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Preparation and Evaluation of Taste Masked Quick Dissolving Film of 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 Quick dissolving film (QDF) 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 Beta Cyclodextrin in different ratios using kneading method by optimizing the kneading time. Taste evaluation was done by human volunteer and UV method. The optimized drug-beta cyclodextrin complex was incorporated in QDF by solvent casting technique using PVA: Pullulan as polymers and PEG 400 as plasticizer. The optimization of concentration of PVA: Pullulan and PEG 400 was done by 3^2 factorial design to observe its effect on disintegration time, drug release in 20 minutes, tensile strength and folding endurance as dependent variable. The optimized batch QDF1 gave disintegration in 22 second and 98 % drug release in 20 minutes with suitable strength and flexibility. It can be concluded that the development of Quick dissolving film of Lornoxicam could give quick relief from the pain of rheumatoid arthritis with greater compliance compared to other conventional dosage forms.

Keywords: Taste masking, beta cyclodextrin, pullulan, Polyvinyl alcohol, Quick dissolving film, tensile strength.

INTRODUCTION

In the field of dosage forms, tablet is the most successful amongst all. But in case of immediate release tablet, it has to pass through several steps including swelling, absorption of water and creation of repulsive force in tablet which can leads to disintegration of tablet. Thus the complete process takes sufficient time. [1] To overcome this steps, innovation in immediate release dosage forms were investigated to prepare quick dissolving film which is a recent and novel approach in the field of immediate release drug delivery system. Some patients, particularly paediatrics and geriatrics have difficulty in swallowing or chewing solid dosage forms. Many pediatrics and geriatric patients are not willing to take these solid preparations due to fear of choking. Thus, formulation of mouth dissolving dosage form fit best for them. [2]

Film possesses more benefits than moulding tablet due to availability of larger surface area which leads to rapid disintegrating and thereby dissolution in the oral cavity. Since the films are flexible they are not as fragile as most of the ODTs. Moreover, there is ease of transportation during consumer handling and storage. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the

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strips. Thus, it was found preferable to formulate quick dissolving film of Lornoxicam (LXM).

LXM has bitter taste. Taste masking is necessary for formulating QDF of LXM. Eudragit EPO masked LXM was not capable to give flexible film; it doesn't give continuous film it detaches from the mould in form of flakes. Ion exchange masked LXM don't give film as it has poor film forming property**.** Thus another approach was required for taste masking. Taste masking by inclusion complexation using beta cyclodextrin was used. Preliminary trials to select polymer and plasticizers were done. Final optimization was carried out using experimental design. Film was optimized for various parameters for disintegration time, flexibility and rapid drug release. Thus the aim of present work was to formulate and evaluate quick dissolving taste masked film of LXM for immediate treatment of pain.

Table 1: Taste masking of LXM using beta cyclodextrin in different molar ratio

Batch No.	Drug: β Cyclodextrin
DCD1	1:1
DCD2	1:2
DCD3	1:3

Table 2: Formulation composition for optimizing the kneading time

S. No.	Drug: Bcd	Time of Kneading
DCD4	1:2	3 hours
DCD5	1:2	4 hours
DCD6	1:3	3 hours
DCD7	1:3	4 hours

MATERIALS AND METHOD

LXM was received as gift samples from Hetero drugs Ltd. (Hyderabad, India). Beta cyclodextrin, Aspartame and citric acid were procured from Himedia Pvt. Ltd. Poly vinyl alcohol was received from CDH laboratory, India. Pullulan PI 20 was procured as gift sample from Hayashibara Biochemical Laboratories (Okayama, Japan). Polyethylene glycol 400 was received from S.D. Fine chemicals, Mumbai. Water used was double distilled and prepared in the laboratory. All other chemicals and reagents used were of analytical grade, procured commercially and used as such without further purification.

Preparation of LXM beta cyclodextrin taste masked granules by kneading method

Beta cyclodextrin was used as inclusion complexing agent. The taste-masked granules of drug and beta cyclodextrin were prepared by kneading method using mortar and pestle by varying different molar ratio of LXM to beta cyclodextrin from 1:1 to 1:3 and water as solvent. Accurately weighed quantity of beta cyclodextrin was taken in mortar and kneaded with water using pestle for 10 minutes. To the above mixture accurately weighed quantity of LXM was mixed and stirred. After kneading the mixture was allowed to dry and dried powder mixture was analysed for micromeritic properties, drug content and taste evaluation.

Optimizing the drug beta cyclodextrin molar ratio

Different batches were prepared as the procedure explained above with kneading time of 2 hours and formulations compositions are mentioned in Table 1.

Optimization of the kneading time

βCD was weighed and kneaded for 10 minutes using water and the drug was added and kneaded in mortar using water for different time intervals as shown in Table 2.

