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DEVELOPMENT AND EVALUATION OF COLON TARGETED COMPRESSED COATING TABLETS OF ETODOLAC

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ABSTRACT

Compression coating is one of the strategies for delivering drug to the colon. The main aim of these formulations to develop Etodolac core tablets compression coated with a mixture of time dependent hydrophilic swellable polymer HPMC K 15M, Eudragit L100 and Xanthan gum in different ratios. The effect of proportion of HPMC, Eudragit and Xanthan gum in the coat on premature drug release in upper part (Stomach and small intestine) of GIT & the amount of drug release in colon target area was studied. The formulations are carried out by using Direct Compression method. Sodium starch Glycolate used for rapid disintegration. FTIR used for Drug-Polymer Interaction studies. The prepare tablets were evaluated for hardness, thickness, friability, *In-Vitro* Dissolution. The F6 Batch Eudragit gives better result than other formulations.

INTRODUCTION:

Colon specific diseases are often in efficiently managed by oral therapy, because most orally administered drugs are absorbed before arriving in the colon. Therefore, colon-specific drug delivery systems, which can release the drugs to the lower gastrointestinal tract without deliver in the upper GI-tract. It can be expected to increase the quality of life for patients suffering from colon specific diseases. Treatment might be more effective if the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and, if so, reduced systemic side effects can be produced by giving lower doses in adequate amounts[1]. Number of serious diseases of the colon might be capable of being treated more effectively if drugs were targeted on the colon. Therefore, it appears that targeted drug delivery with an appropriate release pattern could be crucial in providing effective therapy for these chronic Diseases.

In addition to providing more effective therapy of colon related diseases, colon specific delivery has the potential to address important unmet therapeutic needs including oral delivery of macromolecular drugs[2]. The representatives of colon specific diseases are Inflammatory Bowel Disease (IBD), including Ulcerative Colitis and Crohn's disease, Irritable Bowel Syndromes (IBS), Constipation and Colorectal Carcinoma-I. In particular, patients suffering from colorectal cancer have been apprehensively increasing recently[3]. Etodolac is a Non-steroidal anti-inflammatory drug with anti-inflammatory. Etodolac inhibits the enzyme cycloxygenase (COX) and decreases the peripheral prostaglandins synthesis involved in mediating inflammation. It combinds to the COX enzyme active site upper portion and prevents its substrate, arachidonic acid, from entering the active site[4]. Previously Etodolac is a non-selective COX inhibitor, but now it is known to be 5 – 50 times more selective to the COX-2

than COX-1. The antipyresis may produce by central action on the hypothalamus and resulting in peripheral dilation, subsequent heat loss and increased cutaneous blood flow.

MATERIALS AND METHODS:

Etodolac, Starch, sodium starch glycolate, Poly vinyl propylene K30, Magnesium stearate, Hydroxypropylmethyl cellulose K15M, Eudragit L100, Xanthan gum, Microcrystalline cellulose pH 101 and talc are required for preparing of Etodolac compressed coating tablets[5,6].

Estimation of Etodolac[7]

A spectrophotometric method based on the measurement of absorbance at 279nm in 0.1N HCl and pH 6.8 phosphate buffers are used in the present study for the estimation of Etodolac**.**

Standard solution

100mg of Etodolac pure drug was dissolved in 100ml of 0.1N HCl (stock solution-1000μg/ml), from this 10ml of solution was taken and the volume was adjusted to 100ml with 0.1N HCl (100 μg/ml).

Calibration curve of Etodolac in 0.1N HCl

The above solution was subsequently diluted with 0.1N HCl to obtain the series of dilutions containing 2, 4, 6,8,10 and 12 μg/ml of Etodolac solution. The absorbance of the above dilutions was measured at 279nm by using the UV-Spectrophotometer using 0.1N HCl as blank. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line which is given in Table 1 and figure 1.

