Int. J. Sci. R. Tech., 2025 2(9)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Colon Targeted Drug Delivery System: An Overview on Current Approaches

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ABSTRACT

Recent reports indicate interest in colon as a site where poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have less hostile environment as well as enzyme activity compared to stomach and small intestine. The development of a dosage form that improves the oral absorption of peptide and protein drugs whose bioavailability is very low because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral peptide delivery in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for spatial delivery of candidates like peptides, proteins, oligonucleotides and vaccines. However, drug release is not the end point of oral delivery. The bioavailability of protein drugs delivered at the colon site needs to addressed. The use of drug absorption enhancers into the drug delivery systems is likely to enhance therapeutic efficacy. Studies on drug absorption by the intestinal system have focused on drug transporters that mediate drug influx and efflux and agents which can enhance drug absorption. The colon segment is designed by nature mainly to expel metabolism products rather than to absorb nutrients. Therefore, more research that is focused on the specificity of drug uptake at the colon site is necessary. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

Keywords: Colon targeted drug delivery system, polymer, multiparticulate, IBD

INTRODUCTION

Due to its excellent benefits in the treatment of a number of illnesses, including colorectal infection, ulcerative colitis, crohn diseases, and colorectal cancer, colonic drug administration has lately grown in popularity. Some colonic disorders can be locally treated while avoiding systemic absorption and potential harmful effects by using colonic drug administration. Innovative colon drug delivery strategies may also enable the transfer of medicines, peptides, and proteins that are commonly influenced by abrupt pH changes between the stomach and small intestine [1-5]. When administered orally or recally, the colon may be the primary target. Rectal administration is often reserved for palliative and emergency cases since it is uncomfortable for patients and difficult to target particular areas of the colon. Because it is non-invasive, easy to administer, and practical, the oral route is recommended because these factors increase the likelihood that the patient will take their prescription as prescribed. Additionally, the likelihood that patients will accept it is increased. Additionally, it is a safe distribution technique that does not call for sterile production setting, making such system easier to construct while boosting industrial flexibility and reducing production cost [4,6-8]. But there are special issues with the way oral medications are dispersed. It could be challenging to provide the highest therapeutic dosage without triggering breakdown and absorption in the stomach and small intestine since the colon is the furthest region of the gastrointestinal system. The small intestine proteolytic activity can denature the pharmaceuticals, whilst the stomach's acidic pH levels may expedite the breakdown of proteins and medications that are pH-sensitive. Additionally, there is less water in the colon, which might result in medicine not being well absorbed [3-5] To prevent the substantial physiological changes in the upper GIT and concentrate medicine release in the colon arrange of colon, semi-synthetic polymers have been studied. In order to create a range of Colon targeted drug delivery system (CTDDS), the polymers are used from the matrix tablets to make it more sophisticated osmotic pressure system. Nanotechnology makes it

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.

easier for colon medication to be administered [7,9-10]. A variety of nano-technologies like microsphere, nanoparticles, niosomes, nanocapsules and small tablets etc. are efficient at delaying medication release until it releases to the colon. polysaccharides make the majority of polymer including its derivatives to create matrix tablets formulation [11]. Natural polysaccharides are the first line choice for the industrial manufacturing since they are extensively used.

Various Disease Conditions:

Colon Cancer: Colon cancer happens when cells in the colon develop changes in their DNA. A cells' DNA holds the instructions that tell the cell what to do. The changes tell the cells to multiply quickly. The changes let the cells continue living when healthy cells die as part of their natural lifecycle. This causes too many cells. The cells might form a mass called a tumor. The cells can invade and destroy healthy body tissue. In time, the cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer. [12]

Colonic Polyps: A polyp is an extra piece of tissue that grows inside your body. Colonic polyps grow in the large intestine, or colon. Most polyps are not dangerous. However, some polyps may turn into cancer or already be cancer. To be safe, doctors remove polyps and test them. Polyps can be removed when a doctor examines the inside of the large intestine during a colonoscopy. [13]

Ulcerative colitis: Ulcerative colitis (UC) is a disease that causes inflammation and sores, called ulcers, in the lining of the rectum and colon. It is one of a group of diseases called inflammatory bowel disease. UC can happen at any age, but it usually starts between the ages of 15 and 30. It tends to run in families. The most common symptoms are pain in the abdomen and blood or pus in diarrhea [14].

