INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725]
Journal Homepage: https://www.ijpsjournal.com

Review Article

A Review On Colon Targeted Drug Delivery System

Ruchiket K. Jagtap , Manisha Savle, Gajanan Sanap

Department of Pharmacy, Late Bhagirathi Yashwantraon Pathrikar College of Pharmacy.Pathri dirsct . Chh. Sambhajinagar,India

ARTICLE INFO

Received: 17 Dec 2023
Accepted: 21 Dec 2023
Published: 13 Jan 2024
Keywords:
Crohn's disease, inflammatory Bowel disease, colon drug delivery
DOI:
10.5281/zenodo.10494997

ABSTRACT

Day by day, advancements in the field of colon-specific drug delivery continue to emerge. The delivery of drugs directly to the colon is increasingly important, not only for treating local colon-related ailments like Crohn's disease and ulcerative colitis but also for administering proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive medications, and anti-diabetic agents systemically. Recent advancements have led to the development of new systems and technologies aimed at targeting the colon and surpassing the limitations of previous methods. Despite its promising potential, colon targeting requires further innovative exploration. This review article provides a concise overview covering the basics of the colon, factors influencing drug transition in the colon, colonic diseases, and the latest technologies emerging for colon-specific targeting.

INTRODUCTION

The oral route stands out as the most convenient and vital means of administering drugs for systemic effects. Around half of the drug delivery systems available today are geared towards oral intake, benefitting from patient acceptance and ease of use. Over the past decade, there has been a surge of interest in crafting formulations specifically targeted for the colon. This focus on colonic drug delivery isn't solely for treating local colon-related ailments such as Crohn's disease, ulcerative colitis, irritable bowel syndrome, and constipation; it also aims at delivering proteins, therapeutic peptides, anti-asthmatic, antihypertensive, and antidiabetic medications systemically. Various methods and techniques have emerged to achieve drug targeting in the colon [1,2]. For instance, creating prodrugs, employing pH-sensitive polymer coatings, utilizing biodegradable polymers in coatings, formulating with polysaccharides, implementing timed-release systems, pressure-controlled drug delivery systems, and osmotic pressure-controlled systems. Coating drugs with pH-sensitive polymers represents a straightforward approach for achieving colon-specific drug delivery [5,6].

***Corresponding Author:** Ruchiket K. Jagtap
Address: *Late Bhagirathi Yashwantrao Pathrikar College Of Pharmacy ,Pathri ,Ch.Sambhajinagar ,Maharashtra ,India.*
Email : ruchiketjagtap2002@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of colon targeting drug delivery system[7-9]:-

- The colon serves as an optimal location for delivering treatments to address specific ailments affecting this region of the digestive system.
- Treating a condition locally offers the advantage of necessitating smaller amounts of medication or drugs.
- It decreases the frequency at which doses need to be administered.
- Hence, lower cost of expensive drugs.
- This might result in a lower likelihood of experiencing side effects and potential interactions between drugs. Additionally, the colon presents an appealing location where poorly absorbed drug molecules could exhibit enhanced bioavailability.
- It helps in decreasing gastric irritation often caused by certain drugs, such as NSAIDs (nonsteroidal anti-inflammatory drugs).
- Bye pass initial first pass metabolism.
- Extended daytime or nighttime activity.
- Enhanced patient compliance is facilitated through targeted drug delivery systems that offer prolonged retention within the system. These systems also exhibit a heightened responsiveness to agents that improve the absorption of drugs that are typically poorly absorbed [10].
- The colon presents a favorable environment with lower hostile conditions and reduced peptidase activity. This characteristic allows for the administration of peptides, oral vaccines, insulin, growth hormones, and similar substances through this route, enabling their effective delivery [11].

Limitations of colon targeting drug delivery system:-

- Multiple manufacturing steps.
- The presence of resident microflora in the colon can influence colonic performance by metabolically breaking down or degrading the drug, potentially altering its effectiveness or properties.
- Incomplete release of drug.
- The bioavailability of a drug might be compromised due to potential nonspecific binding of the drug to dietary residues, intestinal secretions, mucus, or fecal matter, leading to reduced absorption or effectiveness.
- For drugs to be absorbed effectively, they need to be in a soluble form. This requirement poses a challenge for drugs with poor solubility, as achieving this soluble state becomes a crucial rate-limiting step in their absorption process.
- With the help of appropriate dissolution testing methods, we can evaluate the dosage form in-vitro [12].
- A significant limitation of the pH-sensitive coating technique is the uncertainty regarding the specific location and conditions under which the coating begins to dissolve. This uncertainty can affect the drug release and targeting accuracy within the digestive system [13].
- In patients with ulcerative colitis, the use of prodrugs is common. However, a notable limitation of the prodrug approach is its lack of versatility, primarily because its formulation relies on the specific functional groups available on the drug moiety for chemical linkage. This dependency restricts its adaptability across various drug types [14].
- Moreover, prodrugs represent novel chemical entities that require extensive evaluation before being employed as carriers for drug delivery. Their introduction necessitates thorough scrutiny and assessment to ensure their safety and efficacy as carriers for medications [15].

