Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206 (Online)**
Sch. Acad. J. Pharm., 2015; 4(1): 1-9 **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Formulation and Evaluation of Colon Targeted Oral Drug Delivery System for Meloxicam

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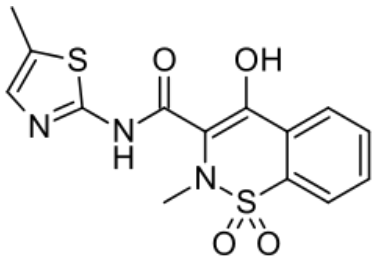
Abstract: In the present research work sustained release matrix formulation of Meloxicam targeted to colon by using various polymers developed. Meloxicam is a selective cyclooxygenase-2 inhibitor with pH-dependent solubility. To achieve pH-independent drug release of meloxicam, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.
Keywords: Colon targeted drug delivery system, Meloxicam, *in vitro* dissolution, release kinetics

INTRODUCTION

The oral route is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and gets absorbed from these regions of the gastrointestinal tract (GIT) depending upon the physicochemical properties of the drug[1]. The rectal route has traditionally been used to administer medicaments in the form of suppositories and enemas to the distal gut, although such formulations rarely succeed in spreading beyond the descending colon. Also, the rectal route is not convenient or acceptable for most patients and hence the oral route is the preferred route of drug administration. However, colonic drug delivery via the oral route is not without its challenges. The colon constitutes the most distal segment of the gastrointestinal tract and so an orally administered formulation must retard drug release in the upper gastrointestinal regions but release the drug promptly on entry into the colon[2,3].

Numerous drug entities based on oral delivery have been successfully commercialized, but many others are not readily available by oral administration, which are incompatible with the physical and/or chemical environments of the upper gastrointestinal tract (GIT) and/or demonstrate poor uptake in the upper GIT [4]. Due to the lack of digestive enzymes, colon is considered as suitable site for the absorption of various drugs. Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes and temporary storage of stools. But now it is accepted as important site for drug delivery[5,6].

Meloxicam is derivative of oxicam and used as a nonsteroidal anti-inflammatory drug (NSAID)[7] with molecular formula $C_{14}H_{13}N_3O_4S_2$ and weight 351.403 g/mol . IUPAC name is 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.



Structure of Meloxicam

There are various strategies for targeting orally administered drugs to the colon are available like

covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, formulation of timed released systems, exploitation of carriers that are degraded specifically by colonic bacteria, bioadhesive systems and osmotic controlled drug delivery systems [8]. There are some prodrugs like sulfasalazine, ipsalazine, balsalazine and olsalazine have been developed that are aimed to deliver 5-amino salicylic acid (5-ASA) for localized chemotherapy of inflammatory bowl disease (IBD)[8].

The aim of the present research work was to develop sustained release matrix formulation of Meloxicam targeted to colon by using various polymers. Meloxicam is a selective cyclooxygenase-2 inhibitor with pH-dependent solubility. To achieve pH-independent drug release of meloxicam, pH modifying agents (buffering agents) were used. Meloxicam matrix tablets containing several retarding agents, were used in order to extend the release of drug over the desired period of time[9].

MATERIALS & METHODS:

The various materials used in our study include Meloxicam, Ethyl cellulose, Eudragit L-100, Eudragit S-100, HPMC K100M, Magnesium Stearate, Micro crystalline cellulose and Talc.

Preformulation parameters:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced.

Angle of Repose:

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. Different ranges of flowability are given in terms of angle of repose. Angle of repose is calculated by formula:

$r = (area/\pi)$ ½

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

Bulk Density:

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another

Tapped density:

After carrying out the procedure as given in the measurement of bulk densitythe cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap= M / V

Compressibility Index:

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

$$\text{Carr's Index (\%)} = \frac{(TBD - LBD)}{TBD} \times 100$$

Hausner ratio:

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The relationship between Hauser's ratio and flow property. Hausner ratio was calculated by using the formula.

