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International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Colon Specific Drug Delivery System

Choudhari Nikita Bapu, Ms.Jyoti Jawale

Institute of pharmaceutical science and research (for girls),swami chincholi Tal-Daund, Dist-pune,pin-413130

ABSTRACT

colon is a site where both local and systemic delivery of drug and takes place local delivery allows topical treatment of inflammatory bowel disease. Day by day there are new developments in the field of colon specific drug delivery systems . colonic drug delivery has a gained increasing importance not just for the delivery of drugs for the treatment of local diseases associated with the colon like crohn's disease, ulcerative colitis etc. but also for the system of delivery of proteins, therapeutic peptides, anti asthmatic drugs.etc[3]. the various approaches that can be exploited to target the release of drug to colon including prodrug formation ,coating with PH sensitive polymers ,coating with biodegradable polymers ,embedding in biodegradable matrices,hydrogel ,timed release systems ,osmotic, and bio adhesive systems .[5].oral colon targeted delivery system have gain enormous attention among researchers in in the last two decades [9]. Usual methods for delivering the drug to the last part of gastrointestinal tract (GIT) that are ph-dependent systems, time dependent systems ,and microbial triggered systems, .

KEYWORDS: colon targeted drug delivery system, approaches, local ,systemic

INTRODUCTION

•What is colon:

The longest part of the large intestine is a tube-like organ connected to the small intestine at one end and the anus at the other.

the oral route is the most convenient and preferred route but other routes for CDDS may be used.

Colonic drug delivery can be achieved by either oral or rectal administration. The rectal routes suppositories and enemas are not always effective because of high variability in the distribution of the drugs administered by this route [9]. In oral colon specific drug delivery systems colon has a large amount of lymphoma tissue.which facilitates direct absorption into the blood,negligible brush border membrane activity, and much less pancreatic enzymatic activity as compared with small intestine[6]. In the past two decades , Pharmaceutical scientists have extensively investigated the area of the colonic region for targeted drug delivery systems. For drugs like proteins and peptides ,for the treatment of disease sensitive to circadian rhythms such as asthma, angina and rheumatoid arthritis and for delivery of steroids ,which are observables[1] in colon. The advent of slow release technologies increase the chances for a drug to be released in the Colon and this organ has an important role to play in drug absorption from oral sustained release formulations [7]. In 1942,svartz discovered that sulfasalazine;a sulfonamide prodrug of 5-aminosalicylic acid (5-ASA) , is effective in the treatment of rheumatoid arthritis and anti-inflammatory disease. The exact mode of which the drug targets itself to the colon is what elucidates which letter in 1970 i.e; colon specific azoreductase splits sulfasalazine causing the release of the active moiety 5-Amino. Salicylic acid . After the several other azo - bonds, containing compounds designed locally [7]. Release 5-amino salicylic acid was synthesized as bensalazine , balsalazide and olsalazine . In 1986, saffron ,and coworkers described the use of azo-containing acrylic polymers to the delivery of protein drugs. Like insulin to the colon (Girish et.al 2006) [7].

•Anatomy and physiology of colon:

Irrespective of therapy desired for local (colonic) or systemic delivery of drugs, the development and aim of the drug delivery to colon remains the same. (Vyas and Roop ,2006), that is

-The drug must not be observed from other regions of the gastrointestinal tract (GIT).

-The release of the drug in the colon should be at eqvi tentatively control rate and the release drug in the colon should be observed from the lumen of the large intestine without any appreciable degradation [7].

-In order to meet these properties, knowledge of the anatomy and physiology of GIT is required .

