



Novel Approaches and Developments in Colon Specific Drug Delivery Systems- A Review

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Novel Approaches and Developments in Colon Specific Drug Delivery Systems- A Review

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Abstract

Colon specific drug delivery has gained increased importance not for the treatment of local diseases associated with the colon but also as potential site for systemic delivery of therapeutic proteins and peptides. Colon is a site where both local and systemic delivery of drug can take place. Treatment could be more effective if it is possible for drug to be directly to colon. Systemic side effects can also be reduced the primary approaches to obtain colon specific delivery is based on prodrugs, pH and time dependent systems (or) microflora activated systems and have achieved limited success only. Most recently new colon – specific delivery systems are developed. These are pressure controlled colon delivery capsules, CODESTM, colon drug delivery systems based on pectin and galactomam coating, hydrogels, osmotic controlled drug delivery system, pulsincap system, time clock system, chronotropic system, enterion capsule technology. The review is aimed at understanding above pharmaceutical approaches to colon targeted drug delivery systems for better therapeutic action without compromising on drug degradation (or) its low bioavailability.

Key words: Colon Specific Drug Delivery System, Advantages, Approaches.

Introduction

The basic goal of drug therapy is to achieve a steady-state at blood or tissue level that is therapeutically effective and non toxic for an extended period of time a basic objective in dosage form design is to optimize the delivery of the medication so as to achieve a measure of control of therapeutic effect in the place of uncertain fluctuations in the in-vivo environment in which drug release takes place. This is usually accomplished by maximizing drug availability, i.e., by attempting to attain a maximum rate and extent of drug action through formulation also implies controlling bioavailability to reduce drug absorption rates. Mainly colon specific or targeted drug delivery system (CDDS). An ideal controlled drug delivery system is one which delivers the drugs at a predetermined rate, locally or systematically, for a

specified period of time. Controlled Released Drug Delivery System interchangeable called as programmed release, sustained release, prolonged release, timed release and extended release.

An ideal targeted drug delivery system is the one which delivers the drugs only to its sites of action and not to the non targeted organs or tissues. This targeted system is employed for the drugs that are destroy by the acidic environment of the stomach or metabolized by pancreatic enzymes are only slightly affected in the colon and this deliver system is used for the treatment of ulcerative colitis, crohn's disease, and colorectal cancer inflammatory bowel diseases. Colonic delivery mainly accomplished by rectal or oral administration. Rectal administration of colonic delivery is not effective widely, oral administration is preferred. Absorption or degradation of active constituent in the upper part of GIT is main obstacle and must be circumvented for successful colonic drug delivery.

New drug delivery system includes, these includes, for instance, transdermal therapeutic system (TTS), where by the active ingredients is absorbed by the skin, subcutaneous injection, where taking pharmaceutical ingredients for controlled release tablet method, in which a predetermined dose of drug can be administered at a predetermined at specific site. In views of CDDS specifically delivering drug to the colon, a lot benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases. First, as for treating localized colonic diseases, i.e. ulcerative colitis, Chron's disease and constipation, etc. The optimal drug delivery system, such as CDDS, should selectively deliver drug to the colon, but not to the upper GI tract. Second, the Colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon. Finally, CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis. The therapeutic advantages of targeting drug to the diseased organ include

(a) Delivery of drug in its intact form as close as

possible to the target site.

(b)The ability to cut down the conventional dose and,

(c)Reduce incidence of adverse side effects.

Colon targeted systems:

The oral route is considered to be most convenient for administration of drugs to patients dosage forms that deliver drugs into the colon rather than upper GIT offers number of advantages Oral delivery of drugs to the colon is valuable in the treatment of disease of drug in the upper GIT. The colon is rich in lymphoid tissue uptake of antigens into mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. This reason of colon is colonized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine.

Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drug apart from retarding of targeting dosage forms, a reliable colonic drug delivery could also be important starting position for the colonic absorption of per orally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidase such specially delivery systems will have a fair chance to get their drug sufficiently absorbed after per orally applied, undigested, unchanged and fully active peptide drug.

Why Colon Targeted Drug Delivery is needed?

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing reduce side effect
- To delay the drug absorption
- 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 and systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, for example Ulcerative Colitis or Crohn's disease. Such inflammatory conditions are usually treated proteins and peptides
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper gastrointestinal tract, highly affected by hepatic metabolism, in particular, therapeutic

Advantages:

- Oral delivery of drugs to the colon is valuable in the

treatment of diseases of colon (ulcerative colitis, Chron's disease, carcinomas and infections)

- minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption
- The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery
- The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.
- This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than the stomach and small intestine.

