Colon Specific Drug Delivery Systems

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***Abstract*: Colonic Disorders: The paper highlights serious colonic disorders, particularly inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, which can lead to severe complications like colon cancer. In India, there are over 66,000 cases of colon cancer annually, contributing to about 15% of cancer-related deaths in the country .Treatment Challenges: It discusses the limitations of traditional medication administration methods for treating IBD and other colon-related diseases. These methods often fail to deliver the drugs effectively to the affected areas, resulting in inadequate treatment .Need for Site-Specific Drug Delivery: The abstract emphasizes the importance of developing site-specific drug delivery systems that can effectively target the colon. Such systems can provide several therapeutic benefits, including:Delivering medication in its intact form as close to the target site as possible , Reducing the standard dosage required for treatment, Minimizing the risk of adverse side effects , Administration Methods: It mentions two primary methods for achieving colonic drug delivery: oral and rectal administration. However, rectal forms like enemas and suppositories are often ineffective due to their limited distribution capabilities. Therefore, oral administration is preferred, although it presents significant physiological challenges that must be overcome to ensure effective drug delivery .Overcoming Barriers: The abstract concludes by stating that effective colonic drug administration requires overcoming the main barrier of drug absorption or breakdown in the upper gastrointestinal tract. This is crucial for the successful treatment of serious colonic disorders, including colorectal cancer.**

***Key words: Colon targeting , pH dependent, Osmotic controlled system,* Pulsincap system .**

I. INTRODUCTION:

Serious colonic disorders are inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, and irritable bowel syndrome. Colon cancer results from untreated ulcerative colitis. According to reports, India sees more than 66,000 cases of colon cancer annually. In India, around 15% of cancer-related deaths are caused by large intestine cancer. In western nations, the prevalence remains elevated. Surgery remains the cornerstone of the treatment for colon cancer. Chemotherapy is typically administered after a partial colectomy, which involves the removal of a portion of the colon. The majority of traditional medication administration methods for the treatment of inflammatory bowel diseases (including Crohn's disease, ulcerative colitis, and irritable bowel syndrome), infectious diseases, and other colon disorders (such as amoebiasis) and colon cancer are not working since the medications are not getting to the affected area at the right amounts. Therefore, using site-specific drug delivery methods to provide an efficient and safe therapy for these colonic illnesses is a hard issue for pharmaceutical technologists. Targeting a medication to the afflicted organ has several therapeutic benefits, including: a) As near to the target site as feasible, administer the medication in its undamaged state. b) The capacity to reduce the standard dosage; and c) A decreased likelihood of unfavorable side effects. Oral or rectal administration are two methods for achieving colonic delivery. Rectal dose forms, such enemas and suppositories, are not usually successful because of the significant distribution variability that is seen with them. Enema solutions can only provide topical treatment to the sigmoid and descending colon, while suppositories are only beneficial in the rectum due to their limited distribution. As a result, oral administration is recommended; however, numerous physiological obstacles must be removed in order to achieve this. A effective colonic medication administration requires overcoming the main barrier, which is the active ingredient's absorption or breakdown in the upper GI tract .[1]

II. NEED OF COLON TARGETED DRUG DELIVERY: Drugs can be sent specifically to the colon to address conditions there, with less systemic side effects and a smaller dosage. Protein and peptide medication administration, as well as extended drug delivery, benefit from colon-specific formulation. Colon targeted drug delivery works well for delivering medications that are polar or prone to enzymatic and chemical breakdown in the upper gastrointestinal tract, which is significantly impacted by hepatic metabolism. Drugs that Target sites Disease condition Drug and active agent Topical action Inflammatory Bowel Diseases, Hydrocortisone , Budesonide Irritable bowel diseases and Prednisolone, Sulfasalazine, Crohn’s disease , chronic pancreatitis Olsalazine , Basalazine Local action Pancreatactomy cysti fibrosis Digestive enzyme supplements Colorectal cancer 5 – Flourouracil Systemic action To prevent gastric irritation NSAIDS , Steroid, Insulin And first pass metabolism Orally ingested drug like Peptide and vaccines target the colon would be more effective in treating serious disorders of the colon. For instance. similar to colorectal cancer, colon cancer. (3,4,5).

