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ADVANCE APPROACHES FOR EFFECTIVE COLONIC DRUG DELIVERY: A REVIEW

[1]Onkar V.Wagh, [2]*Raosaheb S.Shendge, [3]Sneha S.Kardile

[1]Student,Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research,Kopargaon

[2]Professor, Sanjivani College of Pharmaceutical Education and Research,Kopargaon

[3]Student,Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research,Kopargaon

Sanjivani College of Pharmaceutical Education and Research,Kopargaon, India

Abstract: The most preferred route for the treatment of numerous diseases and disorders is oral dosage form, although the gut wall has a number of barriers to drug administration. Colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, allow topical treatment of bowel diseases, ulcerative colitis. Systemic side effects could also be reduced. To achieve successful colonic delivery, a drug must be protected from absorption in the upper gastrointestinal tract (GIT) environment before being released into the proximal colon, which is thought to be the optimum site for colon-targeted drug delivery. Conventional approaches for CDDS (Colon Specific Drug Delivery), which includes prodrugs, pH and time dependent system and microbially triggered system, polysaccharides-based delivery system has achieved limited success and having its limitations. Newly developed CDDS which includes pressure -controlled drug delivery system, CODES technology, and osmotic controlled drug delivery are unique in terms of achieving in vivo site specificity and feasibility. Polymeric approaches CDDS includes reservoir system with rupturable polymeric coating, reservoir system with soluble or eroding polymeric coatings has been achieved. These advance or/and novel approaches are effective and unique in terms of achieving in vivo site specificity and feasibility for colonic drug delivery.

Index Terms - Colonic diseases**,** colon drug delivery system, approaches in drug delivery.

I. INTRODUCTION

In comparison to other drug delivery system techniques, the oral route of administration is always given more attention.[1] Colon targeted drug delivery follows the concept of control or sustained route for drug administration which has received more attention.[2] The oral route is the most appropriate and important way for administering drugs with a systemic effect. Oral D.D.S. (Drug Delivery System) account for around half of all drug delivery systems on the market, and these systems offer additional benefits due to patient acceptability and ease of administration.[3], [4] Colonic drug delivery has gained not only for the delivery of drugs for the treatment of local diseases associated with the colon, such as Crohn's disease, asthma, ulcerative colitis, irritable bowel syndrome, and constipation, but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs, and antidiabetic agents. [5], [6] The colon targeted drug delivery system is not only effective for delivering drugs to the colon for local treatment, but it's also a convenient way to administer protein and peptides and increase their bioavailability.[7] Protein and peptide bioavailability can be achieved if they are protected from acid and enzymes in the stomach and upper intestine, and then released and absorbed in the colon, as well as being protected from degradation in the stomach.[8] Because polymers affect the rate of release and absorption of drugs and play a important role in the design of colon targeted drug delivery systems, degradation of such drugs in the stomach can be prevented by using some polymer, either alone or in combination. [9] Colon drug targeting can be achieved using a variety of methods or techniques, such as the formation of prodrugs, coating with pH-sensitive polymers, coating with biodegradable polymers, designing polysaccharide formulations, timed released systems, pressure-controlled drug delivery systems, and osmotic pressure control systems[10], [11] The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon, i.e., drug release and absorption should not occur in the stomach or small intestine, and neither the bioactive agent nor the dissolution sites should be degraded, but only once the system reaches the colon then the drug should be released and absorbed.[12]

COLON DRUG DELIVERY SYSTEM:

Colonic diseases

1. Angiodysplasia:

After the age of 60, tortuous dilution of submucosal and mucosal blood arteries is most commonly seen in the cecum or right colon. They have a high risk of rupturing and bleeding into the lumen. Significant lower intestine bleeding is caused by 20% of these lesions. A small vascular malformation of the intestine is called angiodysplasia. It's a common cause of gastrointestinal bleeding and anaemia that's otherwise undiagnosed. Multiple lesions are common, and they usually affect the cecum or ascending colon, though they can happen elsewhere. Endoscopic procedures, medicine, and surgery are all options for treatment. Endoscopy, either colonoscopy or esophagogastroduodenoscopy (EGD), is frequently used to diagnose angiodysplasia. [13]

