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RESEARCH ARTICLE

Formulation and Evaluation of Sustained Release Matrix Tablets of Lornoxicam Using Natural Polymers

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ABSTRACT

The objective of the present work is to design of sustained release matrix tablets of Lornoxicam influence of natural polymers on the release rate and *in vitro* evaluation. Lornoxicam is widely used member of non-steroidal anti-inflammatory and analgesic drug with short biological half- life. Lornoxicam is practically insoluble in water because of this reason it is suitable to develop sustained release matrix tablet using hydrophilic polymers. The natural polymers like Okra gum, Locust bean gum, orange peel pectin, Xanthan gum, Lactose were utilized in the formulation of matrix tablets containing Lornoxicam by wet granulation technique and evaluated for its *in-vitro* drug release. Natural polymers are hydrophilic in nature and rate controlling polymers. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, thickness, friability, drug content and weight variations), *in vitro* drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The *in vitro* release study of matrix tablets were carried out in pH 1.2 HCl for 2 hours and pH 6.8 phosphate buffer for the remaining 10 hours as dissolution medium. Among all the formulations, F9 shows 98.89% of drug which was better controlled release at the end of 12 hrs. It has been found that the optimized formulation F9 containing 210 mg of Xanthan gum as drug retarding polymer shows better sustained effect for 12 hours.

KEYWORDS

Lornoxicam, Okra gum, Locust bean gum, Orange peel pectin, Xanthan gum, Lactose, Matrix tablet, Sustained release, Wet granulation

INTRODUCTION

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. Normally conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency.

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The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, matrix erosion have been utilized as formulation

approaches.[1]

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system.[2]

Matrix systems are widely used for the purpose of sustained release. The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.[3]

MATERIAL AND METHODS

Materials

Lornoxicam were purchased from yarrow chemicals Mumbai, Locust bean gum, Xanthan gum, were purchased from SD Fine chemicals Ltd, Mumbai. Orange peel pectin, were purchased from yarrow chemicals Mumbai, *Okra gum (Ladies Finger)* was collected from local market Tumkur, and authenticated at the Botany Department of Sree Siddaganga College Of Arts, Science & Commerce B.H. Road Tumkur, Karanataka. Lactose, Magnesium stearate, Talc, PVP K 30 were purchased from SD Fine chemicals Ltd, Mumbai.

Methods

Compatibility Studies of Drug with Excipients

FTIR spectra of the selected (Optimized) formulation were taken and compared with the spectrum of the pure drug (Lornoxicam) i e (1:1 ratio) by using Agilent Technologies, Cary 630 FTIR.

Formulation of Sustained Release Matrix Tablets

Tablet formulations were prepared by wet granulation method. Lornoxicam SR matrix tablets Proportion of excipients with drug was as given in Table 1. All ingredients were sifted through sieve no.60. The sifted ingredients were mixed thoroughly in a polybag for 15min. PVP K30 was dissolved in DM water and used for wet granulation of the final blend. To get the desired wet mass. This wet mass was passed through sieve # 16. The prepared granules were dried at 60^0C for 1 hour in hot air oven dried granules were sized by passing it through sieve no.20 and lubricated with magnesium stearate and Talc. Finally tablets were compressed at 300 mg weight on a 10 station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 9mm flat-shaped punches. Each tablet formulation was monitored for weight variation, hardness, friability, thickness and drug content.

Extraction of Okra Gum

The fresh fruits of *Abelmoschus esculentus* (2kg) are collected and washed with water. Then they are crushed mechanically with motor and pestle and soaked in water for 5-6hrs. Then they are boiled in a stainless steel container at burner temperature for 2-3hrs. After boiling, keep aside for 1hr, for complete release of mucilage into the water. Then the solution is passed through muslin cloth to remove the marc. To the volume of solution obtained, add 3 times the amount of acetone, to precipitate the mucilage. Then the precipitate is dried in oven at 50-60^0C for 2hrs for complete removal of moisture. After complete removal of moisture it was collected, Powdered with the help of motor and pestle. And it was passed through sieve no. #80. The mucilage obtained is stored in an air tight container[5,6]

Evaluation of Granules[7]

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Table 1: Composition of matrix tablet of Lornoxicam