ADVANTAGES OF CTDDS OVER CONVENTIONAL DRUG DELIVERY: Glucocorticoids and other anti-inflammatory medications are currently used to treat chronic colitis, specifically ulcerative colitis and Crohn's disease. Systemic side effects from the oral and intravenous administration of glucocorticoids, including methylprednisolone and dexamethasone, include immunosuppression, adenosuppression, cushinoid symptoms, and bone resorption. Therefore, targeted drug delivery to the colon may help to minimize systemic negative effects from high doses as well as the necessary dosage. (6,7) .

CRITERIA FOR SELECTION OF DRUG FOR CDDS: The best candidates for CDDS are medications, particularly peptides, that exhibit limited absorption from the stomach or intestine. The medications prescribed for diarrhea, ulcerative colitis, inflammatory bowel disease (IBD), and colon cancer are excellent candidates for local colon administration. Table 2 provides a summary of the selection criteria for CDDS medications. Drug carriers are yet another element that affects CDDS. The physiochemical makeup of the drug and the illness for which the system is intended to be utilized determine which carrier is best for a certain combination of pharmaceuticals. The choice of carrier is influenced by various factors, including the drug's chemical makeup, stability, and

partition coefficient, as well as the type of absorption enhancer selected. Additionally, the selection of a drug carrier is contingent upon the functional groups of the molecule of the medication. An azo bond can be formed, for instance, between a drug's nitro or aniline groups and another benzene group. The carriers may have an impact on the release characteristics and system performance since they contain additives like polymers, which can be utilized as matrices, hydrogels, or coating agents (2)

STRUCTURE AND FUNCTION OF THE COLON: STRUCTURE: The small intestine, large intestine, and stomach make up the GI tract. The large intestine is divided into three main portions that extend from the ileocaecal junction to the anus. These three are the rectum, colon, and anal canal. The colon is made up of the sigmoid colon, ascending colon, descending colon, splenic flexure, hepatic flexure, transverse colon, and cacecum. The transverse colon is the longest and most flexible part, measuring around 1.5 m in length. Its diameter is usually around 6.5 cm, but it can range in the caecum to about 9 cm and in the sigmoid colon to about 2cm. There are four layers that make up the colon wall: i. serosa, ii. muscularis externa, iii. submucosa, and iv. mucosa. The serosa, which covers the outside layer of the large intestine, is made up of areolar tissue and a single layer of squamous mesothelial cells. The muscularis externa is the main muscular coat of the large intestine. This is made up of two layers of fibres: an exterior longitudinal layer and an inner circular layer that encircles the colon. Below the mucosa is a layer of connective tissue called the submucosa. Muscularis mucosae, lamina propria, and epithelium make up the mucosa that lines the colon's lumen. The mucosa's surface is penetrated by crypts that are closely spaced. The smooth muscle layer known as the muscularis mucosa divides the lamina propria from the submucosa. In addition to taking up space, the lamina propria supports the epithelium. It takes up room beneath and in between the crypts. Blood capillaries and lymphatic lacteals are seen in the lamina propria. Along with producing IgA antibodies locally, the area also serves as a reservoir for lymphocytes, plasma cells, neutrophils, eosinophils, macrophage , and lymphocytes. The mucosa's surface and the crypts are covered in a single layer of cells that make up the epithelium. The columnar absorptive cells, goblet cells, and entero endocrine cells are the three main cell types that make up the epithelium. A junctional complex connects neighbouring columnar absorptive cells close to their apical borders. Goblet cells are responsible for the formation of mucus in the Poorly absorbed drug Antihypertensive and Isosorbide, from upper GIT Antianginal drug Theopylline , Ibuprofen Drug that degrade in Peptide and protein Doxorubicin, Insulin upper GIT 5-fiourouracil colon, and the number of these cells rises with age. The superior mesenteric artery provides arterial blood supply to the proximal colon, while the inferior mesenteric artery nourishes the veins of the distal colon. A vast network of capillary plexi is formed when the arterioles and capillary branches connect to the epithelial surfaces in between the crypts.