Evaluation of taste masked powder blend

The powdered blend was evaluated for following physical properties such as angle of repose, compressibility index and Hausner's ratio.

Evaluation of taste masking by UV method

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 ± 0.5°C. 5 ml of sample was withdrawn from the dissolution medium at the specified regular intervals, filtered through whatman filter paper and assayed spectrophotometrically at 378 nm. The cumulative percentage of drug release was calculated and represented graphically.

Evaluation of taste masking by panel method

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, taste masked. This was approved by Institutional ethical committee, Nirma University as per certificate of approval with project no. IEC/NU/III/IP/06. Bitterness scale – sweet taste (++++), non-bitter (+++), less bitter (++) and bitter (+).

DSC Method

A PerkinElmer differential scanning calorimeter was used to obtain the DSC curves of, LXM and LXM-EPO complex. The samples were separately sealed in aluminium cells and heated from 30 to 300°C at a heating rate of 10°C/min. An empty aluminium pan was used as reference.

Fourier Transform Infrared Spectroscopy method

Fourier-transform infrared (FT-IR) spectra LXM and LXM-EPO complex were obtained on JASCO V5300 FT-IR. The pellets were prepared on KBr-press. The spectra were scanned over the wave number range from 400 to 2000 cm^{-1}.

Method for preparation of quick dissolving film

To select ideal proportion of PVA: Pullulan and PEG 400, factorial design approach was used. The design and response summary data was represented in Table 3. Different ratios of polymer or film former as PVA: Pullulan making final concentration as 5% was added to 10 ml of water in beaker to make uniform dispersion. Plasticizer as PEG 400 was added to above dispersion. Sweeteners like aspartame, citric acid as saliva stimulating agent and flavor were added to increase palatability of film. Finally the optimized mixture of LXM βCD was added in accurately weighed quantities.

The clear solution was casted on a 9 cm diameter glass petridish and dried at 45°C in hot air oven. The film was carefully removed from the petridish, checked for regularity and uniformity and cutted in to required size to deliver the equivalent dose of drug per strip. The samples were kept in desiccators at 30% RH until further analysis. Film samples with air bubbles, cuts, or imperfections were excluded from the study.

The polynomial equation was generated using multiple linear regression analysis. This study investigated utility of a 2-factor, 3-level design and optimization process for quick dissolving film of LXM. Proportion of PVA: Pullulan (A) and concentration of PEG 400 (B) were selected as the independent variables whereas disintegration time (Y_1), tensile strength (Y_2) folding endurance (Y_3) and (Y_{15}) Drug release in 20 min (Y_3) were selected as dependent variables. Independent factors were selected at 3 different levels as mentioned in Table 3.

The prepared Quick dissolving film of LXM was evaluated for dissolution study. The design responses and polynomial equation was analyzed using Design expert 9.

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 QDF10 is shown in Table 4.

Evaluation parameters of films [3-6]

Folding endurance: The number of folds on the same crease required to produce crack was taken as a measure of plasticity.

Thickness: It can be measured by micrometer screw gauge at different position.

Mechanical properties: Film of size 10 × 2.5 cm² which is free of physical imperfections was held between two clamps which is 5-cm apart in tensiometer. The 10 × 2.5 cm² dimension was selected because it was the minimum size required for sample testing on the machine. The Film was pulled by the clamp at a rate of 50 mm/min.

Tensile strength

Tensile strength was calculated by following formula.

Tensile strength = Force at break/ Initial cross sectional area of film

Percent Elongation

$$\% \text{ Elongation} = \frac{\text{Increase in length of strip}}{\text{Initial length of strip}} \times 100$$

***In vitro* disintegration studies:** The film containing dose equivalent to 4 mg of drug LXM was placed on a stainless steel wire mesh containing 10 ml of distilled water in a petridish. The time required for the film to break was noted as in vitro disintegration time.

***In vivo* disintegration studies:** The *in vivo* disintegration time was measured in six human volunteers. A film was placed on the tongue of the volunteers and time required for disintegration in the mouth was noted.

***In vitro* dissolution studies:** Test was carried out in simulated gastric fluid, and simulated saliva at 37 ± 5°C at 50 rpm. Each film with dimension (2 × 2 cm²) was submerged into dissolution media. Samples were withdrawn at 2, 4, 6, 8, 10, 12, and 14 min time intervals, and filtered through 0.45µm whatman filter paper, and analyzed spectrophotometrically.

Drug content: Total drug content per film was calculated by random sampling of the all mouth dissolving film of LXM. The drug assay was carried out using UV spectrophotometric method.

Uniformity of drug content: The same procedure was carried out to calculate the uniformity of drug content. 4 cm² pieces were cut from two places and the drug content was calculated using UV spectrophotometric method.

