Review Article

Colon Targeted Drug Delivery – A Review on Primary and Novel Approaches

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ABSTRACT

Colon Targeted drug delivery may provide maximum therapeutic activity by preventing degradation or inactivation of drug during transit to the target site. Meanwhile, it can also minimize adverse effects because of inappropriate disposition and minimize toxicity of potent drugs by reducing dose. An ideal targeted delivery system should be nontoxic, biocompatible, and biodegradable and physic-chemically stable in vivo and in-vitro. The preparation of the delivery system must be reasonably simple, reproducible and cost-effective. The colon targeted drug delivery is beneficial for the localized treatment of several colonic diseases mainly inflammatory bowel diseases (IBD), irritable bowel syndrome and colonic cancer. To achieve clinically relevant bioavailability of poorly absorbed drugs from the upper parts of the gastrointestinal tract because of their polar nature and/or vulnerability to chemical and enzymatic degradation in the small intestine specifically for proteins and peptides. The colonic drug delivery provide more effective therapy of colon associated diseases such as irritable bowel syndrome, IBD including Crohn's disease and ulcerative colitis, and also has potential to deliver macromolecular drugs orally. Colon related pathologies range in seriousness from constipation and diarrhea to the incapacitating inflammatory bowel diseases through to colon cancer, the third most widespread form of cancer in both women and men.

INTRODUCTION

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. 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 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.

Disadvantages of Colonic Drug Delivery

1. There are variations among individuals with respect to the pH level in the small intestine and colon which may allow drug release at undesired colon targeted drug delivery site. The pattern of drug release may differ from person to person which may cause ineffective therapy.
2. The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.

3. The major disadvantage of colonic delivery of drug is poor site specificity.
4. Diet and diseases can affect colonic microflora which can negatively affect drug targeting to colon. Nature of food present in GIT can affect drug pharmacokinetics. In diseased conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site.
5. Enzymatic degradation may be excessively slow which can cause interruption in polymer degradation and thus alters the release profile of drugs.
6. Substantial variation in gastric retention time may cause drug release at the undesired site in case of time dependent colonic drug delivery system.

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 pre-solubilised 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.[3]

Anatomy and Physiology of Colon

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

P^H in the colon

The pH of the GI tract is subject to both inter and intra subject variations. Diet, diseased state, and food intake influences the pH of the gastrointestinal fluid. The changes in the pH along the gastrointestinal tract have been used as a means for targeted colon drug delivery. Radio telemetry shows the highest pH (7.5±0.5) in the terminal ileum. On entry into the colon, the pH drops to 6.4±0.6. The pH in the mid colon is 6.6±0.8 and in the left colon 7.0±0.7. There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce large amounts of lactic acid resulting in pH drop to about 5.0. 1.4.3-Colonic Microflora and Enzymes A large number of anaerobic and aerobic bacteria are present in the entire length of the human GI tract. Intestinal enzymes are used to trigger drug release in various parts of the GI tract. Usually, these enzymes are derived from gut microflora residing in high numbers in the colon. These enzymes are used to degrade coatings or 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 bacteroids. The concentration of bacteria in the human colon is around 1000 CFU/ml. The most important anaerobic bacteria are Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, and Peptostreptococcus, Ruminococcus, Clostridium.

Transit of Material in the Colon

The presence of food material generally increases gastric residence and in some cases with regular feeding, dosage forms have been shown to reside in the stomach for periods in excess of 12 hours. Small intestinal transit is surprisingly constant at 3-4hours and appears to be independent of the type of dosage form and whether the subject is in the fasted or fed state. Compared to other regions of the gastrointestinal tract, movement of materials through the colon is slow. The total time for transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, mobility, stress, disease and drugs. Colonic transit times ranged from 50 to 70 hours. Stool weights increased significantly with the presence of active disease presumably due to exudates form inflamed epithelium, increased mucus secretion, and reduction in re-absorption of fluid and electrolytes.

