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Fabrication and Optimization of Novel Lornoxicam Matrix Tablets Using 3-Factor 3-Level Box-Behnken Statistical Design: *Invitro* and *Invivo* Evaluation

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ABSTRACT

In the present study efforts have been made to prepare sustained release matrix tablets of Lornoxicam. Matrix tablets were prepared by direct compression method by using Hydroxypropyl methyl cellulose K15 (HPMC- K15), Ethyl cellulose (EC) and Sodium carboxy methyl cellulose (Na-CMC) as polymers in different concentrations. A 3-factor 3-level Box-Behnken statistical design was used as an optimization tool having total of 17 experimental runs with 5 central points. All three polymers were selected as independent variables while %age drug release at various time intervals and hardness were used as dependant variables. *In vivo* studies were conducted on human plasma using Tenoxicam as internal standered. All the detections were made on SYKNM HPLC. Foriour Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetery (DSC) studies were conducted and no chemical interaction was found between drug and polymers. The drug release mechanism was mainly governed by non-fickian (anomalous) diffusion and zero-order (case II) transport diffusion. Regression analysis was performed on dissolution data obtained with the selected response variables and polynomial models were constructed. Polynomial models were further validated using one way ANOVA and results indicated that all the polymers used have significant effect on selected response ($p>0.05$). Contour plots and three dimensional response surface curves were drawn. In- vivo studies were conducted on two tablet formulation indicating slow and sustained release of the drug from matrix. From Behnken design it is possible to successfully formulate and optimize Lornoxicam sustained release matrix tablets with three polymers (HPMC- K15, EC and Na-CMC) in combination.

Introduction

Sustained and controlled release dosage forms are making place in pharmaceutical market all over the globe as these provide drug concentrations within the therapeutic window for a desire period of time. This result in reduction in drug related side effects and improves patient compliance. Release of drug contents from the matrix tablets depends upon number of factors like transport of solvent into the dosage form, swelling of polymers, diffusion through swellable matrix and due to breakdown of the swollen matrix [1]. Lornoxicam, a non steroidal anti-inflammatory (NSAID), is a weak acid that belongs to oxicam group of this class. It is used in treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and lower back pain along with analgesic, antipyretic and anti-inflammatory activity. During ulceration even high concentration of Lornoxicam doesn't produce gastro intestinal tract (GIT) as compared to other NSAID's [2] (Hariprasanna et al. 2011). It has short half life of 3 to 5hrs. Due to its acidic nature, sustained release of Lornoxicam occurs in lower part of GIT that results in prolonged release and therapeutic action [2, 3].

Hydrophilic matrix systems are usually preferred for oral delivery particularly HPMC based systems. HPMC has good compressibility nature, wide range of compatibility, non-toxic, gel forming capability and its availability in various viscosity grades. Polymeric chain relaxations occur due to contact with

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water [4, 5]. Ethyl cellulose is an inert and hydrophobic polymer of various viscous grades [6]. It has been used in various techniques like direct compression, wet granulation and hot melt extrusion [7, 8].

Statistical experimental design provides an economical means to obtain desirable information about an experimental method by just performing a few numbers of experimental runs; they also help to determine any type of interactions among study variables and also used to predict the chances of experimental errors. Various types of designs are being used now a day in research and development (R & D) unit of industries i.e. Response surface methodology, Fractional factorial designs, D & A-optimal designs, full factorial designs and Robust experimental designs. Response surface methodology (RSM) is a type of statistical design that is utilized by various pharmaceutical organizations to cope with various research problems, determine relationship between both variables i.e. Dependant and independent, analyze responses and make optimizations of processes even within narrow limits [9]. RSM can be expressed graphically in form of contour plots (three dimensional plots) which are helpful to study the interaction among the independent variables and desired responses. These graphs also help to observe the effect of two variables on response at one time. Response surface methodology (RSM) using 3-factor 3-level Box-Behnken statistical design was used for present study which is an independent, rotatable or nearly rotatable, quadratic design having the treatment combinations at midpoints of the edges of the process space and at the centre [4]. It is preferable as compare to central composite design because it has limited capability for producing orthogonal blocks, and it requires limited number of experimental runs compare to central composite design when we use 3 or 4 independent variables for study. The aim of present work was to fabricate matrix tablets of Lornoxicam containing EC, HPMC and NaCMC in combination for the 1st time in Pakistan using direct compression method. To evaluate the effect of hydrophobic and hydrophilic polymers on the release profile of matrix tablets and optimize the release profile using Box-Behnken statistical design and *in vivo* performance of optimum sustained release tablet formulations was also evaluated.

