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FORMULATION AND CHARACTERIZATION OF COLON SPECIFIC DRUG DELIVERY SYSTEM OF A MATRIX TABLET

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ABSTRACT

The objective of the present study is to develop colon targeted drug delivery system by using Chitosan as a carrier for Mesalamine. Matrix tablets containing various excipients and Chitosan were prepared by wet granulation technique using different binder systems. The prepared tablets were evaluated for Hardness, Weight variation, Drug uniformity, Friability and In-vitro Drug release study. The final product is expected to have the advantage of being biodegradable and pH dependant. The matrix tablet containing Chitosan as a carrier and xanthum gum as binder was found to be suitable for targeting mesalamine for local action in the colon as compare to other matrix tablets containing different binders. Matrix tablets containing Chitosan released 99.99% of mesalamine in simulated colonic fluid. The stability study for prepared tablets at 40°C/75% relative humidity for three months showed no significant change in In-vitro drug release pattern. The results of in-vitro study indicate that matrix tablets containing Chitosan as carrier and xanthum gum as binder are most suitable to deliver the drug specifically in colonic region. The final formulation of mesalamine for colon-specific drug delivery gives pH, time and enzyme controlled release.

KEYWORDS: Mesalamine, Matrix tablet, Chitosan, Hydroxypropyl methyl cellulose.

INTRODUCTION

Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as (ulcerative colitis, crohn's disease) amebiosis, colonic cancer, and for local treatment of local colonic pathologies, and the systemic delivery of protein and peptide

drugs *[Adkin et al., 1993]*. The colon specific drug delivery system (CDDS) should be capable of protecting the drug on route to colon (i.e. drug release and absorption should not occur in the stomach and the small intestine and bioactive agent should not be degraded) *[Ahrabi et al., 2000]* and to allow drug release only in the colon. The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal. *[Sarasija et al., 2000]*. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. *[Kopack et al., 1992]* The right colon consists of the caecum, ascending colon, hepatic flexure and the right half of the transverse colon and the values were shown in Table 1.

Table 1: Measures of different parts of colon

S. No	Large intestine	Length(cm)
1	Caecum	6 – 9
2	Asending colon	20 -25
3	Descending colon	10 -15
4	Tranverse colon	40 -45
5	Sigmoid colon	35 -40
6	Rectum	12
7	Anal canal	3

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen *[Bajpai et al., 2007]*. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. On average, it has been estimated that colon contains only about 220 gm of wet material equivalent to just 35 gm of dry matter. The majority of this dry matter is bacteria. The colon tissue containing the villi, lymph, muscle, nerves, and vessels. The human intestine and colon were shown in Figure1.

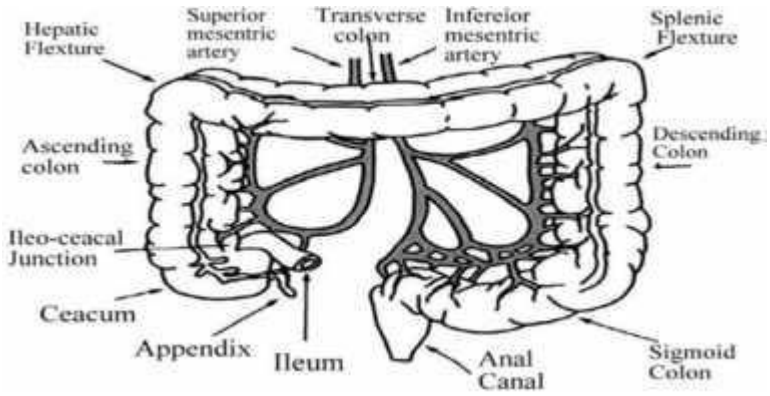

Figure 1: Structure of colon

pH Differences in the Colon: On entry in to the colon, the p^H dropped to 6.4 ± 0.5. The p^H in the mid colon was found to be 6.6 ± 1 and in the left colon, 7.0 ± 1 and the values are shown in Table 2.

