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Novel Colon Targeted Drug Delivery System – Review

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ABSTRACTS: In the most cases of dosage forms Oral administration for colonic drug delivery system (CDDS) is the most common form of administration because of greater patient compliance and flexibility. Targeteddrug delivery many time is known as smart drug delivery.Targeted drug delivery system is a thatsystem in this the dosage form will modified to deliver the drug to target site or at the disease site. Past few year colonic drug delivery has more importance for delivery of drug for the treatment of local diseases of colon like Crohn's disease, ulcerative colitis, etc. associated with colon and systemic delivery therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents.To achieve more effect in colon targeted drug delivery, a drug need to be protected fromdegradation, release and absorption in the upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon.Colon targeted drug delivery it will minimize the systemic side effects.Treatment could be more effective if this will possible to drug directly delivered into the colon system.

This review article includes prodrugs, pH and time dependent systems and microbial triggered systems and the novel approach of colon targeted drug delivery system(CTDDS),this containspressure control colonic delivery capsules (PCDCS), CODES and osmotic controlled drugdelivery are specific technique (ORDS-CT) which are unique in terms of achieving in vivo site specificity, and feasibility of manufacturing process. Also contains IBD treatment. Ulcerative colitis (UC) and Chron's disease (CD) is classified as chronic inflammatory bowel diseases(IBD) this has similar symptoms and lead to digestive disorder and inflammation in the digestive system

Keywords: Colon targeted drug delivery system, Chronic inflammatory bowel disease , pH dependent, Time dependent, New approach etc.

I. INTRODUCTION :

Orally drug administration is the most easy and convenient method of administration of drugs for systemic effect. Commonly 50% of the route of administration of drug delivery systems available in the market are ODDS and these systems will more accepted by patient[1,2].This route of administration has less disadvantages related to other administrations.last ten years there has been interested developing new drugs to target colon . Drugs for colonic drug delivery has more importance to treatment of local diseases of colon like Crohn's disease, ulcerative colitis, etc. associated with colon and systemic delivery therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents[3,4].The colon targeting drug delivery system (CTDDS) should be desirable to protecting the drug in route to the colon i.e. drug must be release and absorption should not occur in to the stomach as well as small intestine, and nor bioactive agent should be degraded either of the dissolution site, but only when released absorbed once the system will reaches the colon[5].

This system contains various methods or techniques through which CTDDS can be achieved, for example, formation of prodrug, coating with pH sensitive biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure-controlled drug delivery systems(PCDDS), osmotic pressure controlled systems(OPCS)[6-8]

Inflammatory bowel disease (IBD) results in the interaction between genetic and

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environmental factors that influence the immune responses. Inflammatory bowel diseases divided into Ulcerative colitis (UC) and Chron's Disease (CD). Ulcerative Colitis disease is similar to Chron's disease, both are classified as chronic inflammatory bowel disease and they cause digestive disorder and inflammation in the gastrointestinal tract. Symptoms of CD & UC includes Diarrhea, Abdominal Pain, Rectal Bleeding, and Weight Loss. This are mainly characterized by inflammation. Chron's disease and Ulcerative colitis both are may occur in adolescents and adults and also affect men and women equally[29]. The symptoms of CD and UC is very similar. Malnutrition is common in CD because the small intestines are responsible for the absorption of nutrients, and CD damages the small intestine [30].

Signs and Diagnosis of the Inflammatory Bowel Diseases(IBD)

To diagnose IBD, need to examine clinical symptoms of disease. Clinical Symptoms of this disease are pediatric growth disorders, anemia, abdominal pain, bloody diarrhea, and arthritis. Common pathogenic bacteria causing IBD is Salmonella, Shigella, Yersinia, Campylobacter, Aeromonas, Clostridium Difficile, E. Coli, and Tuberculosis[33]. Patients who suffer from acute gastroenteritis has been presented a raised risk of growing IBD. Gradel et al, by working on IBD and disclosing about pathogenic bacteria that should cause gastroenteritis disease i.e., campylobacter and salmonella, possibly play an essential role in the IBD etiology[34]. In this initial rectal bleeding in children, that may occur due to hemorrhoids, polyps, or diverticulum, the possibility of IBD should be reported. CD is far more dangerous than the UC; swith more than half of the patients with CD suffered from severe infections in both ileum and colon[35].

