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Research Article

DESIGN AND EVALUATION OF DRUG RELEASE KINETICS OF MELOXICAM SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

Objective: Meloxicam, a potent non-steroidal anti-inflammatory drug which has short half-life, makes the development of sustained release (SR) forms extremely advantageous. The main objective of this work is formulation development of Meloxicam sustained release matrix tablets that provide complete drug release that starts in the stomach to rapidly alleviate the painful symptoms and continues in the intestine to maintain analgesic effect and to understand the kinetics of drug release by applying mathematical and model-dependent approaches.

Methods: Various formulations were developed by using release rate controlling and gel forming polymers like HPMC (K4M, K15M, K100M) by direct compression method. The in-vitro drug release was studied 7.4 pH phosphate buffer using USP dissolution Apparatus 2 at 100 rpm. Zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer et al. models were used to estimate the kinetics of drug release.

Results: It was concluded that the release followed zero order kinetics, as the correlation coefficient (R2 value) was higher for zero order release, so the drug release mechanism is controlled release.

Keywords: Meloxicam, Sustained release drug delivery system, Matrix tablets, HPMC

INTRODUCTION

Meloxicam (an oxicam derivative), (4-hydroxy-2-methyl-*N*-{5-methyl-2-thiazolyl}-*H*-1,2 benzothiazine-3-caboxamide 1,1-dioxide), is a member of enolic acid group of non-steroidal anti-inflammatory drugs [1,2]. It is generally used in the treatment of rheumatoid arthritis, osteoarthritis and other joint pains [3]. It is a relatively new cyclo-oxygenase inhibitor and this enzyme is responsible for converting arachidonic acid into prostaglandin H2 which is the first step in the synthesis of prostaglandins, the mediators of inflammation. It is well known that there are two COX isoforms, COX-1 & COX-2, and that the extent of NSAID-associated relative inhibition of COX-1 & COX-2 activities varies among the drugs. Commonly administered NSAID's such as flunixin, phenylbutazone and ketoprofen, are relatively non-selective and inhibit both COX-1 andCOX-2 to various degrees. Because COX-1-derived prostaglandins play a role in protecting the gastrointestinal mucosa, NSAIDs that inhibit COX-1 have been associated with adverse events such as gastric and intestinal ulcers, gastrointestinal bleeding, and renal injury. This has led to development of newer NSAIDs such as meloxicam with COX-2 selectivity on the order of 5 to 12 times and firocoxib which are more selective for the inhibition of the COX-2 isoenzyme. Meloxicam has most commonly been used for the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders or for the relief of pain associated with equine colic. Meloxicam is available for oral administration or IV daily administration and can be administered once daily for periods up to 14 days.

In order to investigate the mode of release from delayed release tablet, the release data were analyzed using following mathematical models: Zero-order kinetic (Equation 1); First-order kinetic (equation2); Higuchi equation (square root of time equation, equation 3) [4]; and Peppas equation (equation 4) [5].

Eq.1. $Q = k_0 t$

Eq.2. $\ln (100 - Q) = \ln (Q_0) - k_1 t$

Eq.3. $Q = k_H t^{1/2}$

Eq.4. $\text{Log } (Q/100) = k_p t^n$

In equations Q, the percent of drug released is at time t, Q_0, the percent of drug remaining to release and k_0, k_1 and k_H are the coefficients of the equations. K_p is constant incorporating structural and geometric characteristics of the release device, and n is the Release exponent indicative of the mechanism of release.

MATERIALS AND METHODS

Materials

Meloxicam was a gift sample from M/s Natco Pharma, Hyderabad. Hydroxy propyl methyl cellulose (K4M, K15M, K100M) was obtained as gift samples from Colorcon Asia Pvt. Ltd, Micro-crystalline cellulose was obtained as gift sample from Signet Chemical Corporation Pvt. Ltd, Mumbai. Magnesium stearate was purchased from Yarrow-Chem Products; Dombivli.

Methods

Formulation of Meloxicam SR Matrix Tablets

Matrix tablets of Meloxicam with other excipients were prepared by direct compression. The weight of Meloxicam was kept constant in all the prepared tablets at 7.5 mg/tablet. Different viscosity grades of HPMC namely HPMC K4M, HPMC K15M, HPMC K100M were chosen as polymeric matrix materials. Micro crystalline cellulose (MCC) was selected as tablet diluent for increasing the compressibility and flowability of the ingredients, to maintain the tablets at constant weight 120 mg. Magnesium stearate was used as a lubricant at concentration of 2% by weight of tablet. To make powder mixtures, the drug, polymer and MCC were thoroughly mixed for 30 min by means of pestle and mortar. This powder mixture was then lubricated with magnesium stearate then compressed into tablets in 6 mm rotary tablet punching machine. The force of compression was adjusted so that hardness of all the prepared tablets ranges from 5.5-6.5 kg/cm. The detailed compositions of the prepared matrix tablets formulations are given in (Table 1).

Evaluation

Evaluation of Granules

Angle of Repose: The angle of repose of powdered gum was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The Diameter of the powder cone was

measured and angle of repose was calculated using the following equation [6]

$$\theta = \tan^{-1} (h/r)$$

Where h and r are the height and radius of the powder pile respectively

Bulk Density*:* Both bulk density (BD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. BD and TBD were calculated using the following formulas [7]

BD = Weight of the Powder/Volume of the packing

TBD = Weight of the powder /Tapped volume of the packing

Compressibility Index/ Carr's Index: The flow property was also determined by measuring the compressibility index. It is an important measure that can be obtained from the bulk and tapped densities. According to the theory, the less compressible materials are more flowable. A material having values of less than 20 to 30% is defined as the free flowing material. Based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula [8]

