Research Article

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Quality by Design Approach for Optimization and Development of Orodispersible Films of Lornoxicam Inclusion Complexes

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ABSTRACT

Lornoxicam is a non-steroidal anti-inflammatory drug, indicated in the treatment of osteoarthritis and rheumatoid arthritis. Lornoxicam is a poor water-soluble drug and hence possesses dissolution limited bioavailability. The aim of the current research work was to develop and characterize orodispersible films of Lornoxicam to enhance its bioavailability by employing Quality-by-Design (QbD) approach. Solvent casting method was used to formulate the Lornoxicam mouth dissolving films. Three formulation factors viz. amount of polymer, amount of PEG 400 and type of polymer were varied at different levels. The responses selected were disintegration time and percent drug dissolved after 5mins. Under the response surface methodology, historical data design was employed to perform the statistical analysis using Design Expert software. The developed films were found to have good elasticity, folding endurance and favorable tensile strength. The disintegration time was found to be 9 to 17 seconds and drug dissolved after 5 minutes was 49 to 95%. The statistical analysis of the results by ANOVA elucidated that there was a significant effect of all the formulation factors on the selected responses ($p<0.05$). Finally optimization was performed using desirability functions approach to elucidate the best formulation.

Keywords: Orodispersible films, Bioavailability enhancement, Historical data designing, Quality-by-design, Response surface methodology.

1. INTRODUCTION

Lornoxicam (LX) is a new non-steroidal anti-inflammatory drug, indicated in the treatment of osteo arthritis and rheumatoid arthritis belonging to the class oxicam possessing analgesic, anti-inflammatory and anti-pyretic properties. Its potent inhibition of prostaglandin biosynthesis makes it efficient than other oxicam drugs. The half-life of Lornoxicam is 3-5 hours [1]. It inhibits the cyclooxygenase enzymes, which helps to reduce the risk of adverse gastrointestinal (GI) effects seen in most of the non-steroidal anti-inflammatory drugs (NSAIDs). The water solubility of Lornoxicam is 0.0437mg/mL belonging to biopharmaceutical class II drugs [2], having a poor water-solubility and high permeation and hence possesses dissolution limited bioavailability. In order to overcome this problem, Lornoxicam should be developed into a dosage form such that its dissolution is enhanced.

Oral route of administration of drugs has always been the predominantly preferred route of administration owing to its ease of administration, self-medication and also patient compliance with no pain during administration [3]. In the recent trends, fast-dissolving dosage forms have gained a lot of interest as they rapidly disintegrate/dissolve upon administration without the need of water in-take. Patients having dysphagia due to physiological changes, find it easier to administer such mouth dissolving films which get rapidly hydrated by the saliva and release the drug in the mouth and thereby promoting GI absorption of the drug too [4]. It can be inferred from several research studies on these orodispersible films (ODFs) like Wasilewska K *et al.*2019 [5], Foo WC *et al.* 2018 [6] and Khadra I *et al.*2019 [7] that when formulated as ODFs, there is a significant increase in the drug dissolution which promotes the enhancement of the drug bioavailability. The intense literature review carried suggests the scope of development of oral/mouth dispersing films to enhance the drug bioavailability by using different hydrophilic polymers which act as film formers.

Owing to the poor solubility of lornaxicam, its incorporation in the form of cyclodextrin complexes into the films could result in much rapid dissolution. Formation of cyclodextrins (CDs) complexes has always proved to have an added advantage in enhancing the bioavailability of the drug as they tend to form complexes with the poorly water-soluble drugs and thereafter improve its aqueous solubility owing to the increase in the drug dissolution and bioavailability [8]. CDs also help to prevent any GI irritation and also mask the unpleasant taste or smell of the drug thereby improving the patient compliance [9]. The current research involved the development and characterization of Lornoxicam oral dissolving films formulated using solvent casting method, where **γ-cyclodextrin complexes** of the drug were prepared first which were thereafter formulated as orodispersible films.

Historical data design under response surface methodology was employed as the experimental design using Design expert software. The independent factors considered were the type of film formers, amount of film former and amount of plasticizer used. Different grades of hydroxypropyl methyl cellulose (HPMC E3, HPMC E5 AND HPMC E15) polymers were used as the film formers and polyethylene glycol (PEG) 400 being the plasticizer. The response variables considered were tensile strength, folding endurance, disintegration time (DT) and % dissolution after 5minutes (D5%) which are used to determine the desirability of the lornoxicam orodispersible films (LX-ODFs). These results were statistically tested by analysis of variance (ANOVA) for finding their suitability to proceed for the optimization. Finally, the optimization was done by desirability functions approach to find the best combination of the formulation factors towards achieving rapid disintegration and dissolution of the developed films.

2. MATERIALS AND METHODS

2.1 Materials

Lornoxicam was procured from Hetero Drugs Pvt. Ltd, Hyderabad; HPMC E3, HPMC E5, HPMC E15, γ-cyclodextrin and PEG 400 were acquired from Sigma Chemicals Co.; aspartame, citric acid and pineapple flavor were purchased from SD Fine Chemicals, Mumbai. All other chemicals used in this research work were of analytical grade.

