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MICROSPHEERIC DRUG DELIVERY SYSTEM OF MELOXICAM BY IONIC GELATION TECHNIQUE

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ABSTRACT:
Meloxicam is a non-steroidal anti-inflammatory drug (NSAIDs), a class II compound that inhibits the enzymatic activity of cyclooxygenase (COX), reducing the relative risk for developing colorectal cancer. Thus, meloxicam microsphere was prepared by using different polymer concentrations to check the release of the drug. preparation and characterization of colon targeted microsphere of meloxicam made by ionic gelation technique for the treatment of colorectal cancer.

INTRODUCTION:

TARGETED DRUG DELIVERY SYSTEM

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as Ulcerative colitis, Cirrhosis disease, Amoebiasis, Colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon-specific drug delivery system should be capable of protecting the drug in route to the colon i,e.drug release and absorption should not occur in the stomach as well as in the small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but only released and absorbed once the system reaches the colon. A colonic targeted approach was found to be effective in minimizing side effects.[1,2]

Epidemiological studies demonstrated a 40-50% reduction in the risk for colorectal cancer following prolonged use of non-steroidal anti-inflammatory drugs. Recent studies show that cox-2 levels are increased in 85% of colorectal adenocarcinoma. Meloxicam is an NSAID drugs that shows cox-1 IC_{50} of 3.27µm and cox-2 IC_{50} of 0.25µm, 13.1 times more preferential for cox-2 inhibition. Evaluations of selective cox-2 inhibitors for effects on colorectal cancer is currently an area of intense investigation and pre-clinical studies have clearly shown potent anti-tumor properties and several studies are reported in the application of meloxicam for the prophylaxis of colorectal cancer.[3,4]

Various approaches were tried to achieve colonic delivery of drugs include use of prodrugs,pH-sensitive polymer coatings, time-dependent formulations, bacterial degradable coatings, time/pH-controlled deliveries, and intestinal luminal pressure controlled colon delivery capsules.[5] A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it is necessary to deliver the agent to the target tissue in the optimal amount in the right period of time thereby causing little toxicity and minimal side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained and controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free-flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally have a particle size less than 200 µm.[6,7]

In addition, the use of biodegradable polymers such as azopolymers and polysaccharides for colon targeting has been described in the literature. To achieve pH-independent drug release of meloxicam, pH modifying agents (buffering agents) were used. Meloxicam tablets containing polyethylene oxide were dually coated with ethyl cellulose-containing hydrophilic material, polyethylene glycol as an inner coating layer, and methyl acrylate, methyl methacrylate, and methacrylic acid copolymer (eudragit® FS 30D) as outer coating layer for colon targeting.[8]

Mainly colon-specific polymer-based matrix tablets have been reported for meloxicam for colon targeting. However, because of variations in transit throughout the colon, the drug release can be impaired when the colon-specific tablet matrix is not readily disintegrated, and treatment will remain ineffective. This problem could be circumvented by reducing the size of the delivery carrier, since it has been reported that gastrointestinal retention depends upon the size of the carrier, meaning that smaller carriers will lead to a longer residence in the colon.

Hence in the present investigation, we are aimed to develop a colon-specific microsphere delivery system of meloxicam using a natural and enteric polymer as a carrier and to develop the colon-specific delivery that has the potential for use as adjuvant therapy for colorectal cancer.

Advantages of Microspheres [(9)]

They facilitate accurate delivery of small quantities of the potent drug and reduced concentration of drug at a site other than the target organ or tissue. They provide protection for the unstable drug before and after administration, prior to their availability at the site of action. They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution, and cellular interaction of the drug. They enable the controlled release of drug. Examples: Narcotic,

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Microspheres are usually made of polymers. They are classified into two types [9]

1. **Synthetic polymers :**

a)Nonbiodegradable polymer eg: Polymethyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate,

b)**Biodegradable polymers**: Lactides, their glycolides and their copolymers, PolyalkylCyano Acrylate, polyanhydrides

2. Natural polymers: These are obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates. Proteins: Albumin, Gelatin, And Collagen, Carbohydrates: Agarose, Carrageenan, Chitosan, Starch, Chemically Modified Carbohydrates: Poly (acryl) dextran, Poly (acryl) starch

3. Types of Microspheres: Bioadhesive Microsphere, Magnetic Microspheres, Floating Microspheres, Radioactive Microspheres, Polymeric Microspheres,

Techniques used for making microspheres:

1) Single emulsion technique
2) Double emulsion technique
3) Polymerization
a) Normal polymerization
b) Interfacial polymerization
4) Phase separation/ Coacervation
5) Spray drying
6) Ionic gelation technique: Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogels. Since, the use of alginates, gellan gum, chitosan, and pectin for the encapsulation of drug. These anions forms meshwork structure by combining with the polyvalent cations and induce gelation by binding mainly to the anion blocks. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations.

EXPERIMENTAL WORK

1. PREFORMULATION

1) Authentication of Drug
a. UV Spectrometry
b. FTIR
c. Melting point
2) Construction of calibration curve by UV-Visible Spectrophotometer
3) Drug excipients compatibility

2 **MICROSPHERE FORMULATION**

For formulating microspheres following method is used,

a) Ionic gelation technique
b) Formulation trials were done by using different polymers concentration of sodium alginate and Eudragit.