Compressibility Index = Tap density – Bulk density/Tap density x 100

Table 1: Composition of Meloxicam SR Matrix Tablets

Formulation Code	Drug (mg)	Polymer (HPMC) (mg)			Micro Crystalline Cellulose (mg)	Magnesium Steareate (mg)
		K4M	K15M	K100M		
F1	7.5	7.5	-	-	102.6	2.4
F2	7.5	15	-	-	95.1	2.4
F3	7.5	22.5	-	-	87.6	2.4
F4	7.5	-	7.5	-	102.6	2.4
F5	7.5	-	15	-	95.1	2.4
F6	7.5	-	22.5	-	87.6	2.4
F7	7.5	-	-	7.5	102.6	2.4
F8	7.5	-	-	15	95.1	2.4
F9	7.5	-	-	22.5	87.6	2.4

Table 2: Precompression Parameters of Meloxicam SR Matrix Tablets

Formulation code	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)
F1	28.26	0.335	0.413	18.68
F2	28.17	0.331	0.403	17.86
F3	28.93	0.313	0.383	18.25
F4	26.50	0.342	0.420	18.53
F5	28.28	0.305	0.367	16.78
F6	26.20	0.306	0.372	17.73
F7	27.67	0.335	0.418	19.84
F8	29.30	0.330	0.403	17.93
F9	27.16	0.330	0.398	16.87

Evaluation of Tablets

The formulated tablets were evaluated for the following physicochemical characteristics.

General Appearance

The formulated tablets were assessed for its general appearance.

Weight Variation

Formulated matrix tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not. The results are listed in the Table 2.

Friability

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions, after which the tablets were reweighed. The percentage friability was calculated. The results are listed in the Table 2.

Hardness

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The results are listed in the Table 2.

Drug Content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 20mg of Meloxicam was dissolved in 100ml of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 273nm using UV-Visible spectrophotometer (UV 160 Shimadzu, Japan).

Invitro Dissolution Students of Tablets

Procedure

In-vitro drug release studies of all the formulations were carried out using tablet dissolution test apparatus (USP XXII type II Electro lab, Mumbai, India) at 50 rpm. Phosphate buffer pH7.4 was used as the dissolution media with temperature maintained at 37±1ºC. Samples were withdrawn at different intervals (The withdrawn samples replaced with the same volume pre-warmed with fresh dissolution medium); filtered, suitable dilutions were done with distilled water and analyzed spectrophotometrically at 363 nm using Elico UV-Visible spectrophotometer (Labindia, Mumbai, India).

Table 3: Post Compression Parameters of Meloxicam SR Matrix Tablets

Formulation	Weight variation (gm)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Assay (%)
F1	120.01 + 0.075	3.34 + 0.051	6.4	0.46	98.97
F2	119.98 + 0.088	3.21 + 0.054	6.2	0.59	97.28
F3	120.10 + 0.082	3.16 + 0.030	5.9	0.70	99.31
F4	119.83 + 0.077	3.10 + 0.043	6.3	0.53	96.16
F5	120.10 + 0.087	3.08 + 0.023	6.2	0.60	96.37
F6	119.93 + 0.092	3.27 + 0.019	6.0	0.44	98.52
F7	119.89 + 1.03	3.53 + 0.043	6.5	0.48	98.74
F8	120.04 + 0.097	3.25 + 0.032	6.3	0.62	99.53
F9	120.09 + 1.10	3.15 + 0.074	6.1	0.60	98.29

Table 4: Dissolution Data of Meloxicam SR Matrix Tablets

Time (hrs)	Percent Drug Dissolved								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	8.76	5.83	5.07	4.87	3.82	3.79	4.51	3.79	3.02
2	16.32	12.01	10.38	15.13	11.85	8.15	12.71	7.84	7.24
3	30.14	26.32	21.83	26.39	20.17	20.11	21.32	15.53	13.85
4	42.83	39.19	34.76	38.97	34.19	29.25	32.43	27.83	23.91
5	55.08	50.34	44.12	49.67	44.71	37.31	43.78	36.03	32.89
6	64.22	58.93	50.21	56.81	53.58	47.84	51.27	45.87	42.76
7	74.89	69.13	60.86	68.63	65.32	59.72	58.02	56.43	52.67
8	84.77	76.32	68.58	75.93	72.81	68.52	67.24	64.31	60.80
9	90.39	84.73	73.01	82.18	77.29	73.05	71.17	68.71	64.93
10	94.87	88.09	77.84	87.09	81.04	76.20	75.84	72.14	68.18
11	96.72	91.03	81.29	89.23	83.17	78.55	80.39	74.67	70.75
12	98.32	94.09	84.72	91.12	85.08	81.49	84.89	77.93	72.76

Drug Release Kinetics

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al*., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$C = k_0 t$ (1)

Where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$LogC = LogC_o - kt / 2.303$ (2)

Where, C0 is the initial concentration of drug and K is first order constant and t is the time [9]

$Q = Kt^{1/2}$ (3)

Where, K is the constant reflecting the design variables of the system. Hence drug release rate is proportional to the reciprocal of the square root of time. [4]

$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$ (4)

Where, Qt is the amount of drug released in time t, Q0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation as the cube root of the percentage of drug remaining in the matrix vs time. [10]

