



Formulation and Evaluation Of Colon Targeted Drug Delivery System Of Edotolac Tablets

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ABSTRACT

Etodolac is used for the management of rheumatoid osteoarthritis. The site of absorption of Etodolac is in the whole GI tract and has a long half-life of 7 ± 4 hrs. The aim of the study was to develop colon targeted compression coated tablets of Etodolac using HPMC as swellable, time-controlled polymer, Eudragit S 100 as a coating polymer guar gum and chitosan as carriers in the treatment of Osteoarthritis. All the formulations (F1 to F5) were evaluated for the physicochemical parameters and were subjected to *in vitro* drug release studies. The amount of Etodolac released from tablets at different time intervals was estimated by UV spectrophotometer. The formulation F3 released 95.24% of Etodolac. The results of the study showed that formulation F3 is most likely to provide targeting of Etodolac for local action in the colon owing to its minimal release of the drug in the first 5 h. The most satisfactory formulation was stable during stability studies conducted for 60 days as per ICH guidelines. It showed no significant changes in the physicochemical parameters, *in vitro* release pattern. The studies confirmed that, the designed formulation could be used potentially for colon delivery by controlling drug release in stomach and the small intestine.

Keywords: Etodolac, rheumatoid osteoarthritis, HPMC and colon targeted.

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INTRODUCTION

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S and these systems have more advantages due to patient acceptance and ease of administration. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents. There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure-controlled systems. It is a serious drawback in conditions when localized delivery of drug in to colon is required as drug need to be protected from the hostile environment of upper GIT. Targeted drug delivery in to the colon is highly desirable for local treatment of variety of bowels diseases such as ulcerative colitis, cirrhosis and colonic cancer. Coating of the drugs with pH-sensitive polymers provides simple approach for colon specific drug delivery.

Compressed Core Coated Tablets

It is a system in which the entire surface of an inner core is totally surrounded by the coat these coats prevent drug release from the core until the polymeric or drug coat is fully eroded, dissolved or removed. It is simple and unique technology used to provide tablets with a programmable lag phase, followed by a rapid, or rate-controlled drug release. Release of drug depends upon the coating layer and core composition. It has a solvent-free coating and facilitates manufacturing process. It can be used to deliver one or more drugs.

It is one of the approaches which combine the features of both controlled release tablet and instant release tablet in one dosage form. It functions like sugar-coated or film-coated tablets in which the coating may cover a bitter substance, conceal an unpleasant or mottled appearance. Provide a barrier for a substance irritating to the stomach or single inactivated by gastric juice. This gives a far more accurate dose than in the case with sugar coating.

Etodolac

Etodolac is a member of the pyran carboxylic acid group of non steroidal anti-inflammatory drugs (NSAIDs). Etodolac is indicated for acute and long-term management of signs and

symptoms of osteoarthritis and rheumatoid arthritis, as well as for the management of pain.

MATERIALS AND METHOD

Etodolac was obtained from Cadila health care ltd, guar gum, eudragit S 100, chitosan, HPMC, lactose, starch, magnesium stearate and all other reagents and solvents were of analytical grade.

ANALYTICAL METHOD USED IN THE DETERMINATION OF ETODOLAC:

Determination of λ_{\max} using pH 6.8 phosphate buffer.

Absorbance maximum (λ_{\max}) for a drug was determined in pH 6.8 phosphate buffer. Accurately weighed 10 mg of pure Etodolac was transferred into 100 ml volumetric flask. The drug was then dissolved with 10 ml of methanol and diluted up to the mark with buffer to obtain a concentration of 100 μ g/ml as stock solution. From the stock solution aliquot was withdrawn to obtain a concentration of 5 μ g/ml and scanned over the wavelength range of 400 nm to 200 nm using UV-spectrophotometer against same dilutions as blank. The spectrum of absorbance versus wavelength was recorded and analyzed for the absorbance maximum (λ_{\max}) and its wavelength.

