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Implementation of time release technology in formulation development and evaluation of sustained release tablet of Lornoxicam

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ABSTRACT

In present study, the attempts have been made to formulate sustained release tablets of lornoxicam by direct compression method. Based on viscosity grades different proportions of hydrophilic polymers (HPMC K4M, HPMC K15M, HPMC K100M) are used for preparation of lornoxicam sustained release matrix tablet. The drug excipient mixtures were subjected to preformulation studies comprising of micromeritic properties. The tablets were subjected to various studies like as physicochemical studies, in vitro drug release, kinetic studies, etc. FTIR studies shown there was no interaction between drug and polymers. The physicochemical properties of tablets were found within the limits. Lornoxicam is a first generation analgesic, inflammatory & antipyretic agent used in relieving symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute sciatica and low back pain. From developed formulations batch F1 have shown zero order drug release behavior and prolong drug release over a period of 12 h which was deemed as suitable and optimum formulation for sustained drug delivery. Results of the present study indicated the suitability of the low viscous polymer in the proportion of (drug:polymer) 1:1 in the preparation of sustained release formulation of lornoxicam.

1. Introduction

Lornoxicam belongs to Non-Steroidal Anti-inflammatory Drug (NSAID) of the oxicam class. It has analgesic, anti-inflammatory and antipyretic properties. Lornoxicam is used as NSAID in relieving symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute sciatica and low back pain. Like other NSAIDs, lornoxicam inhibits prostaglandin biosynthesis by blocking the enzyme cyclooxygenase. Lornoxicam inhibits both isoforms in the same concentration range in the ratio of COX-1 inhibition to COX-2 inhibition is 1:1. Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract. Maximum plasma concentrations are achieved after approximately 1 to 2 hours. Food protracts the average time to maximum concentration from 1.5 to about 2.3 hours and can reduce the area under the curve (AUC) by up to 20%. The absolute bioavailability of lornoxicam is 90-100%. Mostly lornoxicam is found in the plasma in unchanged form as hydroxylated metabolite [1]. Lornoxicam sustained release formulation is needed because of its short biological half-life of 3.0-5.0 h and also to minimize the gastrointestinal disturbances such as peptic ulceration. Due to very poor solubility in acidic conditions lornoxicam remains in contact with the stomach wall for a long period which might lead to local irritation and ulceration [2, 3].

The oral route is the route most often used for administration of drug. Tablets are the most popular oral formulation available in the market and are preferred by patient and physicians. In long term therapy for the treatment of chronic disease condition, conventional formulations are required to be administered in multiple dosages and therefore have several disadvantages [4, 5]. Implementation of time release technology in formulation and development of sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenances of steady drug plasma concentration. The use of polymers in controlling the release of drugs

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has become an important tool in the formulation of pharmaceutical dosage forms. Sustained release can be achieved by formulating drug as matrix devices using HPMC, sodium CMC and other swellable polymer. Also the matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior. Hydrophilic polymers with high gelling capacity are of particular interest in the field of time release technology [6, 7]. On coming in contact with aqueous medium they hydrate at solid liquid interface and form a viscous layer which retards the release of the drug [8, 9].

Sustained release preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action [10].

Numerous strategies are available for the design and development of modified release drug delivery formulations. Conventional oral dosage forms frequently produce fluctuations in drug plasma level which often exceed safe therapeutic level or suddenly fall below the minimum effective level. Such effects are usually dependent on biological half-life, frequency of dose administration, and release behavior. Most of patients can benefit from modified time release technology dependent formulations intended for chronic administration by maintaining plasma levels within a safe and effective range [11, 12].

In the present work attempts have been made to formulate sustained release tablet of lornoxicam using different grads of polymers like HPMC K4M, HPMC K15M and HPMC K100M by direct compression method. In this work physicochemical characterization, formulation & in vitro evaluation of sustained release tablet of lornoxicam was done.

2. Materials and methods

2.1 *Materials*

Lornoxicam was kindly provided by Cipla Pvt. Ltd. Goa as a gift sample. HPMC K4M, HPMC K15M and HPMC K100M were supplied by Loba Chemie Pvt. Ltd. India. Microcrystalline cellulose and magnesium stearate were also supplied by Loba Chemie Pvt. Ltd. India.

