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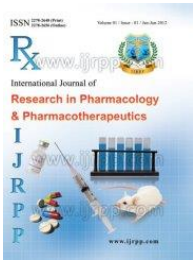

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Review article ***Open Access***

Current trends and approaches of colon specific drug delivery system- a review

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ABSTRACT

The oral route is considered to be the most preferred route for administration of drugs for systemic effect, but the oral route is not suitable to the administration of drug for lower gastrointestinal (GI) diseases, this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract. To overcome this difficulty, colon-specific drug delivery systems have been broadly analyzed during the last two decades. The colon is a site where both local and systemic delivery of drugs can take place. To achieve successful colon targeted drug delivery, a drug need to be protected from degradation, release and absorption in the upper portion of the gastric intestinal tract (GIT) and then to be ensured controlled release in the proximal colon. This review is focused on the merits and demerits, in brief, introduction of colon, factor effecting colonic transition, approaches in the colon targeted drug delivery, and novel emerging technologies for colon targeting.

Keywords: Colonic drug delivery, Drug targeting, Novel approaches, Gastro intestinal tract, Emerging technologies.

INTRODUCTION

The aim of a targeted drug delivery system is to provide a desired drug concentration in the body by delivering a therapeutic amount of drug to a target site. It is suitable and required for the drugs having instability, low solubility, short half-life, a large volume of distribution, poor absorption, low specificity, and therapeutic index. Targeting may provide maximum therapeutic activity (by preventing degradation or inactivation of drug). Meanwhile, it can also minimize adverse effects, the toxicity of potent drugs by reducing dose [1].

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral drug delivery system and these systems have more advantages due to patient acceptance and ease of administration

Apart of these advantages, the oral route is not suitable to the administration of the drug for lower gastrointestinal (GI) diseases; this happened due to their release at upper GI tract (stomach, small intestine), which further minimizes the accessibility of drugs at the lower GI tract.

To overcome this difficulty, colon-specific drug delivery systems have been broadly analyze during the last two decades. By definition, a colonic delivery refers to delivery of drugs accurately into the lower GI tract (by avoiding the drug release in upper GIT), which occurs primarily in the large intestine (*i.e*. colon) [2, 3, 4]. Rectal administration is another route used for colon targeting, but it shows less compliance (uncomfortable) and becomes difficult to reach the colon. Conventional dosage forms that are used in the prevention of colon diseases (ulcerative colitis, crohn's diseases, amoebiasis) are failing as an improper amount of drug reaches site of action. Conventional dosage form affords the drug to be absorbed from the upper part of GIT, *i.e*., stomach. This action of conventional dosage form has a serious drawback for colonic localized delivery. Thus, for efficient and safe therapy, the drug is needed to be preserving from upper hostile environment [3, 5, 6].

Site-specific delivery into the colon is not only needed for local treatment of a variety of colon diseases, like ulcerative colitis, Chron's diseases, amoebiasis, colon cancer, but also systemic delivery of proteins and peptides this is because of less diversity and intensity of digestive enzymes and less proteolytic activity of colon mucosa than that observed in the small intestine. Beside the colon diseases, this system is also helpful in the treatment of asthma, angina and rheumatoid arthritis for taking advantage of chronotherapeutic drug delivery and for delivery of steroids [7].

Need of colon targeted drug delivery [8-11]

- Targeted drug delivery into the colon helpful in treatment of diseases at that site, fewer systemic side effects and dose can be minimized.
- Colon specific formulation is beneficial for the administration of proteins, peptide drugs and also to prolong the drug delivery.
- Colon targeted drug delivery is suitable for delivery of drugs which are polar and/or susceptible to the chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism.
- Serious diseases of the colon are treated more effectively if drugs were targeted to the colon.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.

The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted). A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.

Advantages [12-14]

- Colon is an ideal site for the delivery of agents to cure the local diseases of the colon.
- Local treatment has the advantage of requiring smaller drug quantities.
- Reduces dosage frequency. Hence, lower cost of expensive drugs.
- Reduce gastric irritation caused by many drugs (e.g. NSAIDS).
- Bye pass initial first pass metabolism.
- Extended daytime or nighttime activity.
- Improve patient compliance.
- Useful for the delivery of proteins, peptides which are being delivered by injections
- Used in direct treatment of disease at that site ,low dosing and less systemic side effects
- Molecules that are poorly absorbed in the upper gut, such as peptides, proteins may be better absorbed from the lower GIT.
- The colon is a site where both local and systemic delivery of drugs can take place.
- Local delivery allows topical treatment of inflammatory bowel disease.
- The colon is having high water absorption capacity, the colonic contents are considerably viscous and thus availability of most drugs to the absorptive membrane is low.

