

Design and development of fast disintegrating dosage form of taste masked lornoxicam

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Abstract: Rheumatoid arthritis is the chronic painful disease of joint destruction and functional disability needing immediate action with patient compliance. Pain relieving Fast disintegrating tablet (FDT) will be an accurate patient acceptable solution for this condition. Lornoxicam (LXM) is a non-steroidal anti-inflammatory drug (NSAID) with half life 3-5 hours, complete absorption from GIT (90-100%) having advantage from a tolerability standpoint. LXM has bitter taste thus to improve the palatability, the drug was complexed with Eudragit EPO in different ratios. Taste evaluation was done by human volunteer and UV method. The optimized drug Eudragit EPO complex was incorporated in FDT by direct compression technique using superdisintegrant. The optimization of concentration of Ac-di-sol and Pharmaburst 500 was done by central composite design to observe its effect on disintegration time, drug release and friability as dependent variable. The optimized batch E9 gave disintegration in 8 second and 92 % drug release in 20 minutes with controlled friability. It can be concluded that the development of fast disintegrating tablet of lornoxicam could give quick relief from the pain of rheumatoid arthritis with greater compliance compared to other conventional dosage forms.

Key words: Taste masking, Ac-di-sol, Pharmaburst 500, disintegration time.

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of the joints. Rheumatoid arthritis is a chronic painful illness, last for years, has the potential to cause joint destruction and functional disability. Stiffness in feet and hand movement due to swelling and pain is most common symptom with RA. To relieve this pain various NSAIDS are preferred¹.

Lornoxicam (chlortenoxicam) (LXM) is a non-steroidal anti-inflammatory drug (NSAID) of the oxycam class with analgesic, anti-inflammatory and antipyretic properties. LXM is absorbed rapidly and completely from the gastro-intestinal tract with the half life of 3 to 5 hours. Amongst all NSAIDS, LXM is as effective as other NSAIDS in relieving symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute sciatica and low back pain. Lornoxicam has a tolerability profile characteristic of an NSAID, with gastrointestinal disturbances being the most common adverse events. Limited clinical experience to date suggests that, as with a number of other NSAIDs, lornoxicam may provide a better-tolerated alternative or adjuvant to opioid analgesics for the management of moderate to severe pain. It has also demonstrated potential as an alternative to other NSAIDs for the management of arthritis and other painful and inflammatory conditions. So, LXM is used as model drug medicament for relieving the pain in RA. Thus, it was found advantageous to develop the fast dissolving dosage form of LXM which provide rapid onset of action in severity of pain².

LXM is bitter in taste. As the taste masking is an essential requirement for dosage which are to disintegrated or dissolved in mouth. Thus, it was decided to mask the taste before developing its oral dissolving dosage form. Various techniques are available for taste masking which includes addition of sweeteners and flavors, complexation, inclusion complexation etc. Here solid dispersion technique or mass extrusion technique with Eudragit EPO was used.

The extrusion technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymeric carrier and expulsion of softened mass through the extruder or syringe to get coated granules of bitter drugs to mask their taste while shaping the composite material to form a pharmaceutical product. Eudragit EPO was used as taste masking polymer which is cationic copolymer based on dimethyl amino ethyl methacrylate and ethanol. It has less solubility at salivary pH and provides complete coating to bitter taste of water soluble drug³. Taste masking was carried out by taking trials of different ratios of drug and polymer. Optimized ratio was used for further development of tablet dosage form.

In present study, an attempt has been made to prepare taste masked granules of LXM. Taste masking of LXM was carried out by using Eudragit EPO (Mass extrusion method). These taste masked granules or complex was formulated by systematically optimization into the Fast disintegrating tablet by direct compression method using superdisintegrant. Ac-di-sol gave best disintegration effect due to its ability of rapid swelling and disintegrating tablets rapidly into apparently primary particles. Thus Ac-di-sol was selected as superdisintegrant. Pharmaburst 500 containing tablet has good wettability and Shorter disintegration time and Pharmaburst 500 has taste masking effect also so good for lornoxicam like better drugs. Thus Pharmaburst 500 was finalized as coprocessed excipients. In Pharmaburst 500 -500 stands for quantity of API (up to 500mg API) that can be incorporated in tablet. The optimization of Ac-di-sol as superdisintegrant and Pharmaburst - 500 as a co-processed excipients was done by applying approach of experimental design. The formulations were characterized for different evaluation parameters like friability, hardness, disintegration time and dissolution studies.

Material

Lornoxicam was procured as gift samples from Hetero drugs Ltd. (Hyderabad, India). Pharmaburst 500 was Gifted by SPI pharma, Avicel PH 102 was obtained as gift sample by Lincoln Pharmaceuticals Pvt. Ltd., Ahmedabad, Eudragit EPO was gifted by Roquette Pharma Pvt. Ltd., Magnesium stearate and Talc were obtained from Nice Chemicals Ltd, Cohin, Hydrochloric acid AR, Aerosil was purchased from S.D. Fine Chem Ltd., Baroda, Aspartame, color and flavour were purchased from Himedia lab, Bombay. The double distilled water was used throughout the studies.

Methods

Preparation of LXM Eudragit EPO taste masked granules by mass extrusion technique

The taste-masked granules of drug and Eudragit EPO were prepared by simple mass extrusion technique using 14-gauge needle containing syringe by varying different ratio of LXM to Eudragit EPO from 1:1 to 1:4 and ethanol as a solvent. Fixed amount of drug was mixed with different amount of powdered Eudragit EPO. Formulations compositions are mentioned in table 4.1. Ethanol was added to each mixture. Then gel was prepared using the mixture of the drug and Eudragit EPO which was converted into the taste-masked granules by the extrusion method. The prepared gel was manually extruded (pressed out) using a syringe. After extrusion of the gel, ethanol was removed by evaporation at room temperature for 8 hrs and subsequently the solidified gel in the shape of crystalline lump was crushed into granules using a mortar and pestle. Extruded blend was passed from 60# sieve and evaluated for various parameters.