Calibration curve of Etodolac in Phosphate buffer pH 6.8[7]

Accurately weighed quantity of Etodolac (100mg) was dissolved in methanol and the volume made up to 100ml with the same. 10ml of Stock solution I was further diluted with 100ml of buffer to get a working standard. Aliquots of 5-25µg of stock solution was pipetted into 10ml volumetric flask and diluted up to the volume with buffer. The absorbance was measured at 279nm which is given in Table 2 and figure 2.

Drug–Exicipient interaction study

The pure drug and a mixture of it with the polymers Xanthane gum, HPMC and Eudragit were mixed separately with IR grade KBr in the ratio of 100:1 and corresponding pellets were prepared by applying pressure in a hydraulic press[8]. The pellets were scanned over a wave number range of 4000-400cm-1 in Thermo Nicolet USA, FTIR instrument and graphs given in figure 3.

Pre-compressional parameters [9-12]

Bulk Density:

Bulk density is the ratio of total mass of powder to the bulk volume of powder and it is measured by pouring the weighed sample or powder into a measuring cylinder and the volume was noted.

Tapped Density:

Tapped density is the ratio of total mass of powder to the tapped volume of powder and the tapped volume was measured by tapping the powder to constant volume.

Hausner's ratio:

Hausner's ratio is the fast, simple, and popular methods of predicting powder flow characteristics. It is the ratio of tapped density to bulk density.

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. This is the maximum angle possible between surface of a pile of powder or granules and the horizontal plane.

Carr's Index:

It indicates the ease with which a material can be induced to flow.

Procedure for core tablets: [13-15]

Step 1: Weighing all ingredients and pass through the sieve number 60.

Step 2: Blend the mixture for 15min in double cone blender.

Step 3: Compression in flat faced 6mm circular punches and formulation of each tablet is given in tablet 4.

Procedure for press coated tablets:

Step 4: weigh the other excipients and pass through sieve number 60. Then blend the mixture in a poly bag for 10min.

Step 5: pour the half mixture in die (8.7mm) then place the core tablet and then fill remaining mixture on surface of the core tablet.

Step 6: Then compress the tablets and formulation of each tablet is given in table 5.

Post compressional Parameters: [16-18]

Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually, and then average weight of tablets was calculated. Indi-

vidual tablet weight was compared with the average weight.

Hardness

The hardness of the 6 tablets of each formulation was determined by using the Monsanto hardness tester. This tester operates in a horizontal position. An anvil driven by manually presses the tablet at a constant load rate against a stationary anvil until the tablet breaks.

Friability

The friability of the tablet was determined using Roche Friabilator. The friabilator was operated at 25 rpm for four min.

Thickness

Thickness of tablets was important for uniformity of tablet size. Thickness of the tablet was measured by the using vernier calipers on 3 randomly selected samples.

Content uniformity test

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of drug was transferred into 25 ml volumetric flask and 15 ml water is added. After appropriate dilution, the drug content was determined by measuring the absorbance at 279 nm.

***In-vitro* dissolution study[19-20]**

Acid release: 900 ml of 0.1N HCl was used as dissolution medium and it is placed in vessel. Then the USP apparatus-1 (basket having the tablet) was assembled and the medium was allowed to equilibrate to temperature of $37^0 \pm 0.5^0$C. After that apparatus was operated and the samples are removed at different time intervals in the acid stage (2 hours). The removed aliquots were passed through a suitable 0.45-µm filter. The amount of drug dissolved in acid stage was determined at λ_{max}279 nm by UV Spectrophotometric method.

Buffer stage: After the completion of 2 hours of dissolution in acid stage, immediately the P^H 6.8 phosphate buffer was replaced in the dissolution vessels and further subjected to drug release study. The dissolution samples were collected at 3, 4, 5, 6, 7, 8, 9 and 10 hours time intervals and were passed through a suitable $0.45\mu m$ filter. The amount of drug dissolved in the buffer stage at various time points was determined at λ_{max}279 nm by UV Spectrophotometric method.

***In-vitro* release kinetics[21]**

The dissolution profile of most satisfactory formulation was fitted into zero order, first order, Higuchi model and korsmeyer peppas model to ascertain the kinetic modeling of the drug release. The methods were adopted for deciding the most appropriate model.