Hausner Ratio = Tapped density / Bulk density

Hausner Ratio = V_f/V_0

where V_0 = Initial volume

V_f =Final volume

Formulation development of Tablets:

Colon targeted tablets were prepared by using compression coating technology. Initially internal core tablet containing drug and super disintegrate was formulated. For the prepared core tablet compression coating is done by using various compositions of polymers. Ethyl cellulose, Polymethacrylate polymers such as Eudragit L100 and Eudragit S100 are used as polymers for compression coating.

Tablets are developed in two stages

1. Preparation of core tablet containing drug and super disintegrate.
2. Compression coating of prepared core tablets.

Formulation of core tablet:

The core tablets are formulated by using 15mg of drug molecule, sodium starch glycollate as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively. The composition of core tablet was given in below table 1.

Table 1:Composition of core tablet

Ingredient Name	Quantity (mg)
Meloxicam	15
Sodium starch glycollate	15
Talc	2
Magnesium stearate	2
MCC pH102	28
Total weight	60

Total weight of core tablet was fixed as 60 mg. The tablets are prepared by using 5mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets:

The prepared core tablets were subjected to compression coating by using various compositions of

polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials. The composition of coating layer is given in below table 2:

Table 2: Formulation of various batches of Meloxicam tablets

Ingredient name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (mg)	50	100	150						
Eudragit S100 (mg)				50	100	150			
Eudragit L100 (mg)							50	100	150
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH 102 (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	240	240	240	240	240	240	240	240	240

Compression coating layer was divided into two equal portions i.e., 120mg of each quantity. Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed by using 9mm flat surfaced punch using 8 station tablet punching machine with the hardness of 4-4.5 kg/cm^2.Then the prepared compression coated tablets are evaluated for various post comparameters.

Evaluation of post compression parameters for prepared Tablets

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 3: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Meloxicam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete

solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies:**

Drug release studies of Meloxicam core tablets:

The core tablets containing 15mg Meloxicam of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 270 nm.

Drug release studies of Compression coated Meloxicam tablets:

The release of Meloxicam from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions.

Drug release was measured from compression coated Meloxicam tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm and 270 nm respectively. All dissolution runs were performed for six batch. The results were given with deviation.

Application of Release Rate Kinetics to Dissolution Data :

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics:

The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

RESULTS AND DISCUSSION:

The present study was aimed to developing compression coated Meloxicam formulations for colon targeting using ethyl cellulose and enteric coating polymers like Eudragit L100 and Eudragit S 100. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Meloxicam blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. According to Table 3, the results of angle of repose and compressibility index (%) ranged from 32.74±0.12 to 37.08±0.96 and 13.37±0.38 to 14.72±0.62 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. These results show that the powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Quality Control Parameters For compression coated tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 300 mg. The results of the post compression tablets were given in table 4.

Table 4: Preformulation parameters of core material

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	36.01	0.55	0.645	14.72	0.85
F2	34.8	0.57	0.66	13.63	0.86
F3	32.74	0.53	0.606	14.19	0.858
F4	35.33	0.531	0.613	13.37	0.866
F5	36.24	0.549	0.641	14.35	0.856
F6	36.12	0.564	0.666	15.31	0.846
F7	37.08	0.581	0.671	13.41	0.865
F8	35.12	0.567	0.654	13.12	0.845
F9	35.45	0.571	0.689	13.28	0.855

Table 5: Post compression studies

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%)	Thickness (mm)	Drug content (%)
F1	312.5	4.5	0.52	4.8	99.76
F2	305.4	4.2	0.54	4.9	99.45
F3	298.6	4.4	0.51	4.9	99.34
F4	310.6	4.5	0.55	4.9	99.87
F5	309.4	4.4	0.56	4.7	99.14
F6	310.7	4.2	0.45	4.5	98.56
F7	302.3	4.1	0.51	4.4	98.42
F8	301.2	4.3	0.49	4.7	99.65
F9	298.3	4.5	0.55	4.6	99.12

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-vitro* Drug Release Studies:**

The compression coated tablets containing 15mg of meloxicam were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of meloxicam from compression coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme- free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions. Drug release was measured from compression coated Meloxicam tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm ,319 and 320 nm respectively. All dissolution runs were performed for nine batches.

