MANTECH Publications

Journal of Pharmaceutical Analysis and Drug Research
Volume 1, Issue 1, January-April, 2019

A Review-Targeted Delivery of Drugs into the Lower GI Tract

Lodhi Devendra Singh*, Dr.KuldeepGanj**, Pradeep Patra***

Assistant Professor, Principal**, Associate Professor****

Department of Pharmacy

Sagar Institute of Pharmacy and Technology (Siptec)[, **], SOP, SSSVTMS[***]*

Corresponding author's email id:*devendralodhi86@gmail.com*

Abstract

Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). 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 (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancerother potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction.

Keywords: -*Prodrug approaches, Azo bond conjugate, Glycoside conjugation Pulsincap diverticulitis*

INTRODUCTION

Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). 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 (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction[1,2].

Advantages of colon targeting drug delivery system over conventional drug delivery[3,4]

Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.

- Local treatment has the advantage of requiring smaller drug quantities.

- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Possibly leading to a reduced incidence of side effects and drug interactions.
- The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability.
- Reduce gastric irritation caused by many drugs.
- Bypass initial first pass metabolism.
- Improve patient compliance.
- Targeted drug delivery system.
- It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
- It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin,growth hormones, can be given through this route.

Limitations of colon targeting drug delivery system[4]

- Multiple manufacturing steps.
- Incomplete release of drug.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in- vitro.

Colon anatomy[5]

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 to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. 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 1

Table 1:Parts of Colon

S.NO	Large Intestine	Length(cm)
1	Cecum	6-9
2	Ascending colon	20-25
3	Descending colon	10-15
4	Transverse colon	40-45
5	Sigmoid colRectum	35- 40
6	Anal canal	12-3

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[6]. The human intestine and colon were shown in Figure1 and Figure 2 respectively.

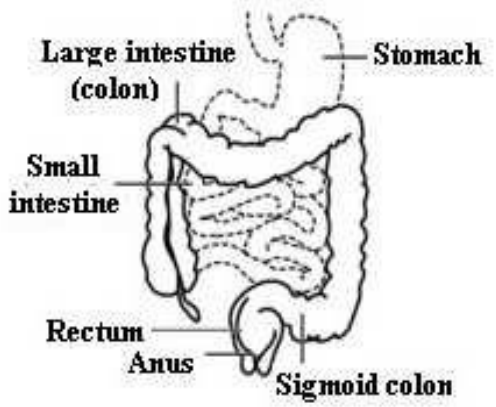

Figure:-1 Structure of human intestine

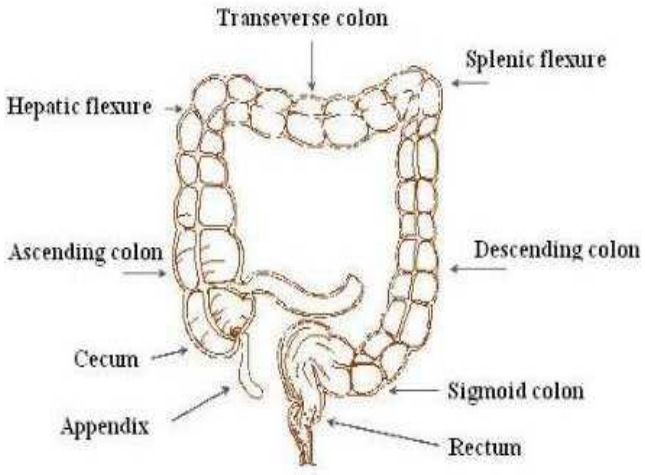

Figure:-2 Structure of colon

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen[2]. The absorptive capacity is very high, each about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed. On average, it has been estimated that colon contains only about 220 gm of wet material equivalent to just 35 gm of dry matter. The majority of this dry matter is bacteria. The colon tissue containing the villi, lymph, muscle, nerves, and vessels

Colonic micro flora

A large number of anaerobic and aerobic bacteria are present the entire length of the human GI tract. Over 400 distinct bacterial species have been found, 20- 30% of which are of the genus bactericides [6]. The upper region of the GIT has a very small number of bacteria and predominantly consists of gram positive facultative bacteria. The rate of microbial growth is greatest in the proximal areas because of high concentration of energy source. The metabolic activity of microflora can be modified by various factors such as age, GI disease, and intake of drug and fermentation of dietary residues.

1. pH differences in the colon

On entry in to the colon, the pH dropped to 6.4 ± 0.5. The pH in the mid colon was found to be 6.6 ± 1 and in the left colon, 7.0 ± 1.

