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ORIGINAL ARTICLE

Optimization, Development, Formulation of Lornoxicam Oral Dispersible Tablets using Central composite Experimental Design

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ABSTRACT
The Present Research investigation was designed to formulate and optimize Oral disintegrating formulations of Lornoxicam by using Qbd approach. To evaluate the input variables and output variables scientifically central composite design was used. Different concentrations of superdisintegrants were taken as predicted variables. In vitro dispersion time,% Drug release were taken as response variables. The quantitative effect at different levels of independent variables on response variables were predicted by utilizing polynomial equations. There is significance in curvature effect and the Design was nonlinear, therefore composite design study was adopted to optimization of the Formulation. FTIR and Differential scanning colorimetric studies concluded that no incompatibility exists among Drug and Excipients. Precompression and post compression parameters were within specified values. As concentration levels of CP and SSG increases % drug release was increased and in vitro dispersion time was decreased. From the Kinetic studies, the release of drug from the formulations obeyed first order, dependent variables and independent variables were demonstrated by utilizing contour plots. By using this statistical model the Predicted, Experimental values were found to be close to each other relatively. The results concluded that the design proposed for the formulation of Lornoxicam oral disintegrating tablets showed better optimized properties.
Key words: Lornoxicam, Superdisintegrants, Central composite design.

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INTRODUCTION

The oral form of administration is the most common preferable way of administering the dosage form . Among different dosage forms tablets are more convenient because of its easy to manufacture, patient compliance , precised dosing, stability compared with capsules and oral liquids [1]. In order to avoid patient discomfort and promote the administration by all age groups orodispersible tablets promotes better patient compliance which disintegrates under salivary pH without the need of drinking water especially in bed ridden conditions and in travelling [2, 3]. Orodispersible tablets were also known as fast dissolving tablets.

Lornoxicam comes under the category of cox2 inhibitor used to cure inflammation, pain occurred by rheumatoid arthritis and osteoarthritis and also post surgical pains. Superdisintegrants provide faster disintegration by water absorption by capillary action and swelling of the formulation which further promotes better disintegration and dissolution properties.

Depending on factorial numbers, levels, their interaction possibilities experimental designs were designed [5]. Box and Wilson design is a better design that has a combined advantages of star design and factorial design or fractional factorial design. This model is validated by using Analysis of variance. There is multidimensional interaction with the design space and combination of input variables and process parameters have been proved to provide the quality of proof based on ICH Q8 (R2)guidelines. In the present research investigation, A Trail was made to prepare oral disintegrating tablets of Lornoxicam by using Box and wilson design to identify activity of superdisintegrants on % drug release .

MATERIAL AND METHODS

Materials:

Lornoxicam (KP Labs Hyderabad), croscarmellose sodium, sodium starch glycolate, and Aspartame (Ranbaxy, Hyderabad). Crospovidone (Msn labs, Hyderabad, India). Sodium saccharin, polyvinylpyrrolidone (PVP), mannitol, and magnesium stearate talc (S.D. Fine Chemicals, Mumbai, India).

METHODS

Compatibility studies

FTIR studies:

The interaction study between the drug and Superdisintegrants SSG, CCS and CP were estimated by FTIR studies. KBR press was used for the preparation of the pellets. The spectra that obtained was observed at a range of 3500 cm^{-1}.

Differential Scanning Calorimeter (DSC)

The drug and excipients were passed via sieve #60 and mixed well. 5 mg of drug was Transferred alone, drug and excipients mixture was placed in aluminum pan of DSC and scanned at 30-350°C with a heating rate of 10°C per min. The thermograms thus obtained were compared for any interactions.

Optimization by Box and Wilson design :

In the present research study, 2^3 full factorial design was conducted with 4 replicates and for the experimental design the tablets were selected. The design was nonlinear and its significance was showed by curvature effect. Therefore for Optimization purpose the study was adopted to central composite design in which Three factors each were estimated in three levels. The concentrations of superdisintegrants, SSG (X1), CCS (X2), CP (X3) were taken as predicted variables and *In vitro* disintegration time, % drug release were taken as response variables. Trials were conducted for all fifteen possible combinations.