Palatability study: Palatability study was conducted on a group of 6 volunteers. The mouth Dissolving films were rated on the basis of taste, after bitterness and physical appearance. All the batches were rated as +, ++, +++ based on decrease in bitterness.

Stability studies: Stability study of optimized film formulation was carried out for 6 months at 65% relative humidity and 30°C temperature in the humidity chamber. After 6 months the placed film were evaluated for the drug content, disintegration time and physical appearance.

Table 3: Independent variable Levels in coded form

Independent variable	Levels		
	-1	0	1
Concentration of PVA: pullulan	10:90	30:70	50:50
Concentration of PEG 400	30%	35%	40%

Table 4: Layout of design

Batch no.	Coded valve		Actual value	
	A	B	Proportion of PVA: Pullulan (%)	Concentration of PEG 400 (%)
QDF 1	-1	1	10:90	40%
QDF 2	1	-1	50:50	30%
QDF 3	0	0	30:70	35%
QDF4	1	0	50:50	35%
QDF 5	0	1	30:70	40%
QDF 6	0	-1	30:70	30%
QDF 7	-1	-1	10:90	30%
QDF 8	-1	0	10:90	35%
QDF 9	1	1	50:50	40%
QDF10	-0.8	0.8	14:86	39%

RESULT AND DISCUSSION

LXM was a bitter drug. Ion exchange resin or Eudragit EPO complexed drug film were not having flexible films. They were with poor tensile strength and texture. Thus inclusion complexation technique was finalized to mask the bitter taste of drug.

Kneading is one of the simple, easy, and economic methods for inclusion complexation of drug with beta

cyclodextrin. Taste masking was carried out using different ratios of LXM and beta cyclodextrin from 1:1 to 1:3 molar ratio with kneading time fixed as 2 hours. Here the batch DCD 3 with drug to βCD molar ratio of 1: 3 gave slight bitter taste while in DCD 1 and DCD 2 the bitter taste of LXM was felt. So LXM was not included in βCD in Batch DCD 1 and DCD2 in 2 hours of kneading time. So from this result it was concluded that we need to either increase the molar ratio or increase the kneading time.

Table 5: Evaluation of LXM βCD complexed mixture

Batch no.	Drug: β Cyclodextrin molar ratio	% Drug content	Taste evaluation	Carr's Index	Hausner's ratio	Angle of repose
DCD1	1:1	93.23±0.35	+	14.17±0.32	1.15±0.26	18.36±0.25
DCD2	1:2	90.52±0.23	++	16.12±063	1.06±0.36	21.36±0.16
DCD3	1:3	93.26±0.36	+++	18.26±0.29	1.10±0.13	20.49±0.36

Table 6: Evaluation of LXM βCD complexed mixture

S. No.	Drug: βCD	Time of Kneading	Taste Masking	Drug Content(%) ±SD)
DCD4	1:2	3 hours	+++	93±0.89
DCD5	1:2	4 hours	++++	94±0.98
DCD6	1:3	3 hours	++++	94±2.05
DCD7	1:3	4 hours	++++	94±1.15

For further optimization of the kneading time, the molar ratio 1: 2 and 1:3 was repeated with increase in kneading time to 3 and 4 hours in batch DCD 4, 5, 6 and 7. Results were as shown in table 8. From the result it was found that by increasing the kneading time from 2 hours to 4 hours the bitter taste was getting completely masked in case of 1: 2 molar ratio of drug to βCD this means LXM was completely included into the cavity of βCD. Thus there was no need of further increasing the molar ratio to 1:3 as once complete LXM has been included into βCD by 1: 2 molar ratio there will be no further inclusion by increasing the molar ratio to 1:3.

The optimized batch showed drug content of 94% in the granules. The physical properties like percentage compressibility, angle of repose and hausner's ratio of complex was found to be 16 %, 21° and 1.06 respectively.

