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COLON TARGETED DRUG DELIVERY SYSTEM: An OVERVIEW

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Abstract

Colonic drug delivery has gained importance for delivery of drug for the treatment of local diseases associated with colon and systemic delivery of therapeutic peptides and proteins. It is possible for drug to be directly delivered to colon for more effective treatment. Local diseases include asthma, Chron's disease, ulcerative colitis and colorectal cancer. Colonic delivery is a good candidature for delivery of proteins, peptides and vaccines where the enzymatic degradation and the hydrolysis of proteins can be minimized and increases the systemic bioavailability. A drug should be protected from the absorption and the upper GI environment to achieve the successful colonic drug delivery. The colon specific delivery of drugs to the target receptor sites has the advantage to reduce the side effects and improves the therapeutic response. Colon specific drug deliveries are being developed by taking advantage of the luminal PH conditions and the presence of microbial enzymes such as azoreductase, pectinase, dextrans etc. This review mainly reveals on the various concepts and approaches include Prodrug, PH and time dependent systems and microbially triggered systems used in the development of colon specific drug delivery. This also focuses on the novel approaches namely Pressure controlled colonic delivery, osmotic controlled drug delivery. In-vitro and in- vivo evaluation parameters has been discussed briefly here.

Keywords: CDDS (colon drug delivery system), Prodrug approaches, Polymers, asthma.

Introduction

The colon drug delivery has a number of important implications in the field of pharmacotherapy. Oral aspect is considered to be most convenient for administration of drugs to Patients. Normally dissolves in stomach field as

intestinal fluid and absorb from these regions of GIT. Nearly 50% of the drug delivery systems available in the market are oral D.D.S and these systems have more advantages due to patient acceptance and ease of administration. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT. Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis and colonic cancer, local treatment of colonic pathologies and, also for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but only released absorbed once the system reaches the colon[1]. Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and / or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries [2-4]. Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systematically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors and antibiotics, which are useful in treatment of IBD and GI infections respectively.

Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. A colonic targeted approach found to be effected in minimizing uncertain side effects[5].So, the colon, as a site for drug delivery, offers distinct advantages on account of near neutral pH, a much longer transit time, relatively low proteolytic enzymatic activity and offers a much greater responsiveness to absorption enhances. Colon specific delivery systems should prevent the release of drug in upper part of GIT and require a triggering mechanism to release the drug on reaching the colon.

Need For Colon Targeted Drug Delivery

To ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. Colon-specific formulation could also be used to prolong the drug delivery. It should be considered as beneficial in the treatment of colon diseases. The colon is a site where both local or systemic drug delivery could be achieved. Topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's Disease. Such inflammatory conditions are usually treated with glucocorticoids and Sulphasalazine. A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted

to the colon. Formulations for colonic delivery are also suitable for delivery of drugs which polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Factors to Be Considered In the Design of Colon-Specific Drug Delivery System

Anatomy and Physiology of Colon

The large intestine extends from the distal end of the ileum to the anus. Human large intestine is about 1.5m long [6] (Table 1). The colon is upper five feet of the large intestine and mainly situated in the abdomen. The colon is a cylindrical tube that is lined by moist, soft pink lining called mucosa; the pathway is called the lumen and is approximately 2-3 inches in diameter [7]. The cecum forms the first part of the colon and leads to the right colon or the ascending colon (just under the liver) followed by the transverse colon, the descending colon, sigmoid colon, rectum and the anal canal (Figure 1)[8]. The physiology of the proximal and distal colon differs in several respects that have an effect on drug absorption at each site. The physical properties of the luminal content of the colon also change, from liquid in the cecum to semisolid in the distal colon.

Table 1.Summary of anatomical and physiological features of small intestine and colon.

