Review Article

ISSN:2230-7346
Journal of Global Trends in Pharmaceutical Sciences
Vol.2, Issue 4, pp -459-475, October–December 2011

COLON TARGETED DRUG DELIVERY SYSTEMS: A REVIEW

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ABSTRACT

Colon drug delivery system is gaining importance in most of the days because colon is a site where in both local and systemic delivery of drugs can take place. Targeting drugs directly to the colon is advantageous in the treatment of colonic disease such as ulcerative colitis, crohn's disease and inflammatory bowel disease. This review mainly comprises the primary approaches for colon targeted drug delivery that include use of prodrugs, coating with pH dependent polymers, coating with independent Biodegradable polymers and delivery system based on the metabolic activity of colonic bacteria. Mainly prodrugs include targeted prodrug design and prodrug design targeting enzymes. This colon targeted drug delivery present in limitations and challenges and evaluation of colon targeted drug delivery.

KEY WORDS: Colon Target, Prodrugs, Permeation Enhancers

1. INTRODUCTION:

Drug delivery selectively to the colon through the oral route has been the subject of new research initiatives. In recent years there has been considerable research activity within the field of colonic drug delivery. This interest has been stimulated by a number of factors like the development of new therapeutic agents for the treatment of colonic disease has required colon specific drug delivery system to maximize the effectiveness of these drugs.The desire to produce oral drug delivery systems for therapeutic peptides and proteins.The introduction of once a day sustained release formulations has required a better understanding of the transit of dosage forms through the colon and of the colonic

absorption of the drugs contained within them.

Colon targeted drug delivery systems are mainly used for

(1) Drugs used for local effects in colon inflammatory bowel disease like ulcerative colon it is and crohn's disease. E.g. 5-amino salicylic acid, Mebeverine hydrochloride, Sulphasalazine, hydrocortisone acetate, 5-fluorouracil, doxorubicin, Nimustine.

(2) Macro molecule structures peptide and proteins for systemic effects, because colonic environments are less hostile to these drugs. e.g.: calcitonin, interleukin, interferon, insulin, growth hormone, erythropotien, analgesic peptides oral vaccines, contraceptives, peptides etc.

(3) Drugs which are poorly absorbed orally, as colon has longer residence time and is highly responsive to agents that enhance the absorption of poorly absorbable drugs.

(4) For the avoidance of hepatic first pass metabolism of drugs.

(5) Where the delay in systemic absorption is therapeutically desirable, especially in disease susceptible to diurnal variation

(6) Some orally administered drugs which exhibit poor uptake in upper gastrointestinal to show enzymatic action. e.g.: Metoprolol, Nifedipine, Isosorbide, Theophylline, Bromopheniramine, Diclofenac, and Ibuprofen.

To successfully modulate a colon drug delivery for maximal gastrointestinal absorption drugs one need to have a fundamental understanding of anatomic and physiological characteristics of human gastrointestinal tract.

2. GASTRO INTESTINAL TRACT:

The gastro intestinal tract is a long tube extending from the mouth to the anus. Although it is one continuous tube, it is described in the following parts, mouth, pharynx, esophagus, stomach, small intestine, large intestine.

2.1 Anatomy of colon:

In anatomy of the digestive system, the colon is the part of the intestine from the caecum to the rectum. Its primary purpose is to extract water from feces. In mammals, it consists of the ascending colon on the right side, the transverse colon, the descending colon on the left side, the sigmoid colon, and the rectum.

2.2 Colonic micro flora: [9, 10]

The sluggish movement of material through the colon allows a large microbial population to succeed there. Over 400

species of bacteria found, for the most part anaerobes and a small number of fungi. The bacterial count (colony forming unit/mL, CFU/mL) is 10^{11}-10^{12} CFU/mL in colon. Most of them are anaerobes. E.g.: Bacteroides, Bificlobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium and Clostridium; others are facultative anaerobes e.g.: E.Coli. Among all of them 20-30% are Bacteroides.