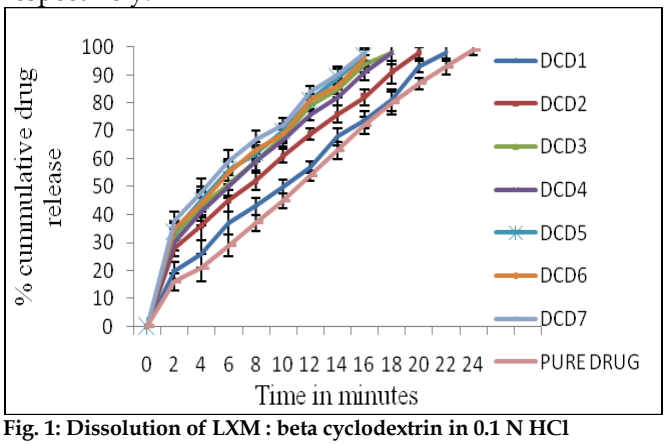

Fig. 1: Dissolution of LXM : beta cyclodextrin in 0.1 N HCl

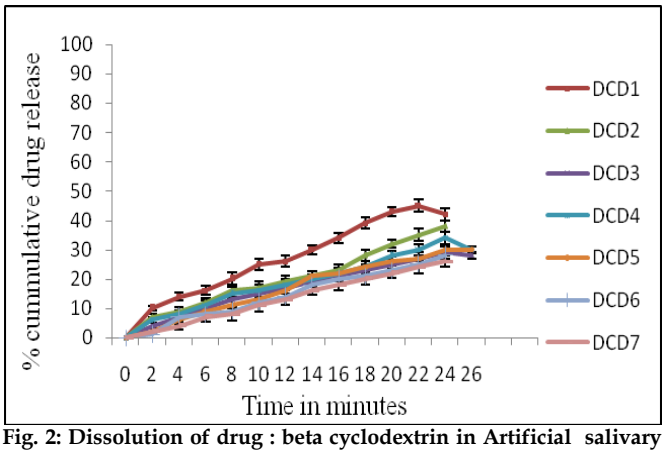

Fig. 2: Dissolution of drug : beta cyclodextrin in Artificial salivary fluid (pH-6.8)

The dissolution of drug: beta cyclodextrin complex was less than 25% in artificial salivary fluid (pH-6.8) as shown in figure 2 which proved that the drug was not released from beta cyclodextrin in saliva so bitter taste of drug was not felt. While in case of dissolution in 0.1 N HCl the drug was completely released from the complex. Thus it was proved that the bitter taste of LXM was completely masked.

Complete taste masking was confirmed by taste acceptability and DSC spectra of pure LXM and complex. The spectra of fig 4 showed absence of sharp endothermic peak of drug, which indicated the complete inclusion of drug in beta cyclodextrin.