2.2 *Methods*

2.2.1 *Preparation of sustained release Lornoxicam tablet*

Direct compression method was used for preparation of Lornoxicam tablets. The weight of Lornoxicam was taken as 8 mg/tablet in all prepared formulation batches. HPMC was used as polymeric material for preparation of matrix tablets. So different grades of HPMC were chosen depending on their viscosity as HPMC K4M, HPMC K15M, HPMC K100M. Magnesium stearate at concentration of 2% by weight of tablet was used as a lubricant. Micro crystalline cellulose (MCC) was selected as tablet diluent to maintain the constant weight of tablet as 200 mg. The powder mixtures of all above mentioned ingredients were thoroughly mixed, sieved through the 60# sieve, lubricated and then compressed into tablets using multi rotary tablet machine (Type: Patel services Pvt. ltd, Ahmadabad) [13]. Each matrix tablet contained 8 mg of lornoxicam and other pharmaceutical ingredients are as shown in (Table 1).

Table 1: Different formulation batches of lornoxicam matrix sustain release tablet

Sr. No.	Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	**Lornoxicam**	8	8	8	8	8	8	8	8	8
2	**HPMC K_4**	8	16	24	-	-	-	-	-	-
3	**HPMC K_{15}**	-	-	-	8	16	24	-	-	-
4	**HPMC K_{100}**	-	-	-	-	-	-	8	16	24
5	**MCC**	180	172	164	180	172	164	180	172	164
6	**Magnesium stearate**	4	4	4	4	4	4	4	4	4
	Total weight	200	200	200	200	200	200	200	200	200

* All values are in ‘mg’.

2.2.2 *Evaluation of preformulation parameters*

Angle of Repose

The angle of repose for the power blend of each formulation was determination by the fixed funnel method. The power blends were poured through the funnel separately until the apex of the conical pile so formed just touches the tip of the funnel. This forms a pile of power on the paper. The angle of repose was calculated by substituting the values of the base radius and pile height in the following equation [14].

$\tan \theta = h/r$ (1)

where, h is the height of heap of pile and r is radius of base of pile.

Bulk Density

Bulk density was determined by placing the power blend in a measuring cylinder and the total volume was measured and total weight of power was measured. Bulk density was calculated by using formula [14].

Bulk density = weight of powder/ Bulk volume (2)

Tapped Density

The tapped density was obtained by dividing the mass of a power by the tapped volume in cm^3. The sample of suitable amount of power from each formulation was carefully introduced into a 10 mL graduated cylinder. The cylinder was dropped onto a hard wooden surface under its own weight form height of 1 inch. The tapping was continued until no further change in volume was noted it was calculated by using equation given below [15].

$Dt = M/V_b$ (3)

where, m is weight of powder taken and V_b is tapped volume.

Carr's Compressibility Index

Carr's compressibility index (CCI) was calculated by using values of bulk density and tapped density as given below [16]:

%CCI = [(TD-BD)*100]/TD .. (4)

Hausner's Ratio

Hausner's ratio is a number that is correlated to the flowability of powder and powder blend. It was calculated using equation given below [14].

Hausner's ratio = TD / BD

(5)

Evaluation of sustained release matrix tablet of lornoxicam
Appearance

The general appearance of a tablet size, shape, color, presence, or absence of an odor, taste, surface texture, physical flows and consistency and legibility of any identifying markings were assessed [15].

Thickness

The thickness of the tablet was measured by using digital Vernier Calliper. A total of 20 tablets from each batch were randomly selected and thickness was measured [15].

Weight variation test

Accurately 20 tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighted individually and the weight variation was determined as per specifications [15, 16].

Hardness

The resistance of tablets to break under conditions of storage, transportation and handling before usage depends on hardness of tablets which was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2 [17-19].

Friability

Friability of the tablet was determined using friability tester made by Electro Lab (India) rotated at 25rpm for 4 min. Percentage friability was determined by following equation [20].

