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Original Article

FORMULATION AND EVALUATION OF SUSTAINED-RELEASE PELLETS OF LORNOXICAM

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ABSTRACT

Objective: The aim of the study was to develop sustained release pellets of lornoxicam using Eudragit RLPO and Eudragit RSPO to reduce the dosing frequency.

Methods: The sustained release pellets of lornoxicam were prepared by extrusion–spheronization technique using Eudragit RLPO and Eudragit RSPO as release retardant polymers and microcrystalline cellulose as spheronizing agent. A 3^2 Full factorial design was applied to investigate the combined effect of the two independent variables i.e. concentration of Eudragit RLPO (X_1) and concentration of Eudragit RSPO (X_2) on the dependent variables, *In vitro* drug release at 1h (Y_1), *In vitro* drug release at 4 h (Y_2) and *In vitro* drug release at 12 h. (Y_3).

Results: The optimized formulation (F0) show *in vitro* drug release 11.24±1.21 %, 43.69±1.28 %, 82.69±1.74 % and 100.24±1.56 % at 1 h, 4 h, 12 h and 24 h respectively. Drug excipients compatibility study by FTIR showed no interaction between drug and excipients. Eudragit RLPO and Eudragit RSPO had a significant effect on *in vitro* drug release.

Conclusion: From all parameters and experimental design evaluation, it was concluded that the drug release rate decreased with an increase the concentration of Eudragit RLPO and Eudragit RSPO. SEM Photomicrograph of pellets revealed that the surface was rough and the pellets were spherical shaped in nature. The *in vitro* release kinetics revealed higuchi model is followed and drug release is by anamolous diffusion.

Keywords: Lornoxicam, Sustained release pellets, Eudragit RLPO, Eudragit RSPO

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INTRODUCTION

The sustained drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [1, 2]. Sustained release drug delivery systems provide a uniform concentration at the absorption site, maintained plasma concentration within a therapeutic range, reduce the frequency of administration and minimizes the side effects [3, 4]. Oral modified drug delivery systems can be classified into two broad groups: single unit dosage forms (SUDFs) and multiple-unit dosage forms (MUDFs), such as granules, pellets or mini-tablets. The production of MUDFs is a common strategy to control the release of drugs as shown by the reproducibility of the release profiles when compared to the ones obtained with SUDFs [5, 6]. Pellet has been used to describe a variety of systematically produced, geometrically defined agglomerate obtained from diverse starting materials utilizing different processing conditions. Their size usually ranges from 0.5 mm to 1.5 mm which is intended mostly for oral administration. Pellets as a drug delivery system offer not only technological advantages but also better flow properties, less friable dosage form, narrow particle size distribution, ease of coating, and uniform packing [7, 8]. It also has therapeutic advantages such as less irritation of the gastrointestinal tract, a low risk of side effects associated with dose dumping and reduction of the variation in gastric emptying rates [9, 10]. Lornoxicam, also known as chlortenoxicam is a member of the oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs) with extremely potent anti-inflammatory and analgesic activities [11-13]. It is widely used for the symptomatic treatment of pain and inflammation in patients with rheumatoid arthritis and osteoarthritis [14]. The bioavailability of lornoxicam is 90–100%. Because of its relatively short plasma half-life, 3-5 h, it is prescribed to take lornoxicam in divided daily doses either twice or thrice daily in order to maintain the therapeutic plasma concentration. These characteristics make lornoxicam a suitable candidate for developing into sustained-release pellets [15]. Hence, the objective of the present research work is to formulate and develop sustained release pellets of lornoxicam using extrusion and spheronization technique. The sustained release pellets were prepared using Eudragit RLPO and Eudragit RSPO as release retardant polymers. The effect of the Eudragit RLPO and Eudragit RSPO on drug release behavior was studied using 3^2 factorial designs.

MATERIALS AND METHODS

Materials

Lornoxicam has obtained a gift sample from Zydus Cadila Healthcare Ltd. Ahmedabad. Eudragit RLPO, Eudragit RSPO and microcrystalline cellulose were purchased form Yarrow chem. Products, Mumbai. Magnesium stearate, talc, and polyvinylpyrrolidone (PVP) K-30 were purchased from Estron Chemicals Limited, Ahmedabad. Isopropyl alcohol was procured from RFCL Ltd. Delhi.