Pre-compression parameters :

Bulk density *:*

The bulk density was estimated by accurately weighing the blend sample in a 100 ml measuring cylinder, the weight of the powder and its initial volume were noted. The ratio of the weight of the blend to its volume gives the Bulk density [7].

Tapped density (TD) :

Tapped density was estimated by weighing the blend sample accurately into a 100 ml of graduated cylinder and was placed in a Electrolab Tapped Density Apparatus (method USP-I). The Initial volume (V_0) of the graduated cylinder was taken and the cylinder was subjected to 10 tappings and measure the volume . Further 500 tappings were made additional and its volume was taken. if there is a difference of more than 2 ml volume that is measured after 10 and 500 tapings Then it continued should be continued up to 1250 tapings.

Hausner's ratio:

It is denoted by the formula

Hausners ratio = Tapped density/Bulk density

Angle of repose(ø) :

It was estimated by pouring the blend through a funnel to a height (h) of the cone was noted and the radius of pile (r) was noted and wascalculated by the formula [7].

$ø = \tan^{-1} (h/r)$

Formulation of Lornoxicam Oral disintegrating tablets:

Fifteen trials of Lornoxicam ODT's (F1 to F15) were formulated by as Sodium Starch Glycolate, Croscarmellose sodium, Crospovidone and is subjected to compression directly for the formulations. The Excipients were subjected to sieving through #60. Drug, MCC, and mannitol were mixed gently by using mortar and pestle. superdisintegrants and aspartame are taken in sufficient quantities and mixed. Menthol, magnesium stearate were added finally. The uniform blends thus obtained were subjected to direct compression by using 7 mm punches to produce tablets of convex faced [8].

Post compression parameters *of the tablets*

Weight variation :

20 tablets were taken at random and individually weighed ,then the avg. wt. of the tablets and their standard deviations were calculated accordingly [9].

Tablet thickness:

Thickness of three tablets were taken by Vernier calipers [9].

Hardness:

3 Tablets were taken and their hardness was estimated with the help of Monsanto hardness tester. Place the tablet in between the two plungers of the hardness tester. The reading should be adjusted to zero. Force was applied by rotating the hardness tester knob and the point where the tablet breaks will be noted [9].

Friability :
Friability is done in order to estimate the tablets mechanical strength and the apparatus used for this estimation is Roche friabilator it should be operated at 25 rpm per min. for 4 min. it was calculated by the formula [9].

Friability = W1 – W2/W1 × 100

Drug content :
Five tablets from each batch were taken and powdered. The Powder equivalent to 8 mg of Lornoxicam was weighed and 10ml of methanol was used to dissolve the powder and the final volume was made to 100 ml with pH 6.8 buffer. Again 1 ml was drawn from this solution, make the final volume using pH6.8 buffer upto 100ml and by using UV–visible spectrophotometer the solution was analyzed at 376nm [7].

***In vitro* Disintegration time :**
According to the I.P. 900 ml purified water was taken and the Disintegration time was noted at room temperature [10].

Water absorption ratio :
Initial weight of the tablet was noted .A filter paper was kept on a a small petridish with 6ml of water and the formulation was kept over it and the time needed for the tablet for completion of wetting was noted. The tablet was then reweighed and it was taken as Final weight and the water absorption ratio is given by the formula[7].

$$\text{Water aborption ratio} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \; x\,100$$

***In vitro* dispersion time:**
A Beaker containing 100ml of pH 6.8 phosphate buffer was taken and the *In-vitro* dispersion time was noted by placing the tablet in to it and the time required for the tablet to disintegrate completely was noted. *In- vitro* dispersion time was noted by taking 3 tablets from each of the batch that is selected randomly [7].