2.3. P^H in the colon: [11]

Radio telemetry has been used to measure the gastrointestinal pH in healthy human subjects. The average pH of the caecum and colon lumen is 6.8 ± 0.85. The highest pH levels (7.5 ± 0.5) were found in the terminal ileum. On entry into the colon, the pH dropped to 6.4 +± 0.6. The pH in the mid-colon was measured at 6.6 ± 0.8 and in the left colon, 7.0 ± 0.7. The fall in pH on entry into the colon is due to the presence of short chain fatty acids arising from the bacterial fermentation of polysaccharides. Colonic pH has been shown to be reduced in disease.

2.4. Function of the colon: [8, 12, 31]

The function of the colon differs significantly from the small intestine; the surface area of the colon is low, although it is increased 10 -15 times compared to that of a cylinder of the same dimensions by the presence of folds and microvillus on the epithelial cells.

*The major function is the consolidation of the intestinal contents into feaces by the absorption of water and electrolytes. The absorptive capacity is very high. In healthy human colon, sodium and chloride ions are usually absorbed and potassium and bicarbonate ions are usually secreted.

*Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements caused by circular muscle and causing the appearance of the sac-like haustra, predominate and resulting in mixing of the luminal contents. Significant propulsive activity, associated with defecation and affected by longitudinal muscle, is less common and occurs an average of three or four times daily.

2.5 Colonic absorption:

Drug absorption from the colon can be limited by a number of barriers. In the lumen itself, specific and non specific drug binding can occur through the interaction of the drug with dietary components for example, a glycoprotein drug molecule could interact selectively through specific sugar residues on the protein with foodstuff lectins. Non selective interaction could occur between regions of the glycoprotein

drug and undigested food stuff, such as waxes and alginates. The drug stays within the lumen it will be passed from the proximal to distal colon by muscular activity. During this passage the bacterial content increases dramatically which could further compensate the drug bioavailability.

I Existence of mucus layer:

The mucus barrier at the epithelial surface can present a formidable physical barrier to uptake as a result of specific and non specific drug binding for example cephalosporin, penicillin and amino glycosides are the notable examples of small molecules of drugs that can bind to the negatively - charged mucus. Then the drug binding to colonic mucus might be a significant problem for certain proteins and peptides. As a, corollary to drug protein binding, drug mucus repulsion, or exclusion could also act to retard the drug from reaching the epithelial surface. The mucus layer due to its highly charged and sieve like nature can present a formidable thermodynamic barrier to the transit of large, negatively - charged delivery structures. Uses of mucolytic agents are attractive for increasing drug absorption but normal colonic function will be altered.

II Occurrence of unstirred layer:

The space between the mucus layer and epithelial cells, termed the unstirred water layer presents another barrier to colonic absorption particularly for lipophilic drugs. The low pH at the colonocyte surface may dramatically alter drug solubility and affect absorption.

III Presence of epithelial layer:

Enzymatic destruction can occur at the epithelial surface due to the resident bacteria's and can be successfully overcome by the use of enzyme inhibitors. Probably the single most significant barrier to epithelial transport of drug in the colon occurs at the level of epithelium. The lipid bilayer of the individual colonocyte and the Occluding Junctional Complex (OJC) between these cells provide a physical barrier to the drug absorption. Drugs that pass from the apical to basolateral surface termed “the transcellular route” or between adjacent colonocyte termed “the paracellular route”. Intercellular OJCS also known as junctional tight complexes, effectively limit the transepithelial movement of essentially all biomolecules larger than small ions. The paracellular route as well as several potential routes of transcellular drug transport is depicted in below figure.

3. FACTORS AFFECTING COLONIC DRUG ABSORPTION: [18, 25, 27, 34,]

Colonic drug delivery can be accomplished from either the oral or rectal route. Rectal delivery, although avoid many of the draw backs identified with oral colonic drug delivery, is generally recognized as being less appealing than oral colonic drug delivery. Successful oral colonic delivery first requires that the drug or drug system reach the proximal colon at a precise time. Precise delivery would result in minimized drug loss due to enzymatic activities of the distal colon.

*The inter patient and intra patient variability in measured GI transit times.