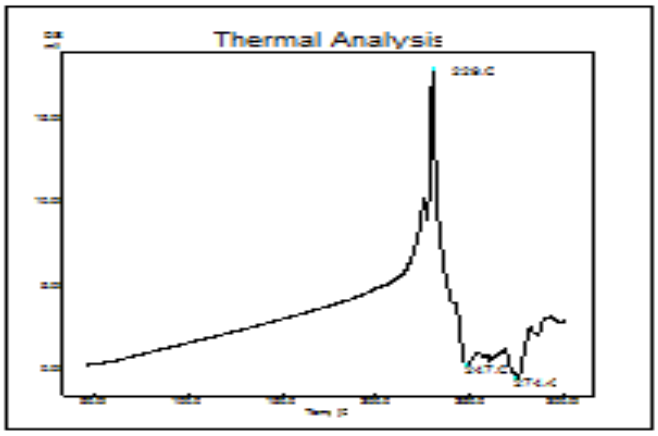

Fig. 3: DSC of LXM

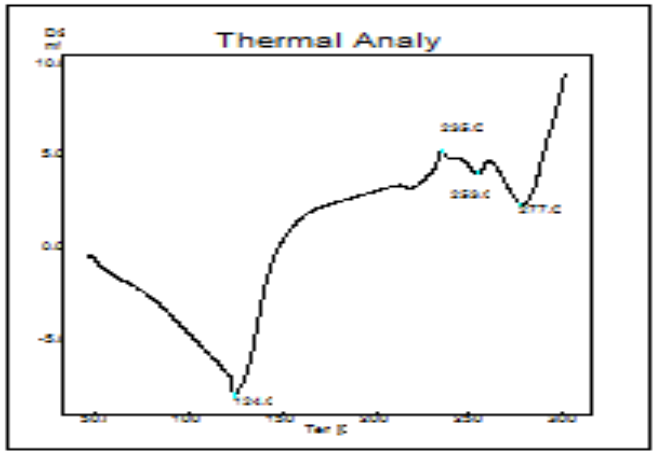

Fig. 4: DSC of LXM-β CD

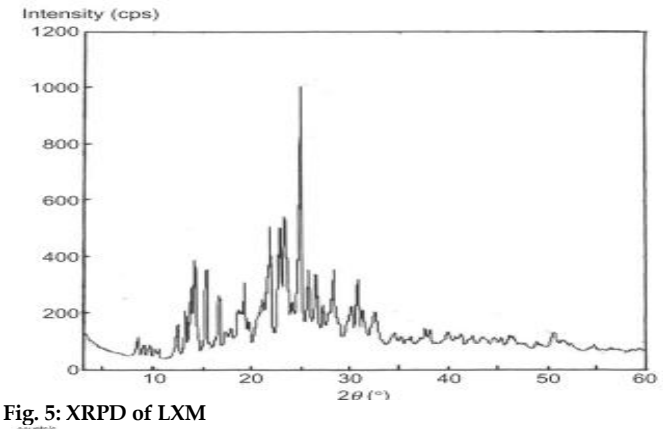

Fig. 5: XRPD of LXM

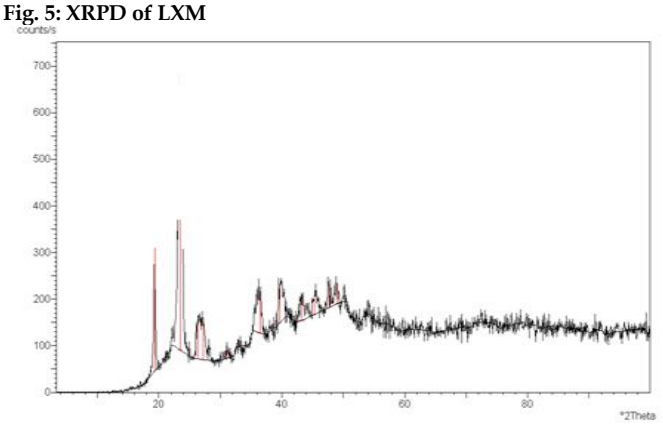

Fig. 6: XRPD of LXM-β CD

Table 7: Results of dependent response

Batch no.	Actual values		Response			
	A	B	DT (sec)	Tensile strength (g)	Folding endurance	Drug release after 20 min (%)
QDF1	**10:90**	**40%**	**22**	**315**	**219**	**98.59**
QDF2	50:50	30%	48	215	135	65.29
QDF3	30:70	35%	39	308	192	75.85
QDF4	50:50	35%	40	438	268	71.49
QDF5	30:70	40%	33	425	245	86.48
QDF6	30:70	30%	43	138	84	69.15
QDF7	10:90	30%	31	78	52	89.12
QDF8	10:90	35%	26	189	110	92.15
QDF9	50:50	40%	37	472	286	81.38
QDF10	14:86	39%	26	321	204	91.25

Table 8: Formulations constraints for dependent and independent variables

Name	Goal	Lower Limit	Upper Limit
Concentration of PVA: Pullulan	In range	10:90	50:50
Concentration of PEG 400	In range	30%	40%
Disintegration Time (sec)	In range	0	30
Tensile strength(g)	In range	78	472
Folding endurance	In range	52	286
Drug release in 20 min (%)	In range	70	100

By XRPD it was concluded that the crystallinity of drug was reduced and drug had become amorphous as the sharpness of the peaks was reduced. Thus, LXM: Beta cyclodextrin in 1:2 molar ratio prepared by kneading with water for 4 hours gave complete taste masking. This taste masked LXM complex was incorporated in to film.

Optimization of Formulation compositions by experimental design

To select ideal proportion of PVA: Pullulan and PEG 400, 3^2 factorial design was applied. After applying design, the response was recorded and analysis of data was carried out using Design Expert 9. The response variable considered for optimization were disintegration time (Y_1), tensile strength (Y_2), Folding endurance (Y_3) and drug release in 20 minutes Y_{20} (Y_4). The results of response were depicted in Table 7.

The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). Constraints were selected based on minimum and maximum limits obtained from each response. Constraints for responses and factors are shown in Table 8.

Statistical analysis of the data and validation of the model

The statistical analysis of the factorial design formulations was performed by design expert 9. In vitro drug release in 15 minutes, disintegration time, folding endurance and tensile strength values for the 9 formulations (QDF 1-9) showed a wide variation; the results are shown in Table 7. The data clearly indicate that the values of in vitro drug release, DT, folding endurance and tensile strength were strongly dependent on the independent variables.

Response 1: Disintegration time (Y1)

The fitted full model equation relating the response disintegration time to the transformed factor is shown in following equation. The equation obtained as follows

Disintegration Time (Y1) =+37.10345+7.66667 * A-5.00000 * B-0.50000 * A*B-3.86207 * A^2 +1.14 * B^2

The disintegration time for the 9 batches show a variation, that is, the response ranged from a minimum 22 sec to maximum of 48sec. The value of correlation co-efficient R^2 was found to be 0.9707, indicating a good fit. b1 is positive and b2 is negative, It may be concluded that at higher levels of A(amount of PVA: pullulan) and lower level of B (amount of PEG 400) the disintegration time increases. The level B shows less significant effect than A on the disintegration time.

The surface and counter plot are shown in Fig. 7.

Response 2: Tensile strength

Tensile strength =+292.31+90.50*A+130.17* B

Positive value of b1 and b2 concluded that With higher level of A (amount of PVA: pullulan) and B (amount of PEG 400) the tensile strength increases. B shows more significant effect on the tensile strength, in comparison to A Value of coefficient correlation r^2 is 0.95 shows good fit. The surface and counter plot are shown in Fig. 8.

