Colonic Drug Delivery System: A Review

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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 protect from degradation, release and absorption in upper portion of the GI tract and then to be ensured abrupt or controlled release in 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.

Keywords: G.I.T, Colon Drug Delivery System, Colonic.

INTRODUCTION
Day by day there are new developments in field of colon specific drug delivery system. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like crohn’s disease, etc. but also for the systemic delivery of anti-asthmatic drugs, antihypertensive drugs and anti-diabetic agents. New systems and technologies have been developed for colon targeting and to overcome previous method’s limitations. Colon targeting holds a great potential and still need more innovative work.

Traditionally solid oral dosage forms have been designed to release their drug load in upper region of G.I.T where conditions are generally more suited to drug dissolution and absorption1. Recently greater emphasis has been placed on controlling the rate and site of drug release from oral formulations for the purpose of patient compliance and treatment efficiency.

The colonic region of G.I.T. is one of that would benefit from the development and such modified release technologies. Although considered by many to be an innocence organ that may simple functions in the form of water and electro light absorption and the formation storage and explosion of fecal material, the colon is valuable to a no of disorders including alternative qualities corn’s disease irritable bower syndrome and carcinomas1,2. Targeted drug delivery to the colon would therefore ensure direct treatment at the disease site lower closing and favour systemic side effects.

In addition to local therapy, the color can also be utilized as a portal for entry of drug into the systemic circulation. E.g.: molecules that are degraded parry absorbed in upper get, such as peptides and proteins, may be better absorbed from more being environment of colon. In addition, systemic absorption from colon can also be used as a means of achieving chemotherapy for diseases that are sensitive to circadian rhythms such as asthma, angina, orthotics1,2.

TARGETING MECHANISM OF DRUG ACTING ON COLON

1. Pre-dependent delivery
2. Time-dependent delivery
3. Pressure-dependent delivery
4. Bacteria dependent delivery

Successful colonic drug delivery requires careful considerations of a number of factors, including the properties of drug, the type of delivery system and its interaction with the healthy or diseased gut1.

1. Pre-dependent Delivery

Pre-sensitive enteric coatings have been used routing to deliver drugs to small intensive. These polymer coatings are insensitive to the acidic conditions of stomach yet dissolve at the higher PH environment of small intestine. This PH differential principle has also been attempted for colonic delivery purposes although polymers used for solenoid targeting and to have a threshold PH for dissolution that is higher than those used in conventional enteric coating application1,7. Most commonly co-
polymers of methacrylic acid and methyl methacrylate that
dissolve at PH 5 or PH 7 have been investigated. / this
approach is based on assumptions that G.I. PH increases
progressively from the small intestine to colon. In fact, the
small intestine is usually around 7.5, while the PH in
proximal colon is closer to 6 these delivery systems
therefore have a tendency to release their drug load prior
to reaching colon2.

To overcome the problem of premature drug release a
copolymer of methacrylic acid, methyl methacrylate and
ethyl threshold PH, has been developed recently.

The inter subject variability in G.I.T. and possibly certain
other intersect various such as electrolyte concentration
and transit time will therefore impact on in vivo behaviour
of PH responsive systems, ranging from early drug release is
small intensive to are release at all with the formulation
passing throughout gut intact the latter situation will also
arise when PH of colon, and possibly the small intensive is
considerably lower than normal as the case in patients
with creative qualities in spite of their limitations, PH
sensitive delivery systems are commercially available for
mesalazine in and budesonide for treatment of ulcerative
colitis and crohn’s disease, respectively.

2. Time Dependent Delivery

It has also been proposed as a means of targeting the
colon. Time dependence systems release their drug load
after a preprogrammed time delay. To attain colonic
release, the log, time should equate to time taken for
system to react the colon. This time is difficult to predict in
advance, although a log time of five hours is usually
considerate sufficient, given that small intestinal transit
time is reported to be relatively consistent at three to four
hours1. One of the earliest systems to utilize this principle
was the pulsincap device. System consist of an importable
capsule fined with drug and stoppered at one end with a
hydroges plug, on contact with gastrointestinal fluids, the
plug hydrates and swells and after a set log time, ejects
from the capsules body, thereby allowing drug release to
occur the log time is controlled by the size and composition
of play.