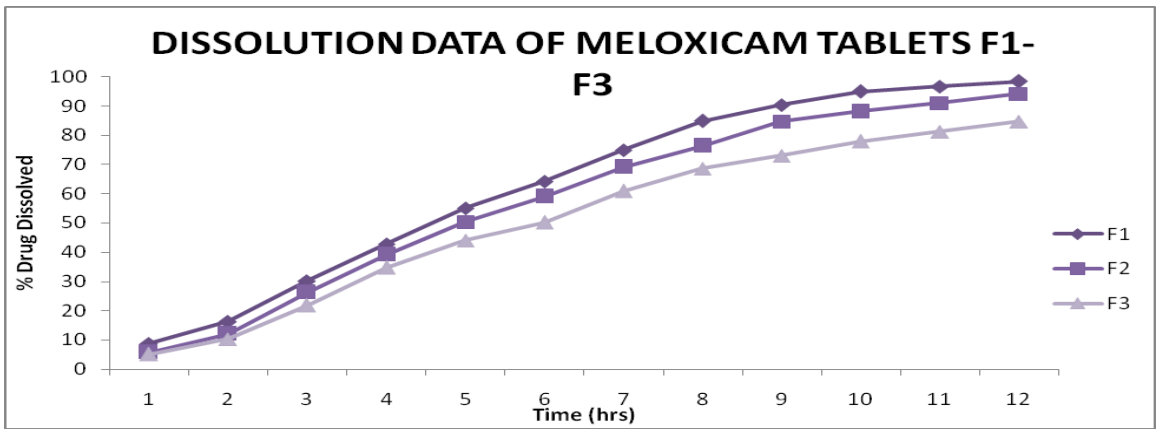
The following plots were made: *cumulative % drug release vs. time* (zero order kinetic model); *log cumulative of % drug remaining vs. time* (first order kinetic model); cumulative *% drug release vs. square root of time* (Higuchi model) *log cumulative % drug release vs. log time* (Korsmeyer model) and *cube root of drug % remaining in matrix vs. time* (Hixson-Crowell cube root law).

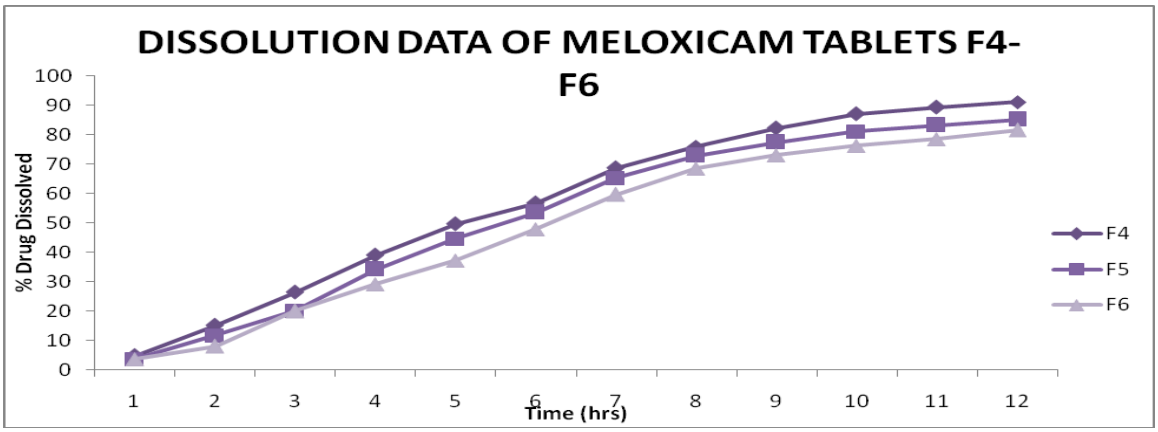
Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model

$Mt/M\infty = Kt^n$ (5)

Where Mt/M∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices.