Table 2: Different pH conditions in gastro intestinal tract

S.No	Location	p^H
1	Stomach	1 - 2
	Fasted condition	<1
	Fed condition	1.5 - 2
2	Small intestine	3 - 5
	Jejunum	5 - 6.5
	Ileum	6 - 6.5
3	Large intestine	6.4
	Right colon	6.7 - 7.3
	Mid colon	7.3 - 7.5
	Left colon	7.5 – 8.0

Opportunities in Colon Targeted Drug Delivery

- In the area of targeted delivery, the colonic region of the GI tract is the one that has been embraced by scientists and is being extensively investigated over the past two decades.
- Targeted delivery to the colon is being explored not only for local colonic pathologies, thus avoiding systemic effects of drugs or inconvenient and painful trans- colonic administration of drugs.
- This is also a potential site for the treatment of diseases sensitive to circadian rhythms such as asthma, angina and arthritis.
- The treatment of disorders of the large intestine, such as irritable bowel syndrome (IBS), colitis, Crohn's disease and other colon diseases.
- The development of a dosage form that improves the oral absorption of peptide and

protein drugs whose bioavailability is very low.

- The bioavailability of protein drugs delivered at the colon site needs to be addressed.

Approaches used for Site Specific Drug Delivery to Colon

The various strategies for targeting orally administered drugs to the delivery system. There are four practical mechanisms by which a delivery system can be targeted to the colon by oral administrations:

- Use of a p^H dependent delivery system
- Use of time dependent delivery system.
- Use of a pressure controlled delivery system
- Use of a bacterially triggered delivery system

p^H- Dependent Delivery: p^H sensitivity enteric coatings have been used routinely to deliver drugs to the small intestine these polymers coatings are insensitive to acidic conditions of the stomach yet dissolve at the higher p^H environment of small intestine. This p^H differential principle has also (7-7.5), has been developed recently.

Time-Dependent Delivery: Time dependent delivery has also been proposed as a means of targeting the colon. Time-dependent system releases their drug load after a pre-programmed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon. This time is difficult to predict in advance, although a lag time is reported to be relatively constant at three to four hours.

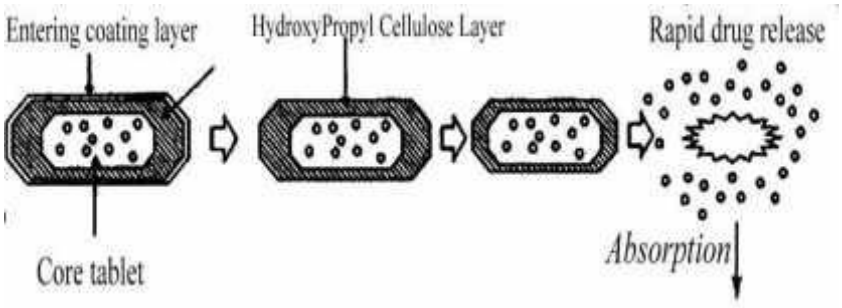

Figure 2: Design of enteric coated timed-release press coated tablet

Pressure-Dependent Delivery: Gastro intestinal pressure has also been utilized to trigger drug release in the distal gut. This pressure, which is generated via muscular contraction of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration

throughout the GIT, with the colon considered to have a higher luminal pressure due to the process that occur during stool formation. Systems have developed therefore to resist the pressure of the upper GIT but rupture in response to the raised pressure of the colon. Capsule shell fabricated from the water insoluble polymer ethyl cellulose has been used for this purpose. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall. *[Sharma Anuj et al., 2010]*.

Bacteria-Dependent Delivery: The resident GIT bacteria provide a further means of effecting drug release in the colon. These bacteria predominantly colonize the distal region of GIT where the bacterial count in the colon is 1011 per gram, as compare to 104 per gram in upper small intestine. Moreover, 400 different species are present. Colonic bacteria are predominantly anaerobic in nature and produce enzymes that are capable of metabolizing endogenous and exogenous substrate, such as carbohydrate and proteins that escape digestion in the upper GIT. Therefore, materials those are recalcitrant to the condition of the stomach and small intestine. *[Anil Philip et al., 2010, Jitender et al.,2011, Vinay Kumar et al.,2011 and Hemant et al.,2012]*.

Prodrug Approach for Drug Delivery to Colon

A prodrug is a pharmacologically inactive derivative of a parent molecule that requires some form of transformation *in vivo* to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. The type of linkage that is formed between the drug and carrier would decide the triggering mechanism for the release of the drug in the colon. This biotransformation is carried out by a variety of enzymes, mainly of bacterial origin, present in the colon. The enzymes that are mainly targeted for colon drug delivery include azoreducatase-galactosidase, β-xylosidase, nitroreductase, glycosidase, deaminase etc. Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky, to minimize absorption from the upper GI tract and, once in the colon, it is converted into a more lipophilic drug molecule that is then available for absorption. *[Rubinstein et al.,1990 and Friend et al.,1991]*

Polysaccharide Based Delivery Systems

The use of naturally occurring polysaccharides is attracting a lot of attention for drug targeting the colon since these polymers of monosaccharides are found in abundance, have

wide availability are inexpensive and are available in a verity of a structures with varied properties. They can be easily modified chemically, biochemically, and are highly stable, safe, nontoxic, hydrophilic and gel forming and in addition, are biodegradable. These include naturally occurring polysaccharides obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) or microbial (dextran) origin. The polysaccrides can be broken down by the colonic microflora to simple saccharides *[ashrod et al., 1993]* Therefore, they fall into the category of "generally regarded as safe" (GRAS).

