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RESEARCH ARTICLE

A REVIEW ON COLON TARGETED DRUG DELIVERY

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ABSTRACT

Colon specific drug delivery system has attracted considerable attention for the last few years in order to develop drug delivery system that are able to release drug specifically in the colon in predictable and reproducible manner. Colonic drug delivery has gained increased importance not just for delivery of drugs for the treatment of local disease associated with the colon like Crohn's disease, ulcerative colitis etc. but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drug, anti-hypertensive drugs and anti-diabetic agents. Colon specific systems is most important delivery of those drug which are normally inactivated in the upper parts of the gastrointestinal tract (GIT). To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in upper portion of GI tract and then to be ensured abrupt or controlled release in the proximal colon. Colon targeting holds a great potential and still need more innovative work. This review article discusses need of colon targeted drug delivery, factors affecting targeted drug delivery, platform technologies for colon targeted drug delivery systems.

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INTRODUCTION

Colon delivery is the targeted delivery of drug to the lower GI tract, which takes place firstly in the large intestine (i.e. colon).[1] Targeted drug delivery into the colon is most advantageous for local treatment of various bowl disease such as ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systematic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should have capacity to protect the drug in route to the colon i.e. drug release and absorption should not happens in stomach as well as small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but not only release absorbed once the system reached the colon [Gilbert S Banker, 2002] Colon targeted Drug Delivery System (CTDDS) may be follow the concept of sustained or controlled drug delivery system, for CTDDS oral route of administration has received much awareness. This is due to the flexibility in dosage form designed for oral than parental route because:

- Patient acceptance for the oral administration of the drug is very high.
- It is relatively safe route of drug administration compared with parenteral route and potential damage at site of administration is lowest (Brahamankar, 1995).

Colon drug delivery has also get significance not just for the systemic delivery of drugs for the cure of local disease, but also potential site for the systematic delivery of therapeutic protein and peptide which are being delivered by injections. These delivery system when orally, allow drugs to release the drug from the delivery system once the drug in the colon.[4, 5] there are so many methods and techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with biodegradable polymers, coating with pH-sensitive polymers, designing formulation using polysaccharides, timed released systems, pressure-controlled drug delivery systems, osmotic pressure controlled systems.[6, 7] Formulations for colonic delivery are also acceptable for delivery of drug 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 [Luck, 2000; Yang 1999]

Need of colon targeted drug delivery:

- Targeted drug delivery into the colon helpful in the cure of disease at that site, fewer systemic sides effects and dose can be minimize.
- Colon specific formulation is beneficial for the administration of proteins, peptide drugs and also to prolong the drug delivery.

- Colon targeted drug delivery is suitable for delivery of drugs which are polar and/or susceptible to the chemical and enzymatic degradation in upper GI tract, highly affected by hepatic metabolism.
- Serious disease of the colon are treated more effectively if drugs were targeted to the colon.

Example: colonic cancers like colorectal cancer [Sarasija, 2000]

Advantages of ctdds over conventional drug delivery: Chronic colitis, named as ulcerative colitis, and Crohn's disease are now cure with glucocorticoids, and other anti-inflammatory agents. Administration of glucocorticoids named as dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppression, cushinoid symptoms, and bone resorption. Thus selective delivery of drugs to the colon could not only lower the required dose but also decrease the systemic side effects caused by high doses. [11]

Advantages of ctdds:

- The site specific delivery of drugs to lower parts of the GI tract is advantageous for localized cure of several colonic disease, mainly inflammatory bowel disease, irritable bowel syndrome, colon cancer.
- Used in treatment of nicotinic addiction.
- Useful for the delivery of protein, peptides which are being delivered by injection.
- Delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most and also reduce the potential side effects and drug instability.
- Used in direct treatment of disease at that site, low dosing and less systematic effects.
- Molecules that are poorly absorbed in the upper gut, such as peptides, protein may be better absorbed from the lower GIT.
- The colon is the site where both local and systemic delivery of drugs can takes place. Local delivery allows topical cure of inflammatory bowel disease.
- The colon is having high water absorption capacity, the colonic contents are considerably viscous and thus availability of most drugs to the absorptive membrane is low.
- The metabolic processes like azoreduction and enzymatic cleavage are takes place in colon which is responsible for the metabolism of many drugs and peptides like insulin (Vyas, 2005; Vinaykumar, 2011; TarakJayraj, 2011).

