass tubes measuring“3 long, open at the top, and held against10”screen at lower end of the basket rack congregation. One tablet positioned in each tube with basket rack positioned in 1000ml beaker containing buffer at 37± 2 ^{0}C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. (Daniel and J. Axel, 2015)

Dissolution Rate Study

Dissolution rate of Lornoxicam tablets prepared was studied in phosphate buffer of pH 6.8 (900 ml) employing eight station dissolution rate test apparatus (ELICO double beam UV spectrophotometer) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 0.2°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter. at different time intervals such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 mins and assayed for Lornoxicam at 376 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

Accelerated Stability Studies

Accelerated three months stability tests were carried out for the optimized FDT in a stability chamber at 40 ^{0}C / 75 % RH post wrapping the FDTs in aluminum foil and sealing into ambered bottles (Irwin J et al., 1999).

Analysis of Data

Dissolution rate (K1) values were analyzed as per ANOVA of 3^3 factorial experiments and FTIR studies.

RESULTS AND DISCUSSION

Preliminary Solubility Studies of Lornoxicam

The solubility of Lornoxicam pure drug is 0.0085±0.09µg/ml. The solubility of physical mixture drug and Soluplus in equimolar ratio exhibits maximum drug solubility of 0.2125±0.13µg/ml, which is 25 times higher than pure drug. The results indicate that Labrosol, PEG 4000, PVP K 25, Kolliphor EL and Aerosil 200 that exhibited low solubility are not involved in Lornoxicam SD formulation (Figure 1)

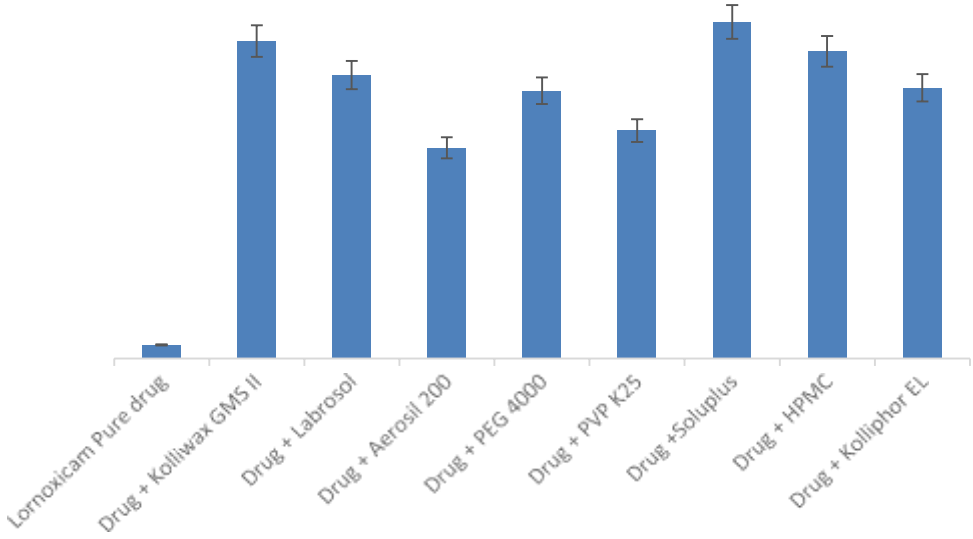

Figure 1: Solubility studies of Lornoxicam physical mixture

Preparation of Lornoxicam SD

Lornoxicam SD prepared by solvent evaporation technique with varying amounts of Soluplus, Kolliwax GMS II, and HPMC in drug: polymer: surfactant (SLS) ratios of 1:1:1, 1:2:1 and 1:3:1(Table 1).Nine Lornoxicam SD formulations were prepared as per the procedure. All the formulations are free flowing fine powders.

Table 1: Composition of Lornoxicam solid dispersions

Ingredients (mg)	SD1 (1:1:1)	SD2 (1:2:1)	SD3 (1:3:1)	SD4 (1:1:1)	SD5 (1:2:1)	SD6 (1:3:1)	SD7 (1:1:1)	SD8 (1:2:1)	SD9 (1:3:1)
Lornoxicam(mg)	8	8	8	8	8	8	8	8	8
Kolliwax GMSII	8	16	24	-	-	-	-	-	-
HPMC(mg)	-	-	-	8	16	24	-	-	-
Soluplus (mg)	-	-	-	-	-	-	8	16	24
SLS(mg)	8	8	8	8	8	8	8	8	8
Ethanol(ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Solubility studies of Lornoxicam SD

Lornoxicam SD subjected to solubility study indicate that the formulation (SD9) comprising drug: Soluplus (1:3) and with SLS displayed maximum solubility of 0.68±0.10µg/ml, that is 75-fold superior to pure drug solubility (0.0085±0.09µg/ml). (Figure 2)