Table 3: Polysaccharides investigated for colon-specific drug delivery.

Drug moiety used	Polysaccharide investigated	Dosage form prepared
Diclofenac sodium	Chitosan	Enteric coated chitosan microspheres
Insulin	Chitosan	Enteric coated chitosan microspheres
indomethacin	Pectin	Matrices
Paracetamol	Amidated pectin	Matrix tablets
imdomethacin	Amidated pectin	Chitosan coated amidated pectin beads
Repavacaine	Amidated pectin	Matrix tablets
dexamethasone	Guar gum	Matrix tablets
Indomethacin	Chondratoin sulphate	Matrix tablets
Theophylline	Locust bean gum	Film

Newly Developed Approaches for CDDS

Novel Colon Targeted Delivery System (CODES ^{TM}): CODES^{TM} was a unique CDDS technology which is a combined approach involving pH dependent and microbially triggered CDDS and was designed to avoid the inherent problems associated with p^{H} or time dependent systems. It was developed by utilizing a unique mechanism involving lactulose, acting as a trigger for site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is coated with acid soluble material Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The final conclusion of this technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying.

Osmotic Controlled Drug Delivery (OROS-CT): The OROS-CT was used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 units, each encapsulated within a hard gelatin capsule (Figure 5). Each bilayer unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane thus it is called as a push-pull unit.

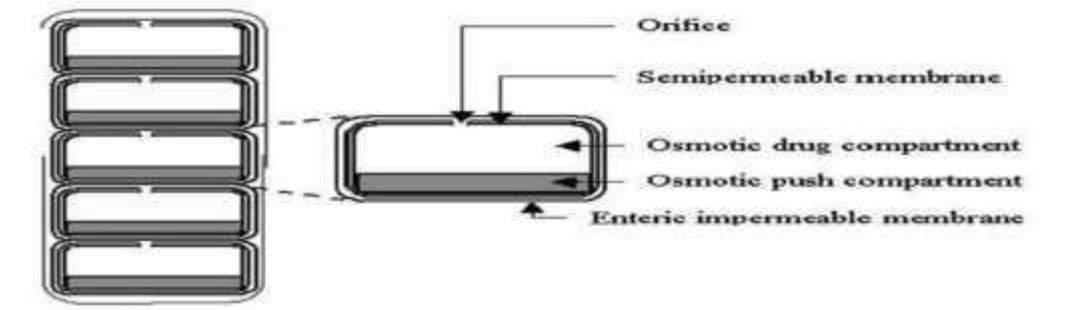

Figure 3: Cross-Section of the OROS-CT Colon Targeted Drug Delivery System

Combination of Different Approaches of CDDS: An oral colonic drug delivery system of 5-aminosalicylic acid was developed using combination of pH dependent, time-based and enzyme degradable approaches. The pellets were coated with three functional layers i.e. the outer EudragitL30D-55 layer for protection against GI fluids, the intermediate layer of ethyl cellulose to inhibit the drug release during passage through the small intestine and the inner layer of pectin for swelling and enzyme degradation. *In-vitro* release studies indicated that the coated pellets completely protected the drug release in 0.1M HCl while the drug release was delayed for 3 to 4 h in pH 6.8 phosphate buffer. *[Pramod Kumar et al., 2013]*.

Hydrogel Based CDDS: Hydrogels are usually formed by the covalent cross linking of linear hydrophilic polymers to form a network of material capable of absorbing water, yet still remaining insoluble. Heterogenous polymer mixture may also be used to form hydrogels without the need for covalent cross linking. *[Ranjit Singh et al., 2012]*.

Other Novel Drug Delivery Systems: A new microparticulate system containing microsponges was prepared by microencapsulation for colon specific delivery *[Kollam Prasad et al., 2011]*.

Polymers Used in the Colon Drug Delivery System

Oral colon targeted drug delivery systems have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration.