3. Pressure Dependent Delivery

G.I pressure has also been utilized drug release in distal
gut. This pressure which is generated via muscular
contraction of gut wall for grinding and proposition of
intestinal contents, varies in intensity and duration
through the gastro intestinal tract, with the colon
considered to have a higher internal pressure due to
process that occur during stool formation. The system
have therefore been developed to resist the pressure of
upper G.I tract but in rupture response to the raised
pressure of colon2. Capsule shells fabricated from water
insoluble polymer entry cellulose have been used for this
purpose. The system can be modified to withstand and
rupture at different pressures by changing the size of
capsule and thickness of capsule shell wall.

Enzymes that are capable of metabolizing endogeneous
and exogeneous substrates such as carbohydrates,
proteins that are escapee digestion in upper G.I tract,
therefore materials that are recalitritant to the conditions
of stomach and small intestine, yet suspicious to
degradation by bacterial enzymes within colon, can be
utilized as carriers for drug delivery to colon.

Eg.: This principle has been exploited commercially to
deliver 5 anniosalicylic acid to the colon by way of a drug
carrier. The prodrug sulphasalazinc consist of two separate
moieties, sulphaphyridine and 5-amonosalicylic acid, linked
by as azo-bond. The prodrug possess through three upper
gut intrac, but once in colon the azo-bond is cleave by the
host bacteria, liberating the carrier molecule sulphaphyridin and pharmacologically active agent 5-
aminosalicylic acid14.

4. Bacteria Dependent Delivery

The resident G.I bacteria provide a further means of
effecting drug release in colon, these bacteria
predominantly colonise the distas region of G.I.tract where
bacterial count in the colon is 10’ per gram as compared with
10’ per gram in upper small intestine moreover, 400
different species are present colon bacteria are pre-
dominantly in nature and produce once of gastric copying
on performance of pulsincap was reduced by a application
of an outer enteric coat1. The outer enteric coat dissolves
on entering the small intestine to reveal by either swelling,
eroding or dissolving over a period of time equivalent to
small intestinal transit.

Although the use of an over enteric coat overcomes to a
certain attempt the availability in G.I. emptying, the
intrinsic problems with such systems is over all inter
and intra subject variability in transit. Transit is slower in
evening as compared with morning.

Table 1: Colon targeting diseases, drugs and sites

<table>
<thead>
<tr>
<th>Target Sites</th>
<th>Disease Condition</th>
<th>Drug active agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical action</td>
<td>IBD Irritable bowel disease</td>
<td>Hydrocortisone, Budenoside</td>
</tr>
<tr>
<td></td>
<td>Crohns disease</td>
<td>Prednisolone</td>
</tr>
<tr>
<td></td>
<td>Cronic pancreatitis</td>
<td>Sulfaselazine, Olasazine, meosalazine</td>
</tr>
<tr>
<td>Local action</td>
<td>Pancreatctomy</td>
<td>Digestive Enzyme supplements</td>
</tr>
<tr>
<td></td>
<td>cystifibrosis Colorectal cancer</td>
<td>5- Flououracil</td>
</tr>
<tr>
<td>Systemic action</td>
<td>To prevent gastric</td>
<td>NSAIDS, Steroid, Insulin</td>
</tr>
<tr>
<td></td>
<td>irritation and first pass</td>
<td>Typhoid</td>
</tr>
<tr>
<td></td>
<td>metabolism of orally</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ingested drugs like</td>
<td></td>
</tr>
<tr>
<td></td>
<td>peptides and vaccines</td>
<td></td>
</tr>
</tbody>
</table>
Advantages of CDDS Over Conventional Drug Delivery

Chronic colitis, namely ulcerative colitis and crohn’s disease are currently treated with glucocorticoids and other anti-inflammatory agents. Administration of glucocorticoid namely dexamethasone and methyl prednisolone by oral and intravenous routes produce systemic side effects including adenosuppression, immunosuppressant, cushiniod symptoms, and bone resorption. Thus selective delivery of drugs to the colon could not only lower the required but also reduce the systemic side effects caused by high dose.

