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DEVELOPMENT OF ORAL FORMULATIONS FOR COLON-SPECIFIC DRUG DELIVERY USING EUDRAGIT, HPMC AND CARBOPOL AS EXCIPIENTS

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ABSTRACT

The aim of present research work was to develop colon targeted controlled drug delivery system of mesalamine tablet by using slight modification in CODES^{TM} technology that protect drug during its passage through the stomach and about first six meters of small intestine. Method: The drug and polymers were directly compressed in tablet press. Mesalamine tablets were prepared in two group A and B. In group A tablets with combination of carbopol with HPMC and in group B alone carbopol were used. Tablets were spray coated with lactulose USP solution then followed with acid-soluble coating material, eudragit E-100 (10%w/w), water-soluble HPMC (10%w/w), enteric-coating material, eudragit L-100 (10%w/w). Mesalamine core and coated tablets were characterized with official methods. No in-vitro release of mesalamine in pH1.2 for first hour and in buffer pH 6.8 for next four hour but in PBS (phosphate buffer saline) pH 5.0 drug releases was observed. Result: in Group A the value of regression coefficient for batch CT-1 and CT-2 was 0.9978 indicating zero order release and in group B the value of regression coefficient for formulation R3 was found to be 0.9935 indicating zero order release.

KEYWORDS: CODES^{TM} technology, mesalamine, IBD.

1. INTRODUCTION

Colon-specific drug delivery is intended to improve the efficacy and reduce side effects by exerting high drug concentrations topically at the disease site. Because of the distal location of the colon in the gastrointestinal (GI) tract, an ideal colon-specific drug delivery system

should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. This requires a triggering mechanism built in the delivery system responsive to the physiological changes particular to the colon. However, the physiological similarity between distal small intestine and the proximal colon presents very limited options in selecting an appropriate drug release triggering mechanism. Commonly used pharmaceutical strategies to achieve a colon-specific drug delivery include timed-release approximating the GI transit time, pH-sensitive polymer coating, prodrug, and colonic microflora activated delivery systems.[1] The representatives of colon specific diseases are inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, irritable bowel syndromes, colorectal carcinoma, and constipation. In particular, patients suffering from IBD have been appreciably increasing in Japan.[2] Unfortunately, they must often take drugs, such as anti-inflammatory, chronically, because IBD recurs as a cycle of acute episodes and remissions.[3] Colon specific diseases are often inefficiently managed by oral therapy, because most orally administered drugs are absorbed before arriving in the colon. Therefore, colon-specific drug delivery systems, which can deliver drugs to the lower gastrointestinal tract without releasing them in the upper GI-tract, can be expected to decrease the side-effects of the drugs and improve the quality of life for patients suffering from colon specific diseases.[4]

Generally, the colon is not as suitable a site for drug absorption as is the small intestine, because the water content in the colon is much lower and the colonic surface area for drug absorption is narrow in comparison with the small intestine.[5] However, the colon is a preferable site for the absorption of protein drugs, because the hydrolytic enzyme activities of the colon are lower than that of the small intestine.[6] Therefore, many researchers have focused on the colon as a potential delivery site for peptide and protein drugs. Many colon-specific drug delivery systems have been investigated, not only to treat the colonic diseases, but also to improve the bioavailability of such drugs.[7] Several approaches utilizing the GI-transit time of various formulation[8] and the change in pH[9] bacterial concentration[10] and pressure[11] in the GI-tract have been reported to achieve colon-specific drug delivery. The pH-sensitive delivery systems have used enteric coating materials such as Eudragit L100[9]. Some new synthetic polymers containing an aromatic azo group, which are degraded by intestinal flora, have been developed and used as coating materials.[10] Orally administered lactulose is not absorbed in the upper GI tract, but degraded to organic acids by enterobacteria in the lower GI tract, especially the colon.[12] In the present study, we have