*Fluctuations in gastric residence time due to the presence of food. The meals and feaces can also affect local nerve activity and therefore alter colonic residence time.

*Emotional stress is capable of increasing the colonic motility and altering the GI transit times. Total transit time can vary from 10 - 60 hrs. Mouth to colon transit in human has been estimated to be 8 - 10 hr with variable transit times through the stomach of 0.5 - 3 hrs and through the small intestine 1 - 6 hrs.

*Combining information from several studies transit through the proximal colon, right colon and sigmoid colon requires approximately 7 - 11 hr, 9 - 11 hr, and 12.5 - 18.5 hr respectively. In total the average transit through the colon varies from 22 - 36 hr.

*Intrinsic components such as leukotrienes, prostaglandins and Nitric oxide (NO) have been shown to modulate the muscular activities of the proximal and ascending colon.

*Both acute and chronic pathological condition can affect drug uptake from the colon, for example, acute cholera diarrhea and increased muscular activity can modify net convective water flow transport resulting in reduced drug uptake. Similarly drugs which locally activate cholinergic neurons of the colonic sub mucosa and stimulate chloride ion secretion could alter colonic drug absorption, changes in the luminal environment can also affect on drug transport.

4. APPROACHES TO OVERCOMING FLUCTUATION IN COLONIC RESIDENCE TIME:

*One approach is by employing bioadhesives in colonic drug formulations. As one might expect, increased colonic residence time improves total drug uptake.

*Use of enzyme inhibitors, more stable analogues and prodrugs specific for colon delivery. For example amino terminal

acylation can decrease enzymatic damages and in some instance colonic peptide uptake.

*Glycoside-conjugate prodrugs of small molecular weight at parent molecules have also shown promise for colon specific delivery. Colonic delivery of 5 ASA can be improved using the pro drug Sulphasalazine which undergoes azo-reduction by the resident bacteria of the colon to produce 5 ASA and Sulphapyridine. Similarly anthracene laxative can be converted to active sennoside by the colonic bacteria.

*Proteolysis resistant insulin analogues as well as the use of protease inhibitors bacitracin has resulted in the lowering of Serum glucose levels. Also an endogenous trypsin inhibitor has been localized to human crypt goblet cells suggesting that resident colonic protease inhibitors exist which may aid in the local stability of proteins and peptides against the action of epithelial and bacterial derived enzyme activities.

*Hyperoxaluria may be caused by a lowered intraluminal pH, accelerating the uptake of oxalate ions thus suggesting that formulations which significantly alter luminal composition might similarly affect the drug uptake.

Increase in luminal osmolality might also increases uptake of molecules from the colonic lumen [21.]

5. FORMULATION DESIGNS:

5.1 Coating with ph dependent polymers[34, 51]

In these systems drugs can be formulated as solid dosage forms such as tablets, capsules and pellets and coated with pH sensitive polymers as an enteric coating. Widely used polymers are methacrylic resins (Eudragits) which are available in water soluble and insoluble forms. Eudragit L and S are copolymers of methacrylic acid and methacrylate. 5-aminosalicylic acid is commercially available as an oral dosage form coated with Eudragit L and S. Other colon-specific delivery systems based on methacrylic resins are described for prednisolone, insulin and quinolones[8,15].

The pH-dependent systems exploit the generally accepted view that pH of the human GIT increases progressively from the stomach (pH 1-2 which increase to 4 during digestion), small intestine (pH 6 - 7) at the site of digestion and it increases to 7-8 in the distal ileum. The gamma scintigraphy technique becomes most popular technique to investigate the gastrointestinal performance of pharmaceutical

