



INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A PROMISING APPROACHES OF COLON TARGETED DRUG DELIVERY SYSTEM

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Accepted Date: 19/04/2014; Published Date: 27/04/2014

Abstract: Oral administration of different dosage forms is the most commonly used method due to greater flexibility in design of dosage form and high patient acceptance, but the gastrointestinal tract presents several formidable barriers to drug delivery. In oral colon-specific drug delivery system, colon has a large amount of lymphoma tissue (facilitates direct absorption in to the blood), negligible brush boarder membrane activity, and much less pancreatic enzymatic activity as compared with the small intestine. Colon-specific drug delivery has gained increased importance not just for the delivery of the drugs for treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides. This review updated the research on different approaches for formulation and evaluation of colon- specific drug delivery system. Reduce the dosage size and frequency, enhance drugs solubility, permeability and bioavailability, accumulation of the particulate carrier system in the desired site may be get by Colon-specific drug delivery system.

Keywords: Colon specific drug delivery system, pH dependent approach, Time dependent approach, pH and Time dependent approach, Prodrug approach, Probiotic approach



PAPER-QR CODE

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Access Online On:

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How to Cite This Article:

Ravi Patel, IJPRBS, 2014; Volume 3(2): 814-826

INTRODUCTION

The colon specific drug delivery system should be capable of drug need to protect from degradation, i.e. drug release and absorption in the upper portion of the gastric intestinal tract and then to be ensured abrupt or controlled release in the proximal colon^{1,2}.

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allow topical treatment of inflammatory bowel disease, ulcerative colitis, crohn's disease, cirrhosis disease, amoebiasis, and colonic cancer, local treatment of colonic pathogens and systemic delivery of protein and peptide drugs².The colon is believed to be a suitable absorption for peptides and protein drugs for following reasons;(i) less diversity, and intensity of digestive enzymes,(ii)comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine. Treatment can be made effective if the drug can be targeted directly into the colon, thereby reducing the systemic side effects. CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability and finally, because the colon has a long residence time which is up to 5 days and highly responsive to absorption enhancer^{1,2}.

ADVANTAGES³⁻⁵

1. It is suitable for drug degraded by the enzymes in stomach and small intestine.
2. It provides enhanced absorption of poorly soluble drug by offering long retention time in colon.
3. The wastage of drug by unnecessary systemic absorption is reduced and intact from of the drug is saving till reaches target site.
4. Predictable, reproducible and short gastric residence time.
5. Less inter- and intra-subject variability.
6. Improve bioavailability.
7. Reduced adverse effects and improved tolerability.
8. Limited risk of local irritation.
9. No risk of dose dumping.
10. Flexibility in design.

11. Ease of combining pellets with different compositions or Release patterns.
12. Improve stability.
13. Improve patient comfort and compliance.
14. Achieve a unique release pattern.
15. Reduce gastric irritation caused by many drug (e.g. NSAIDS).
16. Extended daytime or night time activity.
17. It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.

APPROACH:

- 1) pH-Dependent system
- 2) Time dependent
- 3) pH and time dependent
- 4) Prodrug approaches
- 5) Probiotic approaches
- 6) Microbial triggered approach
- 7) Hydrogel approaches
- 8) CODES technologies
- 9) Osmotic controlled drug delivery system
- 10) PULSINCAP system
- 11) Port system
- 12) Time clock system
- 13) Chronotopic system
- 14) COLAL-PRED system
- 15) Pressure controlled drug delivery
- 16) Multiparticulate approaches
- 17) Pulsatile system
- 18) Nano particulate system

(1) pH-Dependent system:

During fasting the pH range of the stomach is in between 1-2 but on eating its increases. The pH of proximal small intestine is about 6.5 and in the cecum are about 6.4⁶⁻⁸. However, pH values as low as 5.7 has been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and in the descending colon 7.0⁹. Colon targeted drug delivery systems

