Int. J. Pharm. Investigation, 2021; 11(4) : 420-425

Original Article

Orodispersible Films of Meloxicam Inclusion Complexes for Bioavailability Enhancement: Optimization and Development through Quality by Design Approach

Archana Nerella[1,*], MV Nagabhushanam[2]
[1]Department of Pharmaceutics, Acharya Nagarjuna University, Guntur, Andhra Pradesh, INDIA.
[2]Hindu College of Pharmacy, Guntur, Andhra Pradesh, INDIA.

ABSTRACT

Background: Owing to overcome the dissolution limited bioavailability of Meloxicam, the current research involves the development of Oro-dispersible films using Meloxicam by employing Quality by Design. **Methods:** In this work, the Meloxicam oral dispersible films were formulated by solvent casting method by altering three formulation factors viz. amount of film former, amount of the plasticizer, PEG 400 and type of film former (HPMC E3, HPMC E5, HPMC E15). Historical data designing under response surface methodology was selected as the experimental design. Disintegration time, dissolution of Meloxicam after 5 mins, folding endurance and tensile strength of the orodispersible films were taken as the responses. **Results:** All the formulations were found to have favorable tensile strength and folding endurance. The disintegration time values were found to be in a range of 9-15 sec, the values of amount of Meloxicam dissolved after 5 min were found to be in the range of 48-98%. The data obtained from the responses were statistically treated using ANOVA and the effect of the formulation factors were found to be significant. **Conclusion:** The optimization of these formulations indicated that a combined film former of 140mg of HPMC E15 and 50mg of HPMC E3 with 25mL plasticizer was found to be the optimized formulation. The films prepared at this combination showed disintegration time of 8 sec, drug release of 66.5% after 5 min which indicate that the formulated Meloxicam orodispersible films were successfully optimized and developed.

Key words: Oro-dispersible films, Dissolution enhancement, Historical data designing, optimization, ANOVA, Response surface methodology.

Correspondence

Assoc. prof. Archana Nerella
Research Scholar, Department of Pharmaceutics, University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur-52251, Andhra Pradesh, INDIA.

Email id: archana.nerella@gmail.com

DOI: 10.5530/ijpi.2021.4.75

INTRODUCTION

Meloxicam is a non-steroidal anti-inflammatory drug which is used in the treatment of osteoarthritis and rheumatoid arthritis in adults and juvenile rheumatoid arthritis in pediatrics. It is used to relieve the musculoskeletal conditions and also neuropathic pain. The half-life of meloxicam is 20 hr[1] which is longer than most of the other NSAIDs, which helps to give a single dose of the drug without a need for formulation into a sustained/extended-release formulation.[2] It acts by inhibiting the COX-2 enzyme thereby reducing the risk of adverse gastrointestinal effects caused in most of the NSAIDs.[3] The solubility of meloxicam is practically insoluble in water[4] making it a poor water-soluble drug which thereby leads to dissolution limited bioavailability of the drug. Owing to this problem, meloxicam has to be developed into a dosage form where its dissolution is enhanced.

Among all the routes of drug delivery, oral route has always found to has a significant ease of administration, patient compliance and also versatile in formulating several drugs as oral dosage forms. Intense research and development in the oral drug delivery show a promising transition from tablet/capsules to oral disintegrating tablets to oral dispersible films/strips.[5] The orodispersible films (ODFs) have been found to show a promising advantage than other oral dosage forms due to their ease of ingestion, patient compliance, high stability and also the versatility in incorporating higher amounts of drug; also, a rapid disintegration and an enhanced drug dissolution owing to the increase in the drug bioavailability. Several researches on these ODFs like Nishimura M *et.al.*2009,[6] Kulkarni KP *et.al.* 2011[7] and Saini S *et.al* 2012.[8] have elucidated the significant increase in the drug dissolution when formulated as ODFs owing to enhancement in the bioavailability. The widely carried literature review signifies the scope of development of oral/mouth dispersing films by using different hydrophilic polymers which act as film formers.