Response 3: Folding endurance

Folding endurance =+180.92+51.33*A+79.83*B

Positive value of b1 and b2 shows more significant effect of both factors on the folding endurance, effect of B is higher than the effect of A. Value of coefficient correlation r^2 is 0.94 shows good fit. The surface and counter plot are shown in Fig. 9.

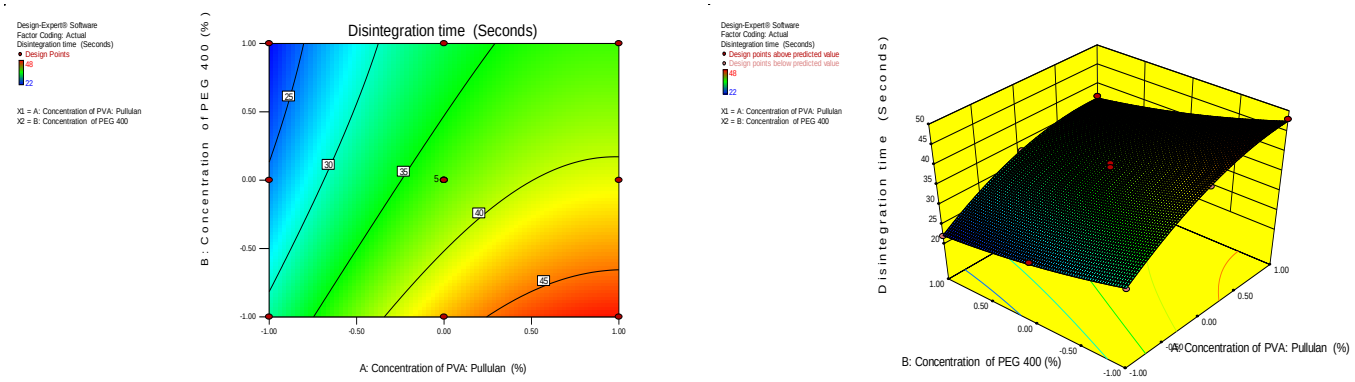

Fig. 7: Contour and surface plot for the effect of A and B on Disintegration time