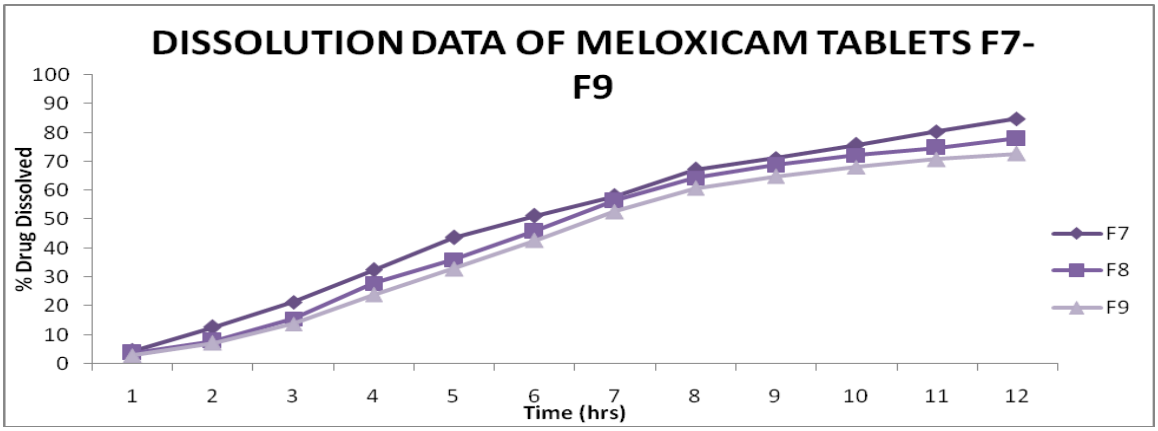


Fig. 1: Dissolution Data of Meloxicam SR Matrix Tablets

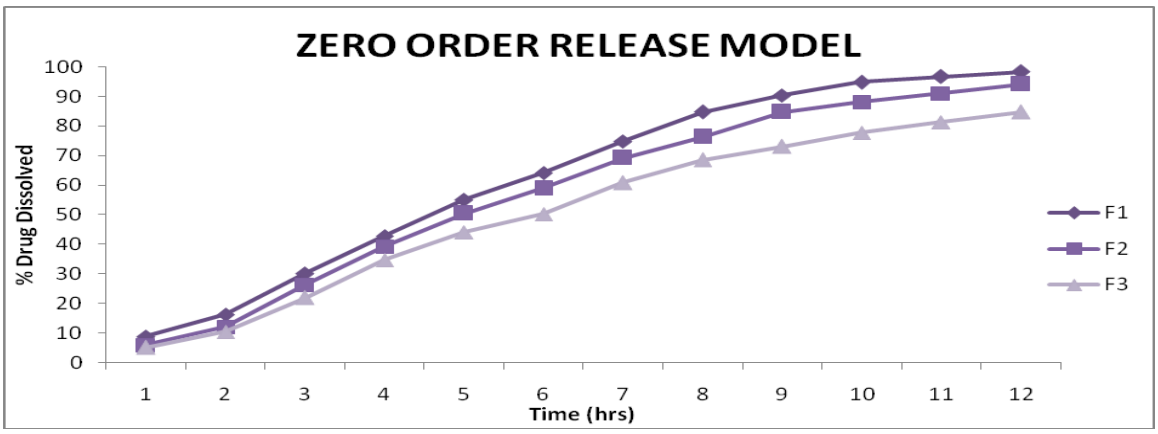
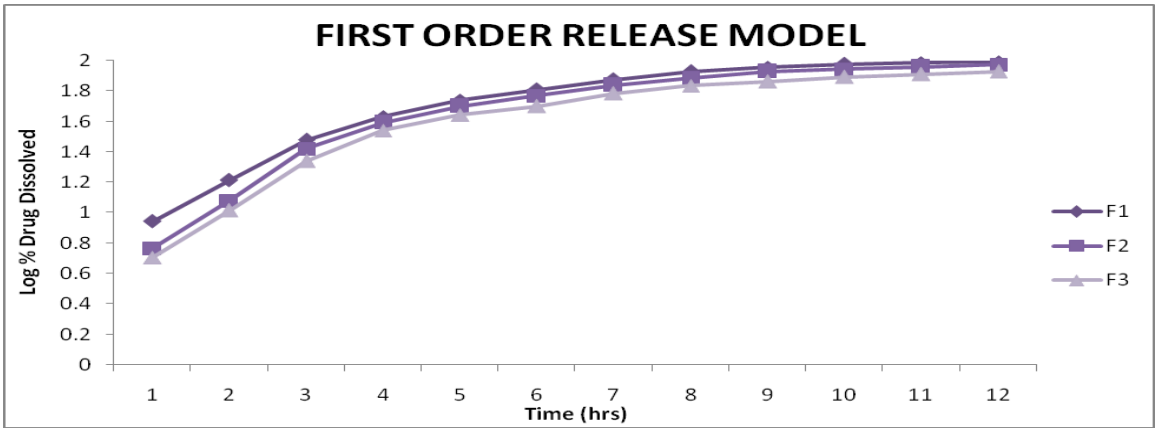
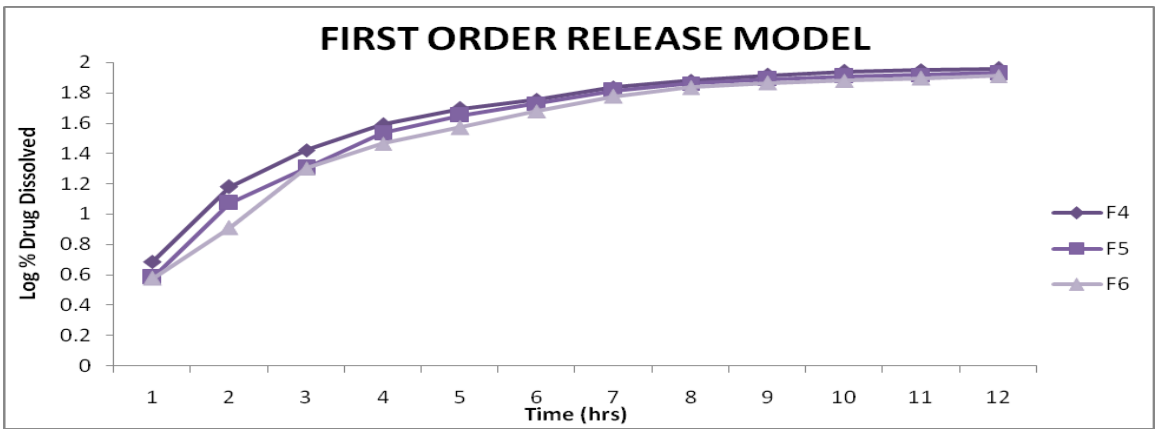