Table: 4.1 Taste masking of LXM using Eudragit EPO

Batch Code	Drug polymer Ratio
A	1:1
B	1:2
C	1:3
D	1:4

Evaluation of taste masked powder blend^{3,4}

The powdered blend was evaluated for physical properties like angle of repose, tapped density, bulk density, Carr's index and Hausner ratio.

In vitro drug release for *in-vitro* taste evaluation

The *in vitro* drug release of optimized LXM-Eudragit EPO was performed. Stimulated salivary fluid pH 6.8 and 0.1N HCl were used as dissolution media and maintained at $37 \pm 0.5^\circ\text{C}$. 5 ml of sample was withdrawn from the dissolution medium at the specified regular intervals, filtered through whattmann filter paper and assayed spectrophotometrically at 378 nm. The cumulative percentage of drug release was calculated and represented graphically.

Taste evaluation by human volunteers

The taste evaluation test was carried out with 6 volunteers for each taste masked drug and the unmasked drug was taken as the control which was compared with the taste masked drug. They were allowed to give interpretations as bitter, slight bitter and taste masked.

Formulation of fast disintegrating tablet

It was carried out to prepare fast disintegrating tablets of LXM using optimized taste masked blend of LXM. Taste masked blend was weighed accurately and mixed with excipients and lubricated sufficiently and directly compressed in rotary tablet machine using 6 mm concave punch. Total weight of each tablet was 100 mg. Minimum 20 tablets were prepared for each batch. Drug polymer complex equivalent to 4 mg of LXM was taken. Ac-di-sol was used as superdisintegrant and Pharmaburst -500 was selected as coprocessed excipients. Lornoxicam has yellow so it gave non- uniformity of color on the surface of tablet so coloring agent was added to make the tablet look uniform in color. Suitable flavour and sweeteners were added.

To select ideal proportion of superdisintegrant (Ac-di-sol) and co-processed excipients (Pharmaburst 500), Central composite design approach was used. The polynomial equation was generated using multiple linear regression analysis⁷.

This study investigated utility of a 2-factor, 3-level design and optimization process for fast disintegrating tablet of LXM. Concentration of ac-di-sol (A) and concentration of Pharmaburst 500 (B) were selected as the independent variables whereas Disintegration time (Y_1), (Y_{20}) - Dissolution at 20 min (Y_2) and Friability (Y_3) were selected as dependent variables. Independent factors were selected at 3 different levels as mentioned in table 4.2. Experimental trials were performed in all 13 formulations.

Table: 4.2 Independent variable Levels in coded form

Independent variable	levels				
	-1.414	-1	0	+1	+1.414
X1: % of Ac-di-sol	1.41	2	3	4	4.414
X2: % of Pharmaburst 500	55	60	70	80	85

The prepared tablets of LXM were evaluated for dissolution study. The design responses were analyzed using ANOVA in MS Excel and polynomial equation was generated for each response.

The response surface methodology is a collection of mathematical and statistical techniques used for modeling and analysis of problems in which a response of interest is influenced by several variable and the objectives is to optimize this response. The run or formulations, which are designed based on central composite design, were evaluated for the response. The response values are subjected to multiple regressions analysis to find out the relationship between the factor used and the response value obtained⁸. The multiple linear regression analysis was done using DESIGN EXPERT 9 version (STAT-EASE) software, which specially meant for effective optimization process. One random check points covering the entire range of experimental domain were carried out to determine the validity of the model generated. Subsequently, the resultant experimental data of the response properties were quantitatively compared with those of the predicted

values. Predicted values were compared with the resulting experimental values and the percentage bias was calculated .

The composition of checkpoint formulations E*14 is shown in Table 4.4

Table: 4.3 Layout of design

Batch no	Coded Values		Actual Values (%)	
	Conc. of Ac-di-sol (A)	Conc. of Pharmaburst (B)	A	B
E1	-1	-1	2	60
E2	-1.414	0	1.41	70
E3	-1	1	2	80
E4	0	-1.414	3	65
E5	0	0	3	70
E6	0	1.414	3	85
E7	1	-1	4	60
E8	1.414	0	4.414	60
E9	1	1	4	80
E10	0	0	3	70
E11	0	0	3	70
E12	0	0	3	70
E13	0	0	3	70
E*14	0.8	0.8	3.2	78

Table: 4.4 Composition of FDT

Ingredients (Quantities in mg.)	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E13	E*14
Drug complex in equivalent to 4 mg LXM	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8	18.8
Ac-di-sol	2	1.41	2	3	3	3	4	4.41	4	3	3	3	3	3.2
Pharmaburst 500	60	70	80	65	70	85	60	60	80	70	70	70	70	7.8
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1	1	1
tartrazine color	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Orange flavor	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Micro crystalline cellulose(AVICEL PH 102)	Qs to 100 mg													

Evaluation of LXM fast disintegrating tablets ^{5,6}

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared FDTs were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator)

In vitro disintegration test

The disintegration time was measured using a modified disintegration method ($n = 5$). For this purpose, a petridish (10-cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the petridish and the time for the tablet to completely disintegrate into fine particles was noted.

In vivo disintegration time study

The time required for the tablets to disperse in mouth cavity was determined by holding the tablets in mouth and then spitting out. The test was performed in 8 healthy human volunteers in the age group of 23 to 40 years.

Wetting time study

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of salivary buffer having pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch and the standard deviations were also determined.

In vitro dissolution studies

In vitro dissolution studies for all the prepared tablet was carried out using USP paddle method at 50 rpm in 900 ml of 0.1 N HCl as dissolution media and maintained at $37 \pm 0.5^\circ\text{C}$. 5 ml of sample was withdrawn from the dissolution medium at the specified regular intervals, filtered through whattmann filter paper and assayed spectrophotometrically at 378 nm. The cumulative percentage of drug release was calculated and represented graphically.

