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FORMULATION AND INVITRO EVALUATION OF COLON TARGETED DRUG DELIVERY OF MELOXICAM TABLETS

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ABSTARCT

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: Meloxicam, Colon targeted drug delivery system, Ethyl cellulose, Eudragit L100, Eudragit S 100.

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[1] of the drug.

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.

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[2] solely responsible for absorption of water, electrolytes and temporary storage of stools. But now it is accepted as important site for drug delivery.

Colon targeting is used to treat

Seriousness from constipation and diarrhea to the debilitating inflammatory bowel diseases(Ulcerative colitis and Crohn's disease) through to colon carcinoma which is two third cause of cancer in both man and women. Colon can be utilized as portal for the entry of drugs into the blood stream for the systemic therapy. Colon having the lower level of luminal and mucosal digestive enzymes as compared with the small intestine reduces the chances of drug degradation. E.g.to facilitate absorption of acid and enzymatically labile materials especially proteins and peptides. Colon delivery also a mean of achieving chronotherapy of disease that is sensitive to circadian rhythm such as asthma and arthritis Colonic drug delivery is also found useful for improving systemic absorption of drugs like nitr-endipine (calcium channel blocker), metoprolol (anti-hypertensive), iso-sorbide mononitrate (anti-anginal. 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. Retardation of drug release in the diverse and hostile conditions of the stomach and small intestine is not easily achieved, since the dosage form will be subjected to a physical and chemical assault that is designed to break down ingested materials. While in the colon, the low fluid environment and viscous nature of luminal contents may hinder the dissolution and release of the drug from the formulation. Moreover, the resident colonic microflora may impact on the stability of the released drug via metabolic degradation. In the context of

colonic targeting, the exploitable gastrointestinal features include pH, transit time, pressure, bacteria and prodrug approach[3].

Anatomy And Physiology Of Colon

The GIT is divided into stomach, small intestine and large intestine. The large intestine extending from the ileo-caecal junction to the anus is divided into three main parts. These are the colon, the rectum and the anal canal. The location of the parts of the colon is either in the abdominal cavity or behind it in the retro-peritoneum. The colon itself is made up of the caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon (Figure 1). It is about 1.5 m long, the transverse colon being the longest and most mobile part and has a average diameter of about 6.5 cm. The colon from the cecum to the splenic flexure (the junction between the transverse and descending colon) is also known as the right colon. The remainder is known as the left colon. Arterial supply to the colon of humans comes from branches of the superior and inferior mesenteric arteries.. Lymphatic drainage[4]. from the entire colon and proximal two-thirds of the rectum is to the paraortic nodes, which then drain into the cisterna chyli. The lymph from the remaining rectum and anus can either follow the same route, or drain to the internal illiac and superficial inguinal nodes.

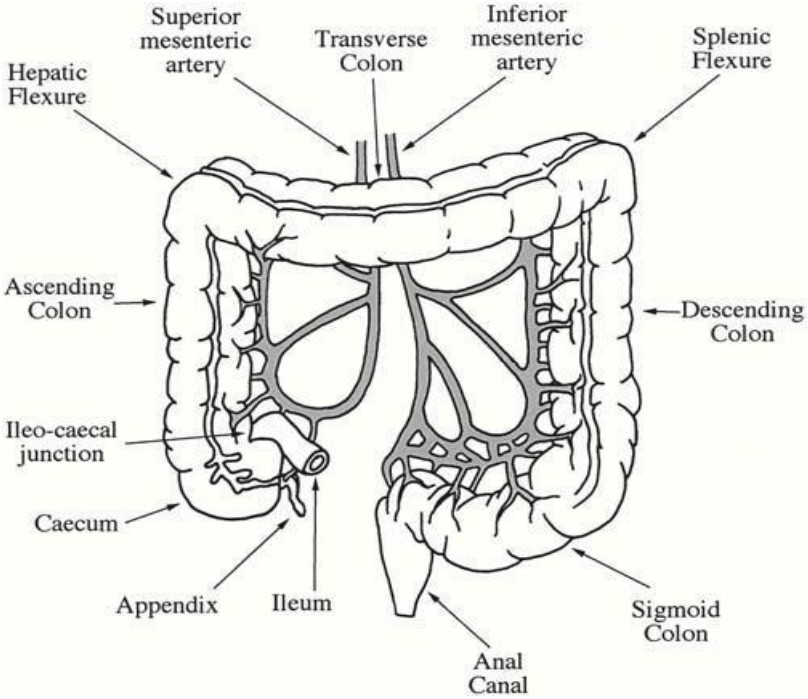

Fig 1: Main Features of the Colon

Functions of Colon[5]

