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Colon Targeted Drug Delivery System: A Review

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Abstract:

The oral route is considered to be most convenient for administration of drugs to patients. After oral administration of conventional dosage drug normally dissolves in the stomach fluid or intestinal fluid and is absorbed from these regions of the GIT. Absorption depends upon the physicochemical properties of the drug. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. Colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. Apart from retarding or targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of per-orally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidases such special delivery systems will have a fair chance to get their drug sufficiently absorbed after per oral application.

Keywords: Crohn's disease, carcinomas, bioavailability, vaccine delivery, oral application.

Introduction

Solid oral dosage forms are designed to release the drug in the upper regions of the gastrointestinal tract. Conditions in upper gastrointestinal tract are favorable to drug dissolution and absorption. Recently, greater emphasis has been placed on controlling the rate and/or site of drug release from oral formulations for the purpose of treatment efficacy. The colonic region of the gastrointestinal tract is one area that will be beneficial from the development and use of such modified release technologies. Some disorders like colon cancer and colitis need drug delivery to colon. In addition to local therapy, the colon can also be utilized as a site for the entry of drugs into the systemic circulation. Molecules

such as peptides and proteins that are degraded/poorly absorbed in the upper gut may be better absorbed from colon. Systemic absorption from the colon can also be used as a means of achieving chronotherapy for diseases that are sensitive to circadian rhythms[1-4].

Successful colonic drug delivery requires careful consideration of properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut. The administered drug must first dissolve in the lumenal fluids of the colon. Overall there is less free fluid in the colon than in the small intestine and hence, dissolution could be problematic for poorly water-soluble drugs. In such cases, the drug may need to be delivered in a presolubilised form or delivery should be directed to the proximal colon.

Modified release formulations are usually based on either a single unit (tablets and capsules) or multi-unit (pellets and granules) design. The biopharmaceutical performances of the two designs are very different. Multi-unit systems tend to exhibit more uniform gastrointestinal transit and absorption characteristics due to their small size and divided nature. Also the slower rate of passage of multi-units through the colon would be advantageous for colonic delivery. From the perspective of cost however, single unit systems are usually more cost-efficient to manufacture[5].

1.1. Factors that have stimulated colon targeted drug delivery

1) The development of new therapeutic agents for the treatment of colonic diseases.
2) The development of the colon specific delivery system to maximize the effectiveness of these drugs.
3) To produce oral delivery system for proteins and peptides.

ADVANTAGES

Drugs that are destroyed by the acidic environment of the stomach or metabolized by pancreatic enzymes are only slightly affected in the colon and can be absorbed from colon, so colon targeted drug delivery will be useful for these drugs. Sustained colonic delivery of the drugs can be useful in conditions in which diurnal rhythm is evident like nocturnal asthma, angina and arthritis. Treatment of ulcerative colitis, Crohn's disease, and colorectal cancer is more effective with the direct delivery of the drugs to the colon.

1.2. The features of the colon that make it suitable for targeting various drugs including proteins and peptides are

Its lower metabolic activities.
Longer residence time (20-30 hrs).
Responsiveness to absorption enhancers.
Targeting opportunities offered by colonic bacterial enzymes.
Trans mucosal and membrane potential difference that is significant in the absorption of the ionized and unionized drugs.

Possibility that bulk water absorption in this region for solvent drag[6].

1.3. Structure and Function of Colon[7].

The large intestine extends from the ileocecal junction to anus and is divided into colon, rectum, and anal canal respectively. The colon comprises of the cecum, ascending colon, hepatic flexure, transverse colon, descending colon, and sigmoid colon. Cecum is the widest part of the colon and is approximately 8.5 cm long. Its main function is 1) To absorb fluids and the salts that remain after the completion of intestinal digestion 2) To mix its contents with mucus for lubrication.

The ascending colon extends from the cecum to the hepatic flexure, which lies laterally to the right kidney and in contact with the inferior surface of the liver. The transverse colon hangs loosely between the hepatic and the splenic flexures. The splenic flexure is usually located higher than the hepatic flexure. The descending colon extends downwards from the splenic flexure to the pelvic brim. The colon then turns towards the midline to form the coiled sigmoid colon. Fig.1 shows anatomy of gastrointestinal tract.

A. Colonic Structure

The wall of the colon is divided into four layers: serosa, external muscular region (muscularis external), sub musoca, and the mucosa. The

squamous epithelium of the serosa is covered with adipose tissue, which forms distended fat pouches, known as appendices epiplocicae. These are larger, more numerous in the distal half of the colon and are one of its distinguishing feature.

B. Blood supply

The blood supply to the colon and upper rectum derives from the superior and inferior mesenteric arteries and venous return is via the superior and inferior mesenteric veins. These join the splenic vein as part of the portal system to the liver. Thus any drug absorbed from the colon and upper rectum is subjected to first pass elimination by the liver. Measurement of blood flow through the colon is difficult and reported values range from 8 to 75 ml/min. Blood flow through colon is considerably less than to the small intestine and the proximal colon receive a greater share of the blood flow than the more distal part.