2.2 Analytical method for estimation of Lornoxicam

Spectrophotometric method was used to develop method for estimation of lornoxicam in the complexes and in the films. Methanol was used to pre-

pare stock solution at 100µg/mL. final dilutions were made as 2, 4, 6, 8 and 10 µg/mL using pH 6.8 phosphate buffer for the purpose of linearity and to develop calibration curve. The dilutions were measured using UV – Visible spectrophotometer at the maximum wavelength of 379 nm. Accuracy was performed by triplicate sampling of known concentration (10µg/mL) of the drug solution. Percent relative standard deviation (% RSD) was calculated from the mean and standard deviation of the absorbances. Precision was performed by taking a series of 10 samples from a homogenous solution of known concentration of the drug. From the mean and standard deviation of the obtained absorbance values, %RSD was calculated to check the precision.

2.3 Preparation of inclusion complexes of lornoxicam

The complexes were prepared using solvent evaporation method [8,9]. Drug to cyclodextrin at three different ratios viz. 2:1, 1:1 and 1:2 were taken and mixture of dimethyl sulfoxide (DMSO) and methanol at 50:50 ratio was taken as the solvent to prepare the complexes. 100 mg of the drug and the corresponding amount of the CD were dissolved in 20 mL of the solvent mixture. The mixture was subjected to evaporation of the solvent using Rotavapor (Buchi Rotavapor R-100) instrument at 65^{o}C under low pressure. After complete removal of the solvent, the obtained powdered complexes were collected and subjected to solubility studies.

2.4 Development of Lornoxicam Orodispersible Films (LX-ODFs)

Design of Experiment

Quality by design (QbD) [10] based approach was employed in the development of LX-ODFs in this work. The quality target product profile (QTPP) was defined for this experiment as the ODFs with sufficient mechanical strength and mainly with rapid disintegration and dissolution were needed. In order to achieve the desired quality, the critical process/formulation parameters (CPPs) or independent factors selected to design the experiment were the three formulation factors viz. A: amount of film former (140-310mg), B: amount of plasticizer (PEG 400, 5-25mL) and C: Type of HPMC used. To represent the desired quality of the ODFs, critical quality attributes (CQAs) or responses considered were the two critical quality attributes of the LX-ODFs which were R1: Disintegration time and R2: Percent drug dissolved after 5 minutes. Experimental runs were taken with all the possible combinations of the factors at all the levels. Under the response surface methodology, historical data designing was employed as the experimental design to analyze the influence of the factors on the responses using Stat Ease Design Expert software. With the combinations of the factors at different levels (shown in Table 1 and 2) 30 runs were designed to formulate the LX-ODFs.

Preparation of Lornoxicam Orodispersible Films (LX-ODFs)

Solvent casting method [11] was employed to formulate the ɣ-cyclodextrin complexes into the oral dissolving films. 108 mg of the drug-cyclodextrin complex equivalent to 36 mg of lornoxicam was dissolved in 20 ml of 50% v/v aqueous methanol. Different grades of HPMC [12] which were used as the film forming polymers in appropriate quantities were soaked for 24 hours for proper hydration and then the solution was stirred for 2hrs at 50rpm on a magnetic stirrer (Remi, 10 MLH Plus). Later, PEG 400 was added and stirred for 30 minutes more. The water-soluble ingredients viz. pineapple flavor, malic acid, aspartame were dissolved in sufficient amount (as shown in Table 1 and 2) of aqueous solvent to form a clear solution which was then added to the drug-cyclodextrin complex solution under constant stirring till the formation of a homogenous solution which was transferred to a petri dish [13] of area of 72 cm^{2}for drying for a period of 6hrs at 45^{o}C. The films obtained were cut into strips of 8 cm^2 (equivalent to 4mg of Lornoxicam), stored and further used to carry out the characterization studies.

2.5 Characterization of the Films

Thickness

Through visualization, the surface appearance and texture of the ODFs was observed. A micrometer screw-gauge was used to measure the thickness [14] at five different points on the LX-ODFs and the results obtained were given as their mean value.

Folding endurance

The ODFs were folded a number of times repetitively till the film was broken to calculate its folding

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Table 1. Combination of factors and their levels with the formulation compositions of F1-F15

Formulation code	Drug-CD complex (mg)	HPMC (mg)			PEG 400 (mg)	Aspartame (mg)	Citric acid (mg)	Pineapple flavor (mL)
		E3	E5	E15				
F1	108	260	-	-	5	8	2	0.1
F2	108	230	-	-	10	8	2	0.1
F3	108	200	-	-	15	8	2	0.1
F4	108	170	-	-	20	8	2	0.1
F5	108	140	-	-	25	8	2	0.1
F6	108	-	260	-	5	8	2	0.1
F7	108	-	230	-	10	8	2	0.1
F8	108	-	200	-	15	8	2	0.1
F9	108	-	170	-	20	8	2	0.1
F10	108	-	140	-	25	8	2	0.1
F11	108	-	-	260	5	8	2	0.1
F12	108	-	-	230	10	8	2	0.1
F13	108	-	-	200	15	8	2	0.1
F14	108	-	-	170	20	8	2	0.1
F15	108	-	-	140	25	8	2	0.1

endurance [15,16]. The final count at which the film broke was considered as the folding endurance point.

Tensile strength

Tensile strength [17,18] is used to determine the maximum stress where the film breaks when applied at a particular point which was determined using the tensile strength tester (HAIDA, HD-B609-S). It was calculated by the following equation.