Region of Gastrointestinal Tract		**pH**
Stomach		1.5-3 (fasted) 2-5 (fed)
Small intestine	Duodenum	6.1(fasted) 5.4(fed)
	Jejunum	5.4
	Ileum	7-8
Large intestine	Cecum	6-7
	Ascending colon	20
	Transverse colon	45
	Descending colon	30
	Sigmoid colon	40
	Rectum	12
	Anal canal	3

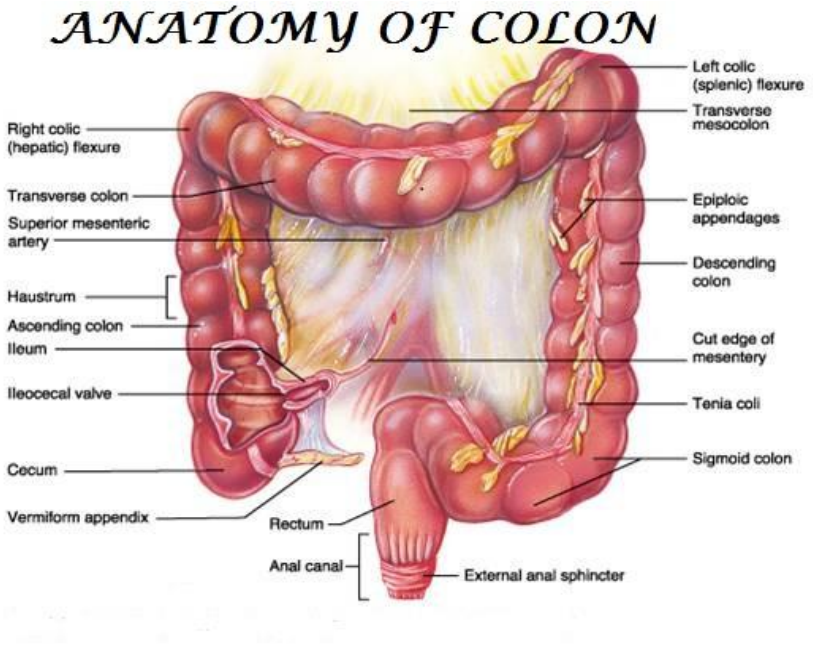
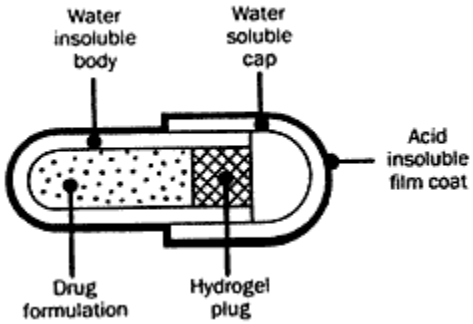


Fig.2. Design of Pulsincap system.



pH in the Colon

The pH of the gastrointestinal tract is subject to both inter and intra subject variations. Diet, diseased state and food intake influence the pH of the gastrointestinal fluid. The change in pH along the gastrointestinal tract has been used as a means for targeted colon drug delivery [9]. There is a pH gradient in the gastrointestinal tract with value ranging from 1.2 in the stomach through 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine (Table 1.). The pH difference between the stomach and small intestine has historically been exploited to deliver the drug to the small intestine by way of pH sensitive enteric coatings. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides.

Transit of material in the colon

Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The arrival of an oral dosage form at

the colon is determined by the rate of gastric emptying and the small intestinal transit time. The transit times of small oral dosage forms in GIT are given in Table 2.

Table 2.The transit time of dosage form in GIT.

Organ	**Transit time (hr)**
Stomach	<1 (Fasting) >3 (Fed)
Small intestine	3-4
Large intestine	20-30

The movement of materials through the colon is slow and tends to be highly variable and influenced by a number of factors such as diet, dietary fiber content, mobility, stress, disease and drugs. In healthy young and adult males, dosage forms such as capsules and tablets pass through the colon in approximately 20-30 hours, although the transit time of a few hours to more than 2 days can occur. Diseases affecting colonic transit have important implications for drug delivery: diarrhea increases colonic transit and constipation decreases it. However, in most disease conditions, transit time appears to remain reasonably constant

Colonic micro flora and their enzymes

Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut micro flora residing in high number in the colon. These enzymes are used to degrade coatings/matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug. Over 400 distinct bacterial species have been found, 20-30% of which are of the genus Bacteroides [10, 11]. The upper region of the GIT has very small number of bacteria and predominantly consists of Gram-positive facultative bacteria. The concentration of bacteria in the human colon is 1011- 1012 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptostreptococcus, peptococcus, Ruminococcus and clostridiums [12]. Summary of the most important metabolic reaction carried out by intestinal bacteria are given in Table.3

Table 3: Criteria for selection of drugs for colon specific drug delivery system.