***In vitro* drug release :**
Invitro dissolution study was performed in 900ml pH 6.8 Phosphate buffer using USP type-II (paddle) apparatus at 50 rpm at a temp. of 37±0.5^{0}c. Five milliliters of the sample were collected at specified time intervals. Aliquots were withdrawn from the dissolution medium at specific intervals of time and equal amount of fresh medium was replaced immediately . The samples were analysed by UV method at 376nm and the cumulative % drug released was calculated accordingly.

Determination of Statistical Data and Optimization:
Design expert(version 7) software was utilised to generate the study design by utilizing the Data obtained. Depending on comparisons of various parameters that were provided by software, selection of best-fit model was done. Regression coefficients of Response variables were identified by ANOVA and significant effects of factors among predicted and response variables was further determined by contour plots. Subsequently, Inorder to generate a technique of graphical optimization for new formulations with desired responses contour plots were used. theoretical prediction was verified by *In vitro* dispersion time and dissolution studies of the prepared optimized formulation. The relative errors (%) among the predicted and response values were calculated [12, 13].

Table 1: Central composite design layout

	Combinations	SSG X1 (mg)	CCS X2 (mg)	CP X3 (mg)
Factorial designs	X1	5.25	4.12	4.12
	X2	3.75	6.37	4.12
	X1X2	5.25	6.37	4.12
	X3	3.75	4.12	6.37
	X1X3	5.25	4.12	6.37
	X_2X_3	3.75	6.37	6.37
	$X_1X_2X_3$	5.25	6.37	6.37
Mid points	Mid-Point	4.5	5.245	5.245
Composite design	X_1At-2L	3.0	5.245	5.245
	X_1At+2L	6.0	5.245	5.245
	X_2At-2L	4.5	2.995	5.245
	X_2At+2L	4.5	7.495	5.245
	X_3At-2L	4.5	5.245	2.995
	X_3At+2L	4.5	5.245	7.495

Stability studies: Stability studies were performed at 40°C ±2°C / 75% ± 5% RH for a duration of 3 months in HDPE containers for an optimized formulation. *In vitro* dispersion time and drug release was performed for optimized formulation for 3 months [14].

RESULTS AND DISCUSSION

Compatibility studies

Fourier transform infrared spectroscopy:

The studies finalized , no physical interaction exists among the Drug and Excepients.

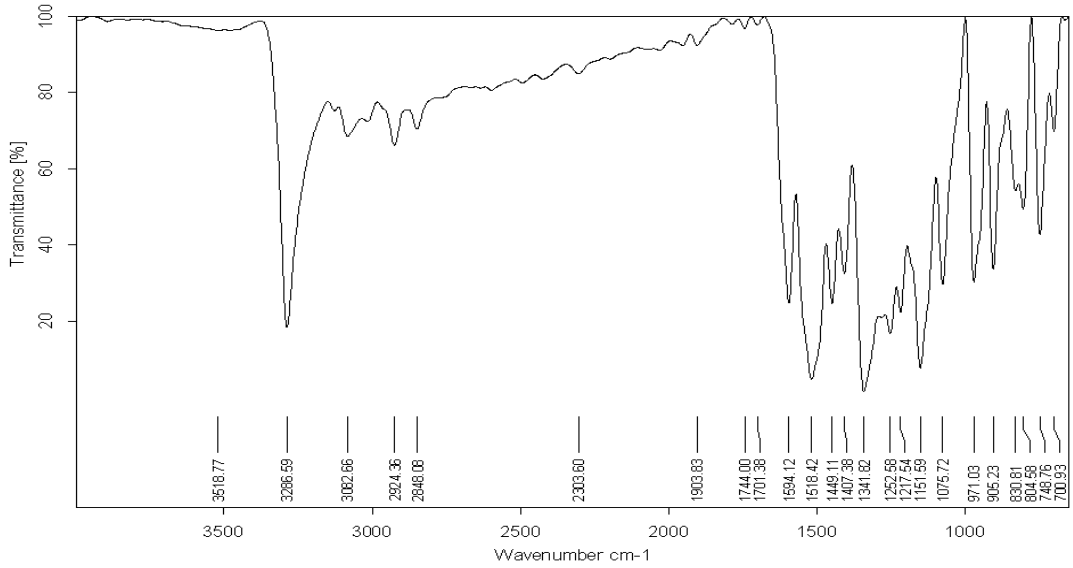

Fig.1: FTIR of pure Lornoxicam

Differential Scanning Calorimeter (DSC) :

DSC thermograms shows an endothermic peak of 218.35°C and that of final formulation is 218.41°C indicating that there is no chemical and physical interaction which is likely to affect the pharmacotechnical properties of the formulation.