Among various methods of enhancement of the bioavailability, formation of cyclodextrin complexes (CDS) has been proved to be advantageous, as they are used as complexing agents with the poor water-soluble drugs to increase their aqueous solubility, thereby enhancing their dissolution and bioavailability.[9] CDs have been used to reduce or prevent gastrointestinal irritation, improve patient compliance by reducing the unpleasant tastes or smell, prevent various drug interactions and also in the conversion of oils and liquid drugs into microcrystalline or amorphous powders.[10] The current work includes the formulation of Meloxicam ODFs by solvent casting method, in which initially the γ-cyclodextrin complexes[11] are formulated using maltodextrin[12] which are then prepared as the mouth dissolving films.

The current study involves the design of experiment using Design Expert software. Historical data designing under response surface methodology has been used to design the formulations. HPMC E3, HPMC E5 AND HPMC E15 were the three film formers used at different concentrations. The independent factors taken in this work are type of film formers, concentration of film formers and the concentration of plasticizers. Disintegration time (DT), percent of drug dissolved after 5 min (D5%),

tensile strength and folding endurance of the ODFs were taken as response variables which thereby determine the desired quality of the ODFs. The developed films were characterized for different physical characteristics and the responses, the results of which were statistically treated with ANOVA.

MATERIALS AND METHODS

Materials

Meloxicam was procured from Hetero Drugs Pvt. Ltd, Visakhapatnam; HPMC E3, HPMC E5, HPMC E15 and PEG 400 were acquired from Sigma Chemicals Co.; Maltodextrin, aspartame, citric acid and pineapple flavor were purchased from SD Fine Chemicals, Mumbai. All other chemicals used in the current work are of analytical grade.

Design of experiment

Three formulation parameters were selected as the independent factors viz. A: amount of film former (140-260mg), B: amount of plasticizer (PEG 400, 5-25mL) and C: Type of HPMC polymer used. The responses were the four critical quality attributes of the MX-ODFs viz. R1: Disintegration time, R2: Tensile strength of the film, R3: Folding endurance and R4: Amount of drug dissolved after 5 min. Historical data design under response surface methodology was employed as the experimental design and has been executed using StatEase Design Expert software. 30 different runs as the combinations of the factors with their levels (Table 1) were used to formulate the MX-ODFs.

Development of meloxicam oral dispersible films

The γ-cyclodextrin complexes[13] were formulated into mouth dissolving films by solvent casting method[14] by employing quality by design (QbD) based approach. Film forming polymers of different grades of HPMC (140-260 mg) and Maltodextrin (50 mg) based on the formulation runs as shown in Table 1 were soaked for 24 hr to ensure complete hydration. The solution was stirred on a magnetic stirrer at 50 rpm for 2 hr, PEG 400 (5-25 mL) was added and stirring was continued for 30 min at 50 rpm. This process ensures the formation of cyclodextrin complexes. In this process, all the water-soluble ingredients (0.1mL pineapple flavor, 2mg citric acid, 8mg Aspartame and 24.75 mg Meloxicam) were dissolved in an aqueous solvent to form a clear solution for each formulation. This solution was added to the cyclodextrin complex solution upon constant stirring till the formation of a homogenous solution which was poured onto a dry petri dish and further dried at 45°C for 6 hr. The obtained film was cut carefully into a shape of 4cm^2 (equivalent to 7.5mg Meloxicam) which were further stored and subjected to different characterization studies.

Table 1: Combination of factors and their levels with the formulation compositions.