Stability testing

The fast disintegrating tablets were packed in suitable packaging and stored at temperature of $40^\circ\text{C} \pm 2^\circ\text{C}$ and relative humidity $75\% \pm 5\%$. The tablets were withdrawn after a period of 6 months and analyzed for visual defects, hardness, friability, disintegrations, dissolution and drug content etc.

Results and Discussion

Lornoxicam was a bitter drug. So, Eudragit EPO was selected for the taste masking of LXM. The taste-masked granules of drug and Eudragit EPO were prepared by simple mass extrusion technique using syringe by varying different concentration of Eudragit EPO.

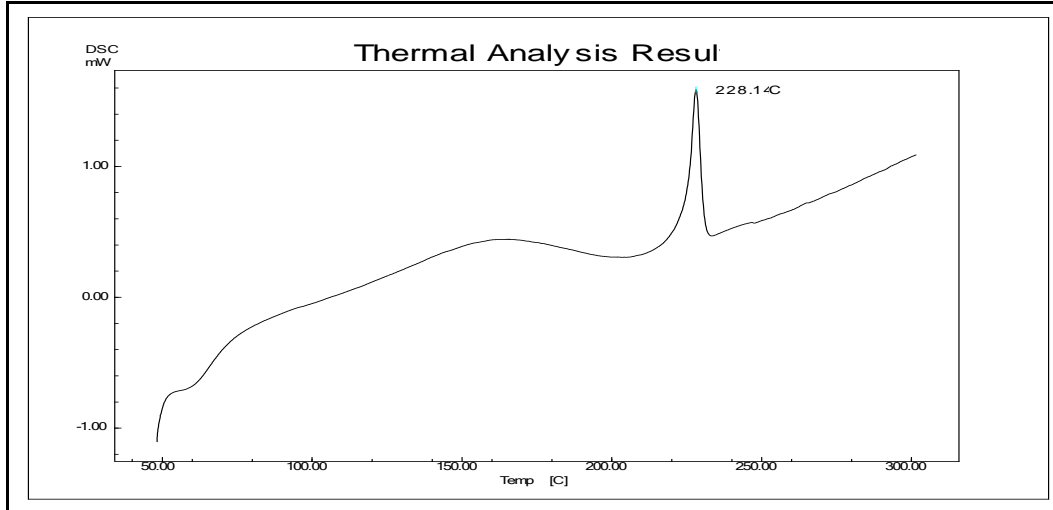
Mass extrusion is one of the simple, easy, novel and economic method for coating of bitter drug particle with polymer. Taste masking was carried out using different ratios of LXM and Eudragit EPO from 1:1 to 1:4. Among all different ratios, batch C having 1:3 drug to polymer ratio showed complete taste masking. It was observed that by increasing the ratio higher than 1:3, % yield was decreased up to 76% and flow property was also decreased. This may be due to increase in the intermolecular forces upon increasing proportion of Eudragit EPO⁵.

The optimized batch showed drug content of 98.89 % in the granules. The physical properties like bulk density, tapped density, angle of repose, percentage compressibility and hausner's ratio of complex was found to be 0.60 g/ml, 0.65 g/ml, 24.5° , 7.69%, and 1.08 respectively. (Table 4.5)

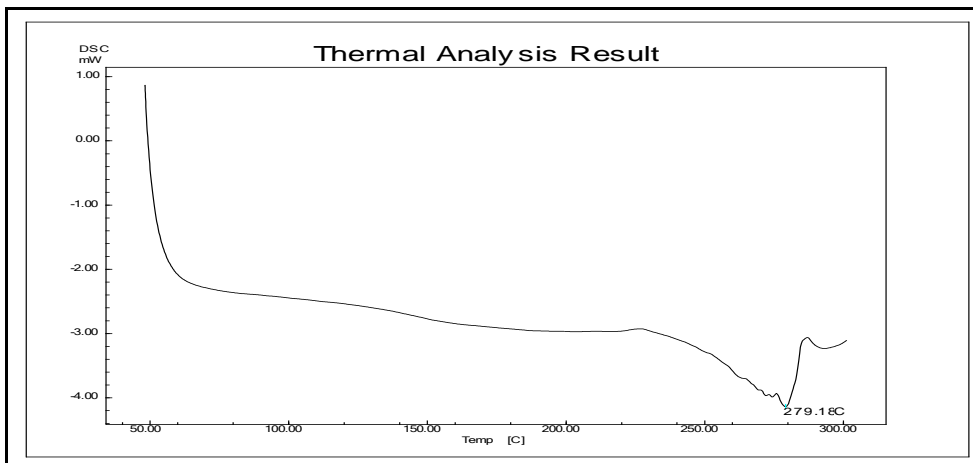
Table: 4.5 Micromeritics properties of LXM Eudragit EPO complex blend

Batch Code	Drug polymer Ratio	% Yield	Taste	Drug content (%)	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	% CI	Hausner's Ratio
A	1:1	95	Very bitter	98.45	0.61	0.68	25.8	10.29	1.11
B	1:2	90	Slight bitter	99.12	0.59	0.67	27.4	11.94	1.14

C	1:3	87	Taste masked	98.89	0.60	0.65	24.5	7.69	1.08
D	1:4	76	Taste masked	98.65	0.53	0.60	26.5	11.66	1.13



A)



B)