FUNCTION: A) Establishing an atmosphere that is conducive to the development of colonic microbes. B) a container for holding excrement. C) the colon's contents being expelled at the proper periods. D) the lumen's absorption of potassium and water, which concentrates the amount of faeces, as well as the secretion and excretion of bicarbonate and potassium. (1)

The following variables will have an impact on the colon targeted medication delivery system's design: There are two primary categories of factors that impact colon medication delivery.(3)
•A Physiological component
•Compound related aspects

1) PHYSIOLOGICAL COMPONENT :

Gastrointestinal Transit: During a fasting state, the digestive tract goes through four phases in a span of two to three hours. The erratic contractile activity during the feeding state disrupts the regular rhythm.
Small Intestinal Transit: The size of the dose form, the presence of food in the stomach, or the patient's physical condition have no bearing on small intestinal transit. To reach the ileocecal junction, the dosage form takes an average of 3–4 hours, and this transit time is constant.

Colonic transit time: The length of time it takes for medications to leave dosage forms can have a significant impact on their bioavailability. The colonic transit time is affected by a number of variables, including the amount of the dose form, the patient's gender, and physiological states including stress, hunger, and illness. Men have a lower colonic transit time than women do, and small particles and solutions move slowly in the proximal colon in humans. Adults take 20 to 35 hours for a capsule to transit through the colon; this period is unaffected by the volume and density of the capsule. (3)
Material movements into and through the Colon: The subject's state of being fed or fasted, as well as the size and density of the dosage form, are the main factors that influence the very varied gastric emptying of dosage forms. In one investigation, it took anywhere from 15 minutes to more than 3 hours to empty non-disintegrating single unit dose forms (12). Medication formulations have been observed to stay in the stomach for longer than 12 hours when fed regularly, and the inclusion of food generally increases this duration (13, 14). Remarkably consistent small intestine transit occurs about 3–4 hours, and it seems to be unaffected by the kind of dose form and if the patient is fasting or fed state (15). Therefore, after oral administration, a dose form may reach at the colon in as short as 4 hours or as long as 12 hours. Materials move more slowly through the colon than they do through other parts of the digestive system. The overall transit time is sometimes very variable and dependent on several factors, including food, including the amount of dietary fibre, movement, stress, illness, and medication use (16).

Under normal circumstances, colonic transit : A group of seventy-three healthy persons' transit times have been estimated using a radiopaque marker approach. 53.3 hours was the mean mouth-to-anus transit time. The average colonic transit time was 35 hours, with the right (ascending + piece of transverse), left (descending + portion of transverse), and recto sigmoid colon having mean segmental transit times of 11.3 hours, 11.4 hours, and 12.4 hours, respectively. Male individuals' total colon transit was noticeably shorter than that of female subjects (17). There is, however, no difference in the transit rates of men and women, according to previous research (18, 19). Gamma scintigraphy is a widely used technique to quantify the passage of medicinal dose forms through the intestines. 5 x 5 mm, non- disintegrating in a scintigraphy investigation Radiolabeled tablets were administered for three days in a row to six healthy people. As the tablets passed through the intestines, they dispersed widely.

There was a considerable difference in the mouth-to-anus transit period of a batch of five pills, ranging from 18 to 72 hours. The mouth to colon section of the entire trip took two or more hours (20).

Diet's impact on colonic transit : Dietary fiber is the main dietary factor that has the potential to influence intestinal motility. Supplementing with dietary fiber is typically thought to shorten intestinal transit times and increase fecal weight, partially through water retention and partially through bacterial mass. For instance, adding 20 g/day of bran to the diet of a group of healthy participants decreased whole gut transit from 73 f 24 hr to 43 f 7 hr and increased stool weight by 127% (21).

Disease's impact on colonic transit : Drug distribution is significantly impacted by conditions that affect intestinal transit; constipation causes a decrease in colonic motility, whereas diarrhea causes an increase in colonic motility. An unusual frequency and fluidity of fecal discharge is known as diarrhea. Diarrhea will arise from an imbalance between the absorption and secretion of water and electrolytes, regardless of the exact cause. Diarrhea will occur if there is a decrease in fluid absorption within the small and large intestines and/or an increase in secretion (22). Numerous chemicals, including some medications like stimulant laxatives (e.g., senna, bisacodyl) and bacterial toxins, can directly stimulate secretion or impede absorption. Due to their poor absorption, certain chemicals such sorbitol, polyethylene glycols, and magnesium salts might retain an excessive amount of fluid in the intestinal lumen, which can lead to diarrhea (23).