C. Mucus

Mucus is produced by goblet cells and acts as a lubricant protecting the colon from abrasion from solid matter, particularly in distal colon. Mucins are degraded by colonic micro-organisms greater, in the distal colon and decreasing proximally towards the terminal ileum.

D. Colonic mucosa

The colonic mucosa is divided into three layers: the muscularis mucosa, the lamina propia and the epithelium.

E. Colonic environment

The colonic environment mainly differs from other parts of the gastrointestinal tract. The absorptive capacity of the colon is much less than that of the small intestine, mainly due to the reduced surface area. The mucosal surface of the colon is similar to that of the small intestine at birth, but rapidly changes by losing villi leaving a flat mucosa with deep crypts. As the gut ages, there is decrease in the number of non-goblet crypt cells.

F. Nervous and Hormonal control

The vagi to the proximal colon and pelvic nerves to the distal colon provide parasympathetic supply to the colon, whereas sympathetic supply is via the splanchnic and lumbar colonic nerves, which supply the proximal and distal colon respectively. Vagal stimulation initiates segmental contractions in the proximal colon whereas pelvic nerve stimulation causes tonic propulsions contractions in the distal colon. Stimulation of either the splanchnic or lumbar sympathetic nerves causes the colonic muscles to relax. A number of hormones influence colonic motility. Gastrin can intensify contractions and may decrease the evacuation time of the colon. Cholecystokinin has been proposed as a mediator of the lipid generated increase in recto sigmoid motor activity. Neurotensin is present in the myenteric plexus and mucosa of the colon and may also play a part in increase in colonic motility seen on ingestion of fat as the serum levels rise.

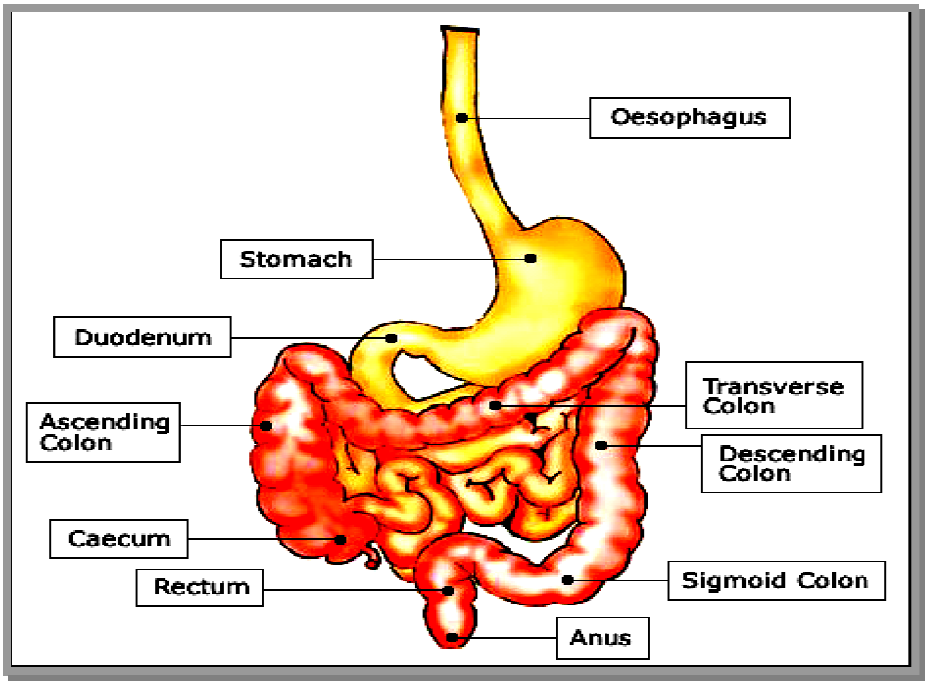
G. Water and electrolytes

The colon has very high absorptive capacity for water entering the colon; the residual water in the stools will be less than 200 ml. The colon is capable of absorbing up to 4 lit of water per day and can withstand an infusion rate of 6 ml/min before there is any increase in fecal water. The colon is responsible for the absorption of sodium and chloride ions in exchange of bicarbonate and potassium ions via water filled channels. A sodium potassium exchange pump system in the basolateral membrane then moves sodium against steep concentration (14 mM to 140 mM) and electrical (-30mV to +20mV) gradients into the intercellular space. In healthy individuals, approximately 10 mEq of potassium enters the colon each day and 5-15 mEq are lost in the feces during the same time period.