3 **MICROSPHERES EVALUATION**

The microspheres were evaluated for % yield, % drug entrapment, in vitro drug release and flow property.

4 STABILITY STUDIES

The optimized batch is subjected to stability studies at 40˚C ± 2˚C/75 % RH ± 5 % RH for duration of two month.

RESULTS AND DISCUSSION

1. PREFORMULATION

1. Authentication of Drug

a. UV spectrum of Meloxicam

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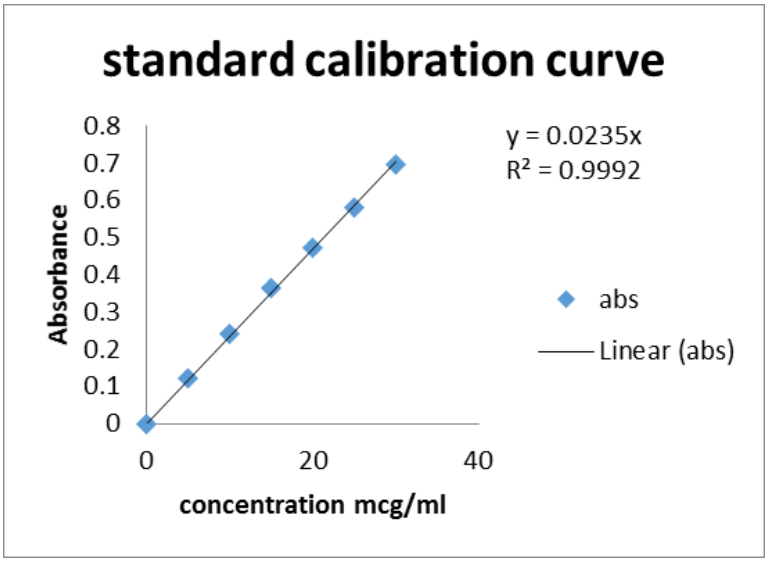
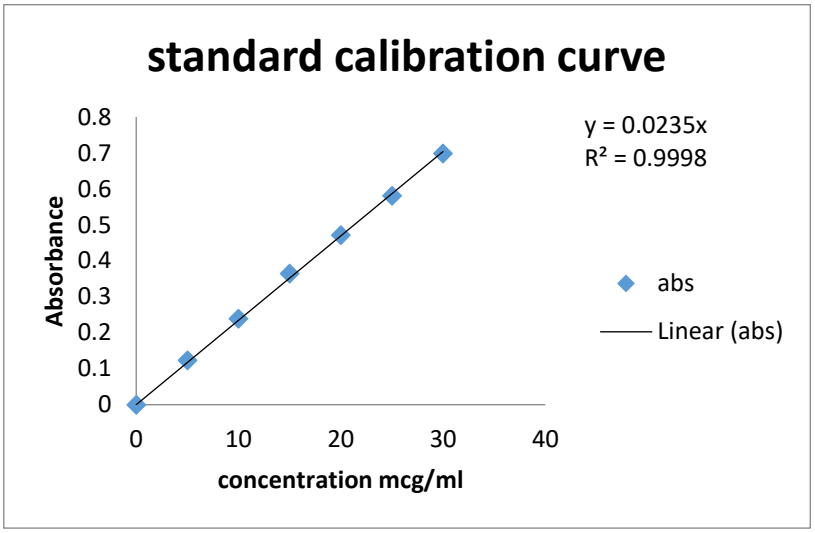
Calibration curve in Acidic pH 1.2 at 365 nm

Sr.no	Concentration	Absorbance
1	0	0
2	50 *µg/ml*	0.1276
3	*100µg/ml*	0.2255
4	*150µg/ml*	0.3178
5	*200µg/ml*	0.4229
6	*250µg/ml*	0.5



Calibration curve in pH 6.8

Sr.no	Concentration	Absorbance
1	0µg/ml	0
2	4µg/ml	0.1446
4	6µg/ml	0.2191
5	8µg/ml	0.3001
6	10µg/ml	0.3635
7	12µg/ml	0.4596
8	14µg/ml	0.5417



