COLON TARGETED DRUG DELIVERY – A REVIEW ON PRIMARY AND NOVEL APPROACHES

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ABSTRACT

Oral administration of different dosage forms is the most common form of administration due to greater patient compliance and flexibility. Targeted drug delivery system is the system in which the dosage form is modified to deliver the drug at the target region or at the disease region. In colon targeted drug delivery system the drug is targeted to the colon. The colon targeted drug delivery system is used for the treatment of various diseases related to colon like inflammatory bowel disease, crohn's disease, colon cancer, etc. This targeting of drug to the disease site lowers the requirement of higher doses of drug thus reducing the dosage frequency and cost of the drugs. Colon targeted drug delivery system will also lower the systemic side effects. This review article compares the different approaches to colon targeted drug delivery like pH and time dependent, prodrug, microbial triggered drug delivery, azo hydrogels, pressure controlled drug delivery, pulsatile drug delivery system, osmotic controlled drug delivery system, etc. The microbial triggered drug delivery system is based on the enzymes released by different microflora in the colon. Of the different approaches the new approaches like pressure controlled, osmotic controlled drug delivery systems are highly effective.

Keywords: colon targeted drug delivery, prodrug, osmotic pressure, microflora, pH sensitivity, time dependence, nanoparticles, etc.

INTRODUCTION

During the past decades research is going on in developing the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ[1]. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases like ulcerative colitis, crohn's disease, intestinal cancer, diarrhoea, for the treatment of diseases sensitive to circadian rhythms like Asthma, Angina, for the delivery of steroids, etc. colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon.

Advantages[2]
1. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis, crohn's disease, etc.
2. Decreases the side effects in the treatment of colon diseases.
3. Prevents gastric irritation resulting due to the administration of NSAIDs.
4. Minimizes first pass metabolism.
5. Provides suitable environment for proteins and peptides that are sensitive to gastric fluid and digestive enzymes.
6. Increased patient compliance.
7. Decreased frequency of administration. Hence decreased cost of drugs.
8. High retention time thus increasing the bioavailability of poorly absorbable drugs.

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Limitations

1. Multiple manufacturing steps.
2. Incomplete release of drug.
3. Lowering of bioavailability due to binding of drugs to intestinal contents.

Several factors like properties of drug, delivery system, interaction with GIT contents play a major role in the successful delivery of drug. The luminal fluid in the colon plays a major role in the absorption of the drugs. The luminal fluid in the colon is less compared to the small intestine. The drug should be in soluble state for the successful absorption. The low contents of the colon effects the absorption of low soluble drugs. To prevent the decreased availability of low soluble drugs the drug should be delivered in presolubilized form. The key factors to be considered while targeting the drug to the specific organ like colon are pH of GIT, drug solubility, contents of GIT, microbial flora, transit time of the intestine, etc.

Table 1: Colon targeted Diseases and drugs[4]

Target sites	Diseases	Drugs
Topical action	Inflammatory bowel diseases (Crohn's disease, Ulcerative colitis) Irritable bowel diseases	Hydrocortisone, Prednisolone, Sulfasalazine, Mesalazine, Mercaptopurine
	Amoebiasis	Metronidazole, Tinidazole, mebendazole.
Local action	Pancreatactomy, Chronic pancreatitis, Cystic fibrosis Colorectal cancer	Digestive enzymes 5- fluorouracil
Systemic action	To prevent gastric irritation To prevent first pass metabolism of orally administered drugs Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroids Insulin Typhoid

**Fig 1:** location of inflammatory bowel disease
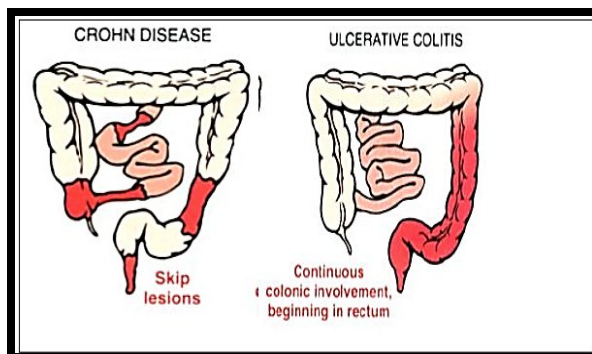
Anatomy of colon

The GIT[4, 6] consists of parts from mouth to anus. It mainly consists of two parts namely stomach, intestine. The intestine includes small intestine and large intestine.