Biodegradable Polymers: Natural polysaccharides are extensively used for the development of solid oral dosage forms for colonic delivery of drugs *[Jain et al., 2006]*. Biodegradable polymers are generally hydrophilic in nature and have limited swelling characteristic in acidic pH. Various bacteria present in the colon secretes many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. β-D-galactosidase, amylase, pectinase, β-D- glucosidase,

dextranase, α-D-xylosidase *[Wilson et al., 2008]*.

Guar gum: Guar gum is derived from the seeds of the *cyomopsis tetragonolobus* (Fam. Leguminosae). Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose. The backbone is a linear chain of β 1, 4-linked mannose residues to which galactose residues are 1, 6-linked at every second mannose, forming short side-branches *[Shirwaikar et al., 2008]*.

Pectin: Pectin is a linear, heterogeneous polysaccharide which is mainly composed of galacturonic acid and its methyl ester. These are predominantly linear polymers of mainly (1→4) linked D-galacturonic acid residue interrupted by 1,2-linked L-rhamnose residue with a few hundred to about one thousand building blocks per molecule *[Shirwaikar et al., 2008]*.

Chondroitin Sulfate: Chondroitin sulfate is a soluble mucopolysaccharide that is used as a substrate by *Bacteroides* species in the large intestine mainly by *B. thetaiotaomicron* and *B. ovatus*. Chondroitin sulphate consists of β-1, 3-D-glucuronic acid linked to N-acetyl-D-galactosamide.

Dextran: Dextran is a polysaccharide consisting of α-1, 6 D-glucose and side chain of α-1,3 D-glucose units *[Wilson et al., 2008 and Jain et al., 2007]*. These highly water soluble polymers are available commercially as different molecular weights with a relatively narrow molecular weight distribution.

Chitosan: Chitosan is functional linear polymer obtained from the alkaline deacetylation of chitin. Chitosan is consisting of the repeated units of (2-amino-2-deoxy-D-gluco-pyranose) which are linked by (1-4) β-bonds. *[Jain et al 2007 and Wilson et al 2008]*.

Mesalamine: Mesalamine is an anti-inflammatory agent which is used to treat inflammatory bowel disease, crohn's disease and ulcerativecolitis. appears to have a topical anti-inflammatory effect on the colonic epithelial cells. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that Mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. Mesalamine has the potential to inhibit the activation of nuclear factor kappa B (NFκB) and consequently the production of key pro-inflammatory cytokines.

MATERIALS AND METHODS

Polymers like HPMC phthalate, Hydroxy Propyl Methyl CelluloseK15M (methocel), Gum karaya, Guar gum, Chitosan, Olibanum gum, Xanthan gum are Commercially procured from Yarrow chem. Products, Mumbai and Mesalamine a Gift sample from Mylan Pharma Ltd, Hyderabad.

Preparation of Mesalamine Standard Dilutions: Aliquots of Mesalamine stock solutions was transferred into 5 volumetric flasks and were further diluted with 7.2 pH phosphate buffer so as to get 5,10,15,20 and 25 µg/ml of standard dilutions of Mesalamine. The absorbance values of above dilutions were measured in ELICO double beam UV-VIS spectrophotometer at 302nm using 7.2 pH phosphate buffer as blank.

Preformulation Studies on Mesalamine: The drug and the polymer or excipient interaction studies were evaluated by checking the physical appearance, drug content and FTIR studies.

Preparation of Mesalamine Matrix Tablets

Mesalamine matrix tablets were prepared by wet granulation method. The Mesalamine matrix tablet formulations consisted of drug, polymer, diluent, gums and effervescing agent. The drug concentration was maintained constantly while polymer proportions were varied. The weight of all the tablet formulations was maintained uniformly by using MCC as diluent.

Table 4: Composition of Various Mesalamine Matrix Formulations

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
	250	250	250	250	250	250	250	250	250	250
Mesalamine	125	62.5	125	62.5	125	62.5	125	62.5	125	62.5
HPMC K15M	62.5	125	-	-	-	-	-	-	-	-
Gum karaya	-	-	62.5	125	-	-	-	-	-	-
Guar gum	-	-	-	-	62.5	125	-	-	-	-
Olibanum gum	-	-	-	-	-	-	62.5	125	-	-
Chitosan	-	-	-	-	-	-	-	-	62.5	125
Xanthan gum	25	25	25	25	25	25	25	25	25	25
Sodium carbonate	76.5	76.5	76.5	76.5	76.5	76.5	76.5	76.5	76.5	76.5
MCC	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Magnesium stearate Talc	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Totaltablet weight(mg)	550	550	550	550	550	550	550	550	550	550

Evaluation of Powder Flow Characteristics

Angle of Repose: Angle of repose for the powder blends were performed by Fixed Funnel Method and is the measure of the flowability of powder. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm over the platform. About 10 gm of powder blend was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured ***[****Lachman et al., 1990]*.