based on meth acrylic resins has described for insulin, prednisolone, quinolones, cyclosporine, salsalazine, beclomethasone dipropionate and naproxane¹⁰. The principle in this method is the coating of the tablets/pellets etc. with various pH sensitive polymers (Eudragit L-100, Eudragit S-100, Eudragit L-30D, Eudragit L-100-55, Eudragit FS 30D, Poly Vinyl Acetate Phthalate, Hydroxy Propyl Methyl Cellulose Phthalate 50, Hydroxy Propyl Methyl Cellulose Phthalate 55, Hydroxy Propyl Ethyl Cellulose Phthalate, Cellulose Acetate Phthalate, Cellulose Acetate Trimellate) which will produce delayed release and also give protection from gastric fluids¹¹. These different polymers having different threshold pH and according to that release the drug at same pH (as shown in the Table 1.4). Mostly the Eudragit L and S are used for the preparation of colon drug delivery, these dissolved at the pH of 6 and 7 respectively⁹. The decrease in the pH from the end of the small intestine to the colon have many problems like increases lag times at the ileocecal junction or fast elimination through the ascending colon, which can affects poor site specificity of the single unit formulation¹². Several factors affects the formulation, such as combinations of different polymers, pH of the media, coating level of the tablets and presence of plasticizers, influence the dissolution rate of Eudragit®.

Table. 1.4: Table showing different pH sensitive polymers and their threshold pH release⁹.

Sr. No.	Polymer	Threshold Ph
1	Eudragit S-100	7
2	Eudragit L-100	6
3	Eudragit FS 30D	>7
4	Eudragit RS 100	<6
5	Eudragit L 30D	5.6
6	Eudragit L100-55	5.5
7	Hydroxy propyl methyl cellulose phthalate	>5.5
8	Shellac	7
9	Hydroxy propyl ethyl cellulose phthalate	5.2
10	Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	
	LF Grade	
	MF Grade	>5.5
	HF Grade	>6.0
		>6.8
11	Polyvinyl acetate phthalate	4.5-4.8
12	Cellulose acetate terimellate	4.8

(2) Time-dependent system:

In this approach, the basic principle is the release of the drug after a predetermined lag time from dosage form at the site of action at right time and in right amount¹³. Both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine, that can be unaffected by particle size, density or composition of the meals, because the time taken to leave the formulation to the stomach was not predicted¹⁴. Ideally, formulation was to be designed that are not affected by the individual difference in gastric emptying time, pH of the stomach, small intestine or presence of anaerobic bacteria in the colon at the site of delivery¹⁵. In this formulation is comprised of three parts first a center core containing a drug and swelling excipients, secondly an inner semipermeable polymer membrane containing a plasticizer which allow water influx but prevents the outward diffusion of drug and lastly an outer enteric-coating which dissolves above pH 5.5¹⁶⁻¹⁷.

Disadvantages of this system

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
- Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhoea and the ulcerative colitis.

(3) pH and Time dependent system:

By combining an enteric coating approach to prevent drug dissolution in the stomach and a delayed-release element that relies on the passage of time, it is possible to targeted release of a drug in the terminal ileum and colon. A typical multi-layered bead formulation used for pH and time dependent drug release. This type of formulation comprises of

- (1) An outermost coating of an enteric polymer such as Eudragit L,S or FS that ensures dosage transit from stomach to some distance into small intestine.
- (2) A second barrier coating of a pH-independent polymer such as Eudragit RS or ethylcellulose that delays drug release for several hours.
- (3) An innermost drug layered nonpareil seed¹⁸.

(4) Prodrug approach:

Prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body in order to release the active drug and improved release properties of parent compound. For colonic delivery, the prodrug is designed to undergo minimal hydrolysis in the upper GIT, and undergo enzymatic hydrolysis in the colon by releasing the active drug moiety from drug carrier¹⁹. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes. Its other linkages susceptible to bacterial hydrolysis especially colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucuronic acids, glucose, galactose, cellulose dextran, cyclodextran etc²⁰⁻²².

(5) Probiotic:

The Probiotic approach is one of the latest approach for colon targeting. In this approach, three components are desirable namely probiotic strain, microbially digestible carrier and triggering temperature. Probiotic strains include inactive micro flora like Bifidobacterium and Lactobacillus species²³. At body temperature, these strains triggered to be active and start digesting the carrier and ultimately release the drug at desired place. This approach gain success in colon drug delivery system because these conditions are only available in colon. Performed this approach for diclofenac sodium using guar gum as the carrier in matrix tablets. They gained success as the formulation containing probiotics show better release of drug than drug alone in carrier²⁴.