From the dissolution values it was evident that the formulations F3 & F9 were retarded the drug release up to 12 hours, they shown drug release of 98.69 and 96.45 % respectively. Formulations F1 –F3 contains ethyl cellulose alone. As the concentration of ethyl cellulose increases retardation nature also increased. F3 formulation contains 150 mg of ethyl cellulose showed almost negligible amount of drug release in first 3 hours, from the 5 th hour onwards it shown drug release as the time proceeds slowly the polymer undergone erosion and allowed the drug to come out from the dosage form. The formulation showed retarded drug release up to 12 hours and it showed maximum drug release in 12 hours i,e., in colon region. Similarly the formulation F9 containing Eudragit L 100 at a concentration of 150 mg also showed similar drug release pattern.

Table 6 : *In-vitro* Drug Release profile for coated formulations (F1-F9)

Time(h	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	5.42	0.26	0.34	2.39	1.11	1.44	8.06	2.65	1.32
2	12.65	0.44	0.54	17.88	1.29	12.30	20.94	7.23	2.14
3	23.56	4.65	1.26	30.45	11.71	24.44	30.26	18.19	2.90
4	66.8	17.87	2.22	40.59	30.22	36.61	45.44	30.27	8.11
5	86.9	29.18	3.05	55.01	40.18	47.30	63.86	42.06	17.72
6	98.35	35.45	18.41	73.85	54.53	55.68	72.93	51.40	30.40
7	-	61.04	30.05	91.92	63.88	67.53	90.23	69.13	51.64
8	-	74.24	48.69	-	80.53	78.72	-	78.45	61.59
9	-	88.13	55.38	-	95.06	83.34	-	85.67	74.97
10	-	96.39	72.34	-	95.18	90.67	-	98.45	84.18
11	-	96.45	87.56	-	-	98.12	-	98.12	96.87
12	-	-	98.69	-	-	-	-	-	96.45