Angle of repose was calculated from the average radius using the following formula

□ = tan^{-1} *(h/r)* Where, □ = Angle of repose, h = Height of the pile, r = Average radius

Table 5: Specifications of Angle of Repose

Angle of Repose	Type of Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

Compressibility Index: A simple test was used to evaluate the flowability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down. The Carr's index can be calculated using the following formula.

Carr's index = (Tapped density – bulk density / Tapped density) X 100

Table 6: Specifications of Flow Properties Corresponding to Compressibility Index

% Compressibility	Flow Description
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

Hausner's ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's ratio= Tapped density/ Bulk density

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Evaluation of Physical Parameters of Mesalamine Matrix Tablets

Uniformity of Weight: Twenty tablets from each batch at random were taken and weighed. The average weight was calculated, then each tablet was weighed individually and weights of each tablet were noted. The weights of individual tablets were then compared with the average weight that was already calculated.

Table 7: IP Limits for the Percentage Deviation of Average Weight

Average Weight	Percentage Deviation
80 mg or less	10
More than 80mg but less than 250mg	7.5
250 mg or more	5

Hardness Test: Hardness of the tablets was determined by using Monsanto hardness tester (Tab-machines, Mumbai). The tablet to be tested is held in fixed and moving jaw and reading of the indicator was adjusted to zero. Then force to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet breaks.

Friability Test: Friability test was performed by using Roche friabilator (Remi Equipments, Mumbai). Ten tablets of a batch were weighted and placed in a friabilator chamber and it was allowed to rotate for 100 revolutions. During each revolution these tablets fall from a distance of six inches to undergo shock. After completion of 100 revolutions, tablets were again weighed and the loss in weight indicated friability.

$$\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X\ 100$$

Uniformity of Drug Content: Matrix tablet of Mesalamine from a batch was taken at random and was crushed to a fine powder. The powdered material was transferred into a 250ml volumetric flask and 200ml of 7.8 pH phosphate buffer was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 250ml by adding 7.2 pH phosphate buffer.

***In Vitro* Dissolution Studies:** Dissolution studies on each formulation were performed in a calibrated 8 station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 0.1N HCl as a dissolution medium for 2 hours, 900 ml of 7.2 pH phosphate buffer for next 6hours, then with 900ml of 7.2 pH phosphate buffer up to 24 hours. The paddles were operated at a 50rpm and the temperature was maintained at

37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 24hrs and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment.

Accelerated Stability Studies

Accelerated Study: The product was subjected to accelerated stability studies at 40 ± 2□C / 75 ± 5% RH for 3 months.

Long Term Study: The product was subjected to long term studies at 25 ± 2□C / 60 ± 5%RH for 6 months.

RESULTS AND DISCUSSION

Table 8: Calibration Curve for the Estimation of Mesalamine in 7.2 PH

S. No.	Concentration (µg/ml)	Absorbance* $\bar{X}$ ± SD
1	0	0
2	5	0.1218 ± 0.001
3	10	0.2411 ± 0.0008
4	15	0.3659 ± 0.002
5	20	0.4865 ± 0.002
6	25	0.6275 ± 0.002

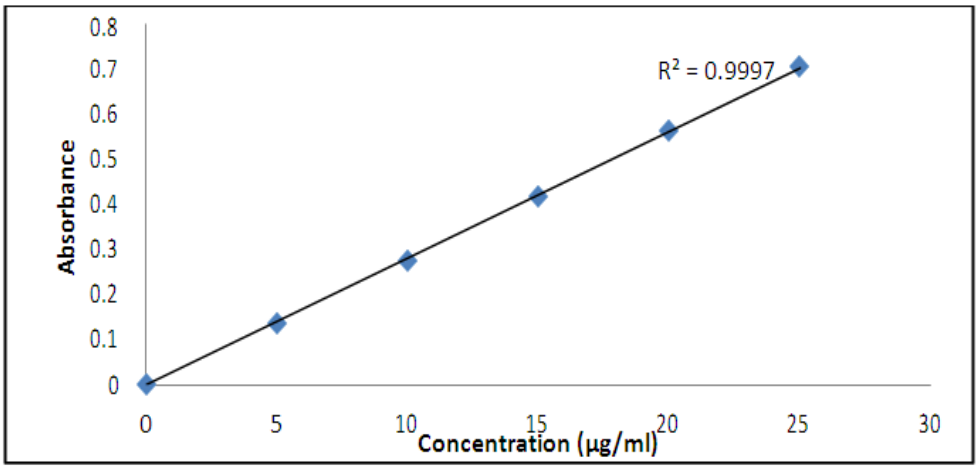

Figure 3: Calibration Curve for the Estimation of Mesalamine in 7.2 pH phosphate buffer