H. pH :-

Studies using a pH sensitive radio telemetry capsule in normal, ambulatory volunteers have shown that the mean pH in the colonic lumen is 6.4 ± 0.6 in the ascending colon, 6.6 ± 0.8 in the transverse colon and 7.0 ± 0.7 in the descending colon. Many factors such as disease, diet, pharmaceutical formulations or therapeutic agents may alter pH between the ascending and descending colon[8].

Fig no. 01: - Anatomy of Gastrointestinal Tract[7].



I. Colonic micro flora:

The gastrointestinal tract is sterile at birth, but colonization typically begins within a few hours of birth, starting in small intestine and increases gradually over the period of several days.

Slow movement of material through the colon allows a large microbial population to live there. The upper region of the GIT has a very small number of bacteria (10^3 CFU/ml). Under normal conditions, the micro flora of the proximal small bowel is similar to those of the stomach, the bacterial concentration being 10^3-10^4 CFU/ml. The lower and the distal ileum have a bacterial concentration of 10^6-10^7 CFU/ml. In the ileocecal sphincter, the bacterial concentration increases dramatically. The concentration of bacteria in the human colon is 10^{11}-10^{12}CFU/ml. The bacterial micro flora is predominantly anaerobic with some aerobic species and is composed of more than 400 strains, like of Bacteroides, Eubacteria, Clostridia, Enterococci, Enterobacteria, and Ruminoccous etc[9]. Approximately 30%of the dry weight of the feces consists of bacteria. Carbohydrates that enter the colon are fermented by the colonic bacteria, polysaccharidases and glycosidases enzymes to short chain fatty acids mainly acetic acid, propionic acid, and butyric acid; carbon dioxide (CO_2), hydrogen (H_2), methane (CH_4) and hydrogen disulfide (H_2S). For fermentation the microflora produces vast number of enzymes like β-glucoronidase, β-xylosidase, β-galactosidase, α-arabinosidase, Nitroreductase, azoreductase, deaminase, and urea dehydroxylase. Table 1. describes various enzymes produced by micro flora of colon.

1.4.1. Transit of Material into and through the colon

Wide ranges of colonic transit times must be taken into consideration during the design of drug delivery system. Table 2 describes anatomical and physiological characteristics of GI tract. Small intestine transit is surprisingly constant at 3 to 4 hrs and appears to be independent of both the dosage form and whether or not the subject is in the fasted or fed state. After the hepatic flexure the consolidation of fecal matter gradually increases the viscosity of the luminal content. This results in increasing difficulty of drug diffusion to the absorbing membrane. Only the ascending colon is sufficiently fluid to present a favorable environment of drug absorption. Absorption of even the most water-soluble drugs is reduced after the mid transverse colon, due to the lack of water. For

example Ciprofloxacin demonstrates a clear reduction in drug uptake with a more distal delivery. On rare occasions, drug absorption can be seen from the distal regions due to the drug affecting the fluidity of the contents of the transverse colon. Total time for the transit is influenced by number of factors such as diet, particular fiber diet, mobility, stress, disease and the drugs.

1.4.2. Drug absorption in the colon

Molecules that are degraded/poorly absorbed in the upper gut, such as peptides and proteins, may be better absorbed from the more benign environment of the colon. Systemic absorption from the colon can also be used as a means of achieving chronotherapy for diseases that are sensitive to circadian rhythms. Successful colonic drug delivery requires careful consideration of a number of factors, including the properties of the drug, the type of delivery system and its interaction with the healthy or diseased gut[10]. In such instances, the drug may need to be delivered in a presolubilised form, or delivery should be directed to the proximal colon, as a fluid gradient exists in the colon with more free water present in the proximal colon than in the distal colon. Apart from drug solubility, the stability of the drug in the colonic environment is also important[11].

1.5. Inflammatory Bowel Disease (IBD)[12]

Inflammatory bowel disease, or IBD, is a collective term encompassing related, but distinct, chronic inflammatory disorders of the gastrointestinal tract, such as Crohn's disease, ulcerative colitis (UC), indeterminate colitis, microscopic colitis and collagenous colitis. Crohn's disease and ulcerative colitis are the most common diseases. Another chronic disorder of the gastrointestinal tract is irritable bowel syndrome (IBS). For most patients, IBD and IBS are chronic conditions with symptoms lasting for months to years. Inflammatory bowel diseases such as ulcerative colitis and Crohn's disease are serious intestinal diseases that can ultimately lead to the surgical removal of the colon. It is most common in young adults, but can occur at any age. It is found worldwide, but it is most common in industrialized countries such as the United States, England, and Northern Europe. For example, IBD affects an estimated two million people in the United States alone.

1.5.1. Pathogenesis:

The exact causes of IBD and IBS are not yet understood. Common hypotheses include, for example, disorders of the immune system and actions of pro- inflammatory cytokines and selective activation of lymphocyte subsets,

Table 1: Drug metabolizing enzymes in the human colon that catalyze reductive reactions.