Fig. 2: Zero Order Release Model of Meloxicam SR Matrix Formulation





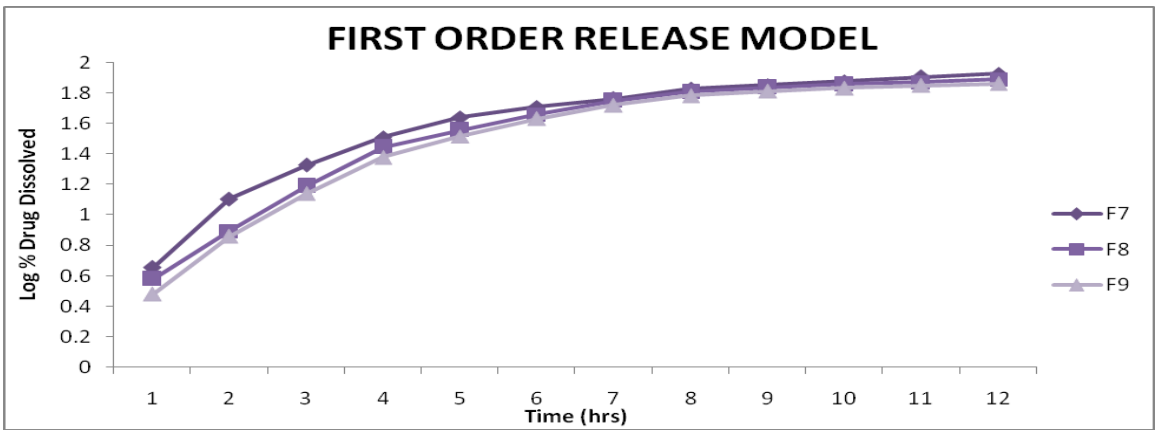


Fig. 3: First Order Release Model of Meloxicam SR Matrix Formulation

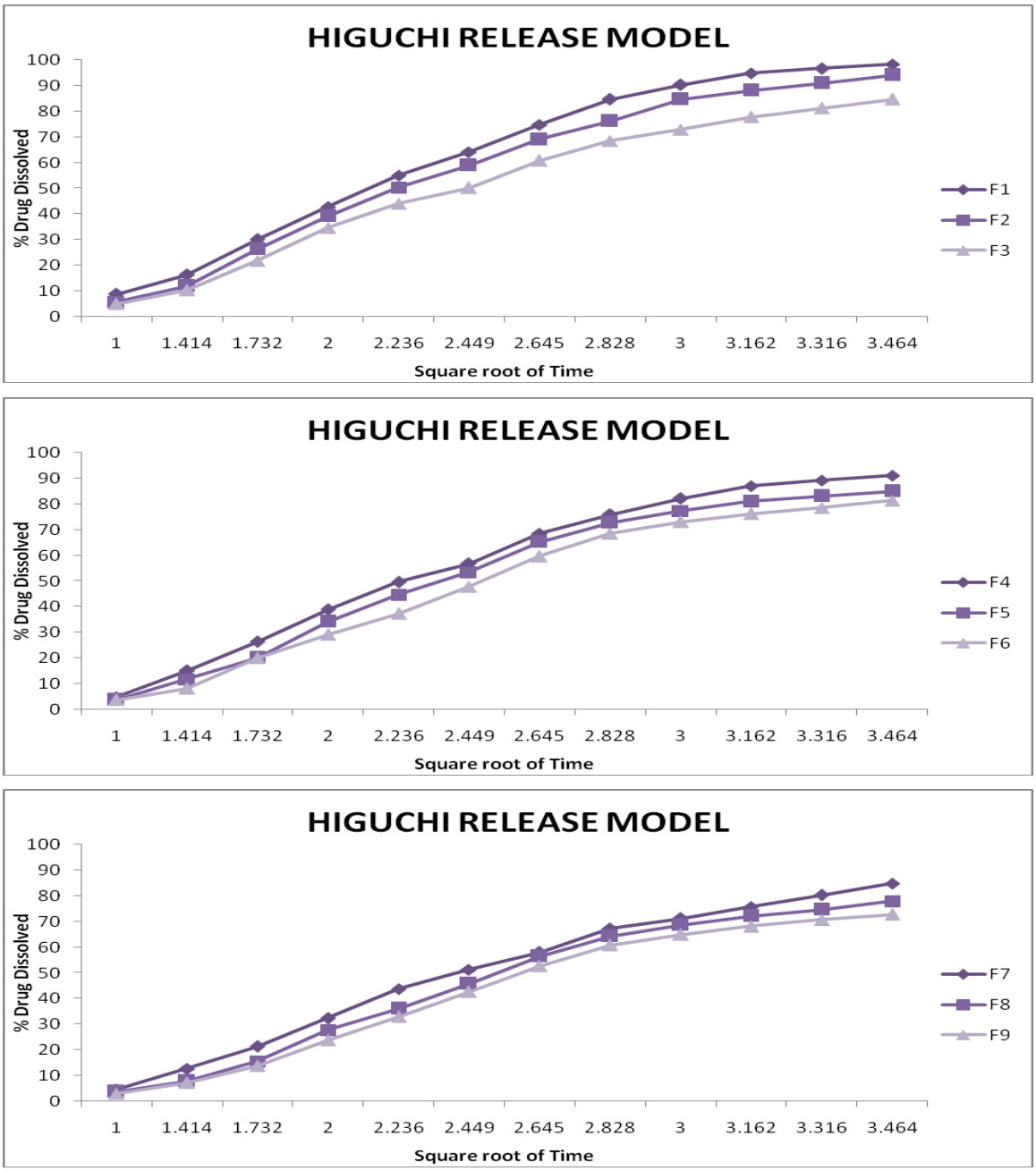
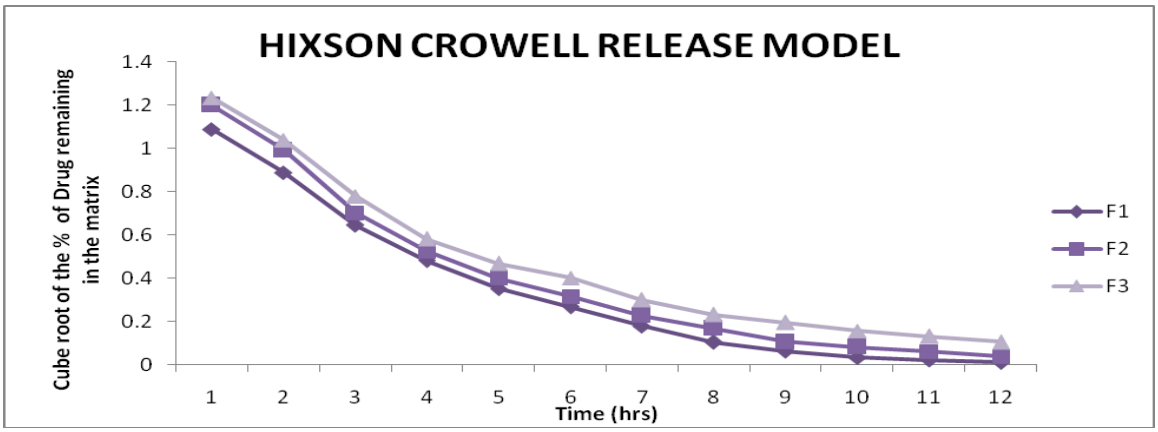