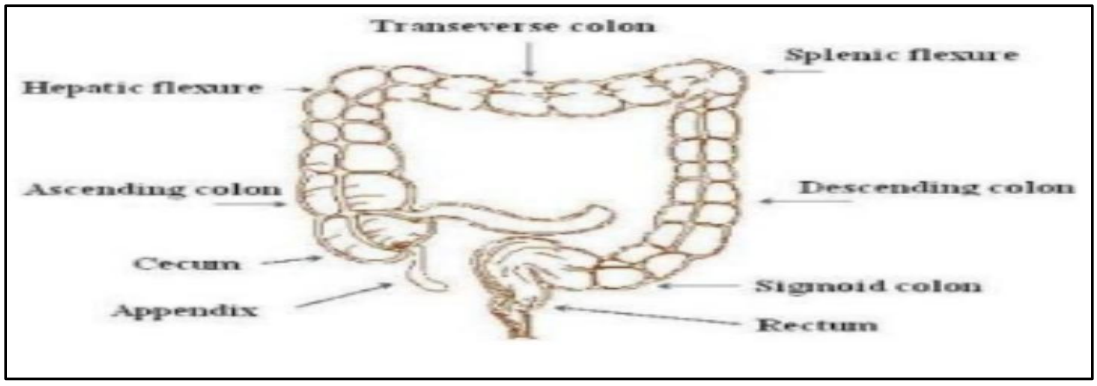

Fig 1.Physiology of colon

-large intestine starts from the ileocecal junction to the anus with a length of about 1.5 m (adults) and is divided into three parts: they are 1.Colon
2.rectum
3.anal canal.

-The colon is cylindrical and lined by mucosa. The cecum, Colon ascends , Colon transverse, Colon descendens and recto sigmoid colon made of the colon.

-The colon is made up of four layers Serosa ,muscularis externa, submucosa and mucosa.

-The column does not have a villi , but due to presence of plicaese militares (crescentic folds) the intestinal surface of the colon is increased to approximately 1300 CM square.

-CDDS is primary dependent on the following physiological factors;

They are the

1.ph level

2.the transit time

3.the microbial environment in the colon

-which are governing the release rate of drugs from different designs of CDDS (Vyas and Roop , 2006, Vincent ey.al 2002) . Different properties of GIT are given in (table number 1) and different enzymes present in the colon , which are responsible for microbial degradation ,were reported by Vincent et al (2002)[7].

•some colon problems:

There are many colon problems affecting the colon and rectum these conditions include:

1] irritable bowel syndrome

2] constipation

3] hemorrhoids

4] anal fissures

5] abscess

6] calitis

7] polyps

8] colon cancer.

•How to identify something is wrong with colon:

-a persistent change in your bowel habits, including diarrhea or constipation change in the consistency of your stool.

-rectal bleeding or blood in your stool

-persistent abdominal discomfort, such as cramps, gas ,or pain ,a feeling that your bowel does not empty completely.

•function of colon: the colon removes water and some nutrients and electrolytes from partially digested food.

•Technology used for colon targeting:

currently Gamma scintigraphy and high-frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

•when your colon is inflamed then :

Eat protein

-low sodium and ud low fat deli meats.

-well- cooked eggs.

-tofu

-There are seven ways to do a natural colon cleanse at home.

1.2. Salt water flush you can also try a salt water flush**…..**

3. High fiber diet**…..**

4. Juices and smoothies**…..**

5. More resistant starches**…..**

6. Probiotics**…..**

7. Herbal teas**…..**

•symptoms:

Symptoms of bowel problems include

1. Abdominal pain
2. Spasms
3. Gas
4. Bloating
5. Inability to defecate or pass gas
6. Rectal bleeding
7. Loose and watery stools
8. Constipation
9. Diarrhea
10. Vomiting
11. Weight loss.

•Drug absorption in the colon:

-The surface area of colon is much less as compared to small intestine and it's compensated by absence of endogenous digestive enzymes and long residence time of Colon (10-24hrs). Different factors affecting colonic absorption are reported by Vincent et al (2002).

-passes through colonocytes { transcellular transport}.

-passes between adjacent colonocytes {paracellular transport}.

1.Drugs shown to be well absorbed include glibenclamide, diclofenac, theophylline, Ibuprofen, metoprolol, and oxprenolol.

2.drugs shown to be less observed include Furosemide, piretanide,,buflomedil, atenolol, cimetidine , hydrochlorothiazide, lithium and ciprofloxacin (sarasija et.al 200).

•Different types of absorption enhancers used in CDDS reported by Vincent et.al(2000).[7].

drugs are absorbed passively by either paracellular or transcellular route.

transcellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes.[3][4]

Ware paracellular absorption involves the transport of drugs through the tight junction between cells and is the route most hydrophilic drugs take. (Vyas and Roop,2006).

the slow rate if transit In colon let the drugs stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area.[3][4]

The concentration of drugs reaching the colon depends on formulation factors, the extent of retrograde spreading and retention time.

foame and suppositories have been shown to be retained mainly in the rectum and sigmoid colon .

while enema solutions have a great spreading capacity [2].

because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient [2].