Calibration curve in pH7.4

Sr.no	Concentration	Absorbance
1	**0µg/ml**	**0**

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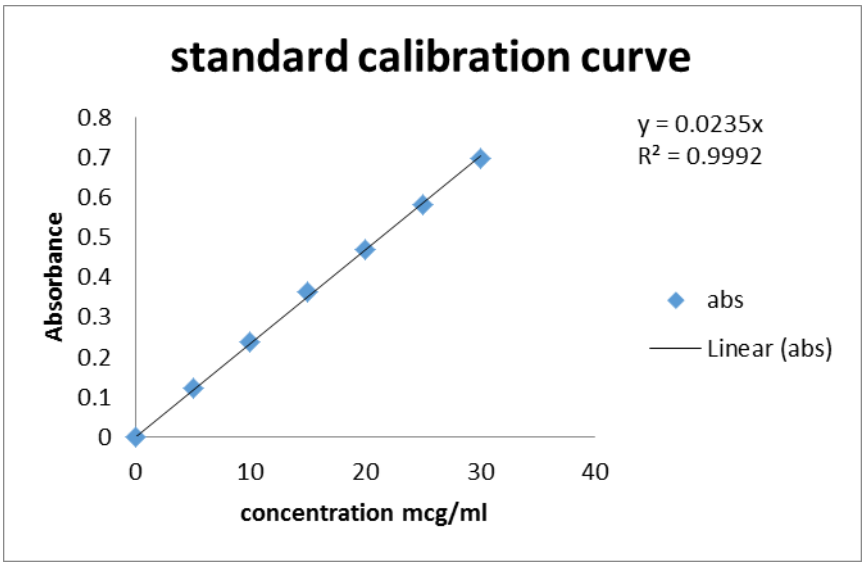
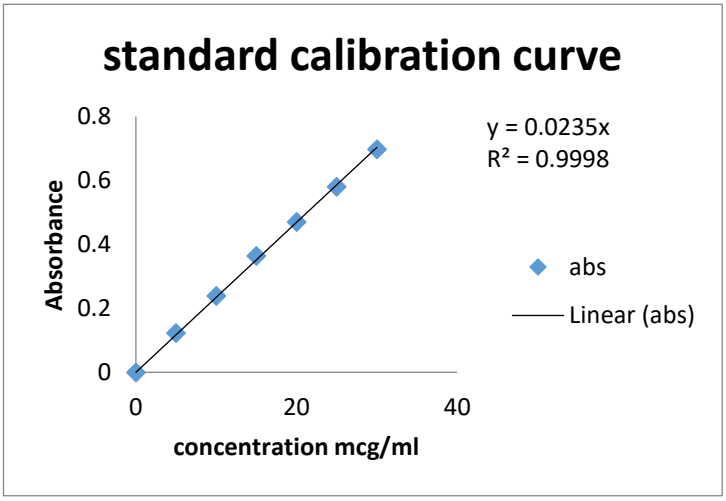
2	5µg/ml	0.1233
3	10µg/ml	0.2393
4	15µg/ml	0.3647
5	20µg/ml	0.4711
6	25µg/ml	0.5812
7	30µg/ml	0.6979

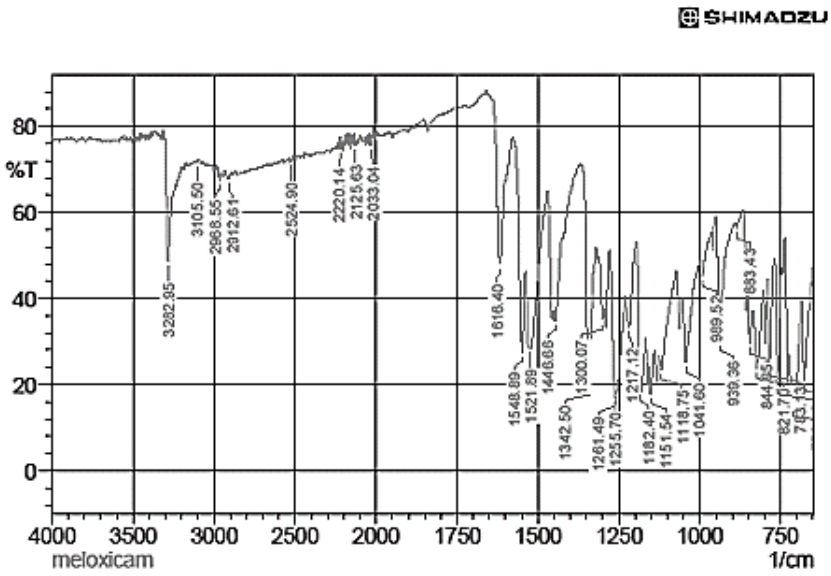


Calibration curve in 0.1N NaOH

Sr.no	Concentration	Absorbance
1	0µg/ml	0
2	2µg/ml	0.1492
3	4µg/ml	0.2835
4	6µg/ml	0.4357
5	8µg/ml	0.5714
6	10µg/ml	0.7645
7	12µg/ml	0.8884