Need for colon targeting drug delivery:-

- Targeted drug delivery to the colon allows for direct treatment at the specific disease site, which enables lower dosing while reducing systemic side effects. This localized approach enhances therapeutic efficacy while minimizing adverse effects on the rest of the body.
- A site-specific or targeted drug delivery system designed for the colon facilitates the oral administration of peptide and protein drugs. Moreover, such formulations tailored for the colon can effectively prolong the delivery of these drugs, optimizing their therapeutic effects.
- Colon-specific drug delivery system is considered to be best in the treatment of colon related diseases [16].
- The colon offers a favorable site for both localized and systemic drug delivery. In managing inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, a common approach involves topical treatment. Glucocorticoids and sulphasalazine are frequently employed to address these inflammatory conditions, specifically targeting the affected areas within the colon for more effective treatment [17].
- Diseases like colorectal cancer could potentially benefit significantly from more effective treatments through targeted drug delivery to the colon. This approach may offer enhanced therapeutic outcomes and better management of such serious colon-related conditions [18].
- Formulations designed for colonic delivery aren't limited to treating specific conditions. They are also beneficial for delivering drugs that are polar, prone to chemical or enzymatic degradation in the upper gastrointestinal tract, or highly affected by hepatic metabolism. This includes therapeutic proteins and peptides, ensuring their effective delivery and optimal therapeutic outcomes [19].

ANATOMY AND PHYSIOLOGY OF COLON:-

Structure of Colon:-

The colon, part of the lower gastrointestinal tract, spans from the ileocecal junction to the anus, encompassing various sections such as the ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anus. In contrast to the small intestine, the colon has a smaller surface area, yet it facilitates effective absorption due to the presence of villi, microvilli, and a prolonged residence time. This cylindrical tube is about 2 to 3 inches in diameter and is lined with a moist, soft pink mucosal lining. Anatomic blood supply is present in both the colon and rectum, with accompanying lymph nodes and blood vessels. Colon activity involves segmenting and propulsive movements. Segmenting movements, primarily caused by circular muscles, create haustral sac-like formations, leading to the mixing of luminal contents. On the other hand, significant propulsive activity, related to defecation and driven by longitudinal muscles, occurs less frequently, averaging around three or four times daily [20].

Functions of Colon:-

1. Appropriate site and environment for the growth of colonic microorganism.

a. These bacteria are very rich in cytochrome. The normal flora of the large intestine and stops the growth of other pathogenic bacteria and serves a very useful purpose.

b. Certain bacteria possess the capability to break down cellulose. Research suggests that individuals experiencing constipation might exhibit a higher ability to break down cellulose compared to those without constipation. lead to a reduction in bulk.

2. Development of stool and storage reservoir of facial contents

3. The colon is responsible for absorbing potassium and water from the digestive lumen, which contributes to the formation of fecal contents. Additionally, substances like saline, glucose, certain anesthetics, and amino acids exhibit better absorption within the colon compared to other parts of the gastrointestinal tract. This absorption process in the colon significantly impacts the composition and characteristics of fecal matter.
4. Secretion and excretion of bicarbonate and potassium, bismuth,arsenic,mercury etc.
5. Microorganisms residing in the colon play a crucial role in synthesizing essential nutrients like vitamin K and folic acid. Additionally, they produce significant amounts of vitamin B12, although the majority of this synthesized B12 isn't absorbed in the colon itself but rather further along in the small intestine.

Absorption of Drugs from the Colon:-

In drug absorption within the colon, drugs passively enter through either the paracellular or transcellular routes. Lipophilic drugs typically use the transcellular route, passing through cells, while hydrophilic drugs favor the paracellular route, moving through tight junctions between cells.Yet, in the colon, the challenge lies in the limited paracellular absorption due to tightly bound epithelial cell junctions. Despite a smaller surface area than the small intestine, the slower transit rate in the colon allows drugs to linger longer near the mucosa. As water absorption increases along the colon, making the colonic content more viscous, drug dissolution slows down and the diffusion of dissolved drugs through the mucosa becomes sluggish, affecting their absorption.

pH of Various Area of Gastrointestinal Region:-

The pH in the stomach typically ranges between 1 and 2, but after eating, it tends to increase. Moving from the ileum to the colon, there's a notable decline in pH. Specifically, in the caecum, the pH is approximately around 6.4.

Region of Gastrointestinal tract	pH
Stomach	1.5 in fasting and 2-5 in fed condition
Small intestine	pH
Duodenum	6.1 in fasting and 5.4 in fed condition
Jejunum	5.4 Ileum 7.8 Large intestine 5.5-7
Rectum	7-8

Table no: 1. Showing pH of gastrointestinal tract.

Diseases of colon:-

I. **Crohn's Disease:**
Crohn's disease is an idiopathic, chronic, and ulcerative inflammatory bowel condition marked by granulomatous inflammation. It predominantly affects a segment of the terminal ileum or colon, though it can impact any part of the gastrointestinal tract.