Code	Drug (mg)	HPMC (mg)			PEG 400 (mL)	Malto-dextrin (mg)	Aspartame (mg)	Citric acid (mg)	Pineapple flavor (mL)
		E3	E5	E15					
F1	24.75	260	-	-	5	50	8	2	0.1
F2	24.75	230	-	-	10	50	8	2	0.1
F3	24.75	200	-	-	15	50	8	2	0.1
F4	24.75	170	-	-	20	50	8	2	0.1
F5	24.75	140	-	-	25	50	8	2	0.1
F6	24.75	-	260	-	5	50	8	2	0.1
F7	24.75	-	230	-	10	50	8	2	0.1
F8	24.75	-	200	-	15	50	8	2	0.1
F9	24.75	-	170	-	20	50	8	2	0.1
F10	24.75	-	140	-	25	50	8	2	0.1
F11	24.75	-	-	260	5	50	8	2	0.1
F12	24.75	-	-	230	10	50	8	2	0.1
F13	24.75	-	-	200	15	50	8	2	0.1
F14	24.75	-	-	170	20	50	8	2	0.1
F15	24.75	-	-	140	25	50	8	2	0.1
F16	24.75	260	50	-	5	50	8	2	0.1
F17	24.75	230	50	-	10	50	8	2	0.1
F18	24.75	200	50	-	15	50	8	2	0.1
F19	24.75	170	50	-	20	50	8	2	0.1
F20	24.75	140	50	-	25	50	8	2	0.1
F21	24.75	50	-	260	5	50	8	2	0.1
F22	24.75	50	-	230	10	50	8	2	0.1
F23	24.75	50	-	200	15	50	8	2	0.1
F24	24.75	50	-	170	20	50	8	2	0.1
F25	24.75	50	-	140	25	50	8	2	0.1
F26	24.75	-	260	50	5	50	8	2	0.1
F27	24.75	-	230	50	10	50	8	2	0.1
F28	24.75	-	200	50	15	50	8	2	0.1
F29	24.75	-	170	50	20	50	8	2	0.1
F30	24.75	-	140	-	25	50	8	2	0.1

Appearance and Thickness

The surface appearance of the ODFs was carried by visualization for a transparent or semi-transparent glossy smooth texture film. Using a micrometer screw-gauge, the thickness of the MX-ODFs was measured at five different points and the obtained results were reported as their mean value.[15]

Folding endurance

By counting the number of times, the film can be folded repetitively until it broke, the folding endurance[16] of the ODFs was determined. Texture analyzer was used to determine the tensile strength of the ODFs.

Tensile strength

The maximum stress applied to a point at which the film specimen breaks, determines the tensile strength.[17,18] It is calculated from the applied load at rupture divided by the strip cross-sectional area given in the equation below from the formula

$$\text{Tensile strength} = \frac{\text{Load at the point of rupture}}{\text{Film thickness} \times \text{film width}}$$

Drug content

A MX-ODF was transferred into a beaker containing 100 mL of the pH 6.8 phosphate buffer and was subjected to constant stirring for 2 hr.[19] The dispersion after filtering was analyzed for the content of Meloxicam using UV-Visible spectrophotometer after suitable dilutions at a wavelength of 362nm. The test was performed in triplicate and the results reported were the mean values.

Disintegration time

The disintegration time of the MX-ODFs was determined using Petri dish method.[20] 10mL distilled water was transferred into the petri dishes and the ODFs of 4 cm^2 were placed in each petri plate. The time at which the MX-ODFs were completely dispersed was taken as disintegration time. The test was performed in triplicate and the results were expressed as the mean of the three values ± SD.[21]

Dissolution study

The dissolution test was conducted in USP type I basket apparatus. 900 mL of 6.8pH phosphate buffer of 900 mL was taken as the dissolution medium.[22,23] Each film (equivalent to 7.5mg Meloxicam) was placed in the dissolution medium and after 1, 3, 5, 7, 9 and 10 min, the samples were collected and replaced with the same buffer. The obtained samples were analyzed under spectrophotometrically under UV at a λ_{max} of 362nm.

RESULTS

Appearance and Thickness

The developed ODFs were visually observed for a smooth, uniform and transparent texture. The results of various physical characterization studies were shown in Table 2.