![Anatomy of the colon](figure1)

**Figure 1:** Anatomy of the colon

Factors Affected in the Design of Colon Specific Drug Delivery System

The anatomy of the colon is shown in figure 1. The GIT 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 to five major segments. The right colon of the cecum ascending colon, hepatic flexure and the right half of the transverse colon and the values were shown in table 2. 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.

<table>
<thead>
<tr>
<th>Table 2: Measures of different parts of colon.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Large intestine</strong></td>
</tr>
<tr>
<td>Ascending colon</td>
</tr>
<tr>
<td>Descending colon</td>
</tr>
<tr>
<td>Transverse colon</td>
</tr>
<tr>
<td>Sigmoid colon</td>
</tr>
<tr>
<td>Rectum</td>
</tr>
</tbody>
</table>

Colon pH

The pH of the GIT is subject to both inter and intra subject variation. 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.

**Colonic microflora and enzymes**

A large number of anaerobic and aerobic bacteria are present in the entire length of the human GIT. Intestinal enzymes are used to trigger drug release in various parts of the GIT. 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, peptostreptococcus, ruminococcus, and clostridium.

Transit of material in the colon

Compared to other regions of the gastrointestinal tract, movement of materials through the colon is slow. 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 excudates form inflamed epithelium, increased mucus secretion and reduction in reabsorption of fluid and electrolytes.

**Drug absorption in the colon**

Drugs are absorbed passively by either paracellular or transcellular route. Tranellular 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 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.

**CRITERIA FOR SELECTION OF DRUG FOR CDDS**

The best candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of inflammatory bowel disease (IBD), ulcerative colitis, diarrhea, and colon cancer is ideally candidates for local colon delivery. The
criteria for selection of drugs CDDS are summarized in table 3 drug carrier is another factor which influences CDDS the selection of carrier for particular drugs depends on the physiological nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Pharmacological class</th>
<th>Non-peptide drugs</th>
<th>Peptide drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used for local effects in colon against GIT diseases</td>
<td>Anti-inflammatory drugs</td>
<td>Oxyprorenol, metoprolol, nifedine.</td>
<td>Amylin, antisense oligonucleotide.</td>
</tr>
<tr>
<td>Drugs poorly absorbed from upper GIT</td>
<td>Antihypertensive, antianginal drugs.</td>
<td>Ibuprofen, isosorbides, theophylline.</td>
<td>Cyclosporine, desmopressin.</td>
</tr>
<tr>
<td>Drugs for colon cancer</td>
<td>Antineoplastic drugs.</td>
<td>Psuedoephidrene</td>
<td>Epoetin, glucagoan.</td>
</tr>
<tr>
<td>Drugs that degrade in stomach and small intestine</td>
<td>Peptides and proteins.</td>
<td>Bromophenaramine, 5-flourouracil, doxorubicin.</td>
<td>Gonadoreline, insulin, interferons.</td>
</tr>
<tr>
<td>Drugs for targeting</td>
<td>Antiarhtritic, antiasthamatic drugs.</td>
<td>Prednisolone, hydrocortisone, 5-aminosalicylic acid.</td>
<td>Somatropin, urotoilitin.</td>
</tr>
</tbody>
</table>

PHARMACEUTICAL APPROACH TO COLON TARGETED DRUG DELIVERY

Coating with biodurabable polymers

The bio environment inside the human G.I.T. is characterized by presence of complex microflora especially the colon that is rich in micro organizing that are involved in the process of reduction of dietary component or other materials. Drugs that are coated with polymers, which are showing degradability due to influence of colonic microorganisms, can be exploited in designing drugs for colon targeting12. These bacterial degradable polymers especially also polymers have been explored in order to release as orally administrated drug in colon.

Actually upon passage of dosage from through G.I.T. it remains intact in stomach and small intestine where very little microbially degrades activity is present that is quiet insufficient for cleavage of polymer coating, release of the drugs from azo polymer coated formulation is supposed to take place after reductionism thus degradation of azo reductase enzymes released by azo batters in colonic microflora1.

Mesalazine is the active component of sulfasalazine exerting a predominant local topical action independent of blood levels17. Its effectiveness depends on the site of ulceration in relation to the drug’s dissolution profile. This is very important when choosing aminosalicylate preparations.