Enzymes	Microorganisms	Metabolic reaction catalyzed
Nitroreductase	*E.coli, Bacteroides*	Reduce aromatic and heterocyclic compounds
Azoreductase	*Clostridia spp., Lactobacilli, E.coli*	Reductive cleavage of azo compounds
N-Oxide reductase, Sulfoxide reductase	*E.coli*	Reduce N-Oxides and Sulfoxides
Hydrogenase	*Clostridia spp. Lactobacilli spp.*	Reduce carbonyl groups and aliphatic double bonds
Esterase and amidases	*E.coli, P.vulgaris, B.subtalis, B.mycoides*	Cleavage of ester or amidases of carboxylic acids
Glucosidase	*Clostridia, Eubacteria*	Cleavage of β-glycosidases of alcohols and phenols
Glucoronidase	*E.coli, A.aerogens*	Cleavage of β- glucoronidases of alcohols and phenols
Sulfatase	*Eubacteria,Clostridia, stretptococci.*	Cleavage of O-Sulfates and sulfamates

which perpetuate unrestrained activation of an inflammatory response in the intestine. Also it has been hypothesized that an intolerance to the normal flora (bacteria) in the gut leads to inflammation and resulting pathology.The pathogenesis of inflammatory bowel diseases is thought to be related, at least to a certain degree, to colonic bacterial microflora. A body of evidence from clinical and experimental observations indicates a role for endogenous digestive microflora in the pathogenesis of IBD. The distal ileum and the colon are the areas with highest luminal bacterial concentrations and represent the sites of inflammation in IBD. Also non-specific inflammation of the ileal reservoir that is the main post-surgical complication in patients with ulcerative colitis, who undergo pan-colectomy, occurs in presence of a bacterial overgrowth.

1.5.2. Ulcerative Colitis:

Ulcerative colitis is a chronic inflammation of the large intestine (colon).It is a disease that causes inflammation and sores, called ulcers, in the lining of the rectum and colon. Ulcers form at sites where inflammation has killed the cells that usually line the colon, then bleed and produce pus

Ulcerative colitis is closely related to another condition of inflammation of the intestines called Crohn's disease. Together, they are frequently referred to as inflammatory bowel disease (IBD).

Ulcerative colitis can occur in people of any age, but it usually starts between the ages of 15 and 30, and less frequently between 50 and 70 years of age. It affects men and women equally and appears to run in families, with reports of up to 20 percent of people with ulcerative colitis having a family member or relative with ulcerative colitis or Crohn's disease. A higher incidence of ulcerative colitis is seen in Whites and people of Jewish descent.

1.5.3. Symptoms of ulcerative colitis:

The most common symptoms of ulcerative colitis are abdominal pain and bloody diarrhea. Patients also may experience.

- Anemia
- Fatigue
- Weight loss
- Loss of appetite
- Rectal bleeding
- Loss of body fluids and nutrients
- Skin lesions
- Joint pain
- Growth failure (specifically in children)

Table 2: Anatomical and physiological characteristics of the gastrointestinal tract.

Sr. No	Region	Length (m)	Surface area (m^2)	pH	Residence Time	Micro-organisms. (CFU/ml.)
1	Oesophagus	0.3	02	6.8	>30 sec	Unknown
2	Stomach	0.2	0.2	1.8-2.5	1-5 hr	$\leq 10^2$
3	Duodenum	0.3	0.02	5-6.5	> 5 min	$\leq 10^2$
4	Jejunum	3	100	6.9	1-2 hr	$\leq 10^2$
5	Ileum	4	100	7.6	2-3 hr	$\leq 10^2$
6	Colon	1.5	3	5.5-7.8	15-48 hr	$\leq 10^{11}$

About half of the people diagnosed with ulcerative colitis have mild symptoms. Others suffer frequent fevers, bloody diarrhea, nausea, and severe abdominal cramps. Ulcerative colitis may also cause problems such as arthritis, inflammation of the eye, liver disease, and osteoporosis. It is not known why these problems occur outside the colon. These complications may be the result of inflammation triggered by the immune system. Some of these problems go away when the colitis is treated.

1.5.4. Pathogenesis:

Many theories exist about what causes ulcerative colitis. People with ulcerative colitis have abnormalities of the immune system, but doctors do not know whether these abnormalities are a cause or a result of the disease. The body's immune system is believed to react abnormally to the bacteria in the digestive tract.

Ulcerative colitis is not caused by emotional distress or sensitivity to certain foods or food products, but these factors may trigger symptoms in some people. The stress of living with ulcerative colitis may also contribute to a worsening of symptoms

Pro-inflammatory products of enteric bacteria like, chemotactic peptides, lipopolysaccharide and peptidoglycan-polysaccharide have a significant potential to trigger potent inflammatory responses that could play a contributing role in the extra-intestinal manifestations of IBD.

1.5.5. Diagnosis

Many tests are used to diagnose ulcerative colitis. A physical examination and medical history are usually the first step.