Clinical eye examinations can also play a very useful role in diagnosing these diseases. Accordingly, rectal examinations can also be performed as well. Thus, in 20-80% of patients with CD, perianal skin tags, itchiness, or pain around the anus should be suggestive of inflammation, fistulization, or abscess around area of anal, that are quite common[36,37]. An increase in the lactoferrin up to 80% is alarming and the suggesting the likelihood of IBD[38,39]. In a comprehensive study of the clinical feature of UC, Moo et al. should reported that some local side effects and external anomalies must be appear in disease[40].

History of Disease Treatment

Kamm can believed that the main objective of the diagnosis and treatment of the disease should to reduce the symptoms and improve the patient's health, to completely eliminate the symptoms of the disease or keep the disease at the fixed stage and surgical treatment should avoid.[41]. He also stated that before to treat IBD , it was necessary that the type of the disease before initiating the treatment. By carefully examining the clinical symptoms of the patient and complete several tests, the disease stage or severity , as well as which area should affected by disease , can be determine. Also important how body will responds to treatment[42]. For mild to moderate disease, aminosalicylates that are proper selective drugs used in different forms. Efficacy of aminosalicylates must be depends on the dosages [43,44].

New formulations of other drugs for IBD: Budesonide and Azathioprine

To treatment of IBD requires consideration in the assessment and design of other existing and novel drugs because the changes in intraluminal intestine and colonic pH in affected patients.

Controlled ileal release budesonide approach the prednisolone in efficacy to treatment of active ileocaecal Crohn's disease[45,46]. Two different pH based formulations of budesonide are now available. Budesonide CR (Entocort CR) gelatin capsules include acid stable micro granules of budesonide suspended in ethyl cellulose with an inert sugar core. Micro granules is coated with layer of methoacrylic copolymer that dissolves at a pH above 5.5 so that 50-80% of an oral dose which absorbed in the ileum or proximal colon in healthy volunteers [47]. More recently launched Budenofalk shows that the Budesonide is released from Eudragit coating [48] when pH exceeds up to 6.4. In this context, it is of interest that Budenofalk appeared not effective in patients with active Crohn's disease confined to the left colon and rectum,[46] in whom low colonic pH [49].

For IBD Azathioprine is an very effective immunomodulating treatment, use of which restricted, by its toxicity, to the patients with refractory disease [50]. A new pH dependent release formulation effectively delivers drug to the terminal ileum and colon with and minimum systemic absorption in healthy volunteers [51]. Formulation has an polymer coating that starts

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releasing the drug in the distal ileum at luminal pH > 7.0. Again, the low colonic luminal pH found in the some patients whichan active colitis could reduce Azathioprine bioavailability and thelimit its therapeutic efficacy.

Benefits and Drawbacks [9 – 11, 31]

Colon is an site for the delivery of agents to cure the local disease of colon. Lowest adverse side effects and drug interaction. Low amount of drug is required.No first pass metabolism. Novel targeted drug delivery system.More patient compliance. Low frequency of administration then minimum cost of drug.

Long process of manufacturing with multiple steps.Drug releases incompletely. Low bioavailability because binding of drug to intestinal content.

Table 1. Colon Targeted Diseases drugs[12]

Target site	Disease condition	Drugs and active agent
Topical action	Inflammatory Bowel Diseases, (Chron's disease, Ulcerative colitis) Irritable bowel diseases Amoebiasis	Hydrocortisone, Prednisolone, Sulfasalazine, Mesalazine, Mercaptopurine Metronidazole, Tinidazole, Mebendazole.
Local action	Pancreatactomy, chronic pancreatitis, Cystic fibrosis, Colorectal cancer	Digestive enzyme 5-Flourouracil
Systemic action	To prevent gastric irritation To prevent the first pass metabolism of orally administered drugs Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroids Insulin Typhoid

Factors to be affected in the design of colon-targeted drug delivery system

1.Anatomy of colon :

GIT [12,13] have part from mouth to anus. Mainly divided into three parts i.e., stomach,small intestine & large intestine. The GIT measures up to 5 meter long. small intestine measures up to 6.9 - 7.1 m long. In small intestines includes i.e., duodenum, jejunum , and ileum.