Fig. 4: Higuchi Release Model of Meloxicam SR Matrix Formulation



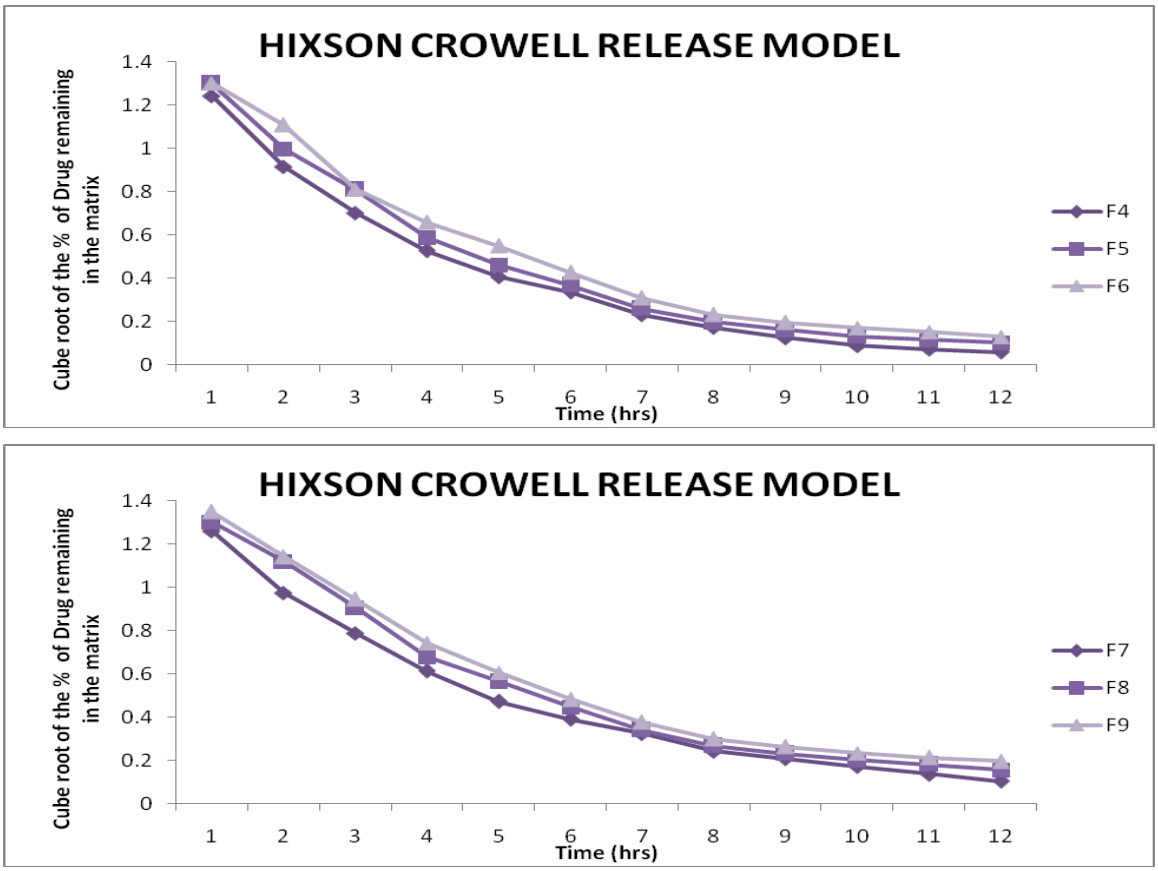
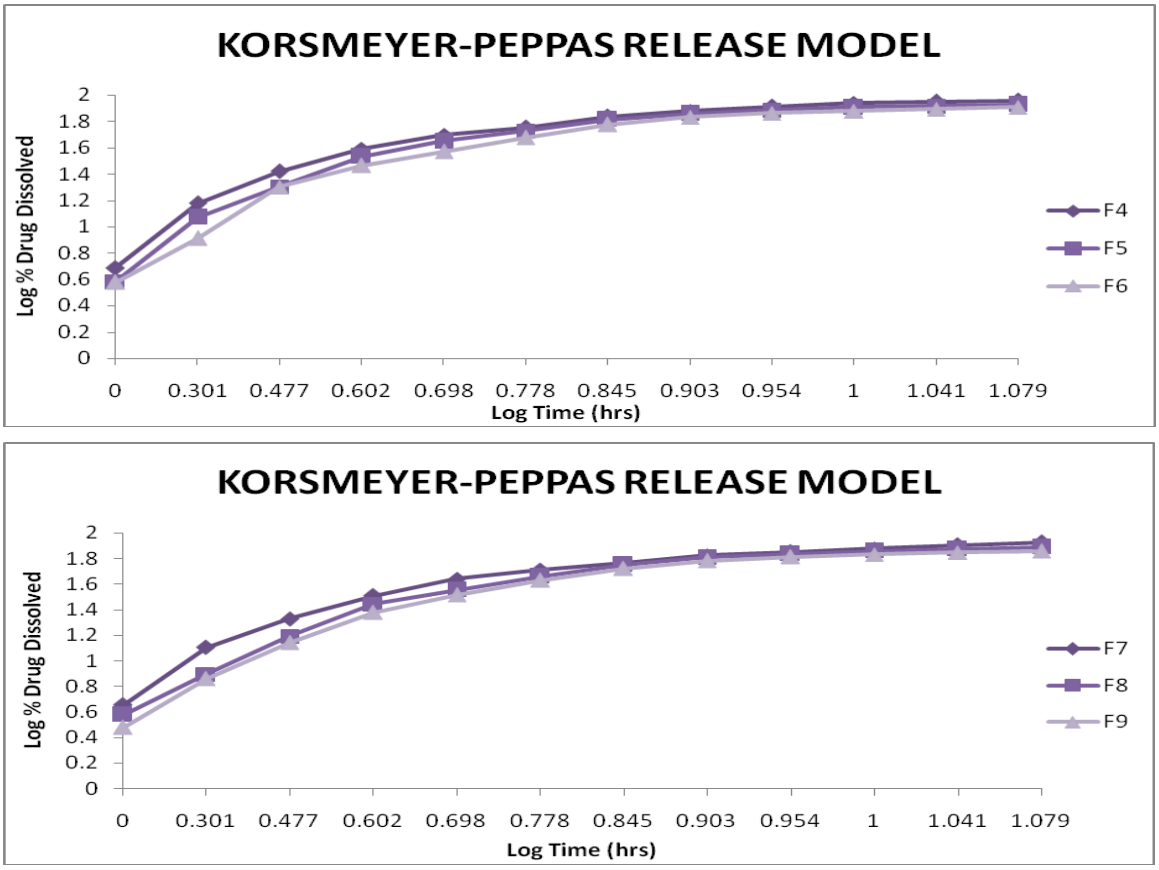