Formulation Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Lornoxicam	16	16	16	16	16	16	16	16	16	16	16	16
Locust Bean Gum	150	180	210	-	-	-	-	-	-	-	-	-
Okra Gum	-	-	-	150	180	210	-	-	-	-	-	-
Xanthan Gum	-	-	-	-	-	-	150	180	210	-	-	-
Orange Peel Pectin	-	-	-	-	-	-	-	-	-	150	180	210
Lactose	110	80	50	110	80	50	110	80	50	110	80	50
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3	3	3	3
PVP K-30	15	15	15	15	15	15	15	15	15	15	15	15

Table 2: Preliminary confirmatory tests for dried gum and mucilage

Sl.No.	***CHEMICAL TEST***	***Okragum***
1.	**Test for Carbohydrate** Molisch's test:	+
2.	**Test for Mucilage** Ruthenium test:	+
3.	**Test for Polysaccharides** Iodine test:	+
4.	**Test for Tannins** Ferric chloride test	–
5.	**Test for Alkaloids** Wagner's test	+

Bulk Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] X 100 / TBD

Where, TPD is Tapped bulk density

LBD is loose bulk density

Evaluation of Tablets

Post Compression Parameters

Thickness and diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

Hardness

The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets.

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

Weight Variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods.

Uniformity of Drug Content

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of Lornoxicam, transfer to a 250 ml volumetric flask. Add about 150 ml of 0.1N HCl, shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 0.1N HCl. Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 0.1N HCl. Measure the absorbance, of the resulting solution at the maxima at about 376 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

Cu/Cs = Au/As * dilution factor

Cu = Concentration of unknown sample,

Cs = Concentration of Standard sample

Au = Absorbance of unknown sample &

As = Absorbance of standard sample [10].

In-Vitro Dissolution Study

In vitro release study was done using the USP Dissolution Test Apparatus II (Electrolab TD T08L). The study was carried out in 900 ml of 0.1 N HCl for 2 h followed by phosphate buffer pH 6.8 for 10 h. The medium was maintained at $37^0C \pm 0.5^0C$ and a paddle rotation speed was 50 rpm. Aliquots of 5 ml sample solutions were analyzed for Lornoxicam at 376 nm using a UV/VISIBLE double beam spectrophotometer (Labindia-25UV/VIS spectrometer, Mumbai, India).

Stability Study

The optimized formulation was subjected to stability at 40^0C ± 2^0C and 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile.

Scanning Electron Microscopy

SEM has been used to determine the surface topography, texture and to examine the morphology of fractured or sectioned surface. The examination of the surface of polymeric drug delivery system can provide important information about the porosity and micro structure of device. The optimized formulation was selected for scanning electron microscopy (SEM) by using JEOL-JSM-840A, Japan. The tablet surface morphology was studied at 2nd, 6th and 12th hours.

RESULTS AND DISCUSSION

Compatibility Studies of Drug with Excipients

Overly IR spectrum of Lornoxicam matches with optimised formulation F-9 and it was found to be similar. Importantly, finger print region of both tested compounds was found to be matching. Indicates no signs of drug-excipients incompatibility.

Table 3: Interpretation of FT-IR

Functional group vibrations	Lornoxicam (Cm^{-1})	Optimized formulation F-9 (Cm^{-1})
C=C, C=N ring stretching	1529.587	1541.628
Asymmetric SO_2 stretching	1324.319	1325.914
Symmetric SO2 stretching	1143.484	1141.549
Aromatic –C-H bending	868.858	875.175
C-Cl bending	687.828	668.566
C-S stretching	767.846	757.177