Properties of Gastro Intestinal Tract: (Figure 1)

Colonic absorption:

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 (Trans cellular transport).
- * Passes between adjacent colonocytes (Para cellular transport).

Transcellular absorption involves the passage of drugs through cells and thus the route for most lipophilic 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, diclofenac, theophylline, ibuprofen, metoprolol and oxyprenolol. Drugs shown to be less absorbed include furosemide, pyretanide, buflomedil, atenolol

Factors affecting colonic absorption:

- * 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.

Methods

APPROCHES TO COLON SPECIFIC DRUG

DELIVERY:

The oral administered drugs to the colon is accomplished by

- (a) Coating with pH dependent polymers
- (b) Time release dosage forms
- (c) Delivery systems based on the metabolic activity of colonic bacteria.

Factors to be considered in the design of colon-specific delivery system:

- (1) pH in the colon
- (2) GI-Transit
- (3) Colonic microflora

Methods for Targeting Drugs to the Colon:

To achieve successful colonic delivery, a drug needs to be protected from absorption and /or the environment of the upper gastrointestinal tract (GIT) and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. The various strategies for targeting orally administered drugs to the delivery system

There are four practical mechanisms by which a delivery system can be targeted to the colon by oral administrations:

- * Use of a bacterially triggered delivery system.
- * Recent advances in colonic drug delivery system.
- * Use of a pH dependent delivery system.
- * Use of time dependent delivery system.
- * Use of a pressure controlled delivery system.

pH-dependent Delivery:

pH sensitivity enteric coatings have been used routinely to deliver drugs to the small intestine these polymers coatings are insensitive to acidic conditions of the stomach yet dissolve at the higher PH environment of small intestine. This pH differential principle has also been attempted for colonic delivery purposes, although the polymers used for colonic targeting tend to have a threshold of pH for those used in conventional enteric coating applications. Most commonly co-polymers of meth acrylic acid and methyl methacrylate that dissolve at a slower rate and at a higher threshold pH (7-7.5), has been developed recently.

The inter and intra-subject variability in gastro-intestinal pH and possibly certain other intrinsic variable such as electrolyte concentration and transit time will therefore impact on the in vivo behavior of pH-responsive system, ranging from early drug release in the small intestine to no release at all, with the formulation passing through the guts intact. The latter intestine, is considerably lower than normal, as is the case in patients with ulcer colitis in spite of their limitation, pH-sensitive delivery system are available for mesalazine and budesonide for treatment of

ulcerative colitis and crohn's disease, respectably

Time-dependent Delivery:

Time dependent delivery has also been proposed as a means of targeting the colon. Time-dependent system releases their drug load after a pre-programmed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon. This time is difficult to predict in advance, although a lag time is reported to be relatively constant at three to four hours.

Pressure-dependent delivery:

Gastro intestinal pressure has also been utilized to trigger drug release in the distal gut. This pressure, which is generated via muscular contraction of the gut wall for grinding and propulsion of intestinal contents, varies in intensity and duration throughout the GIT, with the colon considered to have a higher luminal pressure due to the process that occur during stool formation. Systems have developed therefore to resist the pressure of the upper GIT but rupture in response to the raised pressure of the colon. Capsule shell fabricated from the water insoluble polymer ethyl cellulose has been used for this purpose. The system can be modified to withstand and rupture at different pressures by changing the size of the capsule and thickness of the capsule shell wall.

Bacteria-dependent delivery:

The resident GIT bacteria provide a further means of effecting drug release in the colon. These bacteria predominantly colonize the distal region of GIT where the bacterial count in the colon is 10¹¹ per gram, as compare to 10⁴ per gram in upper small intestine. Moreover, 400 different species are present. Colonic bacteria are predominantly anaerobic in nature and produce enzymes that are capable of metabolizing endogenous and exogenous substrate, such as carbohydrate and proteins that escape digestion in the upper GIT. Therefore, materials those are recalcitrant to the condition of the stomach and small intestine. Yet susceptible to degradation by bacterial enzymes within the colon, can be utilized as carriers for drug delivery to the colon. This principle has been exploited commercially to deliver 5-aminosalicylic acid to the colon by way of a prodrug carrier. The prodrug sulphasalazine consist of two separate moieties, sulphapyridine and 5-aminosalicylic acid, linked by an azo bond. The prodrug passes through the upper gut intact, but, once in the colon, the azo bond cleaved by the host bacteria, liberating the carrier molecule sulphapyridine and pharmacologically active agent 5-aminosalicylic acid. This concept has led to development novel azo-bond based polymer for the purpose of obtaining universal carrier systems. However, issue with regard to safety and toxicity of