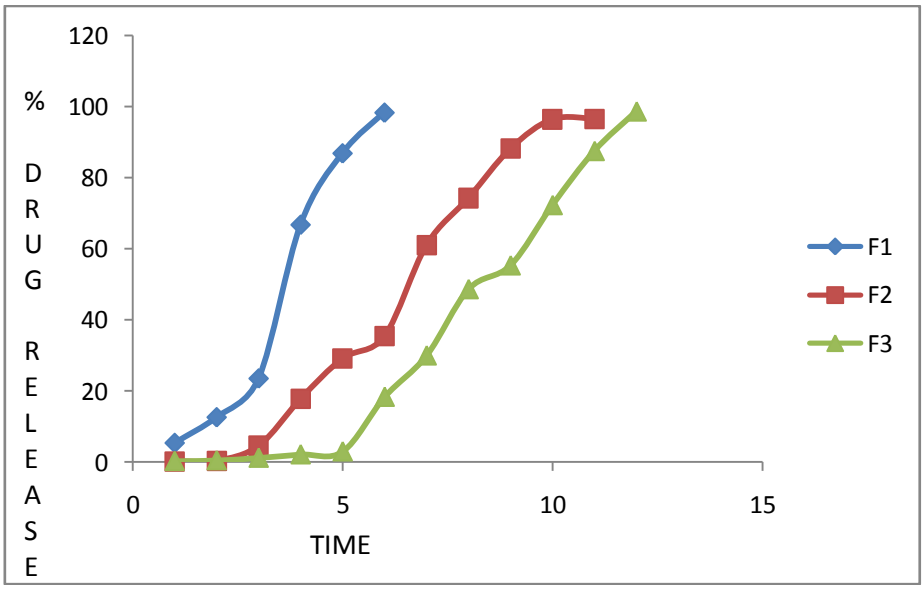


Fig 1: Dissolution of formulations F1-F3

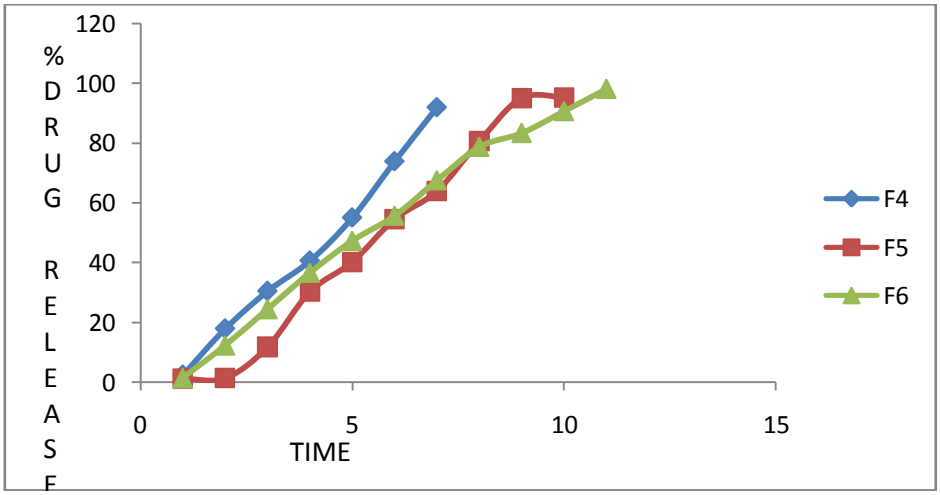


Fig 2 : Dissolution of formulations F4-F6

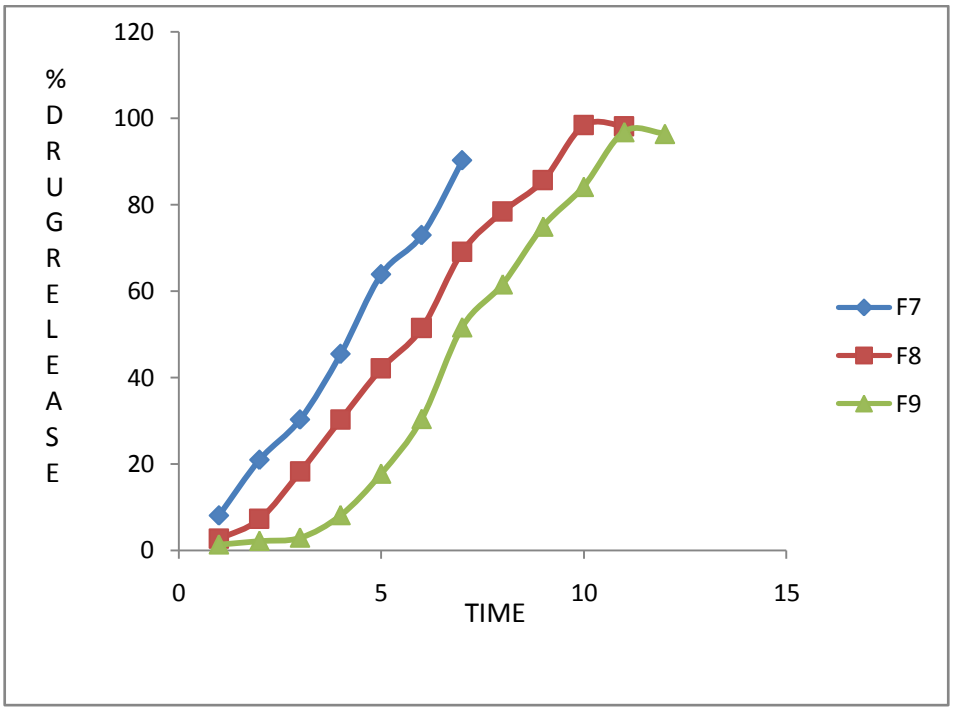


Fig 3 : Dissolution of formulations F7-F9

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 7: Release kinetics data for optimised formulation