2. Gastrointestinal transit

Gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and on the properties of the dosage form such as size and density. The transit times of dosage forms in tract are shown in Table 2

Table 2: Gastrointestinal Transit time of contents

Organ	**Transit Time (hr)**
Stomach	<1(fasting) >3(fed)
Small intestine	3-4
Large intestine	20-30

Diseases affecting colonic transit have important implications for drug delivery, diarrhea increases colonic transit and constipation decreases it. The digestive motility pattern takes place when food is present in the stomach. It is said by regular, frequent contractions (about 4-

5/min.) which affect the mixing intestinal contents and moving them towards the colon in short segments and lasts as long as food remains present in the stomach. The most frequent movements seen in the colon are very slow segmenting movements that typically occurs every 30 minutes [7]

Colonic diseases

1. Crohn's Diseases
2. Ulcerative Colitis
3. Diversional Colitis
4. Ischemic Colitis
5. Diverticular Inflammatory Bowel Disease
6. Colon Cancer
7. Lymphoma of the Colon

Inflammatory Bowel Disease

The cause of inflammatory bowel disease is multi-factoral and it is due to the inflammatory responses, genetic factors such as multiple genetic factors, candidate genes, chromosome location, etc., infectious agents like Escherichia coli, Measles virus, Cytomegalovirus, etc., dietary factors such as saturated fats, milk products, allergic foods etc. It is a general term that has the following two diseases,

1. Ulcerative colitis
2. Crohn's disease

1. Ulcerative colitis occurs only in the large intestine. Ulcers form in the inner lining of the intestine, or mucosa, of the colon or rectum, often resulting in diarrhea, blood, and pus. The inflammation is usually very rigorous in the sigmoid and rectum and usually reduces in the colon.

2. Crohn's disease: Crohn's disease, also called regional enteritis, is a chronic inflammation of the intestines which is usually confined to the terminal portion of the small intestine, the ileum. Ulcerative colitis is a common inflammation of the colon, or large intestine. These diseases and other inflammatory bowel disease have been linked with an increased risk of colorectal cancer.

3. Diverticular disease "diverticulosis" and "diverticular disease" are used to describe the presence of uninflamed diverticula. Diverticular disease of the colon is also a relatively common cause of acute lower gastrointestinal bleeding and is the diagnosis in 23% of patients who present with acute symptoms.[8] The term "diverticulitis" indicates the inflammation of a diverticulum or diverticula, which is

commonly accompanied by gross or microscopical perforation.

APPROACHES FOR COLONIC DRUG DELIVERY

Covalent Linkage of Drug with Carrier

1. Prodrug approaches[9]

Prodrug is a pharmacologically inactive derivative of a parent molecule that requires enzymatic transformation in the biological environment to release the active drug at the target site. This approach involves covalent linkage between the drug and its carrier in such a manner that upon oral administration the moiety remains intact in the stomach and small intestine, and after reached in the colon, enzymatic cleavage regenerate the drug.

a) Azo bond conjugate:

These azo compounds are extensively metabolized by the intestinal bacteria, both by intracellular enzymatic component and extracellular reduction. The use of these azo compounds for colon-targeting has been in the form of hydrogels as a coating material for coating the drug cores and as prodrug. In the latter approach the drug is attached via an azo bond to a carrier[10]. This azo bond is stable in the upper GIT and is cleaved in the colon by the azo-reductases produced by the microflora.Sulphasalazine, used for the treatment of IBD has an azo bond between 5-ASA and sulphapyridine (SP). In the colon, the azoreductases cleave the azo bond releasing the drug, 5-ASA and the carrier SP[10]. (Figure 3)

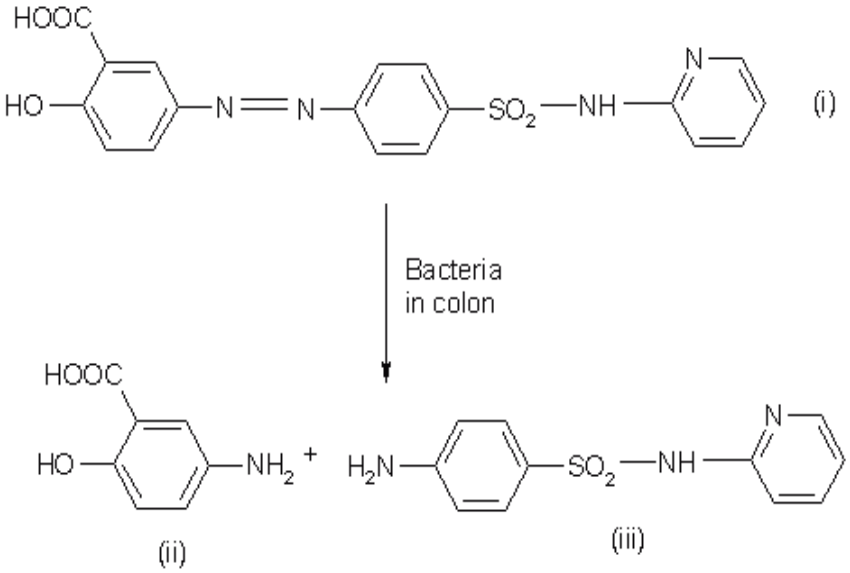

Figure: - 3 Hydrolysis of Sulphasalazine (i) into 5-aminosalicylic acid (ii) &sulfapyridine (iii)

b) Glycoside conjugation:

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Certain drugs can be conjugated to different sugar moieties to form glycosides. The drug part forms the aglycone and is linked to the sugar part, which forms the glycone part of the glycoside. Because they are bulky and hydrophilic, these glycosides do not penetrate the biological membranes upon ingestion. They breakdown upon action of glycosidase, releasing the drug part from the sugar.The presence of glycosidase activity in the small intestine could pose a problem in delivery of these conjugates to the large bowel, because some hydrolysis of the conjugate can be expected in the small intestine. However, the small intestinal transit time, when compared to the large intestinal transit time, is short, and moreover, considering the time required for the hydrolysis of glycosidic bond, these conjugates can be expected to be good colon specific drug carriers. The major glycosidase enzymes produced by the intestinal microflora are β -D-galactosidase, α -L-arabinofuranosidase, β -D-xylopyranosidase, and β –Dglucosidase. These glycosidase enzymes are located at the brush border and hence are accessible to substrate easily.Example: lucosides, galactosides, and cellobiosides of dexamethasone, prednisolone, hydrocortisone, and fludrocortisone. Daxamethasone-21-β-glucoside, Prednisolone-21-β-glucoside.

c) Glucoronide conjugates [11]:

Bacteria of the lower GIT secrete b-glucuronidase and can deglucuronidate a variety of drugs in the intestine. Thus, the deglucuronidation process results in the release of the active drug again and enables its reabsorption. Example: Opiates, when taken for the relief of pain, cause severe constipation by inhibiting GIT motility and secretions. Narcotic antagonists, when given as antidotes for GIT side effects, immediately relieve constipation but precipitate acute withdrawal. This is because these narcotic antagonists are not selective and they not only affect the GIT activity, but also the central nervous system (CNS). A novel approach would be to target these antagonists to the lower bowel so that they are not absorbed systemically. With this purpose, naloxone and nalmefene glucuronide prodrugs were prepared to target these drugs to the colon. When given orally to morphine dependent rats these prodrugs showed increased GIT motility and secretion in the large bowel results in a diarrhea and The resultant

diarrhea flushed out the drug/prodrug from the colon thereby preventing the systemic absorption of the antagonist, which in-turn caused absence of withdrawal symptoms.Budesonide-b-glucuronide prodrug also found to be superior to budesonide itself for the treatment of colitis in the rat.

d) Cyclodextrinconjugates

Cyclodextrins are cyclic oligosaccharides consisted of six to eight glucose units through -1,4 glucosidic bonds and have been utilized to improve certain properties of drugs such as solubility, stability and bioavailability.The interior of these molecules is relatively lipophilic and the exterior relatively hydrophilic, they tend to form inclusion complexes with various drug molecules.They are known to be barely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine however, Colonic bacteria are capable of degrading cyclodextrins for carbon source by stimulating cyclodextranase activity. They are fermented by the colonic microflora to form small saccharides that are then absorbed.This susceptibility to degradation specifically by colonic micro flora together with their property to form inclusion complexes with various drugs makes them particularly useful in carrying drug moieties to the colon.The a- and b-cyclodextrins are practically resistant to gastric acid, salivary, and pancreatic amylases. A clinical study has shown clear evidence that b-cyclodextrin is poorly digested in the small intestine but is almost completely degraded by the colonic microflora.

e) Dextran conjugates[12]:

Dextrans are polysaccharides of bacterial origin where the monosaccharides are joined to each other by glycoside linkages. These linkages are hydrolyzed by moulds, bacteria, and mammalian cells.The enzyme responsible for the hydrolysis of these linkages is dextranase. The dextranase activity is almost absent in the upper GIT, whereas high dextranase activity is shown by anaerobic gram-negative bacteria, especially the Bacteroides, which are present in a concentration as high as 1011 per gram in colon. This led to the use of dextran as carriers for drug molecules to the colon[13].In the colon, dextran's glycosidic bonds are hydrolyzed by dextranases to give shorter prodrug oligomers, which are further split by the colonic esterases to release the drug free in the lumen of the colon. Dextran prodrug approach can be used for colon-specific delivery of drugs containing a carboxylic

acid function (−COOH).NASIDS ware directly coupled to dextran by using carboxylic groups of drugs. Example is Naproxen-dextran conjugate. Glucocorticoids do not possess −COOH group so these are linked to dextran using spacer molecule. e.g. glucocorticoid-dextran conjugates.

f) Amino acid conjugation:

Due to the hydrophilic nature of polar groups like -NH2 and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins.Increase in hydrophilicity and chain length of carrier amino acid; decrease the permeability of amino acids and proteins. So the amino acid conjugate show more enzymatic specificity for hydrolysis by colonic enzyme[14].

g) Polymeric prodrugs[15]:

Newer approaches are aimed at use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers are used for this purpose.Subsynthetic polymers have used to form polymeric prodrug with azo linkage between the polymer and drug moiety

Approaches to deliver intact molecule to colon:

1. pH dependent approach[16]:

This approach utilizes the existence of pH gradient in the git that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0).By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site. The most commonly used pH dependent polymers are derivatives of

a)Coating of the drug core with pH sensitive polymers:

The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.The drug core includes tablets, capsules, pellets, granules, microparticles or nanoparticles.The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The polymers used for colon targeting, however, should be able to withstand the lower pH values of the stomach and of the proximal part of the small intestine and also be able to disintegrate at the neutral of

slightly alkaline pH of the terminal ileum and preferably at the ileocecal junction.The majority of enteric and colon targeted delivery systems are based on the coating of tablets or pellets, which are filled into conventional hard gelatin capsules.The problem with this approach is that the intestinal pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter- and intraindividual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the large intestine Eudragit-L dissolves at a pH level above 5.6 and is used for enteric coating, whereas Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0(attributable to the presence of higher amounts of esterified groups in relation to carboxylic groups), which results in premature drug release from the system. Problem of premature drug release can be overcome by the use of Eudragit FS.