studied that slight modification in CODES^{TM} technology provide controlled release nature of mesalamine in colon. The therapeutic advantage of controlling and targeting mesalamine was to increase local tissue concentration of the drug, hence lesser amount of drug was required to exert therapeutic effect The tablet core containing lactulose and a drug, coated with an acid-soluble coating material, is further coated with an enteric coating material. In the stomach, the drug is not released from CODES^{TM} with the enteric coating layer. In the small intestine where the enteric coating layer, the drug is still not released from the tablet core because of its inner acid-soluble coating layer. However, gastrointestinal fluids penetrate into the tablet core through the acid-soluble coating layer and then lactulose begins to dissolve inside the core during the small intestinal transit.[14]

When CODES^{TM} arrives at the colon, lactulose leaches through the acid-soluble coating layer and is degraded by enterobacteria and produces organic acids. These organic acids should dissolve the acid-soluble coating layer to release the drug. The feature which distinguishes CODES^{TM} from other strategies is the generation of organic acids by bacterial degradation of lactulose in the colon to dissolve the acid-soluble coating layer. The aim of the present study was to establish a new concept, which exploits pH control by bacterial degradation of lactulose in order to develop the CODES ^{TM} and to reduce the dose size of mesalamine tablet.[14]

2.0 EXPERIMENTAL

2.1 Material and Method

Mesalamine was kindly provided as a gift sample from Sarex Overseas, Worli. Lactulose was prepared from the marketed preparation livoiluk manufactured by Panaecea Biotech. New Delhi, India. Hydroxy propyl methyl cellulose procured from central drug house, New Delhi. Eudragit L-100 and Eudragit E-100 was provided as a gift sample from Evonik India private Ltd. Carbopol 934PNF was provided as a gift sample from Noveon Pvt. Ltd. Castor oil was procured from central drug house, New Delhi. Methanol and Potassium di hydrogen phosphate was procured from Qualigens fine chemicals, Mumbai. Sodium hydroxide pellets, n-Octanol and Hydrochloric acid were procured from Central Drug (P) Ltd., New Delhi.

2.2 Preparation method of mesalamine tablets

The core tablet was composed of drug and polymer. These were mixed according to prescribed ratio and then mixture was directly compressed in tablet punching machine. Then after spray coating of lactulose USP solution over the tablet was carried out. The resulted

coated tablet was coated with acid-soluble coating material, Eudragit E-100. A coating solution was prepared by dissolving 10% (w/w) Eudragit E100 in methanol. Coating was performed by a coating machine. The amount of coating was 17.3 mg per tablet core. Second, the tablets were coated with water-soluble coating material, HPMC as an under coating layer. A coating solution was prepared by dissolving 10% (w/w) HPMC in water. The amount of coating was 3.5 mg per tablet core. Finally, the tablets were coated with enteric coating material, Eudragit L100. A coating solution was prepared by dissolving 10% (w/w) Eudragit L100 and 2% (w/w) castor oil in methanol. Coating was performed by the same coating machine. The amount of coating was 19.1 mg per tablet core.[14]

2.3 Characterization of Mesalamine tablets[15]

2.3.1 Uniformity of weight

For determining the uniformity of weight, twenty tablets were weighed individually, calculating average weight and comparing the individual tablet weight to the average. The same procedure was repeated after acid soluble coat and enteric coat.[15] The results are described in table-2, table-3, and table-4.

2.3.2 Hardness

The Hardness of core tablet was determined by Monsanto Hardness Tester.[15] The results are described in table -2.

2.3.3. Friability

The friability of core tablet was found out by Roche fribilator.[15] The values are described in table-2.

2.3.4 Thickness

The thickness of the tablet was determined by screw guage. The determination of thickness was carried out after each coating.[15] The results are described in table-2, table-3 and table-4.

1.3.5 Diameter

The diameter of the core tablet was determined by the help of Vernier Calliper's. The same instrument is used for the determination of acid soluble coated tablet and enteric coated tablet.[15] The results are described in table-2, table-3 and table-4.