Drug content

In a beaker containing 100mL of pH 6.8 phosphate buffer, a LX-ODF was transferred and was subjected to constant stirring for 2 hours. The filtrate of the dispersion was spectrophotometrically analyzed for the drug content [19,20] using UV-Visible spectrophotometer (Thermo Scientific Evolution 201) at a wavelength of 376nm and the results of the triplicate tests were reported as their mean values.

Disintegration time

Petri dish method was used to determine the disintegration time [21,22] of the LX-ODFs. Each petri dish was filled with10mL distilled water in which LX-ODFs of 4 cm^2 were placed. The time taken for the complete dispersion of LX-ODFs was considered as the disintegration time, the results of which were given as their mean.

Dissolution study

USP type I basket apparatus (Labindia, DS 8000) was used to perform the dissolution studies [23,24] and the dissolution medium taken was 900 mL of pH 6.8 phosphate buffer that was maintained at 37°C. The films (each film equivalent to 4mg Lornoxicam) were subjected to dissolution and the samples of 5 mL were collected after 1, 3, 5, 7, 9 and 10 minutes, thereafter replaced with the same amount of buffer. The obtained samples were analyzed using UV spectrophotometer at a λ_{max} of 376nm. The obtained data

Table 2. Combination of the factors and levels with the formulation compositions of F16-F30

Formulation code	Drug-CD complex (mg)	HPMC (mg)			PEG 400 (mg)	Aspartame (mg)	Citric acid (mg)	Pineapple flavor (mL)
		E3	E5	E15				
F16	108	260	50	-	5	8	2	0.1
F17	108	230	50	-	10	8	2	0.1
F18	108	200	50	-	15	8	2	0.1
F19	108	170	50	-	20	8	2	0.1
F20	108	140	50	-	25	8	2	0.1
F21	108	50	-	260	5	8	2	0.1
F22	108	50	-	230	10	8	2	0.1
F23	108	50	-	200	15	8	2	0.1
F24	108	50	-	170	20	8	2	0.1
F25	108	50	-	140	25	8	2	0.1
F26	108	-	260	50	5	8	2	0.1
F27	108	-	230	50	10	8	2	0.1
F28	108	-	200	50	15	8	2	0.1
F29	108	-	170	50	20	8	2	0.1
F30	108	-	140	50	25	8	2	0.1

was subjected to zero-order and first-order kinetics to estimate the dissolution parameters.

3. RESULTS AND DISCUSSION

3.1 Analytical method for estimation of lornoxicam

The measured absorbances (on y-axis) at the prepared dilutions 9on x-axis) were made into a plot which yielded a straight line with the equation of with correlation coefficient of 0.9992. This indicated the developed method was found to produce linearity in the concentration range of 2 – 10 µg/mL. Thus, this can be employed to quantify lornoxicam in the complexes and in the films. The results of accuracy test showed that the % recovery was 100.29% and the %RSD was 0.27%. These values showed that the method was accurate in performing the lornoxicam quantification. The %RSD from the precision test was found to be 0.41%. And as the %RSD values were well below the maximum limit of 2.0%, the developed method was precise enough. All the linearity, range, accuracy and precision results designated that this method was suitable enough to quantify lornoxicam.

3.2 Solubility studies on the lornoxicam inclusion complexes

The complexes prepared at three different ratios of the drug to the γ-CD were subjected to equilibrium solubility studies. The results were obtained as 0.21±0.03, 0.46±0.06 and 0.53±0.04 mg/mL respectively for the complexes at the drug to CD ratios of 2:1, 1:1 and 1:2. The solubility of pure drug was found to be 0.041±0.007 mg/mL which was correlated with that reported by Kalyanappa S *et al.* [2]. Hence, the solubility of Lornoxicam was significantly improved and further, the complexes at the ratio of 1:2 were found to have maximum solubility. This could be due the hydrophilic nature of the γ-CD and upon increase in its concentration, the solubility of

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Table 3. Results of various characterization studies including the responses of LX-ODFs F1–F15

Formulation Code	Results of characterization parameters*					
	Thickness (mm)	Tensile strength (MPa)	Folding endurance	Drug content (%)	R1: DT (sec.)	R2: Drug release after 5mins (D5%)
F1	0.21 ± 0.03	6.3 ± 0.8	98 ± 6	97.69±0.22	12 ± 2	49.79± 5.32
F2	0.19 ± 0.01	5.9 ± 0.6	104 ± 9	97.86±0.66	12± 3	55.49± 3.15
F3	0.18 ± 0.02	6.1 ± 0.3	112 ± 10	97.33±0.09	11 ± 1	73.87± 4.09
F4	0.16 ± 0.04	5.6 ± 1.1	121 ± 5	97.76±0.86	13 ± 4	79.85± 2.78
F5	0.14 ± 0.03	5.2 ± 0.7	127 ± 13	97.70±0.60	12 ± 2	82.53± 6.12
F6	0.24 ± 0.01	6.7 ± 0.4	101 ± 7	96.79±0.44	12 ± 3	63.9± 3.19
F7	0.23 ± 0.03	6.6 ± 0.8	109 ± 11	93.46±0.15	13± 1	63.93± 2.06
F8	0.21 ± 0.04	6.1 ± 1.2	115 ± 9	96.20±0.78	14 ± 1	67.47± 1.62
F9	0.19 ± 0.02	5.8 ± 0.6	128 ± 5	96.89±0.72	12± 2	77.85± 4.52
F10	0.17 ± 0.02	5.6 ± 0.9	136 ± 6	97.38±0.38	13 ± 2	88.85± 3.71
F11	0.28 ± 0.03	6.6 ± 0.5	103 ± 7	96.25±0.14	15± 3	60.46± 2.83
F12	0.26 ± 0.04	6.4 ± 0.3	110 ± 3	95.90±0.65	14± 2	67.52± 2.27
F13	0.23 ± 0.01	6.1 ± 0.7	119 ± 9	96.42±0.68	13± 2	67.17± 1.94
F14	0.21 ± 0.04	5.9 ± 0.6	130 ± 10	98.92±0.95	12± 1	69.8± 3.02
F15	0.19 ± 0.02	5.7 ± 0.4	137 ± 12	98.09±0.15	14 ± 2	79.37± 2.65