The human colon has over 400 distinct species of bacteria as a resident flora, a possible population of up to 1010 bacteria per gram of colonic contents [2].

the colon is believed to be a suitable absorption site for peptides and proteins drugs for the following reasons-

1. 2. Comparative proteolytic activity of colon mucosa is much less than that of observed in the small intestine.

•Drugs suitable for CDDS:

Based on literature review, the following different categories of drugs are suitable for Colon drug delivery[7].

-drugs to treat colonic cancer required local delivery e.g 5 fluorouracil, doxorubicin , and methotrexate.

-protein and peptide drugs- eliminating drug degradation example growth hormones, calcitonin, insulin, interleukin, interferon ,and erythropoietin.

-To treat infectious disease (amoebiasis and helminthiasis) require site specific delivery examples metronidazole ,mebendazole ,and albendazole.

-To treat rheumatoid arthritis (NSAIDS) nocturnal asthma ,angina requires delay in absorption due to circadian rhythms.

-Drugs showing more selective absorption in the colon of the small intestine due to small extent of paracellular transport example glibenclamide, diclofenac, theophylline, Ibuprofen ,metoprolol and oxprenolol[7].

systemic circulation [7].

-An orally administered dosage form has to traverse the entire alimentary canal in order to reach the target site.

-Moreover, the presence of food and metabolic enzymes also increases the physiological complexity[11].

-Another factor is the drug solubility. Due to a low colonic luminal fluid volume, higher viscosity, and a neutral pH, the solubilization of the drug could be a rate-limiting factor for colonic absorption[11].

-The non-specific interactions of the drug with the colonic content e.g., dietary residues, intestinal secretions, mucus, or fecal matter can have a negative influence on the stability of the drug [11]. In addition, the colonic bacterial enzymes may also degrade the drug, rendering it ineffective[11].

•Advantages of colon targeted drug delivery system(CT DDS) over conventional drug delivery:

In targeting larger amounts of drugs can be utilized and are available at targeted site, due to this lesser amount of drug is required. Some of the drugs like dexamethasone and methylprednisolone by oral and intravenous routes produce systemic effects as adenosuppression, immunosuppression, cushinoid symptoms, and bone resorption that can be solved by targeting thus shows effective therapy. It prevents the needless systemic absorption and increases the absorption of poorly absorbed drugs, and prolong drug action thus improving bioavailability. [2][10].

•Why targeted to the colon …..?

-Delay the drug absorption.

-For oral administration of peptide and protein drugs.

-Colon targeting formulation could also be used to prolong drug delivery.

-Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GIT.

-To prevent asthma, arthritis attacks in the early morning[10].

•General consideration for design of colonic formulation:

The design of the colonic formulation is to provide a burst release or to sustained/controlled release when formulation reaches in the. Several important factors like pathology and pattern of the disease or physiology and physiological composition of the healthy decide the formulation approach. Other factors like drug dissolution and release rate of drug in are also considered for the formulations. The pH gradient of the GIT is the most important physiological factor considered in the design of delayed release colonic formulation. [10] .

•Criteria for selection of drug for CTDDS: -Drug Candidate: Drugs which show poor absorption from the stomach or intestine including peptide are most suitable for CT DDS. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea and cancer are ideal candidates for local delivery.

- **Drug Carrier**: The selection of carrier depends on factors such as chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer chosen. In addition, the choice of drug carrier depends on the functional groups of the drug molecule[10].

• **Types or modified release formulations:** These are of two types

1.**Single unit dosage form:**- Ex.- Tablets, Capsules.

2.**Multiple unit dosage form:**- Ex.- Micro granules, Micro spheroids, Beads, Pellets, Microcapsules[10].

•Approaches used for site specific drug delivery to colon :

A**. Primary Approaches for CTDDS:**-

1**. pH -Dependent Polymer Coating Drug Delivery to Colon**. pH- dependent coated methods are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the diseases30. The pH-dependent systems make use of the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increases to 4 during digestion), These enteric polymer coatings are insensitive to the acidic conditions of the stomach but ionize and dissolve at the more neutral pH of 5–6 found in the upper small intestine. This concept has been adapted for targeting [10]. In this system, drugs are formulated into solid dosage forms such as tablets and are coated with pH sensitive polymers as in enteric coating. Eudragit L and Eudragit S are copolymers of methacrylic acid and methyl methacrylate. Eudragit S is water soluble at pH 7 or above and is used to deliver drugs to the end of the small bowel and large intestine [10]. The polymers described as pH dependent in specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. [10]

.The various polymers which are pH-dependent are shown in Table no. I.