Gastric Emptying: Bowel transit time and gastric emptying play a major role in the colon's ability to receive oral medications. The dose form's transit time in the colon is contingent upon the particle size. In comparison to bigger particles, smaller particles have a longer transit time. Patients with diarrhoea experience shorter transit times, while those with constipation experience longer transit times. (24)

Colon pH : (3,26,27,28) varied people have varied GIT pH values. The pH of the gastrointestinal tract is affected by food consumption, illness, etc. The development of colon cancer is attributed to this variation in pH in various GIT regions focused medication delivery methods. The medicine is targeted to the location via coating with various polymers. (3) Inter-individual variability may have an effect on colonspecific medication delivery systems and hence affect the pH of the colon. The status of the disease, regular meals, and food intake capacity all affected the stomach environment. The medication must exhibit appropriate therapeutic efficacy, stabilize in a pH range that is variable, and release at a certain pH region. Because long-chain fatty acids are produced when bacteria ferment polysaccharides, the pH of the colon changes. (26,27, 28)

Enzymes and Colonic Microflora : Numerous enzymes produced by different microbes, including P. vulgaris, B. subtillis, B. mycoides, A. aerogenes, clostridia, E. coli, and clostridium, are found in the gastrointestinal system. These enzymes aid in the breakdown the bonds that bind the active and biodegradable moiety together with metabolism and degrade coating materials. The human colon contains 1011– 1012 CFU/ml of bacteria .(26, 29 and 30).

Absorption in the Colonic System: The colon's surface area is significantly smaller than that of the small intestine, making it less suitable for absorption. Because endogenous enzymes other than those of microbial origin are dividing in the environment, colon is taken into consideration for drug delivery. Colon residents stay there for 10 to 24 hours. Local habitats with optimal absorption can be created in the colon with minimal mixing. Transportation of water affects absorption. ammonia and electrolytes via the mucosa, with a greater concentration in the proximal and distal colon. (3) Passive drug absorption occurs via transcellular or paracellular pathways. Most lipophilic medications are absorbed through transcellular absorption, which includes the drug passing through cells; most hydrophilic pharmaceuticals, on the other hand, are absorbed through paracellular absorption, which involves the drug being transported through the tight junctions between cells. Because epithelial cell connections in the colon are so tightly packed, many medicines have poor paracellular absorption. The colon's slower rate of transit allows the medication to remain in contact with the mucosa for a longer amount of time than the small intestine, making up for the latter's significantly smaller surface area. As one moves deeper into the colon, more water is gradually absorbed, increasing the viscosity of the colonic content. As a result, the medicine dissolves more slowly and diffuses through the mucosa at a slower rate. (34)

Mechanism of absorption :

•Transcellular transport—moving via colonocyte

•Paracellular transport—the movement of colonocytes between neighbouring ones Through a variety of methods, absorption enhancers promote efficient absorption. These are the following: denaturing membrane proteins alters epithelial permeability; altering lipid protein interactions; and colonic enterocytes compromise the integrity of the lipid barrier. Disruption of the intracellular occluding junction complex opens the paracellular pathway. (3)

Macromolecule Absorption in the Colon : The colon absorbs 0.13% of the bovine serum albumin, while the small intestine absorbs 1.7% of it. This results from variations in surface area. (3)

Disease of the Gastrointestinal System: The release and absorption characteristics of colon-specific drug delivery systems may be impacted by Crohn's disease, constipation, diarrhoea, and gastroenteritis. (3)

COLONIC DISORDER :

Angiodysplasia: Usually occurring in the right colon or cecum, tortuous dilution of mucosal and submucosal blood vessels is observed after the age of 60. They frequently burst and leak into the lumen. Twenty percent of substantial lower intestinal beading is caused by such lesions. A minor vascular abnormality of the intestine is called angiosplasia. It is frequently the cause of anemia and otherwise inexplicable gastrointestinal bleeding. Though they can happen anywhere, lesions are usually numerous and usually affect the ascending colon or cecum. Surgery, medicine, or endoscopic procedures may be used as forms of treatment. Esophagogastroduodenoscopy (EGD) or colonoscopy are two common endoscopies used to diagnose angiodysplasia. (35)