Cumulative (%) Release Q	Time (T)	Root (T)	Log(%) Release	Log (T)	Log (%) Remain	Release Rate (Cumulative % Release / T)	1/Cum% Release	Peppas Log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0	0		2.000	0	0	0	100	4.642	4.642	0.000
0.34	1	1.000	-0.469	0.000	1.999	0.340	2.9412	-2.469	99.66	4.642	4.636	0.005
0.54	2	1.414	-0.268	0.301	1.998	0.270	1.8519	-2.268	99.46	4.642	4.633	0.008
1.26	3	1.732	0.100	0.477	1.994	0.420	0.7937	-1.900	98.74	4.642	4.622	0.020
2.22	4	2.000	0.346	0.602	1.990	0.555	0.4505	-1.654	97.78	4.642	4.607	0.035
3.05	5	2.236	0.484	0.699	1.987	0.610	0.3279	-1.516	96.95	4.642	4.594	0.048
18.41	6	2.449	1.265	0.778	1.912	3.068	0.0543	-0.735	81.59	4.642	4.337	0.304
48.69	8	2.828	1.687	0.903	1.710	6.086	0.0205	-0.313	51.31	4.642	3.716	0.926
72.34	10	3.162	1.859	1.000	1.442	7.234	0.0138	-0.141	27.66	4.642	3.024	1.617
98.69	12	3.464	1.994	1.079	0.117	8.224	0.0101	-0.006	1.31	4.642	1.094	3.547