The optimal dose of sulfasalazine to achieve and maintain remission is usually in the range of 2-4gm per day in four divided doses. Acute attacks require 4-8gm per day in divided doses until remission occurs, but at these doses associated side-effects begin to appear1,22. Patients taking sulfasalazine, 30% experience adverse effects that are either dose-related, dependent on acetylator, phenotype or idiosyncreatic non-dose, related reactions. The first group includes nausea, vomiting, headache, malaise, haemolytic anaemia, reticulocytosis, and methamemoglobinemia. The second includes skin rash, hepatic and pulmonary disfunction, aplastic anaemia and reversible azoospermia. Adverse effects usually occur during the first 2 weeks of therapy, the majority being related to serum sulfapyridine levels.

Many of the adverse effects listed above can be avoided by using one of the aminosaliclyate formulations now available1. As mesalazine is unstable in acid medium and rapidly absorbed from the gastrointestinal tract, the new preparations have been developed using three different approaches.

- A mesalazine tablet coated with a pH-dependent acrylic resin.
- Ethy cellulose-coated mesalazine granules diazotization of mesalazine to itself or to an inert carrier.
Asacol contains 400 mg of mesalazine coated with an acrylic resin, eudragit-S, that dissolves at pH 7 and releases mesalazine in the terminal ileum and the colon. Salofalk tablets are similar formulation containing 250 mg mesalazine with sodium carbonate-glycine and a cellulose ether, coated with eudragit-L which dissolves at pH 6 and above, releasing mesalazine in the jejunum and ileum.

**Covalent linkage of the drug with a carrier**

It involves the formation of a covalent linkage between drug and carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine. This approach chiefly involves the formation of prodrug, which is a pharmaceutically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in the biological environment to release the active drug\(^{11}\). Formation of prodrugs has improved delivery properties over the parent drug molecule. The problem of stability of certain drugs from the adverse environment of the upper GIT can be eliminated by prodrug formation, which is converted into parent drug molecule once it reaches into the colon. Site specific drug delivery through site specific prodrug activation may be accomplished by the utilization of some specific property at the target site, such as altered pH or high activity of certain enzymes relative to the non-target tissues for the prodrug-drug conversion\(^6\).

**Azo bond conjugates**

The intestinal microflora is characterized by a complex and relatively stable community of microorganism, many with physiological functions, which play vital roles in health and disease. In addition to protection of the patient against colonization of the intestinal tract by potentially pathogenic bacteria, the indigenous microflora\(^{14}\) are responsible for a wide variety of metabolic processes, including the reduction of nitro and azo\(^{16}\) groups in environmental and therapeutic compounds.

Sulphasalazine\(^{27}\) was introduced for the treatment of rheumatoid arthritis and anti-inflammatory disease. Chemically it is salicylazosulphapyridine (SASP), where sulfapyridine is linked to a salicylate radical by an azo bond. When taken orally, only a small proportion of the ingested dose is absorbed from the small intestine and the bulk of the sulphasalazine reaches the colon intact. There it is split at the azo bond by the colonic bacteria with the liberation of sulphapyridine (SP) and 5 ASA. However sulfapyridine is seems to be responsible for the most of the side effects of sulphasalazine\(^{18}\) and hence various new approaches for the treatment of IBD have emerged.

**Glycoside conjugates**

Steroid glycosides and the unique glycosidase activity of the colonic microflora from the basis of a new colon targeted drug delivery system. Drug glycosides are hydrophilic and thus, poorly absorbed from the small intestine\(^{14}\). Once such a glycoside reaches the colon it can be cleaved by bacterial glycosidases, releasing the free drug to be absorbed by the colonic mucosa.

The major glycosidases identified human feces are b-D-galactosidase, b-D-glucosidase, a-L-arabinofuranosidase, b-D-xlylopyranosidase. These enzymes are located at the brush border and hence access to the substrate is relatively easy. In the plant kingdom numerous compounds are found as glycosides\(^{15}\). Certain drugs act as glycon and can be conjugated to different sugar moieties which results in the formation of glycosides. Due to the bulky and hydrophilic nature of these glycosides, they do not penetrate the biological membrane upon ingestion. Various naturally occurring glycosides, e.g., the sennosides\(^{17}\), have been used for laxative action for ages. When taken orally, intact sennosides are more efficient as laxative than sugar free aglycons. These sennosides are activated are activated by colonic microflora to generate in the once, which gives the desired laxative effect. Glycosidase activity of the GIT is derived from anaerobic microflora in the large bowel or the sloughed or exfoliated cells of the small intestine.