2. Inflammatory Bowel Disease:
Crohn's disease can affect any part of the gastrointestinal tract, from the oesophagus to the anus, but the ileum is the most commonly affected. Inflammatory bowel disease is caused by inflammatory responses, abnormal local immune responses against normal gut flora, genetic factors like multiple genetic factors, candidate genes, chromosome location, infectious agents like E. coli, Measles virus, Cytomegalovirus, and others, and dietary factors like saturated fats, milk products, and allergic foods, among others. Idiopathic inflammatory bowel disease(IBD), which includes Crohn's disease and ulcerative colitis, is a chronic recurrent inflammation disorder with no identified cause. Amino salicylates and corticosteroids are the most common drugs used to treat ulcerative colitis and Crohn's disease. [14]. These and other forms of inflammatory bowel illness have been related to a higher risk of colorectal cancer [15].

Ulcerative colitis: Ulcerative colitis occurs only in the large intestine. Ulcers develop in the mucosa of the colon or rectum, the inner lining of the intestine, leading in diarrhoea, blood, and pus. The sigmoid and rectum are frequently quite irritated, while the colon inflammation is usually mild.
Crohn's disease: Crohn's disease, also known as regional enteritis, is a chronic intestine inflammation that is usually restricted to the ileum, the terminal section of the small intestine.[16]

3. Colorectal cancer
Cancerous growths in the colon, rectum, and appendix are all part of large bowel cancer. Adenocarcinomas account for 98 percent of all malignancies of the large intestine. Several studies have suggested that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can help prevent colon cancer. Adenomatous polyps in the colon cause colorectal cancer. Although most of these mushroom-shaped growths are benign, some do progress to cancer over time. Surgery can be used to treat invasive tumours that are contained within the colon's wall (TNM stages I and II). If left untreated, they progress to regional lymph nodes (stage III), where surgery and chemotherapy can cure up to 73 percent of cases.[17]

4. Constipation:
Constipation (also known as costiveness, dyschezia, and dyssynergia defecation) is characterised by infrequent and difficult-to-pass bowel movements. The most prevalent cause of painful faeces is constipation. Obstipation and faecal impaction are examples of severe constipationDietary changes, laxatives, enemas, biofeedback, and surgery are all options for treatment. Because constipation is a symptom, not an illness, determining the cause may be necessary before treating it.[17]

5. Diarrhea:
The condition of having three or more loose or watery bowel motions per day is known as diarrhoea. Dehydration and electrolyte abnormalities can result from the loss of fluids caused by diarrhoea. Damage to the mucosal lining or brush border causes inflammatory diarrhoea, which results in a passive loss of protein-rich fluids and a reduced ability to absorb these fluids. This type of diarrhoea has characteristics of all three other types of diarrhoea. Bacterial infections, viral infections, parasite infections, and autoimmune illnesses like inflammatory bowel disease can all cause it. Tuberculosis, colon cancer, and enteritis can also causes of it.[18]

6. Ileus:
It is defined as intestinal obstruction. Ileus is a non-mechanical disruption of the normal propulsive motor movement of the gastrointestinal tract. Mechanical bowel blockage, on the other hand, refers to motility issues caused by anatomical anomalies. Postoperative ileus, paralytic ileus, and acute colonic pseudo-obstruction are the three forms of ileus.[19]

7. irritable bowel syndrome:
Irritable bowel syndrome (IBS), often known as spastic colon, is an exclusionary diagnosis. It's a type of functional bowel illness that appears as chronic stomach pain, discomfort, bloating, and stool irregularities in the absence of an organic cause. IBS can develop as a result of an infection or a stressful event in one's life.
Although there is no cure for IBS, there are therapies that can help with symptoms, such as dietary changes, medication, and psychological counseling, patient education and a good doctor-patient relationship are also important. Celiac disease, fructose malabsorption, mild infections, parasite infections such as giardiasis, various inflammatory bowel illnesses, functional chronic constipation, and chronic functional abdominal discomfort are some of the factors that can cause IBS. Routine clinical tests reveal no abnormalities in IBS patients, while specific stimuli, such as balloon insufflation testing, may make the bowels more sensitive. IBS's actual cause is uncertain. Although there may be abnormalities in the gut flora or the immune system, the most popular theory is that IBS is a disorder of the relationship between the brain and the gastrointestinal tract. [20]