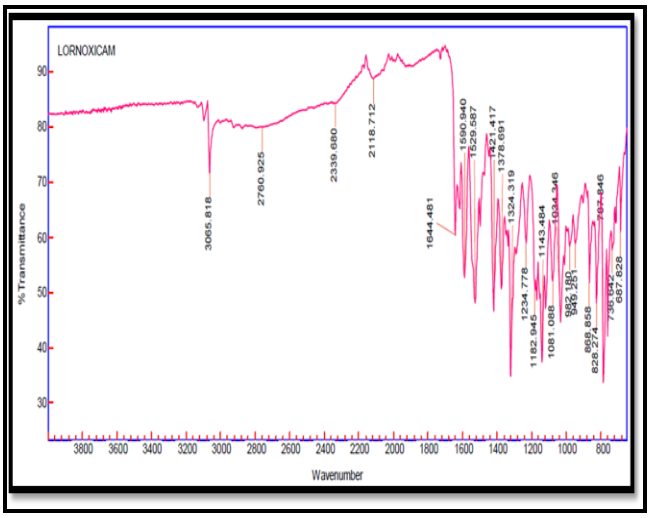

Figure 1: FT-IR of Lornoxicam[3]

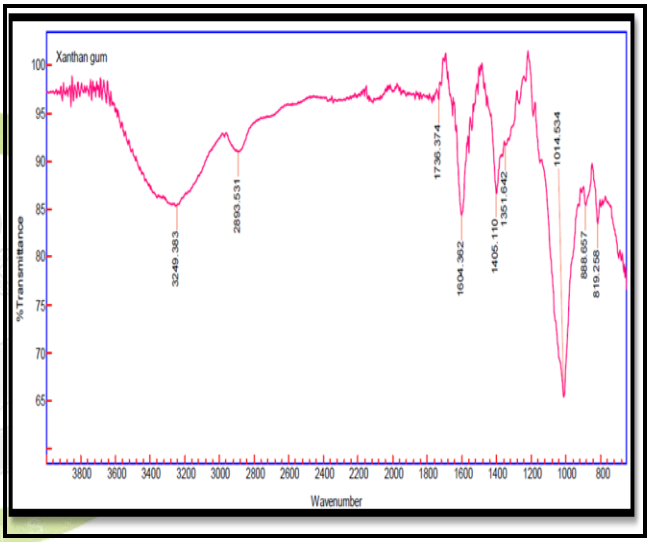

Figure 2: FT-IR of Xanthan gum

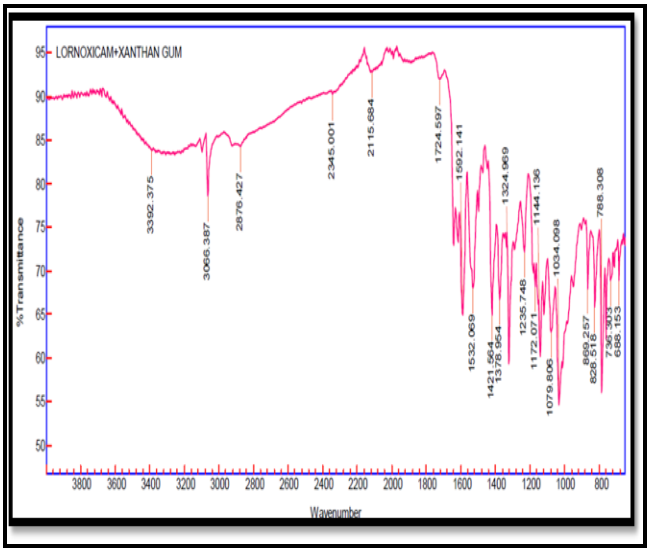

Figure 3: FT-IR of Lornoxicam + Xanthan gum

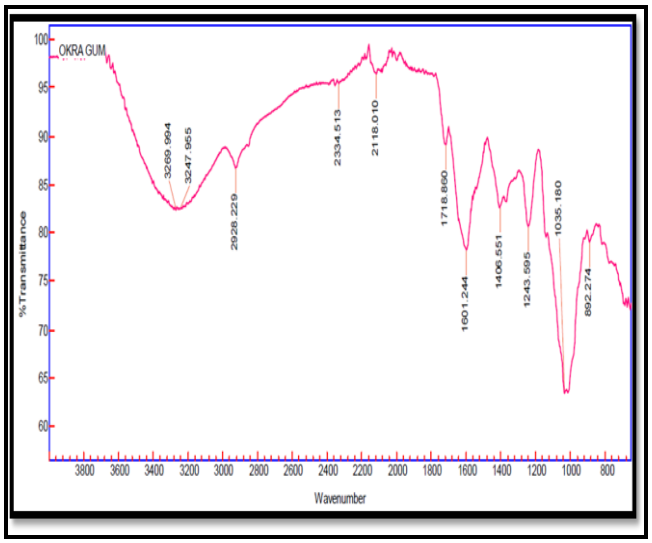

Figure 4: FT-IR of Okra gum

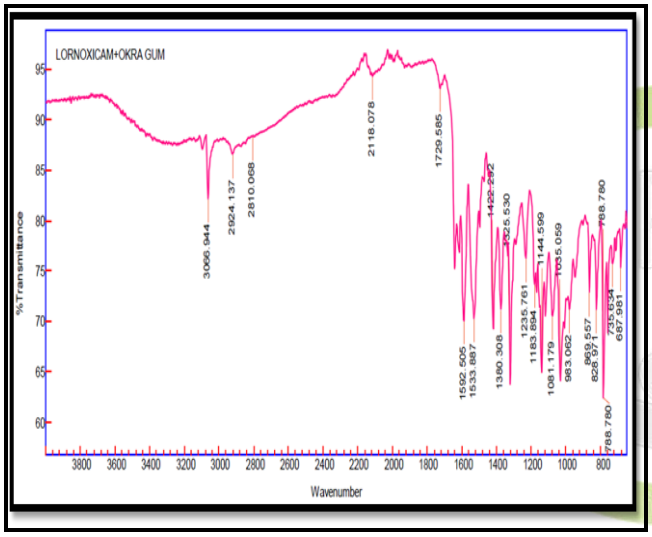

Figure 5: FT-IR of Lornoxicam + Okra gum

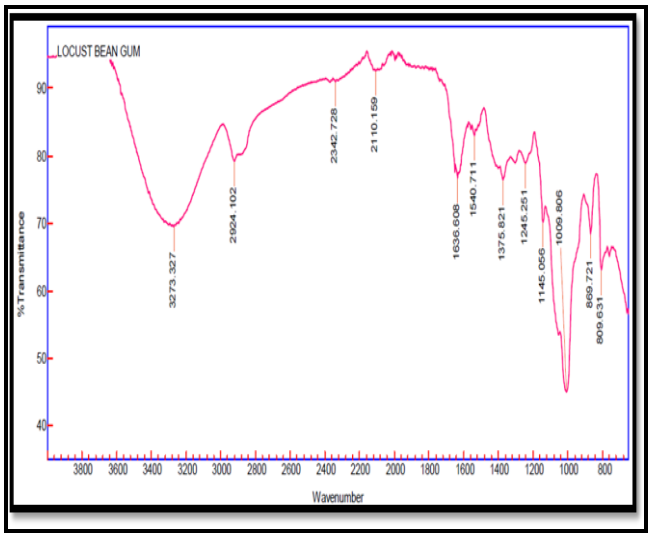

Figure 6: FT-IR of Locust bean gum

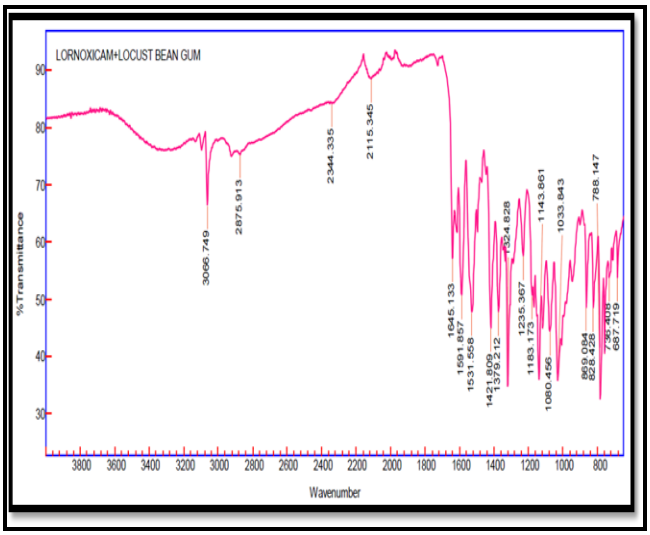