The colon serves four major functions. They are

1. Creation of suitable environment for the growth of colonic microorganisms.
2. Storage reservoir of faecal contents.
3. Expulsion of the contents of the colon at an appropriate time and
4. Absorption of potassium and bicarbonate.

Approaches to colon-specific drug delivery[6-9]

In recent years, a large number of solid formulations targeting the lower parts of the Gastro Intestinal Tract, especially the colon, have been reported. These formulations may be broadly divided into four types, which are:

1. pH- dependent system designed to release a drug in response to change in pH
2. Time controlled (or Time-dependent) system designed to release a drug after a predetermined time.
3. Microbially-controlled system making use of the abundant entero-bacteria in the colon.
4. Enzyme- based system. Prodrug.
5. Pressure-dependent system making use of luminal pressure of the colon.

Among these, first three are most widespread formulation technologies being developed for pharmaceutical market.

Evaluation of colon-targeted drug delivery systems[10-14]

Various *in-vitro and in vivo* evaluation techniques have been developed and proposed to test the performance and stability of colon- specific drug delivery systems.

***In-vitro* dissolution testing**

Dissolution provides decisive information on formulation selection, the critical processing variables in vitro/ in vivo correlation and quality assurance during clinical manufacturing. Currently, four dissolution apparatus are recommended in the USP to accommodate different actives and dosage forms: basket method, paddle method Bio-Dis method and flow-through cell method. For *in-vitro* evaluation of colon-specific drug delivery systems,

the ideal dissolution testing should closely mimic the in vivo conditions with regard to pH, bacteria and types of enzymes, enzymatic activity, fluid volume and mixing intensity.

In-vivo evaluation of colon-specific drug delivery systems

As in other controlled release delivery systems, the successful development of a colon-specific drug delivery system is ultimately determined by its ability to achieve colon-specific drug release and thus exert the intended therapeutic effect. When the system design is conceived and prototype formulation with acceptable *in vitro* characteristics is obtained *in-vivo* studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetics information of the delivery system.

A. Animal studies

Different animals have been used to evaluate the performance of colon-specific drug delivery systems, such as rats, pigs and dogs. To closely simulate the human physiological environment of the colon, the selection of an appropriate animal model for evaluating a colon-specific delivery system depends on its triggering mechanism and system design. For instance, guinea pigs have comparable glycosidase and glucuronidase activities in, the colon and similar digestive anatomy and physiology to that of human, so they are more suitable in evaluating glucoside and glucuronate conjugated prodrugs intended for colon delivery.

B. Gamma-Scintigraphy

In most cases, conventional pharmacokinetic evaluation may not generate sufficient information to elucidate the intended rationale of system design Scintigraphy is an imaging modality, which enables the in vivo per for mance of drug delivery systems to be visualized under nor mal physiological conditions in a non-invasive manner.

Through scintigraphy imaging, the following information regarding the performance of a colon-specific delivery system within human GI tract can be obtained: the location as a function of time, the time and location of initial and complete system disintegration, the extent of dispersion, the colon arrival time, stomach residence and small intestine transit times.

C. Roentgenography

The inclusion of a radio-opaque mater ial into a solid dosage for m enables it to be visualized by the use of X-rays. By incorporating barium sulphate into a pharmaceutical dosage form it is possible to follow the movement, location and the integrity of the dosage for m after oral administration by placing the subject under fluoroscope and taking series of X-rays at various time points.