The GIT measures about 5 meters long. The different parts of GIT are divided into upper and lower gastrointestinal tract. The upper GIT includes oesophagus, stomach, and duodenum. The lower GIT includes small intestine and large intestine.

Fig 2: Anatomy of colon
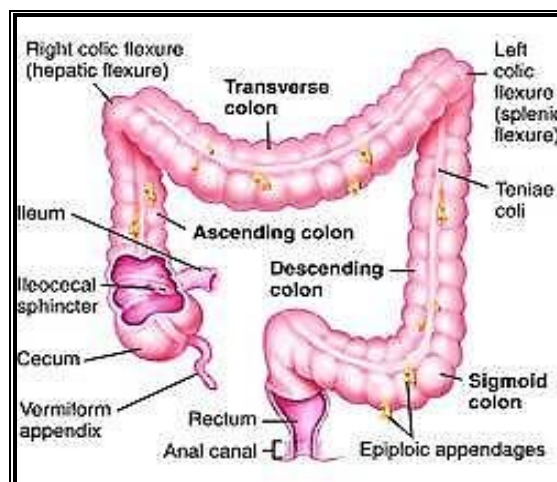
The small intestine measures an average of about 6.9 meters to 7.1 meters. It includes duodenum, jejunum and ileum. The main function of small intestine is the absorption of nutrients and minerals from food. The retention time of small intestine is 3-5 hr.

Table 2: Measures of different parts of GIT

Organ	Length
Small intestine	3m
Duodenum	25cm
Jejunum	1m
Ileum	2m
Large intestine	1.5m
Cecum	6cm
Colon	
Ascending colon	20-25cm
Transverse colon	10-15cm
Descending colon	40-45cm
Sigmoid portion	35-40cm
Rectum	20cm
Anal colon	3cm

The large intestine measures about 1.5 metres long. It includes caecum, colon and rectum. The main function of large intestine is to remove the water and minerals from the food and it sends the indigestible matter to the rectum. It acts as a house for over 700 species of bacteria. The retention time of large intestine is 3-10hr.

The colon consists of four parts: ascending colon, transverse colon, descending colon and sigmoid colon. It extracts water and salts from solid wastes before they are eliminated from the body. The parts of colon are located either in the abdominal cavity or behind it in retro peritoneum. The ascending and descending colon and rectum are retroperitoneal, while transverse colon is intra peritoneal. The pH of colon varies from 5.5 to 7.

Factors affecting colon targeted drug delivery[7]

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors
a. Gastric emptying
Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time of dosage form depends on the size of the particles. Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times.

Table 3: Transit time of different parts of GIT[8]

Part of GIT	Transit time
Fasted state	10min – 2hr
Fed state	>2hr
Small intestine transit	3-4hr
Colon transit	20-35hr

b. pH of colon
The pH of GIT varies between different individuals. The food intake, diseased state, etc. influences the pH of the GIT. This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site.

Table 4: pH in different parts of Colon

Part of GIT	pH
Stomach	Fasted state 1.5-2
	Fed state 2-6
Small intestine	6.6- 7.5
Colon	
Ascending colon	6.4
Transverse colon	6.6
Descending colon	7.0

c. Colonic microflora and enzymes
The GIT contains a variety of microorganisms that produces many enzymes need for metabolism. Growth of this microflora is controlled by the GIT contents and peristaltic movements. The enzymes released by different microorganisms E. coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are responsible for the various metabolic reactions that take place in the GIT.

Table 5: Different microflora, enzymes released and action

Microorganism	Enzyme	Metabolic reaction
E.coli, Bacteroids	Nitroreductase	Reduces aromatic & heterocyclic nitro compounds
Clostridia, Lactobacilli	Hydrogenase	Reduces carbonyl groups & aliphatic double bonds
Clostridia, Eubacteria	Glucosidase	Cleavage of b-glycosidase of alcohols & phenols
Eubacteria, Clostridia, Streptococci	Sulfatase	Cleavage of O-sulphates & sulfamates

2. Pharmaceutical factors

a. Drug candidates:

Due to high retention time of colon, colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. drugs used for treatment of inflammatory bowel diseases, etc. are suitable for colon targeted drug delivery system.