Table 8: Flow Properties of Powder Blends of Mesalamine Matrix Tablets

S. No.	Formulation	Angle of repose (θ)	Compressibility Index (%)	Hausner's ratio
1	F1	24.94 ± 0.02	12.10 ± 0.024	1.120 ± 0.03
2	F2	25.69 ± 0.03	14.20 ± 0.022	1.128 ± 0.02
3	F3	26.42 ± 0.05	11.39 ± 0.009	1.131± 0.05
4	F4	26.85 ± 0.02	14.47 ± 0.017	1.123 ± 0.04
5	F5	27.01 ± 0.03	10.68 ± 0.014	1.128 ± 0.02
6	F6	25.76 ± 0.05	12.07 ± 0.024	1.109 ± 0.01
7	F7	26.40 ± 0.07	13.24 ± 0.019	1.120 ± 0.04
8	F8	27.32 ± 0.09	11.80 ± 0.027	1.117 ± 0.05
9	F9	24.54 ± 0.13	12.75 ± 0.017	1.129 ± 0.05
10	F10	26.87 ± 0.07	11.78 ± 0.014	1.26 ± 0.02

Table 9: Preformulation Studies on Mesalamine

S.No	Description	Method Evaluated	0^{th} day	1 month	3 months
1	Mesalamine	Physical Evaluation	Light pink powder	Complied	Complied
2	Mesalamine + Excipients	Physical Evaluation	Light pink powder	Complied	Complied
3	Mesalamine + Excipients	Assay by UV method	Complied	Complied	Complied
6	Mesalamine	FTIR Studies	3441.54cm^{-1}-1487.98cm^{-1}	Complied	Complied
7	Mesalamine + Excipients	FTIR Studies	3442.29cm^{-1}– 1487.86cm^{-1}	Complied	Complied
4	Mesalamine	DSC Studies	Melting Endotherm was observed at 181.1^{0}C	Complied	Complied
5	Mesalamine + Excipients	DSC Studies	Melting Endotherm was observed at 180.1^{0}C	Complied	Complied

Table 10: Physical Properties of Mesalamine Matrix Tablets

S. No.	Formulation	Weight uniformity (mg)	Hardness (kg/cm²)	Friability (%w/w)	Drug content* (mg/tablet)
1	F1	551± 2.0	5.5 ± 0.4	0.19	248.5 ± 0.5
2	F2	549 ± 3.0	5.7 ± 0.3	0.12	251.3 ± 0.5
3	F3	552 ± 3.0	5.5 ± 0.3	0.18	250.4 ± 0.5
4	F4	548 ± 2.0	5.8 ± 0.2	0.17	251.9 ± 0.2
5	F5	549 ± 4.0	5.5 ± 0.3	0.15	249.2 ± 0.3
6	F6	551± 2.0	5.6 ± 0.2	0.18	249.8 ± 0.5
7	F7	552 ± 3.0	5.7 ± 0.3	0.16	250.6 ± 0.5
8	F8	550 ± 3.0	5.5 ± 0.4	0.18	249.8 ± 0.3
9	F9	551± 2.0	5.8 ± 0.1	0.14	248.2 ± 0.5
10	F10	548 ± 4.0	5.6 ± 0.2	0.20	250 ± 0.2