II. **Ulcerative Colitis:**
It's an inflammatory bowel disease characterized by acute and chronic ulcerative inflammation affecting the mucosa and submucosa of the rectum and often extending to the descending part of the colon, potentially involving the entire length of the colon. Symptoms include acute flare-ups, diarrhoea, rectal bleeding, the formation of ulcers, and pus discharge.

III. **Amoebiasis:**
It is caused by an infection with the parasite Entamoebahistolytica. This infection primarily affects the large intestine. The infection occurs through the ingestion of the cyst form of the parasite, which dissolves in the small intestine, releasing amoebae that then travel to the large intestine. There, they invade the epithelium of the mucosa and subsequently the submucosa, leading to the formation of flask-shaped ulcers.

IV. **Diverticulosis:**
A condition characterized by the formation of outpouchings or herniations in the mucosa and submucosa, typically in the colon. Symptoms may include abdominal pain, constipation, and intermittent bleeding.

V. **Diverticulitis**:

It is the inflamed or infected state of diverticula. It often leads to symptoms like abdominal pain and discomfort, alongside issues such as constipation.

VI. Colon Bleeding:

There are of two types of Varicosities of haemorrhoidalveinsm

a. Internal pile: dilation of superior haemorrhoid plexus.
b. External pile: dilation of inferior plexus. These cause bleeding which we can see in stool.

VII. Salmonellosis:

A bacterial infection caused by non-typhoidal Salmonella, typically contracted after ingesting contaminated food. The infection leads to symptoms like diarrhoea and stomach cramps. Physicians often prescribe antibiotics to eliminate the bacterial infection from the intestine

VIII. Hirschsprung's disease:

A condition that affects the large intestine (colon) and causes problems with passing stool.

IX. Diarrhoea:

It's characterized by an increase in the frequency, volume, and fluid content of feces due to heightened intestinal motility and reduced absorption. This rapid passage of feces through the large intestine can lead to dehydration and imbalances in electrolytes. Various factors such as lactose intolerance, stress, or irritants like certain microbes can contribute to excessive motility and diarrhoea, which sometimes resolves on its own.

X. Traveler's Diarrhoea:

Bacteria like enterotoxigenic Escherichia coli, enteroaggregative E. coli, Campylobacter, Salmonella, and Shigella are frequent culprits behind traveler's diarrhea. These bacteria induce symptoms such as loose stools, nausea, vomiting, and fever in individuals while traveling.

XI. Coloractal Polyps:

Polyps refer to growths or masses that protrude from the mucous membrane into the lumen of an organ. They are most commonly found in the large intestine and the rectosigmoid colon compared to the proximal colon. Polyps can be categorized as either neoplastic (potentially cancerous) or non-neoplastic.

XII. Colon Cancer:

Colon cancer ranks as the fourth most prevalent cancer worldwide, and it leads to approximately 639,000 reported deaths annually [21].

Method of colorectal examination:-

I. Digital rectal examination:

a physician performs a rectal examination by inserting a finger into the rectum to detect any abnormalities, such as polyps or other irregularities in the rectal or colon area .

II. Fecal occult blood testing (FOBT):

Testing a fecal sample for microscopic amounts of blood, known as fecal occult blood testing, can indicate the presence of blood in the stool. While it could suggest a bleeding tumor, it's essential to note that various other factors or conditions might also cause blood to appear in the stool.

III. Barium enema:

a diagnostic procedure used to visualize the rectum and colon. A suspension of barium sulfate is introduced into the rectum, coating the colon's walls and making them visible on X-rays as they appear opaque. This helps in detecting abnormalities in the colon.

IV. Sigmoidoscopy:

It involves inserting a sigmoidoscope, a slender, illuminated tube with a camera on its tip, into the rectum and guiding it through to the sigmoid colon. This diagnostic test assists in detecting polyps, tumors, and various other abnormalities specifically within the rectum and sigmoid colon.

V. Colonoscopy:

This procedure involves using a flexible tube equipped with a tiny camera to thoroughly examine the entire colon. Colonoscopies are highly sensitive and effective for detecting polyps, cancers, and other abnormalities within the entire length of the colon.

VI. Fiberoptic colonoscopy:

It involves a thin, illuminated tube equipped with a camera, but in a colonoscopy, the tube is guided further into the colon to visualize its entirety. During this procedure, the colonoscope pumps air into the colon to aid in visualization while a video camera records images displayed on a screen for the physician to assess in real-time. If abnormal tissues like polyps are detected, they can be removed and biopsied during the same procedure [21].

VII. Colonic pH:

as shown in Table No. 1. These pH fluctuations can be influenced by dietary factors, the type of food consumed, and various disease conditions. Researchers have capitalized on these pH variations by using pH-sensitive enteric coating polymers to deliver drugs specifically to the colon. This strategy allows for targeted drug delivery, aiming to achieve both local and systemic effects based on the pH-sensitive properties of these coatings.

Drug candidates for colon targeting:-

- It's beneficial for them to have poor absorption characteristics in both the stomach and small intestine. This ensures that the drug remains intact until it reaches the colon, where absorption or release can be optimized based on the specific site of action.
- It needs to match the carrier molecule and readily undergo transformation within the large intestine.
- It needs to maintain stability within the alkaline pH environment of the gastrointestinal tract.
- It should exhibit both localized and systemic impacts.
- Medications are employed to address diverse intestinal disorders like ulcerative colitis, amoebiasis, colon cancer, inflammatory bowel disease, and diarrhea [22].