Drug-excipient interaction study by FTIR

FTIR study was carried out to identify the drug sample and to establish drug-polymer compatibility in the physical mixture of drug and polymers. Fourier Transform Infrared Spectroscopy was carried out by diluting the sample with dried potassium bromide and acquiring IR spectrum in the range of 400-4000 cm^{-1}. FTIR spectra of pure drug and physical mixture (drug+Eudragit RLPO+Eudragit RS PO) were taken [16].

Method

Pellets were prepared by the extrusion-spheronization method. Drug, Eudragit RLPO, Eudragit RSPO, microcrystalline cellulose, PVP K-30, talc and magnesium stearate were sifted through sieve no. 40 and accurately weighed. The ingredients were blended in geometric fashion using mortar and pestle for 10 min and water was gradually added in the powder blend to prepare dough mass. The dough mass was extruded through mini screw extruder (1 mm pore size) at speed of 25 rpm. The extrudates were collected and cut it in small size. Small size extrudates were spheronized in spheronizer (Cronimach Machinery, Ahmedabad) at 800 rpm for 20 min. The obtained pellets were dried at 60 °C for 60 min in a hot air oven. Hard gelatin capsules were filled with sustained-release pellets containing 16 mg drug [17, 18].

Experimental design

In this design, two factors were evaluated each at three levels and experimental trials were performed using all possible nine combinations. In this present study, concentration of Eudragit RL PO (X_1) and concentration of Eudragit RSPO (X_2) were selected as independent variables. The *in vitro* drug release at 1 h (Y_1), *in vitro* drug release at 4 h (Y_2) and *in vitro* drug release at 12 h (Y_3) were selected as dependent variables. A statistical model, incorporating interactive and polynomial terms was used to evaluate the response.

Table 1: Variables in 3^2 factorial design

Independent variables	Levels		
	-1	0	+1
X_1 Eudragit RLPO	8% (20 mg)	12% (30 mg)	16% (40 mg)
X_2 Eudragit RSPO	8% (20 mg)	12% (30 mg)	16% (40 mg)

Dependent variables: Y_1: *in vitro* drug release at 1 h, Y_2: *in vitro* release drug 4 h, Y_3: *in vitro* drug release at 12 h

Table 2: Composition of factorial batches

Ingredients	Batches (Qty. in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lornoxicam	16	16	16	16	16	16	16	16	16
Eudragit RL PO	20	30	40	20	30	40	20	30	40
Eudragit RS PO	20	20	20	30	30	30	40	40	40
Microcrystalline cellulose	176	166	156	166	156	146	156	146	136
PVP K-30	8	8	8	8	8	8	8	8	8
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Water	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
Total	250	250	250	250	250	250	250	250	250

Evaluation of pellets

Particle size distribution

The particle size distribution of pellets was carried out by sieve analysis using mesh fractions (American Society for Testing and Materials) 16/18, 18/20, 20/30, 30/44, and 44/60 for 5 min on a mechanical sieve shaker. Pellets retained on each mesh were weighed and the resulting data were used to obtain the mean geometric diameter by plotting cumulative percentage undersize versus the average particle size on log probability paper. The study was performed in triplicate for each batch of pellets [18-20].

Drug content

Pellets were crushed in mortar and pestle. Accurately weighed powder equivalent to 16 mg drug was dissolved in 100 ml phosphate buffer of pH 6.8. The dispersion was sonicated for 15 min and filtered. The filterate was analyzed spectrophotometrically at λmax 377 nm after suitable dilution [13].

Friability

The friability test of pellets was performed to ensure its mechanical strength. Lower friability values indicate good mechanical strength. Pellets of known mass were placed in Roche friabilator and subjected to impact testing at 25 rpm for 4 min [18-21].