**Glucuronide conjugates**

Glucuronide and sulphate conjugation are the major mechanisms for the inactivation and preparation for clearance of a variety of drugs. Bacteria of the lower GIT, however, secrete b-glucuronidase and can de-glucuronidate a variety of drugs in the intestine\(^{18}\). Since the de-glucuronidation process results in the release of active drug and enables its reabsorption, glucuronide prodrugs would be expected to be superior for colon targeted drug delivery.

Morphine-dependent rats were used to evaluate the effects of the narcotic antagonists, naloxone and nalmefene\(^{20}\) and their glucuronide conjugates on the gastrointestinal tract and various parameter of brain-mediated withdrawal. When administered subcutaneously nalmefene hydrochloride caused a dose-dependent tail skin temperature increase, whereas nalmefene glucuronide was ineffective at doses as high as 1 mg/kg, whereas naloxone hydrochloride and nalmefene glucuronide caused diarrhea, withdrawal behavior and tail skin temperature responses by 15 min. in contrast, after per oral administration of the glucuronide conjugate of either narcotic antagonist, diarrhea was delayed for 75 to 203 min. This latency probably reflects the required transit time to the lower gastrointestinal tract\(^{22}\). About 0.2 to 0.5% of the dose of the narcotic antagonist administered orally as the glucuronide was absorbed systemically. These results indicate that per oral administration of the glucuronide conjugates of nalox one and nalmefene results in delivery of the narcotic antagonists to the colon. Haebelin et al. prepared a dexamethasone b-D-glucuronide prodrug\(^{20}\).
**APPROACHES FOR CDDS**

**pH sensitive system**

This approach is based on the pH-dependent release of the drug from the system. In this case the pH differential between the upper and terminal parts of GIT is exploited to effectively deliver drugs to the colon\(^1\). One should not forget that the pH in the intestine and Colon depends on many factors such as diet, food intake and intestinal motility and disease states.

This makes it more challenging for the specialists working in this field to design a delivery system that would be robust enough to withstand the variability in the gastric pH as it moves from the stomach to the small intestine. By combining knowledge of polymers and their solubility at different pH environments, delivery systems have been designed to deliver the drug at the target site\(^6\). Commonly used copolymers of methacrylic acid and methyl methacrylate have been extensively investigated for colonic drug delivery systems. In vitro evolution of Eudragit S and Eudragit FS was performed and it was found that the latter would be more appropriate for drug delivery to the ileocolonic region. Several factors, such as combinations of different polymers, pH of the media, coating level of the tablets and presence of plasticizers\(^6\). Inter and intra-subject variability, electrolyte concentration and transit time are some of the key variables impacting success through this route. In spite of these limitations, pH-based systems are commercially available for mesalazine (5 ASA) and budesonide for the treatment of ulcerative colitis and crohn’s disease, respectively.

**Table 4:** Enteric polymers used in the development of modified release formulations for CDDS

<table>
<thead>
<tr>
<th>Enteric polymers</th>
<th>Optimum pH for dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvinyl acetate phthalate (PVAP)</td>
<td>5.0</td>
</tr>
<tr>
<td>Methacrylic acid copolymer, Type A</td>
<td>≥6.0</td>
</tr>
<tr>
<td>Eudragit F530D</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Hydroxypropylmethylcellulose phthalate (HPMC)</td>
<td>≥5.5</td>
</tr>
<tr>
<td>Methacrylie acid copolymer, Type C (Eudragit L100-55)</td>
<td>&gt;6.0</td>
</tr>
<tr>
<td>Methacrylic acid copolymer, dispersion (Eudragit L30D-55)</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Cellulose acetate trimelitate (CAT)</td>
<td>5.5</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose acetate succinate (HPMCAS)</td>
<td>≥6.0</td>
</tr>
<tr>
<td>Shellac (MarCoat 125 &amp; 125N)</td>
<td>7.0</td>
</tr>
<tr>
<td>Methacrylic acid copolymer, Type B</td>
<td>≥7.0</td>
</tr>
</tbody>
</table>