Drug absorption in the colon

Drugs are absorbed passively by either paracellular or transcellular route. Transcellular absorption involves 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 poor paracellular absorption of many drugs in the colon is due to the fact that epithelial cell junctions are very tight. The slow rate if transit in colon lets the drug stay in contact with the mucosa for a longer period than in small intestine which compensates the much lower surface area. The colonic contents become more viscous with progressive absorption of water as one travels further through the colon. This Causes a reduced dissolution rate, slow diffusion of dissolved drug through the mucosa.

Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum. The oral absorption of the majority of Peptide and Protein drugs are limited because of following reasons

1. Degradation in the acidic environment of the stomach.
2. Enzymatic degradation in the small and large intestine.
3. Rapid small intestine transit.
4. Low mucosal permeability.
5. Extensive first pass metabolism by the absorbing membrane and the liver.[4, 5, 6]

Drug Candidates for Colon Drug Delivery

Drug delivery to the colon through the oral route is becoming increasingly popular for the treatment of large bowel diseases and for systemic absorption of peptide and protein drugs. Inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn's disease would be well treated by selective local delivery of drugs to the colon. Sulfasalazine is the most commonly prescribed medication for such diseases. It is a conjugate of 5 aminosalicylic acid (5-ASA) and sulfapyridine (SP), the active moiety being 5-ASA. When administrated orally, about 20% of the dose is absorbed in the upper part of the GI Tract and the remainder of the dose passes into the colon wherein the colonic azoreductases cleave the azo-bond, thereby liberating 5-ASA and SP. The SP gets absorbed from the small intestine and the colon and produces a number of side-effects. Selective delivery of 5-ASA to the colon is required for therapeutic efficacy with little or no side effects.

The other drugs used in IBD are steroids, such as dexamethasone, prednisolone and hydrocortisone. When these steroids are specifically delivered to the colon, they produce fewer and less intense side effects than when administrated orally orintravenously[7]. Nicotine is currently under investigation for its therapeutic role in the treatment of ulcerative colitis and hence is a promising drug candidate for colonic drug delivery[8]. The site specific delivery of drugs for the treatment of infectious diseases, e.g. treatment of amoebiasis using metronidazole, would be useful for minimizing the side effects associated with the systemic absorption of these drugs. With the development of new peptide and protein drugs through biotechnology, there has been an increasing interest in utilizing the colon as a site for the systemic absorption of these drugs in view of the less hostile environment prevailing in the colon.

A variety of protein and peptide drugs, like calcitonin, interferon, interleukins, growth hormone and even insulin, are being investigated for systematic absorption using colon specific delivery. They have shown that these drugs cross the gastrointestinal tract in significant amounts and that this demonstrates the feasibility of an oral form[9]. Beside peptide and protein drugs, the colon is also a good site for the absorption of drugs that are not stable in the acidic environment of the stomach, that cause gastric irritation (e.g. iron supplements), or that are degraded by small intestine enzymes. Currently, a number of drugs are available in sustained release tablets or capsules for oral administration. This is due to the fact that most of these formulations are supposed to release their drug load slowly over a period of 12 hours, sometimes even 24 hours. The total residence time of these formulations in the stomach and small intestine will be notmore than 5-6 hours. If the drug does not exhibit good absorption properties in the colon, it will be eliminated in the feces.

Drugs that have good absorption properties from the colon include theophylline,Glibenclamide[10], Oxprenolol[11], Diclofenac, Ibuprofen[12],Brompheniramine,Nitrendipine,Nisoldipine, Isosorbide [13], Metoprolol[14], and Nifedipine[15]. Hence these drugs can be investigated for better bioavailability through colon-specific drug delivery[16]. However, piretanide[17], Buflomedil, Atenolol, Cemitidine and hydrochlorothiazide[18] were found to be

poorly absorbed from the colon. This is explained by the pH-partition hypothesis of drug absorption. Approaches to Colon specific Drug Delivery. The targeting of orally administrated drugs to the colon is accomplished by

(i) Coating with pH dependent polymers,
(ii) Timed release dosage forms, and
(iii) Delivery systems based on the metabolic activity of colonic bacteria.