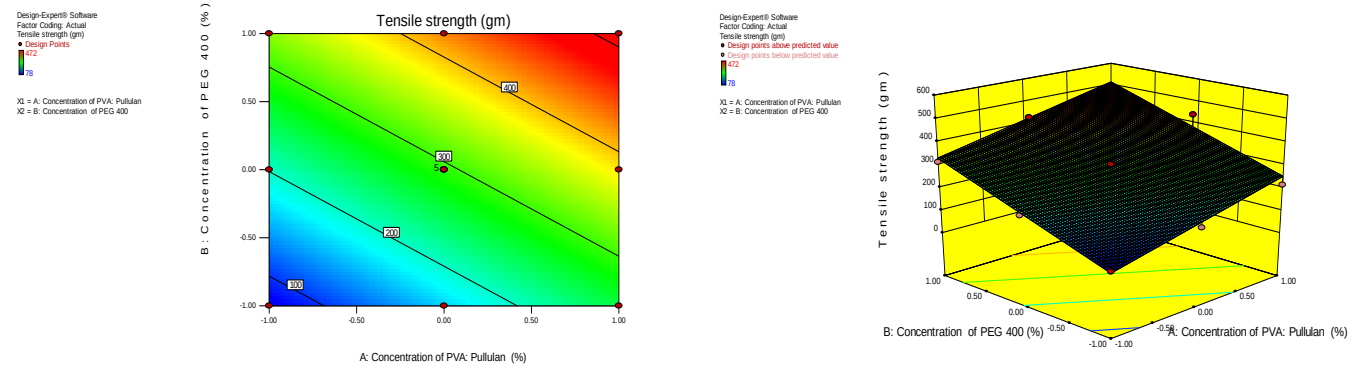

Fig. 8: Contour and surface plot for the effect of A and B on tensile strength

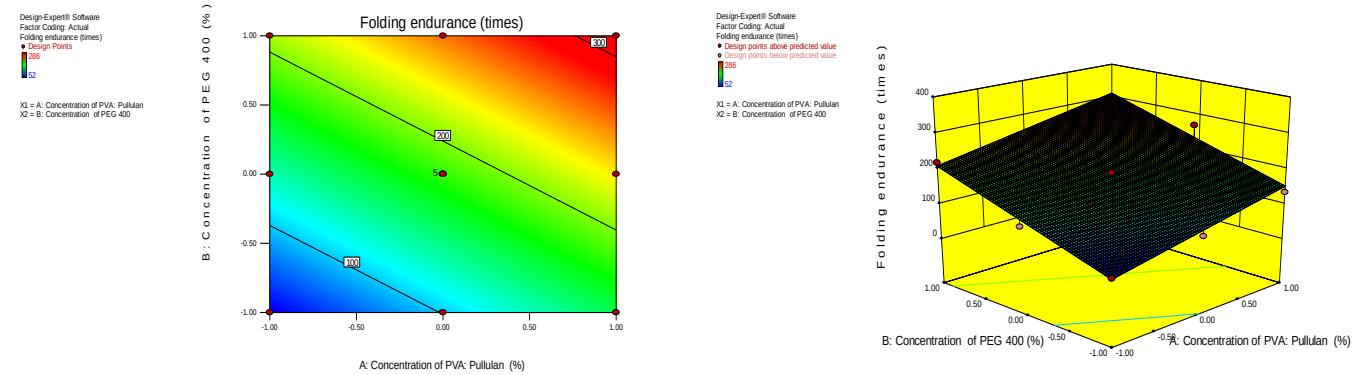

Fig. 9: Contour and surface plot for the effect of A and B on folding endurance

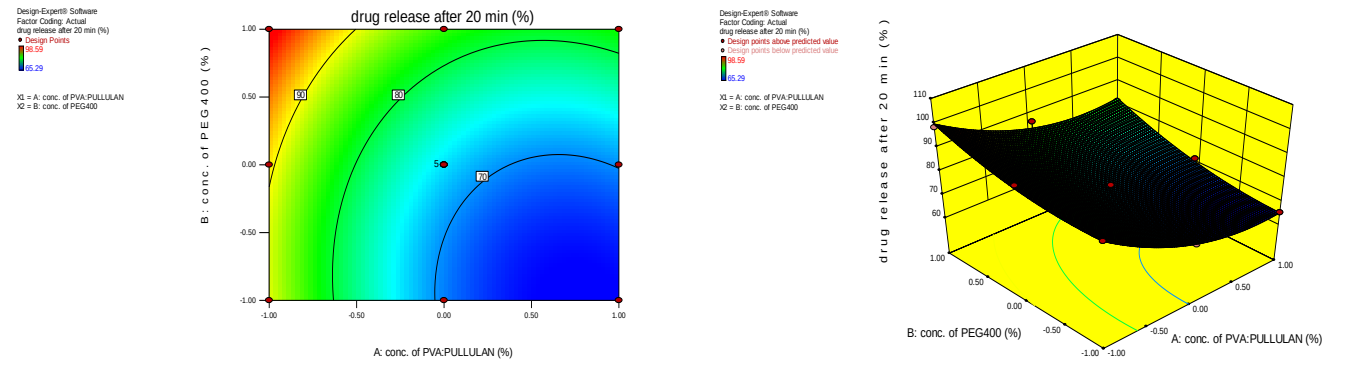

Fig. 10: Contour and surface plot for the effect of A and B on drug release in 20 minutes

Table 9: Results of p values, regression coefficient and F values for various responses.

	p value						R2	F	Significance F
	Bo	b1	b2	b12	b11	b22			
Tensile strength	0.001444	0.00938	0.00331	0.805	0.83832	0.24496	0.98684	22.3497	0.014017
% Drug release in 20 minutes	7.30628E-06	0.00047751	0.001402112	0.117475044	0.012197659	0.185539531	0.996647	89.00911368	0.001849079
Folding endurance	0.002947	0.02066	0.00604	0.79388	0.829	0.39068	0.97922	13.9902	0.027275
DT	0.0000269	0.00053	0.00186	0.45576	0.01356	0.47952	0.99623	79.1189	0.002202

Response 4: Drug release in 20 minutes

rug release after 20 min =+72.77-10.28* A+7.15* B+1.66* A * B+7.74* A^2-3.74* B^2

It may be concluded that at higher levels of A (amount of PVA: pullulan) decrease the effect on amount of drug release up to 20 min. With higher level of B (amount of PEG 400), increase amount drug release. The level A shows negative effect and B shows positive effect. Value of coefficient correlation r^2 is 0.9866 shows good fit. The surface and counter plot are shown in Fig. 10.

The P value for X12, X11 and X22 were found (Table 9) greater than 0.05 (in case of DT, folding endurance and tensile strength) while value for X22 was found (Table 9) greater than 0.05 in case of drug release after 20 minutes, Which rendered insignificant. While p value for other term X1 and X2 were found to be less than 0.05. Thus X1 and X2, has significant effect on dependent variable (DT, folding endurance and tensile strength) while in case of drug release after 20 minutes –X1, X2, X1X2 and $X1^2$ has significant effect on dependent variable.

Formulation Optimization

For the optimization of quick dissolving film of LXM, constraints were fixed for all factors and response. Constraints were set according to formulation of film using minimum amount of excipients, which would give desired response values. In the present study, our aim was disintegration time should be 22 sec and more than 90 % dissolution of drug within 15 min with satisfactory strength and flexibility. In optimization, desirability 1.0 indicated that optimum formulation was achieved at 10:90 ratio of PVA to Pullulan and 40% of PEG 400 as shown in Fig. 11.