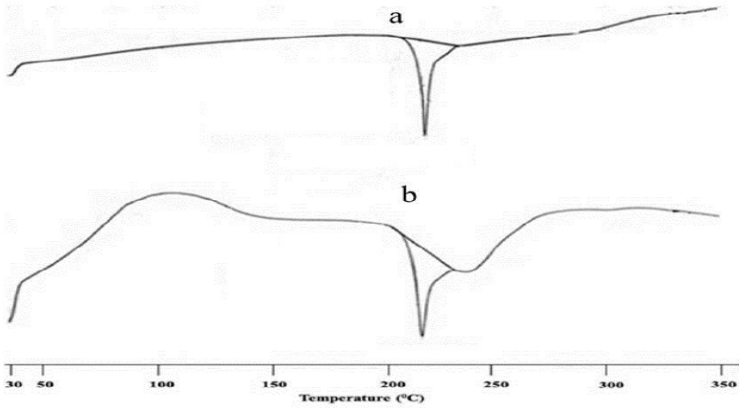

Fig.2 DSC of a)Pure Lornoxicam and b)optimized Formulation

Precompression parameters :

Blend of all the batches were subjected to precompression parameters. The value of compressibility was in the range of 11.78 - 22.37 and Hausners ratio was within the range of 1.14 - 1.28.

Table 2 Precompression parameters

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility Index (%)	Hausner's ratio	Angle of repose(ø)
F1	0.335± 0.041	0.390±0.0.35	14.10±0.341	1.16±0.458	27°.51±0.041
F2	0.320± 0.020	0.408±0.038	21.56±0.263	1.27±0.257	28°.32±0.020
F3	0.314±0.023	0.404±0.019	22.37±0.785	1.28±0.015	35°.63±0.033
F4	0.354±0.041	0.434±0.026	20.27±0.887	1.15±0.036	31°.11±0.021
F5	0.332±0.043	0.406±0.060	13.62±0.772	1.21±0.896	30°.95±0.043
F6	0.324±0.046	0.429±0.023	11.78±0.221	1.25±0.788	34°.03±0.026
F7	0.358±0.028	0.434±0.039	17.73±0.669	1.17±0.168	31°.22±0.048
F8	0.330±0.022	0.399±0.034	20.94±0.054	1.14±0.018	25°.42±0.032
F9	0.311±0.032	0.407±0.014	14.74±0.254	1.22±0.016	31°.23±0.035
F10	0.321±0.036	0.407±0.059	21.01±0.147	1.26±0.367	31°.39±0.039
F11	0.332±0.024	0.433±0.075	18.18±0.011	1.17±0.782	29°.2±0.047
F12	0.334±0.044	0.403±0.013	16.62±0.021	1.26±0.019	25°.21±0.026
F13	0.357±0.029	0.427±0.028	14.64±0.126	1.26±0.089	31°.01±0.031
F14	0.312±0.049	0.394±0.025	15.16±0.148	1.19±0.147	33°.27±0.049
F15	0.357±0.037	0.422±0.029	21.06±0.015	1.17±0.354	30°.06±0.036

± denotes standard deviation (n=3)

Post compression parameters :

All the post-compression parameters were within the pharmacopoeial (I.P) standards. The % drug content of all the batches were within the specified limits. CP due to its wicking, capillary action and SSG due to the easy breakdown of particles, rapid absorption of the drug in the dissolution medium showed faster disintegration time. Due to reduced solubility and increased water absorption ratio CCS disintegrated slowly. Among all formulations, water absorption ratio was more for F3 due to its water penetration and more swelling capacity.