8. Pseudomembranous colitis:
Antibiotic-associated diarrhoea (AAD), also known as pseudomembranous colitis, is a colon infection. Clostridium difficile is frequently, but not always the cause of it . The symptoms of the disease include foul-smelling diarrhoea, fever, and abdominal pain. Life-threatening consequences, such as toxic mega-colon, can arise in severe cases.[21]

9.Haemorrhoids:
Haemorrhoids or piles are the varicosities of the haemorrhoidal veins. These lesions are frequent in the elderly and pregnant women. Increased venous pressure is the most typical cause. Portal hypertension, prolonged constipation and stool straining, heart failure, pregnant venous stasis, inherited predisposition, and rectum tumours are all possible causes.[22]

Drug Treatment:

Table . Marketed drug products for the treatment of various diseases of colon:

S. No.	MARKETED NAME	COMPANY NAME	DISEASE	DRUG
1	Asacol	Win-Medicare Sun pharma, India	Ulcerative colitis, Crohn's disease	Mesalamine
2	BUSCOPAN	German Remedies, India	Colonic motility disorder	Hyoscine butyl bromide
3	COLOSPA	Solvay, India	Irritable colon syndrome	Mebeverine
4	CYCLOMINOL	Neol, India	Irritable colon syndrome	Dyclonine
5	Eldicet	Solvay, India	Irritable colon syndrome, Spastic colon	Pinaverium bromide
6	Ent foam	Cipla, India	Ulcerative colitis	Hydrocortisone acetate
7	Equirex	Jagsonpal Pharmaceutical, India	Irritable colon syndrome	Chlordiazepoxide
8	Intazide	INTA's, India	Ulcerative colitis	Balsalazide
9	Lomotil	RPG Life, India	Mild ulcerative colitis	Diphenoxylate hcl, atropine sulphate
10	Mesacol enema	Sun pharma, India	Ulcerative colitis	Mesalamine
11	Mesacol tablet	Sun pharma, India	Ulcerative colitis	Mesalamine
12	Norma Xin	Systopic labs, India	Irritable colon syndrome	Aclidinium bromide
13	Pro-banthine	RPG Life, India	Irritable colon syndrome	Propantheline bromide
14	SAZO	Wallace, India	Ulcerative colitis, Crohn's disease	Sulphasalazine

Drugs used in colon cancer

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

APPROACHES FOR COLON DRUG DELIVERY SYSTEM

1. Conventional approaches of colon specific drug delivery-
a) PH Sensitive polymer coated drug delivery system.
b) Delayed (Time Controlled release System) release drug delivery system.
c) Microbial triggered system
d) Polysaccharide based delivery system.

2. Newly developed approaches for CDDS-
a) Pressure Controlled drug – delivery system.
b) CODES technology
c) Osmotic controlled drug delivery (OROS-CT)

3.Polymeric Approaches for CDDS-
a) Eudragit L-100-55
b) Eudragit L-30D
c) Reservoir System with Rupturable Polymeric Coating
d) Reservoir Systems with Soluble or Eroding Polymer Coatings

1.Conventional Approaches of Colon specific drug delivery-

A) pH Sensitive polymer coated drug delivery system.

There is numerous invention approaches have been discovered to develop colon drug delivery system. we can use a different type of polymer to target the colon drug delivery system. A pH-dependent polymer can shield a formulation in the stomach and proximal small intestine, but it starts to dissolve in the colon.[23] To promote drug targeting in the colon, a variety of techniques have been developed. Coating the formulation with a natural or synthetic polymer is the most common technique. [24] The drug is placed in the core of the formulation, which is covered with PH-sensitive Polymer in this process. An acid-soluble polymer is used for the first coating, and an enteric polymer is used for the second. [25] The API (Active pharmaceutical ingredient) and excipients are the core of the formulation. The enteric coating does not release the drug in the stomach, when the drug travels through the GI tract, then it dissolves in the small intestine, where the PH is greater than 6. When the drug reaches to the colon, the polysaccharide into organic acid. This lowers the PH of the surrounding system, allowing the surrounding system's acid-soluble coating to dissolve and the drug to be released. [26] Acrylic acid and cellulose derivatives are the most commonly used as pH-dependent polymers.

B) Delayed (Time controlled release system) release drug delivery system.