these synthetic polymers has yet to be addressed. To overcome such concerns, natural materials, essentially those that are polysaccharide-based, offer a viable alternative to the problem. Materials include amylase, chitosan, chondroitin sulphate, dextran, guar gum, inulin and pectin. These materials are not, however without limitations. They are hydrophilic in nature, which renders them to soluble or prone to swelling in an aqueous environment and hence unsuitable as drug carriers. To fully realize the potential of these polysaccharides for colonic delivery, some form of structure modification and/ or formulation strategy is required.

The colonic region of GIT has become an important sites for drug delivery and absorption. Targeted drug delivery would offer considerable therapeutic benefits to patients, in terms of both local and systemic treatment. Systems that rely on gastrointestinal pH, transit time or pressure for release are degraded by bacterial enzyme of colonic origin. Moreover, the cost and ease of manufacture of the delivery system are further consideration that will impact on its likely commercialization and, hence availability to patients. A bacteria-sensitive natural film coating that can be applied to a range of solid oral dosage forms using conventional processing technology would therefore appear to be the delivery system of choice.

Azo bond conjugates:

The intestinal microflora is characterized by a complex and relatively stable community of microorganism, many with physiological functions, which play vital roles in health and disease. In addition to protection of the patient against colonization of the intestinal tract by potentially pathogenic bacteria, the indigenous microflora are responsible for a wide variety of metabolic processes, including the reduction of nitro and azo groups in environmental and therapeutic compounds.

Glycoside conjugates:

Steroid glycosides and the unique glycosidase activity of the colonic microflora form the basis of a new colon targeted drug delivery system. Drug glycosides are hydrophilic and thus, poorly absorbed from the small intestine. Once such a glycoside reaches the colon it can be cleaved by bacterial glycosidases, releasing the free drug to be absorbed by the colonic mucosa.

Amino-acid conjugates:

Due to the hydrophilic nature of polar groups like -NH₂ and -COOH, that is present in the proteins and their basic units (i.e. the amino acids), they reduce the membrane permeability of amino acids and proteins. Various prodrugs have been prepared by the conjugation of drug molecules to these polar amino acids (69-72). Non-essential amino acids such as

tyrosine, glycine, methionine and glutamic acid were conjugated to SA.

Developments

NOVEL DRUG DELIVERY SYSTEMS FOR CDDS:

Now a days the basic CDDS approaches are applied to formulate novel drug delivery systems like Multiparticulate systems, Microspheres, Liposomes, Microencapsulated particles etc.

Multiparticulate systems:

Multiparticulates (pellets, non-peariles etc.) are used as drug carriers in pH-sensitive, time- dependent and microbially control systems for colon targeting. Multiparticulate systems have several advantages in comparison to the conventional single unit for controlled release technology, such as more predictable gastric emptying and fewer localized adverse effect than those of single unit tablets or capsules (Laila and Sanjeev, 2006).

A multiparticulate dosage form was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties. This system was constituted by drug loaded cellulose acetate butyrate (CAB). Microspheres loaded by an enteric polymer (EudragitS). Here the enteric coating layer prevents the drug release below pH 7. After that CAB microspheres efficiently controlled the release of budesonide, which is depended on the polymer concentration in the preparation (Marta, Jose et al. 1998). Azo polymer coated pellets were used for colon-specific drug delivery to enhance the absorption of insulin and (Asu1,7) Eel calcitonin (Hideyuki et al. 2001).

A multiparticulate chitosan dispersed system (CDS) was prepared for colon drug delivery and it was composed of the drug reservoir and the drug release-regulating layer, which was composed of water insoluble polymer and chitosan powder. The drug reservoir was prepared by drug containing multiparticulates like Non peariles in the study. In this study the multiparticulate CDS was adopted not only for colon specific drug delivery but also for sustained drug delivery (Norihito et al. 2003).