Acrylic acid and acidic environment of the stomach and to undergo a lag time of predetermined span of time, after cellulose.

Table 3.Various pH dependent coating polymers

S no.	**Polymer**	**Threshold pH**
1.	Eudragit L 100	6.0
2.	Eudragit S 100	7.0
3.	Eudragit® L-30D	5.6
4.	Eudragit® FS 30D	6.8
5.	Hydroxypropylmethylcellulose phthalate 50	5.2
6.	Hydroxypropylmethylcellulose phthalate 55	5.4
7.	Cellulose acetate trimellate	4.8

b) Embedding in pH-sensitive matrices:

The drug molecules are embedded in the polymer matrix. Extrusion spheronization technique can be used to prepare uniform-size sturdy pellets for colon targeted drug delivery when it is not possible to obtain mechanically strong granules by other methods. Excipients had a significant impact on the physical characteristics of the pellets. Eudragit S100 as a pH sensitive matrix base in the pellets increased the pellet size and influenced pellet roundness.

Citric acid promoted the pelletization process resulting in a narrower area distribution. However, EudragitS100 could not cause statistically significant delay in the drug release at lower pH. An example of this system shown in Figure 4 (Eudracol)

Time dependent delivery:

It is also known as pulsatile release, delayed or sigmoidal release system. This approach is based on the principle of delaying the release of the drug until it enters into the colon. Although gastric emptying tends to be highly variable, small intestinal transit time is relatively constant or little bit variation can be observed. The strategy in designing timed-released systems is to resist the release of drug take place.The lag time in this case is the time mouth to colon. A lag-time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered.

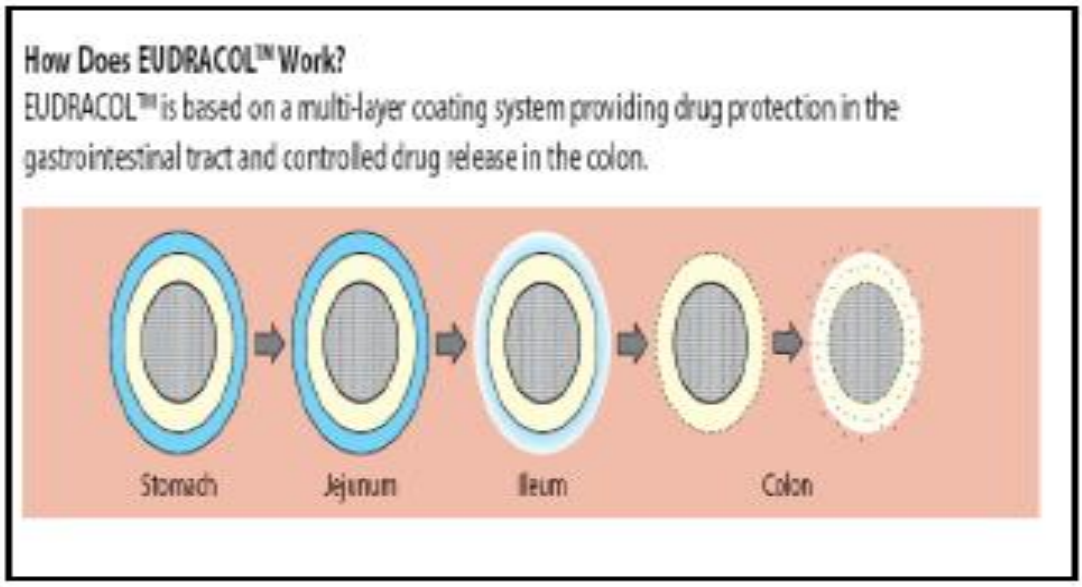

Figure 4 Designs and Working of Eudracol TM

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms.

This system has some disadvantages as follows:

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.

- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.

- Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea and the ulcerative colitis. Therefore time dependent systems are not ideal to deliver drugs to colon specifically for the treatment of colon related diseases. Appropriate integration of pH sensitive and time release functions into a single dosage form may improve requires to transit from the site specificity of drug delivery to the colon.

a) Pulsincap

The first formulation introduced based on this principle was Pulsincap® developed by R.R.Scherer International Corporation, Michigan, US. It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When the capsule enters the small intestine the enteric coating dissolves and the hydrogel plug starts to swell. The length of the plug and its point of insertion into the capsule controlled the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrates. The plug material consists of insoluble but permeable and swell able polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (eg, pectin).