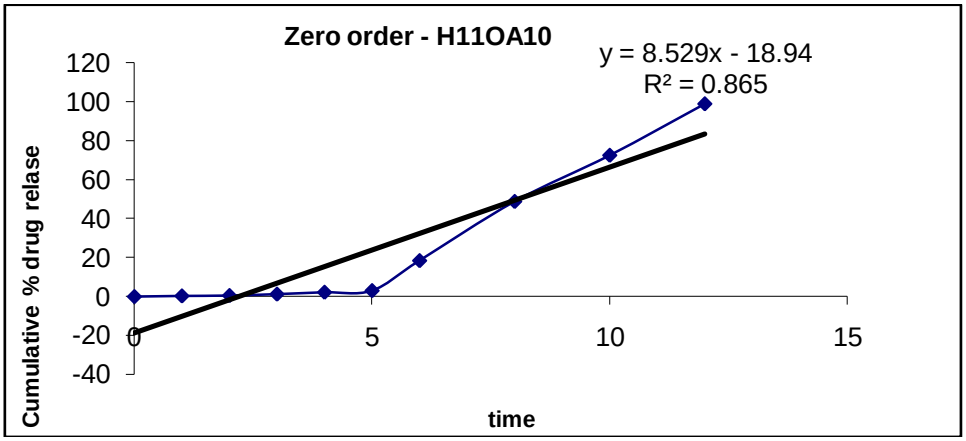


Fig 4 : Zero order release kinetics graph

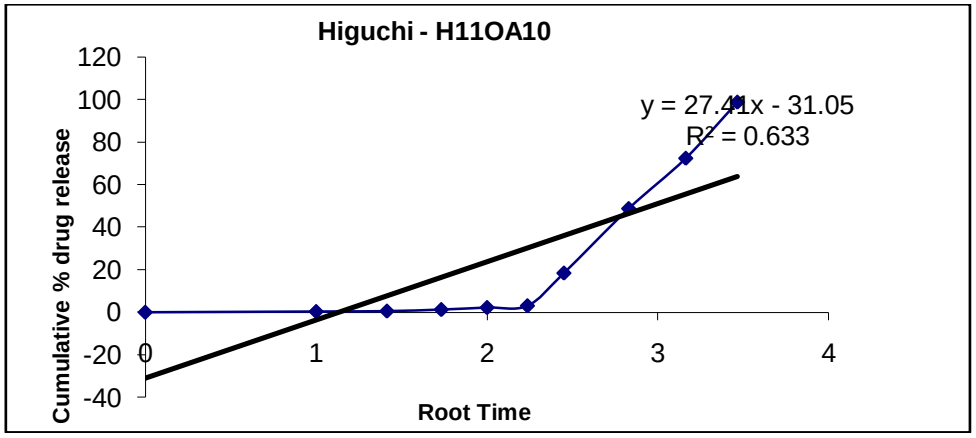


Fig 5 : Higuchi release kinetics graph

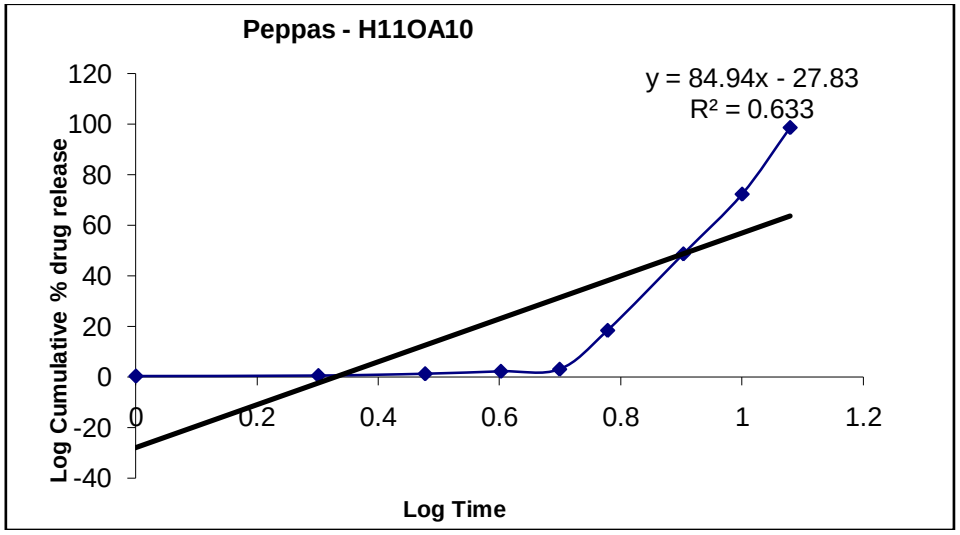


Fig 6: Kars mayer peppas graph

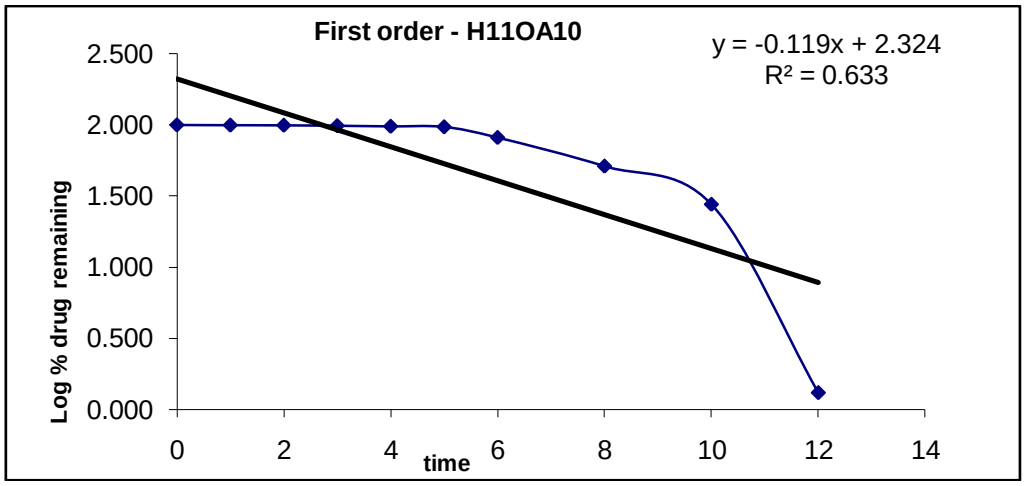


Fig 7: First order release kinetics graph

From the above graphs it was evident that the formulation F3 followed zero order kinetics.

CONCLUSION:

Systematic study was carried involving preparation and evaluation of Colon targeted oral drug delivery system for Meloxicam using release retarding polymers, such as Ethyl cellolose, Eudragit L-100 and Eudragit S-100. Meloxicam is a selective cyclooxygenase-2 inhibitor with pH-dependent solubility. To achieve pH-independent drug release of meloxicam, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were found to be in limits, which indicates free flow. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques, which were found to be in limits. Among all the formulations, F3 formulation was found to be optimized as it retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. From the above investigation it was observed that formulation F3 was found to be best among the prepared formulations which may be used for prolong drug release in colon for, thereby improving patient compliance and bioavailability.

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