A multiparticulate system combining pH sensitive property and specific biodegradability was prepared for colon targeted delivery of metronidazole. The multiparticulate system was prepared by coating cross-linked chitosan microspheres exploring Eudragit L-100 and S-100 as pH sensitive polymers. The in-vitro drug release studies shows that no release of drug at acidic pH and higher drug release was found in presence of rat caecal contents indicating

susceptibility of chitosan matrix to colonic enzymes released from rat caecal contents (Chourasia and Jain 2004). High-Amylose cornstarch and Pectin blend microparticles of diclofenac sodium for colon-targeted delivery were prepared by spray drying technique. The blending of high-amylose cornstarch with pectin improved the encapsulation efficiency and decreased the drug dissolution in the gastric condition from pectin-based microparticles. The drug released in colonic region by the action of pectinase from microparticles (Kashappa, 2005).

Masataka et al. (2006) investigated the effect of sodium glycocholate as an absorption promoter on orally administrated insulin absorption utilizing a colon-targeted delivery system. A novel insulin colon-targeted delivery system (Insulin- CODES) contains insulin, lactulose as a trigger for colon-specific release, citric acid as a solubilizer of insulin, meglumine as a pH adjusting agent and sodium glycocholate as an absorption promoter.

Microspheres of anti-cancer drugs:

Cross-linked guar gum microspheres containing methotrexate were prepared and characterized for local release of drug in the colon for efficient treatment of colorectal cancer. In this method glutaraldehyde was used as a cross-linking agent and guar gum microspheres were prepared by emulsification method. From the results of in vitro and in vivo studies the methotrexate loaded cross-linked guar gum microspheres delivered most of the drug load (79%) to the colon, where as plain drug suspensions could deliver only 23% of their total dose to the target tissue (Mohini et al. 2006).

Colon specific microspheres of 5-fluorouracil were prepared and evaluated for the treatment of colon cancer. In this method core microspheres of alginate were prepared by modified emulsification method in liquid paraffin and by cross-linking with calcium chloride. The core microspheres were coated with Eudragit S-100 by the solvent evaporation technique to prevent drug release in the stomach and small intestine. The results showed that this method had great potential in delivery of 5-fluorouracil to the colon region (Ziyas et al. 2006).

Other novel drug delivery systems:

A new microparticulate system containing budesonide was prepared by microencapsulation for colon specific delivery (Marta et al 2001). In the study by Liu et al. (2003) a novel formulation for bee venom peptide was developed using coated calcium alginate gel beads-entrapped liposome and investigated for colon specific drug delivery in vitro. The release rate of bee venom from formulation was dependent on the concentration of calcium and sodium alginates and the

amount of bee venom in the liposome, as well as coating. A human 99m Tc-scintigraphy technique was used for in vivo studies and the results showed that this formulation had great potential for colon-specific drug delivery. A novel colon specific drug delivery system containing flubiprofen microsponges was designed. Microsponges containing flubiprofen and Eudragit RS100 were prepared by quasi-emulsion solvent diffusion method and/or flubiprofen was entrapped in to a commercial micro sponge-5640 system using entrapment method. Using these flubiprofen microsponges the colon specific tablets were prepared using triggering mechanism. The particulate form (microsponges) has been used to provide more uniform distribution of the drug in the colon and help the drug to spread on the colon surface in an appropriate way (Mine et al. 2006).

EVALUATION OF CDDS:

The drug release in the colonic region from different CDDS is evaluated by different methods of in vitro and in vivo release studies, which show the success rate of different designs of colon drug delivery systems. Depending upon the method of preparation different evaluation methods are proposed. A successful colon specific drug delivery system is one of that remains intact in the physiological environment of stomach and small intestine, but releases the drug in the colon.

In-vitro Evaluation:

Different in vitro methods are used to evaluate the colonic drug delivery systems. In in-vitro studies the ability of the coats/carriers to remain intact in the physiological environment of the stomach & small intestine is assessed by drug release studies in 0.1N HCl for two hours (mean gastric emptying time) and in pH 7.4 phosphate buffer for three hours (mean small intestine transit time) using USP dissolution apparatus. In case of micro flora activated system dosage form, the release rate of drug is tested in vitro by incubating in a buffer medium in the presence of either enzymes (e.g. pectinase, dextranase) or rat/guinea pig / rabbit caecal contents. The amount of drug released at different time intervals during the incubation is estimated to find out the degradation of the carrier under study (Libio et al, 2002).