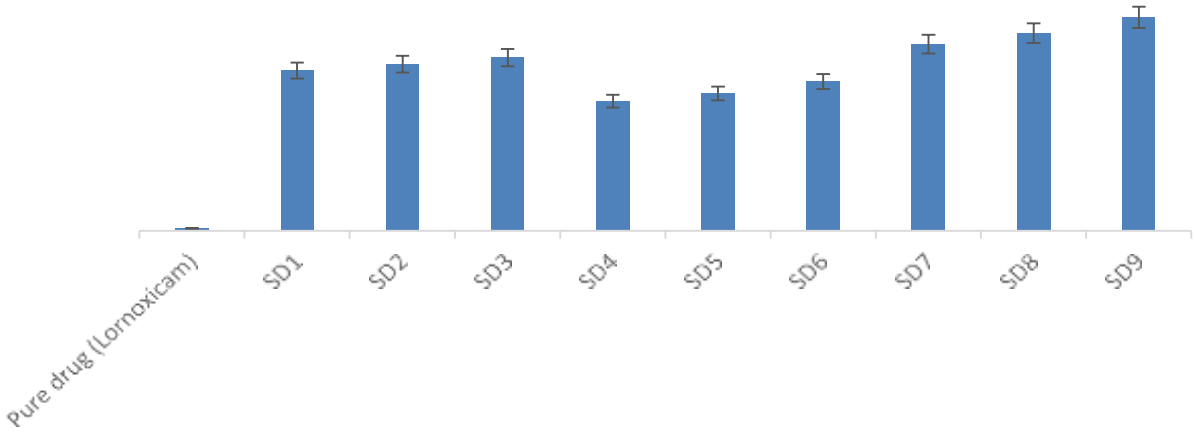

Figure 2: Solubility studies of Lornoxicam SD

Percent practical yield (PPY) and drug content:

The PPY of all the 9 SDs varied between 93.68±0.23 to 98.97±0.49 % and the drug content ranged between 90.47±0.01 to 99.13±0.24%.The Lornoxicam SD formulation SD9 displayed highest PPY and drug content of 98.97% and 99.13% respectively.

In vitro dissolution studies

The dissolution study of all 9 formulations showed a marked increase in the release rate of Lornoxicam from all SDs compared to pure drug. The formulation SD9 containing Lornoxicam: Soluplus: SLS in 1:3:1 ratio displayed maximum dissolution of 98.99±5.29% owing to enhancement in solubility of drug. (Figure 3)

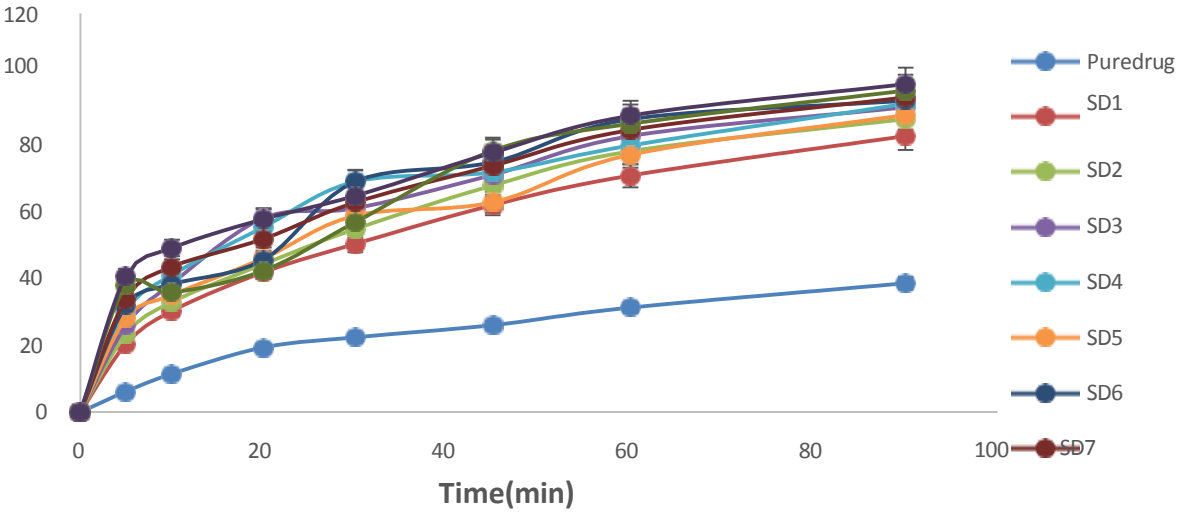

Figure 3: In vitro dissolution profile of pure drug and different formulations of Lornoxicam SD (SD1-SD9)

Characterization of Lornoxicam SD

FTIR Studies

The FTIR spectra of Lornoxicam and compare it with the formulation at 3,333 cm-^{1} (NH stretching), 1,690 cm-^{1}(C=O stretching), 1,529 and 1,492 cm-^{1} (which were assigned to bending vibrations of the N-H group in the secondary amide)1,190, 1,387, and 1,350 cm-^{1} (O=S=O group stretching), 829.42 cm-^{1} (-CH aromatic ring bending) and 744.55 cm-^{1} (C-Cl vibration bending). The distinguishing IR peaks of Lornoxicam were not distorted in the optimized formulation, signifying no chemical interactions amid the drug and excipients. (Figure 4-6)