Disease of the inflammatory bowel : From the esophagus to the anus, every part of the gastrointestinal system can be affected by Crohn's disease, but the ileum is most frequently affected. The aetiology of inflammatory bowel disease is complex and includes inflammatory reactions, aberrant immune responses directed against the gut's normal flora, genetic factors involving multiple genes, chromosome location, and candidate genes, infectious agents such as Escherichia coli, measles virus, cytomegalovirus, etc., and dietary factors like milk products, saturated fats, and allergy foods, among others. inflammatory bowel disease and ulcerative colitis, together referred to as idiopathic inflammatory bowel disease (IBD), are recurrent, chronic inflammation disorders of unclear cause. The primary medications used to treat Crohn's disease and ulcerative colitis are corticosteroids and amino salicylates . There is a connection between these conditions and other inflammatory bowel illnesses and a higher risk of colorectal cancer (36)

Ulcerative colitis: This type of colitis is limited to the large intestine. Pus, blood, and diarrhoea are frequently the results of ulcers that develop in the mucosa, or inner lining, of the colon or rectum. In the sigmoid and rectum, the inflammation is typically fairly severe and then subsides in the colon. Crohn's disease: also known as regional enteritis, Crohn's disease is a chronic inflammatory bowel illness that is typically limited to the ileum, the terminal segment of the small intestine.

Colorectal cancer: Cancerous growths in the colon, rectum, and appendix are included in large bowel cancer. Adenocarcinomas account for 98% of all large intestine cancers. Using aspirin and other NSAIDs may help prevent colon cancer, according to a number of studies. The cause of colorectal malignancies is colonic adenomatous polyps. Although most of these mushroom-shaped growths are benign, some eventually turn into malignancy. A colonoscopy is typically used to diagnose localised colon cancer. Surgery is a treatment option for invasive tumours that are contained within the colon's wall (TNM stages I and II). When left untreated, they progress to stage III regional lymph nodes, where up to 73% can be cured with surgery and chemotherapy. Stage IV cancers that have spread to distant locations are mostly incurable, however treatment survival, and in a few number of instances, the combination of chemotherapy and surgery has helped patients reach a cure. Rectal cancer is treated with radiation (34, 37).

Drugs used in colon cancer (34,38)

1) 5-fluorouracil 2) 9-aminocamptothecin 3) Capecitabine 4) Cetuximab 5) Trinoteca 6) Levamisole hydrochloride 7) Oxaliplatin 8) Trimetrexate 9) UFT (ftorafur and uracil) 10) Bevacizumab 11) Cisplatin.

Constipation-causing Infrequent and difficult-to-pass bowel movements are referred to as constipation (also known as costiveness, dyschezia, and dyssynergic defaecation). A common cause of painful faeces is constipation. Faecal impaction and obstipation are examples of severe constipation. Among the treatments include surgery, laxatives, enemas, biofeedback, and dietary modifications. Since constipation is a symptom rather than an illness, figuring out what's causing it could be necessary before starting treatment.34, 39.

Diarrhoea : Three loose or liquid bowel motions or more in a day is considered diarrhoea. Dehydration and electrolyte abnormalities can result from diarrhea's fluid loss. When the mucosal lining or brush border is damaged, protein-rich fluids are passively lost and the body's capacity to absorb them is compromised. This might result in inflammatory diarrhoea. This type of diarrhoea shares characteristics with the other three categories. It may result from viral, bacterial, parasite, or autoimmune conditions, including inflammatory bowel disorders. Additionally, enteritis, colon cancer, and tuberculosis can cause it (34, 40).

Diverticulitis and Diverticulosis : A diverticulum is a visually impaired pouch that connects to the gut lumen. Congential diverticula are extremely rare and comprise all three gut wall layers. While acquired diverticula can develop anywhere in the gastrointestinal tract, the colon is by far the most typical site. Inflammation of the diverticula leads to diverticulitis. Treatment for an acute diverticulitis episode that occurs initially usually consists of IV fluid resuscitation, bowel rest (i.e., nothing by mouth), and broad-spectrum antibiotics that cover gram-negative rods and anaerobic bacteria. On the other hand, surgery may be necessary either promptly or as an elective procedure in the event of recurrent acute attacks or consequences such as fistula, abscess, or peritonitis [41].