% Friability = [(Initial weight - Final weight)/ Initial weight] x 100 …….. (6)

Drug content uniformity

For the content uniformity test, ten tablets were weighed and pulverized to a fine power, a quantity of power equivalent to 8 mg of lornoxicam was dissolved in 10 mL of 0.1 N NaOH and volume was made up to 100 mL with pH 6.8 phosphate buffer. Suitable concentration of lornoxicam was prepared with appropriate dilutions and determined by measuring the absorbance at 379 nm (using UV-vis spectrophotometer) against pH 6.8 phosphate buffer as a blank. The mean percent drug content was calculated as an average of three determinations [21].

In vitro drug release study

In vitro dissolution studies of the promising sustained release tablets of lornoxicam and commercial conventional tablet formulations were performed according to USP type–II dissolution apparatus employing a paddle stirrer at 50 rpm. Dissolution test was carried out for a period of 12 h using 0.1N HCl (pH 1.2) for first 2 h and then the pH is adjusted to 6.8 for the rest of the period. The temperature of the dissolution medium is maintained at 37±0.5°C.

Aliquots of the dissolution medium (1mL) were withdrawn at specific time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12h) and replaced immediately with equal volume of fresh medium. The samples were filtered through Whatman filter paper and analyzed for drug content by measuring the absorbance at 379 nm. Drug concentration was calculated and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three [22, 23].

3. Results and Discussion

3.1 *Fourier Transform Infra-Red spectroscopy of lornoxicam and optimized formulation*

The IR spectrum of lornoxicam exhibited distinctive peaks at 1529 cm^{-1} due to aromatic rings, 1143 cm^{-1} owing to C-O stretching of the carboxyl ion and at 1375 cm^{-1} because of O-H (Aromatic) as shown in Fig.1.

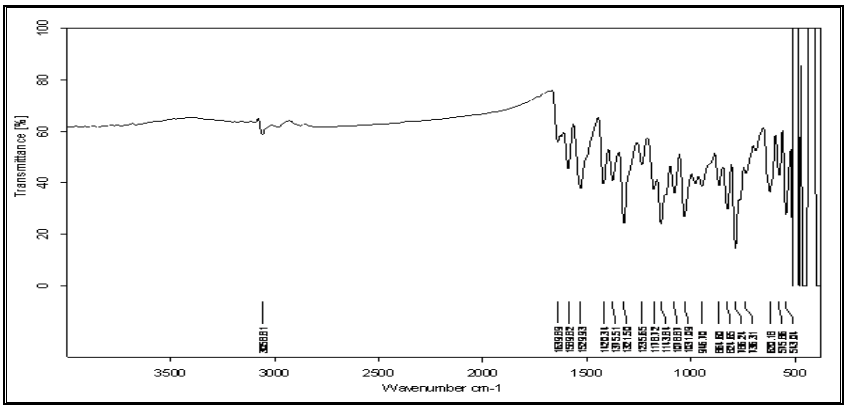

Figure 1: FTIR of lornoxicam

The IR spectrum of optimized lornoxicam matrix sustained release tablet are as shown in Fig.2.

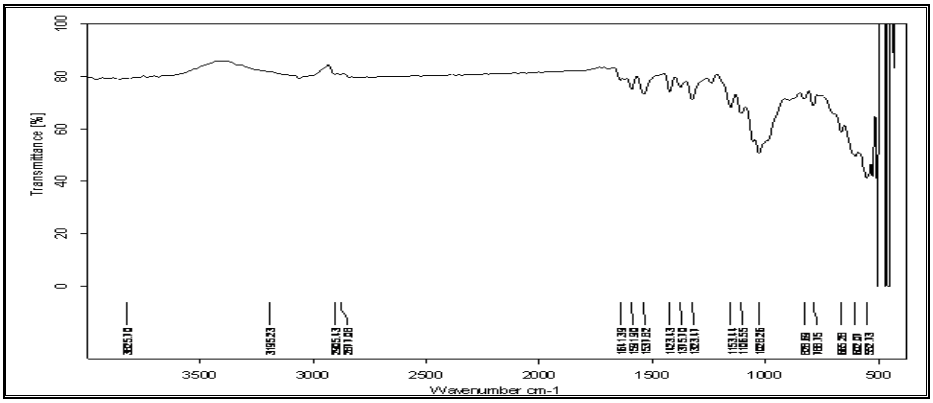

Figure 2: FTIR of optimized lornoxicam sustained release formulation (Batch F1)

Characteristic peaks of lornoxicam and optimized formulation (Batch F1) are as shown in Table 2.