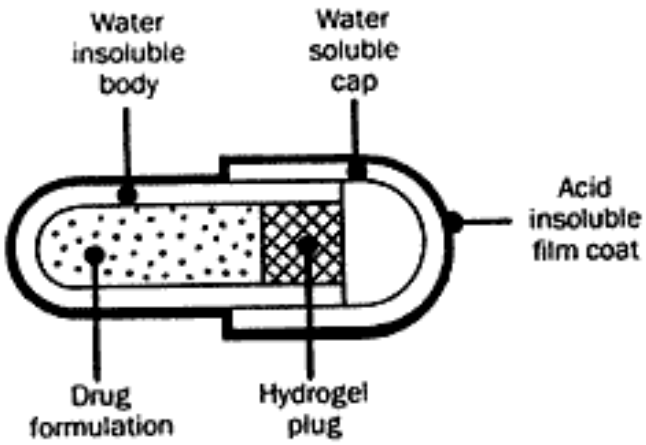

Figure 5.Design of Pulsincap system

b) Colon-Targeted Delivery Capsule based on pH sensitivity and time-release principles: The system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent together with the drug substance. This capsule is then coated with a three-layered film consisting of an acid-soluble layer, a hydrophilic layer, and an enteric layer (Figure 6). After ingestion of the capsule, these layers prevent drug release until the environmental pH inside the capsule decreases by dissolution of the organic acid, upon which the enclosed drug is quickly released. Therefore, the onset time of drug release is controlled by the thickness of the acid-soluble layer.

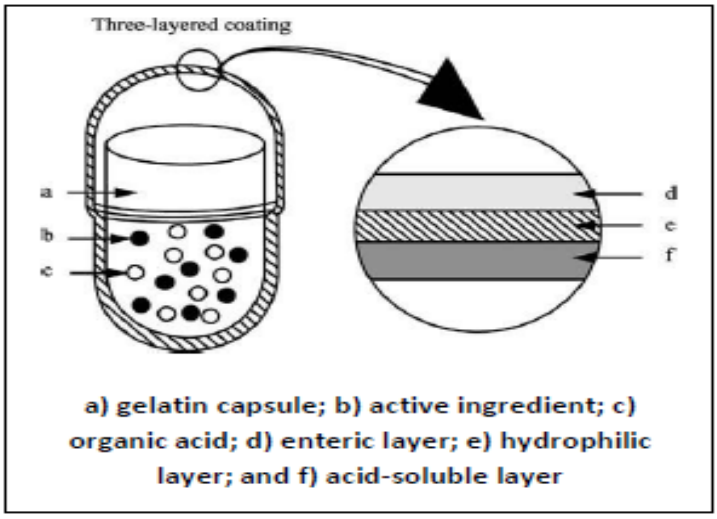

Figure 6 Design of the colon targeted delivery capsule

DIVERTICULITIS

Diverticulum:

A sac-like protrusion of mucosa through the muscular colonic wall [17].Protrusion occurs in weak areas of the bowel wall through which blood vessels can penetrate. Typically 5–10 mm in size. Diverticula are really pseudodiverticular (false diverticula), as they contain only mucosa and submucosa covered by serosa. Diverticular disease consists of: Diverticulosis: the presence of diverticula within the colon • Diverticulitis: inflammation of a diverticulum Diverticular bleeding.

Pathogenesis

Diverticulitis refers to a spectrum of diverticular disease ranging from subclinical inflammation to generalized peritonitis. The pathology of diverticulitis is characterized by inflammation and focal necrosis of diverticula leading to micro- or macroscopic perforation of a diverticulum. Most small perforations are walled off, although some will lead to abscess or fistula formation. The inciting agent of the inflammation was earlier thought to be fecoliths that obstructed diverticular lumens; this, however, turns out to be rare. The main culprit seems to be inspissated food that leads to mucus secretion and eventual bacterial overgrowth within the diverticulum.

Symptoms

The classic presentation of diverticulitis in the western world includes left lower quadrant abdominal pain and tenderness, constipation, fever and leucocytosis. However, the clinical features can be quite variable. Approximately 85% of diverticulitis involves the sigmoid ⁄ descending colon. Seventy percent of patients present with left lower quadrant pain and 25–50% of patients will report having had previous episodes of diverticulitis. Although constipation is present in 50% of patients, 25% to 35% of patients may present with diarrhoea, 20% to 62% may have nausea and vomiting and 10% to 15% may describe urinary symptoms.[18] Abdominal tenderness is present in most patients, and approximately 20% will have a tender mass palpableon exam.[19] Low-grade fever and leucocytosis are also characteristic, but 45% of patients will have a normal white blood cell count.[20] The presentation is particularly apt to be atypical among patients with conditions such as HIV infection, organ transplantation or cancer, in which immune suppression is common[.21,22] Not surprisingly, given the variable

presentation of diverticulitis and the spatial relationship of the colon to other intra-abdominal organs, the differential diagnosis for diverticulitis is broad. Potential diagnostic considerations might include appendicitis, Crohn's disease, colon cancer, ischaemic colitis, pseudomembranous colitis, complicated ulcer disease, ovarian cyst or torsion, or ectopic pregnancy. Nonetheless, the diagnosis is often relatively clear among those patients presenting with typical features.

Diagnosis

The diagnosis of diverticulitis is usually suggested by history and clinical exam. Various adjunctive tests, such as abdominal and chest x-ray, compression ultrasonography and single contrast barium enema have been and are used, although enema examinations are not much used anymore. Increasingly, computed tomography (CT) scans are the test of choice to confirm a clinical suspicion of diverticulitis. The literature has reported excellent test performance characteristics for CT scans, with sensitivity as high as 97% and specificity of up to 100%.[23] Findings on CT scans include soft tissue density in pericolic fat (present in 98%), the presence of colonic diverticula (present in 84%), bowel wall thickening greater than 4 mm (present in 70%), phlegmon and pericolic fluid (present in 35%)[24,25] However, CT findings alone are insufficient to exclude cancer in approximately 10% of cases.[26] Therefore, patients who have not had a colonoscopy yet should have one after resolution of the disease. CT has additional advantages of permitting classification into mild and severe categories, which may aid in predicting success of conservative therapy[27] and in selecting patients for surgery.[28,29] Diverticulitis may be complicated by abscess and fistula formation, peritonitis, or obstruction. CT may help differentiate abscesses that require drainage versus those that can be managed conservative and that behave like uncomplicated diverticulitis; the suggested size cut-off for such a distinction is 5 cm, with smaller abscesses generally responding to medical treatment without drainage.