Limitations of colon targeted drug delivery system:

- Multiple manufacturing steps.
- The resident micro flora could also affect co-ionic performance via metabolic degradation of the drug.
- Incomplete release of drug.
- Bioavailability of drug may be reduce due to potentially binding of drug in a non-specific way to dietary residues, intestinal secretions, mucus or faecal matter.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in vitro (http://www.pharmainfo.net/reviews/colon-targeted-drug-delivery-system-overview).
- An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve. Normal in patients with ulcerative colitis (Nugent, 2001; Jose, 2009).
- Limitations of prodrug approach is that it is not very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage. Furthermore, prodrugs are new chemical entities and need a lot of evaluation before being used as carriers [Gaurav, 2010]

FACTORS AFFECTING COLON TARGETED DRUG DELIVERY: [Obot Solomon Sunday, 2017; George Zhu, 2018, and Prathap, 2014]

There are various factors which are considered for designing of numerous colonic formulations, are listed below:

- Physiological factors
- Pharmaceutical factors
- Physicochemical and biopharmaceutical properties of drug such as solubility, stability, and permeability at the intended site of delivery and;
- The desired release profile of the active ingredients.

Physiological factors:

Anatomy and physiology of colon (Prathap, 2014):

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junctionto the anus is divided into three main parts. These are colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus.

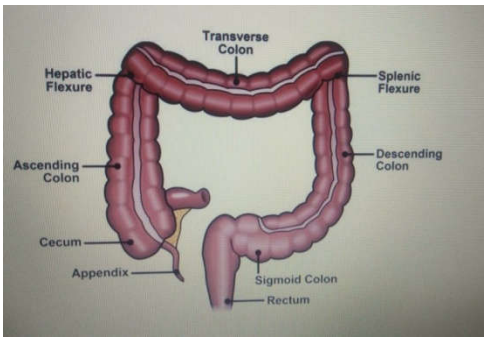

Fig. Main feathers of the colon

Fig: length of different parts of colon (Patel, 2011)

Sr. No.	LARGE INTESTINE	LENGTH(cm)
1.	Cecum	6-9
2.	Ascending colon	20-25
3.	Descending colon	10-15
4.	Transverse colon	40-50
5.	Sigmoid colon	35-40
6.	Rectum	12
7.	Anal canal	3

Gastric emptying: Gastric emptying of dosage form 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 density. Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. Upon reaching the colon the transit time compared of larger particles. Disease affecting colonic transit have important implifications for drug delivery, diarrhea increases colonic transit and constipation decreases it.

pH of colon: The most common physiological factors considered in the design of delayed release colonic formulations is pH gradient of the GI tract. Each individual has a range of pH in GIT which is influenced by various factors such as food intakes, diseased state (inflammatory bowel disease), type of food, fed and fasted state etc. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH = 6.6 + 0.5), to the terminal ileum (pH = 7.5 + 0.4), a decrease in the cecum (pH = 6.4 + 0.4), and then a slow rise from the right to the left colon with a final value of 7.0 + 0.7. pH variation in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is used to develop pH dependent colon drug delivery system.

Colonic micro flora and enzyme: In GIT a variety of microorganism (E. coli, clostridia, lactobacilli, eubacteria, and streptococci) were found that produce many enzymes, these enzymes are responsible for various metabolic reactions that take place in the GIT. The growth of colonic micro flora is controlled by the contents of GIT and peristaltic movements. The metabolic activity of micro flora can be modified by various factors such as age, GI disease, and intake of drug and fermentation of dietary residues.

The large number of anaerobic and aerobic bacteria are present in the entire length of the human GI tract, intestinal enzymes are used trigger drug release in various parts of the GI tract. Usually, these enzymes are derived from gut micro flora residing in high numbers in the colon. These enzymes are used to degrade coating or matrices as well as to break bonds between an inert carrier and an active agents (i.e. release of drug from a prodrug).

Drug absorption in the colon: Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involve the passage of drugs through cells and this is the route most lipophilic drugs takes, where paracellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drug takes. The colon may not be the best site for drug absorption since the colonic mucosa lacks well defined villi as found in the small intestine. The slower rate if transit in colon lets the drug stay in contact mucosa for a longer period than in small intestine which compensates much lower surface area. The colon contents become more viscous with progressive absorption of water as one travels further through the colon. The causes a reduced dissolution rate, slow diffusion of drug through the mucosa.