Disease Status

Colon targeted matrix tablet is one controlled release dosage form, which release the drug in continuous manner at colon. Colon are concerned with number of diseases like IBD, colon cancer etc. The term inflammatory bowel disease (IBD) covers a group of disorders in which the intestines become inflamed (red and swollen). Two major types of IBD are described: ulcerative colitis and Crohn's disease. As the name suggests, ulcerative colitis is limited to the colon (large intestine). Although Crohn's disease can involve any part of the gastrointestinal tract from the mouth to the anus, it most commonly affects the small intestine and/or the colon. Both ulcerative colitis and Crohn's disease usually run a waxing and waning course in the intensity and severity illness. When there is severe inflammation, the disease is considered to be in an active stage, and the person experiences a flare-up of the condition. It is very challenging task to prepare such dosage form which could be target the colon hence, one of active drug Meloxicam (MLX) is an oxicam derivative nonsteroidal anti-inflammatory drug (NSAID) with analgesic and fever reducer effects. Recently has been reported that MLX play important role in cholorectal carcinogenisis therapy

MATERIALS AND METHODS: Meloxicam, Ethyl Cellulose, Eudragit L-100, Eudragit S-100, Hydroxy Propyl Methyl Cellulose K100M, Magnesium stearate, Micro crystalline cellulose, Talc.

Methodology

Analytical method development

a) Determination of absorption maxima

A solution of containing the concentration 10 µg/ ml was prepared in 0.1N HCl, 7.4 pH & phosphate buffer 6.8pH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

b) Preparation calibration curve

10mg of drug was accurately weighed and dissolved in 10ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4,6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.1N HCl, 7.4 pH, and 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 273nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12

psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Differential Scanning Calorimetry (DSC)

DSC scan of samples were obtained in a Perkin Elmer thermal analyzer equipped with a monitor and printer. The instrument was calibrated with indium. Accurately weighed 5 mg of sample were placed in an open, flat bottom, aluminium sample pans. Thermograms were obtained by heating the sample at a constant rate 10 minute. A dry purge of nitrogen gas (20ml/min) was used for all runs sample heated from 35^{o}C to 400^{o}C.

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. The various characteristics of blends tested as per Pharmacopoeia.

- Angle of repose:
- Bulk density:
- Tapped density:
- Measures of powder compressibility:

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.

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.

Table 2.Composition of coating layer

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 coted tablets are evaluated for various post compression parameters as per standard specifications.

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
- Drug content.

***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.

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 invitro drug release studies.

Analytical Method

Graphs of Meloxicam was taken in Simulated Gastric fluid (pH 1.2) and Simulated Intestinal Fluid (pH 6.8 and 7.4).

Table 3: Observations for graph of Meloxicam in 0.1N HCl (275 nm)

No.	Conc [mg/l]	Abs
1	1	0.001
2	3	0.075
3	4	0.128
4	5	0.199
5	6	0.280
6	7	0.343
7	8	0.397
9	11	0.557
10	12	0.623
13	21	0.823
14	22	0.87

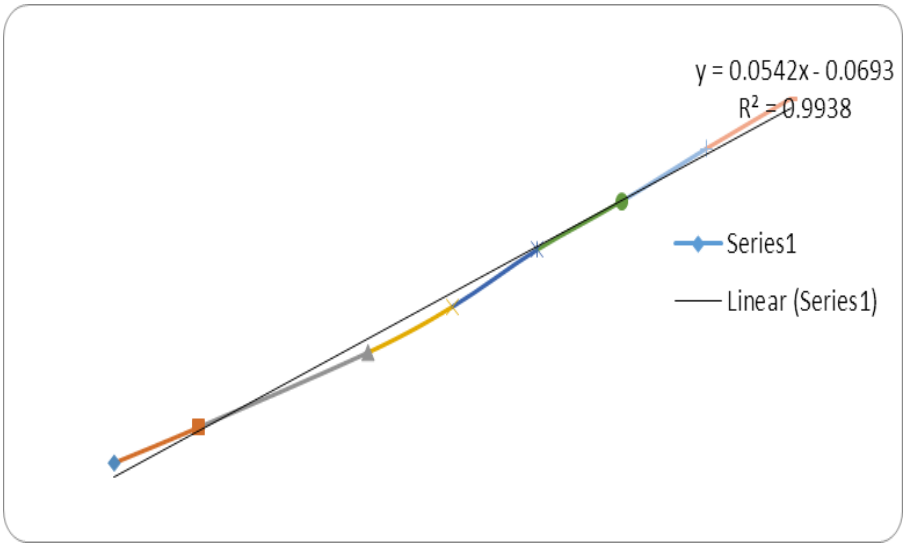

Figure 2: Standard graph of Meloxicam in 0.1N HCl

Table 4: Graph of Meloxicam in 7.4 pH Simulated Intestinal Fluid (319nm)