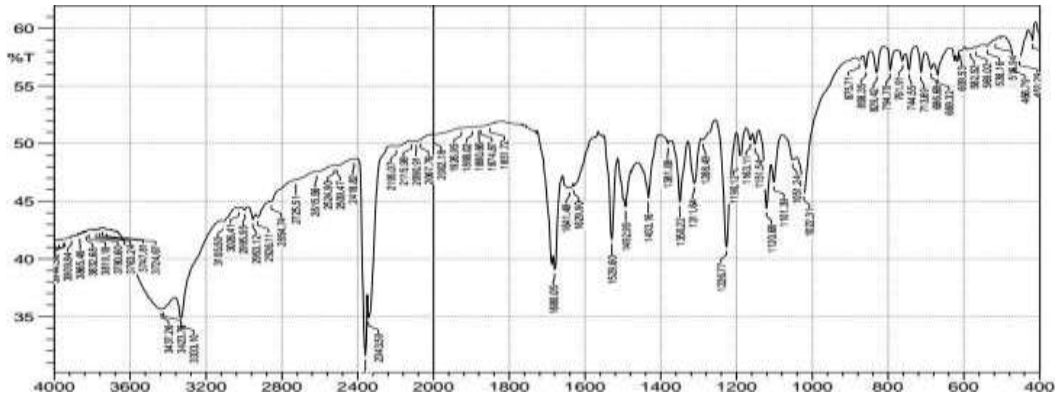

Figure 4: FTIR spectrum of Lornoxicam pure drug

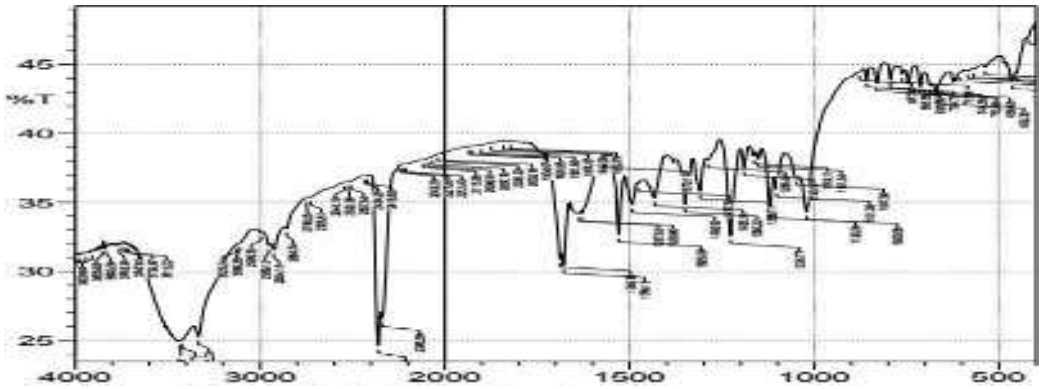

Figure 5: FTIR spectrum of physical mixture

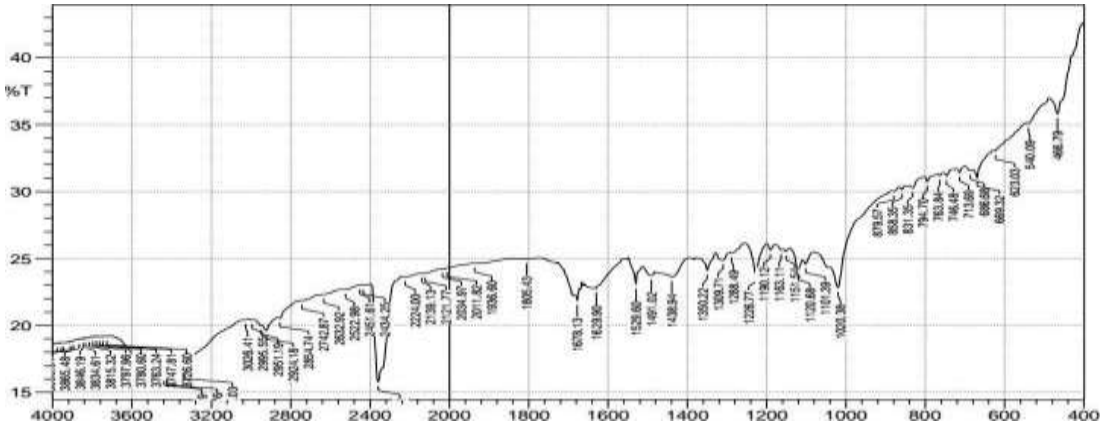

Figure 6: FTIR spectrum of optimized formulation of Lornoxicam

Stability studies

The stability study of SD9 formulation performed for studies for 3 months indicate that the formulation is stable during 3 months with retention of all properties with minor variations. (Table 2)

Table 2: Evaluation parameters of SD9 stored at 40±2^{0}C/75±5%RH

Retest time for optimized formulation	% Drug content	*In-vitro* drug release (%)
0 days	98.53	98.74
30 days	98.09	98.01
60 days	97.15	97.09
90 days	96.11	96.04

MATERIALS AND METHOD

Preparation and Evaluation of Lornoxicam FDT

Twenty-seven formulations of active layer (LF1-LF27) prepared by 3^3 response surface method using plantago ovate mucilage, locust bean gum, gum karaya selected to formulate the Lornoxicam FDT by direct compression technique. FDTs are prepared according to the formula as shown in Table 3. Among all formulations LF24 was found to be having best formulation.