***In vitro* drug release study**

16 mg lornoxicam drug equivalent sustained-release pellets were filled in '1' size hard gelatin capsule. *In vitro* drug release studies were performed using the USP type II dissolution apparatus (Electrolab Dissolution Tester (USP) TDT-08L) in 900 ml 0.1 N HCL pH 1.2 for 2 h and 900 ml phosphate buffer pH 6.8 for 3 to 24 h at temperature 37±0.5 °C. Aliquots (5 ml) were withdrawn at different time intervals. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were analyzed at 377 nm using UV spectrophotometer [22].

Surface morphology

The shape and surface characteristics of pellets were determined by scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling the pellets on the double-sided adhesive tape stuck to an aluminum stub. The stub was then coated with gold. The samples were then randomly scanned and microphotographs were taken on different magnification and higher magnification was used for surface morphology [18].

***In vitro* release kinetic study**

The drug release data of sustained-release pellets were fitted to kinetics models, that is, zero order, first order, Higuchi and Korsmeyer-Peppas to find out drug release pattern and mechanism.

RESULTS AND DISCUSSION

Drug–excipients compatibility study by FTIR

From the IR studies, important function group IR bands of pure drug and physical mixture were identified. Characteristic IR bands of lornoxicam includes the presence of peaks at 1647.21 cm^{-1} (C=O stretching), 3066.91 cm^{-1} (N-H stretching), 3090 cm^{-1} (C-H stretching), 770 cm^{-1} (C-Cl stretching) and 1596.79 cm^{-1} (N-H bending group), which remained unaltered in IR spectrum of physical mixture of drug and polymers. IR analysis revealed that there is no interaction between drug and polymers [15].

Result of batches of lornoxicam pellets

Results of lornoxicam sustained-release pellets as shown in table 3 and 4

Table 3: Evaluation of pellets

Batch no	% drug content	Particle size distribution (mm)	% Friability
F1	97.56±0.07	1.13±0.09	0.57±0.08
F2	98.65±0.09	1.09±0.05	0.78±0.09
F3	96.71±0.12	1.17±0.07	0.24±0.05
F4	98.77±0.12	1.14±0.07	0.63±0.08
F5	97.83±0.17	1.19±0.06	0.86±0.06
F6	99.33±0.06	1.13±0.05	0.56±0.09
F7	99.51±0.15	1.12±0.06	0.69±0.12
F8	97.45±0.14	1.10±0.08	0.84±0.15
F9	98.43±0.07	1.40±0.07	0.78±0.16

Data are represented as mean (X)±standard deviation (SD), n=3

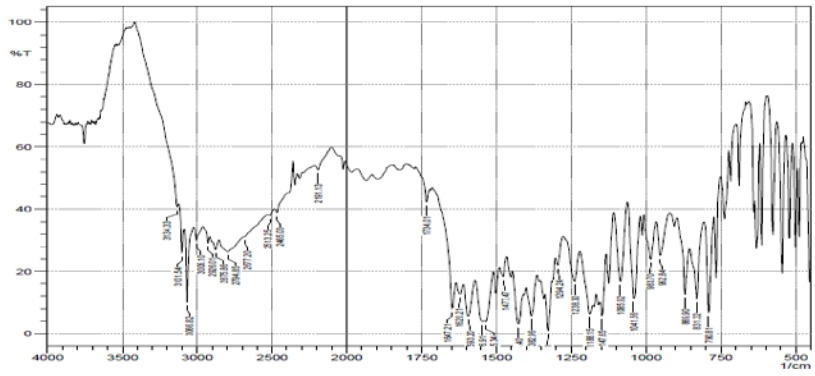

Fig. 1: FTIR of lornoxicam

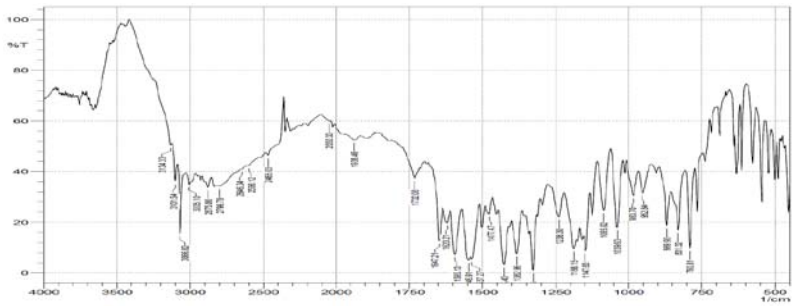

Fig. 2: FTIR of lornoxciam+eudragit RLPO+eudragit RS PO

Table 4: Observed response in 3^2 full factorial design for lornoxicam sustained-release pellets