Blood tests may be done to check for anemia, which could indicate bleeding in the colon or rectum, or they may uncover a high white blood cell count, which is a sign of inflammation somewhere in the body.

A stool sample can also reveal white blood cells, whose presence indicates ulcerative colitis or inflammatory disease. In addition, a stool sample allows the doctor to detect bleeding or infection in the colon or rectum caused by bacteria, a virus, or parasites.

A colonoscopy or sigmoidoscopy are the most accurate methods for making a diagnosis of ulcerative colitis and ruling-out other possible conditions, such as Crohn's disease, diverticular disease, or colon cancer. For both tests, an endoscope—a long, flexible, lighted tube connected to a computer and TV monitor—is used to see the inside of the colon and rectum. Any inflammation, bleeding, or ulcers on the colon wall can be seen. Tissue biopsy confirms these findings. Sometimes X rays such as a barium enema or CT scans are also used to diagnose ulcerative colitis or its complications.

1.5.6. Treatment for ulcerative colitis[10]

Both medications and surgery have been used to treat ulcerative colitis. However, surgery is reserved for those with severe inflammation and life-threatening complications. There is no medication that can cure ulcerative colitis. Patients with ulcerative colitis will typically experience periods of relapse (worsening of inflammation) followed by periods of remission (resolution of inflammation) lasting months to years. During relapses, symptoms of abdominal pain, diarrhea, and rectal bleeding worsen. Remissions usually occur because of treatment with medications or surgery, but occasionally they occur spontaneously, that is, without any treatment.

1.5.7. Drugs for Colonic Delivery[13]

Drug delivery selectively to the colon through oral route is becoming increasingly popular for the treatment of large bowel disease and for systemic absorption of peptide and protein drugs. Inflammatory bowel diseases (IBD) such as Ulcerative colitis (UC) and Crohn's disease require selective local delivery of drugs to the colon. Colonic drug delivery can be achieved by oral or by rectal administration. Conventional rectal delivery forms (suppositories and enemas) are not always effective because of high variability is observed in the distribution of drugs administered by this route. Suppositories are effective in the rectum because of the confined spread and enema solution can only be

applied topically to treat disorders of the sigmoid and descending colon. Therefore, the oral route is preferred. Absorption and degradation is the major obstacle with the delivery of drugs by the oral route and must be overcome for successful colonic drug delivery.

The drugs used in IBD are Sulphasalazine, 5-Aminosalicylic acid[14,15,16], its prodrugs and steroids such as prednisolone and hydrocortisone. When these steroids are specifically delivered to the colon, they produce comparatively few and less intense adverse effects than when administered orally or intravenously. Irritable bowel syndrome is another disorder of the colon. Pinaverium bromide is a drug for the local treatment of irritable bowel syndrome. Advanced UC, if not treated may lead to colon cancer. In such cases, anticancer drugs like 5-Fluorouracil, Doxorubicin, and Nimustine are to be delivered specifically to the colon for an effective and safe therapy. The site-specific delivery of drugs for the treatment of infectious diseases such as amoebiasis (e.g. Metronidazole) would be very much useful in reducing the relapse of these diseases and for minimizing the side effects associated with the systemic absorption of these drugs[17].

With the explosion of new peptide and protein drugs through biotechnology, there has been an increasing interest in utilizing the colon as a site for systemic absorption of these drugs in view of the less hostile environment prevailing in the colon. However, there is significantly protease and peptidase enzyme activity within the colon, arising from the micro flora. Consequently, the stability of peptide and protein drugs within colon is likely to be poor and the opportunities for absorption are still relatively limited.

A variety of protein and peptide drugs like calcitonin, interferon, interleukins, erythropoietin, growth hormone and even insulin are being investigated for their systemic absorption using colon specific delivery. Most of the reports on the colonic absorption of proteins and peptides drugs are in animal models. Few reports exist in the literature on the colonic absorption of therapeutic macromolecules in man[18].

Besides peptide and protein drugs, the colon is a good site for the absorption of drugs that are not stable in the acidic environment of the stomach, cause gastric irritation (e.g. aspirin, iron supplements) or those degraded by small intestine enzymes. Nowadays, a number of drugs are available as sustained released or delayed release or time-release tablets and capsules for oral administration. The different categories of the drugs that are available in this form are anti-inflammatory, anti-hypertensive drugs etc. Unless these drugs have good absorption characteristics in the colon their intended use in the management of respective disorders through sustained release or time released formulations will be in question. This is due to the fact that most formulations are supposed to release their drug slowly over a period of 12 hrs, sometimes even 24hrs. The total residence time of these formulations in the stomach and small intestine will not be more than 5-6 hrs. If the drug is not having inherent absorption properties from the colon, it will be eliminated in the feces as it is. The drugs that are having good absorption properties from colon include theophylline, glibenclamide, oxprenolol diclofenac, ibuprofen, brompheniramine, isosorbide dinitrate, metoprolol, nifedipine etc, and hence can be investigated for the better bioavailability through colon specific drug delivery. However, furosemide, piretanide, bulflomedil, alcohol, cimetidine and hydrochlorthiazide are found poorly absorbed from colon[6].