Diverticulosis: Diverticula are small pouches, or sacs, that bulge outward through weak spots in your colon. They mostly form in the lower part of the colon. Diverticulosis is a condition in which you have these pouches. Most people who have diverticulosis do not have symptoms or problems. But sometimes the pouches can cause symptoms or become inflamed. [15].

Diverticulitis: Diverticulitis is the name for the condition you have when one or more of the pouches get inflamed. Diverticulitis may come on suddenly. It can sometimes cause serious health problems [15].

Irritable bowel syndrome (IBS): irritable bowel syndrome (IBS) is a problem that affects the large intestine. It can cause abdominal cramping, bloating, and a change in bowel habits. Some people with the disorder have constipation. Some have diarrhea. Others go back and forth between the two. Although IBS can cause a great deal of discomfort, it does not harm the intestines. IBS is common. It affects about twice as many women as men and is most often found in people younger than 45 years. No one knows the exact cause of IBS. There is no specific test for it. Your doctor may run tests to be sure you don't have other diseases. These tests may include stool sampling tests, blood tests, and x-rays. Your doctor may also do a test called a sigmoidoscopy or colonoscopy. Most people diagnosed with IBS can control their symptoms with diet, stress management, probiotics, and medicine [16].

Approaches for Design and Development Of Colon-Specific Drug Delivery System:

A. Chemical Approach:

- **Amino Acid Conjugation:** The presence of polar groups, e.g., NH2 and –COOH in proteins, reduces the membrane permeability of amino acids and proteins because of the hydrophilic nature of polar groups. As the hydrophilicity and chain length of carrier amino acid increases, the permeability of amino acids and proteins decreases [17]. Thus, amino acid conjugation results in high enzymatic specificity for hydrolysis by the enzyme of the colon.

- **Dextran Conjugates:** Dextran is a bacteria-based polysaccharide where the monosaccharides are connected by glycosidic linkages. Dextranase is the enzyme that is in charge of the hydrolysis of these linkages. The pro-drug technique of dextran can be applied for colon targeted drug delivery having a carboxylic acid function. In the upper

GIT, dextranase has negligible activity, but anaerobic gram-negative bacteria which is found in a high concentration in the large intestine, shows high dextranase activity. [18]

- **Glucuronide Conjugates:** "Glucuronide conjugation" is the main metabolic pathway of drug. Lower gastrointestinal tract contains a bacteria that produce "β-glucuronidase" and can deglucuronidate various active agents in the intestine. Thus, the active drug is released and reabsorbed by the process of deglucuronidation. This concept is applied for the transporting drug to colon, where the drug is coupled with glucuronide conjugation after oral delivery. [19]

- **Polymeric Pro-drugs:** New approaches in colon targeted formulation involve polymers as a carrier for the delivery of the drug to the colon. All-natural and synthetic polymers can be utilized as drug carriers. Polymeric pro-drugs can be formed with azo linkage between the polymer and the drug by using sub-synthetic polymers. Evaluations of different azo polymers as coating material have been performed. Azoreductase is the enzyme that is responsible for cleaving azo polymers in the large intestine. It has been found that peptide capsules coated with azo polymers prevent the digestion of drugs in the stomach and small intestine. When the capsule reaches colon, azo bonds are reduced, and the medication is released. [20]

B. Pharmaceutical Approach:

- **pH-Sensitive Polymer Coating:** The covering of pH-delicate polymers to the pellets, tablets, and capsules give postponed discharge and shield the dynamic medication from the fluid of gastrointestinal tract. The polymers utilized for aiming medications or in any case ought to have the option to resist the lower pH estimations of the stomach and of the proximal piece of the small digestive system and furthermore have the option to deteriorate at the unbiased of marginally soluble pH of the terminal ileum and ideally at the ileocecal intersection. These procedures dis-seminate the medication all through the digestive organ and enhance the capability of the colon focused on conveyance frameworks. By this approach, the formulation is protected in the stomach and small intestine, but it begins to solubilize when it reaches lower small intestine. So, the formulation will have poor site-specificity [21]

- **Delayed-Release System:** Delayed-release system for colon targeted drug delivery is also known as a time-controlled system in which there is a time-based delay in drug delivery. In this approach, the system is designed in such a way that the individual differences in the gastric emptying rate, availability of anaerobic microorganisms in the large intestine, or pH of the stomach and small intestine do not affect the colonic site. The transit time through the small intestine does not depend on formulation. The designing of a delayed-release system is such that the drug is released after a predetermined lag time. Delayed release formulations usually consist of 4 or 6 h of nominal lag time based on the assumption that this time is needed for the formulation to reach the colonic site [22]