Standard calibration curve of Etodolac in phosphate buffer pH 7.4

100 mg of Etodolac was accurately weighed and dissolved with 10 ml of methanol in a 100 ml volumetric flask and made up to volume using phosphate buffer pH 7.4. Stock solution of Etodolac was subsequently diluted to a series of dilutions containing 2, 4, 6, 8 and 10 μ g/ml of solution using phosphate buffer pH 7.4. The Absorbance of these solutions was measured in UV-Visible spectrophotometer at 274 nm against same dilutions as blank. The graph of absorbance v/s concentration (μ g/ml) was plotted and data was subjected to linear regression analysis.

PRE-FORMULATION STUDIES

Compatibility study

Compatibility of the drug with the excipients is determined by subjecting the physical mixture of the drug and the polymers of the main formulation to infrared absorption spectral analysis (FTIR). Any changes in chemical composition of the drug after combining it with the polymers were investigated with I.R. spectral analysis.

Procedure:

Weighed amount of drug (3 mg) was mixed with 100mg of potassium bromide (dried at 40-50°C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer.

Similar procedure is followed for all relevant excipients used.

Formulation and Development of Etodolac Tablets

Table 1: Composition of Core Tablets of Etodolac

Ingredients (mg)	F1	F2	F3	F4	F5
Etodolac	400	400	400	400	400
Guar gum	25	50	75	100	-
Chitosan	75	50	25	-	100
Lactose	20	20	20	20	20
Starch	20	20	20	20	20
Mg-sterate	10	10	10	10	10
Total	550	550	550	550	550

Table 2: Composition of compression coated tablets of Etodolac

Ingredients(mg)	F1	F2	F3	F4	F5
Core tablet	550	550	550	550	550
Eudragit	150	120	90	60	30
HPMC	30	60	90	120	150
MCC	10	10	10	10	10
MgS	8	8	8	8	8
Talc	2	2	2	2	2
Total	700	700	700	700	700

FORMULATION OF ETODOLAC CORE TABLET Wet Granulation method:**Weighing and mixing****Granulation****Drying of granules****Lubrication****Compression****Figure 1: Flow chart of wet granulation method****FORMULATION OF ETODOLAC COMPRESSION COATED TABLETS****Method of preparation**

- Firstly, core tablet is formulated which is small in size.
- Then for the upper coating, large size punches are used.
- Half amount of coating material is placed in die cavity.
- Then carefully placed a core tablet on it.
- After that remaining half amount of coating material is taken.
- And finally, the tablet is compressed as compression coated tablet.