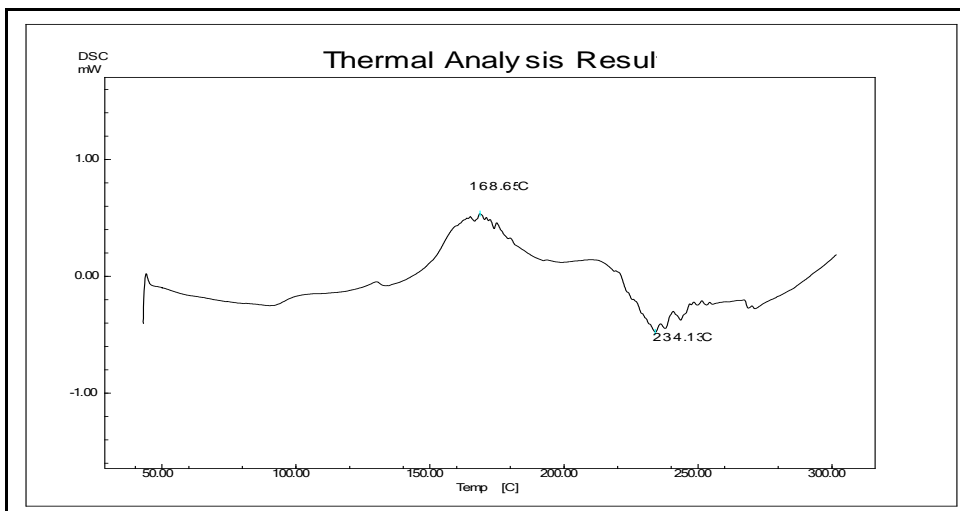
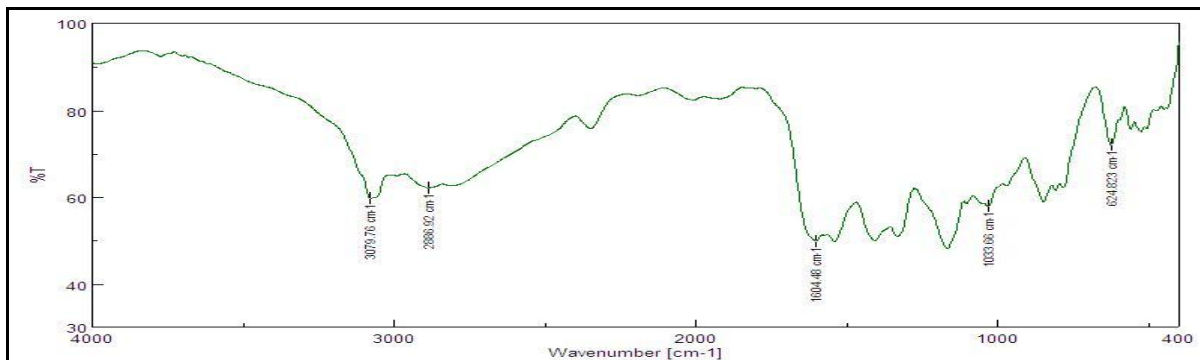


Fig 4.1: DSC spectra of A) LXM B) Eudragit EPO C) Optimized LXM Eudragit EPO complex

The shape of the granules was found irregular. Complete taste masking was confirmed by taste acceptability and DSC spectra of pure LXM and complex. The spectra of batch C showed absence of endothermic peak of drug, which indicated the complete coating of drug as shown in fig 4.1. Above data indicate that granules have good flowability and complete taste masking characteristics.

Lornoxicam (fig 4.2A) showed peaks at 1546 and at 1594 cm^{-1} due to bending vibration (N-H) of secondary amide, peak at 3067 cm^{-1} (N-H stretching vibration), strong absorption peak at 1646 cm^{-1} (C=O stretching vibration) of primary amide. Some peaks appeared at 1146, 1382 cm^{-1} due to stretching vibrations of the O=S=O. Peaks appeared at 830 cm^{-1} showed bending vibration (CH aromatic ring). Peak present in LXM was retained in batch C (1:3) ratio indicating stability of LXM during processing as shown in fig 4.2. Thus, this batch was used for further development of tablet dosage form.

A)



B)

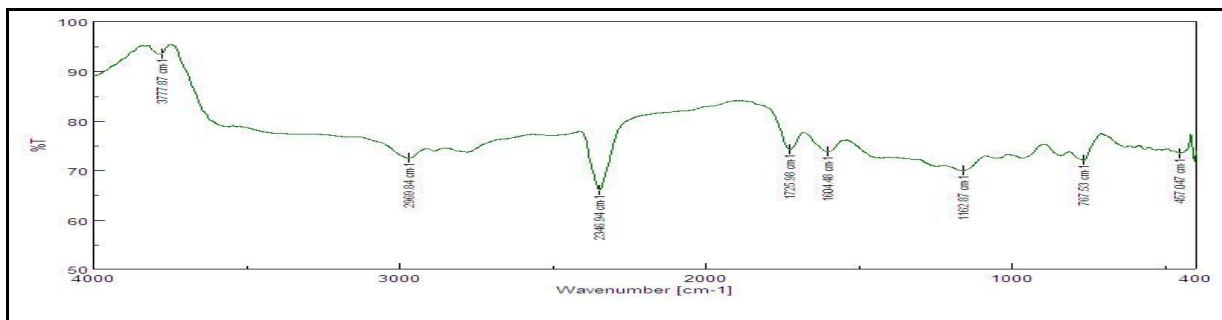


Figure: 4.2 FTIR spectra of A) LXM and B) Optimized LXM Eudragit EPO complex

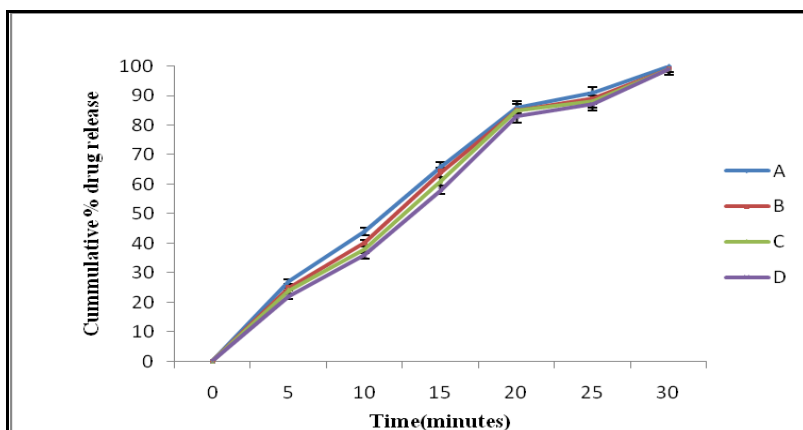


Figure:4.3 In vitro drug release in 0.1 N HCl

The cumulative percentage drug release was calculated for optimized taste masked granules of lornoxicam in 0.1N HCl and Phosphate buffer pH 6.8. From figure 4.3 it was found that in 0.1 N HCl the amount of drug release was found to be more than 95% in 30 minutes in all four batches which proved that drug was freely released in acidic pH of stomach. From the figure 4.4 it was found that there was only 20% drug

release in 30 minutes in batch C and D while in Batch A and B drug release was more about 50% in 30 minutes due to less Eudragit EPO available for drug. Less drug release in phosphate buffer 6.8 pH proved that the drug was not released in mouth and thus there was no bitter taste felt.