3. RESULTS AND DISCUSSION

3.1 Drug content

The uniformity of drug content in each formulation was determined by triturating 20 tanlets and powder equivalent to average eight was added to 100 ml of 5.0 pH PBS followed by stirring for 30 min. The solution was filtered through Whattman filter paper, diluted suitably and absorbance of resultant solution was measured using double beam UV spectrophotometer at maximum wavelength using 5.0 pH PBS.[15]

3.2 In-vitro drug release

The drug release rate from mesalamine tablets were determined by using USP type II dissolution apparatus for batch A tablets[14] and USP type I dissolution apparatus was used for tablets of batch B.[16] Tablet was placed inside the dissolution apparatus. The dissolution test was performed in 900 ml 0.1 N HCl for first two hours and then the tablet was placed in 900 ml PBS pH 6.8 for hr. Finally the tablet was placed in 900 ml PBS pH 5.0.The dissolution was carried out at 50 rpm and the temperature was maintained at 37^0C. At specified time intervals, 1 ml aliquots were withdrawn, filtered, diluted with the same medium and assayed at 230nm in case of 0.1N HCl,214.4nm in case of PBS pH 6.8 and 309.2 nm in case of PBS pH 5.0 for mesalamine using a UV double-beam spectrophotometer (Shimadzu UV-1700 series). Samples with drawn were replaced with equal volume of the same dissolution medium.

3.3 Kinetics of drug release[17] The zero-order rate describes systems where drug release is independent of its concentration and this is applicable to the dosage forms like transdermal system, coated forms, osmotic system as well as matrix tablets with low soluble drugs. The first-order equation describes systems in which the release is dependent on its concentration (generally seen for water-soluble drugs in porous matrix). The Higuchi model describes the release of the drug from an insoluble matrix to be linearly related to the square root of time and is based on Fickian diffusion. The Hixson-Crowell cube root law describes the release of drug from systems where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in the case of systems that dissolute or erodes over time. In order to authenticate the release model, dissolution data can further be analyzed by Peppas and Korsmeyer equation.

Q t = kn t (zero order)

ln Qt = ln Qo – CT1 t (first order)

Qt = kHC t1/2 (higuchi model)

Qo1/3 – Q1/3 = kHC t (Hix. Cro.)

Mt / M∞ = k tn (peppas and korsmeyer)

Where Qt is the amount of drug released at time t; Q0 is the initial amount of the drug in the formulation; k0, CT1, kH, and kHC are release rate constants for zero-order, first-order, Higuchi model and Hixson-Crowell rate equations. Mt is the amount of drug released at time t, and M∞ is the amount released at time∞; k is the kinetic constant, and n is the diffusion coefficient.[16]

3.4 Statistical analysis

In this study the results are given as mean ± SD. Student's t-test and one-way analysis of variance (ANOVA) were applied to find out the significant difference in drug release from different batches by using GRAPH PAD software programme considered statistically significant difference was at $p < 0.05$.[18]

3.5 Stability studies

The selected formulation of coated mesalmine tablet wrapped with alluminium foil was kept at 4±1ºC, 25±1ºC, and 50±1ºC for a period of 15 days and observed for any change in morphology and percentage residual drug content. Sample was analyzed for residual drug content at the time interval of 5 days for 15days.[18]

Table-1 Composition of mesalamine tablets

Ingredients (mg per tablet)	Purpose	CT1	CT2	CT3	CT4	CT5	CT6	R1	R2	R3	R4
Mesalamine	A P I	250	250	250	250	250	250	250	250	250	250
Carbopol	In core tablet	500	500	750	250	-----	250	25	37.5	50	62.5
Sodium CMC	In core tablet	500	750	500	250	250	----	---	----	---	----
Lactulose	polysaccharide	100	100	100	100	100	100	100	100	100	100
EudragitE-100	Acid soluble coat	17.3	17.3	17.3	17.3	17.3	17.3	17.3	17.3	17.3	17.3
HPMC	Avoid interaction between oppositely	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
EudragitL-100	Enteric coat	15.9	15.9	15.9	15.9	15.9	15.9	15.9	15.9	15.9	15.9
Castor oil	plasticizer	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2

Table-2: Physico-Chemical Characterization of core tablets of mesalamine.