RESULTS AND DISCUSSION:

The present study was undertaken to formulate Etodolac compressed tablets. The study involves preformulation studies of drug and exicipients, formulation and processing development along with evaluation of tablets made with the optimized formulation. Finally controlled release tablets were evaluated by *in-vitro* methods. Results of FTIR spectroscopy (figure 3) showed that, functional group frequencies of Etodolac were in the reported range which indicates that the obtained sample was of Etodolac and was pure. Pre compressional parameter studies (table 3) of powder blends of different batches prepared by compression, it was concluded that powder blends of all batches had the good flow properties. From the results tabulated in the table 6 it was observed all physical parameters (Hardness & Thickness) of compressed coated tablets were found to be within the limits.

Table.1: Calibration curve of Etodolac in 0.1N HCl

Concentration (mcg)	Absorbance at 279nm
0	0
2	0.114
4	0.215
6	0.327
8	0.432
10	0.524
12	0.623

Figure.1: Calibration curve of Etodolac in 0.1N HCl

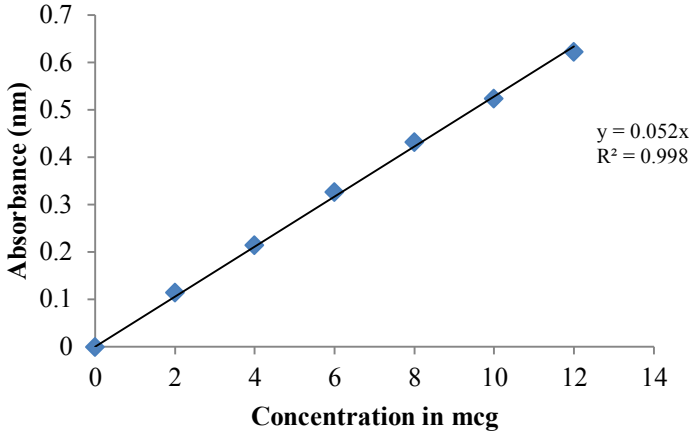

Table.2 Calibration curve of Etodolac in pH 6.8 phosphate buffer.

Concentration (mcg)	Absorbance at 279nm
0	0
5	0.185
10	0.375
15	0.585
20	0.766
25	0.954