Large intestine measures up to 1.5 m long. large intestine starts from distal end of the ileum to the anus. It includes i.e., colon ,rectum and anal canal. Colon measures up to 5 feet (1.5 m) long.[14]

colon itself made up of the caecum,ascending colon ,hepatic flexure, transverse colon,splenic flexure, descending colon, sigmoid colon .colon is cylindrical tube like shape that lined by moist, soft pink lining called mucosa; pathway is called the lumen and is approximately 2-3 inches in diameter[15]

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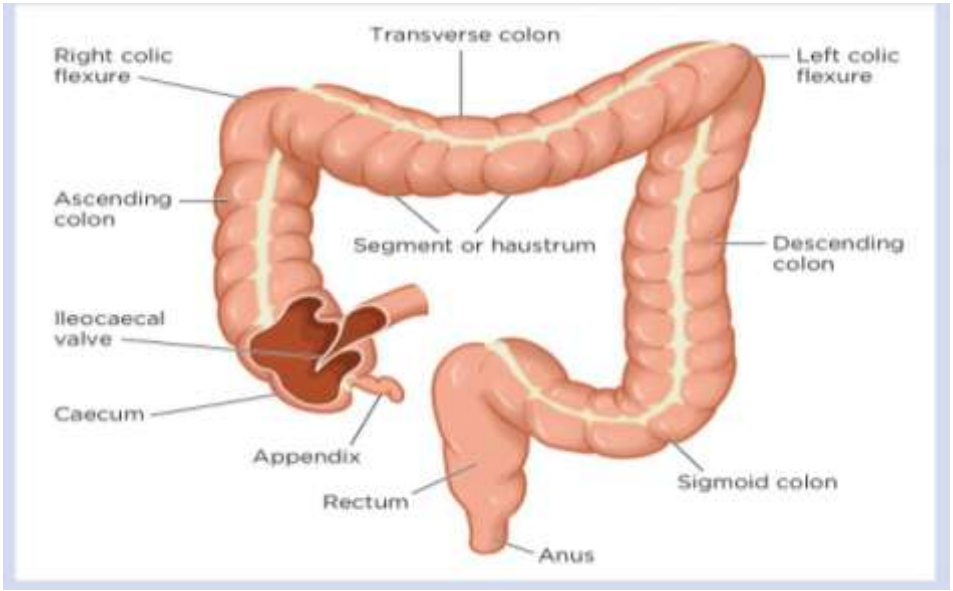

Fig. Anatomy of Colon

Table 2.Measures of different parts of GIT

Organs	Lengths
Small Intestine Duodenum Jejunum Ileum	3m 25m 1m 2m
Large intestine CecumColon Ascending colon Transverse colon Descending colon Sigmoid colon	1.5m 6cm 20-25cm 10-15cm 40-45cm 35-40cm
Rectum	20cm
Anal colon	3cm

2.Colon PH

The PH of gastrointestinal tract is various in two different i.e, inter and intra subjects. Mainly Diet , diseased state, and food intake effect in the PH of gastrointestinal fluid. The changes in the PH along the gastrointestinal tract have been used as a means for novel colon targeted drug delivery.[16]

There is the decrease in the PH due to entry into the colon because presence of short chain fatty acid arising from bacterial fermentation of polysaccharides.

Table : PH in colon

GIT parts	pH
Stomach	Fasted state 1.5-2 Fed state 2-6
Small intestine	6.6-7.5

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Colon Ascending colon Transverse colon Descending colon	 6.4 6.6 7.0

3.Colonic micro flora and enzymes :

Intestinal enzymes used to trigger drug release in GIT parts. Usually, these enzymes are derived from gut micro flora residing in colon. These enzymes must be used for degrade coatings as well as to cut bonds between an inter carrier and an agents(i.e.,prodrug should release from drug).Over 400 distinct bacterial species have been found ,20-30% of which are of the genus Bactericides[17,18].