In-vivo Evaluation:

Like other controlled release delivery systems, the successful development of the CDDS is ultimately determined by its ability to achieve release in colonic region thus exerts the intended therapeutic effect. When the system design is concerned & prototype formulation with acceptable in vitro characteristics is obtained, in vivo studies are usually conducted to evaluate the site specificity of drug release and to obtain relevant pharmacokinetic information of the

delivery system. Although animal models have obvious advantages in assessing colon specific drug delivery systems, human subjects are increasingly utilized for evaluation of this type of delivery systems. The preferable animals to evaluate CDDS are rats, guinea pigs and dogs (Libio et al, 2002).

?-scintigraphic studies were conducted in human volunteers with technetium-99m-DTPA as tracers in sodium chloride core tablets compression coated with guar gum showed that the gum coat protect the drug (tracer) from being released in the stomach and small intestine. On entering the ascending colon, the tablets commenced to release the tracer indicating the breakdown of gum coat by the enzymatic action of colonic bacteria (Krishnaiah et al. 1998a). Technetium-99m-DTPA was used as a tracer for ?-scintigraphy evaluation of colon specific guar gum directly compressed matrix tablets in human volunteers (Krishnaiah et al. 1998b). The scintigraphic evaluation conducted for capsule type colon specific drug delivery system in human healthy volunteers (Ishibashi et al. 1998). In a study by Krishnaiah et al. (2001), showed the effect of metronidazole and tinidazole (antimicrobial agents) on the release of albendazole from guar gum based colon specific matrix tablets. The active antimicrobial agents (7 days) treatment of rat caecal content decreased the release of albendazole due to decreased levels of anaerobic bacteria present in rat. Sangalli et al. (2001) studied the evaluation of chronotropic TM oral system to achieve time and/or site-specific release. In this study in vitro drug release studies were carried out in a USP 24 paddle apparatus. The in vivo testing, performed on healthy volunteers, envisaged the HPLC determination of antipyrine salivary concentration and a ?-scintigraphic investigation to point out the break-up of the units occurred in the colon.

The suitability of different tracers like Tc-DTPA (technisium-99m-diethylene triamine penta- acetic acid) and Tc-sulphur colloid studied for ?- scintigraphy evaluation of CDDS in healthy human volunteers and concluded that DTPA is a suitable targeting for 99m-Tc for evaluation of CDDS containing water soluble drugs by ?- scintigraphy (Krishnaiah et al. 2002). The suitability of locust bean gum and chitosan for bacterially triggered colon specific drug delivery system was studied by in vitro and in vivo drug release studies (Chellan et al. 2002). In vitro evaluation studies were carried out for colon specific tablets containing different binders like xanthan gum, guar gum, chitosan and Eudragit E. From the results formulation with chitosan and Eudragit E would be highly site specific (Sinha et al. 2002). In a study by Jinhe et al. (2002) proved that apparatus III

(reciprocating cylinder method) was more convenient and efficient than apparatus-II (paddle type) by producing various programmable options in sampling times, agitation rates and medium changes and suggested that apparatus-III approach has better potential for in vitro evaluation of CDDS. Summary of general dissolution on conditions for paddle (USP APP-II) and reciprocating cylinder methods (USP APP-III) was reported by Jinhe et al. (2002).

In vitro evaluation studies were conducted for chitosan-containing microparticulate system for colon drug delivery. In this study fluorescein isothiocyanate-labelled bovine serum albumin (FITC-BSA) was used as a model drug. The chitosan hydrogel beads which containing tripolyphosphate as counter ion. The protein release experiments were carried out in vitro under different conditions to simulate the pH and times likely to be encountered drug intestinal transit to the colon. Release of FITC-BSA from the chitosan beads was studied in sealed 25ml conical flasks in a Magniwhirl constant temperature shaker bath at 37°C and 60 SPM. Enzymatic degradations of chitosan by pancreatin and by porcine pancreatic lipase present in simulated intestinal fluid were studied using a viscometric procedure (Hua et al. 2002). The pharmacokinetic evaluation of guar gum based colon-targeted tablets of mebendazole against an immediate release tablet was carried out in human volunteers. Six healthy volunteers participated in the study and a crossover design was followed. In this study, on oral administration of colon-targeted tablets mebendazole started appearance in the plasma at five hours and reached the peak plasma concentration at 9.4 ± 1.7 hrs (T max) where as the immediate release tablets produced at 3.4 ± 0.9 hrs (Tmax) the results of the study indicated that the guar gum based colon targeted tablets of mebendazole did not release the drug in stomach and small intestine, but delivered the drug to the colon resulting in a slow absorption of the drug and making the drug available for local action in colon (Krishnaiah et al. 2003).

