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A REVIEW ON RECENT ADVANCEMENTS IN COLON TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Colon-specific systems might also allow oral administration of peptide and protein drugs, which are normally degraded in the upper parts of the gastrointestinal tract. The treatment of large intestine (colon) disorders such as colon cancer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) i.e. Ulcerative colitis and Crohn's disease, Diverticulitis, and other colon diseases where a high concentration of the active therapeutic agent is required may be efficiently achieved by colon-specific delivery. Prodrugs, pH and time-dependent systems, and microbial triggered drug delivery systems are examples of primary techniques for colon-specific drug delivery (CDDS). In terms of achieving in-vivo drug delivery, newly developed CDDS, which includes pressure-controlled colonic delivery capsules (PCDCS) and osmotic controlled drug delivery, are unique site specificity and feasibility of the manufacturing process. The goal of this analysis is to provide extensive insight into the many colon disorders and tactics used to selectively target therapeutic agents to the colon. The colon is a site where both local and systemic medication delivery can occur. If medications could be targeted specifically on the colon, treatment might be considerably more effective. The colon target drug delivery system has grown in popularity not just for treating local disorders but also for systemic delivery of proteins, therapeutic peptides, anti-asthmatic medicines, antihypertensive medications, and antidiabetic compounds. However, recent attempts have been made to develop colon-specific delivery systems with increased site specificity and variable drug release kinetics to meet a variety of therapeutic demands. The goal of this review is to provide extensive insight into both traditional and novel techniques to targeting therapeutic medicines precisely to the colon.

KEYWORDS: Colon-specific drug delivery, Colon cancer, Conventional, therapeutic peptides and New approaches.

INTRODUCTION

Colon-targeted drug delivery systems may be following the concept of control or sustained route for drug administration has received more attention. At least 50% of the dosage forms available in the market are oral dosage forms because these systems have more advantages due to high patient compliance.[1] Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases. Like Crohn's disease, colonic cancer ulcerative Colitis, amebiosis, and many other disorders. Colon colon-targeted drug delivery system is not only suitable for delivering the drug to the colon for local treatment but it is also a preferable approach for the delivery of protein and peptide and enhancing their bioavailability.

The bioavailability of protein and peptides may be achieved if it can be protected from acid and enzymes in the stomach and upper intestine and released and absorbed in the colon and protect it from degradation in the stomach. Degradation of such drugs in the stomach can be prevented by using some polymer either alone or in a combination because polymers affect the rate of release and absorption of drugs and play an important role in the formulation of colon targets drug delivery system. The oral route is the more preferable and convenient route but other routes for the colon drug delivery system may be used. Administration of drugs through the rectum offers the shortest route for targeting drugsto the colon still reaching the colon proximal part via rectal administration is difficult.[2] Rectal

administration is difficult and painful for patients thus patient compliance decreases. Colon contains a variety of bacteria which is responsible for azo reduction and enzymatic cleavage which is responsible for the metabolism. The colon is a site where both local and systemic drug delivery can take place. A local means of drug delivery could allow topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. The treatment might be more effectiveif the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and systemic side effects might be reduced. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted at the colon.[3]

Anatomy of Colon

The GI tract 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. 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. Peritoneal folds called mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure, and the right half of the transverse colon. The left colon contains the left half of the transverse colon, descending colon, splenic flexure, and sigmoid. The rectum is the last anatomic segment.[4]

The major function of the colon is the creation of a suitable environment for the growth of colonic microorganisms, storage reservoir of fecal contents, the expulsion of the contents of the colon at an appropriate time, and absorption of potassium and water from the lumen. The absorptive capacity is very high, about 2000ml of fluid enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed.

Advantages

- The site-specific delivery of drugs to the lower part of GIT for localized treatment of several colonic diseases.
- Prevent the drug from degradation.
- Ensure direct treatment at the disease state.
- Used to prolong the drug therapy.
- Improved drug utilization.
- Minimizes the first-pass metabolism.
- Suitable absorption site for protein and peptide drugs.

Disadvantages

- On set of actions is low.
- Higher need for excipients.
- Some micro flora may degrade the drug.
- There is less fluid in the colon than in the small intestine and hence, dissolution is a problem for water-soluble drugs.

FACTORS TO BE CONSIDERED IN THE DESIGN OF COLON-SPECIFIC DRUG DELIVERY SYSTEM[5,6,7]

Anatomy of GIT

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. 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 and the right half of the transverse colon.

Colon pH

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 is6.6 ± 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.