METHODS USED FOR DRUG TARGETTING COLON

Formation of prodrugs:-

(example: azo-Prodrug, glucuronide conjugate, etc.)

A prodrug is essentially a dormant medication that becomes effective only after the body transforms or metabolizes it. It involves creating a chemical bond between the drug and a carrier. When takenorally, it reaches the colon without being absorbed in the upper gastrointestinal tract. In the colon, the release of the drug is initiated due to the heightened activity of specific enzymes, which is notably higher compared to the stomach and small intestine [24].

a. Azo bond conjugate: Sulfasalazine is primarily employed in treating inflammatory bowel diseases. It serves as a prodrug for 5-Amino Salicylic Acid (5-ASA). Around 85% of the orally administered dose of sulfasalazine reaches the colon without being absorbed, where it undergoes a reduction due to the anaerobic conditions present, resulting in the formation of 5-ASA and sulphapyridine.Various studies have explored sulphapyridine, leading to the development of other prodrugs such as Olsalazine, Balsalazine, and 4-amino benzoyl-alanine. Intestinal microflora plays a role in producing glycosidase, an important group of enzymes. Evaluations of colon-specific formulations of flurbiprofen utilized azo-aromatic and pH-sensitive polymers, with the conclusion that the azo-aromatic polymer (poly-methyl methacrylate hydroxy rthylmethacrylate:1:5) was effective. Additionally, a mutual azo prodrug of 5-aminosalicyic acid with histidine was synthesized by coupling L-histidine with salicylic acid, aiming for targeted drug delivery to inflamed gut tissue [29].

b. Glucuronide conjugate: Glucuronide and sulfate conjugation represent major mechanisms for deactivating and facilitating the clearance of numerous drugs. Within the lower gastrointestinal tract, bacteria produce glucuronidase, which glucuronidates several drugs in the intestine. Given that the glucuronidation process leads to the liberation of active drug compounds and allows for their reabsorption, glucuronideprodrugs are anticipated to be more effective for targeted drug delivery to the colon [31].

i. Cyclodextrin conjugates: Hydrophilic and ionizablecyclodextrins serve as potent carriers in both immediate and delayed-release formulations, while hydrophobic cyclodextrins can regulate the rate of water release. The most desirable attribute for a drug carrier is its capability to deliver the drug to a specific target site. Creating conjugates of a drug with cyclodextrins offers a versatile approach to develop a new class of colon-targeting prodrugs for soluble drugs. Studies investigated Ibuprofen prodrugs associated with alpha-, beta-, and gamma-cyclodextrins. Additionally, Methotrexate prodrugs linked to alpha- and gamma-cyclodextrins were synthesized, demonstrating their primary purpose in masking the ulcerogenic potential of the free drug. This was

achieved using a 12-fold dose of the normal Methotrexate dose and equivalent doses of the esters [32].

ii. Dextran conjugates: Prodrugs involving dextranesters of metronidazole have been developed and thoroughly examined. Additionally, dextran ester prodrugs of dexamethasone and methylprednisolone were synthesized, demonstrating the effectiveness of these prodrugs in delivering medications specifically to the colon. Methylprednisolone and dexamethasone were linked covalently to dextran using a succinate linker, forming these conjugates for targeted drug delivery [33]

iii. Amino-acid conjugates: The presence of polar groups like NH2 and COOH in proteins and their basic units (amino acids) contributes to their hydrophilic nature, which reduces membrane permeability. Prodrugs have been developed by attaching drug molecules to these polar amino acids. Non-essential amino acids like tyrosine, glycine, methionine, and glutamic acid were conjugated to Salicylic acid in various preparations [34].

Hydrogels:-

Hydrogels offer a means for the targeted delivery of peptide and protein drugs to the colon. These hydrogels consist of acidic components and enzymatically degradable azo-aromatic cross-links. At acidic pH levels, the gels exhibit minimal swelling, offering protection to the drug against degradation in the stomach. However, as the environmental pH increases and becomes more basic, the swelling of the hydrogel increases. This increased swelling facilitates easier access for enzymes like azoreductase, ultimately leading to the release of the drug [35].

Coating with pH dependent polymers:-

The pH levels in the terminal ileum and colon are notably higher compared to other parts of the gastrointestinal tract, making them prime targets for dosage forms that disintegrate at these elevated pH ranges. The pH in the terminal ileum is higher than in the cecum. Dosage forms often experience a delay at the ileocecal junction, demanding careful consideration of the composition and thickness of the enteric coat to ensure that disintegration happens only after the dosage form moves from the terminal ileum into the cecum [36]. Eudragit, also known as Eastacryl, Kollicoat MAE, and polymeric methacrylates, serves as a synonym. Delayed-release tablets containing mesalazine, coated with Eudragit S-100, were studied. These tablets dissolved at a pH level of 7 or higher, releasing mesalazine specifically in the terminal ileum and beyond, targeting inflammatory action in the colon. While the formulation succeeded in delivering mesalazine to the intended site, instances of reported coating failure were noted [37]. Commonly used pH-dependent polymers include derivatives of acrylic acid and cellulose. In colonic drug delivery, drug cores are coated with these pH-sensitive polymers. Various forms such as tablets, capsules, pellets, granules, micro-particles, and nanoparticles are utilized for this purpose [38].