Folding endurance

The folding endurance values of the formulated ODFs ranged from 94 to 115 as shown in Table 2. The folding endurance of the meloxicam OFDs F1-F5 was in the range of 95-98, F6-F10 was in between 94-97, F11-F15 was 101-104, F16-F20 was 104-107, F21-F25 was in a range of 107-110, F26-F30 was between 108-115.

Tensile strength

From the results of the Tensile strength shown in Table 2. It was elucidated from these results that the tensile strength values ranged in between 118 to 428 G which elucidates that formulated films were flexible with a good elasticity owing to the prevention of breaking upon handling.

Drug content

The contents of Meloxicam in all the formulated of MX-ODFs were observed to be in the range of 96.26% - 98.90% as shown in Table 2.

Disintegration time

It was observed that disintegration time of the Meloxicam MDFs films varies from 8 sec to 15 sec as shown in Table 2. The contour plot depicting the effect of amount of film former (HPMC E15+E3) and plasticizer (PEG 400) on the disintegration time of formulation F25 was indicated in Figure 1.

Dissolution studies

The dissolution profiles of Meloxicam were shown in Figure 2. The D5% values for MX-ODFS were presented in Table 2 and the contour plot depicting the effect of amount of film former (HPMC E15+E3) and plasticizer (PEG 400) on the disintegration time of formulation F25 was indicated in Figure 2.

Design validation and optimization

The ANOVA studies on the four responses indicated that the selected model along with the factors A, B and C were found to be significant for DT, Tensile strength and Folding endurance whereas the factor A was found to be insignificant in case of amount of drug dissolved after 5mins (p>0.05) as shown in Table 3. To identify the ODFs formulation having desired responses, the optimization was carried by desirability functions approach using the Design Expert software.

Table 2: Results* of various characterization studies of Meloxicam ODFs F1 – F30.

Code	Evaluation Parameters					
	Thickness (mm)	Tensile strength (G)	Folding endurance	DT (sec.)	Drug content (%)	Drug release after 5 min. (D5%)
F1	0.235±0.03	235±9	98±5	12±0.5	98.69±0.23	59.14±0.64
F2	0.225±0.08	220±6	97±4	12±0.4	98.86±0.64	59.57±0.21
F3	0.222±0.01	217±7	97±3	11±0.3	98.33±0.06	63.89±0.25
F4	0.221±0.09	179±5	96±4	11±0.3	98.76±0.98	68.76±0.75
F5	0.220±0.06	118±8	95±5	10±0.4	98.70±0.68	71.58±0.42
F6	0.237±0.06	289±3	97±2	14±0.5	97.79±0.35	48.56±0.52
F7	0.235±0.05	282±7	96±1	13±0.4	95.46±0.23	58.49±0.68
F8	0.227±0.04	269±6	95±3	12±0.4	97.20±0.89	65.35±0.38
F9	0.225±0.02	191±5	95±3	12±0.3	97.89±0.78	68.5±0.19
F10	0.220±0.06	180±8	94±2	11±0.3	98.38±0.45	67.89±0.35
F11	0.227±0.07	348±2	104±5	14±0.4	96.25±0.44	56.43±0.22
F12	0.225±0.01	311±7	104±4	13±0.3	95.90±0.66	59.86±0.15
F13	0.220±0.06	288±9	103±3	13±0.4	96.42±0.69	65.12±0.72
F14	0.214±0.03	212±5	102±1	12±0.4	98.92±0.95	69.32±0.68
F15	0.210±0.09	179±5	101±3	12±0.5	98.09±0.24	73.24±0.54
F16	0.228±0.04	369±4	107±5	15±0.4	98.49±0.45	60.12±0.29
F17	0.226±0.09	321±7	107±4	14±0.5	97.78±0.56	67.75±0.42
F18	0.225±0.03	280±8	105±1	14±0.3	97.66±0.80	68.46±0.51
F19	0.224±0.05	219±8	105±3	13±0.2	96.76±0.91	69.79±0.16
F20	0.213±0.09	191±6	104±2	13±0.2	98.16±0.87	82.78±0.32
F21	0.226±0.03	419±5	107±3	11±0.5	97.58±0.30	54.55±0.71
F22	0.224±0.02	426±7	108±4	11±0.4	97.59±0.88	59.25±0.81
F23	0.239±0.19	435±8	108±1	10±0.3	95.26±0.77	62.74±0.66
F24	0.227±0.19	441±4	109±3	10±0.5	96.59±0.98	62.55±0.53
F25	0.217±0.09	445±9	110±5	8±0.4	98.90±0.27	66.75±0.92
F26	0.239±0.16	405±6	108±2	11±0.4	97.57±0.43	57.95±0.19
F27	0.238±0.18	429±9	106±4	10±0.3	96.70±0.52	64.22±0.72
F28	0.229±0.15	435±6	105±5	10±0.2	97.90±0.71	79.56±0.57
F29	0.219±0.78	440±7	115±2	9±0.2	96.78±0.61	98.17±0.34
F30	0.202±0.07	428±5	109±3	9±0.3	97.33±0.88	64.56±0.32