b. FT-IR spectral analysis



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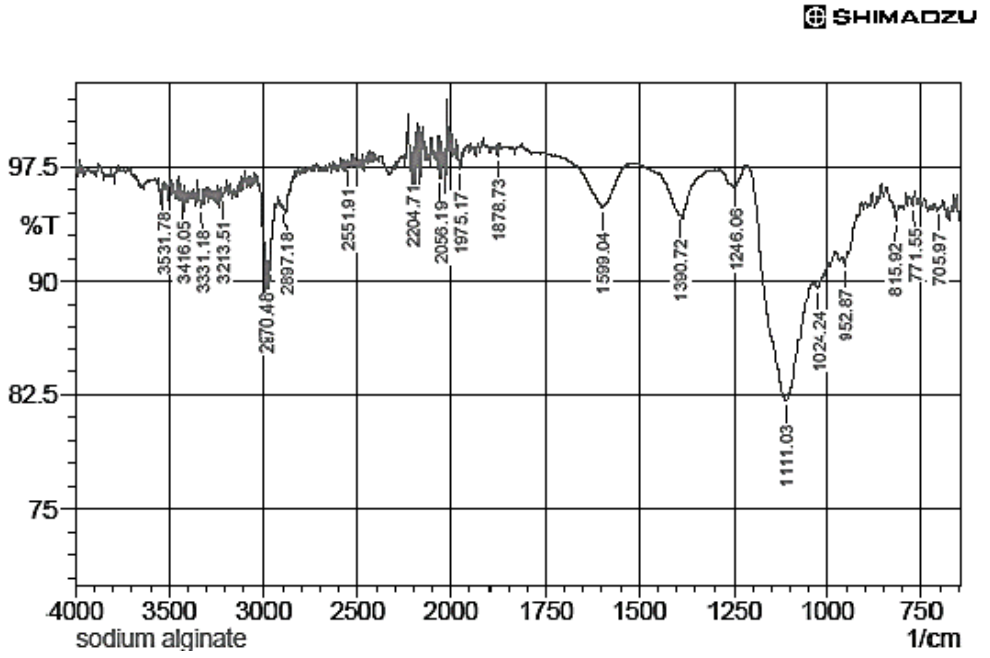
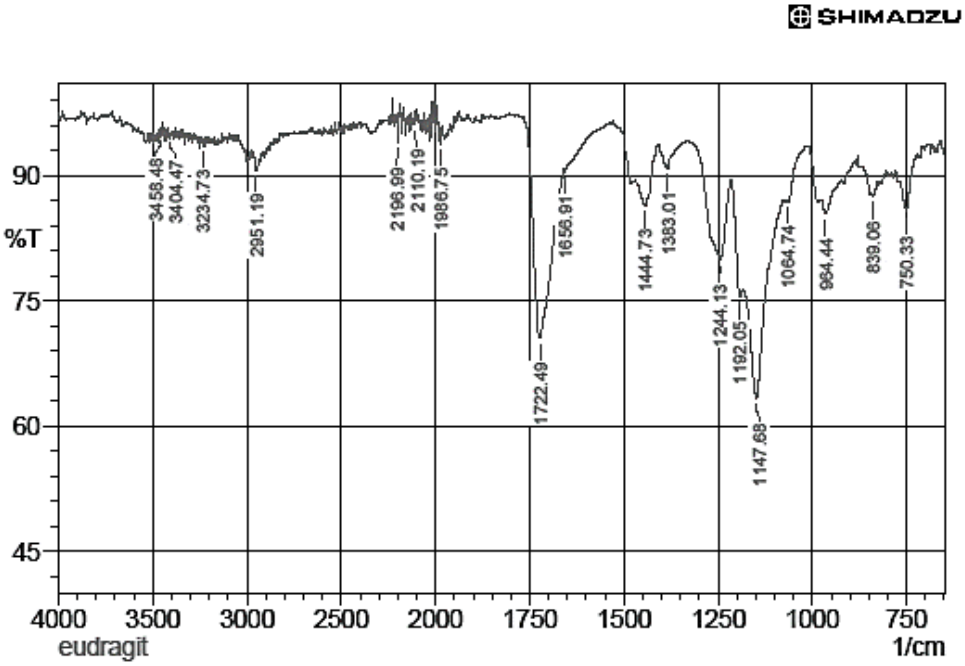
WAVE NUMBER	FUNCTIONAL GROUP
3282.95	**NH Streching**
3105.50	**C-H stretching**
2912.61	**CONH**
1599.04	**SO2**
1548.89	**C=C**





Meloxicam drug +Sodium alginate+eudragit

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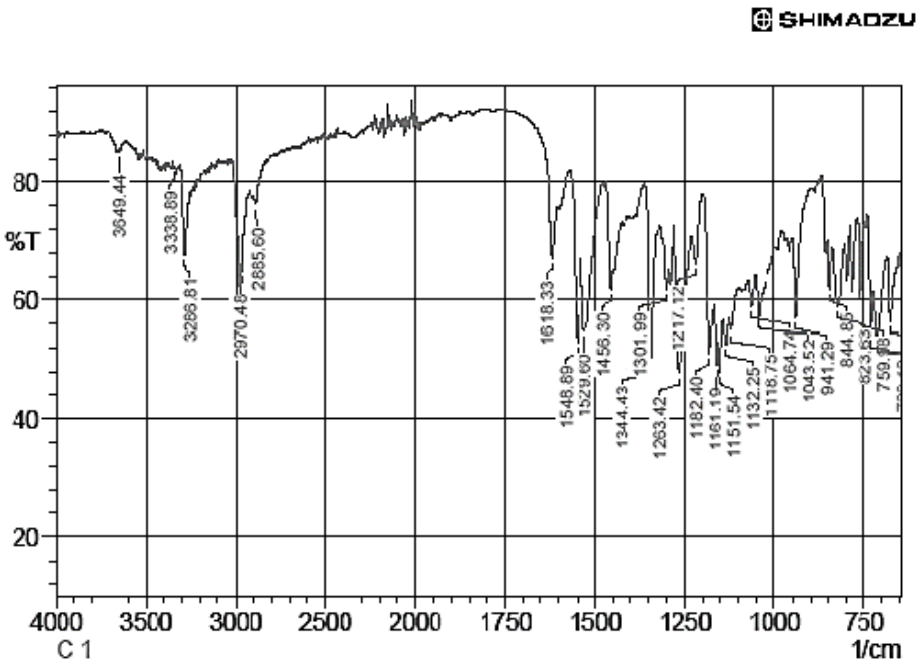