Table I: Polymers used as pH-dependent are as follows.

Polymer.	**Threshold PH**	**polymer**	**Threshold PH**
Eudragit L100.	6.0	cellulose acetate trimiellate.	4.8
Eudragit S100.	7.0.	polyvinyl acetate phthalate(PVAP).	5.0
Eudragit L30D.	5.6.	cellulose acetate trimiellate(CAT).	5.5
Eudragit FS30D.	6.8.	Shellac.	7.0
HPMC phtalate.	5.2.	HPMC phtalate 55.	5.4

2. Delayed (Time Controlled Release System) Release Drug Delivery.

The basic principle involved in the system is the release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount. A nominal lag time of five hours is usually considered sufficient to achieve colon targeting. In this method the solid dosage form coated with different sets of polymers and the thickness of the outer layer determines the time required to disperse in an aqueous environment[10].

1.Microbially Triggered Drug Delivery to Colon.

Amongst all the approaches used for colon targeting, a microbially controlled delivery system is the most appealing as it relies on the unique enzymatic ability of the colonic microflora and enables a more specific targeting, independent of pH variations along the GI tract[10]. These systems are based on the exploitation of the specific enzymatic activity of the microflora (Enterobacteria) present in the colon. The colonic bacteria are predominantly anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escape the digestion in the upper GIT[10]. The presence of colonic microflora has formed a basis for development of colon targeted drug delivery systems. Interest has focused primarily on azo reduction and hydrolysis of glycosidic bonds. Such variation is to be taken into account in the development of colon specific formulations depending on the presence of colonic microflora. There is significant proteolytic activity in the colon, although this is 20-60 times less in the small bowel. with the result that it is exposed longer to proteolytic activity. Because of presence of biodegradable enzymes like glucuronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, xylosidase, azoreductase, deaminase and urea hydroxylase in the colon ,the use of biodegradable polymers for targeted drug delivery seems to be a more site specific approach. These polymers protect the drug from environments of the stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, the polymer may undergo degradation by enzyme or break down and release the drug to [10].

2**. Prodrug Approach for Drug Delivery to Colon**.

Prodrugs can be defined as pharmacologically inert chemical derivatives that can be converted in vivo to the active drug molecules, enzymatically or non enzymatically, to exert a therapeutic effect. Ideally, the prodrug should be converted to the original drug as soon as the goal is achieved[10]. Once in the colon, the drugs are acted upon by enzymes produced by colonic resident bacteria to release the active moiety. Sulphasalazine (SAS) which is used in the treatment of ulcerative colitis, Crohn's disease, and rheumatoid arthritis, is a well known -specific prodrug. It consists of 5-aminosalicylic acid (5-ASA) linked via an azo bond to sulphapyridine (SP). When orally administered, approximately 12% is absorbed in the small intestine, but the main part reaches the colon intact, where bacterial azoreductase cleaves the azo bond, thereby releasing 5-ASA and SP[10].

3**. Polysaccharide Based Approach for Drug Delivery to Colon**.

The important bacteria presents in the such as Bacteroids, Bifidobacterium, Eubacterium, Peptococcus, Lactobacillus, Clostridium secrets a wide range of reductive and hydrolytic enzymes such as β-glucuronidase, β-xylosidase, β-galactosidase, α-arabinosidase, Nitroreductase, Azoreductase, Deaminase and urea hydroxylase. These enzymes are responsible for degradation of di-, tri- and polysaccharides. These dietary polysaccharides thus have the potential as non-toxic carriers for colon specific drug delivery[10]. Several polysaccharides such as sodium alginate, chitosan, guar gum, xanthan gum, pectin, gellan gum have been employed either alone or in combination with their native or modified forms to control the drug release from different types of delivery system [10].

The Polysaccharides polymers which are

mostly used for targeting the colon are shown in Table no. II.

Table II: List of Polysaccharides polymers.

Class.	**Examples.**	**Class.**	**Examples**
Disaccharides.	Lactose.	Polysac.	Alginates
	Maltose.	Harides.	Amylose
	Cellobiose		galactomannan
			(Gugar Gum)
Oligosaccharides.	Cyclo		
	Dextrin		
	Lactulose		insulin
	Stachyose.		Pectins and pectates

•**Advantages of colon targeting drug delivery system**[3]

-colon is an ideal site for the delivery of agents to cure the local disease of the colon.