Drug release methods that are time-dependent or controlled, such as sustained or delayed-release dose forms, are also extremely promising. However, due to possibly considerable variations in dosage from gastric emptying time in people, the Colon arrival time of dosage forms in these procedures cannot be accurately predicted, leading to limited colonial availability[27] The goal of time-released systems is to resist the acidic environment of the stomach and to go through a lag time of a specified amount of time before the drugs are released. In this case, the lag time is the time it takes for food to go from the mouth to the colon; a lag time of 5 hours is usually considered enough because the small intestine takes roughly 3-4 hours, which is relatively constant and unchanged by the nature of the formulation.[28]

C) Microbially triggered system

The colon microflora has a frequency of 1011 -1012 CFU/ml and is primarily made up of anaerobic bacteria, such as Bacteroides. This huge microflora meets its energy needs by digesting various substrates and producing enzymes such as glucuronidase, xyloidine, arabinoside, galactosidase, and etc.[29] Because biodegradable enzymes are exclusively found in the colon, using biodegradable polymers for colon-specific drug delivery appears to be a more site-specific strategy than other methods.[30] These polymers protect the drug from the stomach and small intestinal environments and also allow it to reach the colon. Once they reach the colon, they are degraded by microorganisms, enzymes, or the polymer itself, resulting in a decrease in molecular weight and, as a result, mechanical strength.[31]

D) Polysaccharide Based delivery system-

The use of naturally occurring polysaccharides attracts a lot of attention in the targeting of drugs in the colon because these monosaccharide polymers are widely available, inexpensive, and available in frames with a variety of properties. They are chemically easy to modify and are very stable, safe, and non-toxic, with hydrophilic and gel properties, as well as breakdown. Polysaccharides are obtained from plants (guar gum, inulin), animals (chitosan, chondroitin sulphate), algae (alginates), and microbiological origin are examples (dextran). Colonic bacteria separates this into simple saccharides.[32]–[34]

2- Newly developed approaches for CDDS-

A) Pressure Controlled drug-delivery system

To increase the pressure of the luminal contents of the colon, the pressure-controlled colon drug delivery system capsule is utilised. The reabsorption of water in this region causes a rise in luminal pressure. For the manufacture of such a system, the drug is dispersed in a suppository base and coated with ethyl cellulose. The body's temperature will cause the suppository base to melt and expand in volume, forming an ethyl cellulose balloon that is filled with liquid. This balloon can resist small intestine motions (peristalsis), but it bursts when exposed to a severe contraction in the colon and contents with a higher viscosity. This system is used to create a one-of-a-kind system.[35], [36]

B) CODES technology (combination of PH dependent and microbially triggered CDDS)

CODESTM is an innovative CDDS (colon drug delivery system) technology that minimizes the problems that arose with pH- or time-dependent systems.[37] CODESTM is combined approach of pH dependent and microbially triggered CDDS. It was created by the use of a novel mechanism utilizing lactulose, which acts as a trigger for colon-specific medication release. The system consists of a conventional tablet containing a core containing lactulose, which is then overcoated with an acid-soluble material, Eudragit E, and then an enteric material, Eudragit L. The enteric coating protects the tablet while it is in the stomach and then dissolves quickly after gastric emptying, according to the technology's concept. As the preparation passes through the alkaline pH of the small intestine, the acid soluble material coating protects it When the tablet reaches the colon, bacteria breakdown the polysaccharide (lactulose) into organic acid via enzymes. The pH of the environment around the system is lowered to the point where the acid soluble coating dissolves and the drug is released.[38]

C) Osmotic Controlled Drug Delivery (OROS-CT)

Osmotic controlled drug delivery (Alza Corporation) is a once- or twice-daily formulation for drug delivery to the colon. OROS-CT can be a single osmotic agent or a combination of up to six push-pull osmotic units packed into a hard gelatine capsule.[39] The gelatine capsule dissolves when it comes into contact with GI fluids, and the enteric coating prevents stomach fluids from entering the system.[40] When the coating dissolves in the high pH environment (pH>7) of the small intestine, the drug is released out of the orifice at a rate controlled by the rate of water transport across the membrane, the osmotic pumping action occurs.[41]