Table 3 Post compression parameters

Batch code	Weight Variation (mg)*	Thickness (mm)**	Hardness (kg/cm^2)**	Friability (%)***	Drug content (%)**	Disintegration time (sec)**	Water absorption ratio (%)**
F1	150±2.6	4.18±0.09	2.3±0.110	0.54±0.054	99.37±0.24	23±0.31	92.48±0.19
F2	152±1.6	4.20±0.023	2.5±0.108	0.23±0.112	99.03±0.77	32±0.65	85.25±1.05
F3	148±1.8	4.19±0.518	2.5±0.648	0.44±0.198	97.31±0.31	158±0.28	94.23±3.82
F4	149±1.3	4.10±0.603	2.6±0.751	0.21±1.163	97.45±0.22	151±0.37	81.12±2.63
F5	152±1.1	4.16±0.263	2.4±0.253	0.46±0.682	98.90±0.63	55±0.60	82.22±0.65
F6	150±0.8	4.21±0.648	2.7±0.612	0.33±0.263	99.30±0.34	37±0.63	86.1±0.516
F7	149±0.7	4.16±0.733	2.5±0.115	0.24±0.376	98.36±0.67	28±0.68	88.36±1.06
F8	151±2.7	4.13±0.756	2.5±0.130	0.41±0.358	98.66±0.23	20±0.15	93.41±3.12
F9	148±1.2	4.10±0.758	2.3±0.786	0.43±0.421	97.40±0.71	122±1.32	70.1±0.933
F10	150±1.4	4.19±0.985	2.5±0.263	0.24±0.594	98.90±0.63	61±0.66	86.12±0.33
F11	152±0.9	4.22±0.753	2.5±0.682	0.34±0.113	98.42±0.68	65±0.22	88.0±0.122
F12	148±1.8	4.11±0.467	2.2±0.151	0.48±0.367	97.61±0.24	120±0.77	73.1±0.998
F13	150±1.2	4.18±0.033	2.5±0.170	0.21±0.385	98.63±0.76	63±0.91	86.3±0.132
F14	152±1.3	4.12±0.067	2.5±0.131	0.14±0.412	98.99±0.63	87±0.77	79.1±0.662
F15	151±1.1	4.23±0.054	2.3±0.251	0.36±0.594	99.04±0.67	82±0.88	80.2±0.343

± denotes standard deviation (n=20, n=3**, n=40***)*

***In vitro* Dispersion time :**

Coded factors of the Final equation

$$DT\ (Y1) = 127.6667 - 2.62\,X_1 + 14.75\,X_2 - 30.875\,X_3 - 6.25\,X_1X_2 - 2.5\,X_1X_3 - 90\,X_2X_3 - 4.5\,X_1^2 + 3.2917\,X^2 + 22.0417\,X_3^2. \quad (1)$$

Final equation in terms of actual factors

Dispersion time (Y1) = 128.6667 − 2.62 SSG+ 14.75 CCS- 30.875 CP-SSG CCS- 2.5 SSG CP − 90 CCS CP −4.5 SSG^2 + 3.2917 CCS^2 + 22.0417 CP^2. (2)

From the polynomial equations, magnitude of coefficient and mathematical sign indicates with increase in the concentrations of CP and SSG, the dispersion time was decreased and with increase in the concentration of CCS dispersion time was increased. In order to identify the significant effect, ANOVA was used. F value thus obtained is > critical F-value and the significant result was found at the level of probability (p<0.05).