Table :Different micro flora,Enzymes released and action[31]

Microorganism	Enzyme	Metabolic reaction
E.coli,Bacteroids	Nitroreductases	Reduces the aromatic & heterocyclic nitro compound
Clostridia,Lactobacilli	Hydrogenases	Reduces the carbonyl groups & the aliphatic double bond
Clostridia,Eubacteria	Glycosidase	The cleavage of b-glycosidase of alcohol&the phenol
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavage of O-sulphates &sulfa mates

4.Drug Candidate:

Drugs that shows poor absorption from the stomach as intestine including peptides are most suitable for CDDS.Drugs used in the treatment of inflammatory bowel diseases, ulcerative colitis, diarrhea and colon cancers this are ideal candidates for colon targeted drug delivery system.[19]

Table:Criteria for selection of drugs for CDDS[20]

Criteria	Pharmacological class	Non peptide drugs	Peptide drugs
Drugs used for local action in colon against GIT diseases	Anti-inflammatory drugs	Metoprolol, Nifedipine	Amylin, Oligonucleotide
Drugs used for colon Cancer	Antineoplastic drugs	Pseudoephedrine	Epoetin, Glucagon
Drugs poorly absorbed	Antihypertensive & Antianginal drugs	Ibuprofen, Theophylline	Cyclosporine, Desmopressin
Drugs that undergo extensive first pass metabolism	Nitroglycerine & corticosteroids	Bleomycin, Nicotine	Sermorelin , Saloatonin

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5.Drug Carrier:

The selection of carrier for particular drug candidates depends on the physiochemical nature of the drug as well as the disease for which the system should used.

The factors i.e., chemical nature, stability and partition coefficient of drug and the type of absorption enhancer chosen influence the carrier selection.Drug carrier choice depends on the functional group of drug molecule[21]. The carriers which contain additives like polymers (may be used as matrices and hydrogels as coating agents)may influence the release properties and efficacy o the system.[22]

APPROACHES FOR COLON DRUG DELIVERY SYSTEM

Colon targeted drug delivery system is considered as beneficial in treatment of colon related diseases and the oral delivery of drugs i.e., protein and peptide. Following mechanisms for colon targeted drug delivery system:

1. Coating with pH dependent polymers
2. Osmotic control system
3. Pressure controlled system
4. Coating with pH independent biodegradable polymers
5. Delivery systems based on the metabolic activity of colonic bacteria
6. Pulsating drug delivery system
7. Time controlled or time dependent system

1. Coating with pH dependent polymers

Bio degradable azo polymers with the high hydrophilicity exhibit superior degradation properties and this should be used to coat capsules. The higher degree of hydrophilicity it may cause the drug release from the system before it will reaches to the colon. Azo polymer system it will not suitable for delivery of peptides , hormones, and other drugs with a narrow therapeutic index; however they are suitable for the local drug delivery to colon. Methacrylic acid polymers are mostly used co polymers commonly known as Eudragit L and Eudragit S.Carbonyl polymers forms salt and dissolve at pH 5.5 and disperse in water to form latex and avoid use of organic solvents in coating processes.

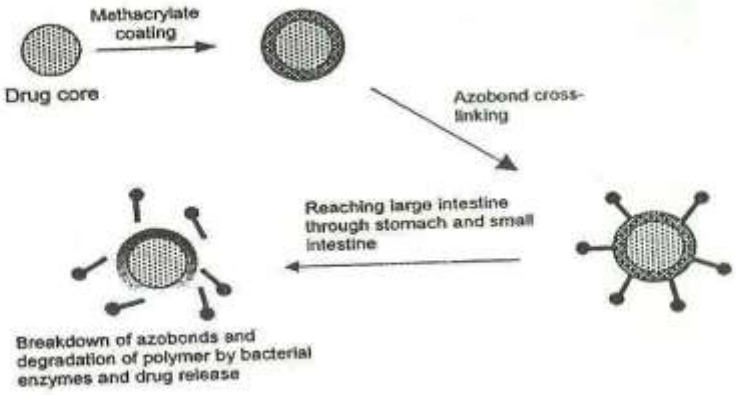

Fig. Working principle of biodegradable azo polymer system.

2.Osmotic Controlled System (ORDS-CT) :

ORDS-CT (Alza Corporation) system must be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsules. Each bilayers push-pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermiable membrane . As the unit enters small intestine the coating dissolves in this higher pH environment compartment.