* The results are expressed in Average ± Standard deviation for n = 3

the drug was further increased. Hence, the complex prepared at 1:2 ratio of the drug to γ-CD was selected to develop the films.

3.3 Characterization studies on the LX-ODFs

Thickness

The visual observation of the developed ODFs determined a smooth and glossy texture of the films. The films were subjected to various characterization studies, the results of which were shown in Table 3 and 4. The thickness values were found to be in a range of 0.14mm to 0.30mm for all the LX-ODFs. It could be inferred from the results that there was an increase in the thickness of the LX-ODFs with the increase in the concentration of the film former. And also the thickness was found to be increased in the order of the E3 < E5 < E15 grades of HPMC. HPMC E3, HPMC E5 and HPMC E15 have viscosities of 3, 5 and 15 cps respectively for a 2% w/v aqueous solution at 20°C. These results could be due to the increase in viscosity of the pre-casting solution at higher polymer concentrations as well as higher viscosity grades of the polymer that resulted in increased thickness of the final films [25].

Tensile strength

From the results of the Tensile strength (as shown in Table 3 and 4), it was inferred that the tensile strength of the LX-ODFs were in a range of 5.2 to 6.9 MPa which depicts flexibility and good elasticity of the developed films which help in avoiding breakage of films upon handling. The tensile strength of the LX-ODFs was found to increase with the increase in the amount of HPMC which might be due to the increased viscosity of the pre-casting solution that could result in stronger films with more strength [25,26].

Table 4. Results of various characterization studies including the responses of LX-ODFs F16–F30

Formulation Code	Results of characterization parameters*					
	Thickness (mm)	Tensile strength (MPa)	Folding endurance	Drug content (%)	R1: DT (sec.)	R2: Drug release after 5mins (D5%)
F16	0.23 ± 0.01	6.6 ± 0.4	101 ± 6	97.49±0.15	13 ± 2	65.44± 2.83
F17	0.21 ± 0.03	6.4 ± 0.7	109 ± 7	95.78±0.68	12 ± 3	67.29± 3.16
F18	0.20 ± 0.04	6.2 ± 1.1	114 ± 3	96.66±0.56	14 ± 1	69.76± 4.06
F19	0.19 ± 0.02	5.9 ± 0.5	118 ± 9	95.76±0.98	15 ± 3	76.97± 2.49
F20	0.17 ± 0.03	5.5 ± 0.3	126 ± 11	97.16±0.90	14 ± 1	85.71± 1.53
F21	0.26 ± 0.04	6.9 ± 0.6	105 ± 8	97.88±0.30	8 ± 1	95.19± 3.06
F22	0.24 ± 0.04	6.5 ± 0.7	109 ± 6	97.87±0.88	12 ± 3	64.59± 1.59
F23	0.23 ± 0.02	6.4 ± 0.9	117 ± 12	95.45±0.77	13 ± 2	59.29± 2.68
F24	0.22 ± 0.03	6.1 ± 1.3	124 ± 7	96.34±0.98	11 ± 2	58.55 ± 1.94
F25	0.19 ± 0.01	5.7 ± 1.1	132 ± 4	97.90±0.28	13 ± 1	65.39± 3.06
F26	0.30 ± 0.05	6.8 ± 0.4	96 ± 9	96.57±0.23	15 ± 3	53.94± 2.11
F27	0.29 ± 0.05	6.6 ± 0.7	103 ± 6	95.70±0.22	15 ± 2	55.36± 3.67
F28	0.26 ± 0.04	6.2 ± 0.9	106 ± 5	96.90±0.51	16 ± 1	56.58± 1.39
F29	0.24 ± 0.01	6.1 ± 1.1	114 ± 10	95.78±0.21	16 ± 4	62.55± 3.06
F30	0.21 ± 0.03	5.6 ± 0.3	123 ± 8	96.33±0.98	17 ± 2	67.44± 2.16

***** The results are expressed in Average ± Standard deviation for n = 3

Folding endurance

The developed LX-ODFs were found to have the folding endurance in the range of96to 137 (shown in Table 3 and 4). It could be inferred from this study that there was a significant increase in the folding endurance with the increase in the amount of the plasticizer which might be due to the increase in the elasticity and the mechanical strength of the obtained films [25]. Further, at a particular amount of the plasticizer, the folding endurance was found to be more with higher viscosity grade of the HPMC. This could be due to the increase in the mechanical strength of the films made with higher viscosity film former which was confirmed with the tensile strength values.