Figure 7: FT-IR of Lornoxicam + Locust bean gum

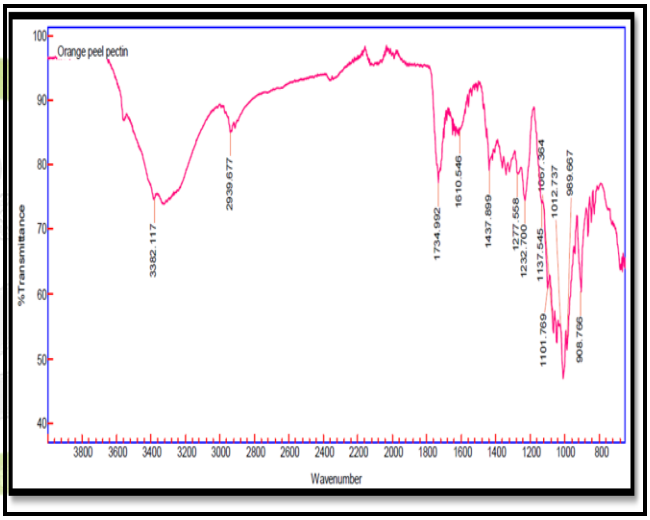

Figure 8: FT-IR of Orange peel pectin gum

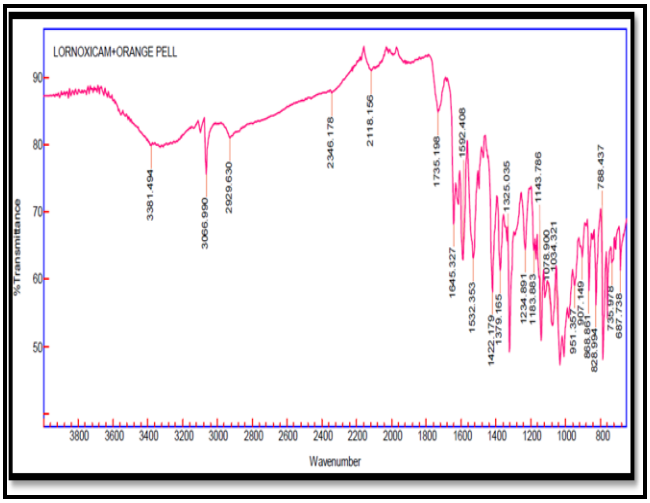

Figure 9: FT-IR of Lornoxicam + Orange peel pectin gum

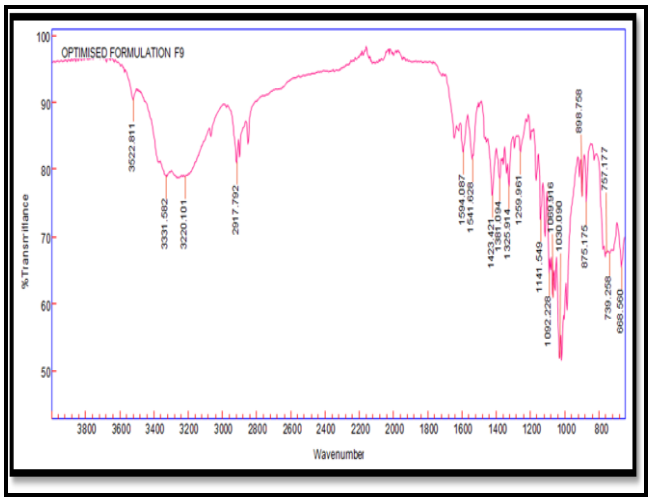

Figure 10: FT-IR of Optimized Formulation F-9

Evaluations of Tablets

All the tablet formulations showed acceptable quality control properties like hardness, friability, thickness, weight variation, drug content uniformity etc. Complied with in the specifications for tested parameters.

From formulation F-1 to F-3 decrease in drug release was observed with higher concentration of polymer like locust bean gum. Rate drug release was faster in F-1 and slower in F-3, as the concentration of polymer increases the drug release decreased. The highest release of drug from formulation F-1 Shows 98.8% drug release after 10 hours, and F-2 & F-3 shows 97.45%, 96.61% drug release after 9hrs respectively.