- **Osmotically Controlled System:** Osmotically controlled system comprises osmotic components. The osmotic components are usually applied as either single component or 5-6 push-pull components which are encapsulated in the capsule made of hard gelatin. Such units are bilayered with semi-permeable membrane within. The middle segment of push pull components comprises of film of active agent. There is an aperture in the semi-permeable membrane which is present besides the film of the active agent. During the course of time, the contents expel out through this aperture. After the administration, the capsule containing the push pull components gets dissolved quickly. Once the formulation reaches the small intestine, the coating gets solubilised due to slightly basic pH. Push layer is swelled as the water enters the unit through the aperture in the semi-permeable membrane. As the push layer swell, it makes the drug content to expel out through the aperture. Thus, the osmotic controlled system delivers the drug for up to 24 h at a perpetual rate [23]

- **Biodegradable Polymer Coating:** The bio-environment of the human gastrointestinal tract is

portrayed by the nearness of complex bacteria, particularly the colon that is wealthy in microorganisms that are engaged with the procedure of decrease of a dietary segment of different contents. Medications covered with the polysaccharides, which indicate degradability because of the impact of the microflora of colon, can be utilized to develop formulations for targeting colonic ailments. These microbially-disruptive polysaccharides, particularly "azo-polymers" have been investigated so as to deliver the orally regulated medication to the site of colon. All things, endless supply of the dose structure through the GIT, it stays unblemished in the stomach and small digestive tract where next to no biodegradable movement is available that hushes up deficient for breaking the polymer layer. Liberation of the medication from azo polymer covered dosage form should happen after reduction and in this manner azo-reductase enzymes available in the micro-flora of the large intestine degenerate azo-bonds [24]

What Is Multiparticulate Drug Delivery System:

Various parameters like GI transit time, residence time in small intestine, colon arrival time, and residence time in colon constitute vital information for in vivo evaluation and establishing in vitro-in vivo correlation of colon targeted dosage forms. [25] In one such study, the GI transit of a multiparticulate dosage form in the form of pellets and a non-disintegrating tablet of metoprolol were studied by Abrahamsson and co-workers [26]. The two formulations were simultaneously administered with breakfast to eight healthy male human subjects. A statically significant difference was reported between the mean gastric emptying time for the pellets (3.6h) and that for the tablet (9.6 h). However, the mean transit through the small intestine did not vary significantly for the two formulations - pellets (3.1 h) and tablet (2.0 h). The pellets were found to have a longer residence ti me in the colon in all subjects as compared with the tablet, with mean colon transit time of 28 h for pellets and 15 h for the tablet. This study helped to highlight the differences in the in vivo behavior of multiparticulate and single unit dosage forms. In another study, the GI transit of five small sized tablets in six patients with ulcerative colitis was monitored by Hardy et al,[27] using radio-labeled imaging techniques. The mean gastric emptying time and small intestinal transit time were found to be 1.6 h and 3.4 h respectively. As the tablets were found to be retained more in the proximal colon for an appreciably long period of time of 6 h, it was concluded that small tablets were a good means of attaining site-specific delivery and controlled release in ulcerative colitis.

Advantages and Disadvantages of Multiparticulate Drug Delivery System:

Advantages:

- Dose dumping avoided.
- Faster gastric emptying.
- Less local irritant and Distribution is better.
- Better stability.
- Desired drug release
- Flexibility in design.
- Increased in Bioavailability.
- Reduced Adverse effects.
- Reduced risk of local irritation.
- Expected gastric emptying. [28]

Disadvantages:

- Drug loading is low.
- Higher need of excipients.
- Huge number of process variables.
- Many formulations steps.
- Huge cost of production.
- Advance technology is needed.
- Trained and skilled person needed. [29]

Types of Multiparticulate Drug Delivery System:

1. Pellets
2. Minitablets
3. Spheroids
4. Granulation

1. Pellets:

Pellets are small, free flowing, systemically produced, in spherical or semispherical shape and its size range from 0.2mm to 2.0mm, obtained from fine powders or granules exploit various pelletization. Orally administered pellets in hard gelatin capsules/ disintegrating tablet release the drug in stomach and

distributed over GIT without loss of any given effect [30-31]. The subunit act as a self-contained store.