FORMULATION OF MICROSPHERES

Sr.no	Ingredient	AI	AII	AIII	BI	BII	BIII	CI	CII	CIII
1	meloxicam	2gm	2gm	2gm	2gm	2gm	2gm	2gm	2gm	2gm
2	Sodium alginate	1gm	1gm	1gm	2gm	2gm	2gm	3gm	3gm	3gm
3	Calcium chloride	2gm	2gm	2gm	2gm	2gm	2gm	2gm	2gm	2gm
4	Eudragit s 100	100mg	200mg	300mg	100mg	200mg	300mg	100mg	200mg	300mg
5	ethanol	7ml	7ml	7ml	7ml	7ml	7ml	7ml	7ml	7ml
6	acetone	3ml	3ml	3ml	3ml	3ml	3ml	3ml	3ml	3ml
7	Span 80	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml	0.1ml
8	N-hexane	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml	50ml

EVALUATION

Formulation	Angle of repose	bulk density (gm/cc)	Tapped bulk density (gm/cc)	Percent Compressibility	Hausner's ratio
A I	26°.85	0.58	0.63	7.936	1.08
A II	24°.22	0.6	0.66	9.09	1.1
A III	27.603	0.56	0.59	5.08	1.05
B I	28.98	0.52	0.58	10.34	1.11
B II	27.15	0.67	0.73	8.22	1.09

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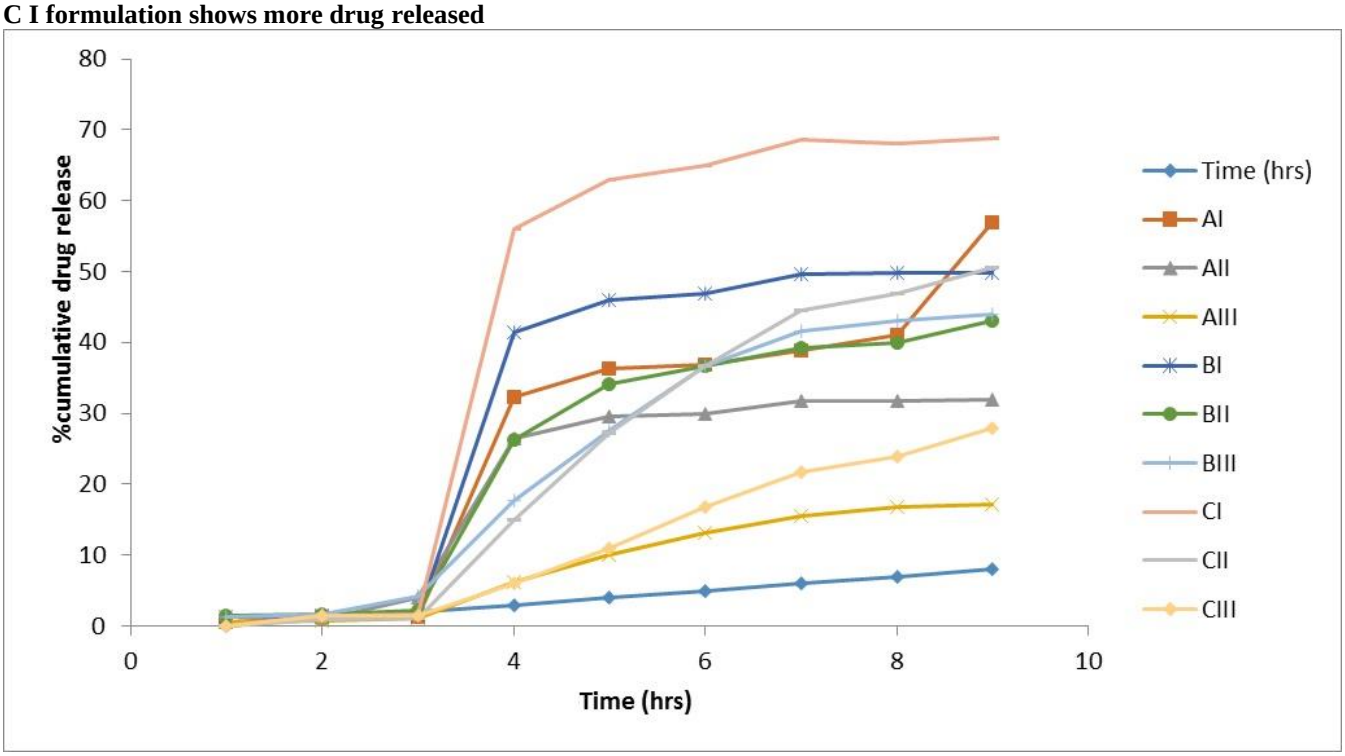
B III	28.05	0.62	0.70	11.42	1.12
C I	29.56	0.56	0.62	9.96	1.10
C II	28.14	0.654	0.728	8.9	1.10
C III	29.34	0.62	0.69	6.25	1.2

Dissolution studies

Drug release profile of Meloxicam by dissolution apparatus.