Criteria	Pharmacological class	Non- peptide drugs	Peptide drugs
Drugs used for local effects in colon	Anti-inflammatory Drugs, Nifedipine	Oxyprenolol, Metoprolol	Amylin, Antisense oligonucleotide

against GI diseases			
Drugs poorly absorbed from upper GIT	Anti hypertensive and anti- anginal drugs	Isosorbides, Theophylline, Ibuprofen	Cyclosporin, Desmopressin
Drugs for colorectal cancer	Anti neoplastic drugs	Pseudoephederine	Epoetin, Glucagon
Drugs that degrade in stomach and small intestine	Proteins and peptides	Bromophenaramine, 5-FU, Doxorubicin	Gonadoreline, Insulin, Interferon
Drugs that undergo extensive FPM	Nitroglycerine and Corticosteroids	Bleomycin, Nicotine	Protirelin, Sermorelin, Saloatonin
Drugs for targeting	Anti arthritic , Anti asthmatic drugs	Prednisolone, Hydrocortisone	Somatropin, Urotoilitin

Criteria for Selection of Drug for Colonic Drug Delivery

Drug candidate

Drugs which show poor absorption from the stomach as intestine including peptide are most suitable for CDDS. The drug used in treatment of IBD, ulcerative colitis, diarrhea and Colon cancers are ideal candidates for local colon delivery [13].

Drug carrier

The selection of carrier for particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of drug and the type of absorption enhancers chosen influence the carrier selection.

Moreover, the choice of drug carrier depends on the functional groups of drug molecule[14]. The carriers which contain additives like polymers (may be used as matrices and hydro gels as coating agents) may influence the release properties and efficacy of the systems[15].

Advantages of CDDS Over Conventional Drug Delivery

- Chronic colitis, namely ulcerative colitis and cirrhosis disease are currently treated with glucocorticoids, and other anti-inflammatory agents.
- Drugs are available directly at the target site.
- Side effects can be reduced [16].
- Utilization of drug is more and lesser amount of dose is required comparatively [17].

- Extended daytime or nighttime activity.
- Targeted drug delivery system.
- Improve patient compliance.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, canbe given through this route.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Reduces dosage frequency. Hence, lower cost of expensive drugs.

Pharmaceutical approaches to colon specific drug delivery system:

The most advanced Pharmaceutical approaches that can be exploited for the development of colon targeted drug delivery systems are given below:

- Time Dependent systems
- Pulsatile Systems
- CODES Technology
- Pressure dependent release systems
- Osmotic controlled drug delivery (ORDS-CT)
- Multiparticulates
- Microspheres

Time-dependent systems:

Time dependent systems are very promising type of drug release systems. The dosage forms also applicable to colon targeting dosage forms by prolonging the lag time of about 5 to 6 hours. However the disadvantages of this system are:

a. Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

b. Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

c. Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis [18].

Therefore, time dependent systems are not ideal to deliver drugs to the colon specifically for the treatment of colon related diseases. Colon targeting could be achieved by incorporating a lag time into formulation equivalent to the mouth to colon transit time. 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[18]. Enteric coated time-release press coated (ETP) tablets, are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy Propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function).The tablet does not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. After gastric emptying, the enteric coating layer rapidly dissolves and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. When the erosion front reaches the core tablet, rapid drug release occurs since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The duration of lag phase is controlled either by the weight or composition of the polymer (HPC) layer. 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 (Table 4) and the thickness of the outer layer determines the time required disperse in aqueous environment.

Table 4- : Materials used in the formulation of CDDS.