Formulation F-4 to F-6, the release rate increase with increases in polymer concentration of polymer like okra gum. The rate of drug release in F-4 it shows 97.86% of drug release up to 11hrs and also in F-5 formulation the drug release shows 97.89% at 9hrs and in F-6 formulation shows at 98.76% drug release at 10 hrs respectively.

Matrix tablet of formulation F-7 to F-9, were containing Xanthan gum as polymer. Among these formulations, the release rate was increased. This result has shown that as the proportion of Xanthan gum increased, the overall time of release of the drug from the matrix tablet was also increased. For F-7 (92.83%) up to 12 hrs, F-8(95.82%) up to 12 hrs, F-9 (98.89%) in 12 hrs. respectively, the rate of drug release was optimized in formulation F-9 (i.e. 98.89%) up to 12 hrs and slower in F-7 formulation (i.e. 92.83%). This result shown that as the proportion polymer concentration increased, the overall time of release of the drug from the matrix tablet was also increased (release retarding). Appears to be suitable for use as a release retardant in the formulating sustained release matrix tablets because of its compatibility, good swelling, good flow properties and drug release characteristics.

The addition of polymer like Orange peel pectin in formulation of F-10 to F-12, it shows the release rate of drug is increased as the polymer concentration increased but the overall time of the drug release is reduced in F-10 formulation 98.23% at 8 hrs , F-11 formulation 97.06% at 9 hrs and F-12 formulation shows that 98.12% at 10 hrs drug release at 10 hrs. The n values obtained from Korsmeyer Peppas plots range from (0.741 to 1.356) indicate that mechanism of release of formulations F-1 to F-12 was Anomalous (non- Fickian) diffusion.

Scanning Electron Microscopy

SEM photomicrographs of tablet surface at different time intervals, indicates the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Lornoxicam from formulated matrix tablets.