3.Polymeric approaches for CDDS-

a.Eudragit L-100-55

The copolymer Eudragit L-100-55 is made up of acrylic and methacrylic acid esters, with the attached functional group (R) determining its physicochemical properties. It is a white, anionic, freely flowing powder that is used for enteric coating and dissolves at pH 5.5 and above.[42] To further manufacture within its enteric-coated tablets, hot-melt extrusion is used to enhance the physicochemical properties of lansoprazole. For the extrusion process, they used Kollidon 12PF polymeric matrix, magnesium oxide (MgO) as an alkalizer, and Lutrol F68 as a plasticizer. When lansoprazole was extruded with Lutrol F68 and Kollidon K12, it was transformed to an amorphous state and released better, but adding MgO-enhanced lansoprazole release and extrudability resulted in over 80% drug release in the buffer stage.[43]

b. Eudragit L-30D

Polymethacrylates are known as Eudragit in industries all over the world. Because of the flexibility of merging with different polymers, it can obtain the necessary drug-release profile at the right moment, in the right place, and even over the required time span. To protect active chemicals in stomach acid and improve its effectiveness, the Eudragit L and S polymers preferred coating polymers.[44] Rohm GmbH and Co. KG holds the trademark Eudragit, which was initially marketed in the 1950s. Polymerization of methacrylic and acrylic acids or their esters, such as butyl ester or dimethyl aminoethyl ester, was used to create Darmstadt in Germany. In 1972, Eudragit L-30D was released. At a pH of 5.5, it dissolves in intestinal fluid and is used to manufacture enteric coatings in its white, anionic, freely flowing state.[45]

c. Reservoir System with Rupturable Polymeric Coating

The reservoir devices in these multiparticulate systems are coated with a rupturable polymeric layer. Many layers are present in such systems. Drug compounds are found in some layers, while rate–controlling polymers are found in others. Individual units are coated with osmotic or swelling chemicals to achieve the rupturing action.[46]This technique can be used to achieve a variety of release patterns, including prolonged release of active pharmaceutical components for absorption across the G.I.T. The drug can be released in either a burst or sustained release profile over a period of 1–12 hours, with a lag time of 4–10 hours.[47] The composition and thickness of the polymer barrier, as well as the lag – time coating itself, determine the length of drug release after the lag – time. For single drugs or a mix of drugs, the multi-particulate system delivers an appropriate release profile. The osmotic pressure created by water infiltration causes the core to rupture, releasing the drug immediately. When the events leading up to a vascular obstruction resulting in a heart attack or stroke most usually occur after the drug is taken in the evening, the explosion of formulation can also be produced by using swelling agents.[48]The formulation has an aspirin core, a swelling agent, and a frangible covering that protects the aspirin from being dissolved by gastrointestinal fluids that are both water soluble and insoluble.[49]

d. Reservoir Systems with Soluble or Eroding Polymer Coatings

Another form of reservoir-type multi-particulate pulsatile system is based on soluble/erodible polymer coatings, in which the barrier dissolves or erodes after a specified lag period, allowing the drug to burst out of the reservoir core. [50]] In general, the thickness of the coating layer can affect the lag time before drug release in this type of system. The basic principle used in these systems is that pH-sensitive polymers have been used to prevent release in the stomach and allow complete release in the intestine due to their significant increase in solubility at the same point in the G.I.T. The hydration of various thicknesses of polymer (Eudragit RS) films in an attempt to distribute drugs to various sites in the G.I.T. which delays the lag times. The lag time could be varied in a theoretical simulation by adjusting the thickness of the coated polymer, which was proportional to the amount of dry polymer in the coating. The outer coating shields the system from stomach acids and dissolves when it reaches the small intestine.[51] An enteric polymer is used in one of the coated membranes, and a mixture of a water-insoluble polymer and an enteric polymer is used in the other.[52] Because the system has pH adjusters that maintain the local acidic environment within the system, this sort of technology has been used for weakly basic pharmaceuticals (which have pH-dependent solubility and are hence insoluble at intestinal pH).

CONCLUSION:

The CDDS (colon drug delivery system) offers patients various therapeutic a9dvantages in both local and systemic treatment. Drug delivery and absorption have become important in the GIT's colonic area. Newer drug delivery methods are being developed for the treatment of a variety of life-threatening diseases and disorders. The colon targeting is for the treatment of diseases like irritable bowel syndrome, ulcerative colitis, colorectal cancer,Crohn's disease, constipation and amebiasis. To specifically target the colon, a variety of conventional, polymeric, and newly developed approaches are used. The current review is an attempt made to advance approaches for an effective colon drug delivery system.

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