- **Ideal characteristics of pellets:**

Coated and uncoated pellets has spherical shape with smooth surface which improves flow property. pellets has a good hardness and low friability which is foremost property of coating it has a high physical strength and integrity and it has a particle size between 500µm to 1000µm which required for efficient coating, prevents segregation during capsule filling and compression. High bulk density of pellets is very important role in achieving of weight uniformity

- **Theories of pellet formulation and growth:**

Granule formation and its growth is important to select and optimize any pelletization process.With trace techniques, results obtained are acceptable.In ordinary classic pellitization which involves rotatory drum,a pan or disc which has three regions regionsnamely nucleation,transition,and ball growth [32]. It is essential to understand the mechanism of pellet formation. Many theories explain the mechanism of pellet formation. Some theories are obtained from experimental results, while others from visual observation.

In these theories, following steps are invoilved in the mechanism of pellet formation [33]

1. Nucleation
2. Transition
3. Ball growth

Mechanism of pellet formation also involves following steps based on the experiment carried out on mechanism of pellet formation.

1. Nucleation
2. Coalescence
3. Layering
4. Abrasion transfer

Nucleation occurs when the powder is wetted with solvent system, which is the first step involved. Once after wetting, it forms 3 phases (air-water-liquid nuclei), by drawing primitive particles together. Transition occurs after nucleation in which growth mechanism is affected by coalescence layering. Coalescence is formed by random collision of well-formed nuclei, which leads to the formation of large particles, which requires slight moisture. As the moisture increases, number of nuclei decreases, whereas the total mass of the system remains constant. In layering, mechanism of growth is slow in which the number of particles does not change. Mass of the system increases due to increase in particle size. The particle size reduction the fragments can be obtained [34]. Abrasion transfer is the transfer of materials from oe granule to another in no specific direction. Total mass of the particle remains constant. Only the size undergoes change until transfer of material exists

2. Minitablets:

Mini-tablets size ranges between 1.0-3.0 mm. Shape of the mini-tablets are flat or slightly curved tablets, which is filled in capsule or compressed into a large tablet or placed in sachet. Minitablets are attractive and alternative to the products of pellets the mini matrices and tableting techniques is used. Various mini-tablets can be individually formulated and designed, which is filled into capsules Minitablets can also be used for immediate release, delayed release, and/or controlled release formulations. Minitablets can improve therapeutic effectiveness of drug and more preferred than pellets. Various mini-tablets can be individually formulated and designed, which is filled into capsules Minitablets can also be used for immediate release, delayed release, and/or controlled release formulations. Minitablets can improve therapeutic effectiveness of drug and more preferred than pellets. [35]

- **Theories of mini-tablets:**

In order EC and HPMC are used as a matrix agent which helps to delay the drug release corresponding to the prolonged release component of dual release system this drug is from the minitablets. For release mechanism of drug the characteristics of the matrix plays an important role. For controlled release drug delivery, one of the most commonly used carriers is HPMC. Which act as a protective barrier when gel becomes a viscous layer to both the influx of efflux and water of the drug in solution. [36] When liquid comes in contact with hydrophilic polymers, gel layer is formed, which is required for the controlled and

sustain release of drugs. More than 40 years in pharmaceutical industry hydrogels are used in the controlled drug delivery from water swellable matrix system. HPMC, a hydrophilic carrier material is used in oral controlled release dosage form, since 1960. The systems are complex because of their underlying mechanism of drug release, and the diffusion, swelling and erosion these are involved in three moving boundaries. HPMC matrix is shown to radial water uptake when drug load swellable high viscosity. [37]

3. Spheroids:

In the recent invention water-insoluble drugs relates to a controlled release pharmaceutical composition for administered to human or animal. The sphecial term "spheroid" means aspherical granule having a diameter between 0.5mm and 2.5mm, especially between 0.8mm. MCC, a non-water-soluble pharmaceutical excipient is used for the formation of spheroids by spheronisation. Greater amount of MCC, helps to form spheroids in a easier way. In contrast, microcrystalline cellulose possesses less control over drug release, so it cannot show controlled release characteristics.