Table 3: Formulation of Lornoxicam FDT

F.NO	Lornoxicam (mg)	Locust Bean Gum(mg)	Gum Karaya(mg)	Plantago Ovata(mg)	Aspartame (mg)	Mannitol (mg)	MCC (mg)	Total (mg)
LF1	40	8	15	32	7	30	62	200
LF2	40	14	15	32	7	30	59	200
LF3	40	8	23	32	7	30	54	200
LF4	40	32	23	30	7	30	32	200
LF5	40	8	15	40	7	30	54	200
LF6	40	16	15	40	7	30	46	200
LF7	40	8	23	40	7	30	46	200
LF8	40	32	23	40	7	30	22	200
LF9	40	8	23	40	7	30	46	200
LF10	40	16	19	36	7	30	46	200
LF11	40	12	15	36	7	30	54	200
LF12	40	12	23	36	7	30	46	200
LF13	40	12	19	32	7	30	76	200
LF14	40	12	19	40	7	30	46	200
LF15	40	12	19	36	7	30	50	200
LF16	40	12	15	40	7	30	50	200
LF17	40	12	15	32	7	30	58	200
LF18	40	12	23	36	7	30	46	200
LF19	40	16	15	36	7	30	50	200
LF20	40	12	23	32	7	30	50	200
LF21	40	16	19	32	7	30	50	200

LF22	40	16	19	36	7	30	46	200
LF23	40	18	18	36	7	30	45	200
LF24	40	8	20	36	7	30	53	200
LF25	40	16	19	40	7	30	42	200
LF26	40	8	19	32	7	30	58	200
LF27	40	12	19	32	7	30	54	200

Note: Magnesium stearate and Talc were added in 3mg each

Physico-Chemical Evaluation of Lornoxicam FDT

The results of bulk densities formulations bearing LF1 to LF27 reported being in the range of 0.50g/cc to 0.59g/cc. The findings of tapped density formulations LF1 to LF27 reported being in the range of 0.54g/cc to 0.68g/cc. The angle of repose of all the formulations was found a satisfactory result. The formulation LF24 was found to be 21.12 having good flow property. The compressibility index values were found to be in the range of 8 to 12 %. These findings indicated that the all the batches of formulations exhibited good flow properties. The Hausner's ratio values in the space of 1.10 to 1.16 %. These findings designated that the all the batches of formulations advertised good flow criterions. Above parameters are communicated as Average ± Standard Deviation; (n=6).The Weight variation of all formulations witnessed to be in the limit allowed that is ± 5% of total tablet weight. The suitable hardness for compressed tablets is considered as a vital function for the end user. The deliberated crushing strength of fabricated tablets of formulations LF1-LF27 trended between 3.0-4.0kg/cm^2 and magnitudes of crushing strength. The thickness of all the formulations between the ranges 4-4.5 mm. The friability of all prepared formulation between 0.52-0.89. The friability properties limits are in between0-1%. The drug content of all formulation is in between 94.11-99.16 %, drug content depends on the angle of repose since the angle of repose indicates uniform flow nature of powder blend which makes the drug to evenly distribute in all the formulation and to maintain content uniformity in all batches. The results are shown in Table 4

Table 4: Physico-chemical parameters of Fast Disintegrating Tablets of Lornoxicam

F.NO	*Weight variation(mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content Uniformity(%)	DT (Sec)
LF1	201.65±1.2	4.0±0.12	3.0±0.12	0.52±0.01	95.23±0.63	49±1.23
LF2	198.69±0.8	4.1±0.06	3.1±0.06	0.55±0.02	97.04±0.06	71±1.51
LF3	198.04±0.5	4.1±0.06	3.1±0.06	0.63±0.03	95.56±0.14	65±1.40
LF4	201.05±0.0	4.2±0.12	3.2±0.12	0.72±0.01	98.11±1.01	55±1.19
LF5	201.54±0.4	4.0±0.00	3.0±0.00	0.62±0.02	94.23±0.8	65±1.25
LF6	200.78±0.4	4.3±0.10	3.1±0.06	0.66±0.01	95.45±0.31	48±1.87
LF7	200.65±0.3	4.1±0.10	3.1±0.10	0.58±0.02	94.11±0.49	57±1.63
LF8	199.57±0.2	4.3±0.25	3.3±0.40	0.69±0.01	97.23±0.51	68±1.37
LF9	200.76±0.35	4.3±0.06	3.3±0.06	0.58±0.00	96.13±0.56	56±1.19