Time interval / **formulation**	**0hrs 1.2pH**	**1hrs 1.2pH**	**2hrs 1.2pH**	**3hrs 7.4pH**	**4hrs 7.4pH**	**5hrs 7.4pH**	**6hrs 6.8pH**	**7hrs 6.8pH**	**8hrs 6.8PH**
A I	0.61	1.22	1.34	32.32	36.36	36.82	38.84	40.98	56.91
A II	0.46	0.93	4.09	26.39	29.64	29.88	31.72	31.75	31.90
A III	0.61	0.66	1.07	6.28	9.99	13.21	15.58	16.76	17.19
B I	1.35	1.37	1.43	41.39	45.99	46.94	49.56	49.77	49.80
B II	1.46	1.65	2.26	26.34	34.21	36.60	39.29	40.05	42.98
B III	1.35	1.59	4.24	17.73	27.53	36.61	41.59	43.12	43.90
C I	1.40	1.48	1.55	56.09	63.02	65.00	68.67	68.10	68.78
C II	0.86	0.96	1.17	15	27.11	36.74	44.58	46.83	50.47
C III	1.35	1.40	1.54	5.99	10.99	16.76	21.63	23.98	27.87

C I formulation shows more drug released



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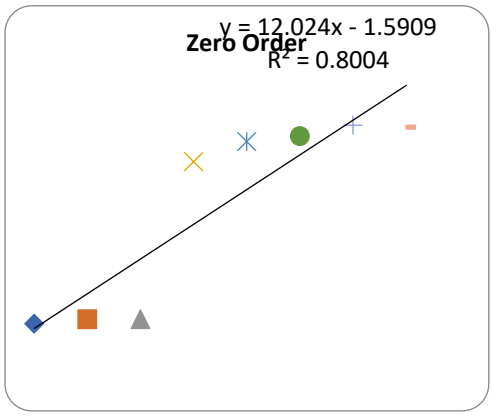
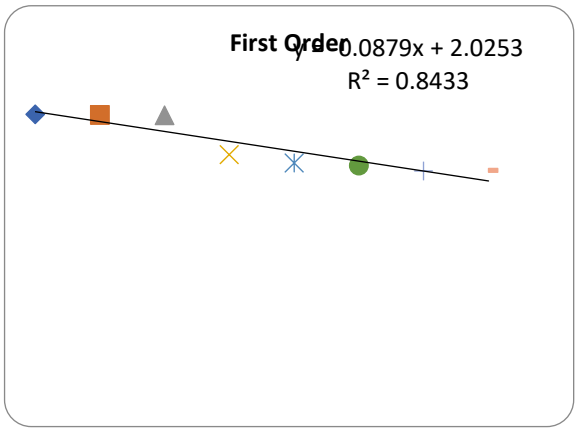
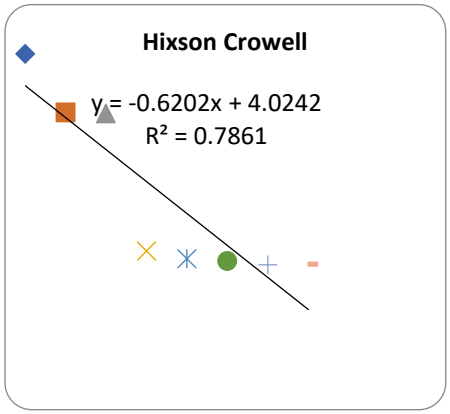
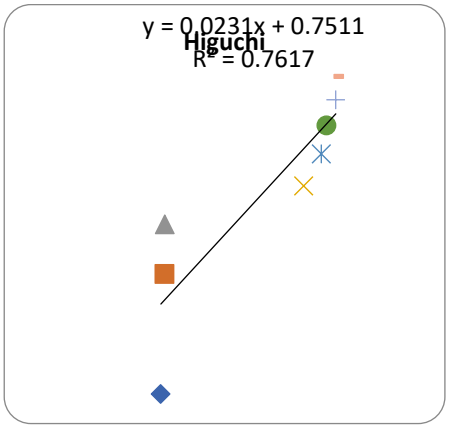
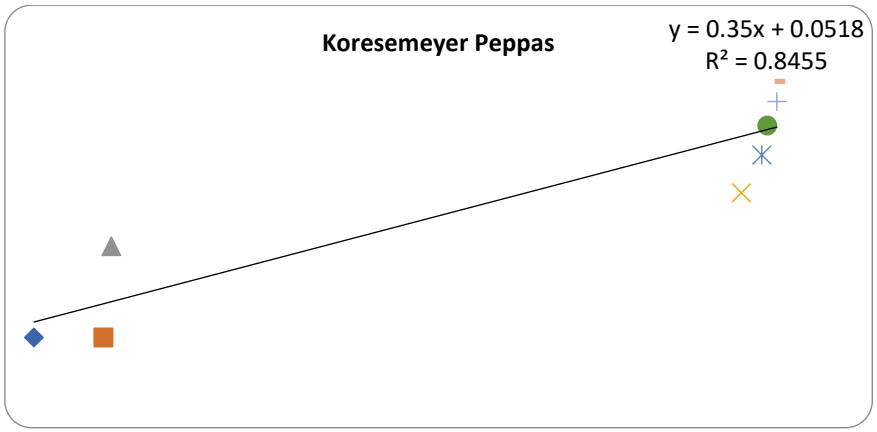
Kinetics of CI batch