Table 6: criteria for selection of drugs for CDDS[9]

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	Nitroglycerin& Corticosteroids	Bleomycin, Nicotine	Sermorelin, Saloatonin

b. Drug carriers:

The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. The various physicochemical factors of drug that effect the carrier selection includes chemical nature, stability, partition coefficient, functional groups of drug molecule, etc.
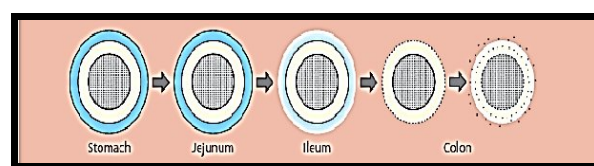
Approaches for colon targeted drug delivery[11]

1. Primary approaches for colon targeted drug delivery
   a. pH sensitive polymer coated drug delivery system
   b. Delayed release drug delivery system
   c. Microbially triggered drug delivery
      i. Prodrug approach
      ii. Polysaccharide based system
2. New approaches for colon targeted drug delivery
   a. Pressure controlled drug delivery system (PCDDDS)
   b. CODE
   c. Osmotic controlled drug delivery system (OROS-CT)
   d. Pulsatile
      i. Pulsincap system
      ii. Port system
   e. Azo hydrogels
   f. Multiparticulate system based drug delivery

a) pH sensitive polymer coated drug delivery system

The pH varies in different parts of the gastrointestinal tract. The pH in stomach ranges between 1 and 2 during fasting. The pH in the proximal part of small intestine is 6.5 and in distal part of small intestine it is 7.5. The pH is 6.4 in caecum, 5.7 in ascending colon, 6.6 in transverse colon and 7.0 in descending colon. The pH dependent drug delivery system is based on the solubility of different polymers at different pH ranges. The polymers are insoluble at lower pH values and get solubilized as the pH increases. As the polymers are insoluble at lower pH values the polymer can protect a formulation in stomach and to some extent in small intestine. In this way by altering the polymers used the release of drug from the formulation can be controlled[18].

Fig 3: Drug release pattern of a multilayer coated system at different pH conditions in GIT

b) Delayed or time controlled release drug delivery system

Time controlled drug delivery system[21] includes sustained or delayed release systems. In this system the delayed release or colon targeted drug delivery is attained by prolonging the lag time. The transit time varies in different parts of gastrointestinal tract. This transit time is responsible for the delayed release of drug. The main drawbacks of this delivery system are that the transit time varies from one person to other and amount of food intake.

It also varies with the peristalsis or contraction in the gastrointestinal tract.

c) Microbial triggered drug delivery system

The various microflora of the colon are Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus, etc. This microflora of gut depends on fermentation of undigested materials in the small intestine for their energy requirements. The microflora performs fermentation by producing a large number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, and deaminase and urea dehydroxylase. These biodegradable enzymes are capable of degrading the polymers used for targeting the drug delivery to colon. Different polymers are used for preventing the release of drug in the stomach and small intestine.

When the coated formulations reach the intestine the biodegradable polymers gets degraded by the enzymes produced by the microbial flora and the drug gets released in the targeted region.

Prodrug[22] is the main approach of microbial triggered drug delivery system in which the drug release from the formulation is triggered by the microflora present in the gut. Prodrug is the inactive form of an active parent drug that undergoes enzymatic transformation to release the active drug. The produrgs are prepared by linking the active drug with hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose, etc. These prodrug molecules get hydrolysed in the presence of the enzymes released by the microflora.