* All the results were indicated as Average ± Std. Dev. for n = 3

DISCUSSION

The thickness values of all the MX-ODFs were found to be in a range of 0.202 to 0.238 mm. The results elucidate that with the increase in the concentration of the film former, the thickness of ODF was found to be increased. This could be due to the increased viscosity of the pre-casted formulation mixture at higher polymer concentrations.[5,7] The thickness of the optimized formulation was found to be 0.217±0.09 mm. The study elucidates that with the increase in the concentration of polymer and plasticizer, folding endurance of mouth dissolving film increases which might be attributed to the increase in the elasticity and flexibility due to the plasticizer.

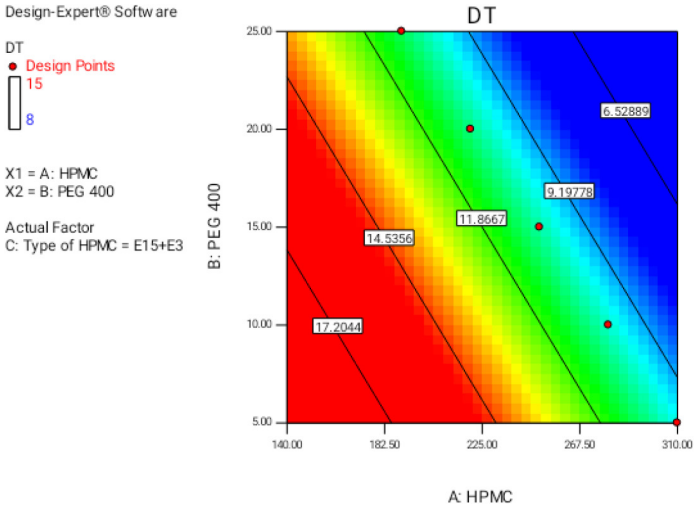

Figure 1: Contour plots depicting the effect of the formulation factors Concentration of polymer and plasticizer on the Disintegration time.

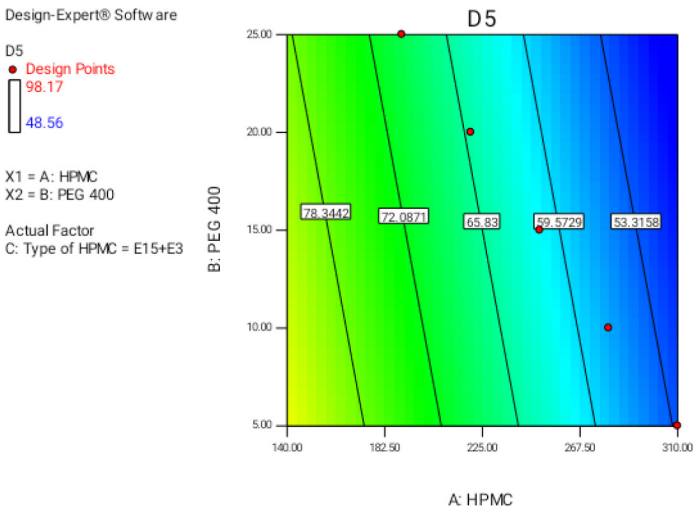

Figure 2: Contour plots depicting the effect of the formulation factors Concentration of polymer and plasticizer on the Dissolution after 5 min (D5%).