Treatment

The treatment of diverticulitis depends on the severity and extent of disease. Recommendations are available from some of the professional societies, such as the American College of Gastroenterology and the American Society of Colon and Rectal Surgeons. Many other countries conform themselves to these general

guidelines with certain exceptions. Patients (70% to 100%) with simple, uncomplicated diverticulitis will improve with conservative measures. Bed rest, only clear liquids or total dietary restriction are the first step. Antibiotics are usually, but not always given. A recent study questions the routine use of antibiotics.[30] Antibiotics are generally chosen to cover Gram negative rods and anaerobes; for example a combination of ciprofloxacin and metronidazole.[31–33] CT scans may be useful for predicting success of conservative therapy.[29,34] A critical decision is whether to hospitalize a patient; this decision may rest on such features as disease severity, ability to tolerate oral intake, age, comorbidity and availability of adequate support systems at home. Complicated disease demands a more intense approach. One commonly used system to group patients according to severity of disease is the Hinchy classification[35] (Table 4). Patients with abscesses larger than 5 cm usually require CT-guided abscess drainage. In cases of peritonitis (Hinchy 3 and 4) emergency surgery is required, where cleansing of the peritoneal cavity and a sigmoid resection with an end-to-end procedure is preferable. Peritonitis carries a high mortality rate of approximately 6% if purulent and 35% if faecal. Fistula will be electively operated, as will patients with obstruction where malignancy cannot be excluded with colonoscopy.

Table 4 Hinchy classification of peritoneal contamination of diverticulitis

STAGE 1	Pericolicor mesenteric abscess
STAGE 2	Walled-off or pelvic absce
STAGE 3	Generalized purulent peritonitis
STAGE 4	Generalized fecal peritonitis

CONCLUSION

Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). 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 (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction.

REFERENCES

1. Abdul B, John B. Perspectives on Colonic Drug Delivery, Business Briefing, Pharmatech, 2003, 185–190.
2. Bajpai S K, Bajpai M, Dengree R. Chemically treated gelatin capsules for colon targeted drug delivery: a novel approach, J. Appl. Polym.Sci., 2003, 89, 2277–2282.
3. Patel A, Bhatt N, Patel KR, Patel NM, Patel MR. Colon targeted drug delivery system: a review system. Journal of Pharmaceutical Science and Bioscientific Research 2011; 01 Suppl 01: 37-49.
4. Singh N, Dr. Khanna RC. Colon targeted drug delivery systems – A Potential Approach. The Pharma Innovation 2012; 01 Suppl 01: 40-47.
5. Sarasija S, Hota A. Colon-specific drug delivery systems, Indian journal of pharmaceutical sciences, 62(1), 2000, 1-8.
6. Colonic Delivery Formulations, Recent Patents on Drug Delivery and Formulation, 1(1), 2007, 55.
7. Hamman et al, Drug Target Insights, 2, 2007, 80.
8. Machicado GA, Jensen DM. Acute and chronic management of lower gastrointestinal bleeding: cost-effective approaches.Gastroenterologist 1997;5:189-201.
9. Encyclopedia of Pharmaceutical Technology Volume 2.
10. Colonic Drug Delivery: Prodrug Approach Pharmaceutical Research, Vol. 18, No. 5, 2001.
11. Modified-Release Solid Formulations for Colonic Delivery Recent Patents on Drug Delivery & Formulation 2007, 1: 53-63.
12. Pharmaceutical approaches to colon targeted drug delivery systems JPPS, 2003; 6(1):33-66.
13. Platform Technologies for Colon Targeted Drug Delivery System: A Review Article Journal of Pharmacy Research 2010, 3(3): 543-547.

14. Primary and Novel Approaches for Colon Targeted Drug Delivery – A Review http://www.arjournals.org/ijdd.html

15. www.drug delivery technology.com

16. Advances in controlled drug delivery system- N.K.Jain.

17. Young-Fadok TM, Roberts PL, Spencer MP, Wolff BG. Colonic diverticular disease. CurrProbSurg 2000;37:457–514 (PMID: 10932672).

18. Ambrosetti P, Robert JH, Witzig JA, et al. Acute left colonic diverticulitis: a prospective analysis of 22 consecutive cases. Surgery 1994; 115: 546–50.

19. 19] Parks TG. Natural history of diverticular disease of the colon. ClinGastroenterol 1975; 4: 53–69.

20. 39 Rao PM, Rhea JT, Novellline RA, et al. Helical CT with only colonic contrast material for diagnosing diverticulitis: prospective evaluation of 150 patients. Am J Roentgenol 1998; 170: 1445–9.