Disadvantages of this method are:-

i. Inconsistency in the dissolution of the polymer at the intended site

ii. .Lack of precision in the pH-dependent systems for targeting specific sites within the gastrointestinal tract leads to variations in polymer dissolution, observed either in the distal portion of the colon or even at the end of the ileum, contingent upon the gastrointestinal motility intensity (Table 2). pH-dependentmicrobeads containing theophylline hydrochloride were developed and assessed using alginate and chitosan through the ionotropic gelation method, followed by enteric coating with eudragit S100. Investigations focused on prednisolone formulations containing 1% eudragit RS PM, displaying complete (100%) drug release. Tablets containing mesalazine were scrutinized, coated with two polymers—eudragit L100 and eudragit S100—in varying ratios: 1:0, 4:1, 3:2, 1:1, 1:5, and 0:1.

Chitosan microspheres containing Ondansetron were prepared via the emulsion cross-linking method, utilizing a combination of eudragit S100 and chitosan polymers. Regression analysis indicated that the potential drug release followed the Peppas model. Mebeverine Hydrochloride microspheres were formulated using eudragit S100 and L100, displaying a biphasic release pattern characterized by non-Fickian diffusion release over 12 hours [39].

Sr. No.	Polymer	pH
1.	Cellulose acetate phthalate (CAP)	5.0
2.	Polyvinyl acetate phthalate (PVAP)	5.0
3.	Hydroxyl propyl methyl cellulose phthalate (HPMCP)	4.8 – 4.8
4.	Cellulose acetate trimelliate	4.8
5.	Eudragit L-30D	5.6
6 .	Eudragit FS 30D	6.8
7.	Eudragit L 100 – 55	5.5
8.	Eudragit L 100	6.0
9.	Eudragit S 100	7.0
10.	Kollicoat 30 D	5.5

Table 2. Various pH dependent polymer.

Timed released systems:-

(example: pulsatile release, pulsincap, delayed release, sigmoidal release system)

The concept revolves around delaying drug release for 3–5 hours after entering the small intestine. This strategy aims for drug release after a set lag time, determined by the transit duration from mouth to colon, which relies on gastric motility and dosage form size. The Pulsincap device, an early approach, comprises a non-disintegrating capsule body sealed with a hydrogel plug and a water-soluble cap, all coated with an enteric polymer. Once in the small intestine, the enteric coating dissolves, and the hydrogel plug starts swelling. The plug is designed to pop out only after a predetermined time, releasing the contents. Another method involves incorporating organic acids alongside the drug in a hard gelatin capsule and sealing the joint with an ethanolic solution of ethylcellulose. The capsule is sequentially coated with an acid-soluble cationic polymer, followed by hydroxypropyl methylcellulose, and finally enterically coated with hydroxypropyl methyl cellulose acetate succinate. After ingestion, the outer enteric layer prevents drug release in the stomach. Upon gastric emptying, water enters the capsule. As the pH decreases due to organic acid dissolution, the acid-soluble layer dissolves, leading to rapid drug release. For treating nocturnal asthma, a chrono modulated drug delivery system for salbutamol sulphate was developed. Cores containing salbutamol sulphate were coated with layers, including an inner swelling layer (hydroxy propyl methyl cellulose E5) and an outer rupturable layer (eudragit RL/RS 1:1), intended for timed release. A combination of pH and time sensitivity was employed in a drug delivery system using press-coated mesalamine tablets with an HPMC E-15 coat, further over-coated with eudragit S100. Additionally, a novel time and pH-dependent system involved compression-coating mesalamine core tablets with HPMC K4M, subsequently coated with eudragit L100. The study revealed that increasing HPMC led to longer lag times and t50 values.Osmotic pressure-controlled systems, also known as OROS, ensure the intact passage of the unit to the colon, where drug release occurs due to the osmotic pressure generated by solvent entry [40].

There are two OROS systems for colon drug delivery [41]:-

1. **Osmet pump:-**

This system involves an enteric-coated semi-permeable shell that surrounds an osmotic layer and a central reservoir filled with the drug, which is impermeable and collapsible. Inside this compartment, there's a delivery orifice connected to the external environment. Once the gastric-resistant film dissolves, water can penetrate through the semi-permeable membrane, increasing pressure within the device [42]. This pressure change causes the inner reservoir to shrink, leading to the pumping out of the drug formulation.

2. **OROS CT:-**

Right after ingestion, the dissolution of the hard gelatin capsule shell takes place [43]. The push and pull unit, coated with an enteric coat, prevents water absorption in the stomach's acidic environment [44-48]. When this coating dissolves,

the osmotic pumping action initiates, enabling the drug to be delivered through the orifice at a controlled rate, governed by the transport rate of water across the membrane [49].