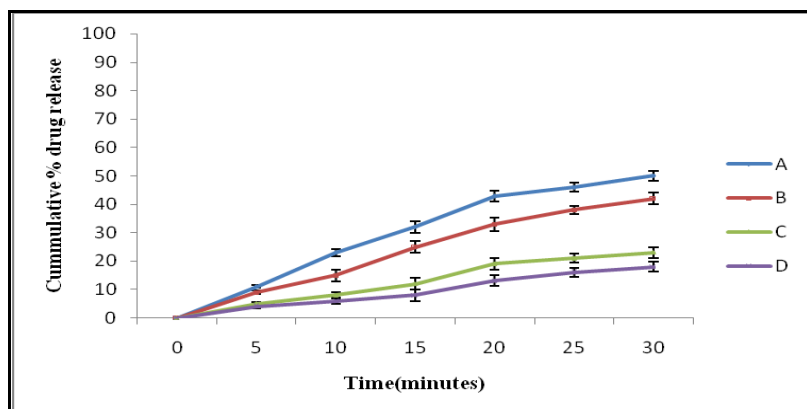


Figure: 4.4 In vitro drug release in Phosphate buffer 6.8 pH

This optimized drug Eudragit EPO was incorporated into Fast disintegrating tablet by direct compression method. Ac-di-sol gives best disintegration and Pharmaburst 500 has good compressibility and taste masking ability and thus used in formulating FDT.

To select ideal proportion of Ac-di-sol and Pharmaburst 500, central composite design was used. After applying design, the response was recorded and analysis of data was carried out using ANOVA in MS Excel. Using the regression coefficient of each factor, the polynomial equation for the each response is generated.

The response variable considered for optimization of disintegration time, Y_{20} and friability. The results of response were depicted in table 4.6.

Table: 4.6 Results of LXM fast disintegrating tablets using central composite design

Batch no	Coded values		Actual values (%)		Dependent variables		
	Conc. of Ac-di-sol (A)	Conc. of Pharmaburst (B)	A	B	DT(SEC)	Drug release in 20 minutes(%)	Friability (%)
E1	-1	-1	2	60	38±1.01	65.26±1.89	0.78±0.003
E2	-1.414	0	1.41	70	47±2.05	57±3.15	0.38±0.001
E3	-1	1	2	80	30±1.26	75.59±2.45	0.31±0.004
E4	0	-1.414	3	65	27±2.54	80.25±4.36	0.86±0.013
E5	0	0	3	70	35±1.81	70.59±1.98	0.75±0.005
E6	0	1.414	3	85	10±1.43	91.65±2.45	0.23±0.002
E7	1	-1	4	60	23±2.28	80.49±3.12	1.25±0.002
E8	1.414	0	4.414	60	18±1.57	85.26±2.73	0.42±0.004
E9	1	1	4	80	8±1.24	92.35±2.84	0.51±0.015
E10	0	0	3	70	32±3.52	71.25±3.89	0.73±0.0014
E11	0	0	3	70	34±3.05	69.58±4.16	0.74±0.002
E12	0	0	3	70	33±2.89	69.89±3.45	0.72±0.0009
E13	0	0	3	70	36±1.56	70.89±1.01	0.73±0.002
E*14	0.8	0.8	3.2	78	10±1.06	90.25±2.45	0.53±0.005

*Check point batch, **n=3 Mean ± SD of 3 experiments

Statistical analysis of the data and validation of the model

The statistical analysis of the central composite design formulations was performed by multiple linear regression analysis carried out in Microsoft Excel 2007. In vitro drug release in 20 minutes, friability and

disintegration time values for the 13 formulations (E1 to E13) showed a wide variation; the results were shown in Table 4.6, 4.7. The data clearly indicated that the values of in vitro drug release, friability and DT were strongly dependent on the independent variables.

Table: 4.7 Evaluation parameters of design batches

Parameters *	Wetting time (sec)	In vivo D.T time (sec)	Hardness (Kg/cm ²)	% drug content
E1	32 ±1.5	36 ±1.3	4 ±0.01	101.5 ±0.4
E2	40±0.5	45 ±1.4	3.8 ±0.02	100.44 ±0.5
E3	25 ±1.2	27±2.5	3.4±0.004	99.2±0.3
E4	22±1.8	25 ±0.6	3.5 ±0.03	101.2 ±0.2
E5	30±1.02	33±2.89	3.9±0.002	101.2 ±1.09
E6	80.2	9±0.59	4.05±0.006	100.06±0.05
E7	15±0.58	20±1.25	3.8±0.004	101.02±0.12
E8	11±1.02	16±1.06	3.5±0.05	100±1.42
E9	4±0.29	7±1.2	3.7±0.003	99.59±0.43
E10	26±1.58	30±1.52	3.9±0.011	101.08±1.26
E11	29±2.12	32±2.31	3.6±0.12	99.53±1.38
E12	27±0.12	31±1.29	4.1±0.02	99.39±1.24
E13	30±0.13	33 ±2.89	4.3±0.09	100.28±1.26
E*14	7±0.05	10±0.02	4.2±0.01	99.98±0.15

Response 1 : Disintegration time(Y₁)

The fitted full model equation relating the responses to the transformed factor is shown in following equation.

$$\text{Disintegration Time}(Y_1) = 34.00 - 9.75 * A - 5.88 * B - 1.75 * A * B - 0.94 * A^2 - 7.94 * B^2 \quad (i)$$

The surface and counter plot are shown in fig.4.6.