Batch no	Independent variables		Dependent variables		
	X_1	X_2	Y_1: *in vitro* drug release at 1 h	Y_2: *In vitro* drug release at 4 h	Y_3: *in vitro* drug release at 12 h
F1	20	20	12.35±1.45	57.12±1.26	95.35±1.03
F2	30	20	13.69±1.46	50.41±1.03	91.24±1.02
F3	40	20	9.92±2.32	48.36±1.45	87.01±1.67
F4	20	30	14.05±1.73	50.42±1.63	92.72±1.16
F5	30	30	11.50±1.63	41.19±1.29	79.91±1.82
F6	40	30	9.19±1.47	38.44±1.12	63.95±1.98
F7	20	40	12.72±1.44	40.06±1.25	65.57±1.26
F8	30	40	10.29±1.35	38.74±1.05	63.51±1.71
F9	40	40	8.34±1.91	34.74±1.62	60.58±1.12

Data are represented as mean (X)±standard deviation (SD), n=6

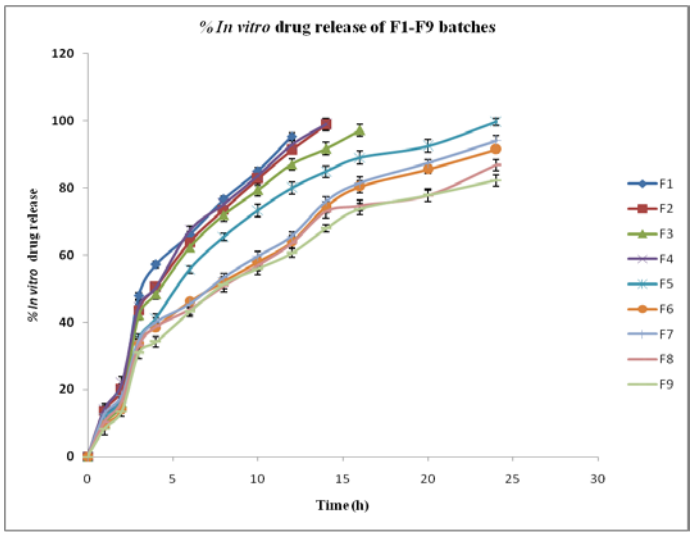

Fig. 3: *In vitro* drug release profile (n=6), error bars represent standard deviations of six replicates

The aqueous medium on contact with polymer matrix gradually begins to hydrate from the periphery toward the center, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium [17]. As the concentration of Eudragit RLPO and Eudragit RSPO were increased, the drug release was decreased. [fig. 3]. It was also observed that the release rate of the drug from Eudragit RLPO pellets was higher than that of Eudragit RSPO pellets because Eudragit RLPO contains higher amount of quaternary ammonium groups, which renders it more permeable and accelerates the drug release. Eudragit RSPO pellets have a thicker polymeric surface as compared to RLPO. The thick polymeric barrier slows the entry of surrounding dissolution medium into the pellets and hence less quantity of drug leaches out from the polymer matrices of the pellets exhibiting slow release [23, 24].