This drawback can be overcome by,

1. Coating the spheroids with controlled release polymer.
2. Amount of MCC is either decreased to 50%w/w or less than the excipients weight and an excipient is added, which does not influence the drug release at a conc of 10% or more than the excipient weight. Disadvantages is associated in both the instances. In the first instance, a step is included, which is uneconomic, whereas in the second instance, less amount of MCC leads to the difficulty in the spheroid production [38]

4. Granulation:

It is the process of conversion of powder to small particles ranging from 0.2-0.4mm in size. Granulation helps to modify the flow properties, compression characteristics, packing arrangement, dissolution-disintegration parameters of powder drug. Depending on the methods granulation could be classified as dry granulation and wet granulation. In wet granulation compact mass of powder drug is prepared with the help of addition of liquid or water and then it is sieved to required size granules. In dry granulation, granules are formed without addition of liquid substances. Effectiveness of granules affected by, type and volume of binder used, less or more time required for preparation of wet mass, amount of force applied and rate of drying of granules.

The most popular novel granulation techniques are;

1. Pneumatic dry granulation
2. Freeze granulation
3. Foamed binder technology
4. Steam Granulation
5. Moisture activated dry granulation
6. Melt granulation technology
7. Thermal adhesion granulation process [39]

Anatomy of Colon Targeting

The importance of targeting the colon is stressed in order to effectively treat colonic illnesses including irritable bowel syndrome and inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis. The colon offers unique advantages as a site for pharmaceutical delivery due to its close to neutral pH, longer transit time, relatively low proteolytic enzyme activity, and noticeably increased responsiveness to absorption enhancers. The greater viscosity of intestinal contents lowered the accessibility of molecules to the epithelium because of the limited space available [40,41]. Individual epithelial colonocytes, lipid bilayers of the occluding junction complex (O.J.C.), and the mucus layer at the epithelial surface, as well as unusual drug interactions with food or metabolites of colonic bacteria in the lumen, are further barriers to colonic absorption [42]. The rate of blood flow to the absorptive epithelium determines medication absorption in the colon. Although arterial blood is delivered to the proximal and distal colons by the superior (proximal colon) and inferior (distal colon) mesenteric arteries, the blood is drained via the superior (proximal colon) and inferior (distal colon) veins. While total colonic blood flow is lower than that of the small intestine, blood flow is stronger in the proximal region of the colon than in the distal section [43]. Because of its smaller surface area, the colon has a lesser absorption capacity than the small intestine. Despite the lack of

villi in the colon, the presence of plicae seminars, or crescentic folds, increases the intestinal surface to around 1300 cm2 [44]. Despite its smaller surface area, the colon has a high absorption capacity for water, electrolytes, and short-chain fatty acids. [45]

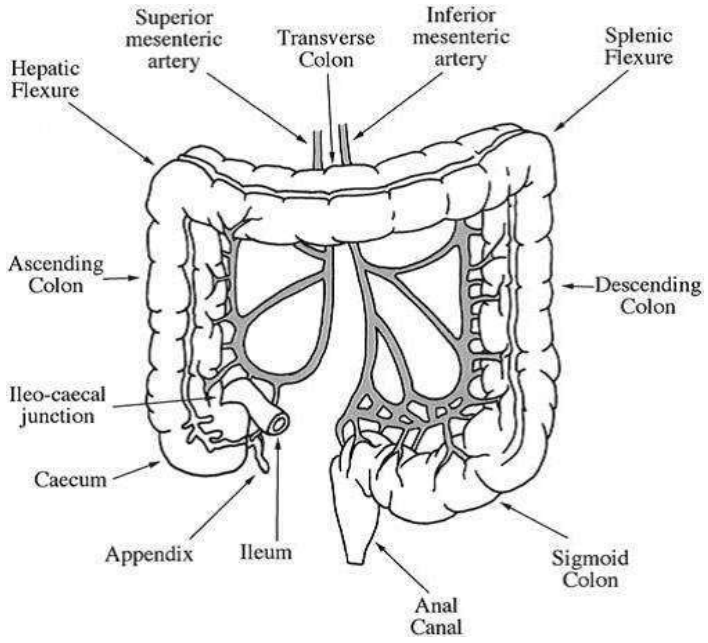

Figure 1: Anatomy of Colon

Need for Colon Targeted Formulation System:

- Site-targeted delivery of medication to the site of the colon has potential application in treating the colon-related disorder.
- Colon-specific formulation is considered to be beneficial in lowering dosing frequency and systemic side effects [46].
- Protein and peptide drugs can be orally delivered by the help of site-specific colon formulation.
- Prolongation of delivery of drug could also be possible by colon targeted formulation.
- Inflammatory conditions such as „ulcerative colitis" or „Crohn"s disease can be managed by the achievement of both local and systemic delivery. Usually, glucocorticoids and sulphasalazine are used to treat such inflammatory ailments [47].
- Major diseases of the colon, such as colorectal cancer, can be managed beneficially by the help of targeted delivery of a drug to the site of disease [48].
- Drugs that are prone to chemical or enzymatic disintegration in the upper GIT can be delivered through colon targeted formulation.