Coating with pH Dependent Polymers In these systems, drugs are formulated into solid dosage forms such as tablets, capsules and pellets and then coated with pH sensitive polymers that behave similarly to material used in enteric coating.

Polymers commonly used for this purpose are based on methacrylic resins (Eudragits), which are available in water soluble and water insolubleforms. Eudragit L and S are copolymers of methacrylic acid and methyl methacrylate. Eudragit L is water soluble at pH 6 or above and is used as an enteric coating polymer. Eudragit S is water soluble at pH 7 or above and is used to deliver drugs to the end of the small bowel and in the large intestine. At present 5-ASA is commercially available as an oral dosage form coated with Eudragit L 100 (Claversal, Mesasal, Colitofalk) or Eudragit S (Asacol)[19]. Studied the usefulness of Eudragit S as a colonic delivery coating material. Thirty capsules filled with sulfa-pyridine and barium sulfaten were coated with Eudragit S and validated in six convalescent patients using X-ray evidence and serum levels of sulfapyridine. After 12 hours, all 36 capsules arrived at the colon. Of those 36, 23 released their contents while 9 remained intact and 4 disintegrated in the ileum. Although the use of Eudragit S provided reliable results, the effect of partially methylating the free carboxylic acid groups of Eudragit S was investigated.

The modified product was found to dissolve at a slightly higher pH value and its effectiveness as a material for colon specific drug delivery was proved in human volunteers. Other oral drug delivery systems for colon delivery based on methacrylic resins are described for prednisolone, and insulin. The disadvantage of this technique is the lack of consistency in the dissolution of polymer at the desired site. Depending on the intensity of the GI motility, the dissolution of polymer can be in the proximal portion of colon or in the distal ileum.

Moreover, many factors, such as the presence of short chain fatty acids, residues of bile acids, carbon dioxide or other fermentation products reduce the colonic pH to approximately 6 and call its pH as a trigger into question. The lack of site specificity of pH dependent systems was demonstrated by Ashford, et al. When Eudragit S was used to coat rapidly disintegrating tablets, these tablets were then administrated to healthy volunteers and studied for their in vivo behavior using gamma scintigraphy. Though the polymer coat protected the tablet during its passage through the stomach and upper small intestine, its site specificity was poor. The disintegrating sites varied from ileum to the sigmoid flexure.

Timed Release Dosage Forms Small intestine transit time is relatively constant and is hardly influenced by the nature of the formulation administered. Studies have shown that, once having left the stomach, the formulation arrives at the ileocecal valve about 3 to 4 hours after dosing[20]. An extension of the pH dependent polymer system is used in the Pulsincap® system.

This delivery system consists of a capsule, half of which is non disintegrating and the other half enteric coated. The enteric coat dissolves on entering the small intestine and a hydrogel plug, stoppering the non-disintegrating part, swells at the rate determined by the degree of crosslinking. After a predetermined time (e.g. 5 hours), the hydrogel plug swells so much that it becomes ineffective at preventing drug release fromthe non-disintegrating bottom half of the capsule.

It must be noted that the swelling of the hydrogen plug is pH independent. However, the site specificity of timed released dosage forms is considered poor because of large variations in gastric emptying times and passage across the ileocecal junction (Davis, et al. 1984).Delivery Systems Based on Metabolic Activity of Colonic Bacteria

Colonic bacteria carry out a variety of metabolic reactions and the most important of them are reduction and hydrolysis. Different strategies were used to target drugs to the colon based on these reactions. The main features of these systems are their site specificity. These strategies are described below. Coating with biodegradable azo polymers. The intestinal microflora has a large metabolic capacity and it appears that reduction of azo bonds is a general reaction of colonic bacteria. The degradation of different types of azo polymers by colonic bacteria was investigated. The influence of the type of azo aromatic group built in the azo polymers and the degree of hydrophilicity of the azo polymer on the degradation by intestinal microflora was studied by. The azo polymers

having a high degree of hydrophilicity were degraded by colonic bacteria. It was alsofound that the chain length of the azo aromatic group in the azo polymers had limited influence on the rate of degradation Colonic drug delivery systems based on biodegradable polyether polyester azo polymers were developed. Since the azo polymers had poor film forming properties, a pH independent Eudragit polymer was mixed with the azo polymer to coat ibuprofen capsules.