-reduce dosage frequency. Hence, lower cost of expensive drugs.

-The colon is an attractive site where poorly absorbed drug molecules have an improved bioavailability.

-Reduce gastric irritation caused by many [2]drugs (example NSAIDS).

-By pass initial first pass metabolism.

-Extended date time or night time activity.

-Improve patient compliance.

-**T**argeted drug delivery system.

-It has a longer retention time and is highly responsive to agents that enhance the absorption of poorly absorbed drugs.

-It has a low hostile environment and less peptidase activity so peptides ,oral vaccines, insulin, growth hormone ,can be given through this route.

-by producing the" friendlier"environment for peptides and proteins when compared to the upper gastrointestinal tract.

•Local delivery of drugs:

CoDDS for local treatment is usually undertaken for various diseased conditions such as IBD, IBS, colon cancer and so on.

IBD is a localized inflammation of the small and large intestines. Drug therapies for these disorders include aminosalicylates, corticosteroids, immunosuppressive agents, nicotine, cationized antioxidant enzymes and genetically engineered bacteria to produce cytokines [9].In addition to IBD, IBS is another common chronic gastrointestinal disorder in which the interaction of psychological, luminal and enteric factors results in disorders of the gut functions. The anticholinergics (e.g., dicyclomine, propantheline), anxiolytics, tricyclic antidepressants (e.g., desipramine and trimipramine), 5-hydroxytryptamine antagonists, calcium channel blockers (nifedipine, nicardipine) and calcium antagonist (pinaverium bromide) have been used for IBS treatment [9].The treatment of colonic cancer using intravenous administration produces severe systemic side effects due to their cytotoxic effect on normal cells. Researchers have reported the use of various lectins and neo glycoconjugates for targeting drugs to cancer cells. They have shown improved specific targeting to the colon on oral administration, with avoidance of the degradation associated with the hepatic first-pass metabolism [9]. Recently, ligand-mediated targeted delivery is being explored for improving the selective toxicity of anticancer therapeutics. The delivery systems used for targeting anticancer drugs to tumor cells or tissues can be improved by a combination of binding drugs with molecules that bind to antigens or receptors that are specific on the target cells as compared with normal cells or tissues [9].

The prodrug laxative sodium sulisatin, an anionic drug, is poorly absorbed and arrives intact to the colon on oral administration. It is then hydrolyzed in the colon by the bacterial arylsulfatase sulfohydrolase to a diphenolic derivative, which is an active laxative [9]. This causes stimulation of water and secretion of electrolytes and causes a laxative effect [9]. The presence of microbial enzymes, and the resulting colonic metabolism are other important factors influencing CDDS performance which is discussed further[11].

•Colonic Enzymes and Metabolism:

The colon is known to consist of over 400 different species of aerobic and anaerobic microorganisms like Escherichia coli and Clostridium species, respectively [11].These bacteria contain several hydrolytic and reductive metabolizing enzymes [11]. The colonic enzymes catalyze a range of reactions, including the metabolism of xenobiotics (e.g., drugs) and other biomolecules (e.g., bile acid), deactivation of harmful metabolites as well as carbohydrate and protein fermentation [11].Polysaccharides such as chitosan, guar gum, pectin, etc., are commonly employed as release rate-controlling components in colon-targeted dosage forms. These polysaccharides are known to be resistant to gastric and intestinal enzymes, but are metabolized by anaerobic bacteria in the colon [11]. Drugs are also known to be susceptible to biotransformation by colonic enzymes. The metabolism of drugs by the colonic enzymes may result in the formation of metabolites that are pharmacologically active, inactive, or sometimes even harmful [11]. Formation of a pharmacologically active metabolite by the colonic metabolism of drugs is a commonly used “prodrug” approach for the colon-specific drug delivery systems[11].

•Formulation Factors:

The formulation factors that influence colonic drug delivery and bioavailability include physicochemical properties of the drugs, the dose, and the dosage form factors. Due to the lower amount (1–44 ml) of colonic fluid available for dissolution, the solubility and the dose of a drug become important factors for its colonic bioavailability. Although the highly potent drug budesonide (dose, 9 mg) has a lower aqueous solubility, it is absorbed well in the colon and is used successfully in the treatment of UC [11]. Mesalamine has a significantly higher solubility (3.64 mg/ml) compared to budesonide (0.24 mg/ml); however, it also has a significantly higher dose (4.8 g daily) which becomes a rate-limiting factor for its colonic absorption [11]. Finally, the technology used in the dosage form development can also influence the colonic bioavailability of drugs. Useris® and Entocort EC® are currently approved budesonide products for the treatment of UC and CD, respectively [11]. Useris® is a multi-matrix (MMX)-based delayed-release tablet, which ensures the drug release in the colon, while Entocort EC® is a capsule which releases the drug in the ileum to treat CD.