Regression analysis

Regression analysis for the effect of X_1 and X_2 on *in vitro* drug release at 1 h

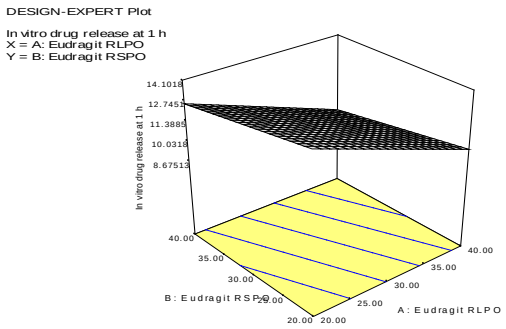

Fig. 4: 3D surface plot of response Y_1

Table 5: Regression statistics Y_1

R Square	0.8042	
Adjusted R Square	0.7650	
Source	Sum of squares	P-value
Model (Linear)	26.24	0.0003
X_1	22.70	0.0001
X_2	3.54	0.0403

Full model equation

$$Y_1 = 11.39-1.95X_1-0.77X_2 \ldots\ldots (1)$$

Higher values of correlation coefficients for drug release at 1 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries. Here p Value for X_1 and X_2 was less than 0.05. So Eudragit RLPO and Eudragit RSPO both had significant effect on *in vitro* drug release at 1 h. [Table 5] Eudragit RLPO and Eudragit RSPO had negative effect on *in vitro* drug release so it was concluded that % drug release decreased with an increase the concentration of Eudragit RLPO and Eudragit RSPO.

Regression analysis for the effect of X_1 and X_2 on *in vitro* drug release at 4 h

Table 6: Regression statistics for Y_2

R Square	0.9620	
Adjusted R Square	0.9348	
Source	Sum of squares	P-value
Model (Quadratic)	460.67	<0.0001
X_1	118.46	0.0003
X_2	307.45	<0.0001
X_1^2	9.38	0.0994
X_2^2	10.91	0.0798
X_1X_2	2.02	0.4079

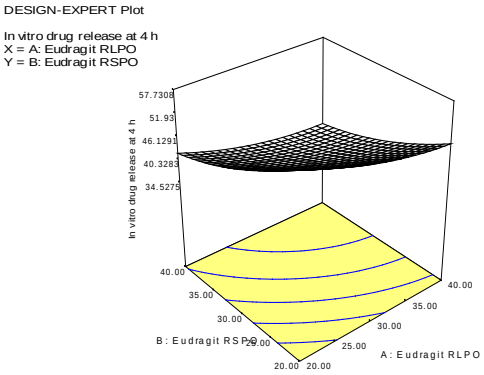

Fig. 5: 3D surface plot of response Y_2

Full model equation

$$Y_2 = 41.59-4.44X_1-7.16X_2+1.84X_1^2+1.99X_2^2+0.71X_1X_2 \ldots\ldots (2)$$

Reduced Model Equation on the basis of p value

$$Y_2 = 41.59-4.44X_1-7.16X_2 \ldots\ldots (3)$$

Higher values of correlation coefficients for drug release at 4 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries. Eudragit RLPO and Eudragit RSPO both had a significant effect on *in vitro* drug release at 4 h. [Table 6] Eudragit RLPO and Eudragit RSPO had a negative effect on *in vitro* drug release so it was concluded that % drug release decreased with an increase in the concentration of Eudragit RLPO and Eudargit RSPO [25]. Here b_2 value is more negative than b_1 which indicated that Eudragit RSPO had a more release retardant effect compare to the Eudragit RLPO at 4 h.

Regression analysis for the effect of X_1 and X_2 on *in vitro* drug release at 12 h

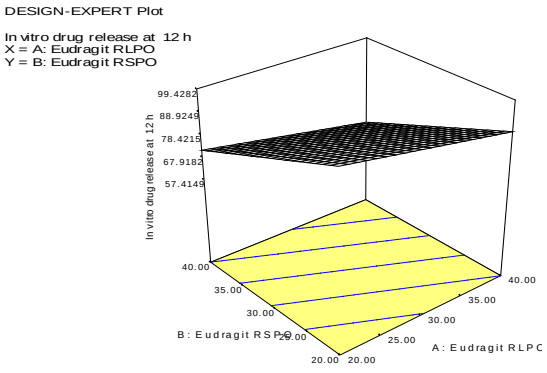

Fig. 6: 3D surface plot of response Y_3

Table 7: Regression statistics for Y_3

R Square	0.8878	
Adjusted R Square	0.8654	
Source	Sum of squares	P-value
Model (Linear)	1469.72	<0.0001
X_1	295.40	0.0026
X_2	1174.32	<0.0001