LF10	200.49±0.2	4.2±0.20	3.2±0.42	0.79±0.02	95.23±0.24	58±1.24
LF11	201.53±0.4	4.2±0.06	3.3±0.06	0.76±0.01	97.97±0.21	63±1.19
LF12	202.58±0.3	4.3±0.00	3.4±0.06	0.73±0.02	97.45±0.76	56±1.40
LF13	201.34±0.2	4.3±0.26	3.8±0.35	0.72±0.02	97.45±0.48	52±1.73
LF14	198.67±0.3	4.1±0.21	3.4±0.21	0.74±0.03	96.98±0.23	55±1.87
LF15	199.65±0.2	4.4±0.06	3.8±0.23	0.75±0.02	96.45±0.36	68±1.35
LF16	200.65±0.3	4.2±0.25	3.4±0.23	0.78±0.01	96.45±0.69	54±1.81
LF17	201.79±0.4	4.5±0.15	3.8±0.32	0.79±0.01	96.34±0.35	53±1.56
LF18	201.87±0.1	4.5±0.25	3.7±0.35	0.82±0.01	97.56±0.23	52±1.12
LF19	199.67±0.3	4.0±0.12	3.±0.12	0.84±0.03	96.29±0.34	57±1.33
LF20	199.32±0.2	4.2±0.12	3.5±0.2	0.63±0.03	97.18±0.81	48±132
LF21	198.27±0.4	4.2±0.06	3.3±0.06	0.66±0.02	96.27±0.11	55±1.27
LF22	200.27±0.1	4.0±0.12	3.0±0.12	0.53±0.03	96.78±0.07	60±1.61
LF23	200.26±0.13	4.3±0.17	3.8±0.4	0.76±0.05	96.14±0.76	68±1.49
LF24	**200.10±0.5**	**4.3±0.13**	**3.7±0.23**	**0.43±0.08**	**99.16±0.12**	**33±1.31**
LF25	199.12±0.6	4.1±0.17	3.6±0.12	0.67±0.02	96.23±0.00	51±1.39
LF26	200.16±0.8	4.4±0.10	3.7±0.21	0.72±0.89	97.34±0.23	69±1.40
LF27	200.29±0.15	4.5±0.29	3.9±0.45	0.89±0.03	97.10±0.40	53±1.77

*Values are expressed in mean ± SD: (n=20) #Values are expressed in mean± SD :(n=3)

Percentage Cumulative Drug Release

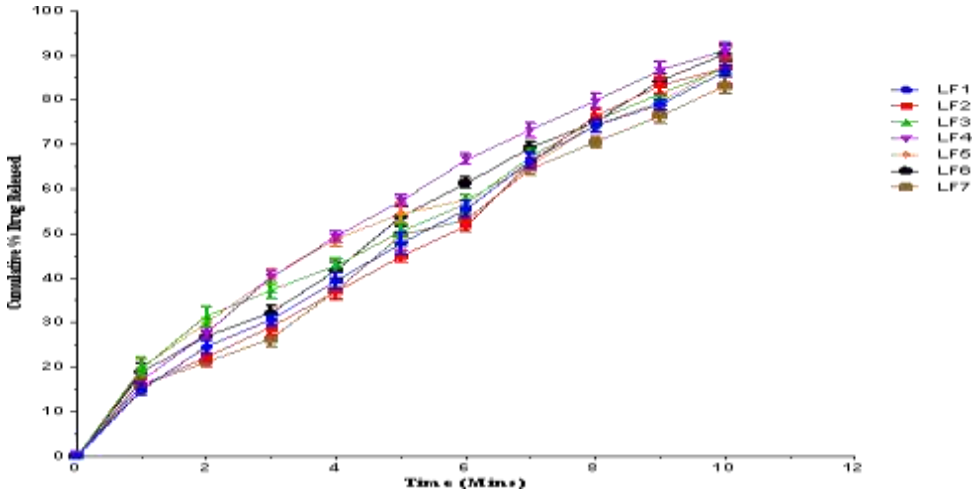

Figure 7: *In-vitro* Drug Release Profile of Fast Disintegrating Tablets of Lornoxicam LF1-LF7

The % CDR of all the formulations LF1-LF27 are shown in the figures 7 to 10

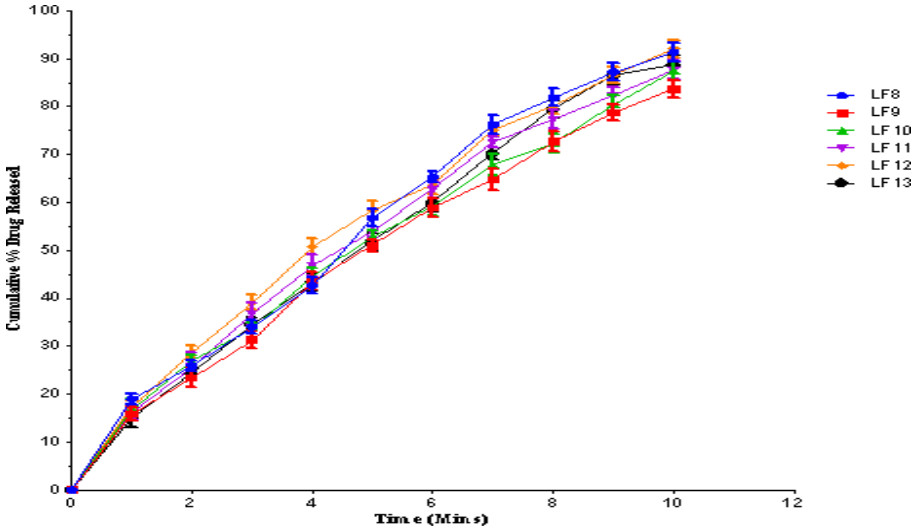

Figure 8: *In-vitro* Drug Release Profile of Fast Disintegrating Tablets of Lornoxicam LF8-LF13