Fig. 5: Hixson-Crowell Release Model of Meloxicam SR Matrix Formulation



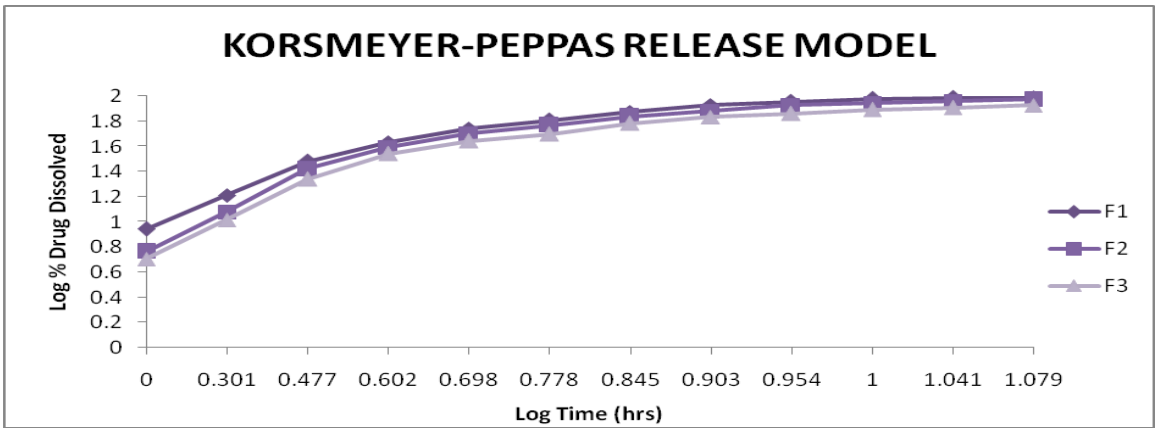


Fig. 6: Koresmeyer- Peppas Release Model of Meloxicam SR Matrix Formulation

Table 5: Diffusion exponent and solute release mechanism for cylindrical shape [11]

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

RESULTS & DISCUSSION

In the present study, Meloxicam matrix tablets were prepared by using HPMC (K4M, K15M, K100M) as a drug retardant polymer. A total number of nine formulations were prepared by direct compression technique. The pre formulation studies such as bulk density, tapped density, angle of repose and carr's index evaluated were found to be within prescribed limits and indicated good free flowing property. The data obtained from physicochemical parameters such as hardness, friability, weight variation, drug content and *in vitro* drug dissolution are shown in (Table 4&5).

Pre-Formulation Evaluation Studies

Development of Calibration Curve of Meloxicam

Accurately weighed 10 mg of Meloxicam was transferred into 10 ml volumetric flask and dissolved in small quantity of distilled water and diluted up to the mark with distilled water to give a stock solution 1000 µg/ml. Further dilutions were made from 50 to 250 µg /ml with distilled water and the absorbance was measured at 345 nm. The scanning of the drug solution in the UV range showed maximum absorbance at 345 nm and hence, the calibration curve was developed at this wavelength.

Table 6: Caliberation Curve of Meloxicam

Concentration (µg/ml)	Absorbance
50	0.16
100	0.33
150	0.49
200	0.66
250	0.83

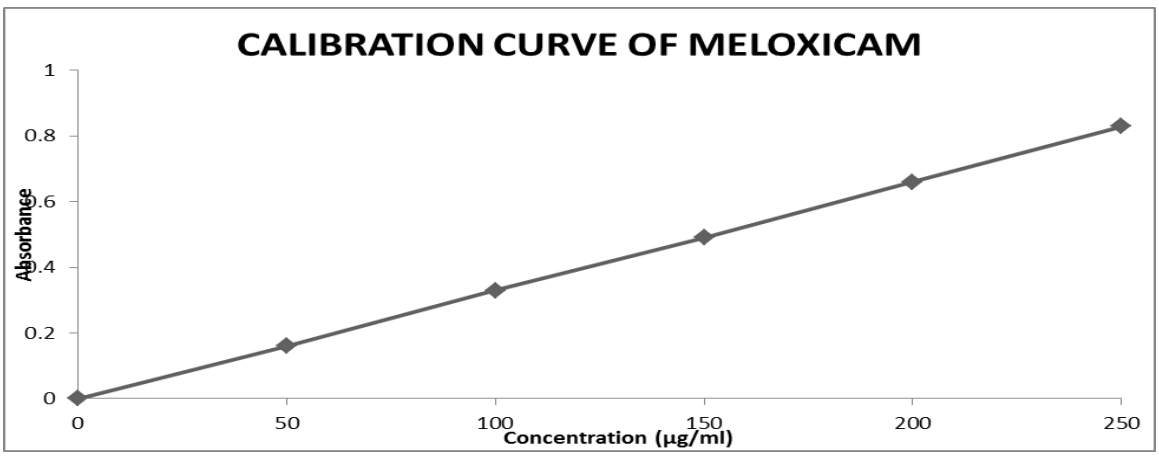


Fig. 7: Calibration Curve of Meloxicam

Formulation Studies

Various formulations of sustained release matrix tablets were developed for Meloxicam by using selected polymers like HPMC K4M, HPMC K15M, HPMC K100M. Microcrystalline cellulose was used as filler and magnesium stearate was used as lubricants. Various formulations of sustained release matrix tablets were prepared by direct compression technique using 6 mm flat punches to an average weight of 120 mg.