Full model equation

$$Y_3 = 78.42\text{-}7.02\ X_1\text{-}13.99\ X_2 \text{ ..... (4)}$$

Higher values of correlation coefficients for drug release at 12 h indicate a good fit. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries. Eudragit RLPO and Eudragit RSPO both had a significant effect on *in vitro* drug release at 12 h. [table 7] Eudragit RLPO and Eudragit RSPO had a negative effect on *in vitro* drug release so it was concluded that % drug release decreased with an increase the concentration of Eudragit RLPO and Eudragit RSPO [25]. Here b_2 value is more negative than b_1 which indicated that Eudragit RSPO had a more release retardant effect compare to the Eudragit RLPO at 12 h.

Validation of design model

Preparation of checkpoint batch from overlay plot

Checkpoint batch C1 and C2 were selected from the overlay plot of responses. The amount of Eudragit RLPO and Eudragit RSPO and according to their amounts the predicted responses were given in the Overlay plot flag or in the solution of overlay data. From that any two batches C1 and C2 were selected for the verification of the model.

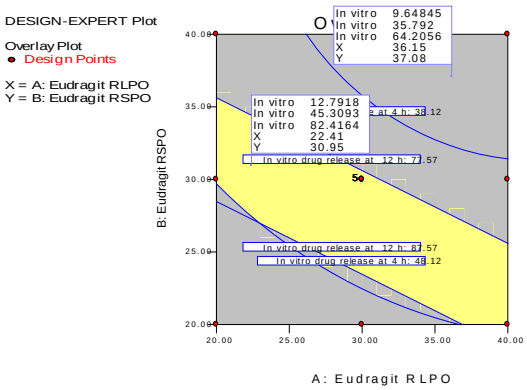

Fig. 7: Overlay plot of response variable

Table 8: Predicted response and the actual response of checkpoint batch

Evaluation parameters	Batch C1			Batch C2		
	Predicted value	Actual value	% Error	Predicted value	Actual value	% Error
In vitro drug release at 1h	12.79	12.25±1.33	4.22	9.64	9.23±1.21	4.25
In vitro drug release at 4 h	45.30	44.38±1,49	2.03	35.79	36.91±1.37	3.12
In vitro drug release at 12 h	82.41	80.11±1.67	2.79	64.20	66.12±1.53	2.99

Data are represented as mean (X)±standard deviation (SD), n=6

Actual response of C1 and C2 batch were measured and compared with the predicted response of checkpoint batch. Error was found to be less than 5% of all the responses. Hence, this model was valid and optimized batch can be selected from the overlay plot of this model.

Optimized batch from overlay plot

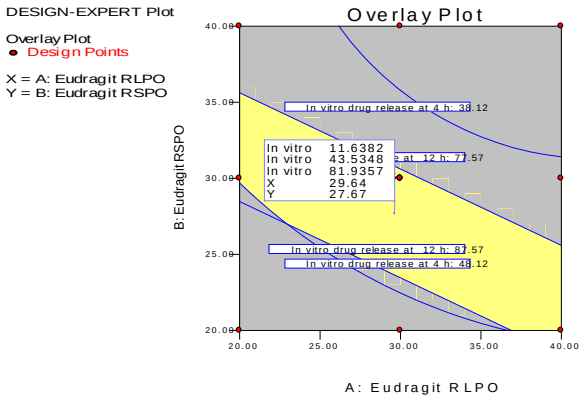

Fig. 8: Optimized batch from overlay plot

The contour plots are evolved for each response which divides the plot surface into desirable and not desirable zone. A contour for each response is then superimposed to locate the area where the targets for all responses are achieved. Here in above fig. 8 shows the yellow area was the optimized area [16].