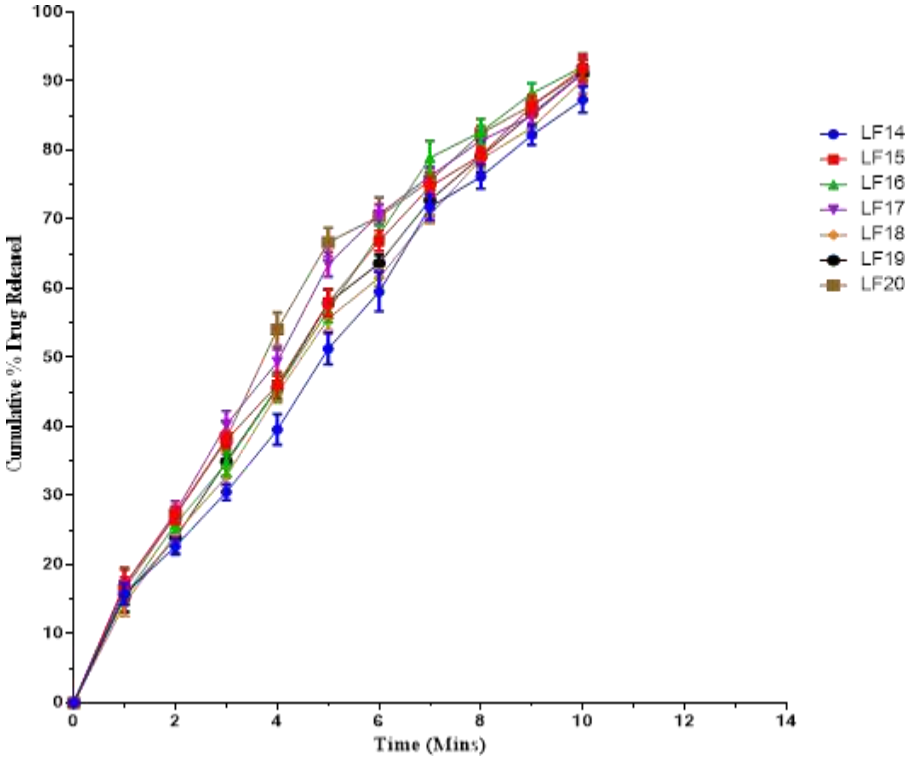

Figure: 9 *In vitro* Drug Release Profile of Fast Disintegrating Tablets of Lornoxicam LF14-LF20

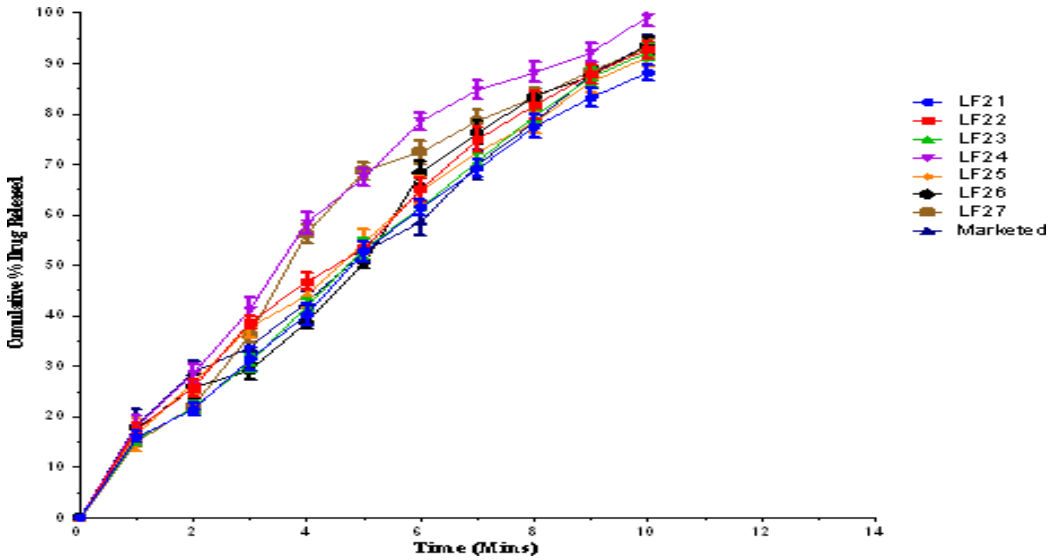

Figure 10: *In vitro* Drug Release Profile of Fast Disintegrating Tablets of Lornoxicam LF21-LF27

Design of Experiments

In this present work the effect of one factor (plantago ovate mucilage) on other two factors (locust bean gum, gum karaya) are explained.