S. No.	Conc [mg/l]	Abs
1	2	0.057
2	3	0.129
3	4	0.204
4	5	0.284
5	6	0.372
6	8	0.566
7	9	0.625
8	10	0.709
9	12	0.893

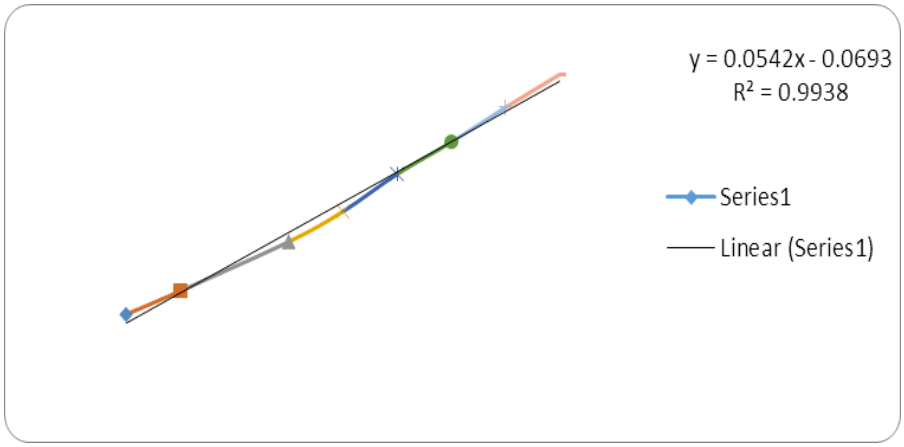

Figure 3: Standard graph of Meloxicam in 7.4 pH

Table 5: Observations for graph of Meloxicam in 6.8 pH (320)

No.	Conc [mg/l]	Abs
1	1	0.001
2	2	0.043
4	4	0.131
5	5	0.185
6	6	0.252
7	7	0.309
8	8	0.371
9	9	0.430
10	10	0.504
13	13	0.684
14	14	0.740
15	15	0.799
16	16	0.896

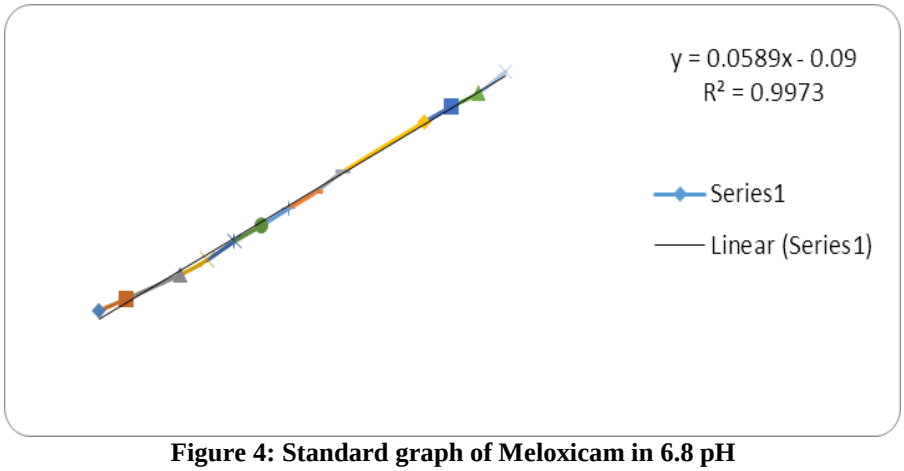

Figure 4: Standard graph of Meloxicam in 6.8 pH

Table 6: 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

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 Tables 7.4, 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 coted 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.

Table 7: Evaluation parameters obtained for coating material

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	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

Invitro quality control parameters for compression coated tablets

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 six batches.