21. Birnbaum BA, Balthazar EJ. CT of appendicitis and diverticulitis. RadiolClin North Am 1994; 32: 885–98.

22. Hulnick DH, Megibow AJ, Balthazar EJ, et al. Computed tomography in the evaluation of diverticulitis. Radiology 1984; 152: 491–5.

23. 42 Padidar AM, Jeffrey RB, Mindelzun RE, et al. Differentiating sigmoid diverticulitis from carcinoma on CT scans; mesenteric inflammation suggests diverticulitis. Am J Roentgenol 1994; 163: 81–3.

24. Ambrosetti P, Robert J, Witzig JA, et al. Prognostic factors from computed tomography in acute left colonic diverticulitis. Br J Surg 1992; 79: 117–9.

25. Ambrosetti P, Grossholz M, Becker C,et al. Computed tomography in acute left colonic diverticulitis. Br J Surg 1997; 84: 532–4.

26. Hachigian MP, Honickman S, Eisenstat TE, et al. Computed tomography in the initial management of acute left-sided diverticulitis. Dis Colon Rectum 1992; 35: 1123–9.

27. Gear JS, Ware A, Fursdon P, et al. Symptomless diverticular disease and intake of dietary fibre. Lancet 1979; 1: 511–4.

28. Thompson WG, Patel DG. Clinical picture of diverticular disease of the colon. ClinGastroenterol 1986; 15: 903–16.

29. Larson DM, Masters SS, Spiro HM. Medical and surgical therapy in diverticular disease: a comparative study. Gastroenterology 1976; 71: 734–7.

30. Hjern F, Josephson T, Altman D, etal.Conservative treatment of acute colonic diverticulitis: are antibiotics always mandatory? Scand J Gastroenterol 2007; 42: 41–7.

31. Detry R, Jamez J, Kartheuser A, et al. Acute localized diverticulitis: optimum management requires accurate staging. Int J Colorectal Dis 1992; 7: 38–42.

32. Chautems RC, Ambrosetti P, Ludwig A, Mermillod B, Morel P, Soravia C. Longtermfollow-up after first acute episode of sigmoid diverticulitis: is surgery mandatory?: a prospective study of 118 patients. Dis Colon Recutum 2002; 45: 962–6.

33. Wolff BG, Ready RL, MacCarty RL, et al. Influence of sigmoid resection on progressionof diverticular disease of the colon. Dis Colon Rectum 1984; 27: 645–7.

34. Benn PL, Wolff BG, llstrup DM. Level of anastomosis and recurrent colonic diverticulitis. Am J Surg 1986; 11: 269–71.

35. Hinchey EJ, Schaal PG, Richards GK.Treatment of perforated diverticular disease of the colon. AdvSurg 1978; 12: 85–109.

36. Asha Patel1*, Nilam Bhatt1, COLON TARGETED DRUG DELIVERY SYSTEM: A REVIEW SYSTEMJPSBR:

Volume 1, Issue 1: July-August 2011 (37-49).

37. TarakJayraj Mehta1*, Mr A.D.Patel2, NEED OF COLON SPECIFIC DRUG DELIVERY SYSTEM: REVIEW ON PRIMARY AND NOVEL APPROACHES VOV-3/ISSU 1/MARCH/014.

38. Anil K. Philip, Betty Philip Colon Targeted Drug Delivery Systems: A Review on Primary and Novel ApproachesVolume 25, Issue 2, April 2010.

39. P.S. SalveDevelopment and in vitro evaluation colon targeted drug delivery system using natural gums. Vol. 1: Issue 4, Pg 91-101.

40. K.V. Vinay Kumar,T. Sivakumar Colon targeting drug delivery system: A review on recent approachesInt J Pharm Biomed Sci 2011, 2(1), 11-19.

41. Anish A. Sheth, M.D, Walter Longo, Diverticular Disease and Diverticulitis (Am J Gastroenterol 2008;103:1550–1556)

42. Danny O. Jacobs, N Engl J Med 2007;357:2057-66.

43. M. M. SZOJDA, M. A. CUESTA Review article: management of diverticulitis Aliment PharmacolTher 26 (Suppl 2), 67–76.

44. Dr. T. Murphy Prof. R.H. Hunt Diverticular Disease World Gastroenterology Organisation,

45. 2007, 1-16.

46. Pramod Kumar Biswal, AnantKumarDESIGN AND EVOLUTION OF COLON SPECIFIC DRUG DELIVERY SYSTEM IJPCBS 2013, 3(1), 150-167 .

47. SunenaSethi, SL Harikumar REVIEW ON ADVANCES IN COLON TARGETED DRUGDELIVERY SYSTEM IJPSR, 2012; Vol. 3(9): 2989-3000.

48. Jitender Kumar Sharma, N. V. SatheeshMadhavDIFFERET APPROACHES TO COLON SPECIFIC DRUG DELIVERY: A

REVIEW Pharmacologyonline 2: 1341-1254 (2011).

49. Ankita Patel, DhruvitaPatel Novel Approaches for Colon Targeted Drug Delivery System ISSN 2229 – 6832.

50. Asija Rajesh, Chaudhari Bharat ORAL COLON TARGETED DRUG DELIVERYSYSTEM: A REVIEW ON CURRENT AND NOVEL PERSPECTIVES JPSI 1 (5), Sept – Oct 2012, 6-12.