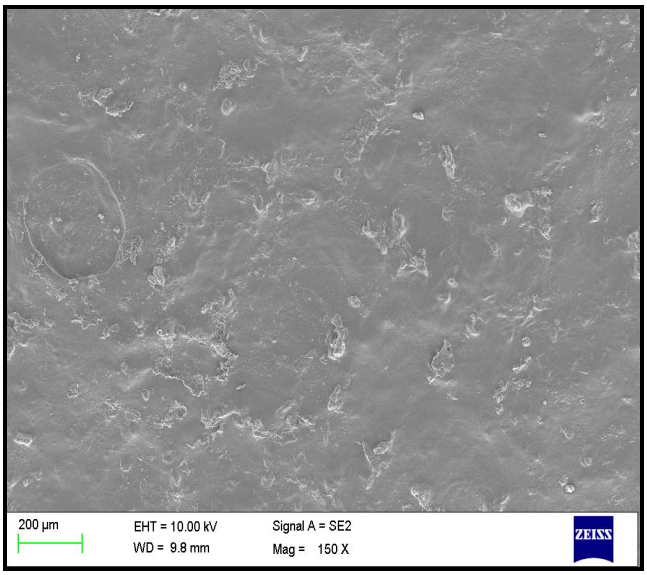

Figure 11 (a): 2nd hrs

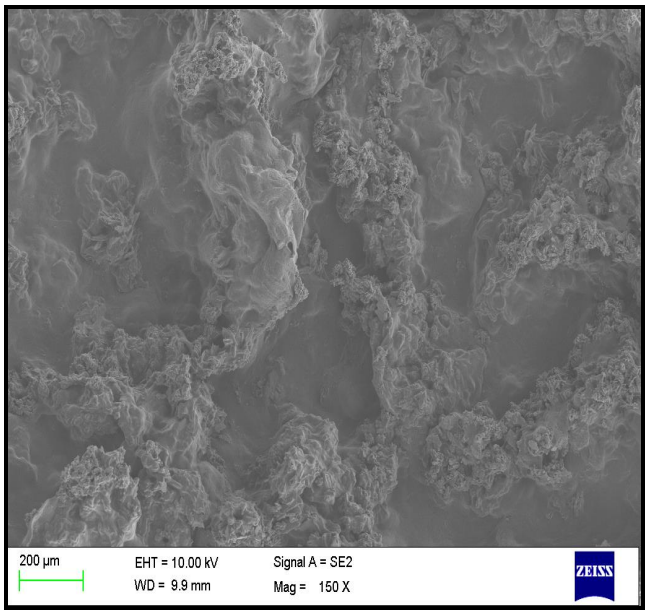

Figure 11 (b): 6th hrs

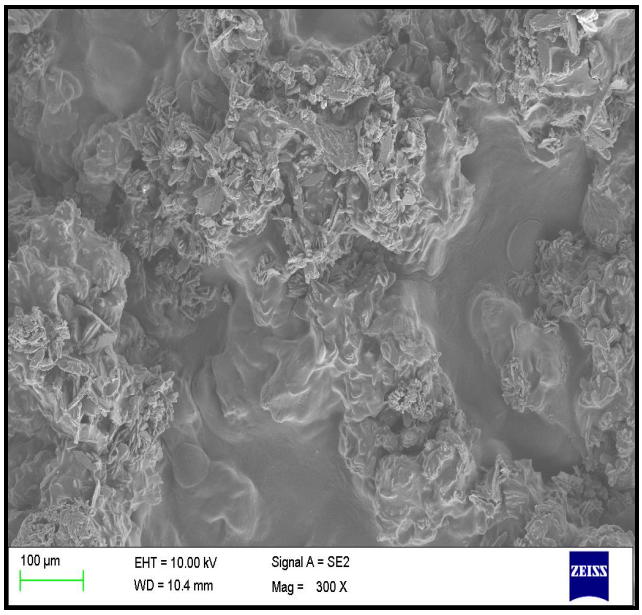

Figure 11 (c): 12th hrs

Table 4: Evaluation of Pre-Compression Parameters

Formulations	Bulk Density* (g/ml)	Tapped bulk* density (g/ml)	Carr's index (%)	Angle of repose*
F1	0.289 ± 0.002	0.295±0.019	11.34±1.41	27.66±1.42
F2	0.284 ±0.005	0.311 ± 0.012	11.18±0.78	26.62±1.25
F3	0.299 ± 0.006	0.289 ± 0.014	9.71±1.32	27.12±1.12
F4	0.291 ±0.008	0.329 ± 0.014	10.46±1.31	26.58±1.32
F5	0.286 ± 0.006	0.316 ± 0.015	9.49±1.41	28.03±1.86
F6	0.296 ±0.004	0.328 ±0.016	11.5±1.39	27.17±1.61
F7	0.302 ± 0.001	0.325 ± 0.016	8.54±0.75	27.33±1.74
F8	0.266 ± 0.006	0.294 ±0.011	10.20±1.44	26.71±1.14
F9	0.292 ± 0.003	0.326 ± 0.013	10.42±1.36	26.22±1.78
F10	0.286±0.004	0.310±0.016	11.63±1.63	27.20±1.18
F11	0.251 ± 0.005	0.277 ± 0.010	9.38±1.32	26.12±1.42
F12	0.282 ±0.004	0.322 ± 0.017	12.42±1.43	28.37±1.44

*The values represent mean ± SD, n=3.

Table 5: Evaluation of Post -Compression Parameters

Formulation code	Thickness* (mm)	Hardness* (kg/cm^2)	Friability (%)	Drug content (%)
F1	3.55±0.08	6.2±0.09	0.26±0.09	98.99±0.14
F2	3.52±0.12	6.3±0.1	0.26±0.22	99.21±0.16
F3	3.52±0.10	6.6±0.06	0.29±0.10	99.64±0.12
F4	3.58±0.02	5.9±0.18	0.31±0.16	98.23±0.14
F5	3.56±0.08	6.2±0.20	0.30±0.13	99.15±0.29
F6	3.57±0.13	6.4±0.06	0.27±0.116	98.99±0.14
F7	3.56±0.05	6.7±0.11	0.33±0.19	98.92±0.23
F8	3.65±0.04	6.3±0.08	0.25±0.24	98.29±0.13
F9	3.62±0.07	6.6±0.06	0.31±0.10	99.09±0.13
F10	3.58±0.04	6.1±0.15	0.35±0.31	98.58±0.24
F11	3.65±0.05	6.2±0.20	0.30±0.12	99.15±0.19
F12	3.55±0.02	6.1±0.08	0.27±0.12	99.02±0.16

*The values represent mean ± SD, n=3.