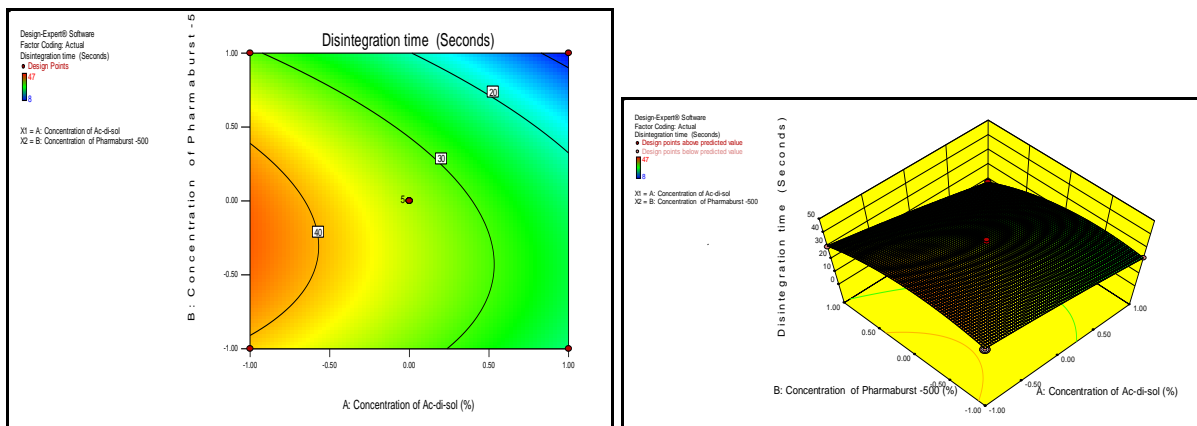


Figure: 4.6 Contour and surface plot for the effect of A and B on Disintegration time Response 2: Drug release in 20 min (Y₂₀) :

The full model polynomial equation obtained was as follows

$$Y_{20} = \text{Drug release after 20 min}(\%) = +70.44 + 8.99 * A + 4.79 * B + 0.38 * A * B + 0.32 * A^2 + 7.73 * B^2$$

.....(ii)

The coefficients b₁ and b₂ are negative. In this case A, B, AB is significant model terms. The disintegration time for the 13 batches show a variation, that is, the response ranged from a minimum 10 sec to maximum of 47 sec. It may be concluded that at higher levels of A (concentration of Ac-di-sol) and B (concentration of Pharmaburst 500) the disintegration time decreases. The level B shows less significant effect

than A on the disintegration time. This might be due to increase more water absorption capacity of tablet upon increasing their concentration which leads to rapid bursting of tablet. The value of correlation co-efficient R^2 was found to be 0.9912, indicating a good fit.

In this case A, B is significant model terms. For Y_{20} response ranged from a minimum 57 % to a maximum of 92.35%. The level A and B shows positive effect. It may be concluded that at higher levels of A (concentration of Ac-di-sol and B (concentration of Pharmaburst 500), increase amount drug release. This may be observed due to rapid disintegration of tablet which leads to higher drug release. The value of correlation co-efficient (R^2) was found to be 0.99 indicating a good fit.

Surface and counter plot are shown in fig.4.7

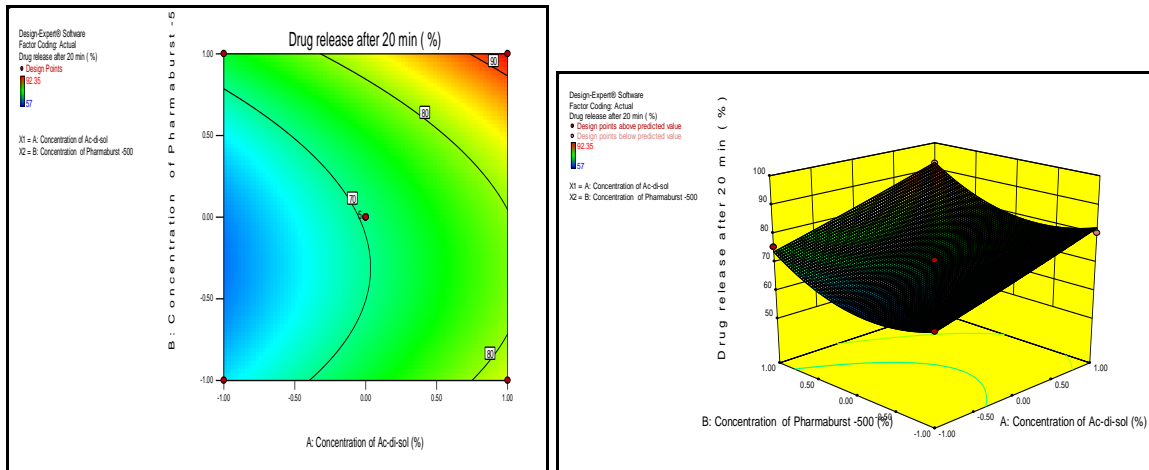


Figure: 4.7 Contour and surface plot for the effect of A and B on Y_{20} Response 3: Friability(Y_3)
 $Friability(Y_3) = +0.51 + 0.22 * A - 0.41 * B - 0.12 * AB + 0.049 * A^2 + 0.089 * B^2$