1.6. Nomenclature for selection of dosage form[19].

A. Modified release dosage forms

Modified release dosage form is one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutics or convenience objectives not offered by conventional dosage forms such as solutions, suspensions and immediate release solid dosage forms.
Modified release dosage forms can be classified as delayed release and extended release dosage forms.
1. Delayed release dosage forms

A delayed release dosage form is one that releases drugs at a time other than promptly after administration.

2. Extended release dosage forms

An extended release dosage form is one that allows

at least a two fold reduction in dose frequency or significant increase in therapeutic performance as compare to that presented as a conventional dosage forms (e.g. as a solution or an immediate release solid dosage form). The terms controlled release, prolonged action and sustained release are used synonymously with extended release.

1.6.1. Approaches in Colon-specific drug delivery systems[20]

There are several ways in which drugs can be targeted on the colon when they are given by mouth. In time-dependent formulations the drug concerned is released during the period of gastrointestinal transit time. Formulations that contain pH-dependent polymers, in that release takes place on the change in pH which is higher in the terminal ileum and colon than in the upper parts of the gastrointestinal tract. The colon is also home to large number of bacteria of many kinds. Prodrugs and dosage forms from which drug release is triggered by the action of colonic bacterial enzymes have therefore been devised. By definition, an oral colonic delivery system should retard drug release in the stomach and small intestine but allow complete release in the colon. The fact that such a system will be exposed to a diverse range of gastrointestinal conditions on passage through the gut makes colonic delivery via the oral route a challenging proposition. Nevertheless, a variety of approaches have been used and systems have been developed for the purpose of achieving colonic targeting. These approaches are either drug-specific (prodrugs) or formulation-specific (coated or matrix preparations).

The most commonly used targeting mechanisms are:

- Drug release based on variation of pH
- Drug release based on gastrointestinal transit time
- Drug release based on the presence of colonic microflora
- Pressure-controlled drug-delivery systems

1.6.2. Drug release based on variation of pH[21]

In the stomach pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal part. From the ileum to the colon pH declines significantly. It is about 6.4 in the caecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6, and in the descending colon it goes up to 7.0. Use of pH-dependent polymers is based on these differences in pH levels. The polymers described as pH-dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. There are various problems with this approach, however. The pH in the gastrointestinal tract varies between and within individuals[21].

It is affected by diet and disease; for example, during acute stage of inflammatory bowel disease colonic pH has been has been found to be significantly lower than parts of the colon. Although a pH dependent polymer can protect a formulation in the stomach and proximal small intestine. Failure of enteric-coated dosage forms, especially single-unit dosage forms, because of lack of disintegration has been reported. The decline in pH from the end of the small intestine to the colon can also normal. In ulcerative colitis, pH values between 2.3 and 4.7 have been measured in the proximal result in problems. Lengthy lag times at the ileo-caecal junction or rapid transit through the ascending colon can also result in poor site-specificity of enteric-coated single-unit formulations. Eudragit™ products are pH-dependent methacrylic acid polymers containing carboxyl groups. Fig 2 gives structure of these polymers.

Eudragit™ S is soluble above pH 7 and Eudragit™ L above pH 6. Eudragit™ S coatings protect well against drug release in the upper parts of the gastrointestinal tract and have been used in preparing colon-specific formulations[19]. Eudragit™ S coatings have been used to target the anti-inflammatory drug 5-aminosalicylic acid (5-ASA) in single-unit formulations on the large intestine. Eudragit™ L coatings have been used in single-unit tablets to target 5-ASA on the colon in patients with ulcerative colitis or Crohn's disease. Eudragit™ S has been used in combination with another methacrylic acid copolymer, Eudragit™ L100-55, in colon-targeted systems to regulate drug delivery. Dissolution studies showed that drug release profiles from enteric-coated single-unit tablets could be altered in vitro by changing the ratios of the polymers, in the pH range 5.5 to 7.0.

Hydroxypropylmethylcellulose acetate succinate (HPMCAS) has been included in outer layers of single-unit press-coated tablets with a view to preventing drug release in the stomach and small intestine. In vitro dissolution studies suggested that such tablets could be useful as colon-specific formulations[23].