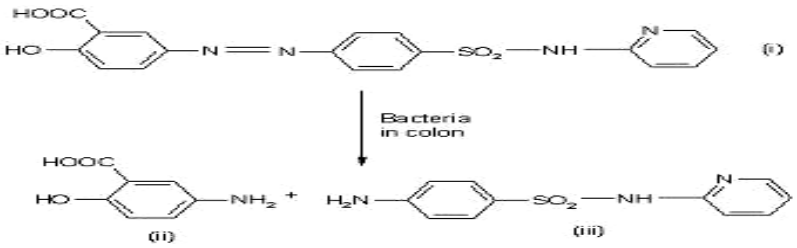
formulations. Mostly used polymer most commonly used pH-dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S more specifically Eudragit L and S. Eudragit L100 and S100 are the copolymers of methacrylic acid and methyl methacrylate. Carboxyl polymer form salts and dissolve above pH 5.5 and disperse in water to form latex and thus avoid the use of organic solvents is the coating process. Eudragit L100-55 polymers with ionizable phthalic acid groups dissolve much faster and at a lower pH than those with acrylic or methacrylic acid groups[16].

5.2 Coating with ph independent polymers:[34, 51]

Drugs that are coated with the polymers, which are showing degradability due to the influence of colonic microorganisms, can be exploited in designing drugs for colon targeting in order to release an orally administered drug in the colon. The intestinal microflora has a large metabolic capacity and it appears that reduction of azo bonds is a general reaction of colonic bacteria. The azo polymers having a high degree of hydrophilicity were degraded by colonic bacteria[15,16]. The copolymers of styrene and 2-hydroxy mehyl methacrylate which were cross linked with divinyl azo benzene and N.N^1 bis (β-styrene sulphonyl) - 4, 4^1-diamino azo- benzene to coat oral dosage forms of insulin and vasopressin. On arrival at the colon the coating is degraded by bacterial azo reductases there by releasing the drug.

5.3 Prodrugs:[17, 18, 20]

Prodrugs[8] of steroids having a hydroxyl group at C-21 position were prepared using poly-l-aspartic acid carrier. The ester prodrug of dexamethasone with poly-l-aspartic acid when subjected to *in vitro* drug release studies in gastro intestinal tract homgenates released dexamethasone because of the cleavage of the ester bond by bacterial enzymes. The polymeric prodrugs of sulfasaslazine, is used in the treatment of ulcerative colitis and crohn's disease. Chemically sulfasaslazine is 5-aminosalicylic acid (5-ASA) coupled with sulphapyridine by azo bonding. On arrival at the colon the azo bond is reduced by colonic azo reductases to 5-ASA and sulphapyridne[17, 18].



Hydrolysis of sulfasalazine (i) into 5-aminosalicylic acid (ii) and sulfapyridine

Classical prodrug design often represents a nonspecific chemical approach to mask unwanted drug properties such as low bioavailability, less site specificity, and chemical instability. On the other hand, targeted prodrug design represents a new strategy for directed and efficient drug delivery. Particularly, prodrugs targeting to a specific enzyme or a specific membrane transporter, or both, have potential drug delivery system especially for cancer chemotherapy. Site specific targeting with prodrugs can be further improved by the simultaneous use of gene delivery to express the requisite enzymes or transporters. This review highlights evolving strategies in targeted prodrug design, including antibody directed enzyme prodrug therapy, gene directed enzyme prodrug therapy, and peptide transporter-associated prodrug therapy[19].The use of prodrugs has been actively pursued to achieve very precise and direct effects at the "site of action," with minimal effect on the rest of the body. There are at least three factors should be optimized for the site specific delivery of drugs by using the prodrug approach[12,13].

1. The prodrug must to reach the target for the site of action as early as possible, and uptake from the site must be fast and essentially perfusion rate limited.

2. Once the drug reached to the site, prodrug must be selectively liberated to the active drug relative to its conversion at other sites.

3. Once selectively liberated at the site of action, the active drug must be somewhat retained by the tissue.

5.4. Absorption enhancing agents for colon drug delivery system[26, 32]

Co administration of absorption enhancers offers a potential means of overcoming this barrier.

6. LIMITATIONS:

*A complex series of events occur before absorption of drug molecules form the colon.

*Successful colonic uptake of a drug species requires enzymatic stability

*The colonic epithelial permeability is insufficient to allow for the transport rate required for a therapeutic delivery.

*One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system *in-vitro*. This is due to the rationale after a colon specific drug delivery system is quite diverse.