Surface and counter plot are shown in fig.4.8

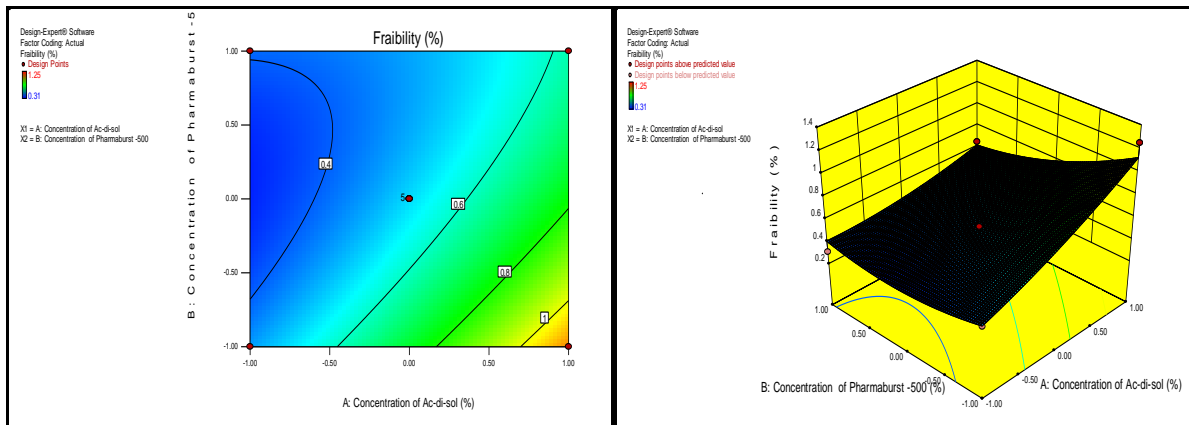


Figure: 4.8 Contour and surface plot for the effect of A and B on friability (Y_3)

The coefficients b_1 was positive and b_2 was negative. In this case A, B, AB was little significant model terms. The friability for the 13 batches show a variation, that was, the response ranged from a minimum 0.31% to maximum of 1.25 %. It was concluded that at higher levels of A (concentration of Ac-di-sol) and lower level of B (concentration of Pharmaburst 500) the friability increases. The level A shows less significant effect than B on the friability. It was found that superdisintegrant increased the friability while pharmaburst -500 gave good compressibility and reduced the friability. The value of correlation co-efficient R^2 was found to be 0.96, indicating a good fit.

A Central composite design was adopted, using the amount of Ac-di-sol and amount of Pharmaburst 500 as independent variables. The response variables subjected for this analysis were disintegration time, % drug release in 20 min and friability.

It was logically decided to obtain the values of the disintegration time 20 sec from the formulated products. Ac-di-sol had the ability of rapid swelling and disintegrating tablets rapidly into apparently primary particles leading to fast disintegration. Pharmaburst 500 has high tendency to create repulsive force leads to bursting of the tablet.

In case of dissolution rate after 20 min, successively increase in concentration of ac-di-sol and Pharmaburst 500; increased the release rate of drug above 85 % within 20 min. Here, logically predecided to obtain 85 % drug dissolved within 20 min.

In friability, By increasing concentration of ac-di-sol showed rise in the friability value even above 1%. This may be due to its less compressibility.

Formulations E6,E8 and E9 showed total disintegration time and drug release near to desired value. Exact amount of Ac-di-sol and pharmaburst 500 required for achieving desired responses were found out from optimization by desirability plot.

For the optimization of Fast disintegrating tablet of LXM, constraints were fixed for all factors and response. Constraints were set according to formulation of tablet using minimum amount of excipients, which would give desired response values. In the present study, our aim was disintegration time should be 20 sec and more than 85% dissolution of drug within 20 min with controlled friability^{9, 10}. In optimization, desirability 1.0 indicated that optimum formulation was achieved at 4% of Ac-di-sol and 80% of Pharmaburst 500 as shown in fig. 4.9.

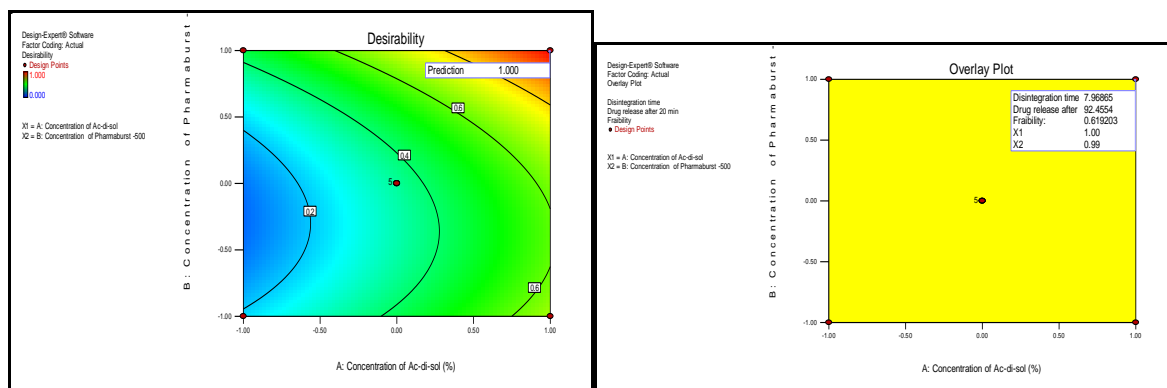


Figure: 4.9 Desirability and overlay plot for optimization

Validation of optimization technique done by preparing checkpoint batch E*14 and response were evaluated. Check point batch was compared for predicted value with observed value in table 4.8. Observed value was found close to the predicted value, which indicated good correlation of results.

Table: 4.8 Comparison of predicted value and observed values of all response for E*14 batch

Comparison of predicted value and observed values of all response						
Batch	Disintegration time(sec)		Drug release in 20 minutes(%)		Friability (%)	
	Observed value	Predicted value	Observed value	Predicted value	Observed value	Predicted value
E*14	10	10.23	90	90.21	0.53	0.54

Drug release profile of design batches were shown in fig 4.10.

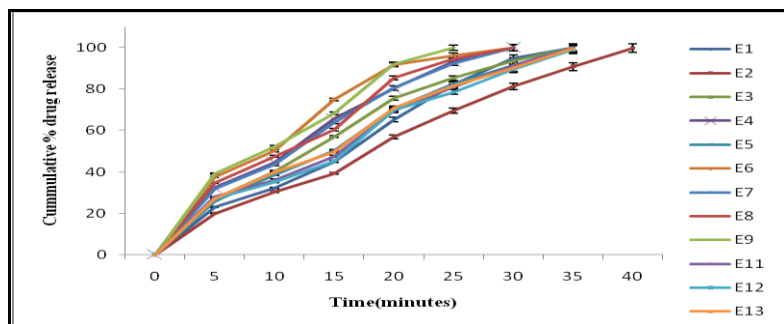


Figure: 4.10 Drug release profile in 0.1 N HCl of design batches

Optimized batch E9 having disintegration time of 8 seconds and 92% drug release within 20 min.