Materials and Methods

Materials

Lornoxicam was obtained as generous gift from Hilton Pharmaceutical (pvt) Ltd (Karachi, Pakistan) used as model drug. Tenoxicam (as internal standard of HPLC method) was donated by Pearle pharmaceutical (pvt) Ltd. (Islamabad, Pakistan). Hydroxypropyl methyl cellulose (HPMC) K15M was purchased from Fluka chemie AG (Switzerland). Ethyl cellulose 100 cp (EC), Sodium Carboxy methyl cellulose (NaCMC), Tri chloro acetic acid (TCA) and NaOH used were of analytical grade and were purchased from Sigma-Aldrich (Germany). Magnesium stearate, Lactose, Methanol, KH_2PO_4 and Acetonitrile HPLC grade purchased from E. Merck co. (Germany). Distill water and phosphate buffer were prepared in Pharmaceutics research lab of The Islamia University of Bahawalpur. Human Studies were approved by ethical committee of the Islamia University Bahawalpur.

Methods

Direct Compression Method

All the ingredients as shown in Table.1 were weighed on electronic weighing balance (Shimdazu AUX 220) and mixed properly for 15 minutes in cubic mixer except magnesium stearate. Lubricant (magnesium stearate) was added to the powder blend and mixed again for 5minutes. Powder blend was compressed on single punch rotary machine using concave tooling to produce matrix tablets of average weight of 200mg [10].

Table 1:Composition of Lornoxicam Matrix Tablet

Code	Lornoxicam mg	HPMC mg	EC Mg	NaCMC mg	Magnesium stearate mg	Lactose (q.s) mg	Total Wt mg
A1	08	20	50	18	02	102	200
A2	08	24	48	20	02	098	
A3	08	28	46	22	02	094	
A4	08	32	44	24	02	090	
A5	08	42	36	26	02	086	
A6	08	40	40	28	02	082	
A7	08	44	38	30	02	078	
A8	08	38	38	38	02	084	
A9	08	52	34	34	02	070	
A10	08	80	32	36	02	066	
A11	08	60	30	38	02	062	
A12	08	64	28	40	02	058	
A13	08	68	26	42	02	054	
A14	08	72	24	44	02	050	
A15	08	76	22	46	02	046	
A16	08	80	20	48	02	042	
A17	08	84	18	50	02	038	

***In- vitro* characterization:**

All the precompression studies i.e. bulk density, tapped density; Carr's index, hausner ratio and angle of repose for all 17 formulations were conducted. In process tests such as weight variation, hardness, thickness and friability tests were performed on all different 17 formulations. Weights of 20 tablets was measured individually using analytical weighing balance (Shimdazu AUX 220) and then calculate average weight and percentage variation in each batch separately. Digital hardness tester (Curio HT901, Pakistan) was used to measure the hardness of 10 tablets from each batch and then average hardness and S.D of each batch was calculated. Friability test was performed using Roche friabilator (Emmy, Pakistan) by placing 20 tablets after weighing into the rotating chamber and set at a speed of 25rpm for four minutes. Now the difference in original and final weight was determined and percentage decrease in weight was calculated for each batch. According to compendia the acceptable limit of friability test was less than 1% decrease in tablet. Verneir caliper was used to measure the thickness of 10 tablets from each batch and determined the average value and S.D for each batch. All the results obtained were within the official limits.

Fourier transforms infrared spectroscopy studies

FTIR studies on active drug, other formulation excipients and optimized formulations before and after compression were carried out using Bruker FTIR (Tensor 27 series, Germany) with attenuated total reflectance technology (ATR).