Fig 4: Prodrug approach for CDDS
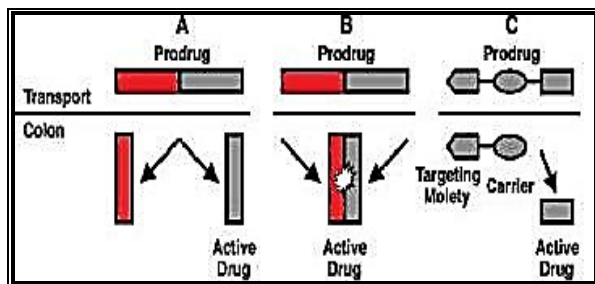
Table 7: Examples of Prodrug system for CDDS

Drug	Carrier	Linkage hydrolysed
5-ASA	Azo conjugates	Azo linkage
Dexamethasone	Saccharide carriers	Glycosidic linkage
Prednisolone, hydrocortisone, fludrocortisone	Glucose, galactose	Glycosidic linkage
Salicylic acid	Amino acid conjugates, glycine	Amide linkage

The main drawback of this approach is that the formulation depends on the functional groups available on drug moiety for chemical linkage. The prodrugs formed upon linkage results in the formation of new chemical entities that need a lot of evaluation before using them as carriers.

The most widely used prodrug approach is the metabolism of azo compounds by intestinal bacteria. Polysaccharide based delivery system is the other form of microbial triggered drug delivery system. Naturally occurring polysaccharides like guar gum, xanthan gum, chitosan, alginates, etc. are used in targeting the drug delivery. These are broken down by the colonic microflora to simple saccharides.

Table 8: Different polymers used for CDDS based on Microbial drug delivery system[22]

| Class	Examples
Disaccharides	Lactose, Maltose
Oligosaccharides	Cyclodextrins, Lactulose, Raffinose, Stachyose
Polysaccharides	Alginates, Amylose, Cellulose, Chitosan, Starch, Chondroitin sulphate, pectin, xanthan gum, etc.

d) Pulsatile colon targeted drug delivery
i) Pulsincap system

In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents.

The capsule[27] gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxy propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body.

Fig 6: Pulsincap system
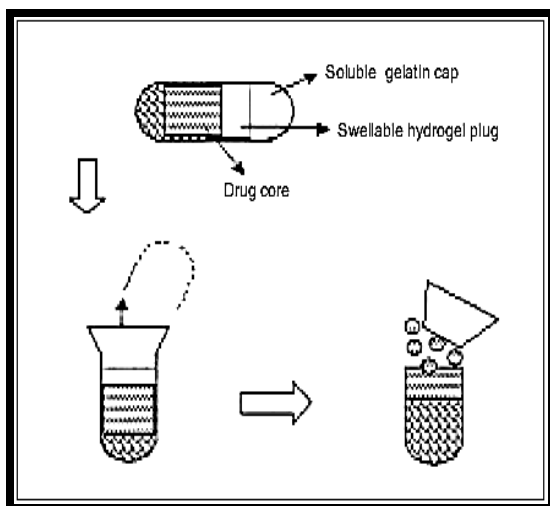
ii) Port system

In this system the capsule body is enclosed in a semipermeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation.

When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals[24].
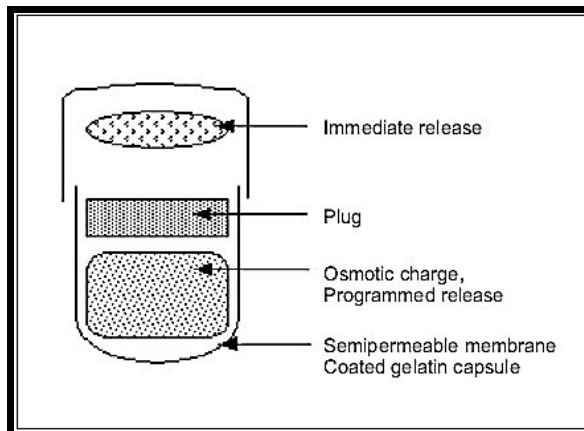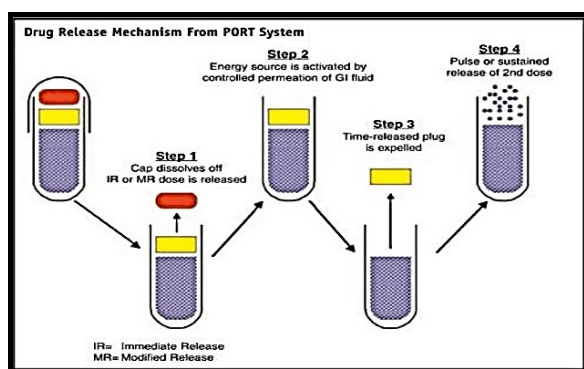
Fig 7: Port system