Disadvantages [15-17]

- A longer residence time of 3-5 days results in elevated plasma levels of the drugs and therefore higher bioavailability in general, but especially for drugs that are substrates for this class of enzyme.

- Single unit colon targeted drug delivery system has the disadvantage of un intentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology.
- Development of colon specific drug is difficult due to many biological barriers
- Cytochrome (P450) class of drug metabolizing enzymes has lower affinity in the colonic mucosa.

Limitations [18]

- Colon offers a near neutral pH, at the site of drug delivery, reduced enzyme activity, a long transit time and increased responsiveness to absorption enhancers
- Wide range of pH values and different enzymes present throughout the gastro intestinal tract, through which dosage form has to travel before reaching target site
- For better drug delivery it should be in solution form before it arrives in the colon
- Fluid content in the colon is much lower and it is more viscous than in the upper part of GI tract.
- Stability of drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a non-specific way to dietary residues, intestinal secretions, mucus or fecal matter.
- The resident microflora could also affect colonic performance via metabolic degradation of the drug
- Lower surface area and relative tightness also affects the bioavailability of drugs.

ANATOMY AND PHYSIOLOGY OF COLON

The anatomy of the colon is shown in Figure 1. The GIT is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts [19]. These are the colon, the rectum and anal canal. The entire colon is about 5 feet (150 cm) long and is divided in to five major segments. The right colon consists of the cecum, ascending colon, hepatic flexure. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus [20].

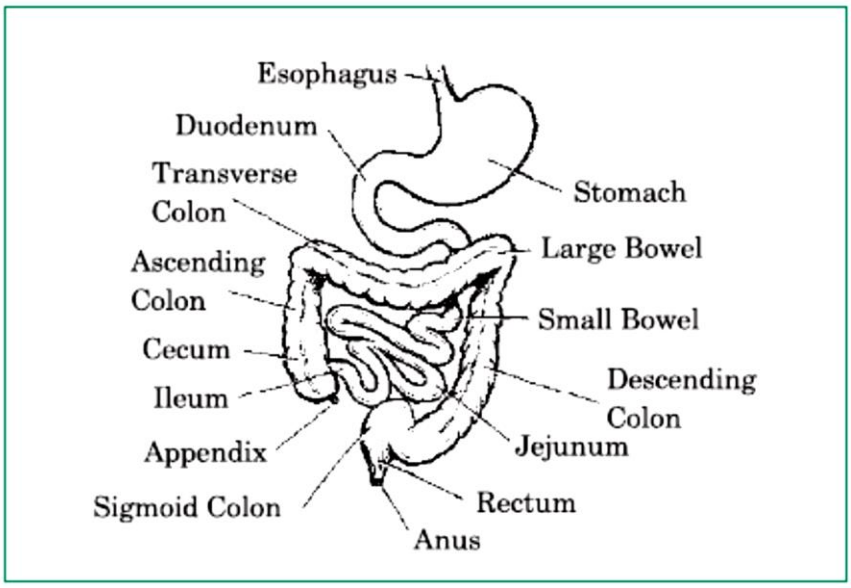

Fig 1: Anatomy of the colon

Function of colon

- The consolidation of the intestinal contents into feces by the absorption of the water and electrolytes and storage of feces until excreted from the body.
- To provide a favorable environment for the growth of colonic microorganisms.
- Absorption of H2O and Na+ from the lumen, and secretion of K+ and HCO3.

Colon pH [21]

The pH of the GIT is subject to both inter and intra subject variations. Diet, diseased state and food intake influences the pH of the gastrointestinal fluid. The changes in the pH along the gastrointestinal tract have been used as a means for targeted colon drug delivery. Radio telemetry shows the highest pH (7.5 ± 0.5) in the terminal ileum. On entry into the colon, the pH drops to 6.4 ± 0.6. The pH in the mid colon is 6.6 ± 0.8 and in the left colon 7.0 ± 0.7.There is a fall in pH on entry into the colon due to the presence of short chain fatty acids arising from bacterial fermentation of polysaccharides. For example lactose is fermented by the colonic bacteria to produce large amounts of lactic acid resulting in pH drop to about 5.0

Table1: pH of GIT at various sites.

