

COLON TARGETED MICROBEADS: A NOVEL APPROACH IN NDDS

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ABSTRACT

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. Different approaches are designed based on prodrug formulation, pH-sensitivity, time-dependency (lag time), microbial degradation and osmotic pressure etc to formulate the different dosage forms like tablets, capsules, multiparticulates, microspheres, microbeads, liposome for colon targeting. The efficiency of drug

delivery system is evaluated using different in vitro and in vivo release studies. This review updated the research on different approaches for formulation and evaluation of colon-specific drug delivery systems (CDDS).

KEYWORDS: Colon Specific Drug Delivery System, Microbial Degradation, Osmotic Pressure, pH-sensitivity, Prodrug, Time Dependency.

INTRODUCTION

In the past two decades, the pharmaceutical scientists are extensively investigated in the area of colonic region for targeted drug delivery system. Targeted drug delivery to the colon is mainly for the treatment of colonic diseases, for drugs like proteins and peptides, for the treatment of diseases sensitive to circadian rhythms such as Asthma, Angina and Rheumatoid arthritis and for delivery of steroids, which absorbable in colon. The advent of slow release

technologies increase the chances for a drug to be released in the colon and thus this organ has an important role to play in drug absorption from oral sustained release formulations. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This region of the colon is having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine. Additionally, the colon has a long retention time and appears highly responsible to agents that enhance the absorption of poorly absorbed drugs. The simplest method for targeting of drugs to the colon is to obtain slower release rates or longer release periods by the application of thicker layers of conventional enteric coating or extremely slow releasing matrices.

ANATOMY OF COLON

Colon is divided into the cecum, ascending colon, transverse colon, rectum and anal canal (as shown in the Fig. 1). The cecum has a dilated portion, which is blinded interiorly and is continuous with the ascending colon superiorly. Ascending colon passes upwards from the cecum to the level of the liver where it bends acutely to the left at the right colic flexure to become transverse colon. The transverse colon, that extends across the abdominal cavity, in front of the duodenum and the stomach to the area of the spleen. The descending colon passes down the left side of the abdominal cavity then bends towards the midline. Pelvic colon describes an S-shaped curve in the pelvic, then continuous downwards to become the rectum. Colon consists of layer of tissues, i.e. the longitudinal muscle fiber, sub mucous layer, mucous membrane lining. Arterial Blood supply in the colon is mainly by superior and inferior mesenteric arteries and venous drainage is mainly by the superior and mesenteric vein.

Physiologically, the human colon can be divided into three functional areas.

- The transverse colon, the motor patterns of which may hold material in the proximal colon or propel it distally but that may also be an important site for the absorption of water and the rectum.
- Proximal colon acts as a reservoir for fecal material and allows defecation to be delayed until socially convenient.
- The cecum and proximal colon, which act as a fermentation chamber.

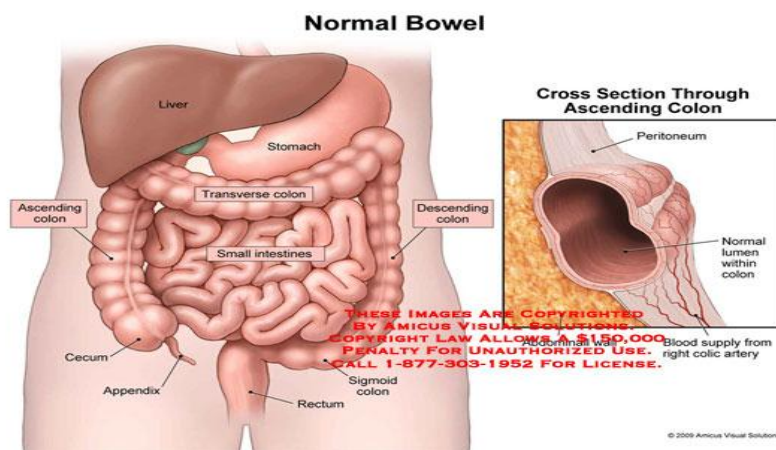


Fig.1 ascending colon and descending colon.

PH IN THE COLON

The pH is different in the GI tract starting from oral cavity to the large intestine. The pH changes appear in stomach, small and large intestine, because of presence of different factors such as diet, food intake, intestinal motility and disease states. This variability in the GIT pH makes it more challenging for the specialists working in this field to design a delivery system that would be robust enough to withstand these changes. The colonic drug delivery uses this variation in pH along the GIT to target the drug. The pH gradient in GIT range from 1.2 in the stomach, 6.6 in the proximal small intestine to a peak of about 7.5 in the distal small intestine. The right, mid, and left colon have pH values approximately 6.4, 6.6 and 7.0 respectively. The pH of the colon is often lower than the pH of the small intestine, which is as high as 8 or 9.20. There is a fall in pH on the entry into the colon due to the presence of short chain fatty acids produced by bacterial fermentation of polysaccharides. This fall in pH has to be targeted to deliver the drug to the small intestine by the way of pH-sensitive enteric coatings.