Table 2: Characteristic peaks of pure drug lornoxicam and optimized formulation

Sr. No.	Pure drug lornoxicam (Wave no. cm^{-1})	Optimized formulation (Batch F1) (Wave no. cm^{-1})	Functional Group Associated
1	786.24	788.82	C-Cl
2	1031.09	1106.55	C-C
3	1143.84	1140.40	C-O
4	1375.51	1375.70	O-H
5	1529.93	1537.92	Aromatic Rings
6	3058.81	3020.23	Aromatic Rings

By observing infrared spectrum of the pure drug and optimized formulation, the principal functional peaks of pure drug sample were also observed in the formulation and no any extra peaks was observed. So it can be concluded that drug in formulation is stable and compatibility with excipients is observed.

3.2 *Preformulation study of lornoxicam matrix sustained release tablet*

Preformulation parameters with micromeritic properties for lornoxicam sustained release matrix tablets are as shown in Table 3.

Table 3: Micromeritic properties for lornoxicam sustained release matrix tablets

Formulation code	Angle of repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility Index (%)	Hauser's ratio
F1	30.56±0.04	0.421±0.02	0.484±0.04	13.01±0.03	1.14±0.05
F2	32.06±0.02	0.432±0.02	0.5±0.04	13.6±0.02	1.15±0.06
F3	31.94±0.03	0.457±0.03	0.51±90.02	12.01±0.02	1.13±0.04
F4	30.54±0.02	0.444±0.01	0.5±0.01	120.1±0.03	1.12±0.06
F5	30.83±0.01	0.465±0.05	0.53±30.03	12.7±50.01	1.14±0.01
F6	32.88±0.02	0.42±10.04	0.484±0.05	13.02±0.02	1.14±0.03
F7	31.85±0.03	0.5±0.01	0.592±0.03	15.54±0.03	1.18±0.01
F8	30.44±0.02	0.449±0.03	0.533±0.02	15.75±0.01	1.18±0.06
F9	31.00±0.03	0.457±0.01	0.522±0.02	12.45±0.02	1.14±0.04

* All values are expressed as: Mean ± SD, n=3.

For each formulation, blend of drug and excipients were prepared and evaluated for various parameters like angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index. Using the bulk and tapped density data, Hausner's ratio and compressibility index was calculated. The powder blend of all the formulations had Hausner's ratio of 1.18 or less indicating good Flow ability. The compressibility index was found between 12.00 and 15.00 % and the compressibility flow ability correlation data indicated a fairly good flow ability of the blend. The angle of repose (range of 30-31.95), which is below 40° indicating good flow ability [1, 20-22].

3.3 *Physicochemical parameters for sustained release matrix tablet of lornoxicam*

Physicochemical parameters of sustained release matrix tablet of lornoxicam are as shown in Table 4.

Table 4: Post formulation parameters of lornoxicam sustained release matrix tablets

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (kg/cm^2)	4.50±0.29	4.71±0.39	5.10±0.38	4.90±0.27	5.01±0.23	4.49±0.26	5.10±0.39	4.90±0.32	4.70±0.39
Friability (%)	0.40±0.04	0.40±0.01	0.50±0.04	0.46±0.01	0.43±0.02	0.41±0.08	0.44±0.08	0.45±0.04	0.46±0.01
Thickness (mm)	3.90±0.018	3.91±0.019	3.89±0.014	3.91±0.015	3.88±0.016	3.89±0.015	3.87±0.015	3.90±0.019	3.92±0.017
Weight variation (%)	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Drug content	99.12±0.89	99.28 ±1.50	96.63 ±1.89	95.67 ±1.91	97.40 ±2.34	96.10 ±1.78	97.89 ±2.10	98.89 ±1.45	98.10 ±1.76

* All values are expressed as: Mean ± SD, n=3.