S.NO	ORGAN	pH
1	Stomach	1.5-2(fasted state) 2-6(fed state)
2	Small intestine	6.6-7.5
3	Right colon	6.4
4	Mid colon	6.6
5	Left colon	7

Colonic microflora and enzymes

A large number of anaerobic and aerobic bacteria are present in the entire length of the human GIT. Intestinal enzymes are used to trigger drug release in various parts of the GIT. Usually, these enzymes are derived from gut microflora residing in high numbers in the colon. These enzymes are used to degrade coatings or matrices as well as to break bonds between an inert carrier and an active agent (i.e., release of a drug from a prodrug). Over 400 distinct bacterial species have been found 20 - 30% of which are of the genus bacteroids. The concentration of bacteria in the human colon is around 1000 CFU / mL. The most important anaerobic bacteria are bacteroides, bifidobacterium, eubacterium, peptococcus, peptostreptococcus, ruminococcus, and clostridium [22].

Colonic absorption [23, 24]

The surface area of the colon is much less compared to small intestine and is compensated by absence of endogenous digestive enzymes and long residence time of colon (10-24 hours). Different factors affecting colonic absorption were reported

- Passes through colonocytes (Transcellular transport).
- Passes between adjacent colonocytes (Paracellular transport).

Transcellular absorption involves the passage of drugs through cells and thus the route for most lipophillic drugs takes, whereas paracellular absorption involves the transport of drug through the tight junctions between the cells and is the route of most hydrophilic drugs. Drugs shown to be well absorbed include glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, buflomedil, atenolol.

Factors affecting colonic absorption [25]

- Physical properties of drug such as pKa and degree of ionization.
- Colonic residence time as commanded by GIT motility.
- Degradation by bacterial enzymes and metabolite products.
- Local physiological action of drug.
- Selective and non-selective binding to mucus.
- Disease state.
- Transit through GIT.

APPROACHES FOR COLONIC DRUG DELIVERY SYSTEMS

pH dependent systems

This approach is based on the pH-dependent release of the drug from the system. In this case the pH differential between the upper and terminal parts of GIT is exploited to effectively deliver drugs to the colon. One should not forget that the pH in the intestine and colon depends on many factors such as diet, food intake and intestinal motility and disease states.

In GIT there is presence of pH gradient which approximately ranges from 1.2 in stomach, 6.6 in proximal small intestine, 7.5 in distal intestine & pH of colon is about 6.4. Generally Eudragit S is used for the colon delivery it dissolves at pH greater than 7.0, which results in premature drug release from the system. It is concluded that pH of GIT was not a reliable criteria for colonic targeting.

Time controlled or time dependent system

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GIT. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time based. In these systems, the site of drug release is decided by the transit time of a formulation in the GIT, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. Ideally, formulations are designed such that the site of delivery (i.e. colon) is not affected by the individual differences in the gastric emptying time, pH of the stomach and small intestine or presence of anaerobic bacteria in the colon. On an average, an orally administered dosage form takes about 3 hrs to travel through the length of the small intestine to the beginning of the colon. Compared to gastric emptying rate, the small intestinal transit time is relatively consistent.

A system in the form of a tablet formulation (patent assigned to Hoffman-La Roche Inc.), which could release the drug consistently in the colon via a time-dependent explosion mechanism. The formulation is comprised of three parts: (i) a central core containing the drug and swelling excipients (ii) an inner semi-permeable polymer membrane containing a plasticizer which allows water influx but prevents the outward diffusion of drug and (iii) an outer enteric-coating which dissolves at or above pH 5.5. The outer enteric coat keeps the tablet intact until it reaches the small intestine. Upon arrival in the small intestine, the enteric coat dissolves allowing for GI fluid to diffuse through the semipermeable membrane into the core. As a result, the core swells during the transit of the tablet through the small intestine. Finally, after a consistent period of 4-6 h transit in the small intestine, the swollen core burst the semi-permeable membrane releasing the drug in the colon [26-28].