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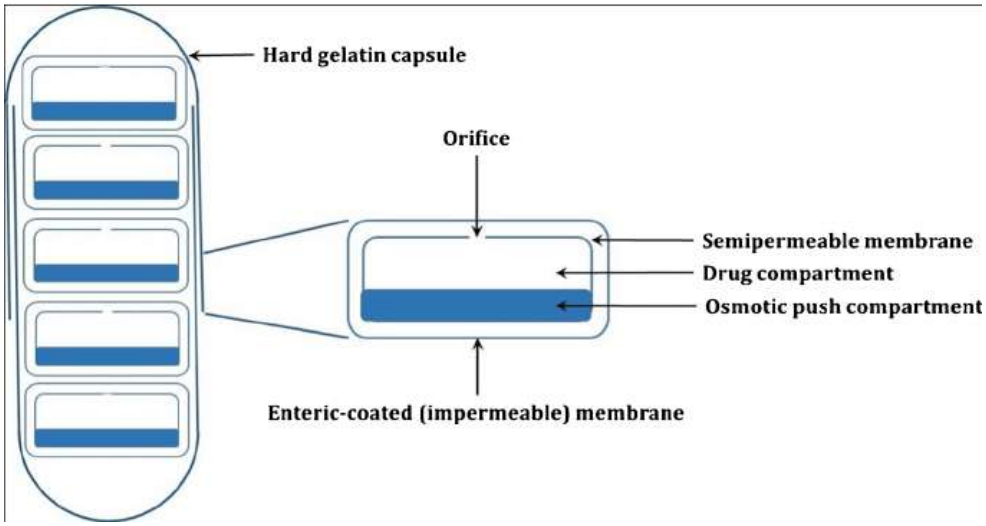

Fig.2 Cross section of the OROS-CT colon targeted drug delivery system

Mechanism :

The muscular contractions of the gut wall will generate pressure,which is responsible for grinding and propulsion of the intestinal contents. This pressure must be responsible for release the drug from the capsule shell.

3.Pressure controlled System

Luminar pressure within the colon, which forms the basis for design of pressure that controls system. The particular delivery which is in the form of capsules that is resistant to the pressures of upper GIT but it is collapsed in the large intestine due to increased pressure. The digestive processes in that theGIT involves contractile activity of the stomach and peristalsis movements for propulsion of intestinal contents. These strong peristalsis waves in the colon are short duration, occurring only 3-4 times a day. The ethyl cellulose use to fabricate the capsule shell and collapse time of the capsule in large intestine can be controlled by adjusting the thickness of the capsule shell wall.

4.Coating with pH independent biodegradable polymers

Polymers that use to coat the drug, which are showing degradability because of the influence of colonic microorganisms, it can be exploited in designing drugs to targeting colon in order to release an orally administered drug directly in the colon. The Styrene and 2- Hydroxyl Methyl Methacrylate has copolymers were cross linked with divinylazo benzene to coat oral dosage forms of Insulin and Vasopressin. The intestinal microflora has a huge metabolic capacity and it appears that resuction azobonds is a general reaction of colonic bacteria.

5.Delivery systems based on the metabolic activity of colonic bacteria

Prodrugs

It designs to represents a nonspecific chemical approach to mask unwanted drug properties i.e., low bioavailability, less site specificity and chemical in stability. Prodrugs use to targeting a specific enzymes or a specific membrane transporter or both have potential drug delivery system specially for colon cancer chemotherapy.

Example – Sulphasalazine in treatment of ulcerative colitis and Chron's Disease.

Hydro gels

In hydro gels acidic co-monomers and enzymatic degradable azo aromatic cross links contains. A number of drug delivery systemshould proposed to deliver drug for efficient therapy. Controlled release active antimicrobial agents from the polymeric matrix well reported.

Example-Amoxicillin, Metronidazole, Ox tetracycline, Tetracycline-HCL.

6.Pulsating Drug Delivery

In this delivery drug released should rapidly after lag time. The lag time prior to rupture is commonly controlled by the permeation, mechanical properties of the polymer coating and the swelling behavior of the swelling layer methods for pulsatile drug delivery system this are capsular system, Osmotic system, Solubilisation or erosion of membrane and rupture of membrane.