Gastro Intestine Transit

The movement of materials through the colon is slow than other regions of the gastrointestinal tract. The total time for transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, mobility, stress, disease, and drugs. Colonic transit times ranged from 50 to 70 h. Stool weights increased significantly with the presence of active disease presumably due to exudates from inflamed epithelium, increased mucus secretion, and reduction in reabsorption of fluid and electrolytes.

Colonic Micro flora and Enzymes

A large is 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).

Drug Absorption in the Colon

Drugs are absorbed passively by either par cellular or Trans cellular route. Trans cellular absorption involves the passage of drugs through cells and this is the route most lipophilic drugs takes, whereas par cellular absorption involves the transport of drug through the tight junction between cells and is the route most hydrophilic drug takes. The slow rate of transit in the colon lets the drug stay in contact with the mucosa for a

longer period than in the small intestine which compensates for the much lower surface area.

Drug

Drugs that show poor absorption from the stomach or intestine including peptides are most suitable for CDDS. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery.

Drug Carrier

The selection of a carrier for a particular drug candidate depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. The factors such as chemical nature, stability and partition coefficient of the drug, and the type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule, for example, aniline or nitro groups on a drug may be used to link it to another benzene group through Azo bond.

CONVENTIONAL TECHNIQUES[8]

- Prodrugs
- Colon-specific biodegradable delivery system
- Matrix-based systems
- Time-release systems
- Bio-adhesive systems
- Multi-particulate systems
- Polysaccharide-based delivery systems
- Colon targeted by coatings.

ADVANCED/NOVEL TECHNIQUES[9]

- Pressure-controlled delivery system
- Osmotic controlled delivery system
- Pulsincap system
- Port system
- CODES Technology
- Enterion capsule Technology
- Time clock system
- Multiparticulate system drug delivery
- Azo hydrogel
- Pro-biotic approach

Pressure-controlled delivery system

In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule as a result of pressure in the lumen of the colon. The thickness of the ethyl cellulose membrane is the most important factor for disintegration of the formulation. 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 ethyl cellulose single-unit capsules the drug is in a liquid. Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to human.[10]

Osmotic controlled delivery system

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. 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.33 Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semipermeable membrane. An orifice is drilled through the membrane next to the drug layer. 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.34,35,36 Various in vitro / in vivo evaluation techniques have been developed and proposed to test the performance and stability of CDDS.

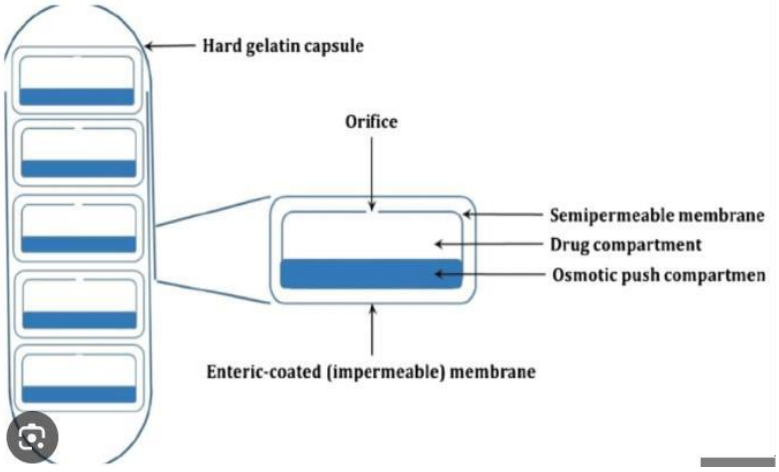

Fig. 1: Osmotic controlled CDDS.

Pulsinicap system

In this system the formulation is developed in a capsule form. The plug placed in the capsule controls the release of the drug. Swellable hydrogels are used to seal the drug contents. The capsule gets swelled when it comes in contact with the dissolution fluid and after a lag time the plug gets pushed off from the capsule and the drug will be released. Polymers such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate are used as hydrogel plugs. The lag time is controlled by the length and point of intersection of the plug in the capsule body.[11]

