A Review on Colon Targeted Drug Delivery System

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***Abstract*- Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in upper portion of the GI tract and then to be ensured abrupt or controlled release in the proximal colon. This review is focused on the merits and demerits, novel approaches in the colon targeted drug delivery, clinical evaluation techniques and some information on the marketed dosage forms.**

INTRODUCTION

Colon delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. Colon).(1) The site specific delivery of drugs to lower parts of GIT is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (crohn's disease and ulcerative colitis), Irritable bowel syndrome and colon cancer. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CTDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. Oral controlled release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug release pattern that are not achieved with traditional immediate or sustained release products.(2). Colon drug delivery has also gained increased importance not just for the systemic delivery of drugs for the treatment of local diseases, but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the drug reaches in to the colon. (3, 4)

NEED OF COLON TARGETED DRUG DELIVERY

Targeted drug delivery into the colon helpful in treatment of diseases at that site, fewer systemic side effects and dose can be minimized.

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 the upper GI tract, highly affected by hepatic metabolism

Serious diseases of the colon are treated more effectively if drugs were targeted to the colon.

Example. Colonic cancers like colorectal cancer. (5,6)

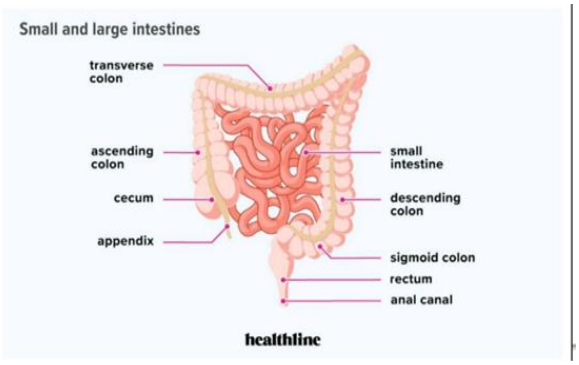

Fig 1: Colon and its segments

The entire colon is about 5 feet (150 cm) long and is divided into 5 major segments. The GI tract is divided into stomach, small intestine and large intestine. Large intestine extending from the ileocecal junction to the anus and it is divided into 3 main parts. (Figure - 1) They are colon, rectum, and anal canal. Perinatal folds are called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon and hepatic flexure. The left colon consists of descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus .The colon tissue contains the villi, lymph, muscle, nerves and vessels. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which 90% of fluid is absorbed. The adult colon is line by atleast 8 distinct epithelial cell types, viz columnar or absorptive cells, deep crypt secretary cells, vacuolated cells, microfold or M cells, undifferentiated crypt cells, multivesicular or caveolated cells, goblet cellsand variety of endocrine cells. (3,5,7)

ADVANTAGES

The site specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease, irritable bowel syndrome, colon cancer.

Used in treatment of nicotinic addiction

Useful for the delivery of proteins, peptides which are being delivered by injections

Delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most and also minimize the potential side effects and drug instability

Used in direct treatment of disease at that site, low dosing and less systemic side effects

Molecules that are poorly absorbed in the upper gut, such as peptides, proteins may be better absorbed from the lower GIT.

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment 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. (7, 8, 9)

DISADVANTAGES

A longer residence time of 3-5 days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.

Single unit colon targeted drug delivery system has the disadvantage of un intentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology

Development of colon specific drug is difficult due to many biological barriers

Cytochrome (P450) class of drug metabolizing enzymes has lower affinity in the colonic mucosa. (8,10)

LIMITATIONS

Colon offers a near neutral pH, at the site of drug delivery, reduced enzyme activity, a long transit time and increased responsiveness to absorption enhancers

Wide range of pH values and different enzymes present throughout the gastro intestinal tract, through which dosage form has to travel before reaching target site

For better drug delivery it should be in solution form before it arrives in the colon

Fluid content in the colon is much lower and it is more viscous than in the upper part of GI tract.