Drug content

The drug content in the developed LX-ODFs was found to be in the range of 93% to 99% as shown in Table 3 and Table 4. It could be inferred from these results that uniformity in drug content was present in all the films formulated which could be due to the homogeneity of the pre-casting solution. Hence, this confirmed that the solvent and the conditions used were suitable for the preparation of the films.

Disintegration time

The disintegration time of LX-ODFs was found to in a range of 9 sec to 17 sec (shown in Table 3 and 4). The influences of the factors on disintegration time were shown as contour and 3D-surface plots in Figure1. With the increase in the amount of the polymer, the disintegration time of Lornoxicam was found to be decreased. This could be owing to the easy penetration of the medium into the film due to the use of low molecular weight polymers [26]and also highly hydrophilic nature of the HPMC polymers [27] thereby promoting fast disintegration. Upon increase in the amount of PEG 400, the disintegration time was found to be decreased. This could be attributed

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to the increased hydrophilicity of the films at higher plasticizer concentration [28]. At a particular amount of HPMC and PEG 400, the disintegration time was found to be increased in the order of E3 < E5 < E15 grades of the HPMC and also found to be more in case of combinations of HPMC types than in single type (shown in Fig 2(a)). This could be because of the increased molecular weight of the film former that could cause more time for swelling followed by disintegration.

Dissolution studies

Figure 2 depicts the contour and 3D-surface plots for the influence of the factors on dissolution of LX-ODFs. The results of the D5% values for LX-ODFS were shown in Table 3 and 4. Drug dissolution from all the formulations were found to follow first-order kinetics. It can be elucidated fromFigure2 that the amount of drug dissolved after 5mins was not significantly influenced with respect to the amount of HPMC but was found to be increased with the increase in the amount of PEG 400.This could be because of increased hydrophilicity of the film as

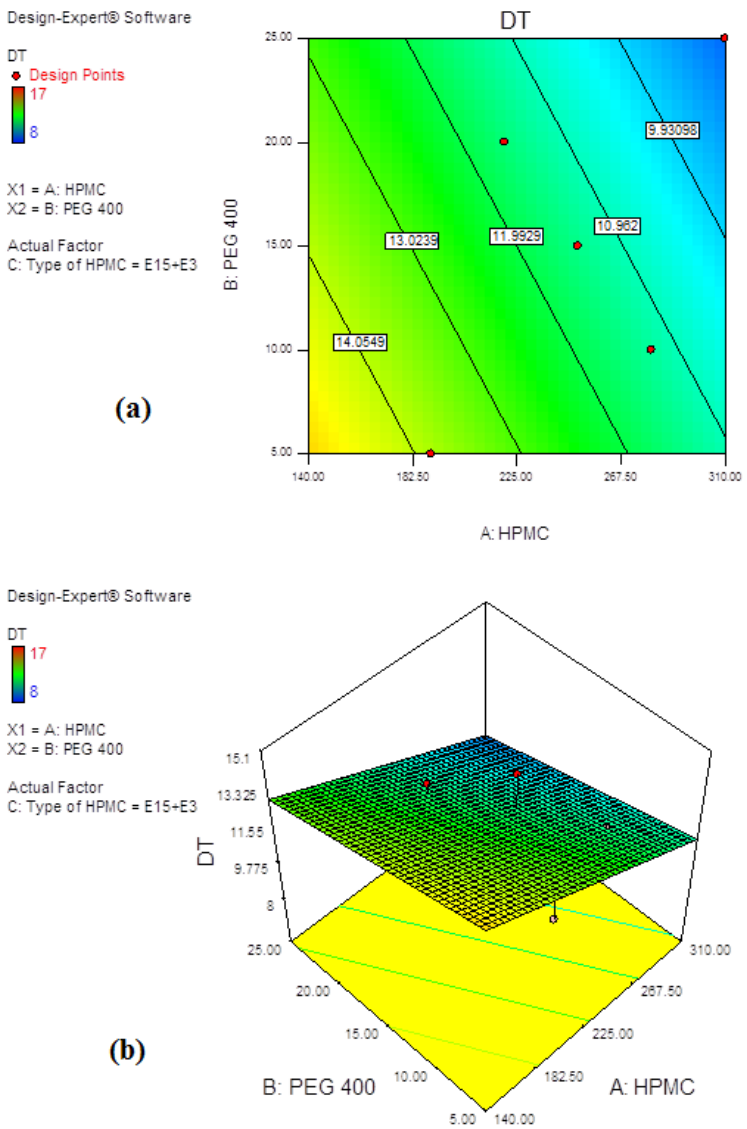

Fig 1. (a) Contour plot (b) 3D-surface plot indicating the effect of the amount of HPMC (factor A) and amount of PEG 400 (factor B) on the disintegration time (R1)