Aganglionosis, or Hirschsprung's disease: Hirschsprung disease arises when the migration of cells generated from the neutral crest along the alimentary canal stops at some point before it reaches the anus during development. The absence of ganglia and ganglion cells in the muscle wall and submucosa of the afflicted segment is the essential lesion in Hirschsprung disease [42]. A uncommon congenital (existing from birth) disorder called Hirschsprung's disease causes blockage due to faulty intestinal function. The majority of the time, it is in men. Children with Down syndrome frequently have it. It could be a persistent disorder or something more dangerous. The most common symptoms in a newborn are unwillingness to eat, green, bile-stained vomiting, inability to pass a meconium stool within 24 to 48 hours after birth, and distension in the abdomen. In the early stages of life, the infant experiences episodes of diarrhea, vomiting, constipation, and stomach distension Severe and sometimes fatal symptoms of enter colitis, an inflammation of the colon, include explosive watery diarrhea, fever, and tiredness. Let the doctor know right away if your kid experiences these symptoms. As children get older, the symptoms can become chronic and include constipation, visible peristalsis (the intestines moving like waves), abdominal distension, and the passing of foul-smelling, ribbon-shaped faces. Typically, the older child is malnourished and anemic. [43]

III. Ileus : It means obstruction of the intestinal tract. Ileus is a non-mechanical source of disruption of normal propulsive gastrointestinal motor action. On the other hand, structurally-based motility issues are referred to as mechanical bowel blockage. There are three forms of ileus: acute colonic pseudo obstruction, paralytic ileus, and postoperative ileus (44).

IV. Intussusception : Similar to how the components of a collapsible telescope slide into one another, an intussusception is a medical disorder where a portion of the intestine has invaded into another section of the gut. The lower receiving section is referred to as the intussusceptions, and the telescoped segment as the intussuscepted. This frequently leads to a blockage. The intussuscepted is the part that prolapses into the other, and the intussusceptions is the part that receives it. Children and newborns are most commonly affected by the illness [45]. Usually, there is no immediate danger to life from the illness. An air-contrast

enema, barium or water soluble contrast enema, or both can be used to cure the intussusception. These methods not only successfully treat the condition but also confirm its diagnosis diminishes it. There is more than 80% success rate. But between 5 and 10% of these happen again in a day [46].

V. Irritable bowel syndrome : An exclusion diagnosis is made for conditions like spastic colon or irritable bowel syndrome (IBS). Chronic stomach pain, discomfort, bloating, and changes in bowel habits without a discernible organic cause are the hallmarks of this functional bowel illness. An infection or a tense life experience may trigger the onset of IBS. IBS is no known cure, although there are therapies that aim to manage symptoms, such as dietary changes, medication, and counselling. A positive doctor-patient rapport and patient education are also crucial. A number of illnesses, such as coeliac disease, fructose malabsorption, minor infections, parasite infections such as giardiasis, several inflammatory bowel diseases, functional chronic constipation, and persistent functional abdominal pain, can manifest as IBS. Routine clinical testing for IBS shows no abnormalities, yet the bowels may respond more readily to specific stimuli, such balloon insufflation tests. It's unclear what specifically causes IBS. The most widely accepted explanation for IBS is that it is a dysfunction of the brain-gastrointestinal tract relationship, though immune system or gut flora abnormalities may also be present. (47).

VI. Colitis that is pseudomembranous : One colon illness that goes by the name of pseudomembranous colitis (AAD) is also known as antibiotic-associated diarrhea. The bacterium Clostridium difficile is frequently, but not always, the cause. Intensely smelly diarrhea, fever, and stomach pain are the symptoms of the sickness. Hazardous consequences, such toxic mega colon, can arise in extreme situations. [48].