To evaluate the interaction among drug and polymers used before and after compression Opus data collection software was used [11]. FTIR spectra were taken by just placing the small amount of powdered sample directly into the pike miracle ATR cell in such a way that ZnSe crystal surface was covered by sample. Now rotate the arm of assembly so that a compact mass of powdered material was formed. Background spectrum was taken before taking spectrum of any sample with empty cell plate. Now the different samples were scanned between the ranges of wave numbers 4000 to 400 cm^{-1}.

In-vitro drug release studies

Dissolution studies of various matrix tablet formulations were performed using automatic dissolution apparatus (USP apparatus II, paddle rotating method) rotated at 50 rpm which was attached to the auto sampler (Watson Marlo, Stockholm, Sweden) and 900 ml of phosphate buffer solution of pH 7.4 was used as dissolution medium at 37°C ± 0.5° C. Dissolution studies for each batch were performed in triplicate while maintaining the same experimental condition for each formulation. Aliquots of 5ml were filtered and withdrawn at regular interval of 30minutes for 24 hrs by auto sampler. UV-Spectrophotometer (U2020, Irmeco, Germany) was used to analyze various samples at 382nm. The percent drug release was obtained as shown in Fig.1 by comparing the absorbance of standard with the absorbance of sample taken at different time intervals using following formula:

Percent drug release= Abs. of sample solution/Abs. of standard solution X 100

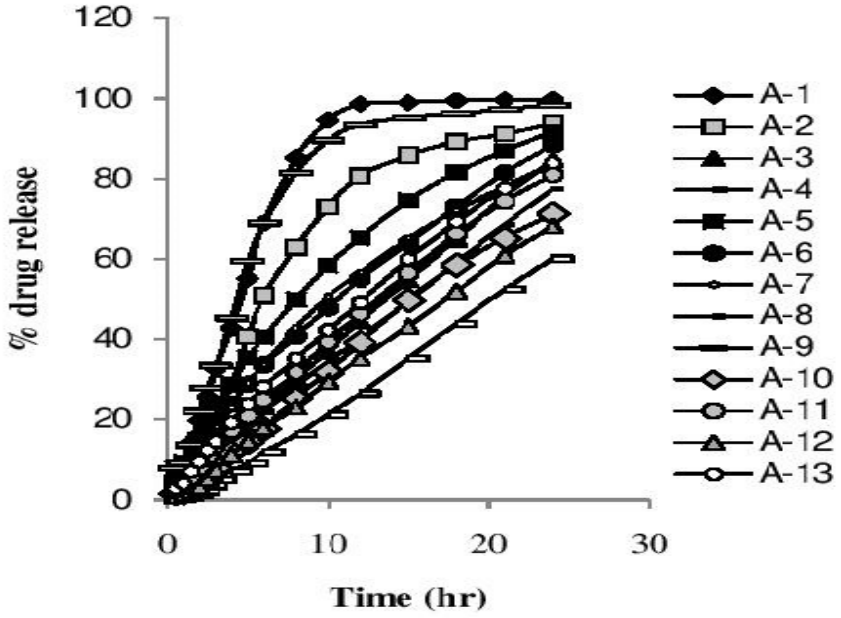


Figure.1: Cumulative %age release of A1-A13

Experimental statistical design

A 3-factor, 3-level Box-Behnken statistical design was applied to evaluate main, quadratic, and interaction effects of polymers on release of matrix tablets [4]. Quadratic response surface and second order polynomial models within least number of experimental runs were obtained by using design expert software [12].

Kinetic modeling of drug release studies

The kinetic models such as zero order, 1st order, Higuchi model and Korsmeyer-Peppas model were used to evaluate *in-vitro* release. These models can be represented by following equations:

Zero order $Qt=K_0t$

First order $\log Qt = \log Q_0 - K_1t$

Higuchi' model $Qt= K_H t^{1/2}$

Korsmeyer-Peppas $Mt/M_0= K_{kp}t^n$

Where

Qt is the initial drug amount of drug that released at time t,

K_0, K_1, K_H, and K_{KP} are release rate constant for zero order, 1st order, Higuchi model, and Korsmeyer-Peppas model respectively

t is the time.