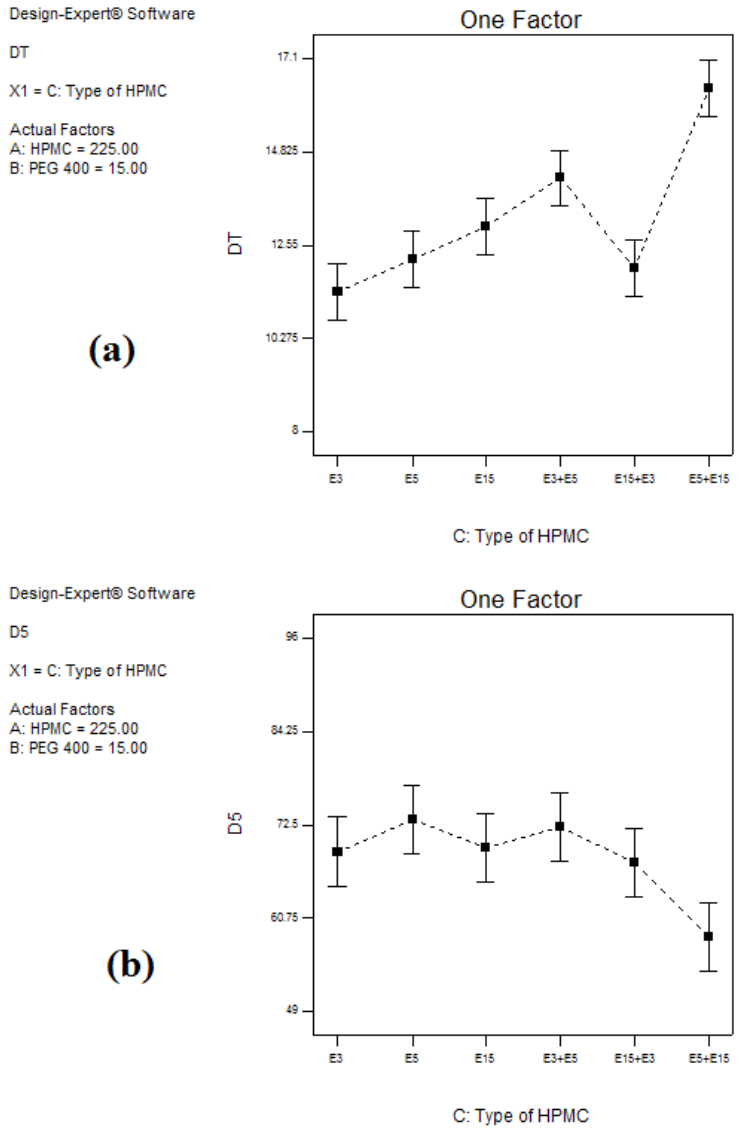

Fig 2. Effect of type of HPMC on (a) Disintegration time (DT, R1); and on (b) Drug dissolved at 5 min. (D5, R2)

well as increased free space between the polymer chains at higher plasticizer concentration [28]. The results obtained were correlated with those reported by Aguirre *et al.* 2013[29]. At a particular amount of HPMC and PEG 400, the dissolution and the amount dissolved at 5 min. (D5) were found to be decreased in case of combinations of HPMC than those in single type HPMC in the order of E3+E5 > E3+E15 > E5+E15 (shown in Fig 2(b)). This could be because of the increased molecular weight of the film former that could cause more time for swelling, disintegration and dissolution. These results were correlated with the disintegration time results.

3.4 Design validation

Historical data design was used in this research work to investigate the influence of the formulation factors on the responses and for further optimization using Design Expert software. Sequential model sum of squares was performed to identify the statistical model to be selected to understand the influence of the factors on the responses. From this analysis (shown in Table 5), it was observed that linear model was suggested to perform the ANOVA test. From the results of the ANOVA for the suggested response surface linear model, it can be inferred that the effect of all the three factors was found to be significant

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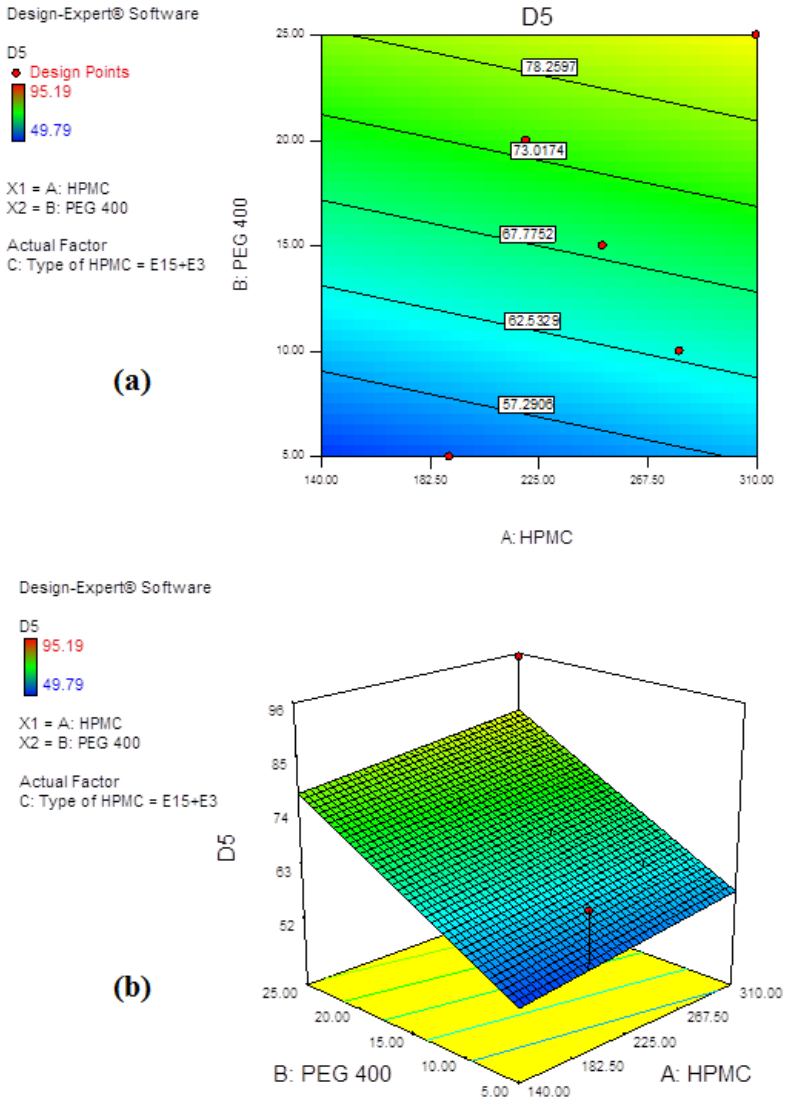