*As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, a long transit time and increased responsiveness to absorption enhancers; however, the targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.

*Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or, alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract.

7. EVALUATION OF COLON SPESIFIC DRUG DELIVARY SYSTEMS:

- Consecutive dissolution tests in different buffers for different periods of time best simulate the transit of a formulation through the gastrointestinal tract. In gradient dissolution studies a particular formulation unit is exposed to buffers representing successive conditions in the gastrointestinal tract. Enteric-coated capsules for colon-specific drug delivery have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4.
- The relationship between percentage of drug released in vitro and percentage of drug absorbed in vivo was observed when pulsatile-release tablets were tested in vitro for two hours at pH 1.2 followed by a dissolution study at pH 6.8.

- Fukui et al. (2000) kept enteric-coated tablets in a buffer at pH 1.2 for 16 hours. A dissolution study was then carried out at pH 6.8. It was concluded that the dissolution profiles of formulations that had not been kept in buffer at pH 1.2 did not differ markedly from dissolution profiles of formulations that had been kept in buffer at pH 1.2. Exposure to acid in the stomach should therefore not affect the dissolution properties of such formulations in the lower gastrointestinal tract. On the basis of these findings it is obvious that sufficient information regarding dissolution properties of formulations can often be obtained using parallel dissolution tests. Gradient dissolution tests are usually unnecessary.
- To allow the performance of colon-specific delivery systems containing biodegradable polymers to be assessed, the contents of animal caecum have been used in dissolution studies. Such studies provide no information about the physical and chemical functionality of a system.
- In vivo bioavailability tests in human beings are important in developing controlled-release drug delivery systems. From the results of bioavailability tests, sites of drug liberation in vivo can be determined, if the formulation has been administered to the subjects in the fasting state.
- However, it is impossible to predict times of arrival of formulations in the colon accurately, because gastric emptying times vary so greatly. In recent years gamma scintigraphy has become the most popular means of investigating the gastrointestinal performance of pharmaceutical dosage forms, especially site-specific dosage forms. By means of gamma scintigraphic imaging, information can, for example, 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. Gammascintigraphy studies can also provide information

about regional permeability in the colon. Information about gastrointestinal transit and the release behaviour of dosage forms can be obtained by combining pharmacokinetic studies and gammascintigraphy studies (pharmacoscintigraphy). Good correlations between appearance of a drug in plasma and observed disintegration times have been recorded.

- Although the tablets disintegrated completely in the colon it was concluded that gammascintigraphy did not allow exact information about the mechanism of disintegration to be obtained.
- Many pharmacoscintigraphy studies have been reported. Stevens et al. (2002) used gammascintigraphy to identify the site of release from a Pulsincap™ formulation, intended to release drug after a five-hour lag time.

Plasma concentrations of the model drug were also followed. A good correlation was found between release times determined scintigraphically and pharmacokinetic profiles. A correlation between pharmacokinetic and gammascintigraphy data was also found when times and anatomical locations of break-up of colon-specific formulation were determined by Sangalli et al. (2001)

8. CONCLUSION:

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Colon targeted drug delivery offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. The 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 targeted drug delivery systems, and the uncertainty of current dissolution methods in establishing possible evaluation 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 can be used routinely in an industry setting for the evaluation of colon targeted drug delivery systems

FIX	CLASS	EXAMPLES	TARGET DRUGS
I	NSAIDS	Indomethacin Diclofenac Phenylbutazone Salicylates	Ampicillin Cefmetazole Cefoxitin Insulin, Lidocaine
II	Chelating Agents	EDTA Enamines Trisodium Citrate	Heparin Ampicillin Sulfanilic acid
III	Surfactants	Sodium lauryl sulphate Brij 35 Brij 58	Cefoxitin Lincomycin Insulin
IV	Phenothiazenes	Perphenazine Ether promazine	Cefoxitin Gentamycin
V	Mixed micelles	Oleic acid - Polyoxy ethelene hydrogenated caster oil	
VI	Other Agents Acylamino acids Dicarboxylic acids	PhenylaminoNon am ethylene oxalic acid	Ampicillin

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