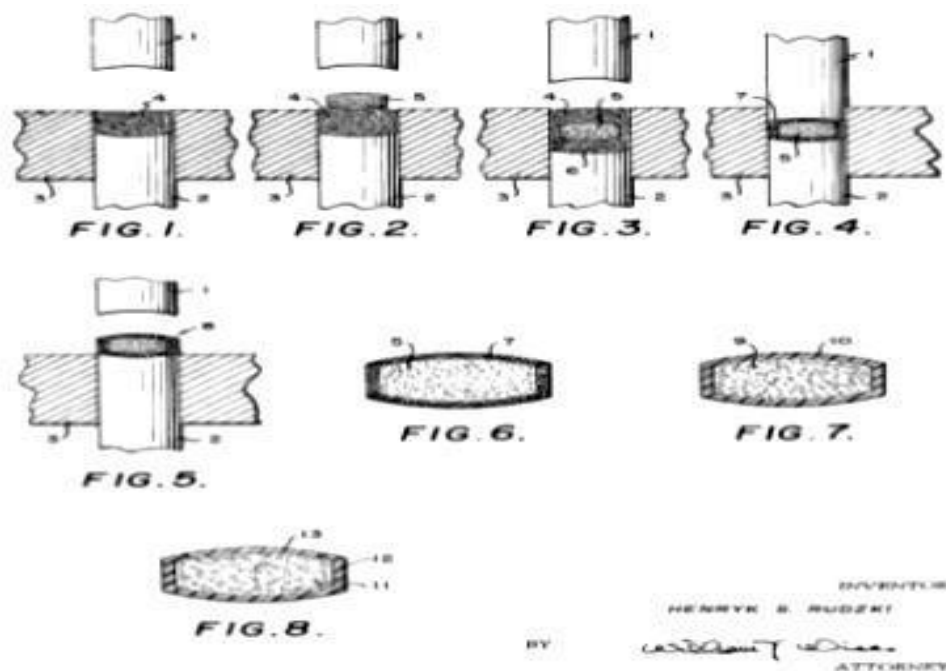


Figure 2: compression coating technique

All ingredients are weighed accurately and passed through 40 no sieves. All ingredients except magnesium stearate was transferred in to the motor and mixed thoroughly for 5 min to obtain a uniform mixed powder and blend homogenously for 15 min by triturating with the help of pestle. The above blend mixture was granulated with 10%w/v starch paste till a coherent mass was formed and passed through mesh no. 10 to form granules. The collected granules were dried at 40 °C. and passed through sieve 20. Granules were lubricated by blending with magnesium stearate and evaluated for pre compression parameter and then subjected for tablet compression.

Pre-compression parameters

Angle of Repose:

The angle of repose is the constant, three-dimension angle (relative to horizontal base) assumed by a cone like pile of material formed by any of several different methods. When the angle of repose exceeds 50degrees, the flow is rarely accepted for manufacturing purpose.

Bulk Density:

The bulk density was determined by transferring the accurately weighed sample of powder to the graduate cylinder. The initial volume and weight were noted. Ratio of weight of the sample was calculated by using the following formula.

$$\text{Bulk Density} = \text{Mass} / \text{Bulk volume.}$$

Tapped Density:

Weighed powder sample was transferring to a graduated cylinder and was placed on the tap

density apparatus, was operated for fixed number of taps (100). The tapped density was determined by the following formula.

$$\text{Tapped Density} = \text{Mass} / \text{Tapped volume.}$$

Percentage compressibility:

Based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by the following formula

$$\% \text{ Compressibility} = \frac{\text{Tapped density} - \text{Bulk density} \times 100}{\text{Tapped density.}}$$

Hauser's Ratio:

It is measured by the tapped density to bulk density.

$$\text{Hauser's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

POST COMPRESSION PARAMETERS

Tablet thickness:

Randomly 5 tablets were taken from each formulation trial batch and their thickness was determined by using screw gauge.

Weight variation test:

20 tablets were randomly selected from each formulation trial batch and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight.

Measurement of tablet hardness:

Hardness of 10 tablets was found using Monsanto hardness tester, mean and standard deviation were computed and reported. It is expressed in kg/cm^2 .

Friability:

10 tablets were weighed and placed in Roche friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. The Friabilator was operated at 25 rpm for 4 mins. After 100 revolutions, tablets are removed, deducted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

Content Uniformity

Crush four (4) tablets and take average weight of tablet powder equivalent to 10 mg of Etodolac and dissolve in 100 ml of pH 6.8 phosphate buffer. Tablets was allowed to dissolve in the solution and 5 ml of filtrate was dilute to 50 ml with the same buffer and analysed spectrophotometrically at 274 nm.

***In-vitro* dissolution studies**

In-vitro dissolution study was performed by using USP Type II Apparatus (Basket type)

[Electrolab (ETC-11L) Tablet Dissolution Tester] at 100 rpm for 2 h in 0.1 N HCl (900 ml). Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for 3 h as the average transit time of small intestine is 3 h. After 5 h, the dissolution medium was replaced with pH 6.8 phosphate buffer and tested for next 10 h. At the end of the time period 5 ml of the sample were taken and analyzed for Etodolac content as described previously. 5 ml of filtrate was diluted to 50 ml with the same buffer and analysed spectrophotometrically at 274 nm.

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

First order kinetics

This type of model to analyse drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t / 2.303$$

Where Q_t is the amount of drug released in time t , Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant.

Korsmeyer Peppas model

Korsmeyer developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Q_t / Q_a = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism.