***In vitro* drug release**

The %drug release for all batches found to be 64.4-102.4%

Final equations of coded factors

$$\text{Drug release (Y2)} = 83.0306 + 0.375X_1 - 0.975X_2 + 4.487X_3 + 0.825X_1X_2 + 1.95X_1X_3 + 11.6X_2X_3 + 2.6806X^2 + 0.486X^2 + 0.8306X_3^2. \quad (3)$$

Final equations in terms of actual factors

Drug release (Y2) = 83.0306 + 0.375 SSG- 0.975 CCS + 4.487 CP + 0.825 SSG CCS + 1.95 SSG CP+ 11.6 CCS CP + 2.6806 SSG^2 + 0.486 CCS^2 +0.8306 CP^2. (4)

From the results of regression analysis indicates with increase in Croscarmellose sodium, the drug release was decreased and with increase in crospovidone and Sodium starch glycolate drug release was increased. To identify the significant effect ANOVA was used. The calculated F value and p-value for a response (Y2) indicate a significant effect of the three factors. To identify the significant effect ANOVA was used. F value Obtained is greater than critical F-value and there is a significant result at the level of probability (p<0.05). The best fit model with high correlation coefficient values (R^2) for all the batches obeyed First order release kinetics .

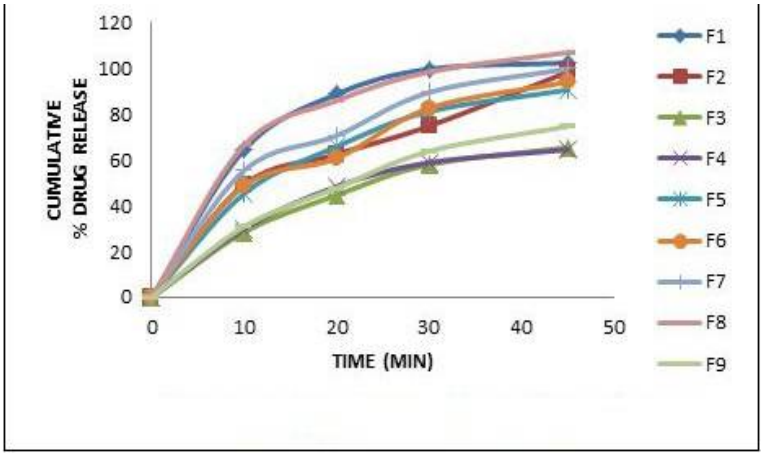

Fig.3: Comparative dissolution profile for F1 –F9

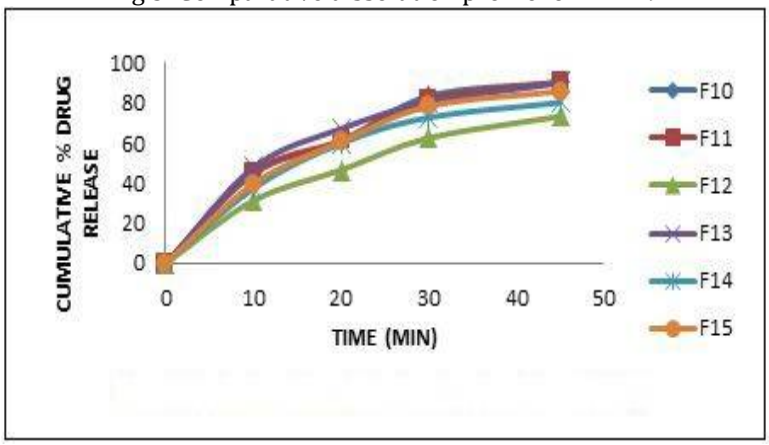

Fig.4: Comparative dissolution profile for F10 –F15

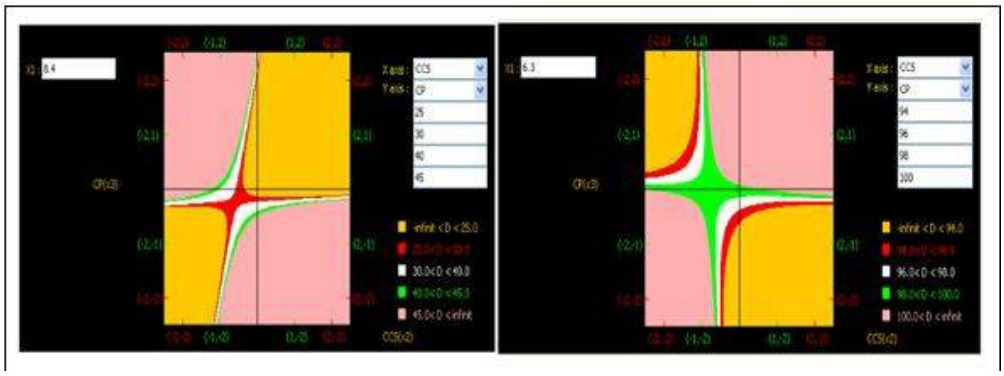

Fig.5: Contour plots of Lornoxicam oral dispersible tablets

Table 4: Comparative results of Experimented with predicted responses for Lornoxicam Orodispersible tablets formulation