Table 8: *In-vitro* Drug Release profile for coated formulations (F1-F9)

Time(hrs)	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

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 was increased.F3 formulation containing 150 mg of ethyl cellulose was show 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 was undergone erosion and allowed the drug to come out from the dosage form. The formulation was 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 in the concentration of 150 mg also showed similar drug release pattern.

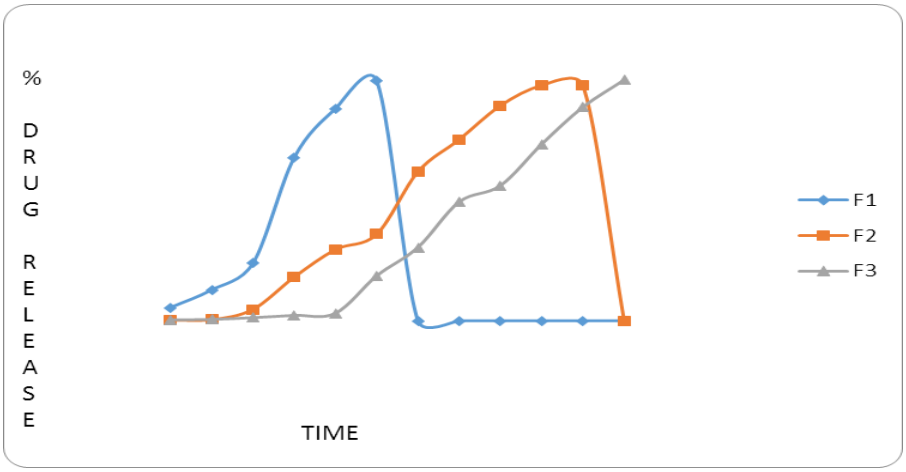

Fig 5 : Dissolution of formulations F1-F3

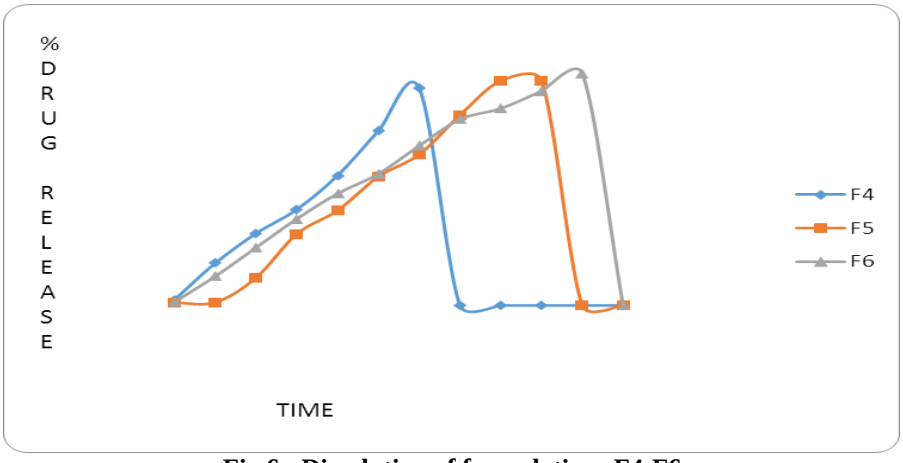

Fig 6 : Dissolution of formulations F4-F6

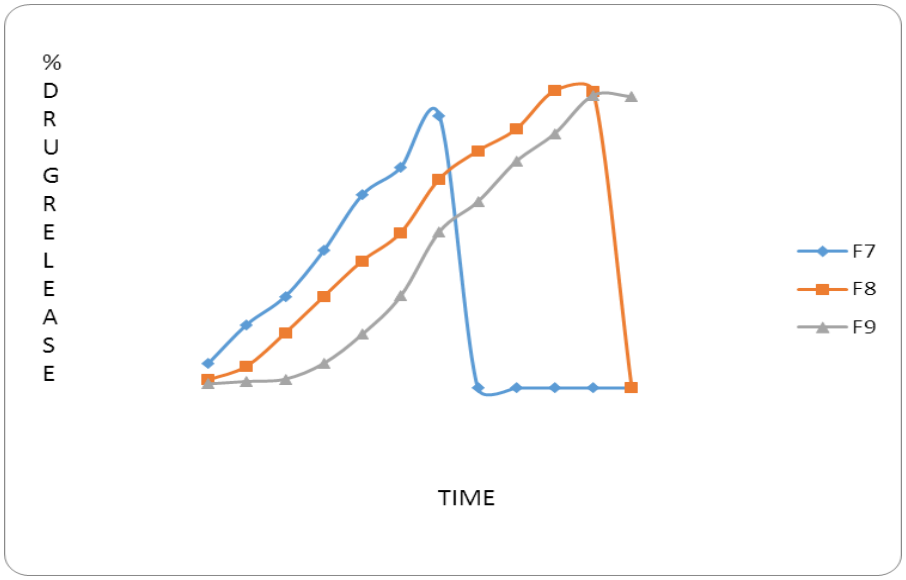

Fig 7 : Dissolution of formulations F7-F9

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 9: 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