Table 2: kinetic model

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Higuchi Model

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus concentration indicates that the drug

release follows strict Fickian diffusion.

$$Q_t = K_H t^{1/2}$$

Where

Q_t = the amount of drug released at time t and

K_H = the Higuchi release rate

RESULTS AND DISCUSSION

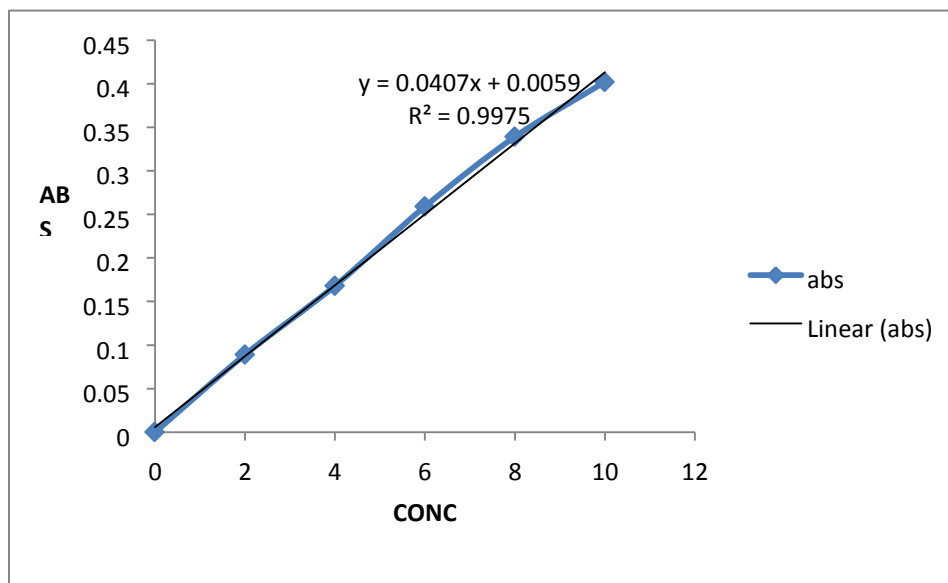


Figure 3: Standard calibration curve for Etodolac in phosphate buffer pH 7.4