Table 11: Drug Release Profiles of Mesalamine Matrix Tablets

S.No	Time (hrs)	Cumulative % Drug Released					
		F1	F2	F3	F4	F5	F6
2	1	8.804 ± 0.13	15.09 ± 0.78	5.13 ± 0.27	12.16 ± 1.73	10.09 ± 0.78	23.17 ± 0.24
3	2	14.76 ± 0.86	26.97 ± 1.2	11.79 ± 1.82	18.13 ± 0.46	21.83 ± 0.34	35.93 ± 0.59
4	4	27.81 ± 0.47	44.13 ± 0.94	24.13 ± 0.46	32.17 ± 0.73	36.91 ± 0.46	53.32 ± 0.63
5	6	40.98 ± 0.53	57.51 ± 0.65	34.99 ± 0.74	45.14 ± 0.84	49.76 ± 0.57	66.67 ± 0.17
6	8	51.04 ± 0.65	68.37 ± 0.34	45.18 ± 0.92	55.30 ± 0.98	59.99 ± 0.31	77.72 ± 0.53
7	10	59.84 ± 0.34	76.91 ± 0.12	53.26 ± 0.31	64.70 ± 0.52	68.94 ± 0.14	85.13 ± 0.14
8	12	66.7 ± 0.83	83.32 ± 0.18	61.20 ± 0.91	72.21 ± 0.95	76.13 ± 0.16	90.70 ± 0.67
9	16	78.67 ± 0.92	91.40 ± 0.35	73.79 ± 0.48	83.13 ± 0.45	87.42 ± 0.52	97.03 ± 0.12
10	20	88.26 ± 0.56	96.19 ± 0.69	84.31 ± 0.29	92.14 ± 0.23	95.17 ± 0.38	98.84 ± 0.43
11	24	98.2 ± 0.45	99.01 ± 0.24	97.96 ± 0.47	98.79 ± 0.89	98.42 ± 0.69	99.29 ± 0.32

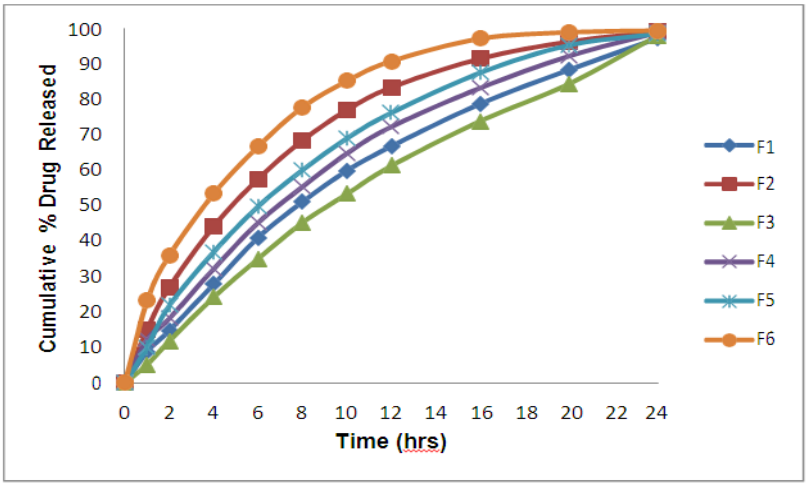

Figure 4: Drug Release Profiles of Various Matrix Tablet Formulations of Mesalamine

Table 12: Drug Release Profiles of Mesalamine Matrix Tablets

S.No	Time (hrs)	Cumulative % Drug Released			
		F7	F8	F9	F10
1	1	8.73 ± 0.32	19.39 ± 0.27	12.74 ± 0.43	25.13 ± 0.18
2	2	18.97 ± 0.54	32.2 ± 0.84	25.31 ± 0.61	39.48 ± 0.48
3	4	36.82 ± 1.35	50.79 ± 0.52	43.94 ± 0.73	58.77 ± 0.92
4	6	50.26 ± 0.73	64.93 ± 0.42	58.60 ± 0.93	72.19 ± 0.43
5	8	61.24 ± 0.52	76.12 ± 0.37	69.48 ± 0.83	82.13 ± 0.27
6	10	69.73 ± 0.49	84.70 ± 0.56	77.81 ± 0.84	89.98 ± 0.18
7	12	76.13 ± 0.83	90.32 ± 0.95	84.42 ± 0.39	94.83 ± 0.37
8	16	85.20 ± 0.52	95.89 ± 0.31	91.74 ± 0.98	98.70 ± 0.29
9	20	91.17 ± 0.56	98.08 ± 0.54	95.70 ± 0.41	98.88 ± 0.69
10	24	98.51 ± 0.93	99.92 ± 0.82	99.90 ± 0.96	99.99 ± 0.57