Bacteria dependent delivery [29]

In this system colonic bacteria are utilized to degrade the substrate. The bacterial amount has been estimated about 10-11 per gram in the colon & having around 400 species (anaerobic in nature). Earlier polymer cross linked with azo aromatic groups was used but due to potential carcinogenic activity now a day's natural polysaccharides are used. Natural polysaccharides generally undergo premature drug release so they are chemically modified or mixed with hydrophobic polymers. This polymer shows good film forming properties, resistant to pancreatic enzymes but they will undergo degradation due to bacterial enzyme.

NEWLY DEVELOPED APPROACHES FOR CDDS

Pressure controlled drug-delivery systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya developed pressure controlled colon-delivery capsules prepared using ethylcellulose, which is insoluble in water [30]. In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation [31, 32]. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could

present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethylcellulose single unit capsules the drug is in a liquid [33]. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

Novel colon targeted delivery system (CODESTM)

CODESTM is an unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems [34, 35]. CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon, (Fig. 2). The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently over coated with an enteric material, Eudragit L. The premise of the technology is that the enteric coating protects the tablet while it is located in the stomach and then dissolves quickly following gastric emptying. The acid soluble material coating then protects the preparation as it passes through the alkaline pH of the small intestine [36]. Once the tablet arrives in the colon, the bacteria enzymetically degrade the polysaccharide (lactulose) into organic acid. This lowers the pH surrounding the system sufficient to affect the dissolution of the acid soluble coating and subsequent drug release

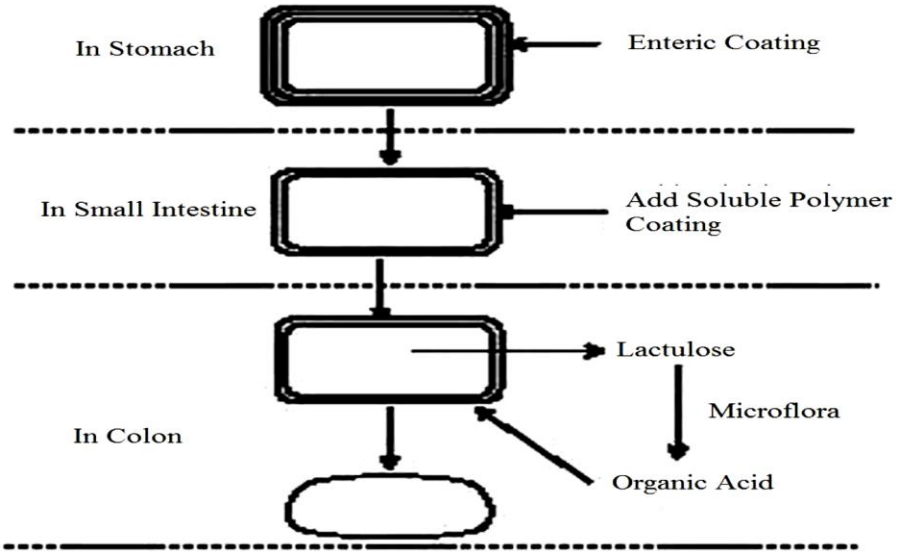

Figure 2: Schematics of the conceptual design of CODES

Osmotic controlled drug delivery (ORDS-CT)

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable [37].The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, (Fig. 3). Each bilayered [38] push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer. Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment to swell, and concomitantly creates a flowable gel in the drug compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semipermeable membrane. For treating

ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon [39-42].Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

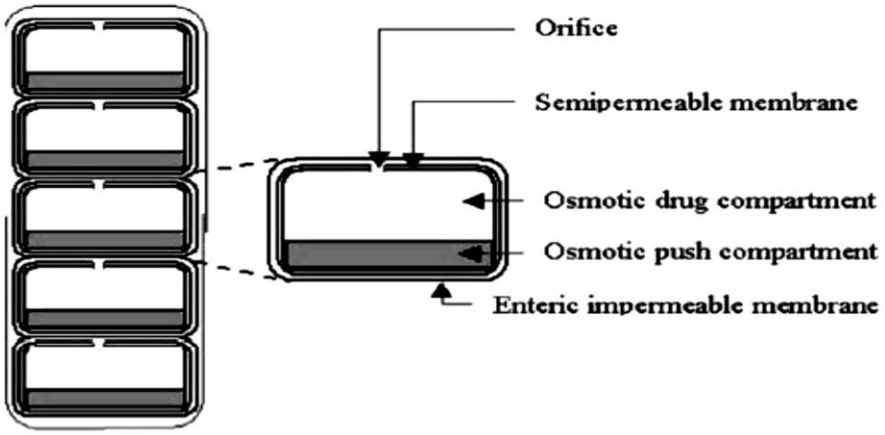

Figure 3: Cross-Section of the OROS-CT colon targeted drug delivery system

Evaluation tests

There is different in-vitro methods are used to evaluate different carrier systems for their ability to deliver drugs specifically to the colon.