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7.Time Controlled/ Dependent System:

This process is helpful from synchronous delivery of a drug. Transit time through small intestine i.e., independent type of formulation. Effects of variance in gastric resident time this minimized by using systems this are protected in the stomach and drug release is colon targeted by means of formulation release drug after a certain time of gastric emptying. Combinations of hydrophilic (HPMC) and hydrophobic polymers have been used as coating for tablets they release drug drug from a core after lag time. Time controlled formulations also have been prepared using water insoluble ethyl cellulose and swallable polymers.[17,18,23-27]

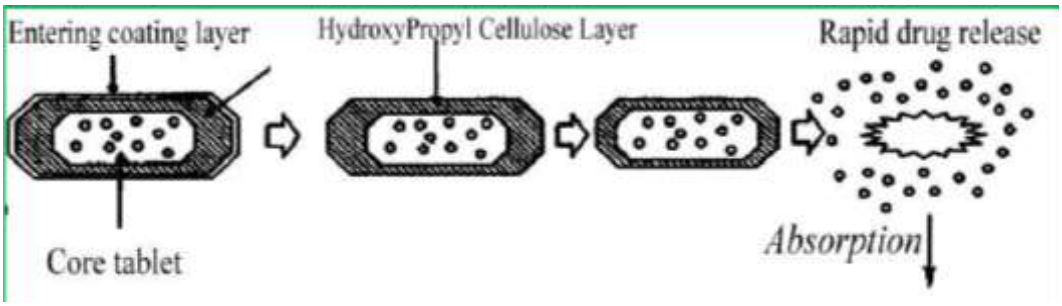

Fig. Design of Enteric Coated Timed- Release Press Coated Tablet (ETP Tablets)

EVALUATIONS

In-vitro evaluations

standardized evaluations techniques are not available for evaluations of CDDS as an ideal in vitro model should possess in -vivo conditions of GIT such as PH, volume, stirring, bacteria, enzymes, enzyme activity and components of food.These conditions are influenced by diet and physical stress.The in-vitro evaluations of colon targeted drug delivery system includes in-vitro dissolutions study and in-vitro enzymatic test.

1.In -vitro dissolution test :

Dissolutions of controlled -release formulations used for colon-specific drug delivery are usually complex, and dissolutions method should described in the USP can't wholly mimic in vivo conditions such as those relating to PH , bacterial environment and mixing forces. The dissolutions testing relating to CDDS may be carried outsing the conventional basket method.

The dissolutions testing in different buffers to characterize the behavior of formulations at different pH levels.

The different media should used for the dissolutions testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid ,pH 6.8 to simulate small intestine,pH7.4 to simulate large intestine.

The colon targeted drug delivery systems are tested for 2hr in 0.1N HCL ,3hr in pH 6.8 phosphate buffer and finally at pH7.4 phosphate buffer .Buffer of the above pH this is prepared to evaluate the novel colon targeted drug delivery system.

2.In-vitro enzymatic test:

Two type of tests for the in-vitro enzymatic test.

-The carrier drug system is incubated in fermented containing suitable medium for bacteria (Streptococcus facciumor B.ovatus). The specific amount of drug will released at different time interval is determined.

-Drug release study is performed in buffer medium containing enzymes pectinase, dextranse or rat or guinea pig or rabbit cecal contents. The specific amount of drug will released in a particular time i.e, directly proportional to the rate of degradation of polymer carrier.

In vivo Evaluations:

Number of animals i.e, dogs, guinea pigs, rats and pigs this are used to evaluate the drug delivery to colon because they resemble the anatomic and physiological conditions as well as the microflora of human GIT.While choosing a model for testing a CDDS,relative model for the colonic diseases should also be considered.Eg.Guinea pigs are commonly used for experimental IBD model .The distributions of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluations of CDDS a novel model has been proposed. In this model the human fatal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which vascularises within 4 weeks ,matures and becomes

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capable for developing of mucosal immune system from host.

Clinical Evaluations

Drug absorptions into colon will monitored by colonoscopy and intubation.

Recently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery system.

•High frequency capsule:

Smooth plastic capsule containing small latex balloon, drug and radiotracer administered orally.