Table. 1: average PH in the git.

portion of gi tract	ph range
Oral cavity	6.2-7.4
Oesophagus	5.0-6.0
Stomach	Fast condition-1.5-2.0 Fed condition-3.0-5.0
Small intestine	Jejunum-5.0-6.5 Ileum-6.0-7.5
Large intestine	Right colon-6.4 Mid colon & left colon-6.0-7.5

DIFFERENT APPROCHES USED FOR COLON TARGETING

- Prodrug approaches.
- Probiotic approaches.
- Hydrogel approaches.
- pH-Dependent system.
- Time dependent.
- Microbially triggered system.
- CODES technologies.
- Osmotic controlled drug delivery system.
- Pulsin cap System.
- Port system.
- Time clock system.
- Chronotropic system.
- Colal pred system.
- Pressure controlled drug delivery.
- Multiparticulate approaches.
- Pulsatile colon delivery.
- Nanoparticulate system.

Prodrug approach: Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires biotransformation *in vivo* to release the active drug from the carrier. The enzymes like azoreductase, galactosidase, xylosidase, nitroreductase, glycosidase and deaminase are mainly targeted for colonic drug delivery.

Probiotic approach: The Probiotic approach is one of the latest approach for colon targeting. In this approach, three components are desirable namely probiotic strain, microbially digestable carrier and triggering temperature. Probiotic strains include inactive microflora like Bifidobacterium and Lactobacillus species.

Hydrogel approach: 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.

Ph-dependent

During fasting the pH range of the stomach is in between 1-2 but on eating it increases. The pH of proximal small intestine is about 6.5 and in the cecum are about 6.4. 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 7.2 Colon targeted drug delivery systems based on meth acrylic resins has described for insulin, prednisolone, quinolones, cyclosporine, salsalazine, beclomethasone dipropionate and naproxane.

Time dependent approach

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 amount 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 predicted.

Microbial triggered approach

The basic principle involved in this method is degradation of coated polymers on the drug delivery system by microflora present in colon and release of drug in colonic region. The microflora of the colon is in the range of 10^{11} - 10^{12} 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 microflora from external source which assist the interior flora. Polysaccharides offer an alternative substrate for the bacterial enzymes present in the colon. Many of these polymers are already used as excipients in drug formulations or are constituents of the human diet and are therefore generally regarded as safe. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems.

CoDESTm

This technology was introduced to avoid viscero-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 L. Outermost coat of Eudragit L

protect the ultimate tablet to be dissolved in gastric fluids and former Eudragit protects the preparation as it passes through the alkaline pH of the small intestine. Microbial triggered degradation of lactulose starts when the tablet arrives in the colon.

Osmotic controlled drug delivery (ords-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 upto 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.

Pulsincap system

This technique was introduced by R.R.Scherer International Corporation, Michigan, US, to target a water insoluble capsules. This formulation possess seal coat with swellable hydrogel plug to enclosing the drug reservoir into the capsule body. At particular lag time, capsule was come to in contact with dissolution fluid, swelling take place and drug release rapidly. The different grade and viscosity of polymers was used to design the hydrogel plug, that includes polymethyl methacrylate, hydroxyl propyl methyl cellulose, poly vinyl acetate and poly ethylene oxide.

Port system

This technique was introduced by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of insoluble plug of drug and osmotically active agent coated with a semi permeable membrane of the capsule. System used to delivered methylphenidate to school age children and shows good in-vivo and *in-vitro* correlation in humans for the treatment of attention deficit hyper activity disorder (ADHD).

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 respectively.

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.

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 indevelopment, 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. COLAL-PRED has a coating that is broken down only in the colon, by locally occurring bacteria.

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 organs The thickness of the ethyl cellulose membrane play a very vital role in the disintegration of the capsule.

Multiparticulate approach

Multi particulate 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.

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 layers.

Nanoparticulate system

Nanoparticle size colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting. Orally administered nanoparticles serve as carriers for different types of drugs and have been shown to enhance their solubility, permeability and bioavailability. The use of nanoparticles for bioadhesion purposes have also been investigated. Nanoparticles have a large specific surface, which is indicative of high interactive potential with biological surfaces. Since the interaction is of nonspecific nature, bioadhesion can be induced by binding nanoparticles with different molecules.

PREPARATION OF HYDROGEL BEADS BY USING DIFFERENT TECHNIQUES:

Ionotropic gelation technique

Emulsion internal Ionotropic gelation.

Ionotropic gelation under a high voltage electrostatic field.

Ionotropic gelation followed by coacervation.

Multi polyelectrolyte hydrogel beads.

Ionotropic gelation followed by compression.

METHOD OF PREPARATION**Beads can be prepared by the following method**

1. Ionotropic gelation technique
2. Cross-linking
3. Emulsification gelation technique

Following these three methods show many advantages

- Easy and mild, inexpensive preparation techniques.
- No organic solvent or high shear force to be used.
- These method would be use for broad categories of drugs such as macromolecules, protein, others Stable.