Fig 8: Drug release mechanism of port system

e) Pressure controlled drug delivery system

Digestion mainly occurs due to the contractility of the stomach and peristaltic movement of the intestine. The contractility movement of stomach leads to the digestion or breakdown of larger particles to smaller ones which are then transferred to intestine. The peristaltic movement of intestine is responsible for the passage of bolus from one part of GIT to the next part. The peristaltic movement of ascending colon transfers the bolus to transverse colon called as mass peristalsis. These peristaltic movements occur in limited number i.e. three to four times a day.

These peristaltic movements of intestine results in an increase in the luminal pressure. This increase in luminal pressure is the key point in the development of pressure controlled drug delivery system.

The pressure controlled drug delivery system[25] consists of a capsule in which the drug is present. These gelatin capsules are coated with water insoluble polymer like ethyl cellulose on their inner side. The drug is introduced into the capsule along with suppository base. The thickness of ethyl cellulose coating determines the disintegration capacity of the capsule. After administration the suppository base dissolves at body temperature. The water from intestinal contents is absorbed resulting in increased viscosity which leads to an increase in the pressure in the capsule. The pressure in the capsule expels the drug into the colon.

The intestinal pressure developed varies with the circadian rhythms, state of body, food administration, etc.

f) CODES technology

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings[27].

Fig 9: CODES system
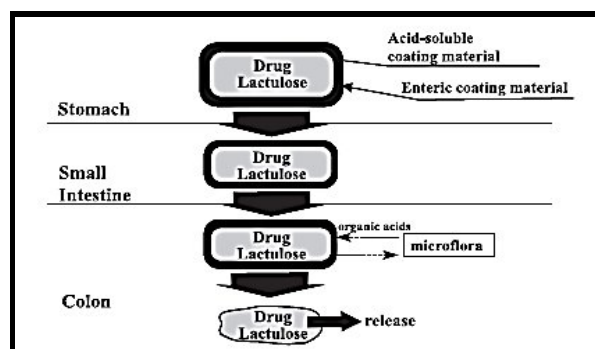
The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes though the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E. This layer allows the release of lactulose present in the inner core. This released lactulose gets metabolized into short chain fatty acids that lower the surrounding pH where the Eudragit E layer dissolves. The dissolving of Eudragit E

results in the exposure of the drug. The other polysaccharides that are used along with the drug in the core tablet are mannitol, maltose, etc. The bacteria present in the colon are responsible for the degradation of polysaccharides that are released from the core tablet. The degradation of polysaccharides results in organic acids formation that lowers the pH of the contents surrounding the tablet.

g) Osmotically controlled colon targeted drug delivery system

This system[30] consists of osmotic units. The osmotic units are used either singly or as many as 5-6 push pull units that are encapsulated in a hard gelatin capsule. The push pull units are bilayered with outer enteric impermeable membrane and inner semi permeable membrane. The internal or central part of the push pull consists of the drug layer and push payer. The semipermeable membrane which is present next to the drug layer consists of an orifice through which the drug contents are expelled during the course of time.

Fig 10: Osmotically controlled CDDs[31]
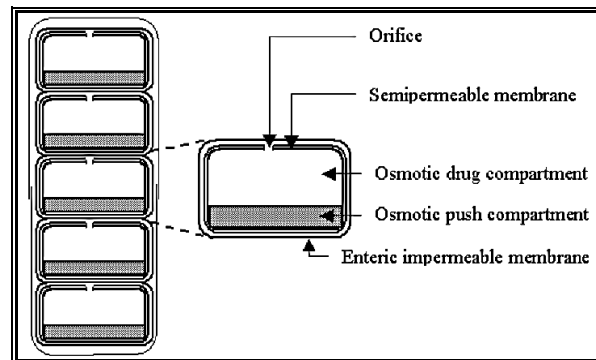
The capsule body enclosing the push pull units gets dissolved immediately after administration. During the passage of the push pull units through the GIT the enteric impermeable membrane prevents the water absorption into the unit. The coating gets dissolved once it reaches the small intestine due to higher pH (>7). Water enters the unit through the semi permeable membrane causing the push layer to swell. The swelling of the push compartment forces the drug into the surrounding environment through the orifice. These osmotic controlled drug delivery systems deliver the drug at a constant rate for up to 24hr.