Table 6: Correlation coefficients of different mathematical models for formulations F- 1 to F-12

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R^2	Slope n
F1	0.9969	0.8889	0.961	0.9818	0.8897
F2	0.9983	0.7993	0.9816	0.989	1.3569
F3	0.9962	0.81	0.974	0.994	0.9732
F4	0.9925	0.8449	0.9683	0.9918	1.1491
F5	0.9899	0.7329	0.9624	0.9769	1.0726
F6	0.9848	0.8986	0.9238	0.9666	0.8647
F7	0.9936	0.9092	0.9853	0.9962	0.8098
F8	0.9913	0.8684	0.9845	0.9966	0.7417
F9	0.9995	0.8951	0.7147	0.9979	0.9735
F10	0.9991	0.9189	0.9769	0.9987	1.0051
F11	0.9986	0.9119	0.9766	0.998	1.0231
F12	0.9981	0.9119	0.9714	0.996	0.9408

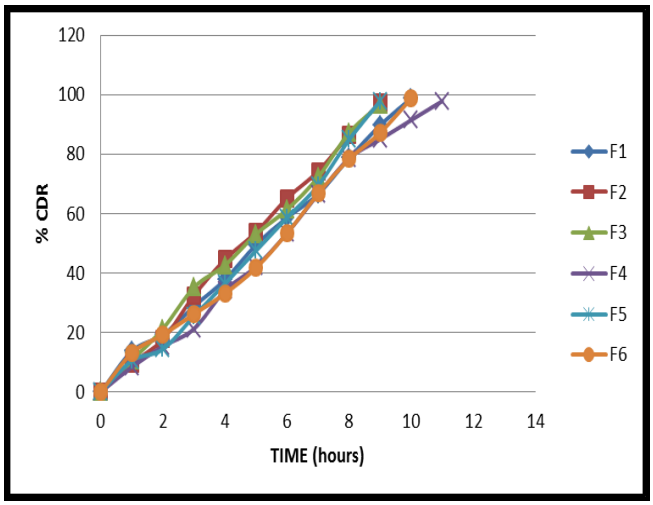

Figure 12: *In Vitro* Dissolution Profile of F-1 to F-6 Formulations

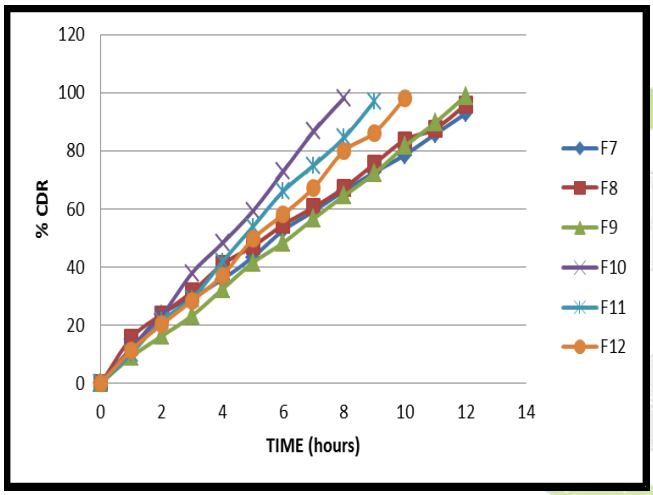

Figure 13: *In Vitro* Dissolution Profile of F-7 to F-12 Formulations

Stability Study

Stability studies were conducted for the optimized formulations as per ICH guidelines. There was not much variation in matrix integrity of the tablets at all the temperature conditions. There was no significant change in drug content, physical stability, hardness, friability and drug release for the selected formulation F-9 after 90 days.

CONCLUSION

Matrix tablet of Lornoxicam can be prepared successfully by using wet granulation method, using Locust bean gum, Okra gum, Xanthan gum, Orange peel pectin, polymers as retardant and by using Lactose as diluent. From the above observations it was concluded that slow and sustained release of Lornoxicam over a period of 12 hours was obtained from matrix tablets F-9. It was found that increase in the polymeric concentration in polymeric ratio increases the drug release.

This can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Lornoxicam tablets.

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