Ionotropic gelation technique**Steps involved in the preparation of micro-beads by ionotropic gelation technique**

1. Weigh accurately all the materials including the drug used, sodium alginate and calcium chloride.
2. Distilled water is added to the weighed quantity of sodium alginate to make mucilage pest and allowed to heat for 5-10 minutes in a hot plate.

3. After that, distilled water is also added to the weighed quantity of calcium chloride to make a solution.
4. The mucilage pest of sodium alginate is then stirred in a magnetic stirrer at a suitable speed for several minutes.
5. The Drug is dispersed in the mucilage pest of sodium alginate and stirred at suitable speed in the magnetic stirrer.
6. The micro-beads are formed by dropping the calcium chloride solution in it through a glass syringe with the help of a needle.
7. The micro-beads are filtered & washed thoroughly with distilled water.
8. Dried at room temperature subsequently for few hours.

Cross-linking

Steps involved in the general preparation of beads by cross-linking

1. The cross-linking polymer solutions of different concentrations were prepared by dissolving in water under slow agitation.
2. Drug was added in the polymer solution under constant stirring for 2 min for uniform distribution throughout the solution.
3. Finally, drug and polymer solution was extruded drop wise through a 1.2-mm diameter needle into of stirred calcium chloride solution at room temperature.
4. And then micro-beads were formed and beads were allowed to remain in the stirred solution for 10 min curing time.
5. The micro-beads were filtered and washed with distilled water and beads dried at room temperature.

Emulsification gelation method

1. In emulsion gelation technique polymer sodium alginate were dissolved in the water.
2. The drug was added in to the polymer solution and mixed uniformly.
3. The polymer solution was then added in a thin string of heavy liquid paraffin solution contained in a beaker.
4. Then calcium chloride solution was added into the emulsion and stirring for 15 min to formed spherical micro-beads.
5. The micro-beads were collected by decantation and washed with petroleum ether.
6. The micro-beads were then air dried to obtain discrete microcapsules.

ADVANTAGES

- Increased therapeutic efficiency as more drug reaches to target site.
- Avoid risk of toxicity.
- Plasma concentration of drug is maintained for prolonged period.
- Better absorption as surface area is increased.
- Patient compliance will be increased because of taste masking Improved stability.
- The synthetic polymers have ability to tailor mechanical properties and degradability.
- They are also attractive because it can be fabricated into various shapes.
- Polymers can be designed with chemical particular functional groups.

DISADVANTAGES

- It is always higher in cost; the production cost is also much in higher compared with natural polymer.
- Some synthetic polymer are not biocompatible and produces toxicity.
- During synthesis of synthetic polymer it causes environment pollution.
- It also produces side effect (acute and chronic effect).
- And poor patient compliance.

Application**The alginate micro-beads have various therapeutic uses**

1. NSAID like Diclofenac micro-beads, it show reduced release in the stomach. It is reduces the adverse effects and avoids direct contact between the drug and the gastric mucosa.
2. The micro-beads loaded with the antibiotics (like Oxytetracycline) is useful for the oral administered for the treatment of gastric and intestinal disease.
3. Lamivudine is a synthetic nucleoside analog that is being increasingly used as the core of an Antiretroviral regimen for the treatment of HIV infection and it formulated in the alginate beads so that their controlled release can be obtained for the prolonged therapeutic effect.
4. Ranitidine, peptic ulcer drug, it designed in micro-bead form in such a way that it will be retained in stomach for sufficient time. So, it could open new treatment of gastric ulcer and acidity.
5. Sustained release of Prednisolone from chitosan gel beads, and it increses the therapeutic efficacy and decreases side effects by minimizing the reaching of the drug to the systemic circulation against inflammation.

6. Theophylline, a poorly water soluble bronchodilator and the targeted drug for controlled delivery, and reduces drug release under physiologically simulated pH conditions (acidic and neutral). So, it could be formulated into modified dosage form.
7. 5-Fluorouracil encapsulated alginate micro-beads for the treatment of breast cancer can be formulated in the alginate beads so that their controlled release can be obtained for the prolonged therapeutic effect.
8. Metformine Hydrochloride, an antidiabetic drug, using albumin are degraded in to acidic medium when it given orally. Formulating them in the modified alginate micro- beads can deliver them in to intestinal region without degradation in the stomach region.
9. Insuline, an antidiabetic drug, formulating them in the modified alginate beads can directly delivers them in the intestinal region without drug degradation in the stomach.
10. Piperine was fabricated into alginate beads using sodium alginate. The main aim to develop the sustained release of piperine from alginate beads by *in vitro* evaluation. The drug release studies were showed that the alginate beads sustained the release.
11. Rifampicine, first line drug used to treat tuberculosis, so the sustained and the controlled release of ampicillin can be useful to overcome its short half-life.
12. Salbutamol sulphate is a short-acting β_2 -adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma, so their therapeutic effect enhanced by the use of the sodium alginate interpenetrating network beads.
13. Microspheres are also being use in cancer treatment. Cancer microsphere technology is the latest trend in cancer therapy.
14. Developing of calcium alginate–gelatin based microspheres for controlled release of Endosulfan act as a model pesticide.

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