Prodrug conjugates	**pH sensitive polymers**	**Materials used in Time Dependent System**	**Microbial degradable polymers**
Azo bond conjugates	Eudragit L-100, Eudgrgit S-100	Hydroxyl propyl methyl cellulose	Chitosan
Amino acid (polypeptide conjugates**)**	Eudragit L-30 D, Eudragit L-100-55	Hydroxy ethyl cellulose	Pectin, Lactulose, Cyclodextrin
Glycoside conjugates	Eudragit F S 30 D	Ethyl cellulose	Guar gum
Glucuronide conjugates and sulphate conjugates	Poly vinyl acetate phthalate, Cellulose acetate phthalate	Microcrystalline cellulose	Dextran, Alginates
Polymeric conjugates	Hydroxyl propyl ethyl cellulose	Hydroxyl propyl methyl cellulose	Inulin, Amylose

	phthalate	acetate succinate	
Cyclodextrin conjugates, dextran conjugate	Hydroxy propyl methyl cellulose, cellulose phthalate 50	Lactose/ behinic acid	Locust bean gum, Boswellia gum

Hydroxy Propyl Methyl Cellulose (HPMC) compression coated tablets of 5-fluorouracil were studied for colon drug delivery that based on time-dependent approach. In this, the core tablet was prepared by wet granulation method and then coated with 50% of HPMC/lactose coat powder by compression-coating method. Drug release characteristics were evaluated in distilled water by using a Chinese pharmacopoeia rotatable basket method[19].

Pulsatile Systems:

The first formulation introduced based on this principle was Pulsincap® developed by R.R.Scherer International Corporation, Michigan, US. It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap as shown in fig.2. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell. The length of the plug and its point of insertion into the capsule controlled the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glycerylmonooleate), and enzymatically controlled erodible polymer (eg, pectin)[20].

CODES™ technology:

The design of CODES™ exploited the advantages of certain polysaccharides that are only degraded by bacteria available in the colon. This is coupled with a pH-sensitive polymer coating. Since the degradation of polysaccharides occurred only in the colon, this system exhibited the capability to achieve colon delivery consistently and reliably. In this technology the core tablet coated with three layers of polymer coatings. The first coating (next to the core tablet) is an acid-soluble polymer (e.g. Eudragit E®) and outer coating is enteric with a HPMC barrier layer in between to prevent any possible interactions between the oppositely charged polymers. The core tablet is comprised of the active, one or more polysaccharides and other desirable Excipients. The polysaccharides, degradable by enterobacteria to generate organic acid, include mannitol,

maltose, stachyose, lactulose, fructooligosaccharide etc. During its transit through the bacteria will enzymatically degrade the polysaccharide into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release[21].

Pressure dependent release systems

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. The preferred thickness of the capsule wall is about 35-60 μm. The system also appeared to depend on capsule size and density. In pressure-controlled ethyl cellulose single- unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human[22].

Osmotic controlled drug delivery:

The OROS-CT system (Figure 3) can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated within a hard gelatin capsule. Each push-pull unit is bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. In principle semipermeable membrane is permeable to the inward entry of water and aqueous gi fluids and is impermeable to the outward exit of the drug. An orifice is drilled into the semipermeable membrane to the drug layer. The outside surface of the semipermeable membrane is then coated by eudragit®S100 to delay the drug release from the device during its transit through the stomach. Upon arrival on the small intestine the coating dissolves at pH≤7. As a result water enters the unit causing the osmotic push compartment to swell forcing the

drug out of the orifice into colon. For treating ulcerative colitis, each push pull unit is designed with a 3-4 hour post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 h in the colon.

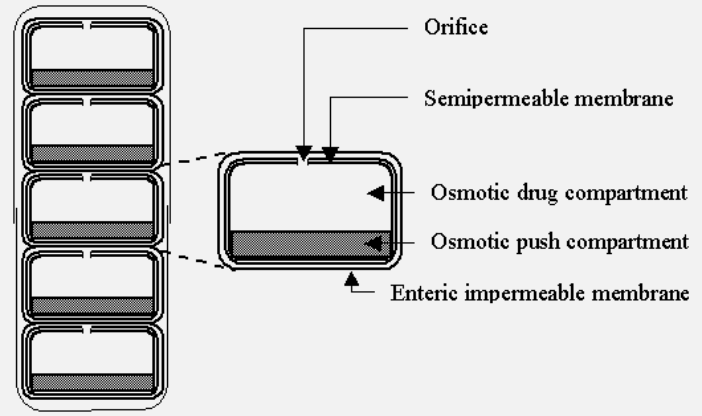


Fig.3. Cross section of the OROS-CT colon targeted drug delivery system.