Stability of drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a non-specific way to dietary residues, intestinal secretions, mucus or fecal matter

The resident microflora could also affect colonic performance via metabolic degradation of the drug

Lower surface area and relative tightness also affects the bioavailability of drugs.(7,8)

Factors Governing the Colon Drug Delivery

Factors which influence colon drug delivery are mainly divided into 2 types;

Physiological factors

Pharmaceutical factors

Physiological Factors

Gastrointestinal Transit

Gastrointestinal motility in fasted state proceeds through 4 phase over a period of 2-3 hours. The feeding state affects the normal pattern by irregular contractile activity.

Small Intestinal Transit

Small intestinal transit is not influenced by the physical state, size of the dosage form and the presence of food in the stomach. The mean transit time of the dosage form is about 3-4 hours to reach the ileocecal junction and the time period is consistent.

Colonic Transit

The bioavailability of drugs released from the dosage forms can be highly influenced by the colonic transit time. Various factors like gender and size of the dosage form and physiological conditions such as stress, presence of food and diseased state influence the colonic transit time. Small particles and solutions pass slowly through the proximal colon and in human being, Men shows shorter colonic transit time than women. The colonic transit time of capsule in adults is 20-35 hours, the transit time of capsule is independent of the capsule density and volume.

Gastric Emptying

Gastric emptying is fastest and most consistent. Emptying completes from 5-10 min up to 2 hrs, depending on phase of stomach at the time of drug administration. Gastric emptying can be considerably slowed by fed state.

Stomach and Intestinal pH

Release and absorption of orally administered drugs are influenced by the gastro intestinal pH.

Colonic Microflora and Enzymes

The human alimentary canal is highly populated with bacteria and other microflora at both ends, are oral cavity and the colon /rectum. Azoreductase produced by the colonic microflora plays an important role in development of a number of delivery systems, particularly in catalyzing the release of 5-amino salicylic acid, from a variety of prodrugs. Other enzymes are glycosidase and glucuronidases produced by lactobacilli, bacteroids and bifidobacteria. The activity of enzyme is associated with the concentration of bacteria in particular region.

Colonic Absorption

The surface area of colon is much less compared to small intestine, and hence not ideally suited for absorption. Colon is considered for drug delivery because the environment is dividing of endogenous enzymes other than microbial origin. Resident time of colon is 10-24 hours. Little mixing in the colon makes it possible to create local environments with optimal absorption. Absorption is influenced by the transport of water, electrolytes and ammonia across the mucosa and it as more in the proximal colon and distal colon.

Mechanisms of Absorptions

Passing through colonocytes (trancellular transport)

Passing between adjacent colonocytes(paracellular transport)

Absorption enhancers facilitate effective absorption through various mechanisms .They are disruption of the intracellular occluding junction complex opens the paracellular route, modification of epithelial permeability by denaturing membrane proteins and modification of lipid protein interactions and disruption of the integrity of lipid barrier by colonic enterocytes.

Colonic Absorption of Macromolecules

The absorption property of Bovine serum albumin is 0.13% from colon and 1.7% through small intestine. This is due to surface area difference.

Gastrointestinal Diseased State:

Crohn's disease, constipation, diarrhea and gastroenteritis may affect the release and absorption properties of colon specific drug delivery systems.

PHARMACEUTICAL FACTORS

Drug Molecules

Drugs which show poor absorption from the stomach or intestine including peptide drugs are most suitable for colon specific drug delivery systems. Sulphasalazine and 5-ASA are widely used drugs for treatment of IBD and other diseases.

Drug Carriers

The selection of carrier for particular drug candidate depends on physicochemical nature of drug as well as disease for which the system is to be used. Chemicalnature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. (7,11,12)

Targeting Approaches to Colon

Colon specific drug delivery is considered as beneficial in the treatment of colon related diseases and the oral delivery of protein and peptide drugs. Various mechanisms following for colon targeted drug delivery are:

1. Coating with pH dependent polymers
2. Osmotic control system
3. Pressure delivery systems
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

CONCLUSION

Drug delivery to the diseased colon are advantageous in reducing systemic side effects, lower dose of drug, supply of the drug only when it is required and maintenance of the drug in its intact form as close as possible to the target site. Better colonic delivery could be achieved by protecting the drug from absorption and /the environment of the upper GIT and then abruptly released in to proximal colon, which is the site for colonic targeted delivery of drigs

All the approaches provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbed drugs .The colon is rich in microflora which can be used to target the drug release in the colon.

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