The colon-specific matrix tablets of mesalazine with guar gum were evaluated in vitro and in vivo studies. In vitro dissolution studies using a flow-through cell apparatus with and without galactomannase enzyme. In-vivo studies conducted in healthy humans using X-ray imaging technique to monitor the tablets throughout the GI system in which barium sulphate as a marker (Fatmanual et al. 2004). Tablets consisting of flubiprofen microsponges were developed for colon specific delivery and dissolution test was conducted in USP rotating paddle apparatus at $37 \pm 0.5^\circ\text{C}$ and 50 RPM. Initial drug release studies were done in 750 ml

of 0.1 N HCl for two hours. Then 250 ml of 0.2 M trisodium phosphate solution was added to the dissolution media and the pH was adjusted to 6.8 with 2N HCl for eight hours. Samples were withdrawn after regulated time intervals and analyzed spectrophotometrically at 248 nm. For the study of enzymatic degradation same method was used, but at eighth hour pectinexultra SP-L was added to the dissolution media to simulate the enzymatic action to the colonic bacteria (Mine et al. 2006).

Conclusion

From past two decades, considerable amount of research work has been carried out in the area of colon targeting. By considering the advantages of CDDS like providing friendlier environment for protein and peptide drugs that reducing the adverse effects in the treatment of colonic diseases, site-specific release to treat colonic cancer, amoebiasis, and helminthiasis etc, minimizing the extensive first pass metabolism of steroids and produces delay in absorption of drugs to treat rheumatoid arthritis, angina and nocturnal asthma etc., different approaches are designed to develop colonic drug delivery system. The release of drug load in colon region is depended on pH of GIT, gastro intestinal transit time and microbial flora and their enzymes to degrade coated polymers and breaking bonds between carrier molecule and drug molecule. The preferred CDDS is that should release maximum drug load in colon region. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro intestinal pH, but gives better results with combination of time-dependent system, microbially activated system and others. Different polymers are used to prepare CDDS by various approaches and are evaluated for their efficiency and safety.