In-vitro dissolution test

Dissolution of controlled-release formulations used for colon-specific drug delivery are usually complex, and the dissolution methods described in the USP cannot fully mimic in vivo conditions such as those relating to pH, bacterial environment and mixing forces [43]. Dissolution tests relating to CDDS may be carried out using the conventional basket method. Parallel dissolution studies in different buffers may be undertaken to characterize the behavior of formulations at different pH levels. Dissolution tests of a colon-specific formulation in various media simulating pH conditions and times likely to be encountered at various locations in the gastrointestinal tract have been studied [44]. The media chosen were, for example, pH 1.2 to simulate gastric fluid, pH 6.8 to simulate the jejunal region of the small intestine, and pH 7.2 to simulate the ileum segment. Enteric-coated capsules for CDDS have been investigated in a gradient dissolution study in three buffers. The capsules were tested for two hours at pH 1.2, then one hour at pH 6.8, and finally at pH 7.4 [45].

In vitro enzymatic tests

Incubate carrier drug system in fermenter containing suitable medium for bacteria (strectococcus faccium and B. Ovatus). The amount of drug released at different time intervals are determined. Drug release study is done in buffer medium containing enzymes (ezypectinase, dextranase), or rat or guinea pig or rabbit cecal contents. The amount of drug released in a particular time is determined, which is directly proportional to the rate of degradation of polymer carrier.

In-vivo evaluation

A number of animals such as dogs, guinea pigs, rats, and pigs are used to evaluate the delivery of drug to colon because they resemble the anatomic and physiological conditions as well as the micro flora of human GIT. While choosing a model for testing a CDDS, relative model for the colonic diseases should also be considered. Guinea pigs are commonly used for experimental IBD model. The distribution of azoreductase and glucouronidase activity in the GIT of rat and rabbit is fairly comparable to that in the human46. For rapid evaluation of CDDS, a novel model has been

proposed. In this model, the human fetal bowel is transplanted into a subcutaneous tullel on the back of thymic nude mice, which bascularizes within four weeks, matures, and becomes capable of developing of mucosal immune system from the host.

Drug delivery index (DDI) and clinical evaluation of colon-specific drug delivery systems

DDI is a calculated pharmacokinetic parameter, following single or multiple dose of oral colonic prodrugs. DDI is the relative ratio of RCE (Relative colonic tissue exposure to the drug) to RSC (Relative amount of drug in blood i.e. that is relative systemic exposal to the drug). High drug DDI value indicates better colon drug delivery. Absorption of drugs from the colon is monitored by colonoscopy and intubation. Currently, gamma scintigraphy and high frequency capsules are the most preferred techniques employed to evaluate colon drug delivery systems.

CONCLUSIONS

The advancement of colon-targeted oral drug delivery systems has increased expanding enthusiasm among formulation researchers as of late. As discussed above, colon-specific drug delivery systems give critical therapeutic advantages to the patients as far as wellbeing, adequacy, and patient compliance. Factors including the physicochemical characteristics of the drug, detailing and procedure factors, just as the GI physiological factors impact, and may introduce a test to the effective plan of a colon-specific drug delivery system. The formulation approaches used to conquer these difficulties principally center around an individual component of drug delivery, including bypassing the complex pH condition of the upper GIT by the measurement structure, forestalling the drug release and drug-absorption in the upper GIT, and discharging the drug in the colon for absorption. The using limit of the colon catalysts is additionally being investigated as a way to deal with target drug delivery specifically in the colonic region. To ensure a balance between efficiency, target-specificity, cost, and patient compliance, apparently a mix of traditional and more current methodologies is the way in to the advancement of colon-specific drug delivery systems. Notwithstanding the joined methodologies, the investigation of nanotechnology is by all accounts a region of future research for colon targeting of drugs.

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