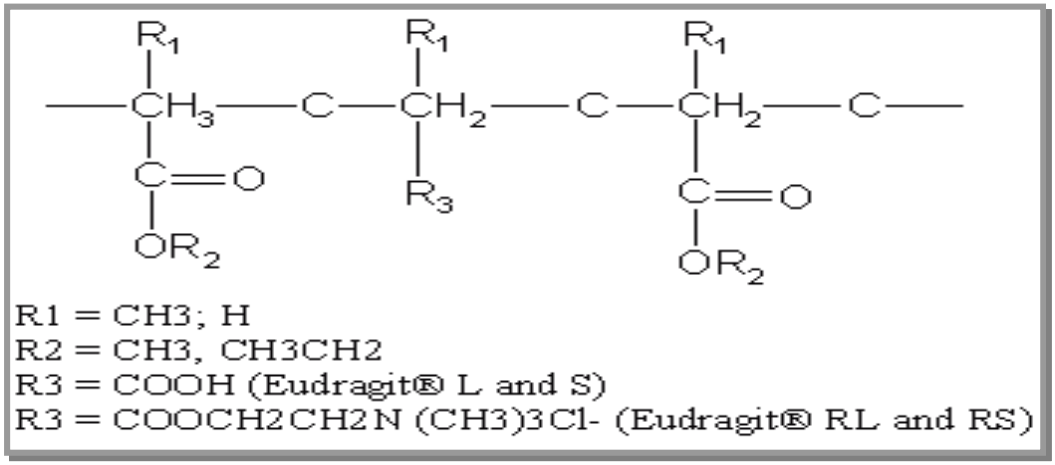
1.6.3. Drug release based on gastrointestinal transit time[8].

The transit time through the small intestine is independent of formulation. It has been found that both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine. Transit time through the small intestine is unaffected by particle size or density, or by the composition of meals.

Table 3: Threshold pH of commonly used polymers

Polymer	Threshold pH
Eudragit® L-100	6.0
Eudragit® S-100	7.0
Eudragit® L-30D	5.6
Eudragit® FS-30D	6.8
Eudragit® L-100-55	5.5
Poly vinyl acetate phthalate	5.0
Hydroxy propyl methylcellulose phthalate	4.5 - 4.8
Hydroxy propyl methylcellulose phthalate 50	5.2
Hydroxy propyl methylcellulose phthalate 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0

Figure 2. The number of esterified carboxyl group's that affects the pH level.



Because the time taken by formulations to leave the stomach varies greatly the time of arrival of a formulation in the colon cannot be accurately predicted. However, using systems that are protected in the stomach can minimize the effects of variation in gastric residence time, and drug release can be targeted on the colon by means of formulations that release the drug after gastric emptying. Such formulations pass through the stomach and small intestine and drug is then released at the end of the small intestine or beginning of the colon. Accordingly, formulations

that depend for drug release on transit time through the small intestine also depend on changes in pH in the gastrointestinal tract. Transit times through the colon that is lesser in patients with irritable bowel syndrome, diarrhea and ulcerative colitis.

Combinations of hydrophilic and hydrophobic polymers have been used as coatings for tablets that release drug from a core after a lag time. Time-controlled formulations have also been prepared using water insoluble ethylcellulose and swellable polymer (HPC) [24,18]. Each of the formulations consisted of a core, drug, swelling agent and a water-insoluble membrane. A drug delivery system (Pulsincap™), from which there is rapid drug release after a lag-time, has been developed to allow release of drug in the large intestine. The system involves an insoluble capsule body with a hydrogel plug. The plug is ejected from the capsule when it has swelled after a particular lag-time. A release profile is characterized by a period during which there is no release followed by rapid and complete drug release[25,26].

1.6.4. Drug release based on the presence of colonic microflora[27-30].

Both anaerobic and aerobic microorganisms inhabit the human gastrointestinal tract. In the small intestine the microflora is mainly aerobic, but in the large intestine it is anaerobic. About 400 bacterial species have been found in the colon, and some fungi. Most bacteria inhabit in the proximal areas of the large intestine, where energy sources are greatest. Carbohydrates arriving from the small intestine form the main source of nourishment for bacteria in the colon. Protease activity in the colon can result in cleavage of proteins and peptides. In the proximal colon the pH is lower than at the end of the small bowel because of the presence of short-chain fatty acids and other fermentation products. Diet can affect colonic pH[27].

The presence of colonic microflora has formed a basis for development of colon-specific drug delivery systems. Interest has focused primarily on azo reduction and hydrolysis of glycoside bonds. Prodrugs have been used in targeting drugs on the large intestine. Sulphasalazine is a colon-specific prodrug used in the treatment of ulcerative colitis. In the colon sulphasalazine is split by bacterial azoreduction into 5-ASA and sulphapyridine.