Drug release studies carried out in rat cecal content medium showed that capsules coated with three layers of polymer coat containing 15% polyethylene glycol (PEG in coating solution resulted in higher drug release due to enhanced hydrophilicity of the coating) were useful for colonic drug delivery. The relationship between the swelling properties and enzymatic degradation of azo polymers, designed for colon specific drug delivery, was also studied. The release profiles indicate that the degradation of the azo polymer coatings depends on their degree of swelling, due to a higher accessibility of the azo bonds for the bacterial azo reductase [21]. Prodrugs A well known colon specific prodrug, sulfasalazine, is used in the treatment of ulcerative colitis and Crohn's disease. Chemically, sulfasalazine is 5-aminosalyclic acid (5-ASA) coupled with sulfapyridine by an azo bond. On reaching the colon, the azo bond is reduced by colonic azoreductases to 5-ASA and sulfapyridine.

The active moiety is 5-ASA and sulfapyridine simply acts as a carrier to deliver 5-ASA intact to the colon. A recent novel approach is the use of a water soluble copolymer, N-(2-hydroxy propyl) methacrylamide together with a bioadhesive sugar moiety complementary to mucus lectins of the GI tract. In this approach, 5-ASA was linked through an azo bond to the polymeric carrier and fucosylamine (sugar moiety) serves as the bioadhesive material.

Glycosidases are a prominent group of enzymes produced by the intestinal microflora. Drug glycosides are poorly absorbed from the small intestine due to theirhydrophilicity[22]. Glycoside prodrugs were also prepared and studied for their efficacy in different animal models. Pro-drugs of Dexamethasone were prepared and were subjected to stability studies in the homogenates of the different segments of the rat gastrointestinal tract with an objective of achieving colon-specific drug delivery.

The contents of the cecum and colon show greater hydrolytic activity than the contents of the small intestine and stomach.A class of macromolecules, such as Dextran-Naproxen ester prodrugs, has been the focus of increasing interest in colon-specific drug delivery. These prodrugs, on reaching the colon, are acted upon by colonic esterase, resulting in the release of the active moiety.

Dextran ester prodrugs of naproxen were synthesized and tested for drug release in homogenates of various segments of the pig gastrointestinal tract. Drug release was found to proceed 15-17 times faster in cecum and colon homogenates than in homogenates of the small intestine. The drug release was attributed to the initial depolymerization of dextran chains by dextranases of the pig colonic bacteria and the resultant fragments act as substrates for esterases and other hydrolases.

The bioavailability of naproxen after oral administration of aqueous solutions of various dextran-naproxen ester prodrugs in pigs was found to be close to 100%.Polysaccharides as Carriers Natural polysaccharides, such as pectin and xylan, are not digested in the human stomach or small intestine, but are degraded in the colon by resident bacteria. Bacterial enzymes are capable of degrading a wide variety of polysaccharides present in the diet; the bacteria ferment polysaccharides to gases, such as methane, CO_2, and hydrogen, and to short chain fatty acids, thus accounting for the drop in pH of the colon[23].

These dietary polysaccharides thus have the potential to act as nontoxic carriers for colon-specific drug delivery. A number of polysaccharides that are under vestigation for colon-specific drug delivery are detailed below. Pectin, an anionic lysaccharide extracted from plant primary cell walls, was used by Ashford, et al. To develop a colonic drug delivery system. The in vitro studies demonstrated that high methoxy pectin, when applied as a compression coat,protected the core tablet from disintegration and dissolution in the upper part of the gastrointestinal tract.