In general the amount of coating required depends upon the solubility characteristics (solubility, dose/solubility ratio) of the drug, desired release profile and surface area of the formulation, and composition of the coating solution/dispersion. Coating approach is one of the simplest formulation available for colon-specific delivery. It also offers significant advantage in terms of cost and ease of manufacture\(^8\). From formulation standpoint, coated dosage forms may be either single-unit system or a multi-particulate system and each of these may be a single layer product or a multi-layer product.

In case of single layered products, the coating may be composed of a single enteric polymer that has a pH-dependent solubility or a mixture of two polymers one of which is pH-dependent while other is pH independent. On the other hand, in case of multilayer products, the coating is applied in successive layers which could be either based on two enteric polymers that have different pH-dependent solubility profiles, or two polymers one of which is enteric while other has a pH independent solubility but permeable to intestinal fluids. In either case, the coating can be applied to a wide variety of solid core formulations such as tablets, capsules, minitablets, pellets or granules. When coated pellets or granules are filled into a gelatin capsule or compressed together with conventional excipients in the form of tablets, the formulation is regarded as multi-particulate dosage form. The tablets or capsules coated pellets or granules can be further coated with a suitable enteric polymer which may be same or different than that used for coating of pellets or granules\(^12\). Modified-release formulations that are based on the combination of a pH-dependent and pH-independent polymer are described in a European patent assigned to aktiebolaget hassle. The approach involves coating of an active ingredient (e.g., mesalazine) with a mixture of an anionic acrylic polymer soluble just at pH 5.5 (e.g., eudragit L) and a cationic acrylic polymer insoluble in water (e.g., eudragit RS or RL)\(^12\). The quantities of an anionic acrylic polymer can range from 10 to85% while that of pH independent polymers may vary from 15 to 90%. The blending with one or more polymers having a pH independent solubility thus prevents the active ingredient from being released too rapidly, once the soluble polymer has reached the optimum pH of solubilisation\(^8\).

**USES**

**a. Local actions**

1) Ulcerative colitis.
2) Chron’s disease.
3) Irritable bowel syndrome.
4) Metastatic human colon cancer.

**b. Systemic actions**

1) Molecules degraded/poorly absorbed from upper GIT such as peptides and proteins are better absorbed from colon.
2) For achieving chemotherapy for diseases that are sensitive to cardiac rhythm such as asthma, angina, arthritis\(^25\).
ADVANTAGES AND DISADVANTAGES

Advantages

i. Patient compliance the treatment efficacy.
ii. Useful in treatment of ulcerative colitis, chron’s disease, irritable bowel syndrome and carcinomas.
iii. Low dose is required, so less side effects.
iv. Used for local and systemic action.
v. Gastric irritation can be avoided.

Disadvantage

i. There is less fluid in colon than in small intestine and hence dissolution is a major problem for water soluble drugs.
ii. Binding of drug to dietary residues, intestinal secretions etc reduce concentration of free drugs.
iii. Some microflora may degrade the drug.
iv. Small luminal surface area and relative tightness of tight junctions in colon, delay the systemic absorption.
v. Onset of action is slow.

CONCLUSION

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. Drug targeting to the diseased colon is advantageous in reducing the systemic side effects, lowering dose of a 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. All the approaches of colon drug delivery provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. 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, makes the reliability, delivery efficiency of formulation and targeting to colon complicated.

In summary two controlled release mechanism, i.e, time and pH-dependent, could achieve colonic specific drug delivery following oral administration. In addition, both CDDS were relatively in expensive and easy to be manufactured using conventional pharmaceutical coating technique, and provided the promising candidates for specifically delivering drug to targeted colon region, in particular for DS and 5-ASA in this study, respectively.

ABBREVIATIONS

Colonic drug delivery system (CDDS); example (e.g); gastrointestinal tract (GIT); that is (i.e.); kilogram (kg); milligram (mg).


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