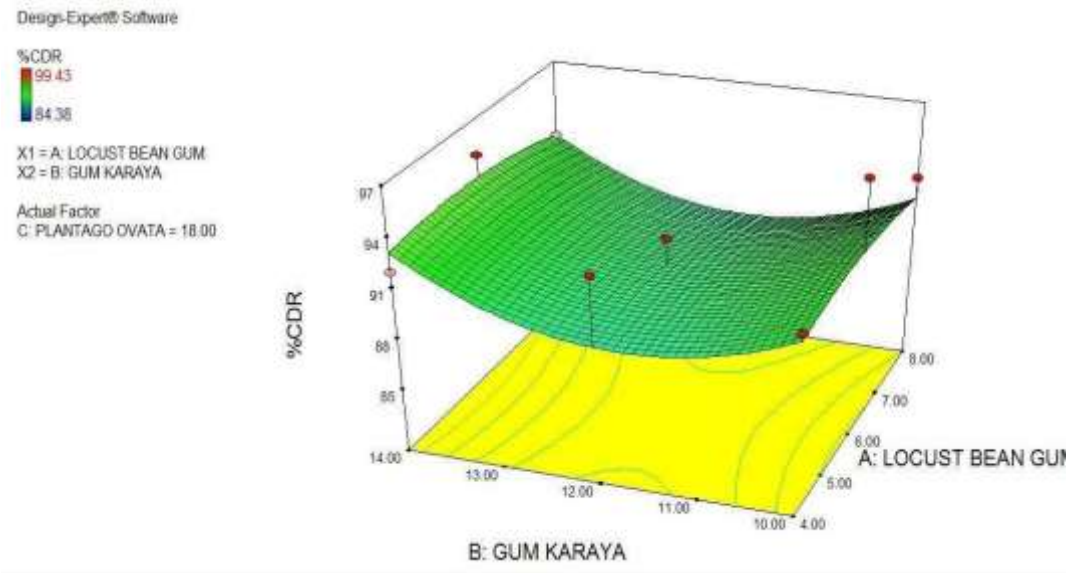

Figure 11 Response surface plots showing the influence of amount of Super disintegrants on the release profile of Lornoxicam.

The graph represents the effect of plantago ovate mucilage on DT release which indicates a significant effect of super disintegrant on DT. As concentration of + super disintegrants increase, the DT decreases.

Response 1 %CDR

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Block	73.00	2	36.50			
Model	135.71	9	15.08	1.86	0.1260	not significant
A-LOCUST BE	*1.82*	*1*	*1.82*	*0.22*	*0.6418*	
B-GUM KARA	*9.06*	*1*	*9.06*	*1.12*	*0.3048*	
C-PLANTAGO	*0.000*	*1*	*0.000*	*0.000*	*1.0000*	
AB	*0.13*	*1*	*0.13*	*0.016*	*0.9006*	
AC	*52.17*	*1*	*52.17*	*6.43*	*0.0207*	
BC	*0.62*	*1*	*0.62*	*0.076*	*0.7853*	
A^2	*3.60*	*1*	*3.60*	*0.44*	*0.5140*	
B^2	*60.78*	*1*	*60.78*	*7.49*	*0.0136*	
C^2	*4.75*	*1*	*4.75*	*0.59*	*0.4542*	
Residual	146.14	18	8.12			
Lack of Fit	*145.72*	*17*	*8.57*	*20.25*	*0.1732*	*not significant*
Pure Error	*0.42*	*1*	*0.42*			
Cor Total	354.85	29				

Design Summary

Study Type	Response Surface	Runs	27
Initial Design	3 Level Factorial	Blocks	No Blocks
Design Model	Quadratic		

Factor	Name	Units	Type	Low Actual	High Actual	Low Coded	High Coded	Mean	Std. Dev.
A	LOCUST BEAN (	mg	Numeric	4.00	8.00	-1.000	1.000	6.000	1.500
B	GUM KARAYA	mg	Numeric	10.00	14.00	-1.000	1.000	12.000	1.500
C	PLANTAGO OV.	mg	Numeric	16.00	20.00	-1.000	1.000	18.000	1.500

Response	Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio
Y1	%CDR	%	0	Polynomial	No Data	No Data	No Data	No Data	N/A
Y2	DT	%	0	Polynomial	No Data	No Data	No Data	No Data	N/A

Figure 12: ANOVA for Response Surface Mean Model of release profile of Lornoxicam for % Cumulative Drug Release.