The coat was susceptible to enzymatic attack in the colon, thereby releasing the drug. In vivo gamma scintigraphic studies confirmed the in vitrofindings. The same research group carried out further studies on matrix formulations with different types of pectin (high and low methoxy pectin) using different concentrations of pectinase enzyme and calcium salts. It was concluded that an ideal pectin for colonic drug delivery should consist of either high methoxy pectin or low methoxy pectin with controlled

calcium levels. Another promising matrix system was developed by with calcium pectinate, which was evaluated for colonic drug delivery using indomethacin as a model drug. Pectin, as a component of a compression coat, was evaluated for drug targeting to the colon by an in-vitro system for the evaluation of these formulations was developed and used to carry out the drug release studies with isolated enzymes. The study showed that hydration is an important consideration with polysaccharide based dosage forms since they must absorb water to swell before they are open to attack by bacterial enzymes.A biodegradable coating containing pectin and ethyl cellulose was evaluated by Wakerly, Fell et al[24] for colon specific drug delivery. They showed that ethylcellulose and pectin can provide protection to a drug in the upper gastrointestinal tract while allowing enzymatic breakdown and drug release in the colon. The suitability of hydrogel beads based on amidated pectin for potential use as colon specific drug delivery matrices was investigated using indomethacin and sulfomethoxazole as model insoluble and relatively soluble drugs, respectively, by Wakerly, Fell et al drug release from the beads was found to be a function of media pH and drug loading. In simulated gastric and small intestine conditions, drug release was greater with the more soluble sulfomethoxazole but release of both drugs could be reduced to satisfactory levels by the formation of a chitosan polyelectrolyte complex around the beads. All the preparations released the drug in simulated colonic conditions within 135 minutes also studied the potential of amidated pectins for colonic drug delivery and suggested that these materials might be of value in the form of a coating.

Evaluation test of Colon Drug Delivery System

In vitro evaluation No standardized evaluation Technique is available for evaluation of CDDS as 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 and physical stress. The in-vitro Evaluation of colon targeted drug delivery systems includes the in-vitro dissolution study and in-vitro enzymatic test.

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 behavior 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[25].

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 erformed 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[26].

In- vivo evaluation

The in-vivo evaluation of the CDDS is done in dogs, guinea pigs, rats and pigs as they resemble the anatomic and physiological conditions, microflora of human GIT. The distribution of arious enzymes in GIT of rat and rabbit is comparable to that in human[27].

Analysis of Drug Release Kinetics

To understand the mechanism of drug release from core, the modeling of drug release kinetics was done for the data obtained in various dissolution media (SGF, water and SIF) but only after confirm ing the drug stability profiles in the these dissolution media. The goodness of fit of the drug release data was tested with Higuchi matrix model and Hixson-Crowell cube root laws as Described below.

1. Higuchi Matrix model

Q = k tl/:

So a plot of Q vs t l/: yields a straight line. The release rate (k) was calculated from the slopes of the release profile plotted as Q vs. t 1/2

2. Hixson-Crowell Cube Root Dissolution Law

$$W_o^{1/3} - W^{1/3} = Kt$$

Where Wo is the initial weight (expressed as 100%) and W is the percent remaining un dissolved at time t. K is an apparent dissolution rate constant.

Statistical Analysis

Various statistical tests were performed using a statistical software (Graph PAD Instat®. california. USA).

Correlation tests

For the evaluation of the correlations, Pearson's correlation test was performed, and the Correlation coefficients and associated probability values (two tailed) were calculated. This test was used to determine if there is any significant correlation between

1. Drug loading and drug solubility in various divalent chloride solutions,
2. Drug loading and drug solubility in various molar concentrations of calcium ions, and
3. Solubility in various divalent chloride solutions versus melting points of divalent halides.

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 in-vitro 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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