Batch Code	Uniformity of weight	Thickness	Diameter	Friability	Hardness
K 1	1248 ± 2.44	2.5 ± 0.0	14.0 ±.05	0.65 ± .05	8.25±180
K 2	1494 ± 3.74	3.15 ± .05	14.015 ± .05	.60 ± .04	9.1 ± 0.1
K 3	1493 ± 2.44	3.15 ± .05	14.0 ± 0.05	.65 ± .05	9.1 ± 0.0
K 4	748 ± 2.44	1.35 ± .05	12.01 ±.05	.75 ± .05	8.0 ± 0.0
K 5	493 ± 2.44	1.25 ± .05	12.0 ± 0.5	.60 ± .04	8.1 ± 0.0
K 6	493 ± 2.44	1.25 ± .05	12.0 ± 0.5	.65 ± .03	8.25 ± .05
R 1	260 ± 11.66	1.05 ± .05	12.01 ± 0.05	.68 ±.02	8.3 ± 0.0
R 2	285.4 ± .49	1.055 ± .05	12.01 ± 0.05	.69 ± .02	8.15 ± .05
R 3	293 ± 2.44	1.15 ± .05	12.0 ± 0.05	.55 ± .04	8.4 ± 0.0
R 4	310.4 ± 0.8	1.25 ± .05	12.01 ± 0.05	.59 ± .02	8.15 ± .05

Table-3: Physico-Chemical Characterization of acid soluble coated tablets of mesalamine.

Batch Code	Uniformity of weight	Thickness	Diameter
K 1	1363 ± 2.44	2.80 ± 0.0	14.1 ± 0.05
K 2	1612 ± 2.44	3.65 ± .05	14.115 ± 0.05
K 3	1613 ± 2.44	3.45 ± .05	14.01 ± 0.05
K 4	865.4 ± 0.49	1.85 ± .05	12.05 ± 0.05
K 5	614 ± 2.0	1.7 ± 0.0	12.05 ± 0.05
K 6	614 ± 2.0	1.8 ± .05	12.04 ± 0.05
R 1	388 ± 2.44	1.5 ± 0.0	12.04 ± 0.05
R 2	402 ± 2.44	1.55 ±0.5	12.05 ± 0.00
R 3	415 ± 0.0	1.75 ± .05	12.04 ± 0.05
R 4	425.2 ± 0.89	1.75 ± .05	12.05 ± 0.05

Table-4: Physico-Chemical Characterization of coated tablets of mesalamine

Batch Code	Uniformity of weight	Thickness	% Drug content
K 1	1372 ± 11.22	3.725 ± .083	98.5 ± .05
K 2	1631 ±2.44	4.25 ± .05	98.6 ± .05
K 3	1636 ± 1.36	4.25 ± .05	97.5 ± .05
K 4	885.4 ± .94	2.45 ± .05	98.9 ± .05
K 5	634 ± 2.0	2.35 ±.05	99.1 ± .05
K 6	634 ± 2.0	2.25 ± .05	98.2 ± .05
R 1	414 ±2.0	2.05 ± .05	98.3 ± .05
R 2	423.2 ± 2.64	2.055 ± .05	98.5 ± .05
R 3	434.2 ± 2.13	2.15 ± .05	98.4 ± .05
R 4	450.8 ± .96	2.25 ± .05	98.6 ± .05

Table-5: Kinetics *in-vitro* mesalamine release from mesalamine tablets.