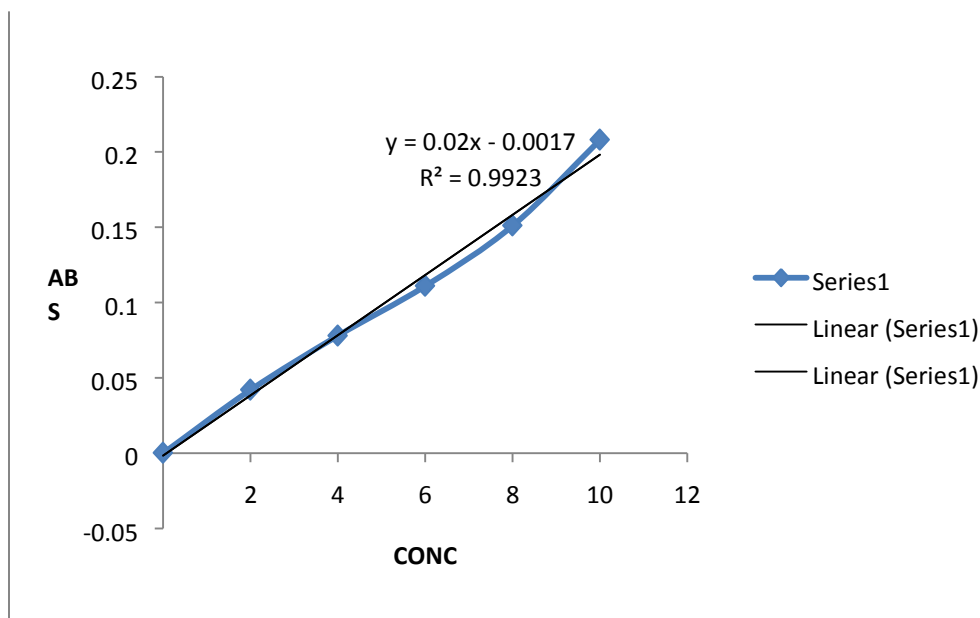


Figure 4: Standard calibration curve of Etodolac in phosphate buffer 6.8 pH

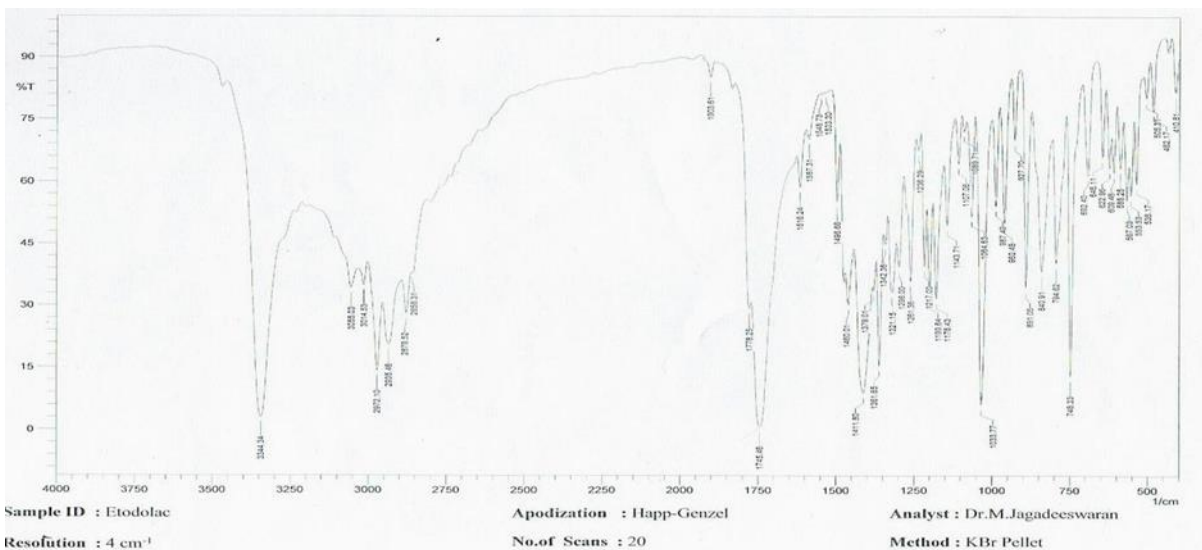


Figure 5: FTIR spectrum of pure Etodolac

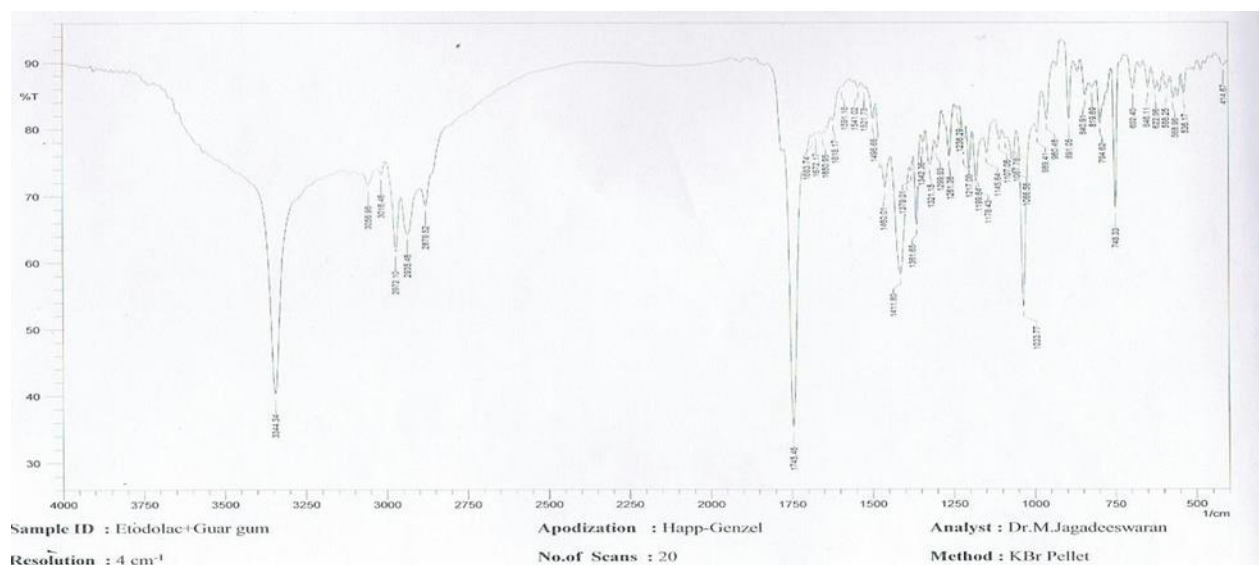


Figure 6: FTIR spectrum of Etodolac with polymers

EVALUATION OF COLON TARGETED ETODOLAC TABLETS

Pre compression evaluation parameter

Table 3: Pre-Compression Parameter results