Ingredient	Composition (mg/tab)	Response	Predicted value	Experimental value	Standard error
SSG	5.25	Y1(DT) (sec)	41.04	38.05	1.49%
CCS	5.25	Y2(DR) (%)	102.1	99.8	1.10%
CP	7.49				

CONCLUSION

In this study, the concentration of various superdisintegrants was known to have a intense and interactive effect on the dispersion time and drug release as shown by the model obtained using Box and Wilson design. The observed data concluded that the design was successfully utilized for optimizing the concentrations of different superdisintegrants and to prepare Orodispersible tablets of Lornoxicam with specified characters of less dispersion time and increased % drug release. It can be finalized that the Box and Wilson design can be applied successfully for the preparation of Lornoxicam Orodispersible tablets with better quality attributes and less number of trials.

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CONFLICT OF INTEREST

No conflict of interest are declared.

REFERENCES

1. Chein Yie W. (1992).Oral drug delivery and delivery systems. 2nd ed. Marcel Dekker. New York.
2. Bi Y, Sunada H, Danjo K, Otsuka A. (1996). Preparation and evaluation of a com- pressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull. 44 (11): 2121-7.
3. Pabari RM, Ramtoola Z. (2012). Effect of disintegration mechanism on wetting, water absorption and disintegration time of Orodispersible tablets. J young Pharm.;4:157-63.
4. Indian Pharmacopoeia, (1996). Government of India, ministry of health and family welfare. 4th ed. New Delhi: Controller of Publication of India.
5. Venkata Naveen Kasagana SSK, Thirumal M. (2012). Formulation and Evaluation of fast dissolving Piroxicam tablets using different Superdisintegrants. Int J Pharm Pharm Sci.; 4(2):334-7.
6. Suryaprakash Reddy Chappidi, Y Padmanabha Reddy, Nayakanti Devanna. (2016). Formulation and Optimization of the extended release tablets of Dalfampridine by 23 factorial design. Journal of Pharmaceutical and Scientific Innovation. ;5(1):27-37.
7. Bansod YD, AE Shirsat. (2014). Quality by Design approach to the development of Verapamil Hydrochloride floating matrix tablet. Am J Pharm Tech Res. 4:890-904.
8. Amaresh Prusty, Amiya kanta Mishra, Bijon Kumar Gupta. (2016). Development and evaluation of matrix tablet by taking new chemicals combination of chitosan and eudragit-I 100. J Young Pharm.8(3):168-76.
9. Gohel M PM, Amin AM, Agrawal R, Dave R, Bariya N. (2004). Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS Pharm Sci Tech. 5:36.

10. Milind Wagh P, Chetan Yewale P, Santosh Zate U, Paresh Kothawade I, Ganesh Mahale H. (2010). Formulation and evaluation of Fast Dispersible tablets of Aceclof- enac using different Superdisintegrants. Int J Pharm Pharm SciInt J Pharm Pharm Sci. ;2:154-7.
11. Ravi Kiran N, Palanichamy S, Rajesh M, Godwin T, Rajadhas, Anusha V, Parasakthi N, Thanga Thirupathi A. (2010). Formulation and evaluation of orodispersible tablets Piroxicam tablets. J Pharm Sci Res. 2(10):615-21.
12. Pabari RM, Ramtoola Z. (2012). Effect of disintegration mechanism on wetting, water absorption and disintegration time of Orodispersible tablets. J Young Pharm.4:157-63.