Batch code	Zero order		First order		Matrix		Peppas		Hix. Crow.	
	R	K	R	k	R	k	R	K	R	K
CT 1	.9978	3.9179	.8787	-0.0844	.8844	12.9921	0.9896	3.7065	0.9415	0.0202
CT 2	0.9978	3.9342	0.8800	-0.0847	0.8870	13.0659	0.9902	3.7907	0.9429	-0.0203
CT 3	0.9964	3.8983	0.8721	-0.0840	0.8698	12.8206	0.9937	2.8011	0.9359	-0.0202
CT 4	0.9154	4.6716	0.9012	-0.1050	0.9709	16.4031	0.9857	14.5804	0.9660	-0.0246
CT 5	0.8241	15.4273	0.9190	-0.3652	0.9729	35.3458	0.9347	43.0534	0.9377	-0.0863
CT 6	0.9577	15.8161	0.9523	-0.3103	0.9874	33.1441	0.9875	29.3166	0.9797	-0.0799
R 1	0.9528	4.0961	0.9803	-0.0673	0.9213	14.0591	0.9634	7.0526	0.9847	-0.0186
R 2	0.9809	3.7162	0.9679	-0.0598	0.9089	12.5687	0.9766	5.7290	0.9855	-0.0167
R 3	0.9935	3.5198	0.9633	-0.0555	0.9116	11.8585	0.9888	4.5119	0.9869	-0.0156
R 4	0.9877	3.0459	0.9824	-0.0430	0.9021	10.2388	0.9692	3.2881	0.9913	-0.0126

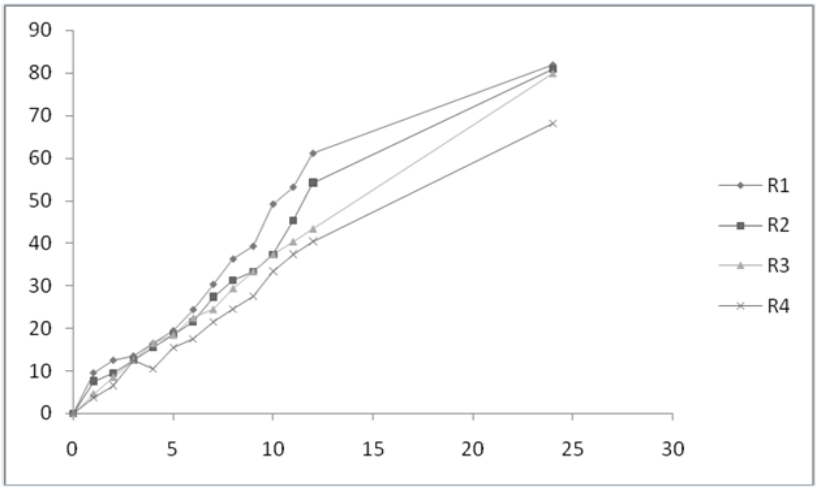

Fig1. Effect of carbopol on release profile of mesalamine from tablets (batch R1,R2,R3,R4) in pH 5.0 PBS.

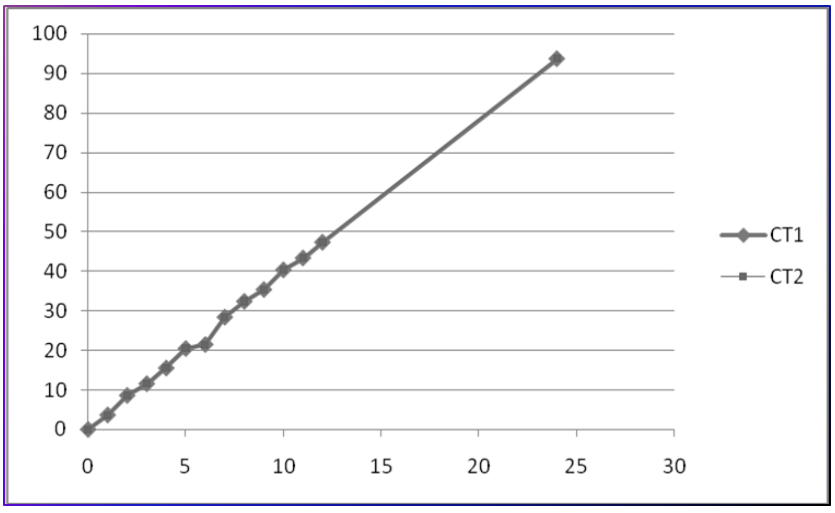

Fig.-2 Effect of Sodium CMC on release profile of mesalamine from tablets (Batch CT1, CT2) in pH 5.0 PBS-