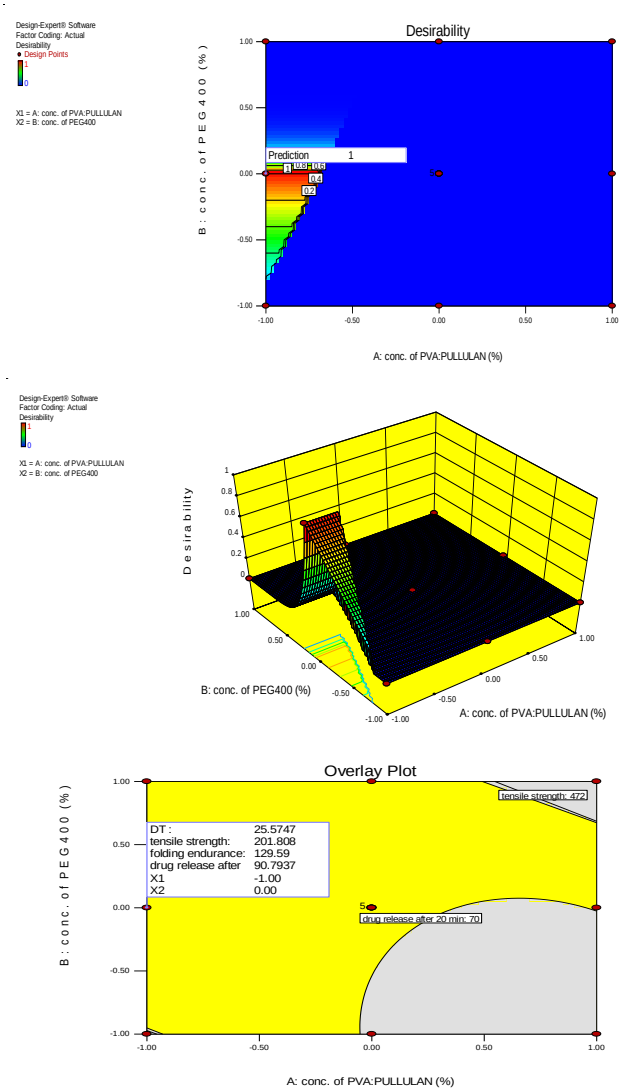

Fig. 11: Desirability and overlay plot for optimization

Table 10: Comparison of predicted value and observed values of all response for QDF 10 batch

Batch	Comparison of predicted value and observed values of all response							
	Disintegration time (sec)		Drug release in 20 minutes (%)		Folding endurance		Tensile strength(g)	
	Observed value	Predicted value	Observed value	Predicted value	Observed value	Predicted value	Observed value	Predicted value
QDF 10	26	25.5	91.053	91.25	204	203.72	321	432

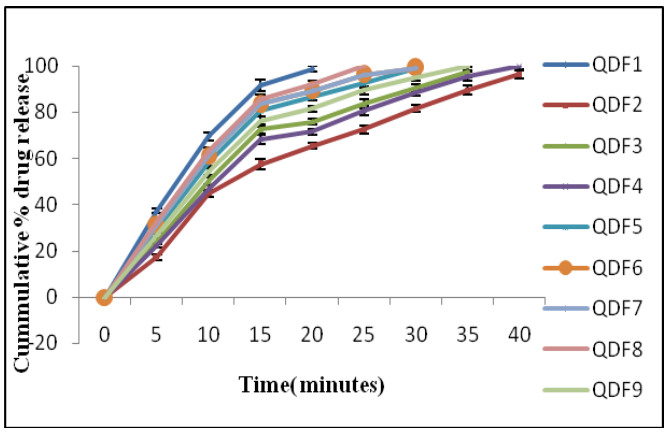

Fig. 12: Drug release profile in 0.1 N HCl of design batches of Quick dissolving film

Validation of optimization technique done by preparing checkpoint batch QDF 10 and response were evaluated. Check point batch was compared for predicted value with observed value in table 10. Observed value was found close to the predicted value, which indicated good correlation of results.

Drug release profile in 0.1N HCl of design batches were shown in Fig. 12.

Optimized batch QDF 1 having disintegration time of 22 seconds and 98.59 % drug release within 20 min.

Stability studies

Optimized batch was subjected to stability study at 25C±2°C and 40%±5 RH for 6 month. The film were found to be stable at such condition and other parameters were found to be unaffected

From all results, it was found that optimized formulation of taste masked QDF of LXM present a better alternative to any other dosage form because it will give quick symptomatic relief from pain for

rheumatoid arthritis. Moreover, LXM-QDF can be taken anywhere anytime without preventing patient from living an active life which promotes very high patient acceptance and compliance.

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