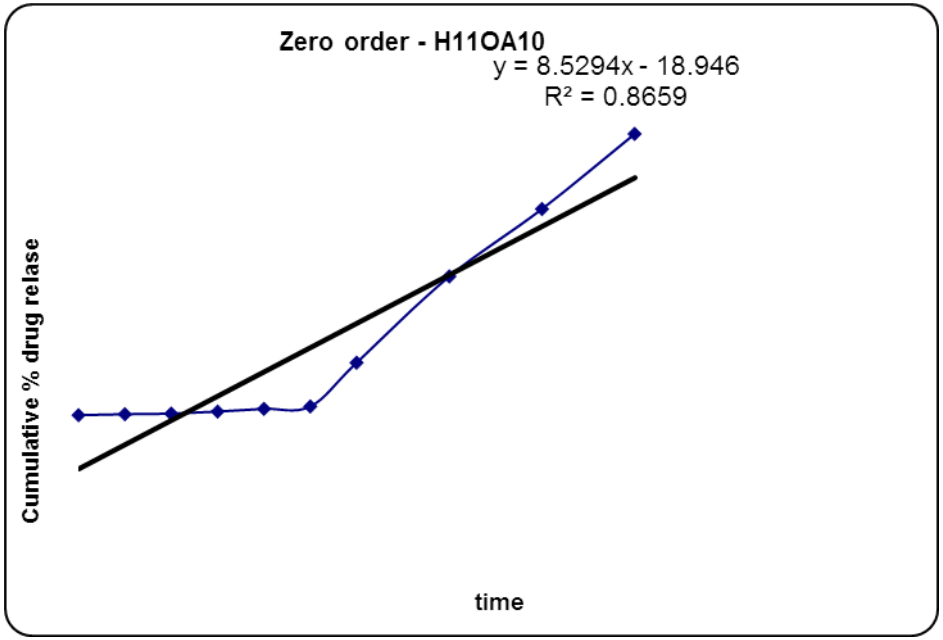

Fig 8 : Zero order release kinetics graph

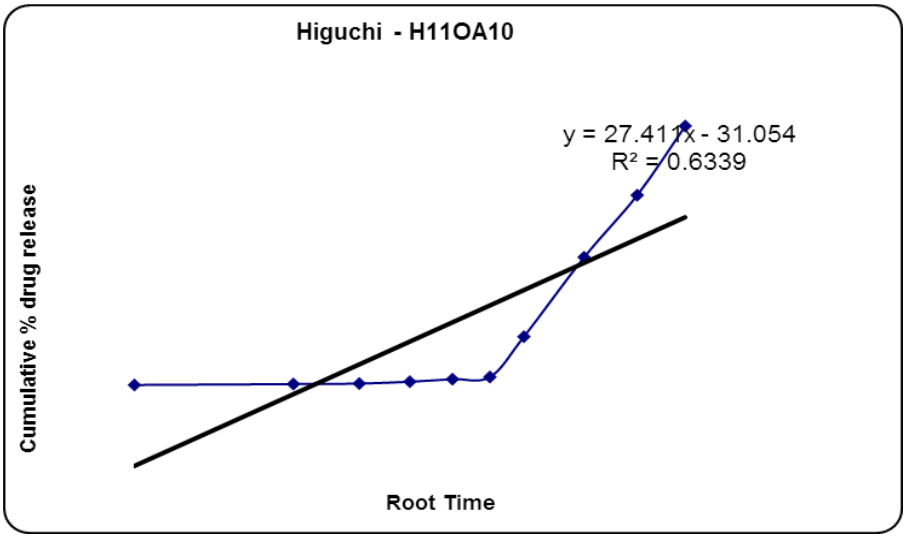

Fig 9 : Higuchi release kinetics graph

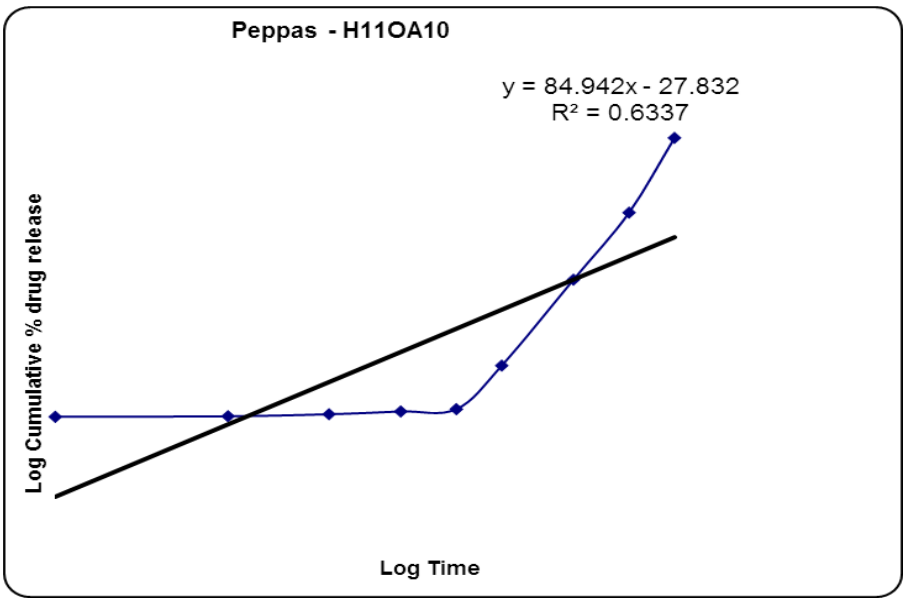