Factorial design:

Factorial of batches

	Factor 1	Factor 2	Response 1
Run	A:Sodium alginate	B:Eudragit S-100	CPR
	gm	mg	%
1	1	100	56.91
2	1	200	31.9
3	1	300	17.19
4	2	100	49.8
5	2	200	42.98
6	2	300	43.9
7	3	100	68.79

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8	3	200	50.47
9	3	300	27.87

Response 1 CPR

ANOVA for Response Surface Linear model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob> F**	
Model	1530.14	2	765.07	10.23	0.0117	significant
A-Sodium alginate	*281.95*	*1*	*281.95*	*3.77*	*0.1002*	
B-Eudragit S-100	*1248.20*	*1*	*1248.20*	*16.69*	*0.0065*	
Residual	448.73	6	74.79			
Cor Total	1978.87	8				

The Model F-value of 10.23 implies the model is significant. There is only a 1.17% chance that an F-value this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B is a significant model term.Values greater than 0.1000 indicate the model terms are not significant.If there are many insignificant model terms (not counting those required to support hierarchy),model reduction may improve your model.

Std. Dev.	8.65		R-Squared	0.7732
Mean	43.31		Adj R-Squared	0.6977
C.V. %	19.97		Pred R-Squared	0.4721
PRESS	1044.68		Adeq Precision	8.523
-2 Log Likelihood	60.72		BIC	67.32
			AICc	71.52

The "Pred R-Squared" of 0.4721 is not as close to the "Adj R-Squared" of 0.6977 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effector a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs."Adeq Precision" measures the signal-to-noise ratio. A ratio greater than 4 is desirable. Your ratio of 8.523 indicates an adequate signal. This model can be used to navigate the design space.

	Coefficient		**Standard**	**95% CI**	**95% CI**	
Factor	**Estimate**	**df**	**Error**	**Low**	**High**	**VIF**
Intercept	43.31	1	2.88	36.26	50.37	
A-Sodium alginate	6.86	1	3.53	-1.78	15.49	1.00
B-Eudragit S-100	-14.42	1	3.53	-23.06	-5.78	1.00

Final Equation in Terms of Coded Factors:

CPR=+43.31+6.86*A-14.42*B

The equation in terms of coded factors can be used to make predictions about the response forgiven levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels of the factors are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

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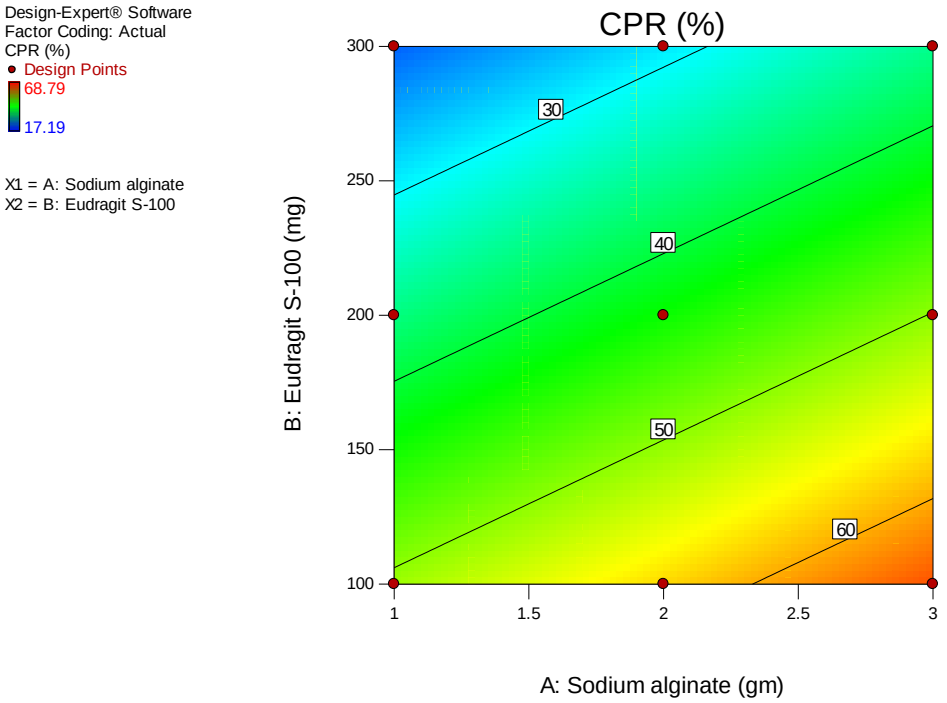