Table 9: Result of evaluation parameters of optimized batch (F0)

Parameters	Result
% Friability *	0.71±0.06
Particle size distribution *	1.13±0.12 mm
% drug content *	99.73±0.09
In vitro drug release at 1 h #	11.24±1.21 %
In vitro drug release at 4 h#	43.69±1.28 %
In vitro drug release at 12 h #	82.69±1.74 %

*n=3, # n=6, (mean±SD)

***In vitro* release kinetic study**

The In vitro release profile of the drug from all the formulations could be best expressed by Higuchi model, as the plot shows high linearity (R^2 = 0.9572,). (table 10) To confirm the diffusion mechanism, the data were fit into the Korsmeyer-Peppas equation; here 'n' value was found to be 0.7167 so it follows anomalous diffusion mechanism. This behavior was responsible for maintaining zero-order release in which the increase diffusion path length due to swelling is balanced with the decrease in diffusion path length due to matrix erosion [18].

Surface morphology (SEM analysis)

Shape analysis and surface morphology of pellets of the optimized batch were carried out by SEM. SEM photomicrograph of pellets revealed that the pellets were spherical shaped in nature and the surface was rough. This could be due to the deposition of fines produced by attrition of pellets during spheronization [26] [fig. 9].

Table 10: *In vitro release* kinetic study

Model	Kinetic model data of optimized batch			
	Zero order	1st order	Higuchi	Peppas
R^2	0.8587	0.6740	0.9572	0.9480

Slope (n)	3.935033	0.034878	24.75161	0.716766
Intercept	24.48383	1.377144	-8.69492	-0.88167

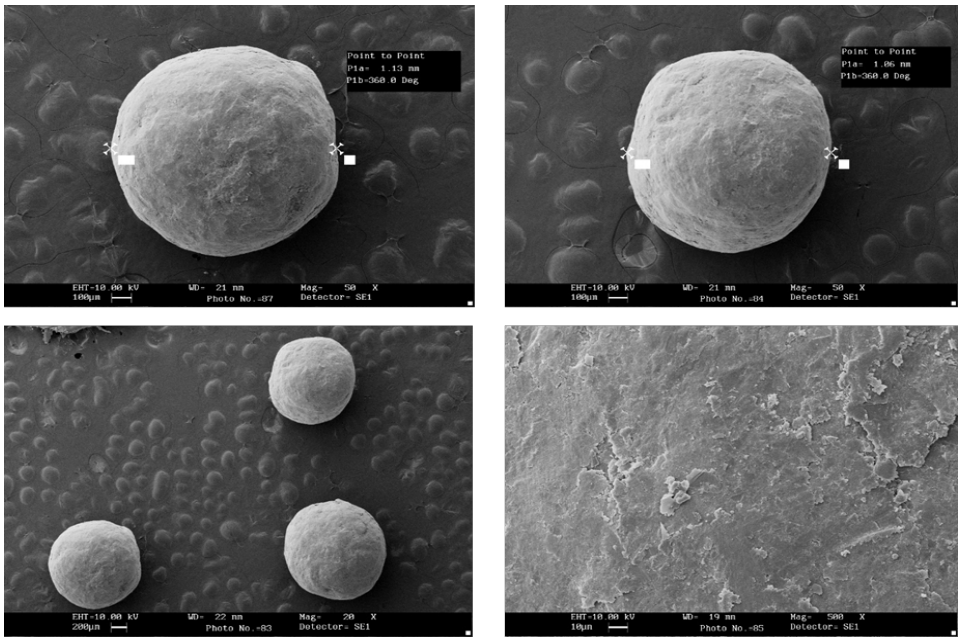

Fig. 9: Scanning electron microscopy images (surface morphology) of batch F0

CONCLUSION

The sustained release pellets of lornoxicam are prepared by extrusion and spheronization method using polymers such Eudragit RLPO and Eudragit RSPO to reduce dosing frequency. Concentration of Eudragit RLPO and Eudragit RSPO had a significant effect on % *in vitro* drug release. It was found that increase the concentration of polymers resulted that decreased release rate. Here Eudragit RSPO had more release retardant effect than Eudragit RLPO. The optimized batch F0 containing 30 mg Eudragit RLPO and 28 mg of Eudragit RSPO was considered as the best product with respect to size, shape of pellets, and *in vitro* drug release up to 24 h. SEM study confirmed that the prepared pellets was spherical in nature. The *in vitro* release kinetics revealed Higuchi model is followed and drug release is by anomalous diffusion.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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