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Illustrations

Illustration 1

Figure 1

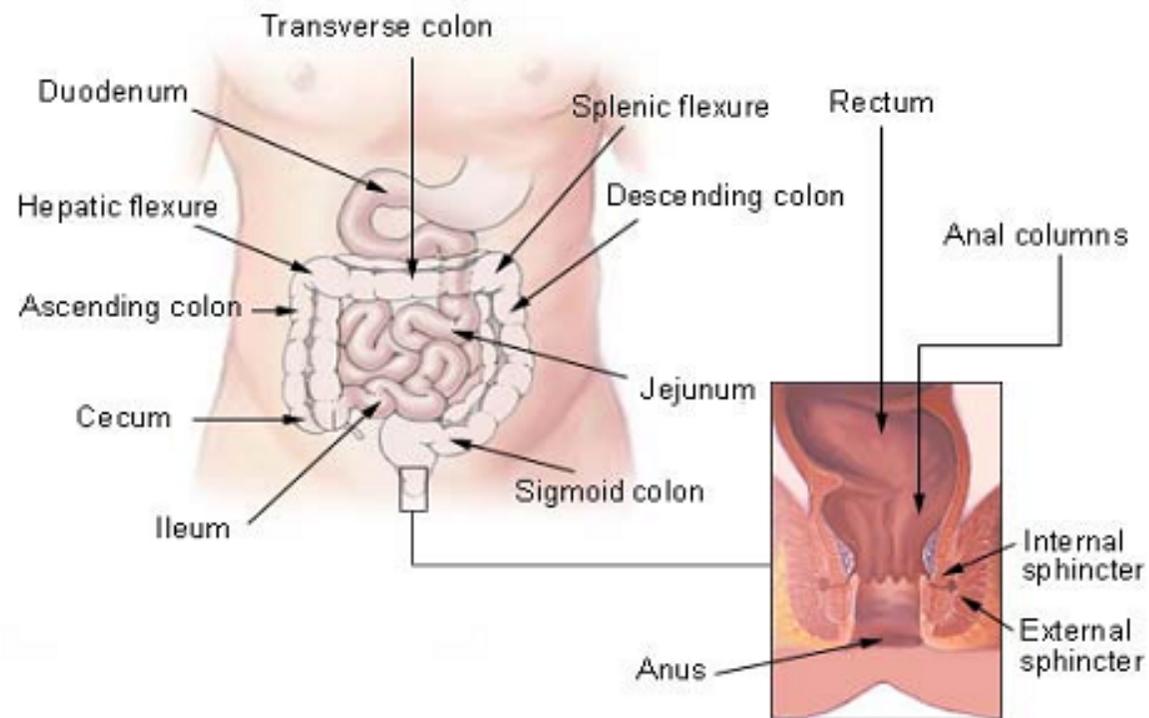


Figure 1: Anatomical features of Small and Large Intestine

Illustration 2

Table 1

Table 1: Region of GIT Property Measured value³

| Region of GIT | Surface area /length |
|------------------------|-----------------------------------|
| Total GIT | 2-10 ⁶ cm ² |
| Small intestine | |
| Duodenum | 20-30cm |
| Jejunum | 150-250cm |
| Ileum | 200-350cm |
| Large intestine | |
| Cecum | 6-7cm |
| Ascending colon | 20cm |
| Descending colon | 45cm |
| Transverse colon | 30cm |
| Sigmoid colon | 12cm |
| Rectum | 3cm |

Illustration 3

Table 2

Table 2: Transit Time of Dosage Forms in GIT³

| Organ | Transit time |
|-----------------|-----------------------|
| Stomach | <1(Fasting) , >3(Fed) |
| Small intestine | 3-4 |
| Large Intestine | 20-30 |

Illustration 4

Table 3

Table 3: various pharmaceutical approaches to colon targeted drug delivery system⁴:

| SL.NO | APPROACH | BASIC FEATURES |
|------------|---|--|
| 1.0 | Covalent linkage of a drug with a carrier | |
| 1.1 | Azo conjugate | The drug is conjugated via an azobond |
| 1.2 | Cyclodextrin conjugates | The drug is conjugated with cyclodextrin |
| 1.3 | Glycoside conjugates | The drug is conjugated with glycoside. |
| 1.4 | Glucuronate conjugates | The drug is conjugated with glucuronate. |
| 1.5 | Dextran conjugates | The drug is conjugated with dextran. |
| 1.6 | Ploypeptide conjugates | The drug is conjugated with Ploy (aspartic Acid) |
| 1.7 | Ploymeric Conjugates | The drug is conjugated with Polymers |
| 2.0 | Approaches to deliver the intact molecule to the colon | |
| 2.1 | Coating with Polymer | |
| 2.1.1 | Coating with pH Sensitive Polymers | Formulations coated with enteric polymers release drug when pH moves towards alkaline range. |
| 2.1.2 | Coating with biodegradable polymers | Drug is released following degradations of the polymer polymers due to the action of colonic bacteria. |

| | | |
|-------|--|---|
| 2.2 | Embedding in matrices | The embedded drug in polysaccharide matrices |
| 2.2.1 | Embedding in biode-Redox sensitive polymers gradable matrices and hydro gels | Released by swelling and by the biodegradable. action polysaccharides |
| 2.2.2 | Embedding in PH sensitive matrices | Degradation of the PH sensitive polymer in the GIT release embedded drug |
| 2.3 | Timed release systems | Once the multicoated formulation passed the stomach, drug is released after the drug is released after a lag time of 3-5 hrs that is equivalent to small intestine transit time |
| 2.4 | Redox sensitivity polymers | Drugs formulated with azo polymer and disulfide polymers that responds to redox potential of colon provides colonic delivery |
| 2.5 | Bioadhesive systems | Selectively provide adhesion to colonic mucosa may release drug in colon |
| 2.6 | Coating with micro particles | Drugs linked with micro particles. |
| 2.7 | Osmotic controlled drug delivery | Drug released through semi permeable membrane due to osmotic pressure |

Illustration 5

Table 4

Table 4: Ranges of pH of Gastrointestinal Tract

| Region | pH |
|----------------------------|-----------|
| Stomach (during digestion) | 1- 3.5 |
| Duodenum | 5-7 |
| Jejunum | 6-7 |
| Ileum | 7 |
| Colon | 5.5-7 |
| Rectum | 7 |

Illustration 6

Table 5

Table 5: Threshold pH of commonly used polymers

| Polymers | Threshold pH |
|--|---------------------|
| Eudragit L100 | 6.0 |
| Eudragit S 100 | 7.0 |
| Eudragit L-30D | 5.6 |
| Eudragit FS 30D | 6.8 |
| Poly vinyl acetate phthalate | 5.0 |
| Hydroxyl methylcellulose phthalate | 4.5-4.8 |
| Hydroxyl methyl cellulose phthalate S0 | 5.2 |
| Hydroxyl methyl cellulose phthalate SS | 5.4 |
| Cellulose acetate phthalate | 5.0 |