VII. Haemorrhoids : The veins that cause hemorrhoids are varicose. These are also known as piles. In older people and expectant mothers, these are prevalent lesions. Most often, elevated venous pressure is the cause. Heart failure, venous stasis during pregnancy, rectum tumors, inherited predisposition, persistent constipation, and straining at the stool are among the potential reasons. (34)

PHARMACEUTICAL ASPECTS

Medication substances: Drug delivery systems designed specifically for the colon are most suited for medications that exhibit poor absorption from the stomach or intestine, such as peptide medicines. Drugs like 5-ASA and sulphasalazine are frequently used to treat IBD and other conditions.

Drug-Carrying individuals : The physicochemical makeup of the drug and the illness for which the system is intended to be utilized determine which carrier is best for a certain drug candidate. The carrier selection is influenced by the drug's chemical makeup, stability, and partition coefficient as well as the kind of absorption enhancer selected (49,50,51).

APPROACHING COLONIZATION WITH A TARGETEDSTRATEGY

1. Applying a coating using pH-dependent biodegradable polymers : Capsules are coated with biodegradable azo polymers that are very hydrophilic and have outstanding breakdown characteristics. Increased hydrophilicity may lead to the medication being released from the body prior to entering the colon. The azo polymer systems work well for local drug delivery to the colon, but they are not appropriate for the delivery of hormones, peptides, or other medications with a limited therapeutic index. The most widely utilized polymers are eudragit L and eudragit S, which are co-polymers of methacrylic acid. By forming salts and dissolving at pH 5.5, carboxyl polymer can be used to create latex without the need for organic solvents during the coating process. The way biodegradable systems of azo polymers (3)

2. (ORDS-CT) Osmotic Controlled System : The ORDS-CT system from Alza Corporation has the option of having one osmotic unit or as many as five or six push-pull units, each measuring four mm and enclosed in a hard gelatin capsule. Every bilayer push-pull unit has two layers: one for drugs and the other for osmotic push, both encased in a semipermeable membrane . The coating dissolves in the higher pH environment of the small intestine when the unit passes through it. (3)

3. The design of targeted Prodrugs : A non-specific chemical method is frequently used in the design of classical prodrugs to hide undesirable drug features such chemical instability, limited bioavailability, and less site specificity. In contrast, a novel approach to focused and effective drug delivery is targeted prodrug design. Prodrugs that target a particular enzyme, membrane transporter, or both in particular have the potential to be used as a drug delivery method, particularly in cancer chemotherapy. When designing a strategy to target a certain enzyme or carrier substrate specificity, one must possess extensive knowledge about the molecular and functional properties of that particular enzyme or carrier system in order to overcome numerous undesirable pharmacological properties.

   These characteristics can be classified into two categories:
   (i) Concentrating on particular enzymes Since they are hydrophilic, glycoside derivatives are poorly absorbed from the small intestine. However, once they reach the colon, bacterial glycosidases can effectively liberate them, releasing the free medication and facilitating the mucosa of the colon's absorption. Although the parent medication was absorbed in the small intestine, the glycosidic prodrug, dexamethasone glucoside, seemed to be a better option. Approximately 60% of the prodrug reached the caecumas free steroids.
   (ii) Specializing in particular membrane transporters Oral administration of free steroids resulted in nearly complete absorption in the small intestine and less than 1% of the oral dose reaching the colon. Hydrogels have been used to coat the drug cores and as a coating medium when using azo compounds for colon targeting pro-drugs. It was eventually discovered that sulphasalazine, which was once used to treat rheumatoid arthritis, may also be useful in the management

of inflammatory bowel disease. An azo bond is present in this chemical between sulphapyridine and 5-amino salicylic acid.

(iii) Systems based on polysaccharides The polymer of monosaccharide, known as a polysaccharide, maintains its structural integrity due to its resistance to the digestive action of gastrointestinal enzymes. The polysaccharide matrices are considered to be intact in the physiological environment of the stomach and small intestine; however, upon reaching the colon, they are subjected to bacterial polysaccharidases, which cause the matrixes to degrade. Due to its huge number of derivitizable groups, wide range of molecular weights, variable chemical composition, and form most with moderate toxicity and biodegradability but high stability, the family of natural polysaccharides has appeal in the field of drug delivery. Pectin is a polysaccharide that has side chains of D-galactose and D-arabinose together with α-1,4 Dgalactouronic acid and 1,2 D-Rhamnose. A new medicine delivery method through the colon is looked into. When applied as a compression coat, high methoxy pectin was shown in in vitro trials to be vulnerable to enzymatic attack and to coat tablets in conditions that stimulated the gastrointestinal environment. (2)