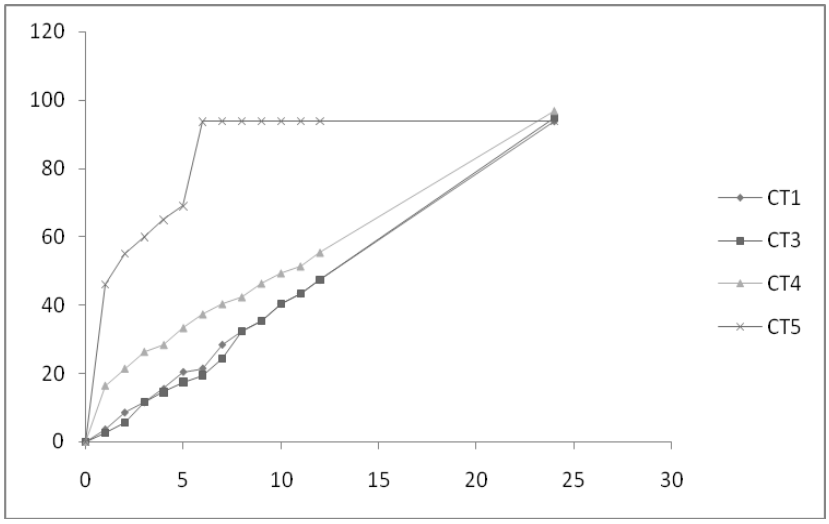

Fig.-3 Effect of Sodium CMC on release profile of mesalamine from tablets (Batch CT1, CT3, CT4, CT5) in pH 5.0 PBS.

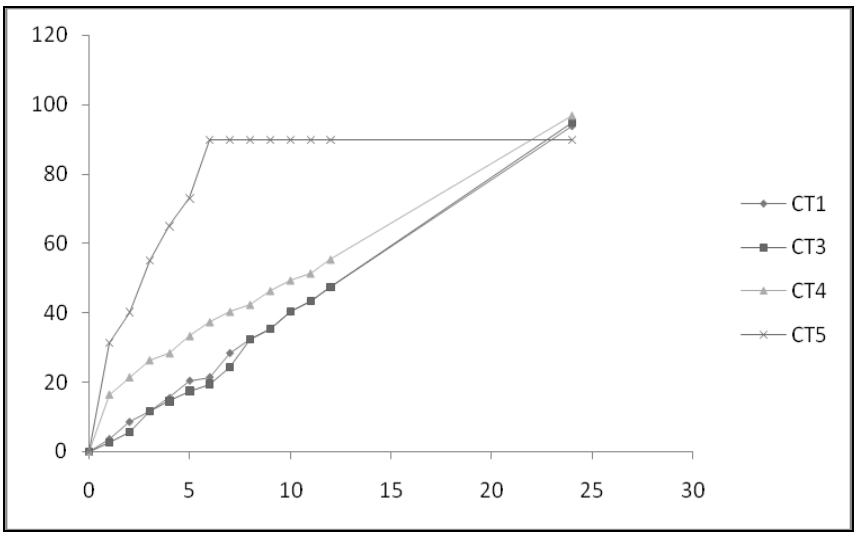

Fig.-4 Effect of carbopol on release profile of mesalamine from tablets (batch-CT1, CT3, CT4, CT5) in pH 5.0 PBS.

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