(6) Microbial triggered approach:

The basic principle involved in this method is degradation of coated polymers on the drug delivery system by micro flora present in colon and release of drug in colonic region. The micro flora of the colon is in the range of 10¹¹-10¹² CFU/ml consisting mainly of anaerobic bacteria, e.g. Bacteroides Bifidobacterium, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This approach is different from probiotic approach because in probiotic approach, we are providing micro flora from external source which assist the interior flora. Polysaccharides offer an alternative substrate for the bacterial enzymes present in the colon.^{25, 26}

(7) Hydrogel system:

Hydrogels incorporating drugs was also found to be used as oral colon drug delivery devices. Many studies show that this system has significant potential. Various type of hydrogel based CDDS were reported by different researchers. These are of three types, namely azo cross-linked, alcohol cross-linked and aldehyde cross-linked hydrogels. Azo hydrogels produced colon

specificity by mutual involvement of pH sensitive monomers and azo cross linking agents. This synthetic approach for colon targeting can be obtained by cross-linking polymerization of N-substituted (meth)acrylamides, N-tart-butyl acrylamide and acrylic acid with 4,4'-di(methacryloylamino) azobenzene and N- N'-methylene bisacrylamide . The hydrogels were also prepared by polymer–polymer reaction using the same polymeric precursor with the corresponding copolymer containing side chains terminating in NH₂ groups.

(8)CODES Technology:

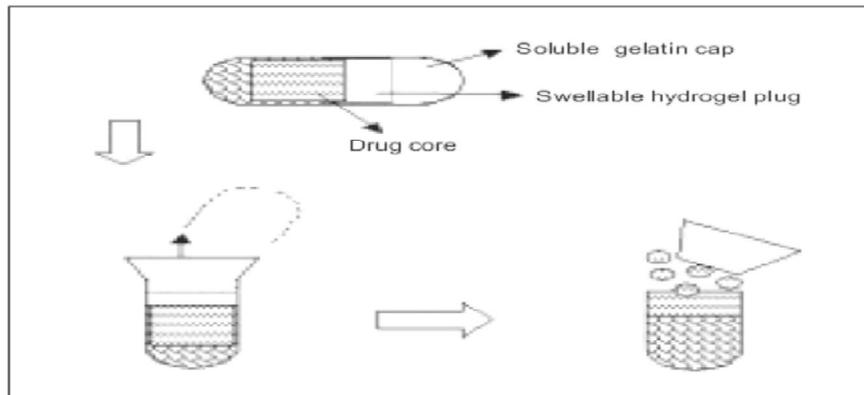
This technology was introduced to avoid viscera-colonic problems associated with time or pH. CODESTM is a combinational approach of microbially triggered and pH dependent CDDS. It has been developed for the site specific release in the colon by utilization of a unique triggered mechanism involving lactulose. In this system, lactulose is incorporated in the core, followed by coat of Eudragit E which is acid soluble in nature and then subsequently over coated with an enteric material, Eudragit L²⁷.

(9) Osmotic controlled drug delivery (OROS-CT)

A novel CDDS was introduced by Alza Corporation, to target the drug locally to the colon, which is known as OROS-CT. The OROS-CT system include either single osmotic unit or up to 6 push pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule. In this system a semi permeable membrane surrounds both osmotic push layer and drug layer. Next to the drug layer orifice is drilled through the membrane. The push-pull unit was dissolved after the OROS-CT is swallowed in the gelatin capsule. Because of the enteric coating of the impermeable drug, there is no drug release in the stomach due to push-pull unit prevents the absorption of drug in the acidic environment²⁸.

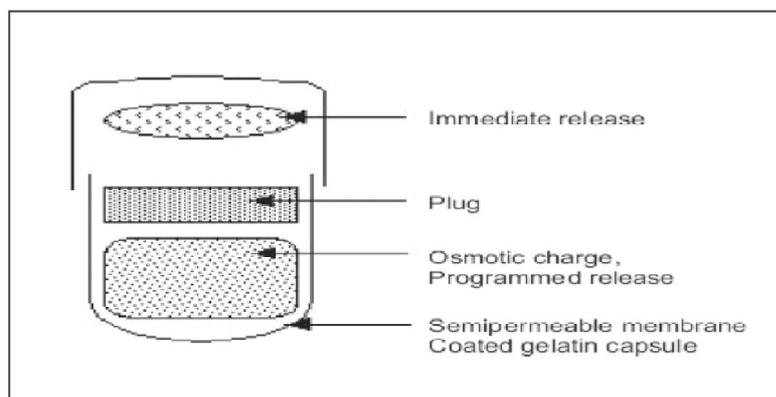
(10) PULSINCAP system

Single-unit systems are mostly developed in a capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion and the drug is released as a “Pulse” from the insoluble capsule body. One such system comprises of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule comes in contact with the dissolution fluid, it swelled and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for the hydrogel plug were different viscosity grades of hydroxypropyl methyl cellulose (HPMC), poly methyl methacrylate, polyvinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time^{29, 30}.