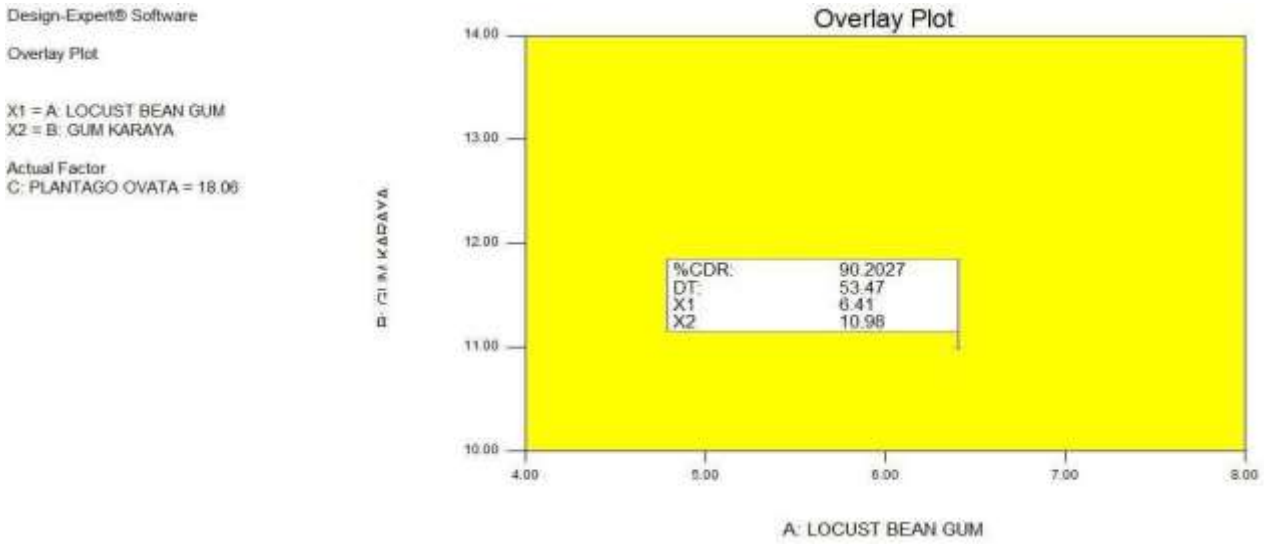

Figure 13: ANOVA for Response Surface Mean Model of release profile of Lornoxicam for Disintegration Time.

Stability Studies

The optimized formulation evaluated for stability for 6 months as per ICH guidelines. The results conclude that the formulation is stable and retained all their original properties like hardness, DT and dissolution studies with minor variations. (Table 5)

Table 5: Stability studies of optimized formulation

Retest Time for Optimized formulation (F24)	#Hardness (Kg/Cm^2)	Disintegration test (Sec)	*_In-vitro_ drug Release profile (%)
0 days	4.3±0.13	33±1.31	99.21±1.87
30 days	4.3±0.11	33±0.09	99.20±1.23
60 days	4.3±0.08	34±0.15	99.20±1.15
120days	4.3±0.04	34±0.11	99.18±1.20
180days	4.3±0.04	34±0.05	99.18±1.13

*Values are expressed in mean ± SD: (n=6)

CONCLUSION

Lornoxicam is anti-inflammatory drug used for inhibition of prostaglandin and thromboxane synthesis through the inhibition of both COX-1 and COX-2. It is used for treatment of pain, fever, swelling. Lornoxicam belong to BCS class II with lower solubility and high per permeability. The current research is aimed at formulating and evaluating Lornoxicam FDT prepared by incorporating the Lornoxicam solid dispersion to enhance dissolution and solubility. The first step involves formation of Lornoxicam SD. preliminary solubility study indicate that the Lornoxicam pure drug solubility is 0.0085±0.09µg/ml. The solubility of drug physical mixture comprising Soluplus in equimolar ratio enhanced the drug solubility by 25 folds (0.2125±0.13µg/ml). Nine SD formulations prepared with varying concentrations of PEG 4000, Labrosol, Soluplus, Kolliphor EL, Kolliwax GMS II, HPMC, Colloidal Silicone dioxide (Aerosil 200), and PVPK-25 in three different drugs : polymer : surfactant (SLS) ratios of1:1:1,1:2:1 and 1:3:1 by solvent evaporation method and evaluated. The solubility study indicates that formulation (SD9) containing drug : Soluplus (1:3) And SLS displayed superior solubility of 0.68±0.10µg/ml, which is75-fold higher than pure drug. The formulations also displayed maximum percentage yield and drug content. The drug release of Lornoxicam SD is 98.99±5.29 % which is superior to that of pure drug. The drug-polymer interactions using FTIR do not display any incompatibility between them. The optimized Lornoxicam solid dispersion (SD9) was further used to prepare FDT by direct compression method using 3^3 Response surface method (3 variables and 3 levels of super disintegrants) by using Design of experiments of ware with super disintegrants like locust bean gum, gum karaya, plantago ovata. Total 27 Lornoxicam FDTs formulated using natural super disintegrants locust bean gum, gum karaya, plantago ovate mucilage with varying concentrations by design of experiment tool. The

plots indicate a synergistic effect when super disintegrants are used in combinations. There is a significant effect of plantago ovata mucilage in formulations on drug release rate from the tablets and disintegration time was also increased. All the formulations evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, disintegration time, *in vitro* drug release studies. The formulation LF24 showed highest drug release of 99.21±1.87 % at 10 mins. On the basis of different evaluation parameters and *in-vitro* dissolution studies LF24 was found to be optimized formulation which contains different concentrations of locust bean gum, gum karaya, plantago ovate mucilage .FTIR analysis revealed that there was no interaction between the drug and super disintegrants. The % CDR of Lornoxicam FDT (LF24) was much higher than that of Lornoxicam marketed formulation. Thus, it can be concluded that Lornoxicam FDTs using natural super disintegrants like locust bean gum, gum karaya, plantago ovate mucilage were suitable candidature for fast disintegrating tablets for Lornoxicam based on information reported here.

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