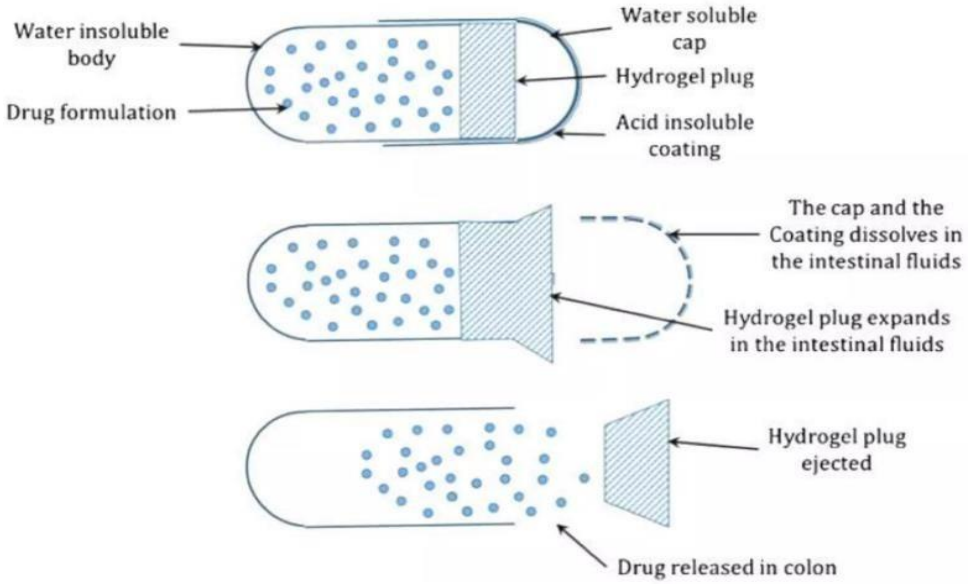

Fig. 2: Pulsinicap system.

Port system

In this system the capsule body is enclosed in a semi permeable membrane. The capsule body consists of an insoluble plug consisting of osmotically active agent and drug formulation. When the capsule comes in contact with the dissolution fluid the semi permeable membrane permits the fluid flow into the capsule resulting in the development of pressure in the capsule body which leads to release of drug due to expelling of the plug. The drug is released at regular intervals with time gap between the successive intervals. It consists of a gelatin capsule coated with a semi-permeable membrane housing an insoluble plug and an osmotically active agent along with the drug formulation. When in contact with an aqueous medium, water diffuses across the semi-permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time.

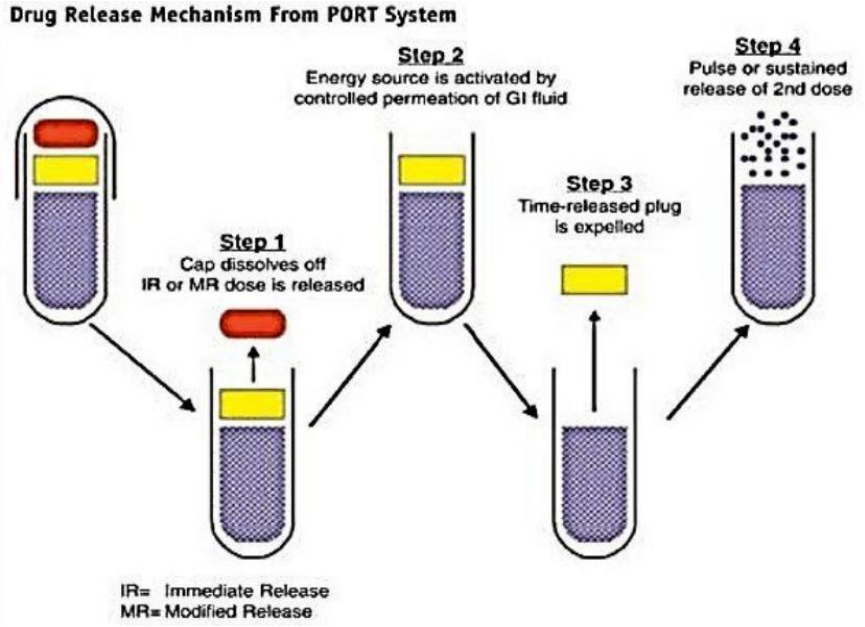

Fig. 3: Drug release mechanism of port system.

CODES Technology (colon specific drug delivery systems)

This method is developed to minimize the problems associated with the pH and time dependent drug delivery systems. In this system the pH sensitive polymers are used along with the polysaccharides that are degraded only by specific bacteria present in the intestine. This system consists of a core tablet coated with three layers of polymer coatings. The outer coating is composed of the polymer Eudragit L. This coating gets dissolved once the tablet passes though the pyloric and duodenum and exposes the next coating. The next coating is composed of Eudragit E.[12]

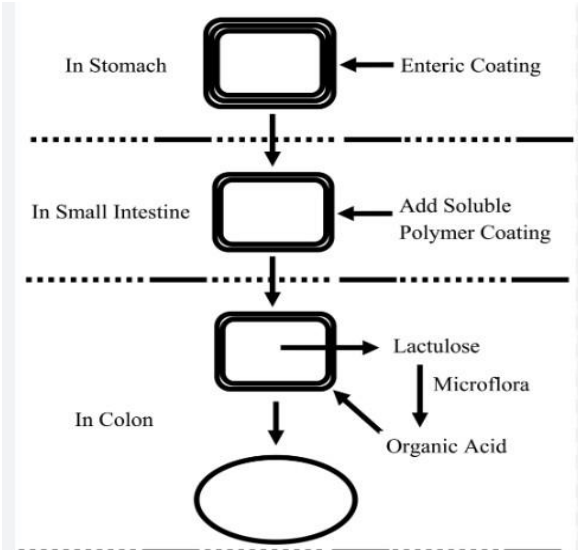

Fig. 4: Mechanism of CODESTM.