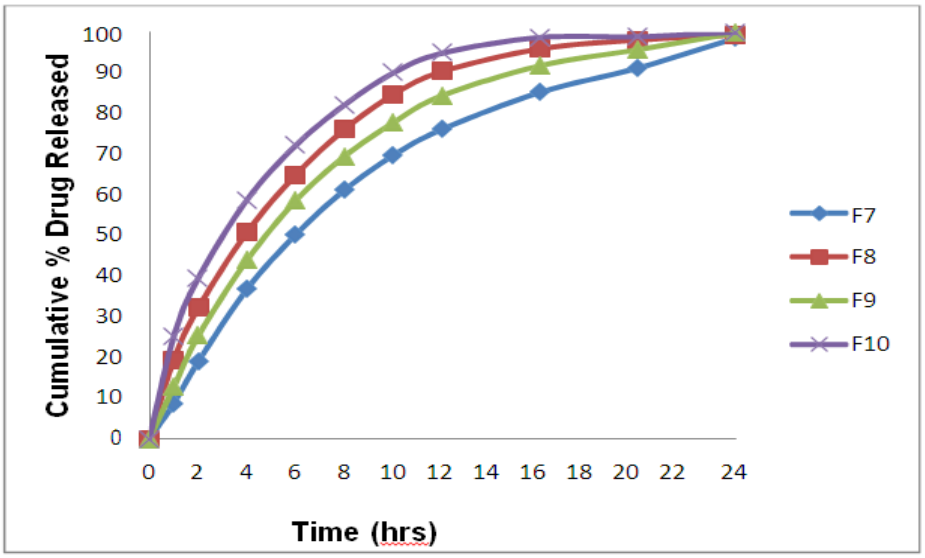

Figure 5: Drug Release Profiles of Various Matrix Tablet Formulations of Mesalamine

Table 13: Physical Parameters of Mesalamine Matrix Tablet Formulations Before and After Storage at Different Conditions

Formulation	Storage Condition	Weight Uniformity (mg)	Hardness (Kg/cm^2)	Friability (% w/w)	Drug Content (mg/tab)
F9	Before storage	549±1.0	5.6± 0.3	0.12	250.4±0.2
	$25±2^0C$, 60±5% RH	549±1.0	5.6± 0.3	0.12	250.3±0.2
	$40±2^0C$, 75±5% RH	549±1.0	5.6± 0.3	0.11	249.4±0.2
F10	Before storage	550±3.0	5.8±0.3	0.18	249.3±0.4
	$25±2^0C$, 60±5% RH	550±3.0	5.8±0.3	0.18	249.3±0.4
	$40±2^0C$, 75±5% RH	550±3.0	5.8±0.3	0.18	249.3±0.4

Table 14: Drug Release Profiles of Mesalamine Matrix Tablet Formulation (F10) Before and After Storage at Different Conditions

Time (hrs)	Before Storage	$25 ± 2^0C$, 60 ± 5% RH	$40 ± 2^0C$, 75 ± 5% RH
1	1.97	1.965	1.962
2	7.39	7.36	7.31
4	27.60	27.54	27.48
6	44.03	43.85	43.73
8	57.65	57.59	57.47
10	70.29	70.18	70.11
12	78.20	78.05	78.01
16	87.61	87.54	87.32
20	94.14	94.03	93.97
24	95.88	95.63	95.57

SUMMARY AND CONCLUSIONS

The objective of developing a Colon Drug Delivery System (CDDS) is to minimize the disadvantages associated with existing dosage form (DF) and optimize therapy. Despite tremendous advancements in drug delivery, the oral route remains the most promising route of drug delivery because of the low cost of therapy and high levels of patient compliance. An important requisite for the successful performance of CDDS is that the drug should have good absorption in colon, preferably by passive diffusion, to ensure continuous absorption of the released drug. A major constraint in colon drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Such drugs are said to have an absorption window, which identifies the drug's primary region of absorption in the GIT. This limitation could be overcome, for various judiciously selected drugs, by prolonging drug release over a extended period of time.

The drug candidate Mesalamine is selected for formulation as colon targeted drug delivery, which is an anti-inflammatory agent used in the treatment of ulcerative colitis and in mild to moderate Crohn`s disease. Mesalamine is slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and dilute hydrochloride. It undergoes rapid and extensive hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability between 20 % and 30%, peak plasma concentration occurs 1 hr after oral administration, and protein binding is around 76%, metabolism occurs in liver. Mesalamine is mainly excreted as unchanged form in urine and mean elimination half life is 5 hr after initial dose and 7 hr at steady state, thus necessitating frequent administration for a prolonged period of time to maintain constant therapeutic drug levels. Mesalamine is found to have drawbacks, such as adverse side effects resulting from accumulation of drug in multi-dose therapy, poor patient compliance and high cost. To minimize the problems as stated above, Mesalamine may be formulated as matrix tablets in order to extend the drug release from the dosage form. These studies were carried out by investigating the effect of temperature on the physicalproperties of the tablets and on drug release from the matrix tablets F10 containing Mesalamine.

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