Fig 3. (a) Contour plot (b) 3D-surface plot indicating the effect of the amount of HPMC (factor A) and amount of PEG 400 (factor B) on the drug dissolved at 5 min. (R2)

on both the responses except the effect of amount of HPMC was found to be insignificant on the percent drug dissolved after 5mins ($p > 0.05$) as shown in Table 6. Further, the model was also found to be significant in case of both the responses. The Normal plot of residuals for both the responses (shown in Fig 4) indicated a straight line but not any sigmoid shape thus indicating the suitability of the selected model elucidating the influence of the factors on the response. Hence, these validation results indicated that this model can be directed for optimization.

3.5 Optimization

Optimization was performed using the Design Expert software. The desirability criteria were set to minimizing the DT with the upper limit of 10 sec and maximizing the D5 with lower limit of 80%. The resulted overlay plot indicating the design space was shown in Fig 5. The design space is the area inside which any combination of the factors would result in the desired response values. Any level of the factors present in the design space (yellow region) in the plot can be used to formulate the LX-ODFs with desired response of minimum disintegration time and

Table 5. Sequential model sum of squares analysis for selecting model to analyze the influence of the factors on the responses

Source	Sum of squares	Degrees of freedom	Mean square	F value	p-value	Inference
R1: DT						
Mean vs Total	5227.20	1	5227.20			
Linear vs Mean	73.66	7	10.52	10.95	< 0.0001	Suggested
2FI vs Linear	7.08	6	1.18	1.34	0.2950	
Quadratic vs 2FI	1.48	1	1.48	1.77	0.2031	
Cubic vs Quadratic	4.82	6	0.80	0.93	0.5157	
Residual	7.75	9	0.86			
Total	5322.00	30	177.40			
R2: D5						
Mean vs Total	$1.403x10^5$	1	$1.403x10^5$			
Linear vs Mean	2611.68	7	373.10	9.56	< 0.0001	Suggested
2FI vs Linear	245.18	6	40.86	1.07	0.4221	
Quadratic vs 2FI	454.86	1	454.86	43.07	< 0.0001	
Cubic vs Quadratic	90.68	6	15.11	2.01	0.1668	
Residual	67.73	9	7.53			
Total	1.438E+005	30	4793.77			

Table 6. ANOVA test results of the two response variables for response surface linear model

Response	Source	SS[a]	Df[b]	MSS[c]	F Value	p-Value	Inference[d]
DT	Model	73.66	7	10.52	10.95	<0.0001	Significant
	A- Amount of HPMC	14.04	1	14.04	14.61	0.0009	Significant
	B- Amount ofPEG400	8.04	1	8.04	8.37	0.0084	Significant
	C-Type of HPMC	71.69	5	14.34	14.92	<0.0001	Significant
	Residual	21.14	22	0.96			
	Cor Total	94.80	29				
D5%	Model	2611.7	7	373.10	9.56	<0.0001	Significant
	A- Amount of HPMC	27.30	1	27.30	0.70	0.4119	Insignificant
	B- Amount ofPEG400	1156.6	1	1156.6	29.64	<0.0001	Significant
	C-Type of HPMC	639.93	5	127.99	3.28	0.0231	Significant
	Residual	858.44	22	39.02			
	Cor Total	3470.1	29				

Note:[a]-Sum of Squares; [b]-Degrees of Freedom; [c]-Mean Sum of Squares; [d]-p-Value less than 0.05 indicates model terms are significant