Results and Discussion

Precompression Studies

These studies were conducted for all seventeen formulations i.e. bulk density (0.201 – 0.668 g/ml), tapped density (0.256 – 0.608mg/dl), Carr's index (10.166 – 21.484%), Hausner ratio (1.11 – 1.27) and Angle of repose (16.29 – 32.64) as shown in Table.2. All the results were found within the limits and have proven that powder has good flow properties to be compressed. Statistically results were evaluated by using One way ANOVA, the p-value of all the results was greater than 0.05 that have proved that all the results within the groups were insignificant.

Table 2: Bulk density, Tapped density, Carr's Index, hausner's ratio, Angle of repose

Formulation Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index %	Hausner's Ratio	Angle of Repose (θ)
A1	0.306	0.347	11.816	1.13	29.03
A2	0.473	0.531	10.923	1.12	23.85
A3	0.336	0.414	18.841	1.23	19.88
A4	0.201	0.256	21.484	1.27	18.18
A5	0.386	0.448	13.839	1.16	22.45
	0.226	0.262	13.740	1.16	16.29
A7	0.267	0.316	15.506	1.18	32.64
A8	0.222	0.269	17.472	1.21	27.69
A9	0.298	0.358	16.760	1.20	21.57
A10	0.347	0.405	14.321	1.17	26.39
A11	0.433	0.482	10.166	1.11	30.48
A12	0.668	0.752	11.170	1.13	30.61
A13	0.474	0.566	16.254	1.19	31.45
A14	0.283	0.352	19.602	1.24	29.98
A15	0.545	0.608	10.362	1.12	26.08
A16	0.377	0.427	11.710	1.13	28.66
A17	0.442	0.495	10.707	1.12	30.40

In process evaluation of Lornoxicam matrix tablets

In process evaluation was carried out and all the tablets were found within the USP limits. Average weight of the tablets was in range of 200.16mg-204.1mg, hardness (1.92 – 3.24 kg/cm^2), thickness (3.914mm- 4.629mm) and friability of tablets was found (0.47% to 0.89%) as shown in Table.3. Results have shown that tablets can withstand with hazards during handling, storage and transportation.

Table 3: Hardness, Thickness, Friability and Avg. weight

Code	Thickness* (mm)	Avg. wt. of tabs (mg)	Hardness (kg/cm²)	Friability * (%)
A1	4.126±0.02	195.40	2.75	0.733±0.014
A2	4.146±0.05	189.50	2.59	0.846±0.019
A3	4.437±0.09	200.62	2.51	0.686±0.013
A4	4.198±0.005	201.54	2.40	0.629±0.011
A5	4.05±0.01	199.76	2.38	0.515±0.007
A6	4.082±0.01	204.16	2.72	0.567±0.009
A7	4.126±0.02	196.21	2.69	0.679±0.012
A8	4.03±0.002	202.55	2.35	0.772±0.016
A9	4.629±0.06	200.16	1.97	0.636±0.011
A10	3.914±0.03	203.68	1.92	0.582±0.009
A11	4.095±0.012	197.11	3.16	0.478±0.006
A12	3.974±0.05	198.57	3.24	0.525±0.007
A13	3.983±0.06	200.90	3.18	0.785±0.016
A14	4.186±0.04	200.43	3.47	0.893±0.021
A15	3.954±0.011	203.32	2.79	0.734±0.014
A16	4.329±0.01	198.18	2.95	0.672±0.012
A17	4.015±0.03	204.00	3.11	0.551±0.008

*Average of three determinations; Standard Deviation (S.D).

Fourier Transform Infrared Spectroscopy Studies (FTIR)

FTIR studies of pure drug and polymers were carried out to check any incompatibility among them. Lornoxicam was confirmed by sharp peak due to stretching vibration of NH group and stretching vibration of C=O group of primary amide at 3090 cm^{-1} and 1642 cm^{-1} respectively. Presence of major groups showed resemblance with actual drug structure and the purity of drug substance [13].No significant difference in peak intensities and wave numbers was observed that concludes that compression force has no significant effect on drug stability and no drug-polymer interaction and deformation was found as shown in Fig 5A.

DSC Studies

DSC studies were conducted to check any incompatibility among drug and polymers. DSC thermograms of drug and polymers were taken alone and in combination [14].The particular DSC thermogram data was scanned. All thermograms have not exhibited any change in shift of peaks as shown in Fig.2. This study confirmed that there was present no interaction among Lornoxicam and polymers.