Illustration 7

Figure 2

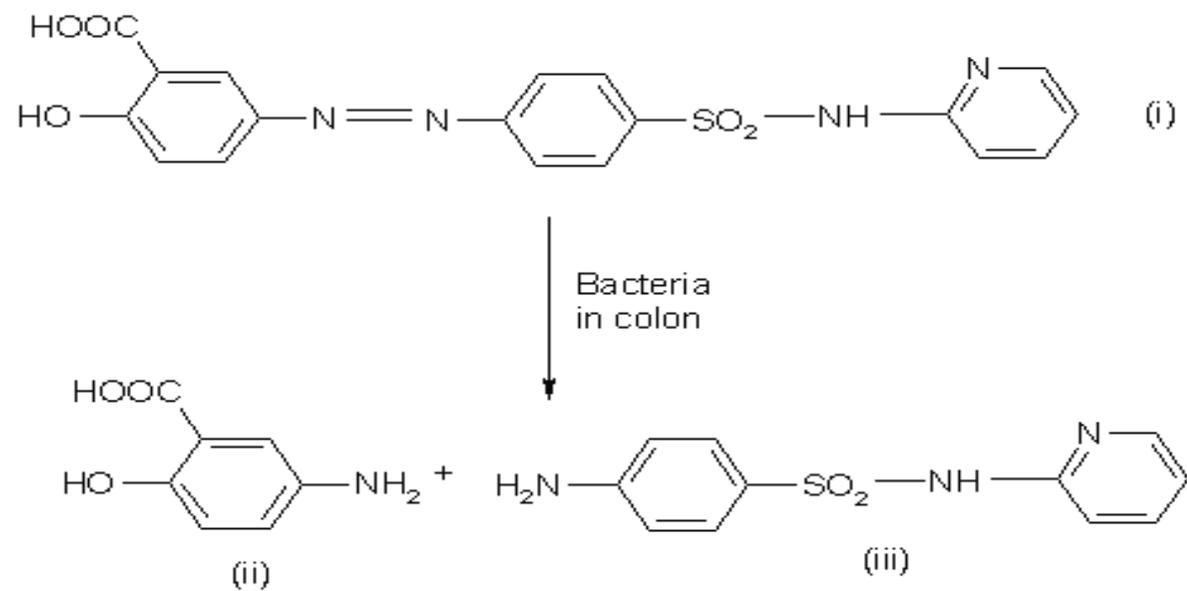
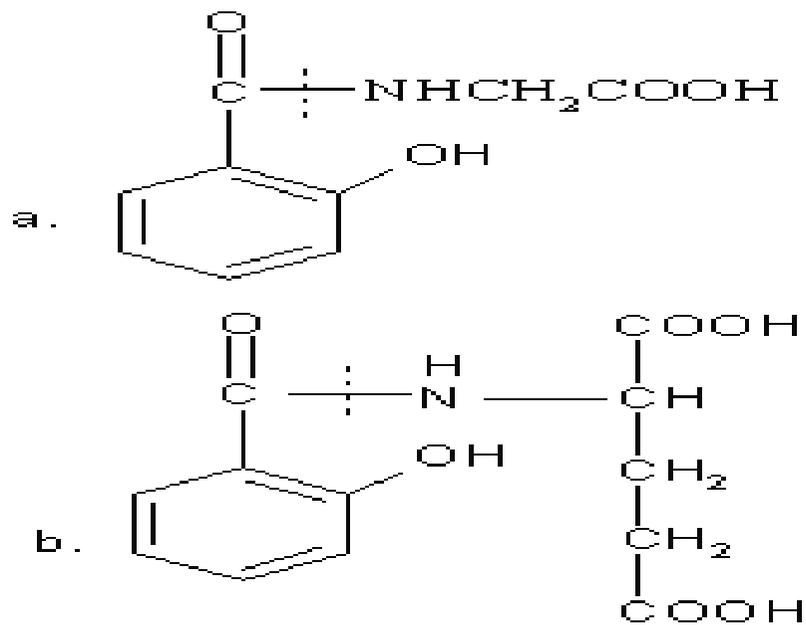
**Figure 2: Azo bond conjugates of p-amino Salicylic acid and sulfapyridine**

Illustration 8

Figure 3

Figure 3: Glycine and glutamic acid conjugates of salicylic acid. (a) Salicylic acid. (b) Salicyl-glutamic acid conjugate



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