Enterion capsule technology

The capsule can be loaded with either a liquid formulation or a particulate formulation. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high-tensile strength polymer filament. When the capsule reaches the target site the drug is released by the action of the magnetic field. This magnetic field induces power in a tuned coil antenna, embedded in the capsule wall. This power is fed to a tiny heater resistor located in a capsule. This greater resistor increases temperature releases the spring and drives the piston. The resulting increase in pressure within the drug reservoir forces off the O-ring sealed cap and ejects the drug or drug formulation into the surrounding GI fluids.

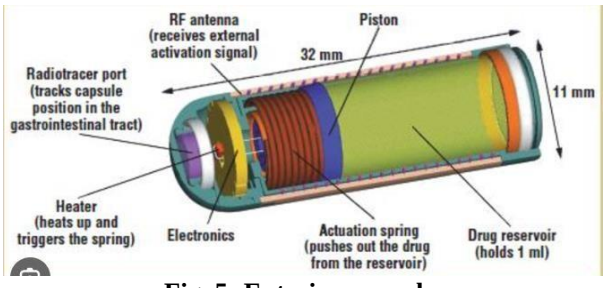

Fig. 5: Enterion capsule.

Time clock system

It is composed of a solid dosage form coated with a hydrophobic surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. The outer layer re-disperses in the aqueous environment at a time proportional to the thickness of the film and the core is then available for dispersion.[13]

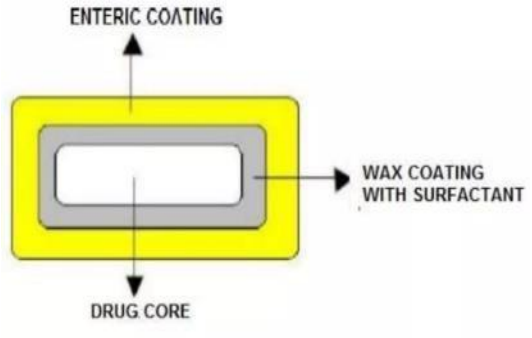

Fig. 6: Time clock method.

Multiparticulate system-based drug delivery

Multiparticulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics (NS Dey et al., 2008). The various advantages of this system are increased bioavailability, reduce risk of local irritation, and reduce risk of systemic toxicity. The various multiparticulate approaches include pellets, micro particles, granules and nano-particles (Nalanda and Prashant, 2015). To administer or to recommend total dose these subunits are compressed into a tablets or filled into a sachets or encapsulated. These are capable of protecting the drugs from the chemical and enzymatic degradation in GIT resulting in an increase in their stability and absorption of through the intestinal epithelium.[14]

Azo hydrogel

The pH-sensitive monomers and azo cross-linking agents in the hydrogel produce the colon specificity. During their passage through GIT, these hydrogels swell as the pH increases. This swelling of hydrogels cleaves the cross-links in the hydrogel network causing the release of drugs entrapped in the hydrogel (Rama Krishna et al., 2014). These hydrogels are prepared by cross-linking polymerization of N-substituted (Meth) acrylamides, N-tertbutyl acrylamide, and acrylic acid with 4, 4-di (methacryloyl amino)azo benzene as cross-linking agents. The degradation rate of hydrogen is associated with the degree of swelling and is inversely proportional to the cross-linking density.

Pro-biotic approach

The pro-biotic approach is one of the modern techniques for colon targeting. In this approach three components are desirable namely probiotic strain, microbial digestible carrier, and triggered temperature. Pro-biotic stains include inactive micro flora like bifid bacterium and lactobacillus species. At body temperature, these

strains are triggered to be active and start digesting the carrier and ultimately release the drug at the desired place. This approach gains success in the colon drug delivery system because these conditions are only available in the colon.[15]

CONCLUSION

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon-targeted drug delivery systems provide benefits of local and systemic effects. The main advantage of a colon drug delivery system is that the colon offers a long transit time, near neutral PH, reduced enzymatic activity, and increased responsiveness to absorption to absorption enhancers. Finally, it concluded that novel techniques of colon-targeted drug delivery systems aremore effective than the conventional methods because these methods increase the pharmacological activity, reduce dose frequency, minimize side effects, and prevent thedrug from degradation.

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