Tablets were prepared using direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variations as per pharmaceutical specifications. The hardness of the tablets between 4.4 to 5.1 kg/cm^2. The hardness of the tablet was found to be satisfactory so that the tablet will resist the mechanical shock during transportation and storage. Friability of the tablets was found less than 1 % indicating good mechanical resistance of tablets [24].

3.4 *Uniformity of drug content*

The drug content in all prepared formulations lies in the range of 95.67 ±1.91 to 99.28 ±1.50 as shown in Table 4. Maximum drug content have shown by batch F2 as 99.28 ±1.50 and minimum shown by batch F4 as 95.67 ±1.91. Drug content shown by all formulations meets standards as per official standard specifications [24].

3.5 *In vitro drug release study*

The release of lornoxicam from sustained release marix tablets varied according to the types & proportion of marix forming polymers. The percentage cumulative drug release form all formulations of lornoxicam sustained release matrix tablets are as shown in Table 5.

Table 5 : % Cumulative drug release of lornoxicam formulation batches (F1-F9).

Time (Hour)	F1 % CDR	F2%CDR	F3% CDR	F4% CDR	F5%CDR	F6%CDR	F7%CDR	F8%CDR	F9%CDR
0.5	2.12± 0.31	1.93±0.46	1.80± 0.55	2.08± 0.44	1.75± 0.34	1.58±0.44	2.58±0.44	1.58±0.64	1.19±0.45
1	5.08± 0.32	4.22±0.49	3.78± 0.38	4.82± 0.43	3.78±0.39	3.25± 0.43	3.21± 0.43	2.89±0.34	2.52±0.45
1.5	12.21±0.12	10.5±0.43	8.32± 0.43	10.78±0.44	9.17± 0.44	8.28±0.49	8.78±0.46	7.53± 0.75	6.51±0.34
2	14.03±0.22	13.3±0.46	12.22±0.49	13.57±0.43	10.1±0.45	9.24± 0.46	10.2±0.49	9.22±0.42	8.15± 0.51
3	20.34±0.40	19.2±0.47	18.02±0.43	19.32±0.39	16.2±0.43	14.7±0.43	15.7±0.43	12.2±0.46	10.7±0.51
4	34.22±0.46	33.7±0.26	32.21±0.43	31.42±0.36	29.3±0.41	25.7±0.44	28.3±0.42	25.2±0.53	23.5±0.43
5	45.32±0.29	43.2±0.41	42.00± 0.42	44.53±0.49	42.2±0.45	40.9±0.43	42.7±0.42	40.2±0.34	38.2±0.49
6	50.24±0.46	48.4±0.39	46.28±0.36	49.78±0.23	47.7±0.46	44.7±0.46	45.5±0.44	42.7±0.34	36.2±0.41
7	62.37±0.43	59.3±0.48	56.27±0.49	60.71± 0.33	58.3±0.43	55.7±0.43	54.7±0.48	50.9±0.39	42.7±0.47
8	78.81±0.34	76.7±0.48	74.29±0.46	73.23± 0.46	71.9±0.3	67.5±0.42	68.5±0.51	64.2±0.44	60.8±0.43
9	80.33±0.39	78.9±0.49	76.03±0.49	78.22± 0.48	75.5±0.51	73.7±0.41	70.2±0.50	68.1±0.43	63.2±0.44
10	85.52±0.45	83.2±0.46	82.21±0.38	81.22±0.49	78.6±0.45	74.5±0.43	73.7±0.43	70.1±0.43	66.2±0.41
11	93.22± 0.45	92.7±0.43	90.03±0.44	90.21±0.50	85.8±0.44	83.7±0.41	78.8±0.49	72.8±0.43	69.8±0.44
12	96.70± 0.43	94.2±0.45	92.38±0.41	93.29±0.51	88.2±0.44	86.1±0.41	80.8±0.65	78.7±0.42	75.4±0.45