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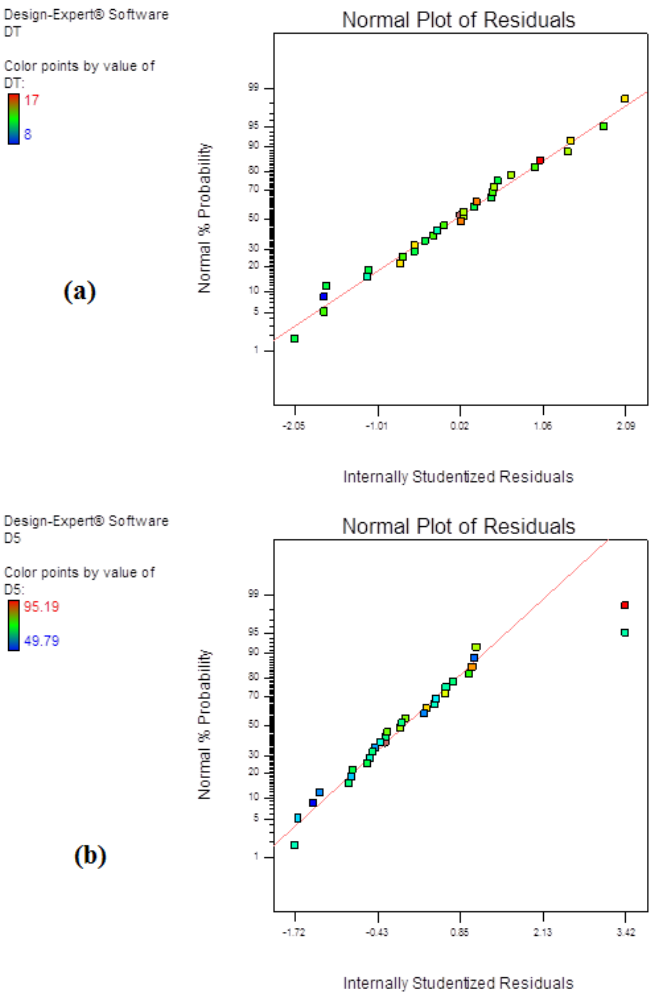

Fig 4. Normal plot of residuals for the (a) R1: Disintegration time and (b) R2: Drug dissolved at 5 min.

rapid dissolution. Among the suggested combination, the combination with factors A: 260mg (HPMC E15) and 50mg (HPMC E3), B: 25 mg and C: HPMC E15+ E3 which was selected as the optimized formulation with the maximum desirability of 0.894.

A new LX-ODF formulation at this combination was prepared and subjected to disintegration and dissolution tests. The DT was found to be 9.8 sec. and the D5 was found to be 87.52%. These values were found to be with in the 95% confidence interval level of the predicted values by the software (shown in Table 7). Hence, it can be inferred that LX-ODFs were optimized successfully in order to have rapid disintegration and dissolution.

4. CONCLUSION

In the current research work, LX-ODFs were formulated by employing QbD with an aim to enhance the bioavailability of LX by improving its dissolution. Design expert software was used in designing the formulations by altering different formulation factors under response surface methodology employing historical data designing. The statistical studies carried out using ANOVA depicts the effect of the formulation factors on the considered responses was significant and suitability of the model for optimization. Upon optimization, the suggested combination of the factors produced ODFs with DT of 9.8 sec and D5 of 87.52%. Further, the use of statistical QbD approach makes the findings more reliable and valid. These results indicated that the dissolution limited

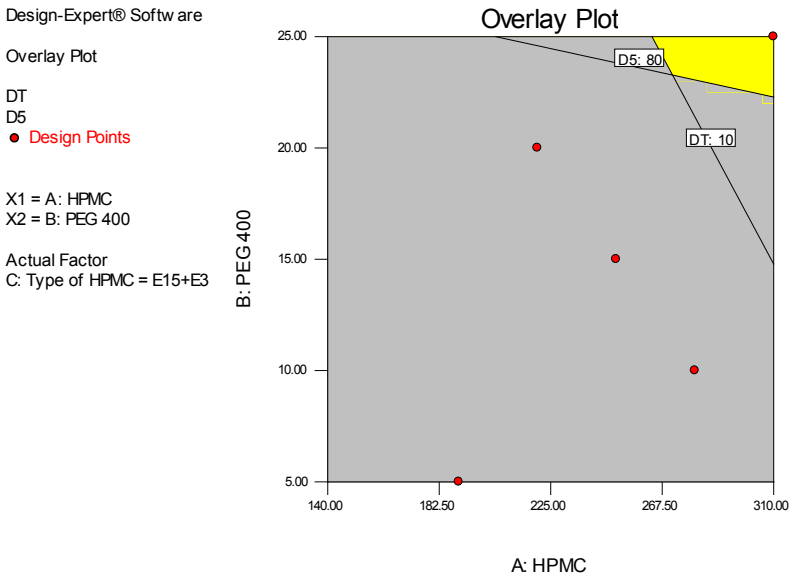

Fig 5. Overlay plot indicating the design space (the yellow region)

Table 7. Comparison of the predicted and observed values of the responses for the optimized LX-ODFs

Factors combination	Responses	Predicted values	95% CI low	95% CI high	Observed values
A: 310 mg of HPMC B: 25 mg of PEG400 C: E15 + E3 as the type of HPMC	R1: DT (sec.)	8.9	7.2	10.6	9.8
	R2: D5 (%)	83.5	72.66	94.34	87.52

bioavailability of lornoxicam was successfully overcome in this work by developing into ODFs.

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Conflict of Interest

The authors have no conflicts of interest regarding this investigation

Statement of Contribution of Researchers

Both the authors are having susbstantial contribution to conception. Actively involved in acquisition, analysis and interpretation of data. Participated in drafting the article and final approval of the version to be published.

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