Fig 10: Kars mayer peppas graph

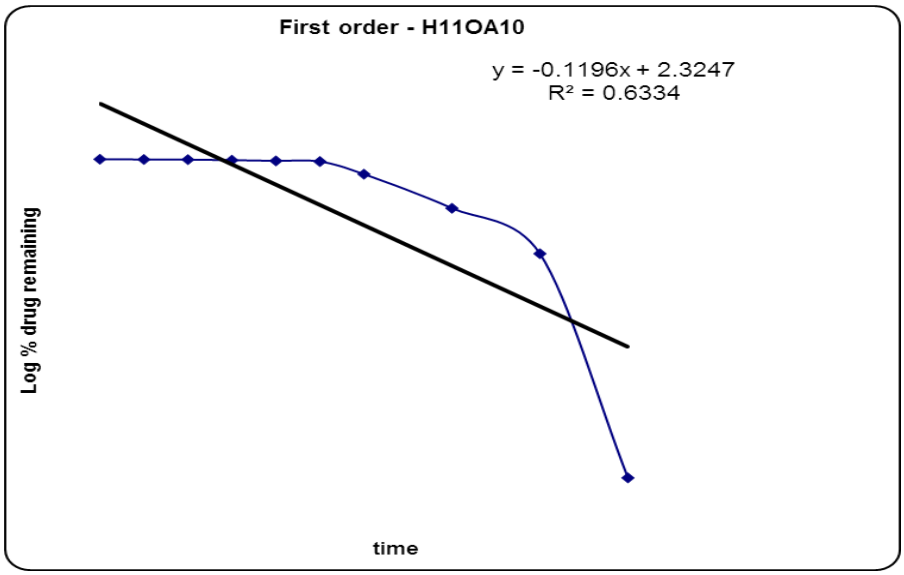

Fig 11: First order release kinetics graph

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

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