***** All values are expressed as: Mean ± SD, n=3.

From F1 formulation (drug: HPMC,1:1), the marked percentage drug release was observed up to 8 h with initial burst phase. After 8 h the release rate decreased slightiy & a sustained release pattern was observed for 12 h. The matrix of HPMC controlled the lornoxicam release effictively for 12 h. It was observed that formulation with drug polymer ratio 1:1 (F1, F4, F7) showed high drug release of 96.70 ± 0.43, 93.29 ± 0.51, 80.8 ± 0.65% when compared to 1:2 ratio (F2, F5, F8) which showed drug release as 94.20 ± 0.45, 88.2 ± 0.44, 78.7 ± 0.42 % and those 1:3 ratio (F3, F6, F9) which showed a drug release rates in the range of 92.38 ± 0.41, 86.10 ± 0.41, 75.40 ± 0.45% over a period of 12h . The order of drug release from a selected polymers were fonud to decrease in the following order HPMC H4 M > HPMC K15 M > HPMC K100 M.

Amongst the three grades of polymer used, the tablets prepared with lower viscosity grade i.e HPMC K4M have shown higher drug release as compared to higher viscositiy grade polymer i.e HPMC K15M and HPMC K100M [22].

3.6 *Model fitting for dissolution studies*

From prepared formulation batches, batch F1 showed higher correlation coefficients of 0.991 for zero order relase as compared to other kinetic models. Batch F4 and F7 also showed higher correlation as 0.978 and 0.955 respectively for zero order release over remaining kinetic models. In vitro drug dissoluion profiles for above mentioned formulations are as shown in Fig.3

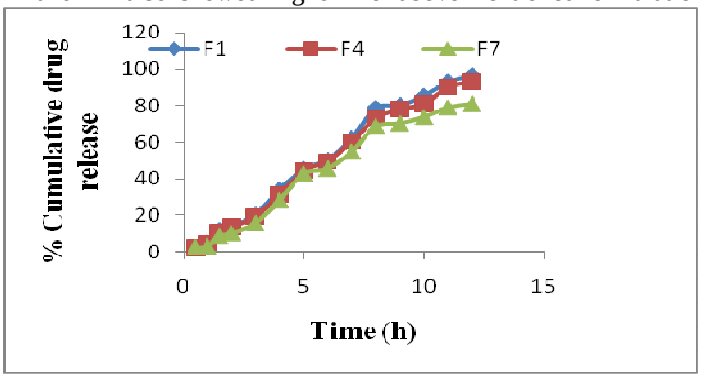

Figure 3: % cumulative drug release of formulations showing zero order drug release

All remaining batches didn't show predominantly zero order release patterns hence not considered as an optimum candidates for sustained drug rlease [25]. But amongst prepared formulations showing zero order drug release behaviours, F1 batch was optimized as it has higher value of correlation coefficient (0.991) and percentage cumlative drug release (96.70±0.43) over a period of 12 h. Hence F1 formulation is considered as an ideal candidate for sustained drug delivery.

4. Conclusion

The study shows that sustained release tablets of lornoxicam can be successfully prepared by using direct compression technique which is selected for better patient compliance and effective therapy. The formulation and evaluation of extended release tablets can be prepared by trial and error method. The prepared tablets have shown satisfactory result for various physiochemical evaluation tests like tablet dimension, hardness, friability, weight variation, content uniformity and in vitro dissolution study. Release rate controlling polymers like HPMC K4M, HPMC K15M, HPMC K100M were used for development of formulations. Polymers were used with varying proportions and depending upon increase in the range of viscosity grade. It has been cleared that as increase in the polymer viscosity have negative correlation with drug release over a period of 12 h by avoiding phase of burst release which is an essential behavior for maintenance of therapeutic drug level along with sustainment in loading dose. From amongst all developed formulations F1 batch was optimized as it has higher value of correlation coefficient for zero order drug release (0.991) and percentage cumlative drug release (96.70±0.43) over a period of 12 h. Hence F1 formulation is considered as an ideal candidate for sustained drug delivery.

Conflict of interest statement: None

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