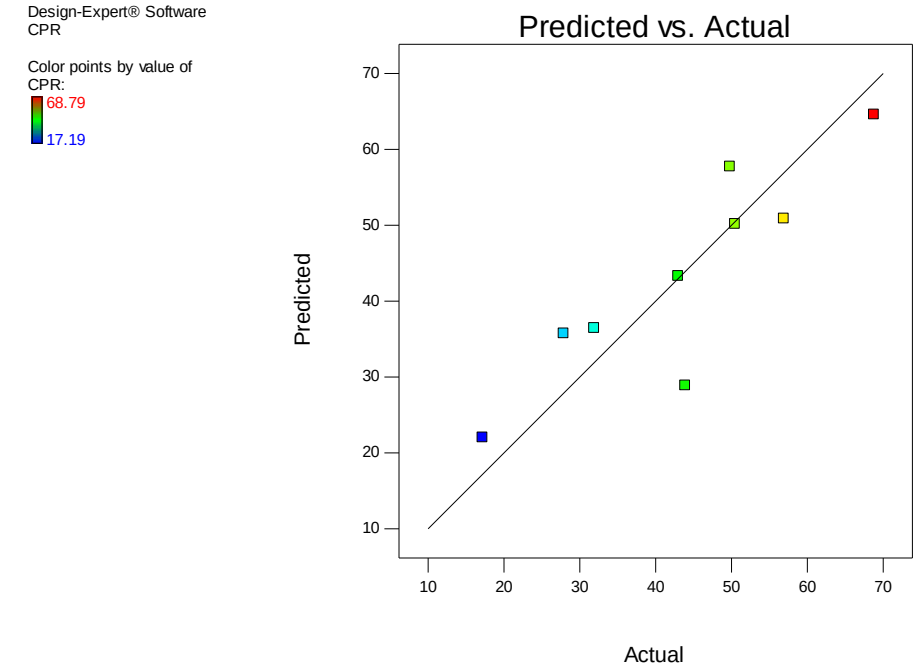

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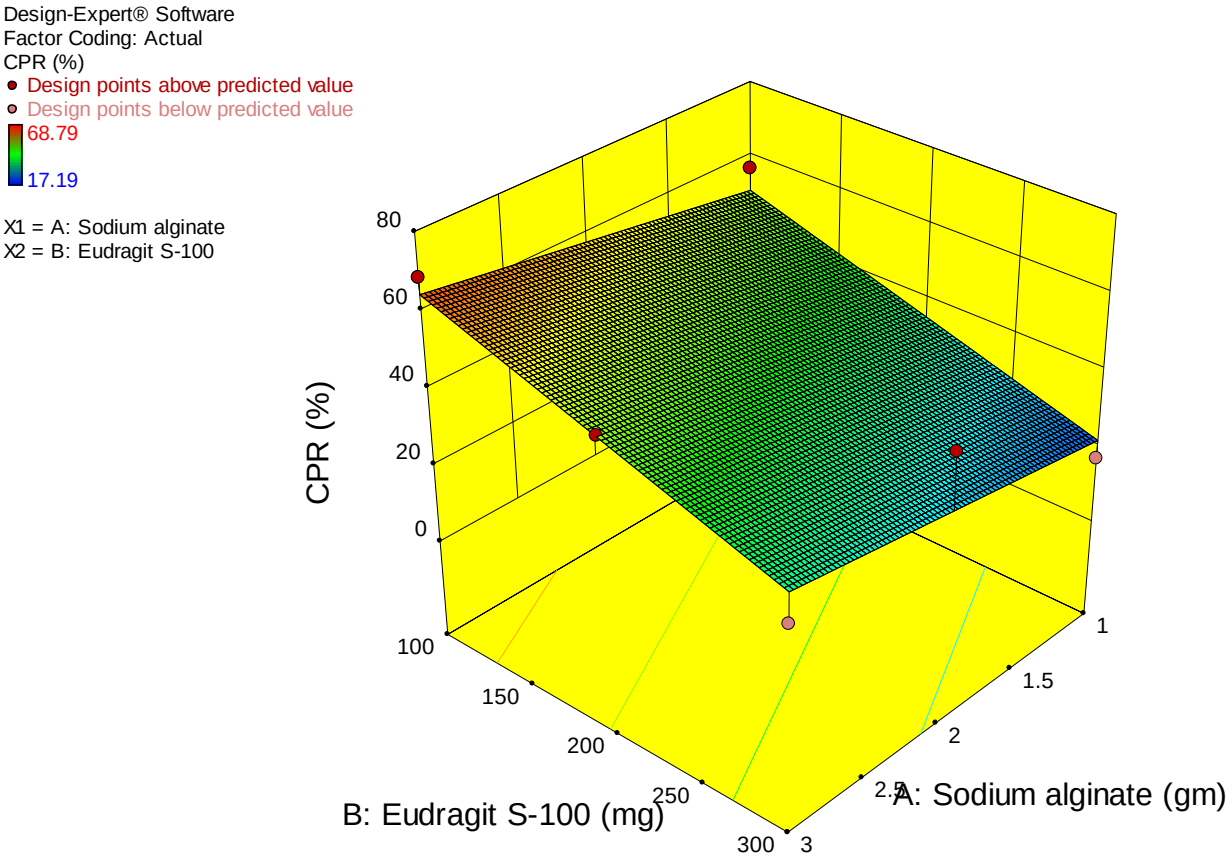

CONCLUSION

The results of my study clearly indicate that there is great potential in delivery of Meloxicam to the colonic region as an alternative to the conventional dosage form. However, more extensive pharmacokinetic and pharmacodynamics studies are needed before establishing colonic delivery of Meloxicam as an alternative. Sodium alginate is a biocompatible polymer; we expect it to cause no harmful effects if used for prolonged periods.

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