Designing formulations using polysaccharides:- (example: bacterial enzymes)

Dosage forms benefit from the protective influence of polysaccharides in the upper gastrointestinal tract (GIT), with drug release occurring in the colon due to the swelling and biodegradable action of polysaccharidases. Polysaccharides sourced from plants (e.g., pectin, guar gum, inulin), animals (e.g., chitosan, chondroitin sulfate), algae (e.g., alginates), or microbes (e.g., dextran) have been investigated for colon targeting. These polymers are broken down by colonic microflora into simple saccharides by saccharolytic species like bacteroides and bifidobacteria. Upon arrival in the colon, the hydrolysis of glycosidic linkages triggers the release of the enclosed bioactive [50]. While specifically degraded in the colon, many of these polymers are hydrophilic and swell under upper GI conditions, causing premature drug release. To address this, natural polysaccharides are chemically modified and mixed with hydrophobic, water-insoluble polymers. Alternatively, in formulations, they are often coated with pH-sensitive polymers. For instance, a pectin/chitosan-based colonic delivery system has been developed. Calcium pectinate was used as a carrier based on the assumption that, like pectin, it can be decomposed by specific pectinolytic enzymes in the colon while retaining its integrity in the small bowel's physiological environment. Derivatives such as methoxylated and amidatedpectins have also been developed. Guar gum-based matrix tablets of metronidazole/tinidazole were formulated, studying the impact of co-administering these drugs on the effectiveness of guar gum as a carrier for colon-specific drug delivery. Khaya gum-coated fast-disintegrating core tablets of budesonide followed by eudragit S100 coating exhibited varying release profiles in the upper digestive tract and with or without rat cecal contents, suggesting that khaya gum alone might not suffice for colon targeting.

Tablet formulations using pectin as a carrier and diltiazem HCl and indomethacin as model drugs were also developed. Coating these tablets with inulin followed by shellac showed promise for effectively targeting both water-soluble and insoluble drugs to the colon [51].

Bio adhesive systems:-

Bio adhesion is an essential concept in formulating drug delivery systems aimed at specific organs, such as the colon. It involves the dosage form adhering to a particular organ for an extended period, leading to increased local drug concentration or improved absorption, especially beneficial for poorly absorbable drugs [52].Several polymers, such as polycarbophils, polyurethanes, and copolymers of polyethylene oxide and polypropylene oxide, have been extensively studied as potential materials for bio adhesive systems. These polymers possess properties that enable them to adhere to the mucosal surfaces of the colon, enhancing the residence time of the drug at the site of absorption or action. This extended contact can facilitate better drug absorption or sustained drug release, contributing to improved therapeutic outcomes for drugs targeting the colon [53].

Osmotic drug delivery:-

The osmotic drug delivery system for metronidazole involves a core comprising the drug and osmotic agents (like mannitol and fructose), prepared through direct compression. This core is coated with a semipermeable membrane consisting of cellulose acetate, PEG400, and guar gum dissolved in acetone and methanol, forming a membrane with a thickness of 90µm. Additionally, an enteric polymer coating, specifically eudragit

S100, is applied. During the gastrointestinal transit, the enteric polymer prevents dissolution in the stomach but dissolves in the higher pH of the small intestine, allowing intestinal fluid to enter the tablet core. This fluid interacts with the osmotic agents, creating osmotic pressure. As the system progresses to the colon, the guar gum, acting as a pore former, degrades due to colonic microflora, forming pores. The generated osmotic pressure eventually leads to the rupture of the core, resulting in drug release in the colon. Another system, OROS-CT, involves a drug core surrounded by a semipermeable membrane and coated with an enteric polymer. This setup delays drug release for 2-4 hours to prevent early release in the upper gastrointestinal tract. This controlled release mechanism maintains consistent drug delivery for up to 24 hours and is utilized in the treatment of conditions like ulcerative colitis, Crohn's disease, and idiopathic proctitis [54].

CONCLUSION:-

The colonic region has gained significance in drug delivery and absorption, offering substantial therapeutic advantages for local and systemic treatment through Controlled Drug Delivery Systems (CDDS). Achieving specificity for the colon is better realized through systems utilizing natural materials broken down by enzymes from colonic bacteria. Despite the sophistication of colon-specific drug delivery systems, challenges persist.One significant challenge involves establishing a reliable dissolution method that mirrors the physiological conditions of the colon. This method should ideally correlate with in-vivo behavior. Presently, uncertainties exist in the capability of current dissolution methods to achieve this correlation accurately. Pharmaceutical scientists are tasked with developing and validating dissolution techniques that capture the intricate features of the colon's environment while remaining practical for routine use in the industry for evaluating Controlled Drug Delivery Systems (CDDS). This pursuit aims to ensure that the performance of drug delivery systems in lab settings aligns closely with their behavior inside the human body.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