4. Pulsincap system : The Pulsincap system represents an innovative amalgamation of a time-dependent release mechanism and a pH-sensitive methodology. Sole reliance on time-dependent systems for the purpose of colon-targeted drug delivery is inadequate, owing to the variability in gastric emptying rates, fluctuations in gastrointestinal transit provoked by peristaltic movements, and other colonic pathologies such as irritable bowel syndrome (IBS). The architecture of the Pulsincap system consists of a water-insoluble capsule body encompassing the therapeutic agent [52]. The hydrogen plugs are fabricated from compounds such as hydroxy-propyl methylcellulose (HPMC), polymethyl methacrylate (PMMA), and polyvinyl acetate (PVA) [53]. The terminal end of the capsule body or capsule cap is comprised of water-soluble material and is sealed with a hydrogel plug. The therapeutic substance is shielded from the acidic environment of the stomach by an acid-insoluble film layer coating [52]. Upon entering the small intestine, the enteric coating dissolves and the hydrogel plug undergoes swelling. The swelling of the hydrogel plug in the small intestine facilitates a delay in drug release and ensures a prolonged release profile in the colon. The duration of the lag time is contingent upon the dimensions of the plug and its degree of insertion [54,55].

5. CODES™ : CODES™ represents a budesonide pellet utilizing CODES™ technology, which is characterized by its pH-dependent and microbial-dependent combination system . This innovative combination effectively addresses the challenges that hinder the efficacy of pH sensitive formulations and time-dependent systems . It comprises a core based on lactulose, which serves as a trigger for site-specific drug release within the colon. The core material is enveloped by two distinct coating layers. The initial coating is formulated from an acid-soluble compound, such as Eudragit E, while the secondary coating, which overlays the primary layer, consists of an enteric-coated material, exemplified by Eudragit L . The distinctive architecture of CODES™ ensures that the drug remains unaltered in the gastric environment due to the protective enteric coating; nevertheless, it dissolves expeditiously following gastric emptying. The drug is safeguarded owing to the presence of an acid-soluble coating. The coating layer disintegrates within the small intestine. The pH level of the small intestine is acidic, and the acidic coating of the formulation inhibits the premature release of the drug as it traverses the acidic milieu of the small intestine. There exists minimal penetration of dissolution media and subsequent swelling of the formulation within the small intestine. However, the polysaccharide (lactulose) is liberated in the colon and diffuses through the coating layers as a consequence of the enzymatic degradation of lactulose. This process is facilitated by the bacterial flora present in the colon, which metabolizes lactulose into organic acid.(56)

In vitro technique: Using USP dissolution rate test apparatus or flow through dissolution apparatus, drug release studies are typically conducted in 0.1 N HCl for 2 hours (mean gastric emptying time) and pH 7.4 Sorensen's phosphate buffer for 3 hours (mean small transit time) to evaluate the ability of coats/carriers to remain intact in the physiological environment of the stomach and small intestine. Using this procedure, tablets coated in pectin compression coats were assessed, and it was discovered that the medication was not released during the testing period. By exposing the delivery system to buffer medium containing either enzymes (such pectinase) or rats, guinea pigs, or rabbits, the system's capacity to release the medicine in the colon is evaluated in vitro.(1)

In vivo techniques:

Animal models: A variety of animal models are employed to assess colon-specific drug distribution from a dexamethasone glucoside prodrug in vivo. Rats are among the numerous animal models that are employed in vivo to assess colon-specific drug delivery systems. Methods for tracking the activity of human colon-specific delivery devices in vivo A range of methods such include : 1.String methodology 2. Endoscopy 3.Using radiotelemetry 4.entradiography 5.Gamma-ray scintigraphy were employed to track the oral dose forms' behaviour in vivo.(1)

CONCLUSION: The paper suggests that ongoing research and development in colon-specific drug delivery systems are crucial for improving treatment outcomes for colonic disorders. This includes exploring new materials and technologies that can enhance the effectiveness and safety of drug delivery.

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