Advantages of Colon Drug Delivery System [49]:

- Bioavailability is increased.
- Dosing frequency is reduced.
- Dose size is reduced.
- Patient compliance is improved
- Formulation development is flexible.
- It provides site-specific delivery of drug in its intact form.
- Adverse side effects are lowered.
- It protects the mucosa from drugs that cause irritation.
- It is economical for patients

Limitations of Colon Drug Delivery System [49]:

- Dose loading is low.
- There is a high requirement for excipients.
- It has multiple formulation steps.
- There is a large number of the process variable.
- It requires advanced technology.
- There is a lack of reproducibility and efficacy.
- Manufacturing of colon drug delivery system requires a skilled person.

FUTURE PROSPECTS:

Nowadays, most of the researchers are focusing on the colonic site-specific absorption of the drug for treatment of diseases mainly colonic cancer which

requires highly specific absorption of drug. Targeting drug to the colonic site is one of the chief area on which the researchers are putting their efforts for maximum uptake of drug in optimum amount at the site of disease for treatment of colonic ailments. One of the major challenges is to improve the oral absorption of protein and peptide drugs as they are having less bioavailability because they are not stable in the gastrointestinal tract. Thus, multiparticulate systems can be beneficial for the delivery of drug moieties such as oligonucleotides, protein, and peptides. So, these studies will be beneficial in the near future. [67] Three-dimensional (3D) printing technology is also being implemented in colon-specific delivery systems because of its significant role in personalized medicine. For the patient suffering from IBD, each patient requires personalized drug delivery, which can be addressed by 3D printing technology. This process involves layer-by-layer addition of active ingredient and excipient to design a particular structure in such a way to release the drug when coming in contact with the mucosa of colon. [68] The precision of colon targeting with the designing of novel in-vitro methods relevant to complicated in-vivo conditions will lead to the development of novel and innovative delivery systems. In the coming future, the mixture of novel and conventional systems is the key to design colon targeting systems as they improve efficiency, targetability, specificity, reduces cost, and increase patient compliance. For targeting the drug to the colon, the exploration of nanotechnology seems to be an area of research in the near future [69, 70, 71]

CONCLUSION:

The oral administration of medications belonging to the anti-inflammatory groups has frequently employed colostomy drug delivery. Medication supply decreasing only when necessary, retaining the drugs intact form as near to the treatment site as feasible, and limiting systemic adverse effects are all benefits of drug targeting to the sick colon. Based on the drug's accessibility to the sick region, all of these methods are generally acknowledged. They are a way of addressing the poorly absorbed drug's local intestinal and systemic absorption. The gastrointestinal system comprises a broad range of pH levels and several enzymes that the dosage form must pass through before reaching the target area. Colonic targeting, formulation dispersion efficacy, and dependability are difficult to achieve. The major focus of the formulation techniques used to address these issues is on a specific mode of drug administration, such as avoiding the complicated pH environment of the upper G.I.T. with the dosage form, blocking drug release and absorption in the upper G.I.T., and releasing the medication for absorption in the colon. Additionally, the capacity of colon enzymes to digest drugs is being researched as a way to concentrate the delivery of medications to the colon. Combining traditional and cutting-edge approaches will be necessary to create colon-specific medication delivery systems that strike a compromise between effectiveness, target-specificity, affordability, and patient compliance. Future research on colon cancer and combination therapies may focus on the study of nanotechnology.

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HOW TO CITE: Onkar Shepal, Pooja Rasal*, Om Pawar, Nikhil Sandhan, Aniket Thul, Colon Targeted Drug Delivery System: An Overview on Current Approaches, Int. J. Sci. R. Tech., 2025, 2 (9), 198-208. https://doi.org/10.5281/zenodo.17164445