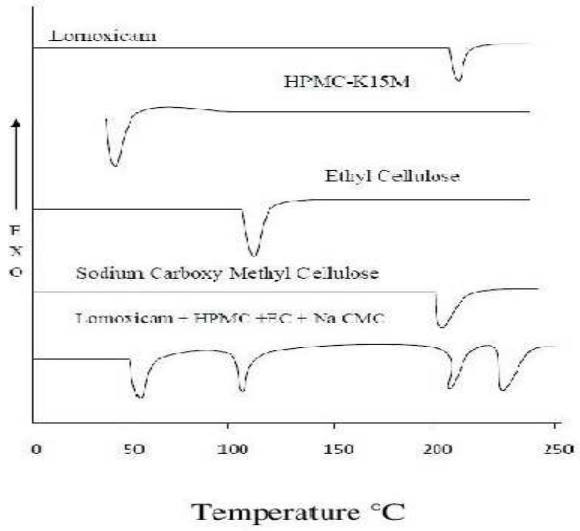


Figure 2: DSC Thermogram

***In-vitro* Drug release studies**

3-factors, 3-level Box-Behnken design was applied for cumulative percent drug release of all formulations. Various concentrations of the polymers i.e. hydrophilic and hydrophobic were compared for their release retarding effect as shown in figure (10) and best formulation (A8) was determined.

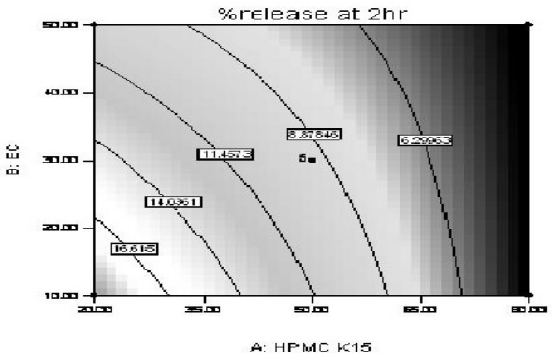
Release kinetic data obtained is shown in figure (10). It was found that formulations containing higher total polymeric ratio followed Zero order kinetics. Formulations A5 and A7 were having high concentrations of HPMC and lower level of EC regression line becomes more linear and value of R^2 reaches up to 0.998. When matrix tablets come in contact with dissolution media a rapid gel layer was formed that responsible for primary release rate [5]. EC is a hydrophobic polymer that follows erosion mechanism. Korsmeyer-Peppas model was also applied and critical value n (diffusion coefficient) was found between 0.534-1.117 indicating non-fickian diffusion (anomalous) mechanisms of drug release.

Optimization results by using RSM (Box-Behnken statistical design)

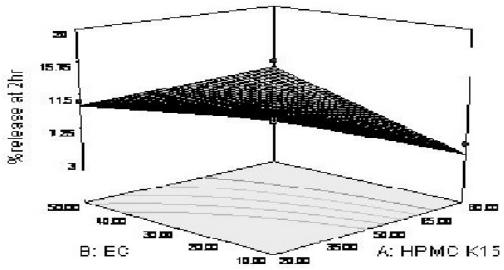
3-factors-3-level Box-Behnken statistical design was applied for optimizing using dependant (Y1, Y2 and Y3) indicating percent drug release at 2hrs, 12hrs and hardness (Kg) respectively and independent X-1(HPMC K15), X-2(EC), X-3(NaCMC) variables.