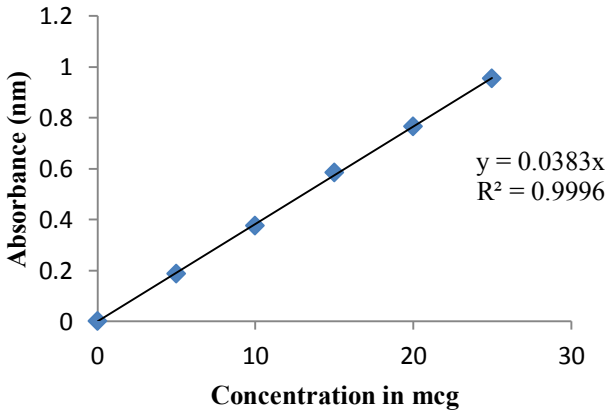

Figure 2: Calibration curve of Etodolac in pH 6.8 phosphate buffer

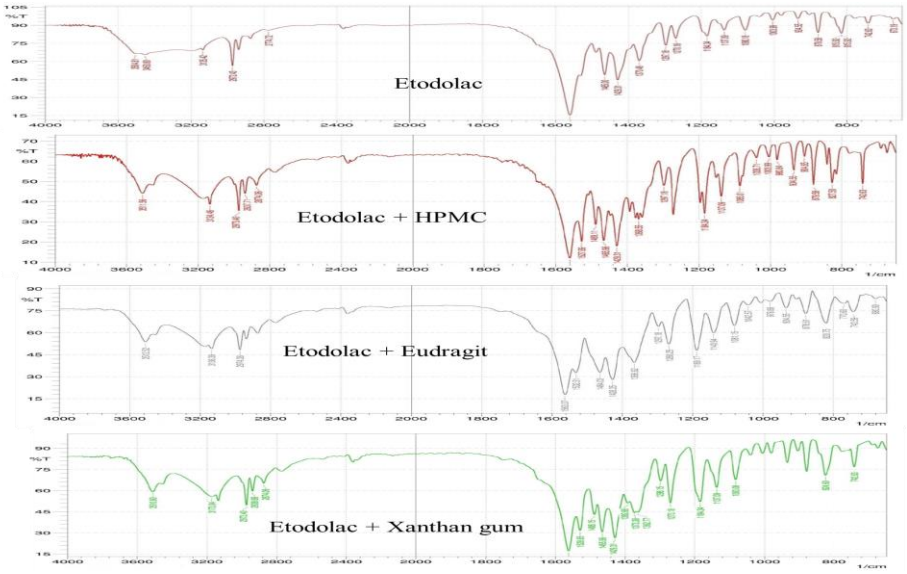

Figure 3: FTIR Graphs

Table 3: Pre Compressional properties of different blends:

F Code	Bulk Density ±SD* (gm/ml)	Tapped Density ±SD* (g/ml)	Carr's Index ± SD* (%)	Hausner ratio ±SD*	Angle of repose ± SD*
F1	0.52±0.06	0.65±0.05	14.04±0.12	1.21±0.04	26.1±0.2
F2	0.55±0.04	0.64±0.06	12.72±0.15	1.16±0.03	28.6±0.2
F3	0.49±0.02	0.57±0.04	13.20±0.15	1.15±0.02	27.2±0.2
F4	0.48±0.04	0.55±0.06	12.72±0.14	1.14±0.04	24.1±0.4
F5	0.50±0.05	0.58±0.05	13.79±0.16	1.16±0.03	27.5±0.3
F6	0.53±0.05	0.61±0.06	13.11±0.14	1.15±0.01	26.8±0.2
F7	0.52±0.04	0.60±0.01	13.33±0.16	1.15±0.05	28.5±0.2
F8	0.55±0.06	0.64±0.01	14.06±0.12	1.16±0.02	24.6±0.4
F9	0.48±0.05	0.56±0.05	14.28±0.14	1.06±0.05	26.7±0.2

Table 4: Formulation for Core tablet:

Ingredients	Quantity per Tablet (mg)
Etodolac	100
Starch	27
Sodium starch glycolate	15
PVP K30	5
Magnesium Stearate	3
Total Wt	150

Table 5: Composition of press coated tablet

F Code	Core tablet (mg)	HPMC K15M (mg)	Eudragit L100 (mg)	Xanthan gum (mg)	MCC pH 101	Talc (mg)	Total tablet weight (mg)
F1	150	60	-	-	84	6	300
F2	150	80	-	-	64	6	300
F3	150	100	-	-	44	6	300
F4	150	-	60	-	84	6	300
F5	150	-	80	-	64	6	300
F6	150	-	100	-	44	6	300
F7	150	-	-	60	84	6	300
F8	150	-	-	80	64	6	300
F9	150	-	-	100	44	6	300

Table 6: Post formulation studies:

F Code	Hardness* (kg/cm2) ± SD	Friability (%) ± SD	Thickness (mm) ± SD	Weight variation ± SD
F1	5.4 ±0.05	0.62±0.05	3.8±1.46	298±0.06
F2	6.1±0.05	0.64±0.05	3.6±1.45	299±0.04
F3	5.5±0.05	0.76±0.05	3.9±0.63	301±0.54
F4	5.2±0.10	0.89±0.10	3.8±0.92	304±0.07
F5	5.1±0.05	0.64±0.05	3.8±0.75	294±0.82
F6	5.2±0.05	0.46±0.15	3.8±0.66	296±0.14
F7	5.4±0.15	0.65±0.05	3.5±0.75	299±0.16
F8	5.2±0.05	0.55±0.10	3.6±1.45	301±0.54
F9	5.5±0.05	0.64±0.05	3.8±0.92	300±0.045