51. SM Chickpetty, Raga Baswaraj STUDIES ON DEVELOPMENT OF NOVEL COMBINED TIME AND Ph dependent SOLVENTLESS COMPRESSION COATED DELIVERYSYSTEMS ISSN 0974-2441 FOR COLONIC DELIVERY OF DICLOFENAC SODIUM Vol.3 Issue 2, April-June 2010.

52. Nirav Patel, Jayvadan Patel Novel Pharmaceutical Approaches For Colon Specific Drug Delivery: An OverviewJournal of Pharmacy Research Vol.1.Issue 1. July-September 2008.

53. www.evonik.com

54. Alpar O et al. The compression properties of lactose. J Pharm Pharmacol 1970; Dec(Suppl.): VromansH et al. Studies on the tableting properties of lactose: the effect of initial particle size on binding properties and dehydration characteristics of a-lactose monohydrate. Rubinstein MH, ed. Pharmaceutical Technology:Tableting Technology., vol. 1: Chichester: Ellis Horwood, 1987; 31–42.

55. Thwaites PM et al. An investigation of the effect of high speed mixing on the mechanical and physical properties of direct compression lactose. Drug Dev Ind Pharm 1991; 17: 503–517.

56. Riepma KA et al. The effect of moisture sorption on the strength and internal surface area of lactose tablets. Int J Pharm 1992; 87: 149–159.C¸ elik M, Okutgen E. A feasibility study for the development of a prospective compaction functionality test and the establishment of a compaction

data bank. Drug Dev IndPharm 1993; 19: 2309–2334.

57. Lerk CF. Consolidation and compaction of lactose. Drug Dev Ind Pharm 1993; 19: 2359–2398.Otsuka M et al. Effect of humidity on solid-state isomerization of various kinds of lactose during grinding. J Pharm Pharmacol 1993; 45: 2–5.

58. Paronen P. Behaviour of some direct compression adjuvants during the tabletting process. STP Pharma 1986; 2: 682–688.

59. Zuurman K et al. The relationship between bulk density and compactibility of lactose
60. granulations. Int J Pharm 1994; 102: 1–9.

61. Patel H et al. The effect of excipients on the stability of levothroxine sodium pentahydrate tablets. Int J Pharm 2003; 264: 35–43.

62. Kirk RE, Othmer DF. Encyclopedia of Chemical Technology, 4th edn, vol. 1: New York: Wiley, 1995; 107.

63. Tugrul TK et al. Solid-state interaction of magnesium oxide and ibuprofen to form a salt. Pharm Res 1989; 6(9): 804–808.

64. Nada AH et al. In vitro adsorption of mepyramine maleate onto some adsorbents and antacids. Int J Pharm 1989; 53: 175–179.

65. Khalil SA et al. The in vitro adsorption of some antibiotics on antacids. Pharmazie 1976; 31: 105–109.

66. Naggar VF et al. The in-vitro adsorption of some antirheumatics on antacids. Pharmazie 1976; 31: 461–465.

67. Singh A, Mital H. Adsorption of atropine sulfate and hyoscyaminehydrobromide by various antacids. Acta Pharm Technol 1979; 25(3): 217–224.

68. Iwuagwu MA, Aloko KS. Adsorption of paracetamol and chloroquine phosphate by some antacids. J Pharm Pharmacol 1992; 44: 655–658.SPI Pharma Group.

Technical literature: Advantose 100 maltose, 2004.

69. Bowe KE et al. Crystalline maltose: a direct compression pharmaceutical excipient. Pharm TechnolEur 1998; 10(5): 40.

70. Mulderrig KB. Placebo evaluation of selected sugar-based excipients in pharmaceutical and nutraceutical tableting. Pharm Technol 2000;24(5): 34, 36, 38, 40, 42, 44.

71. Palevsky PM et al. Maltose-induced hyponatremia. Ann Intern Med 1993; 118(7): 526–528.

72. Allen LV. Featured excipient: capsule and tablet diluents. Int J Pharm Compound 2000; 4(4): 306–310324–325.

73. Yoshinari T et al. Improved compaction properties of mannitol after moisture induce polymorphic transition. Int J Pharm 2003; 258(1–2):121–131.

74. Debord B et al. Study of different crystalline forms of mannitol: comparative behaviour under compression. Drug Dev Ind Pharm 1987;13: 1533–1546.

75. Molokhia AM et al. Aging of tablets prepared by direct compression of bases with different moisture content. Drug Dev Ind Pharm 1987; 13:1933–1946.

76. Mendes RW et al. Wet granulation: a comparison of Manni-Tab and mannitol. Drug CosmetInd 1978; 122(3): 36, 38, 40, 44, 87–88.

77. Bouffard J et al. Influence of processing variables and physicochemical properties on the granulation mechanisms of mannitol in a fluid bed top spray granulator. Drug Dev Ind Pharm 2005; 31: 923–933.

78. Daoust RG, Lynch MJ. Mannitol in chewable tablets. Drug CosmetInd 1963; 93(1): 26–2888, 92, 128–129.

79. Cavatur RK et al. Crystallization behavior of mannitol in frozen aqueous solutions. Pharm Res 2002; 19: 894–900.