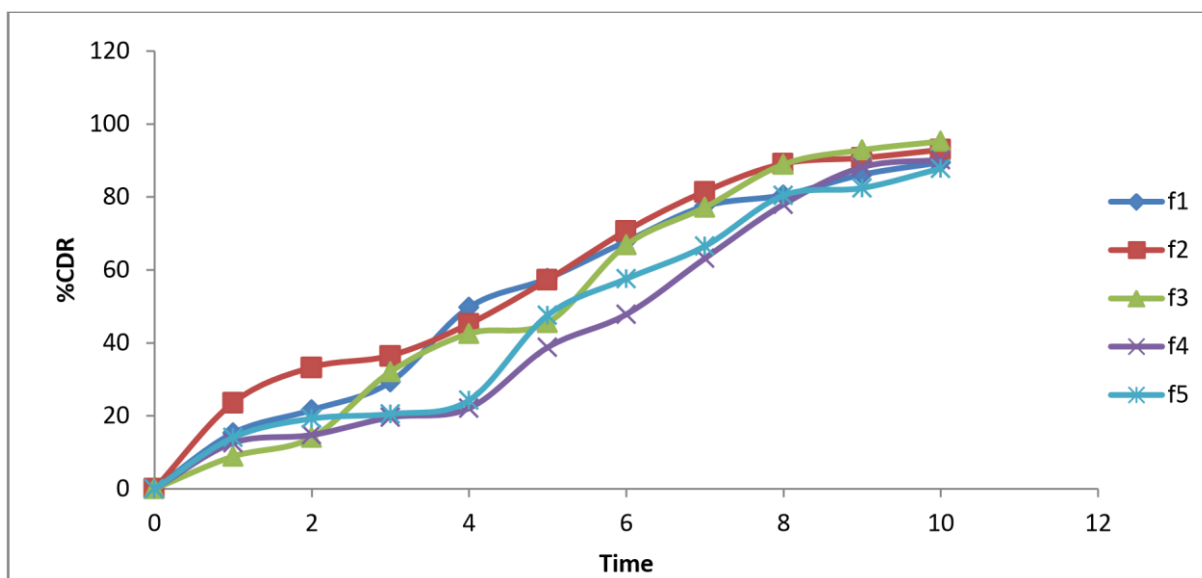
Formulation	F1	F2	F3	F4	F5
Bulk density g/cm ³	0.41±0.016	0.45 ± 0.03	0.378±0.055	0.350±0.036	0.40 ± 0.027
Tapped density g/cm ³	0.51±0.012	0.48 ± 0.06	0.472 ± 0.03	0.406 ± 0.07	0.45 ± 0.05
Angle of repose(°)	18 ± 0.383	19 ± 0.370	18 ± 0.212	19.3 ± 0.41	18.5 ± 0.296
Carr's index%	19.60±0.185	6.25±0.153	20 ± 0.182	13.79 ± 0.22	11.11 ± 0.24
Hausner's ratio	1.24±0.0176	1.06±0.099	1.24±0.0101	1.16±0.0172	1.125±0.0102