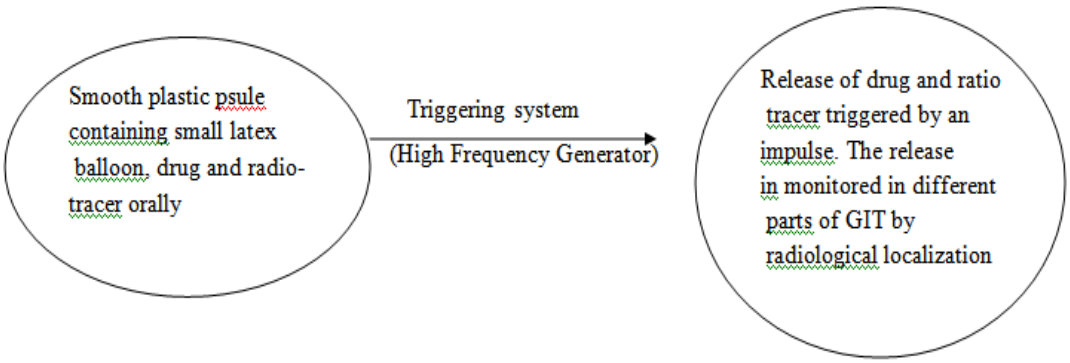
Triggering system is high frequency generator . Release of drug & radiotracer triggering by an impulse, the release is monitored in different parts of GIT by radiological localizations. It will checks the absorption properties of drug in colon.

- **Gammascintigraphy:**

By means of gammascintigraphic imaging, information can be obtained regarding time of arrival of a colon-specific drug delivery system in the colon, times of transit through the stomach and small intestine ,and disintegration.Information about the spreading or dispersion of a formulation and the site at which release from it takes place can also be obtained . Gammascintigraphic studies can also provide information about regional permeability in the colon. Information about GIT and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharmacoscintigraphy)[28].

- **High Frequency Capsule Method :**

This method is used to check absorption properties of drug in colon. The relative bioavailability of colonic drug delivery system should be evaluated by high frequency capsules. Advantages is relative bioavailability from any site of GIT should be evaluated and drug release at many sites of GIT within same object may be used to compare absorption parameters.



Tab..Techniques Employed In Marketed Drugs.

Techniques Employed	Polymer used	Drug used
pH dependent	Eudragit L100 & S100	Mesalazine, Diclofenac sodium & 5ASA
	Eudragit S, Eudragit FS, Eudragit P4135F	Prednisolone
	Eudragit L 30D55, Eudragit FS30D	Paracetamol
Time dependent	Hydroxy propyl methyl cellulose	Pseudoephedrine HCL
	Hydroxyethyl cellulose, Ethyl cellulose	Theophylline

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	Microcrystalline cellulose, Lactoseor Behinic acid	Indomethacine
Bacteria dependent or polysaccharide based	Chitosen	Diclofenac Sodium
	Pectin	Indomethacine
	Guar gum	Dexamethasone

Table . Formulation and Doses of Marketed Drugs. [32]

DRUG	TRADE NAME	FORMULATION	DOSE
Budesonide	Entocort	Eudragit 'L' coated tablets	9mg/day
Mesalamine	Asacol	Eudragit's' coated tablets	0.8-2.4g/day
Mesalamine	Pentaza	Controlled release EC coated tablets	1.5-4g/day
Mesalamine	Salotac	Eudragit 's' coated	1-4g/day
Mesalamine	Claversal	Eudragit 'L' coated tablets	1-2g/day
Olsalazine	Dipentum	5-ASA dimmer as capsules and tablets	1g/day
Sulfasalazine	Salazopyrin	5-ASA linked to sulfa pyridine as tablets	1-2g/day

II. CONCLUSION :

The colonic region of the GIT has become an mostly important site for drug delivery and absorption.CDDS offers therapeutic benefits to patients in both terms i.e, local and systemic treatment.Colon specificity is more likely to be achieved with systems that utilizes natural material that are degraded by colonic bacterial enzymes. Considering the sophistication of novel colon – specific drug delivery system, and the uncertainty of current dissolution methods in establishing possiblein-vitro/in-vivo correlations, challenge must be remain for the pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

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Conflict of Interest: There is no any conflict of interest.

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