REFERENCES

1. Luppi, Barbara, et al. "pH-sensitive polymeric physical-mixture for possible site-specific delivery of ibuprofen." European journal of pharmaceutics and biopharmaceutics 55.2 (2003): 199-202.
2. Lachman, Leon, Herbert A. Lieberman, and Joseph L. Kanig. The theory and practice of industrial pharmacy. Philadelphia: Lea & Febiger, 1976.
3. Antonin, K. H., et al. "The absorption of human calcitonin from the transverse colon of man." International journal of pharmaceutics 130.1 (1996): 33-39.
4. Tozaki, Hideyuki, et al. "Chitosan capsules for colon-specific drug delivery: improvement of insulin absorption from the rat colon." Journal of pharmaceutical sciences 86.9 (1997): 1016-1021.
5. Van den Mooter, Guy, and Renaat Kinget. "Oral colon-specific drug delivery: a review." Drug delivery 2.2 (1995): 81-93.
6. Prasad, YV Rama, Y. S. R. Krishnaiah, and S. Satyanarayana. "In vitro evaluation of guar gum as a carrier for colon-specific drug delivery." Journal of controlled release 51.2-3 (1998): 281-287.
7. Jain, Vikas, Shikha Jain, and S. C. Mahajan. "Nanomedicines based drug delivery systems for anti-cancer targeting and treatment." Current drug delivery 12.2 (2015): 177-191.
8. Halsas, M., et al. "Time-controlled release pseudoephedrine tablets: bioavailability and in vitro/in vivo correlations." Die Pharmazie 56.9 (2001): 718-723.

9. Kinget, Renaat, et al. "Colonic drug targeting." Journal of drug targeting 6.2 (1998): 129-149.
10. Yang, Libo, James S. Chu, and Joseph A. Fix. "Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation." International journal of pharmaceutics 235.1-2 (2002): 1-15.
11. Rathod, S., A. Ram, and G. Thiru. "Colon targeted pulsatile drug delivery: A review." Pharmainfo net 5.2 (2007): 1-11.
12. Kaur, Apninder, et al. "Polymeric drug delivery approaches for colon targeting: A review." Drug Delivery Letters 4.1 (2014): 38-48.
13. Nugent, S. G., et al. "Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs." Gut 48.4 (2001): 571-577.
14. Jose, S., et al. "Colon targeted drug delivery: Different approaches." Journal of young pharmacists 1.1 (2009): 13.
15. Gaurav, Tiwari, et al. "Primary and novel approaches for colon targeted drug delivery-A review." International Journal of Drug Delivery 2.1 (2010): 01-11.
16. Malik, K., et al. "A review on colon targeting drug delivery system: Novel approaches, anatomy and evaluation." The pharma innovation 1.9, Part A (2012): 1.
17. JASRA, KHUSHBOO, et al. "COLON TARGETED DRUG DELIVERY SYSTEM: A SYSTEMIC REVIEW." NeuroQuantology 20.12 (2022): 84.
18. Sarasija, S., and A. Hota. "Colon-specific drug delivery systems." Indian journal of pharmaceutical sciences 62.1 (2000): 1-8.
19. Qureshi, Altamash M., et al. "Colon targeted drug delivery system: A review on current approaches." Indian J Pharm Biol Res 1.4 (2013): 130-47.
20. Pye, G., et al. "Gastrointestinal intraluminal pH in normal subjects and those with colorectal adenoma or carcinoma." Gut 31.12 (1990): 1355-1357.
21. Wong, Tin Wui, Gaia Colombo, and Fabio Sonvico. "Pectin matrix as oral drug delivery vehicle for colon cancer treatment." Aaps PharmSciTech 12 (2011): 201-214.
22. Leddin, Desmond, et al. "Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: guidelines on colon cancer screening." Canadian Journal of Gastroenterology and Hepatology 18 (2004): 93-99.
23. Qureshi, Altamash M., et al. "Colon targeted drug delivery system: A review on current approaches." Indian J Pharm Biol Res 1.4 (2013): 130-47.
24. Singh, Nishant, and R. C. Khanna. "Colon targeted drug delivery systems-A Potential Approach." The Pharma Innovation 1.2 (2012).
25. Klotz, Ulrich. "Clinical pharmacokinetics of sulphasalazine, its metabolites and other prodrugs of 5-aminosalicylic acid." Clinical pharmacokinetics 10.4 (1985): 285-302.
26. Chan, Rosalind P., et al. "Studies of two novel sulfasalazine analogs, ipsalazide and balsalazide." Digestive diseases and sciences 28 (1983): 609-615.
27. Jain, S. K., M. K. Chourasia, and R. Dengre. "Azo polymers for colon targeted drug delivery." Indian journal of pharmaceutical sciences 67.1 (2005): 43-50.
28. Nagpal, Deepika, et al. "Mutual azo prodrug of 5-aminosalicylic acid for colon targeted drug delivery: synthesis, kinetic studies and pharmacological evaluation." Indian journal of pharmaceutical sciences 68.2 (2006)
29. Scheline, Ronald R. "Drug metabolism by intestinal microorganisms." Journal of

pharmaceutical sciences 57.12 (1968): 2021-2037.