Stability studies

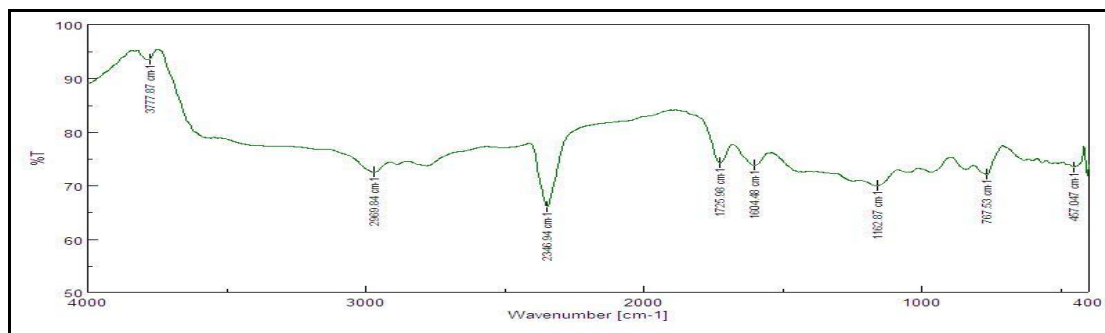


Figure: 4.11 FTIR of Fast disintegrating tablet of LXM-Eudragit EPO

Optimized batch was subjected to stability study at 40°C±2 °C and 75%±5 RH for 6 month. The tablets were found to be stable at such condition and other parameters were found to be unaffected as shown in table 4.9.

Table: 4.9 Stability study of optimized Fast disintegrating tablet of LXM

Months	Drug release in 20 minutes	Drug content (%)	Disintegration time(second)	Hardness (Kg/cm ²)	Friability (%)
0	93.24±1.15	99.15±1.21	8±0.21	4.5±0.52	0.7±0.02
1	93.14±1.45	98.9±1.26	8±1.05	4.5±0.21	0.7±0.04
2	92.21±1.59	98.7±1.06	9±1.03	4.5±0.11	0.7±0.05
3	92.25±0.98	98.56±1.24	9±1.06	4.4±0.58	0.7±0.03
4	91.12±1.87	98.41±1.09	9±1.1	4.4±0.26	0.6±0.12
5	92.13±0.82	98.45±1.11	9±1.2	4.4±0.19	0.6±0.21
6	92.2±0.79	98.15±1.43	9±0.98	4.4±0.11	0.6±0.25

Peak present in LXM was retained in optimized batch indicating stability of LXM during processing as shown in fig 4.11. Thus, this optimized batch was found to be stable tablet dosage form.

DSC spectra of LXM-Eudragit EPO was found similar to that of final optimized dosage form (figure 4.12) and thus the optimized dosage form was found to be stable.

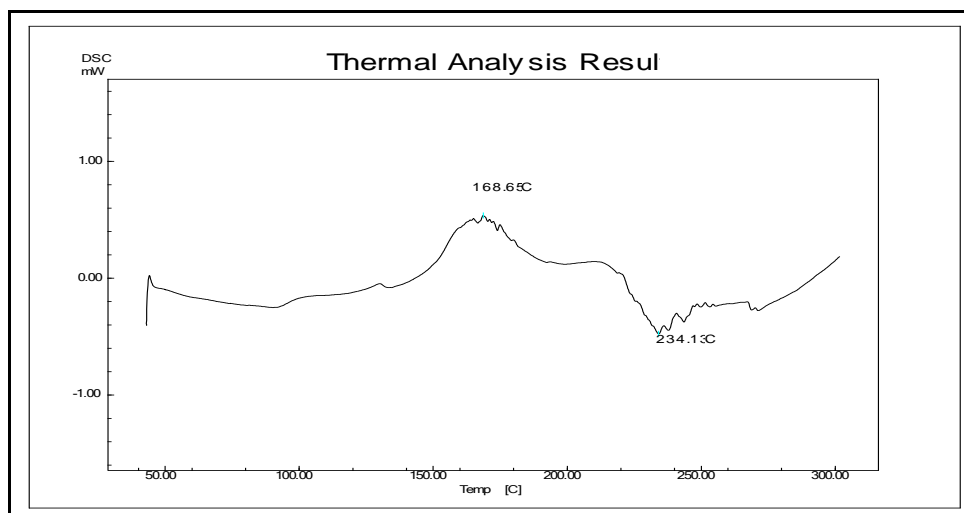


Figure: 4.12 DSC spectra of Optimized fast disintegrating tablet of LXM

4.5 Conclusion

From all results, it was found that optimized formulation of directly compressible taste masked FDT of lornoxicam present a better alternative to any other dosage form because it will give quick symptomatic relief from pain for rheumatoid arthritis. Moreover, lornoxicam -FDT can be taken anywhere anytime without preventing patient from living an active life which promotes very high patient acceptance and compliance.

4.6 References

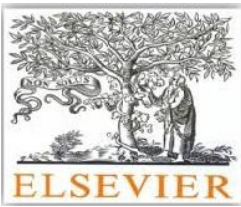

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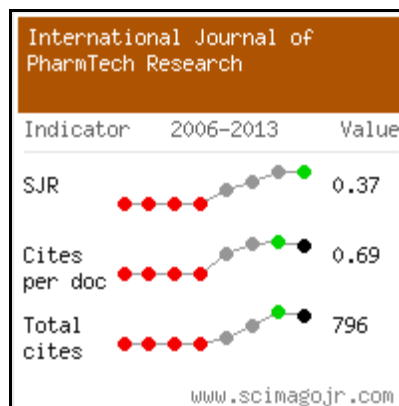
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