Table 3: ANOVA test results of the four 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 of PEG 400	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				
Tensile Strength	Model	$2.278x10^5$	7	32536.0	66.54	< 0.0001	Significant
	A- Amount of HPMC	13224.21	1	13224.2	27.04	< 0.0001	Significant
	B- Amount of PEG 400	9580.74	1	9580.7	19.59	0.0002	Significant
	C- Type of HPMC	78114.44	5	15622.9	31.95	< 0.0001	Significant
	Residual	10757.39	22	488.97			
	Cor Total	$2.385 x10^5$	29				
Folding endurance	Model	717.10	7	102.44	156.84	< 0.0001	Significant
	A- Amount of HPMC	2.96	1	2.96	4.54	0.0446	Significant
	B- Amount of PEG 400	38.16	1	38.16	58.43	< 0.0001	Significant
	C- Type of HPMC	488.27	5	97.65	149.51	< 0.0001	Significant
	Residual	14.37	22	0.65			
	Cor Total	731.47	29				
D5%	Model	2611.68	7	373.10	9.56	< 0.0001	Significant
	A- Amount of HPMC	27.30	1	27.30	0.70	0.4119	Insignificant
	B- Amount of PEG 400	1156.56	1	1156.56	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	3470.12	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

It can be inferred from the results of tensile strength that, the increase in the concentration of the plasticizer resulted in the increase in the tensile strength owing to the entwinement of the plasticizer with the film formers thereby reducing the brittleness of the ODFs similar to the results of Jayarao YR *et al.* (2014)[24] and Sanyang ML *et al.* (2016)[25] The folding endurance and % elongation values were correlated proportionally with tensile strength and increased upon increase in the plasticizer concentration.

The results elucidate good content uniformity among all the films as there is no significant difference in the drug content among all the formulations. The drug content of all the formulations was found be within the limit. The *in vitro* disintegration time of Meloxicam was found to decrease with the increase in the concentration of the polymer, which might be attributed to the ease of the medium to reach the disintegrants as the polymers used are of low molecular hydrophilic polymers owing to easy penetration of the medium into the film similar to the findings of Roy *et al.* (2009)[26] and Swamy SK *et al.* 2016.[27] The ANOVA results infer that all the factors play a significant effect on the disintegration time ($p<0.05$) as shown in Table 3.

It can be inferred from the ANOVA study as shown in Table 3 that there is a significant effect of the type of polymer and the amount of plasticizer used on the dissolution of the drug ($p<0.05$). The effect of the amount of HPMC used at these levels was found to be insignificant on the dissolution of Meloxicam ($p>0.05$). From the effect of the factors on the dissolution time it can be inferred that with the increase in the amount of plasticizer or the viscosity of the film forming polymer, the amount of drug dissolved after 5 min was found to be decreased which might be attributed to the increase in the complexity of the film former matrix prepared from high viscous polymer solution. At high thickness of the films, a higher diffusion path lengths may delay the diffusion of the drug thereby its dissolution. The results obtained were correlated with those of Zhang L *et al.* 2018.[28]

All the four responses DT, folding endurance, tensile strength and D5% when as minimum as possible may increase the dissolution thereby enhancing the bioavailability of Meloxicam. Hence, this was taken as the desirability to proceed for the optimization. Among the various combinations of formulations with all the formulation factors A: 140mg (HPMC E15) and 50mg (HPMC E3), B: 25 mL and C: HPMC E15+ E3, had the maximum desirability of 0.848 (Figure 2). It can be inferred from the overlay plot that any value of the factors which are present within the overlaid region (yellow region/design space) in the plot can be used to formulate the MX-ODFs to obtain desired responses by 84.8% accuracy as shown in Figure 3 and the overlay plot indicating the optimized design space in Figure 4.