30. Tanaka, Hiroshi, et al. "Synthesis of doxorubicin-cyclodextrin conjugates." The Journal of Antibiotics 47.9 (1994): 1025-1029.
31. MHASKE, Deepali V., et al. "Synthesis and pharmacological evaluation of cyclodextrin conjugate prodrugs of ibuprofen." Indian journal of pharmaceutical sciences 67.4 (2005): 432-437.
32. Gupta, D., et al. "Synthesis and evaluation of pharmacological activities of cyclodextrin conjugates of methotrexate." Indian journal of pharmaceutical sciences 66.1 (2004): 26-30.
33. Johansen, Marianne, and Claus Larsen. "Stability and kinetics of hydrolysis of metronidazole monosuccinate in aqueous solution and in plasma." International journal of pharmaceutics 21.2 (1984): 201-209.
34. NAKAMURA, Junzo, et al. "A novel prodrug of salicylic acid, salicylic acid-glutamic acid conjugate utilizing hydrolysis in rabbit intestinal microorganisms." Chemical and pharmaceutical bulletin 40.8 (1992): 2164-2168.
35. Brøndsted, Helle, and Jindřich Kopeček. "Hydrogels for site-specific oral drug delivery: synthesis and characterization." Biomaterials 12.6 (1991): 584-592.
36. Rowe, Raymond C., Paul Sheskey, and Marian Quinn. Handbook of pharmaceutical excipients. Libros Digitales-Pharmaceutical Press, 2009.
37. Schroeder, Kenneth W., William J. Tremaine, and Duane M. Ilstrup. "Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis." New England Journal of Medicine 317.26 (1987): 1625-1629.
38. Ashford, Marianne, et al. "An in vivo investigation into the suitability of pH dependent polymers for colonic targeting." International journal of pharmaceutics 95.1-3 (1993): 193-199.
39. Khan, M. S., B. K. Sridhar, and A. Srinatha. "Development and evaluation of pH-dependent micro beads for colon targeting." Indian Journal of pharmaceutical sciences 72.1 (2010): 18.
40. Sahib, Mohanad Naji, Shaymaa Abdalwahed Abdulameer, and A. A. Rasool. "Design and in vitro evaluation of prednisolone tablets as a potential colon delivery system." Asian journal of pharmaceutical and clinical research 2.4 (2009): 84-93.
41. Khan, M. Zahirul I., Helena P. Štedul, and Nevenka Kurjaković. "A pH-dependent colon-targeted oral drug delivery system using methacrylic acid copolymers. II. Manipulation of drug release using Eudragit® L100 and Eudragit S100 combinations." Drug Development and industrial pharmacy 26.5 (2000): 549-554.
42. Jose, S., et al. "Multiparticulate system for colon targeted delivery of ondansetron." Indian journal of pharmaceutical sciences 72.1 (2010): 58.
43. Dandagi, P. M., et al. "pH-sensitive mebeverine microspheres for colon delivery." Indian Journal of Pharmaceutical Sciences 71.4 (2009): 464.
44. Kumar, Manoj, et al. "Report on pharmaceutical approaches to colon targeted drug delivery systems." J Pharm Res 3.3 (2010): 157-159.
45. Ishibashi, Takashi, et al. "Design and evaluation of a new capsule-type dosage form for colon-targeted delivery of drugs." International journal of pharmaceutics 168.1 (1998): 31-40.
46. Qureshi, J., et al. "Chronomodulated drug delivery system of salbutamol sulphate for the

treatment of nocturnal asthma." Indian journal of pharmaceutical sciences 70.3 (2008): 351.

47. Mukesh C. G., Rajesh K. P., Stavan A. N., MaheshR. D. / Pharm. Dev. Technol. 2008. V. 13.P. 447 – 456.
48. Patel, Mayur M., et al. "Design, development and optimization of a novel time and pH-dependent colon targeted drug delivery system." Pharmaceutical development and technology 14.1 (2009): 65-72
49. Theeuwes, Felix, George V. Guittard, and Patrick SL Wong. "Delivery of drug to colon by oral disage form." U.S. Patent No. 4,904,474. 27 Feb. 1990.
50. Ofori-Kwakye, Kwabena, and John T. Fell. "Biphasic drug release: the permeability of films containing pectin, chitosan and HPMC." International journal of pharmaceutics 226.1-2 (2001): 139-145.
51. Krishnaiah, Y. S. R., et al. "Guar gum as a carrier for colon specific delivery; influence of metronidazole and tinidazole on in vitro release of albendazole from guar gum matrix tablets." J Pharm Pharm Sci 4.3 (2001): 235-43.
52. Prabhu, Prabhakara, et al. "Investigation of colon specificity of novel polymer Khaya gum." Indian J Pharm Educ Res 44 (2010): 56-65.
53. Ravi, V., and TM Pramod Kumar. "Novel colon targeted drug delivery system using natural polymers." Indian journal of pharmaceutical sciences 70.1 (2008): 111.
54. Lenaerts, Vincent M., and Robert Gurny. Bioadhesive drug delivery systems. CRC press, 1989.

HOW TO CITE: Ruchiket K. Jagtap ,Manisha Savle ,Gajanan Sanap, A Review On Colon Targeted Drug Delivery System., Int. J. of Pharm. Sci., 2024, Vol 2, Issue 1, 142-154. https://doi.org/10.5281/zenodo.10494997