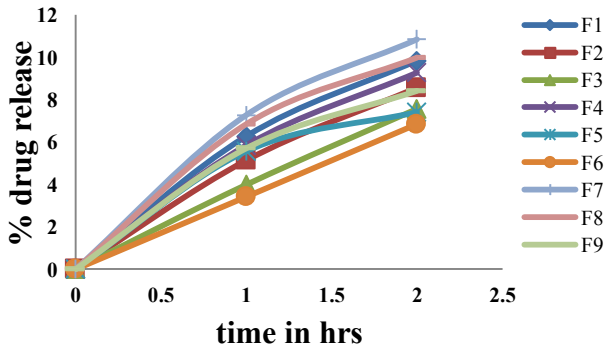

Figure 4*: In-vitro* drug release in Acidic stage

Figure 5*: In-vitro* drug release in buffer stage

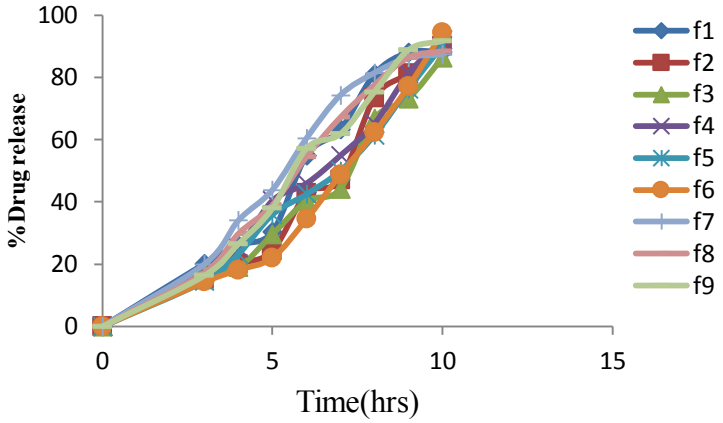

Table 7: *In-vitro* release kinetics for F6

S.no	Kinematic model	R^2	n-value
1	Zero order plot	0.956	1.385
2	First order plot	0.851	
3	Higuchi model	0.902	
4	Hixson Crowell plot	0.823	
5	Korsmeyer-peppa's plot	0.979	

In vitro dissolution studies of all formulations of colon tablets were carried out in 0.1N HCl for first 2 hours (figure 4) and remaining 8hours in 6.8 Phosphate buffer. The study was performed for 10hrs and the cumulative drug release was calculated at every hour interval. It was observed that the type of polymer influences the drug release pattern. All the formulations contained different amounts of rate retarding agents hydroxypropylmethylcellulose (HPMC) and methacrylic acids (Eudragit L100) and natural polymer Xanthan gum. The *In-vitro* drug release for formulations (figure 5) with polymer HPMC K4M (F1 to F3) was ranged from 88.18% to 86.26 % for 10hrs. The *In-vitro* drug release for formulations with polymer Eudragit L100 (F4 to F6) was ranged from 92.06% to 94.32% for 10hrs. The *In-vitro* drug release for formulations with polymer Xanthan gum (F7 to F9) was ranged from 87.36% to 91.65% for 10hrs. The maximum drug release was observed from the formulations based on Eudragit and xanthan gum polymer. Varying the amount of 94.32% and 91.65% affect the drug release. All 9 formulation were showing better drug release profile in both medias, but Formulation F6 shows better drug release retards up to 6hr, when the tablet enters in to colonic region is after 7 hrs it shows maximum release profile. Hence, the F6 is best formulation. According to above R^2 value (table 7), best formulation, i.e., F-6 formulation follows zero order kinetics. From the Korsmeyer peppas model which may shows that drug release is case-2 relaxation or super case transport-2 and refers to erosion of the polymeric chain (If n = 0.89 and above indicates case-2 relaxation or super case transport-2)

CONCLUSION

Etodolac compressed coating tablets were prepared by direct compression coating method by using HPMC K 15 M, Eudragit L100 and Xanthan gum polymers. Among all the formulations F6 showed 94.32% controlled drug release at the end of 10 hours. The stability studies were conducted as per the ICH guidelines no significant changes occur in the best formulation.

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