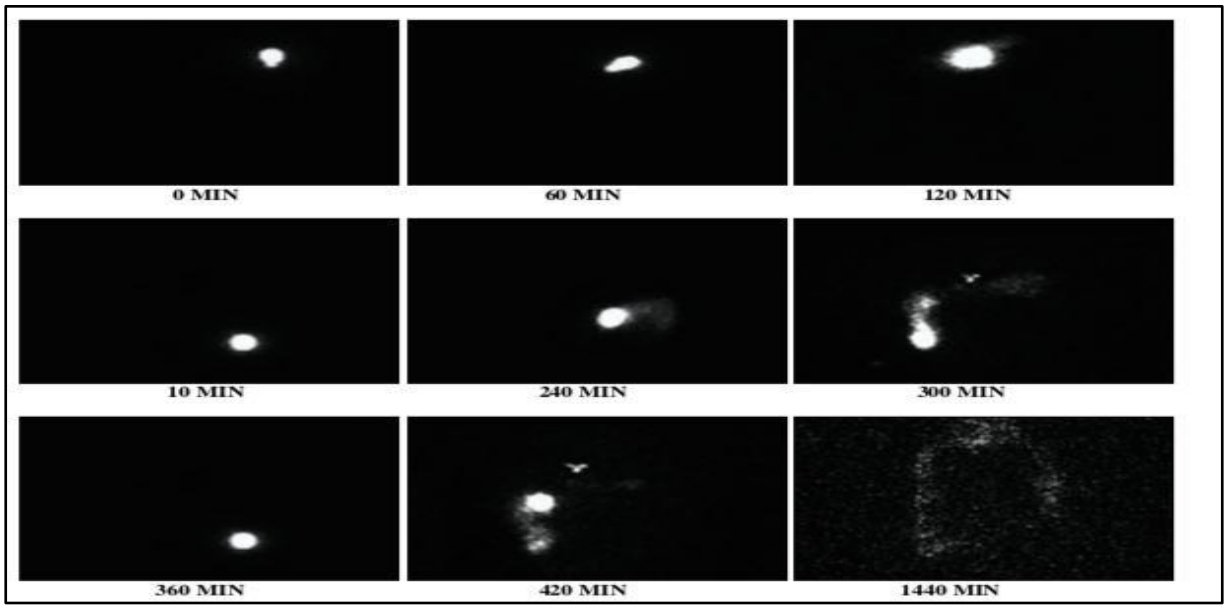

Fig 2. Scintigraphic images of subject after oral administration of 99MTC- labeled formulation at time interval 12

DISCUSSION

The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of The dissolution site but only released and absorbed once the system reaches the colon.

The colon specifically is more likely to be achieved with systems that utilize natural material that are degraded by colonic bacterial enzymes. The significance of this site specific drug delivery system can be measured by its usefulness for delivering a variety of therapeutic agents.both for the treatment of local disease or for systemic therapies. With the arrival of newer innovations , a large number of breakthrough technologies have emerged for targeting a drug molecule to the colon.

On the other hand the major drawback of administering the drug by oral route are absorption and degradation of drug in the upper part of the GIT. Hills in the design of per oral controlled release drug products colon targeted drug delivery system (CODDS) have gained a tremendous interest for delivering a variety of drugs.However, the treatment can be made effective if the drugs can be targeted directly into the colon ,thereby reducing the systemic side effects.

CDDS protect peptide drugs from hydrolysis and enzymatic degradation

In duodenum and jejunum and eventually released drug into an ileum for: which leads to greater systemic bioavailability and finally because the colon has a long residence time which is up to 5 days and its highly responsive to absorption enhancers.

CONCLUSION

The colonic region of GIT has become an increasingly important site for drug delivery and offers considerable therapeutic benefits to patients in terms of both systemic and local treatment. Targeted drug delivery to the colon is mainly for the treatment of colonic disease for drugs like proteins and peptides.

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