Contour plots and response surface analysis

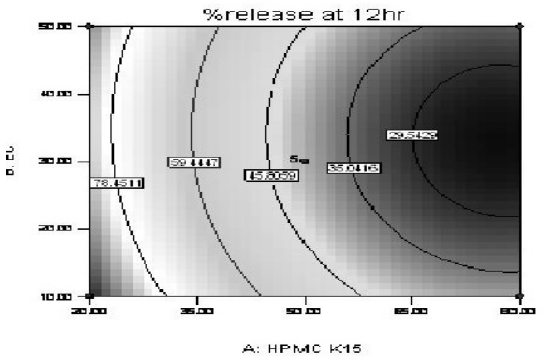
From Fig. 3A & Fig.3B, it is clear that at 2hrs interval HPMC K15 and EC has linear relationship with each other at 2hr interval as almost straight lines were obtained and inhibitory effect on release of drug increased with increasing concentration of all the polymers. As the time reaches to 12hrs non linear relation occurs among HPMC K15 and EC as shown in Fig.3C & Fig.3D.It is also clear that HPMC K15 at its lower concentration release drug up to 78.45% but when its concentration increases up to 80mg its inhibitory effect also increases and it release the drug up to 29% because polymer become more swelled when its concentration increased. But, when combined effects of HPMC are observed with EC, inhibitory effects are further increased. Relationship of hardness shown in Fig.4A & Fig 4B is non linear between HPMC K15 and EC and with increasing concentration of both polymers. Hardness of tablets also increased resulting in decreased release rate of drug.



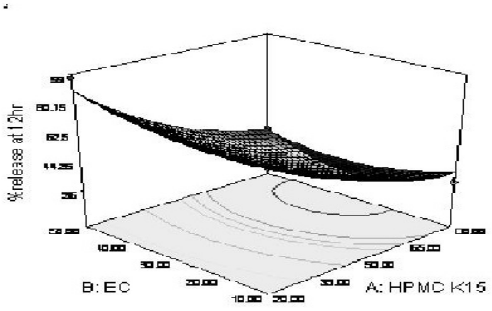
(A) Contour plot showing effect of HPMC(X_1) and EC(X_2) on response Y_1



(B) Response surface plot showing effect of HPMC(X_1) and EC(X_2) on response Y_1

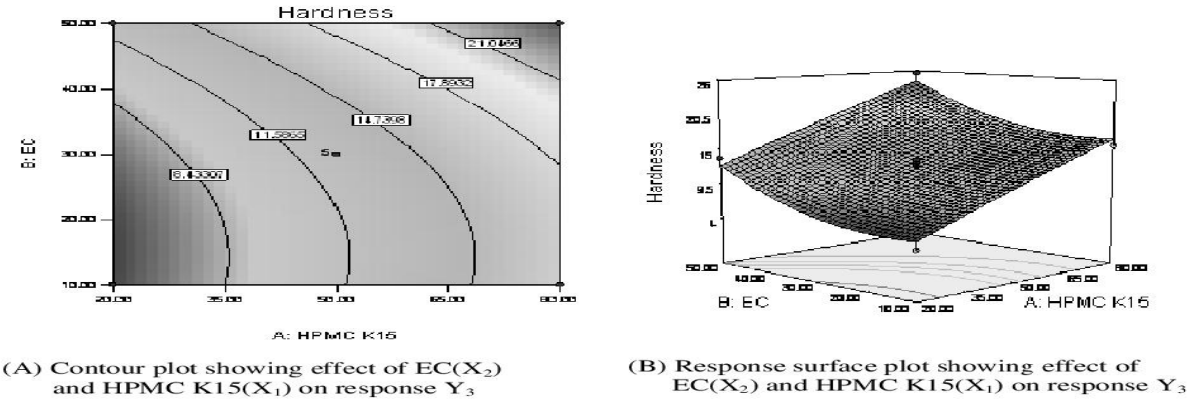


(C) Contour plot showing effect of HPMC(X_1) and EC(X_2) on responseY_2



(D) Response surface plot showing effect of EC(X_2) and HPMC(X_1) on responseY_2

Figure 3: Contour plots and Response Surface Plots



(A) Contour plot showing effect of EC(X_2) and HPMC K15(X_1) on response Y_3

(B) Response surface plot showing effect of EC(X_2) and HPMC K15(X_1) on response Y_3

Figure 4: Contour plots and Response Surface Plots

***In Vivo* Evaluation of optimum sustained release tablets of Lornoxicam**

***In-vivo* study protocol**

Ten healthy male volunteers between 20 - 25 years of age and 50 – 60 kg of weight were included into the study. Health conditions were confirmed by various laboratory tests including blood and urine samples. They have not used any sort of drug from the last one month. Cross over design was employed for formulation delivery to volunteers. Ethical Committee of the Islamia University has approved the current study. During first experiment one group was given formulation A4 and other group received A8 with one full glass of water in morning with fasting state. Volunteers were not given any sort of food and liquid after treatment. Sampling tubes were used to collect blood samples of 5ml at predetermined intervals through previously inserted butterfly cannula in forearm. Samples were centrifuged for 20minutes at 3000 rpm; supernatant was collected and stored in glass tubes in freezer for further studies.