h) Multi particulate system based drug delivery

The various advantages of multiparticulate systems are increased bioavailability, reduced risk of local irritation, reduced risk of systemic toxicity. The various multiparticulate approaches include pellets, microparticles, granules and nanoparticles. Multiparticulates systems are preferred over single unit dosage forms as the multiparticulate systems enables the drug to reach the colon quickly and retained in colon for long period of time. These systems pass through the GIT easily due to their smaller size. Multiparticulate systems are dispersed more uniformly in the GIT resulting in more uniform drug absorption.

Nanoparticles

The preparation of nanoparticles[32] is simple and these are capable of protecting the protein and peptide drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium. The polymeric nanoparticles are prepared by various techniques like polymerization, nanoprecipitation, inverse microemulsion. The methods involve the use of organic solvents, heat and agitation. The drawback of these methods is that the heat, agitation is harmful to proteins and peptide drugs. Ionic gelation technique is the most widely used method for proteins and peptide drugs.

i) Azo hydrogels

The pH sensitive monomers and azo cross linking agents in the hydrogel produce the colon specificity. During their passage through the GIT these hydrogels swell as the pH increases. This swelling of hydrogels cleaves the cross links in the hydrogel network causing the release of drug entrapped in the hydrogel. These hydrogels are prepared by cross linking polymerization of N- substituted (meth) acrylamides, N- tert- butyl acrylamide and acrylic acid with 4, 4-di (methacryloylamino) azobenzene as cross linking agents. The hydrogels are also prepared by crosslinking polymeric precursors, polymer- polymer reaction using same polymeric precursor with the corresponding copolymer containing side chains terminating in NH_2 groups. The degradation rate of hydrogel is associated with the degree of swelling and inversely proportional to the cross linking density[32].

In-vitro evaluation

No standardized evaluation technique is available for evaluation of CDDSas 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 & physical stress. The invitro evaluation[34] of colon targeted drug delivery systems includes the in-vitro dissolution study & in-vitro enzymatic test

1. In-vitro dissolution test

The dissolution testing is done using the conventional basket method. The dissolution testing is done in different buffers to characterize the behaviour of formulations at different pH levels. The different media that are used for the dissolution testing of colon targeted drug delivery are pH 1.2 to simulate gastric fluid, pH 6.8 to simulate small intestine, pH 7.4 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 pH 7.4 phosphate buffer. Buffers of the above pH are prepared to evaluate the colon targeted drug delivery systems.

2. In-vitro enzymatic test:

There are 2 tests for the in-vitro enzymatic test.

- The carrier drug system is incubated in fermenter containing suitable medium for bacteria. The amount of drug released at different time intervals is determined.
- Drug release study is performed in buffer medium containing enzymes pectinase, dextranase or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is directly proportional to rate of degradation of polymer carrier.

In- vivo evaluation

The in-vivo evaluation of the CDDS is done in dogs, guinea pigs, rats & pigs as they resemble the anatomic and physiological conditions, microflora of human GIT. The

distribution of various enzymes in GIT of rat and rabbit is comparable to that in human.

CONCLUSION

Colon targeted drug delivery system offers benefits of local and systemic effects. The main advantage of CDDS is that the colon offers near neutral pH, a long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers. The novel approaches are more specific compared to the primary approaches. The biodegradable polymers are used for the colon specific delivery of the drug. For the invitro evaluation of the system the current dissolution techniques are not suitable. Research is going on to develop suitable dissolution methods to evaluate the colon targeted drug delivery systems.

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