Olsalazine consists of two molecules of 5-ASA linked by an azo-bond. Ipsalatsine and balsalatsine are other 5-ASA containing prodrugs. Polymers and polyamides containing azo groups have been used to convey 5-ASA to the large intestine. Azo polymers have been used as colon specific film coatings[30]. Hydrogels containing azo-aromatic cross-links have been investigated in connection with site-specific drug delivery of peptide and protein drugs. In the low pH range of the stomach the gels have a low equilibrium degree of swelling and the drug is protected against digestion by enzymes, but at high pH levels they swell. So in the stomach a drug will be protected, but released in the colon, where cross-links become degraded[31]. Pectin is a polysaccharide, found in the cell walls of plants. It is totally degraded by colonic bacteria but is not digested in the upper gastrointestinal tract. One disadvantage of pectin is its solubility. This can however be adjusted by changing its degree of methoxylation, or by preparing calcium pectinate. The film-coating properties of pectin have been improved through use of ethylcellulose. Pectin has also been used with chitosan and HMPC[32,33,34].

Cross-linked guar gum has been used as a drug carrier in matrix tablets[35]. It was concluded that guar gum is suitable for preparation of colon-specific formulations and is particularly suitable as a carrier of drugs that are not very soluble in water. However, the guar gum formulations mentioned have only formed the subjects of in vitro dissolution studies and in vivo evaluation in rats. Dextran ester prodrugs have been investigated as means of transporting drugs to the colon. Chitosan is a high-molecular-weight polysaccharide that is degraded by colonic microflora. Insulin and 5-ASA have been administered to rats in enteric-coated chitosan capsules. A multiple-unit formulation containing chitosan and drug has also been prepared[34]. This formulation depended for drug delivery on both variations in gastrointestinal pH and the presence of colonic micro flora.

1.6.5. Pressure-controlled drug-delivery systems[26]

Gastrointestinal pressure has also been utilized to trigger drug release in the distal gut. The pressure, which is generated via muscular contractions of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration throughout the gastrointestinal tract. Systems have been

developed to resist the pressures of the upper gastrointestinal tract but rupture when come in contact with to the increasing pressure of the colon. Capsule shells fabricated from the water-insoluble polymer ethyl cellulose have been used for this purpose. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall. Proof of concept studies has been conducted in dogs and, to a limited extent, in humans. Although the results appear promising, it has not been proven firmly that rupture occurs in the colon.

1.7. In vitro and in vivo evaluation of colon specific drug-delivery systems[19]

In vitro dissolution testing is important in the development of solid dosage forms. The method used should simulate the environment to which the dosage form being developed will be exposed in the gastrointestinal tract. In the United States Pharmacopoeia (USP) dissolution procedures are described for conventional oral formulations, and for extended-release and delayed-release formulations (USP 23). In the case of enteric-coated formulations the test for delayed-release articles should be used. However, controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP[19] cannot wholly mimic in vivo conditions such as those relating to pH, environment and mixing forces. The conventional method involving dissolution in various buffers is useful for assessing the ability of an enteric-coating to prevent drug release in the stomach and small intestine. Dissolution studies of this kind can be used in relation to both time-release systems and formulations with enteric coatings. Dissolution tests relating to colon-specific drug delivery systems may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon-specific formulation in various media simulating pH conditions at various locations in the gastrointestinal tract. The media chosen can be pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.4 to simulate the ileal segment. Consecutive dissolution tests in different buffers for different periods of time can best simulate the transit of a formulation through the gastrointestinal tract.

1.8. Conclusions concerning colon-specific drug delivery methods

During the last decade many investigations have been carried out with the aim of discovering an ideal formulation for colon-specific drug delivery. Many approaches have been demonstrated. All have some disadvantages. The micro flora of the colon can split polymers. However, such enzymatic degradation is usually excessively slow. The bioavailability of drugs from such formulations can be low. In addition, little is known about the safety of the polymers and few have been accepted for use in relation to medicines. Most studies relating to biodegradable polymers have been carried out only in vitro or in laboratory animals.

Time-controlled formulations have also been investigated and developed in connection with targeting of drug delivery on the colon. Formulations of this kind need to be manufactured in such a way that they remain intact in the stomach, in the presence or absence of food. Manufacture of such formulations on an industrial scale is often complicated and expensive. Formulations involving enteric polymers that react to changes in gastrointestinal pH have been extensively used in connection with colon specific drug delivery. Enteric polymers have been shown to be safe, and have been accepted for use in drug products. The enteric polymers that have been used are soluble above pH 6 to 7. The pH at the end of the small intestine is about 7.5. It is therefore obvious that drug release from enteric-coated formulations can begin from the end of the small intestine.

pH levels also decline from the ileum to the colon; if an enteric-coated formulation is still intact after passage through the small intestine there may be a significant delay in relation to drug release in the colon, where the pH value is lower. Rapid drug release in the ascending colon is however usually required when colon-specific formulations are used, e.g. in treating colon disease. It is advantageous if drug release from a formulation can begin

immediately after it enters the colon, even though drug release may subsequently be retarded. It may be concluded that no ideal formulation for colon-specific drug delivery yet exists. Drug release from an ideal formulation should begin in the ascending colon, at a predetermined rate. The manufacturing process for the formulation should also be simple and not to expensive.

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