RP-HPLC Method for Lornoxicam estimation in plasma

Concentration of Lornoxicam was determined by a reversed-phase high-performance liquid chromatographic (HPLC) SYKNM HPLC apparatus at room temperature. S 3210 UV/VIS detector (Germany) detector was set at 382nm wavelength. Potassium hydrogen phosphate (0.1M) and Acetonitrile (60:40) were used as mobile phase and pH was adjusted by acetic acid. Flow rate was kept 1ml/min., Rheodyne sample injector fitted with a 50 µl sample loop. The detector was operated using a sensitivity range of 0.005 AUFS and wavelength was set at 382nm. Data Processing Modular was connected with the detector and the signals of detector were analyzed by HPLC Software clarity. Chromatographic separation was performed iso-cratically at room temperature using Hypersil ODS, C_{18} (150mm x 4.6mm, 5µm particle size) column. Mobile phase consisted of 0.1M KH_2PO_4 and ACN (60:40) and pH was adjusted at 3.0 with acetic acid. Mobile phase was filtered (0.45 µm membrane filters) and degassed (Sonicator) for 2-3 minutes to avoid any bubble and choking of apparatus.

Stock Solution and Standard Solution

Stock solution of Lornoxicam (LOR) was prepared by dissolving 100mg of LOR into 100ml of 0.2M NaOH and labeled it as D1 (dilution one), 1ml was taken from D1 and further diluted with 100ml of mobile phase to obtain final concentration 100µg/ml in measuring flask. Finally, it was filtered and sonicated for further analysis. Similar procedure was adapted to prepare internal standard Tenoxicam. A six point calibration curve was prepared by spiking required volume of working solution of LOR and IS into blank plasma to obtain final concentration of 0.312, 0.625, 1.25, 2.5, 5and 10 µg/ml for LOR.

Chromatogram of spiked plasma having 5µg/ml lornoxicam and IS (2.5µg/ml) is shown in Fig.5C indicating peaks of IS at 2.5 min and lornoxicam at 4.7min. It shows good peak separation and peak shape for both lornoxicam and IS with no significant interaction with plasma components and total run time is quite shorter (`~6min). The chromatogram of plasma samples taken from a volunteer at 12.0 hour after dosing of lornoxicam tablet A-4 as shown in Fig.5B. The recovery values for lornoxicam were more than 70% at 0.3125µg/ml and 0.625µg/ml. The sensitivity of the assay method was approximately 0.01µg/ml.

Statistical Analysis

The kinetic models such as zero order, 1st order, Higuchi model and Korsmeyer-Peppas model were used to evaluate *in-vitro* release. The results are shown in Table 4.