Multiparticulate systems:

Single unit colon targeted drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action in the colon. Report suggests that drug carrier systems larger than 200 μm possess very low gastric transit time due to physiological condition of the bowel in colitis. And for this reason and considering the selective uptake of micron or submicron particles by cancerous and inflamed cells/ tissues a Multiparticulate approach is expected to have better pharmacological effect in the colon[23].

Recently, much emphasis is being laid on the development of multiparticulate dosage forms in comparison to single unit systems because of their potential benefits like,

a. Multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time and hence increased bioavailability.
b. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily, leading to less inter- and intra subject variability.
c. Moreover, Multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption.
d. Reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying.

Microspheres:

Cross-linked guar gum microspheres containing methotrexate were prepared and characterized for local release of drug in the colon for the treatment of colorectal cancer. In this method, glutaraldehyde was used as a crosslinking agent and guar gum microspheres were prepared by Emulsification method. From the results of in vitro and in vivo studies themethotrexate loaded crosslinked guar gum microspheres delivered most of the drug loaded (79%) to the colon, where as plain drug suspensions could deliver only 23% of their total dose to the target tissue[24]. Colon specific microspheres of 5-fluorouracil were prepared and evaluated for the treatment of colon cancer. In this method core microspheres of alginate were prepared by modified emulsification method in liquid paraffin by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by solvent evaporation technique to prevent drug release in the stomach and small intestine. The results showed that this method had great potential in delivery of 5- fluorouracil the colonic region[25]. Besides the above discussed systems, the others include Prodrug approach, PH Dependent systems and Microbial triggered systems.

Evaluation [26-28]

***In Vitro* Evaluation**

No standardized evaluation technique is available for evaluation of CDDS because an ideal *in vitro* model should posses the *in vivo* conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity and other components of food. Generally these conditions are influenced by the diet and physical stress and these factors make it difficult to design a slandered in vitro model. *In vitro* model used for CDDS are:

***In vitro* dissolution test:**

Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot wholly mimic *in vivo* conditions such as those relating to pH, bacterial environment and mixing forces. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon- specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileal segment. Enteric-coated capsules for CDDS have

been investigated in a gradient dissolution study in three buffers. In vitro test for intactness of coatings and carriers in simulated conditions of stomach and intestine Drug release study in 0.1 N HCl for 2 hours (mean gastric emptying time) Drug release study in phosphate buffer for 3 hours (mean small intestine transit time)

***In vitro* enzymatic test:**

For this there are 2 tests:

1. Incubate carrier drug system in fermenter containing suitable medium for bacteria (*Streptococcus faccium*or *B.ovatus*) amount of drug released at different time intervals determined.

2. Drug release study is done in buffer medium containing enzymes (enzyme pectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

***In Vivo* Evaluation**

A number of animals such as dogs, guinea pigs, rats and pigs are used to evaluate the delivery of drug 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 distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human. For rapid evaluation of CDDS a novel model has been proposed. In this model the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which vascularizes within 4 weeks, matures and becomes capable of developing of mucosal immune system from the host.

Clinical Evaluation

Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

High frequency capsule:

Smooth plastic capsule containing small latex balloon, drug and radiotracer taken orally. Triggering system is high frequency generator. Release of drug & radiotracer triggered by an impulse, the release is monitored in different parts of GIT by radiological localization. It checks the absorption properties of drug in colon.

Gammascintigraphic:

By means of gammascintigraphic imaging, information or reports 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 gastrointestinal transit and the release behavior of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphic studies (pharmacoscintigraphy).

Conclusion

Many systems are currently being investigated as potential means for targeting of drugs to colon. CDDS offers considerable and many therapeutic benefits to patients in the form of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific drug delivery systems and the uncertainty of current dissolution methods in establishing possible in-vitro/in-vivo correlation, challenges remain for 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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Authors Contributions

All the authors have contributed equally.

Conflict of Interest

We declared that this review does not have any conflict of interest.

Abbreviations

CDDS - Colon Drug Delivery System

GIT - Gastrointestinal Tract

IBD – Inflammatory Bowel Disease

CFU/mL- Colony-Forming Units Per Milliliter

NSAID – Non-Steroidal Anti-Inflammatory Drugs

ETP- Enteric Coated Time-Release Press Coated

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