Micromeritic Properties

Angle of repose

The results of angle of repose were ranged between 26.20° to 29.30° (Table 4) which indicates good flow properties of powder.

Compressibility index

The compressibility index values were found to be in the range of 16.78% to 19.84% (Table 4). These findings indicated that the powder mixture of all batches of formulation exhibited good flow characters and hence, were suitable for direct compression into matrix tablets.

Evaluation of Physicochemical Parameters

Tablet Hardness

Hardness of the developed formulations F1 to F9 varied from 5.9 to 6.5kg/cm2 (Table 7) in all the formulation indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling.

Tablet Thickness

Thickness of the developed formulations F1 to F9 varied from 3.08mm to 3.53mm (Table 7) in all the formulation and the average thickness are within the range of ± 5%. Each sample was analyzed in triplicate.

Friability

The loss in total weight of the tablets due to friability was in the range of 0.44% to 0.70% (Table 7) in all the formulation and the friability value is less than 1% which ensures that formulated tablets were mechanically stable.

Weight variation

The maximum % deviation was found to be ± 1.10% (Table 7) from all the formulations. As none of the formulation showed a deviation of more than ± 7.5% (I.P. limit) for any of the tablets tested, the prepared formulations comply with the weight variation test, thus it fulfils the I.P. requirements [11].

Uniformity of drug content

The drug content in different tablet formulations was highly uniform and in the range of 96.16% to 99.53% (Table 7). The maximum % drug content for all the formulation was found to be 99.53%. The minimum % drug content for all the formulation was found to be 96.16%. It is in the limits specified by IP [11].

In Vitro Drug Dissolution Study

The release of Meloxicam from sustained release matrix tablets varied according to the types and proportion of matrix forming polymers. Ideally, a sustained release tablet should release the required quantity of drug in order to maintain an effective drug plasma concentration. From in vitro drug dissolution profile of Meloxicam matrix tablet, it was found that 98.32% of the drug was released till 12 h from F1 formulation (Drug: HPMC 1:1). The hydrophilic matrix of HPMC controlled the Meloxicam release effectively for 12 h. It was observed that formulation with the drug polymer ratio 1:1 (F1, F4, F7) showed high drug release rates in the range of 98.32% to 84.89% when compared to 1:2 ratio (F2, F5, F8) which showed a drug release rates from 94.09% to 77.93% and those of 1:3 ratio (F3, F6, F9) which showed a drug release rates in the range of 84.72% to 72.76% over a period of 12 h.

The order of drug release from the selected polymers were found to decrease in the following order HPMC K4M > HPMC K15M > HPMC K100M. Among the three grades of polymer used the tablets prepared with lower viscosity grade i.e. HPMC K4M, have shown drug release rate (98.32% to 84.72%) and the higher viscosity grade polymers i.e. HPMC K15M (91.12% to 81.49%) and HPMC K100M (84.89% to 72.76%). But the much difference was not found in the drug release profiles of tablets prepared with HPMC K4M and HPMCK15M.

Kinetics Modeling of Drug Dissolution Profiles

The in vitro release data obtained were fitted into various kinetic models. Correlation coefficients of formulation F1 batch showed higher correlation with zero order plots than higuchi and first order. So, predominant drug release mechanism is controlled release.

Table 7: Correlation Coefficient and Constants of Different Kinetic Models

Code	Zero order		First order		Higuchi equation		Hixson- crowell equation		Koresmeyer peppas equation		
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_m	n
F1	0.9999	3.138	0.9925	0.212	0.9778	1.606	0.9975	0.115	0.9892	0.165	0.544
F2	0.9742	3.3	0.9914	0.234	0.9675	1.469	0.9960	0.131	0.9849	0.157	0.468
F3	0.9784	3.361	0.9952	0.264	0.9631	1.303	0.9984	0.145	0.9870	0.135	0.435
F4	0.9996	3.183	0.9696	0.235	0.9947	1.461	0.9890	0.131	0.9990	0.218	0.525
F5	0.9896	3.306	0.9791	0.268	0.9963	1.282	0.9949	0.147	0.9984	0.204	0.465
F6	0.9860	3.444	0.9880	0.307	0.9433	1.096	0.9928	0.164	0.9806	0.234	0.199
F7	0.9971	3.273	0.9757	0.281	0.9959	1.216	0.9923	0.153	0.9991	0.190	0.482
F8	0.9747	3.456	0.9987	0.319	0.9682	1.043	0.9987	0.169	0.9912	0.191	0.202
F9	0.9829	3.478	0.9942	0.357	0.9796	0.896	0.9975	0.185	0.9978	0.109	0.211

CONCLUSION

The straight line of linear regression analysis indicates zero order of the data yields the equation of best line with R^2 value 0.9999 and the slope of line corresponds to the zero order rate constant was 3.138. The best linearity was found in Higuchi's equation plot (R^2 = 0.9778) indicating the release of drug from matrix as a square root of time dependent process based on Fickian diffusion. The dissolution data was also plotted in accordance with Hixson Crowell cube root law. Applicability of data (R^2 = 0.9975) indicates a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time. According to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxation release are the limits of this phenomenon.

Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxation release is the drug transport mechanism associated with stresses

and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. The value of the release exponent in *Meloxicam* extended release was obtained as 0.544 which follows Anomalous transport ($0.45 < n < 0.89$).

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