Table 4: Data for post compression studies of the prepared formulation for core tablet

Parameters	F1	F2	F3	F4	F5
Thickness(mm)	3.831 ± 0.0516	3.830 ± 0.0527	3.831 ± 0.0483	3.825 ± 0.0632	3.822 ± 0.0707
Hardness(kg/cm ²)	5.836 ± 0.5851	5.96 ± 0.1476	5.88 ± 0.5782	5.90 ± 0.1989	5.83 ± 0.5731
Friability (%)	0.31% ± 0.0730	0.39% ± 0.0312	0.45% ± 0.0115	0.30% ± 0.0422	0.28% ± 0.0456
Weight variation (mg)	547.66±0.062%	549.66±0.08%	550.66±0.061%	547± 0.182%	548± 0.183%
Drug content (%)	95.01%±0.2435	90% ± 0.31	99.86%±0.3107	90.03%±0.3094	94.5% ±0.3573

Post compression studies compressed coated tablet**Table 5: Data for post compression studies of the prepared formulation for compressed coated tablet**

Parameters	F1	F2	F3	F4	F5
Thickness(mm)	5.12 ± 0.0568	5.18 ± 0.0675	5.17 ± 0.0516	5.14 ± 0.0632	5.16 ± 0.0675
Hardness(kg/cm ²)	6.4 ± 0.2983	6.5 ± 0.3464	6.7 ± 0.2781	6.8 ± 0.2635	6.8 ± 0.1792
Friability (%)	0.24% ± 0.1009	0.34% ± 0.1299	0.38% ± 0.1229	0.2% ± 0.1010	0.24% ± 0.1348
Weight variation (mg)	748.3±0.04%	750 ± 0.1%	750.6 ± 0.05%	747.3 ± 0.04%	748.6 ± 0.08%
Drug content (%)	94.53%±0.135	89% ± 0.117	95% ± 0.271	90.5% ± 0.309	91.02% ± 0.067

In Vitro Drug Release Study of Formulations**Figure 7: In vitro drug release study of formulations (F1- F5) in phosphate buffer (pH 6.8)****Table 6: Kinetics modelling data**

Formulation code	Zero order (r ²)	First order (r ²)	Higuchi (r ²)	Krosmeypapas (r ²)	(n)
F1	0.97	0.67	0.98	0.98	0.71
F2	0.95	0.59	0.98	0.98	0.70
F3	0.95	0.80	0.99	0.92	0.73
F4	0.95	0.77	0.92	0.94	0.69
F5	0.96	0.73	0.91	0.96	0.69

CONCLUSION

The present investigation was aimed to develop novel oral colon targeted compression coated tablet formulations of Etodolac for safe and effective therapy of rheumatoid arthritis by using Eudragit S 100 and HPMC mixture as a coating material the pre-formulation studies and post compression studies of Etodolac complied with IP standards. The FTIR spectra revealed that, there was no interaction between polymer and drug polymers used were compatible with Etodolac. *In vitro* drug release kinetic study revealed that Etodolac tablet formulation F1 to F5 release drug with Higuchi kinetics, whereas tablet formulation F4 and F5 release drug with Zero order kinetic. From the korsmeyer-peppas model, it revealed that the drug release profile tablet formulation F1 to F6 follow non-Fickian transport mechanism. The susceptibility of the core tablet to the enzymatic action of colonic bacteria was assessed by performing the drug release studies in medium containing pH 6.8 phosphate buffer using guar gum and Chitosan mixture in ratio (3:1) as carriers. In conclusion, the core tablets compression-coated with Eudragit S 100 : HPMC as a coat material in the ratio (1:1) released only 6% of drug in the physiological environment of stomach and small intestine and released more than 95% of the drug in the target area i.e. physiological environment of colon Thus, based on these results, the tablets containing optimum proportion of Eudragit S 100:HPMC mixture (1:1) is most likely to target Etodolac to the colon without being released significantly in stomach and small intestine.

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