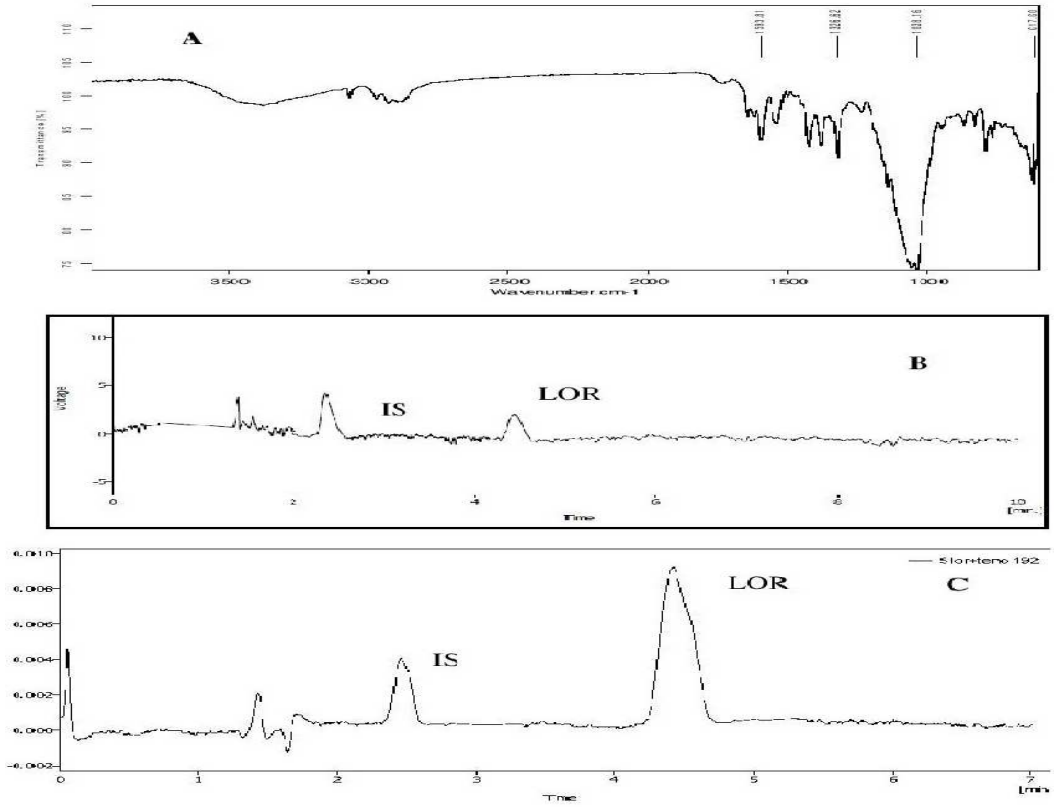


Figure 5: (A) FTIR Spectrum of A4 formulation after compression
(B) Chromatogram obtained from plasma sample at12 hrs after administration of A4 tablet
(C) Chromatogram showing peaks of IS and LOR from spiked plasma

Table 4: Modeling of dissolution data showing release kinetics of lornoxicam sustained release matrix tablets

Code	Zero Order		1st Order		Higuchi		Koresmeyer-Peppas		
A1	5.893	0.604	0.17	0.959	23.612	0.888	21.655	0.534	0.891
A2	5.068	0.823	0.11	0.973	19.739	0.897	13.277	0.656	0.934
A3	3.514	0.997	0.051	0.948	12.888	0.8015	3.031	1.052	0.998
A4	2.505	0.996	0.032	0.969	9.161	0.793	2.027	1.075	0.998
A5	4.545	0.863	0.088	0.998	17.71	0.951	12.207	0.647	0.987
A6	3.812	0.993	0.059	0.968	14.216	0.85	4.8	0.918	0.997
A7	4.063	0.919	0.07	0.998	15.654	0.932	9.243	0.707	0.991
A8	3.262	0.997	0.046	0.966	12.102	0.833	3.532	0.972	0.997
A9	5.831	0.61	0.167	0.97	23.367	0.902	21.555	0.532	0.905
A10	3.111	0.994	0.043	0.969	11.452	0.811	3.043	1.008	0.994
A11	3.54	0.992	0.053	0.976	13.217	0.852	4.553	0.911	0.996
A12	2.586	0.993	0.033	0.959	9.42	0.781	1.855	1.117	0.998
A13	3.355	0.997	0.048	0.963	12.458	0.835	3.674	0.968	0.997
A14	5.145	0.994	0.022	0.914	13.144	0.686	3.654	0.555	0.991
A15	4.254	0.914	0.035	0.952	19.251	0.654	4.521	0.705	0.957
A16	3.985	0.954	0.055	0.914	15.321	0.768	6.251	0.856	0.986
A17	5.056	0.981	0.086	0.924	16.851	0.896	7.456	0.794	0.944

Conclusion

Modified sustained released tablets of lornoxicam were fabricated, characterized for *In vitro – In vivo* characterization and optimized by using 3-factor 3-level Box Behnken design. ANOVA indicated effect of polymer concentration on release and hardness of tablets. A4 formulation was found best and optimized one from our studies.

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Conflict of interest statement

We declare that we have no conflict of interest.

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