CONCLUSION

Meloxicam ODFs were developed in an aim to improve its dissolution thereby enhancing the bioavailability of MX. Historical data designing was employed using three different formulation factors using Design Expert software. The physical characterization studies including the response variables of the ODFs have shown that the formulated films were efficient. The suggested optimized formulation of the ODFs with 50mg HPMC E3 and 140mg HPMC E15; 25mL of PEG 400 was developed, upon optimization by desirability functions approach has a maximum desirability of 0.848. The ANOVA studies show the significant effect of all the three factors on the responses with a probability < 0.05. The study elucidates the development of the MX-ODFs using these factors can produce desirable responses thereby improving the bioavailability by enhancing the dissolution of Meloxicam.

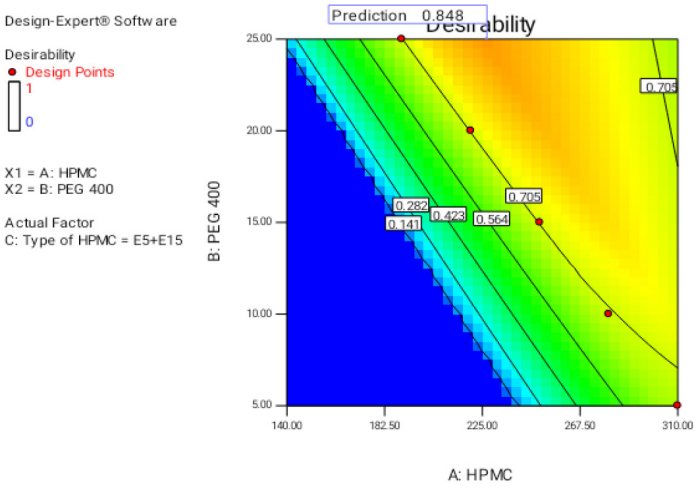

Figure 3: Desirability plot for the optimization.

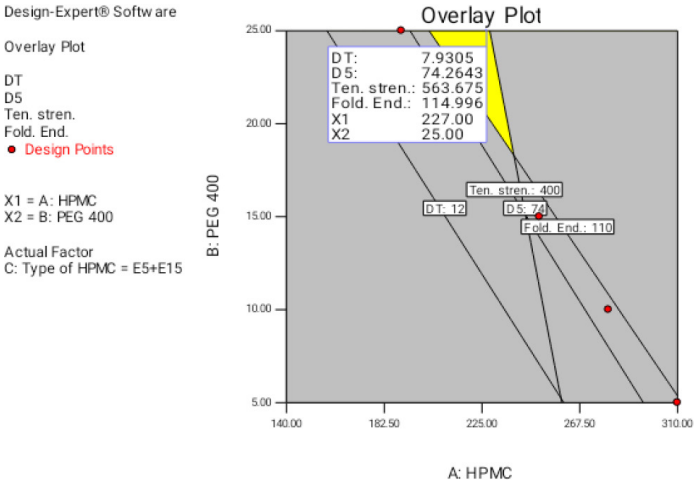

Figure 4: Overlay plot indicating the design space and the optimized combination of the three factors and predicted response values.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation

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Article History: Submission Date : 17-10-2021; Revised Date : 07-11-2021; Acceptance Date : 04-12-2021.
Cite this article: Nerella A, Nagabhushanam MV. Orodispersible Films of Meloxicam Inclusion Complexes for Bioavailability Enhancement: Optimization and Development through Quality by Design Approach. Int. J. Pharm. Investigation. 2021;11(4):420-5.