(11) Port system:

The Port[®] system consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. When this capsule come in contact with the dissolution fluid, the semipermeable membrane allow the entry of water leading to the pressure development inside the capsule and the insoluble plug expelled after a lag time. The dosage form is designed in such a manner that upon ingestion, the first drug release pulse occurs within 1-2 h, followed by period during which no release occurs. Second dose is released in 3-5 h of ingestion. This is again followed by a second no-release interval. Release of third dose occurs within 7-9 h of ingestion. This system avoids the second time dosing³⁰



Advantages

- Extended daytime or night-time activity
- Reduced side effects
- Reduced dosage frequency

- Reduction in dose size
- Improved patient compliance
- Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism

(12) Time clock system:

In this technique, an aqueous dispersion is used for coating of the solid dosage form. In this coating is a hydrophobic surfactant layer to which a water soluble polymer is added to improve adhesion to the core. The rehydration of the system results when it comes in contact with dissolution fluid, and redisperses also. In this system, the lag time could be controlled by proportional varying the thickness of the coating material. The effect on the lag time may be different in high calorie and low calorie meal that was studied by using gamma scintigraphy. The mean lag time of the drug release was 5.5 and 5.7 hours respectively³¹.

(13) Chronotropic system

In this technology a drug release after a particular lag time that is surrounding with a soluble barrier layer, which consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC. The coating of additional enteric coating film outside that layer to overcome the gastric emptying variability and lag time of the drug was controlled by coating thickness and viscosity grade of the HPMC²⁸.

(14) COLAL-PRED system

COLAL-PRED is a proprietary gastrointestinal product developed by Alizyme for the treatment of ulcerative colitis (US). It has arisen from combining Alizyme's proprietary colonic drug delivery system, COLAL, with an approved generic steroid (Prednisolone sodium metasulfobenzoate). It is an effective anti-inflammatory treatment for UC without the typical side effects of steroids. There are currently no competitor products, either on the market or in development, with the same profile of product. A 'Safe steroid' product with the profile of COLAL-PRED would represent a significant advance in the management of UC^{32,33}.

(15) Pressure controlled drug delivery system:

Peristaltic movements of intestines along with gastric contractile activity are responsible for the propulsion of intestinal contents. These peristaltic movements constitute elevated luminal pressure conditions in the colon. The design of pressure controlled drug delivery system is based upon above mechanism. Intensity and duration of this pressure varies with the muscular contractions in the visceral organs³². It consists of a capsule shaped suppositories coated with the water insoluble polymer like ethyl cellulose (EC). Once taken orally, they behave like ballon of ethyl cellulose because the base of the capsule was liquefy at the body temperature²⁷

(16) Multiparticulate approach

Multiparticulate approach tried for colon delivery include formulations in the form of pellets, granules and microparticles. Researchers developed biodegradable colon targeted multi particulate system by using guar gum. In that study, the drug loaded pellets were coated with aqueous guar gum slurry and after in vitro evaluation the drug release after 4.5 h lag time in presence of enzyme and lag time increases in absence of enzyme which indicates the enzyme triggered system for colonic release. Multi particulate system has also be used for colon targeting^{27, 34}.

(17) Pulsatile colon delivery

Pulsatile drug delivery systems (PDDS) can be classified in site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastro intestinal tract, e.g., on pH, presence of enzymes, and the pressure in the gastro intestinal tract. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers³⁵.

CONCLUSION:

The colon specific deliveries are those which rely on condition encountered in this system which can be degraded by colonic bacteria are very attractive and promising site. Although the surface area in the colon is low compared to the small intestine relatively poor drug absorption this is because of slow rate of transit. It is selective site for absorption of hydrophobic drugs, which are absorbed by transcellular transport. It is best for orally delivery of protein and peptides.

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