Pharmaceutical factors:

- **Drug candidate:** colon has longer retention time that enhance the absorption of poorly absorbed agents like peptides. Drugs used for the treatment of inflammatory bowel disease etc. are suitable for colon targeted drug delivery system.
- **Drug carrier:** The selection of carrier for CDDS depends on the nature of the drug, disease for which the drug is used. Selection of drug carriers depends on various physicochemical factors of drug that include chemical nature, stability, partition coefficient, functional groups of drug molecule etc (Ratnaparkhi Mukesh).
- **Polymers used in colon drug delivery (**Singh, 2014; Sinha, 2001**):** A polymer is a large molecule, or macromolecules, composed of many repeated subunits. These are nowadays used in formulating various pharmaceutical products. There are various synthetic polymers which are used for colon targeted drug delivery. These can also be called as pH dependent polymers are derivatives of acrylic acid and cellulose. Naturally found polymer, which include gummy exudates, proteins, enzymes, muscle fiber, polysaccharides.

Platform technologies for colon targeted drug delivery systems: Nowadays design of dosage form is becoming complex because there is a vast use of technology in the dosage forms for controlling various aspects. Few examples are mentioned in case of colon targeted drug delivery:

Codes: CODES is a unique colon targeted drug delivery system that was designed to avoid the inherent problems associated with pH or time dependent systems. It consists of core tablets coated with three layers of polymer coating. The first coating is an acid soluble polymer (Eudragit) and outer layer is enteric with a HPMC barrier layer in between to prevent any possible interaction between the oppositely charged polymers. The core tablet is comprised of the active ingredients and one or more polysaccharides. The polysaccharides are degraded by enterobacteria to generate organic acid. During its transit through GIT, CODES remain intact in the stomach due to enteric protection, but the enteric barrier coating dissolves in the small intestine, where pH is above 6. Because Eudragit-E coating is only slightly permeable and swellable in small intestine. Upon entry into the colon, the bacteria enzymatically degrade the polysaccharides into organic acid.

Pulsincap: Pulsincap was the first formulation developed based on time-release principle. It was similar in appearance to hard gelatin capsule. It consists of water insoluble body water soluble enteric coated cap. The contents are plased with in body plugged with hydrogel plug. When it is administered, after predetermined time the enteric coat dissolves and hydrogel plug starts to swell.

Port System: It consist of a gelatin capsule coated with a semi-permeable membrane (e.g. cellulose acetate) housing an insoluble plug (e.g. lipidic) and an osmotically active agent along with the drug formulation. When in contact with aqueous medium, water diffuses across the semi-permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time.

Oros System: There are two OROS systems for colon drug delivery:

Osmet pump: It consists of an enteric coated semi-permeable shell which encloses an osmotic layer along with a central impermeable and collapsible reservoir filled with drug. The interior of this compartment is connected with the external environment through a delivery orifice at one end. After dissolution of the gastric-resistant film, water is allowed to penetrate through the semi-permeable membrane, thus raising the pressure inside the device which cause inner reservoir to shrink and drug formulation to pump out.

Oros CT: Immediately after ingestion, the hard gelatin capsule shell dissolves. The push and pull unit is prevented from absorbing water in the acidic medium of stomach by enteric coating. The osmotic pumping action results when the coating dissolves in the drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane. Alza Corporation developed OROS-CT an osmotically controlled dosage form. It can be used to target the drug locally to the colon for the management of diseases, which are not responding to the systemically absorbed drug. It can be made up of single unit or may incorporate as many as 5-6 push pull units, each with in 4mm diameter, encapsulated within hard gelatin capsule. When it reaches to small intestine the enteric coating get dissolved and water enters through the semi-permeable membrane, causing osmogen to swell and the drug compartment gets converted in the flow.

Time clock system: It consist of a solid dosages form with lipidic barriers containing carnauba-wax and bee-wax along with surfactants, such as polyxyethylene sorbitan monooleate, in order to prevent the pre mature release of drug in the small intestine the system was further coated with enteric polymers. The release of drug is independent of the pH and the digestive state of the gut. The release mainly depends upon the thickness of the coat applied. As soon as the coat erodes or emulsifies in the aqueous environments after predetermined lag time, the core gets exposed to the colonic environment resulting in complete release of drug.

Cronotropic System: It consists of a drug containing core coated by hydrophilic swellable HPMC, which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric resistant enteric film, the variability in gastric emptying time can be overcome, and a colon specific drug release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and viscosity grades of HPMC.

Targit Technology: It is based on the application of pH sensitive coating onto injection- molded starch capsules. It is designed for site-specific delivery of drugs to the colonic region. This system has been developed for the treatment of local pathologies of lower GI disease. The clinical data generated has of lower GI disease. The clinical data generated has showed its suitability in colon targeted drug delivery.

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