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A Comprehensive Analysis of the Colon Specific Drug Delivery System

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Abstract

Many pharmacological entities based on oral delivery have been successfully marketed, but many others are not easily accessible by oral administration due to incompatibility with the physical and chemical conditions of the upper gastrointestinal tract (GIT) and inadequate absorption in the GIT. Because of the absence of digestive enzymes, the colon is thought to be a good place for medication absorption. The key difficulty for scientists over the last two decades has been to target medications particularly to the colonic portion of the GIT. Previously, the colon was thought to be a harmless organ responsible only for the absorption of water, electrolytes, and the temporary storage of faeces. However, it is increasingly recognised as a significant location for medication delivery. This review concentrated on various ways to colonic delivery and significant uses of colonic medication delivery systems.

Keywords: *Pharmacological, Drug Delivery System, Colon, Enzymes*

INTRODUCTION

Oral medication administration to the colon is becoming popular for the treatment of major intestine disorders and for systemic absorption of protein and peptide medicines. Because of the less hostile environment found in the colon, there has been a growing interest in using it as a location for systemic absorption of these medications. A wide range of protein and peptide medications, including calcitonin, interferon, interleukins, erythropoietin, and insulin, are being studied for absorption by colon specific

drug delivery. IBDs such as ulcerative colitis and Crohn's disease necessitate targeted local delivery of medications to the colon.

The most typically given medicine for such conditions is sulfasalazine. Selective medication distribution to the colon is necessary for therapeutic effectiveness with little or no adverse effects. Steroids such as dexamethasone, prednisolone, and hydrocortisone are also used to treat IBD. Anticancer medications such as 5-flurouracil, doxorubicin, and nimustine are to be administered precisely to the colon in colonic cancer. Drugs such as metronidazole, mebendazole, and albendazole are used in the treatment of infectious disorders such as amoebiasis and helminthiasis.

In addition to peptide and protein medications, the colon is an excellent location for the absorption of pharmaceuticals that are unstable in the acidic environment of the stomach, induce gastric discomfort (e.g., aspirin, iron supplements), or are destroyed by tiny intestinal enzymes.

Anti-inflammatory, anti-hypertensive, and other medications are available as sustained release, delayed release, or timed release tablets or capsules for oral administration. Unless these medications have adequate intestinal absorption qualities, their intended usage in the treating of respective illnesses via sustained release or timed release formulations will be a question. Theophylline, glibenclamide, and oxprenolol are examples of medicines with good absorption abilities from the colon. Diclofenac, ibuprofen, nitrendipine, isosorbide, metoprolol, nifedipine, and other drugs can therefore be studied for improved bioavailability by colon specific drug administration.

APPROACHES TO COLON-SPECIFIC DRUG DELIVERY

In recent years, a large number of solid formulations targeting the lower parts of the GI tract, especially the colon, have been reported. These formulations may be broadly divided into four types, which are

1. pH-dependent system designed to release a drug in response to change in pH,
2. Time controlled (or Time-dependent) system designed to release a drug after a predetermined time,
3. Microbially-controlled system making use of the abundant enterobacteria in the colon,
4. Enzyme-based systems – Prodrug

5. Pressure-dependent system making use of luminal pressure of the colon.

PH-DEPENDENT SYSTEMS

Solid formulations for colonic delivery that are based on pH-dependent drug release mechanism are similar to conventional enteric-coated formulations but they differ in target site for delivery and the type of enteric polymers. In contrast to conventional enteric-coated formulations, colonic formulations are designed to deliver drugs to the distal (terminal) ileum and colon, and utilize enteric polymers that have relatively higher threshold pH for dissolution. Most commonly used polymers (Table 1) are derivatives of acrylic acid and cellulose. These polymers have ability to withstand an environment ranging from low pH (~1.2) to neutral pH (~7.5) for several hours. Apparently, it is highly desirable for pH-dependent colonic formulations to maintain their physical and chemical integrity during passage through the stomach and small intestine and reach the large intestine where the coat should disintegrate to release the drug locally. It should be however noted that GI fluids might pass through the coat while the dosage form transits through the small intestine. This could lead to premature drug release in the upper parts of GI tract and as a result loss of therapeutic efficacy may occur. One approach to overcome this problem is to apply higher coating levels of enteric polymers; however, this also allows influx of GI fluids through the coat, and the thicker coats often rupture under the influence of contractile activity in the stomach. In general, the amount of coating required depends upon the solubility characteristics of the drug, surface area of the formulation, and composition of the coating solution/dispersion.

To overcome the problem of premature drug release, a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate (Eudragit® FS), which dissolves at a slower rate and at a higher threshold pH (7–7.5), has been developed recently. A series of in vitro dissolution studies with this polymer have highlighted clear benefits over the Eudragit® S polymer for colonic targeting .

Colon targeted drug delivery systems based on methacrylic resins has described for insulin, quinolones, salsalazine, cyclosporine, beclomethasone dipropionate and naproxane [10]. pH-sensitive delivery systems are commercially available for mesalazine (5-aminosalicylic acid) (Asacol® and Salofalk®) and budesonide (Budenofalk®

and Entocort®) for the treatment of ulcerative colitis and Crohn's disease, respectively.

Table 1. Threshold pH of commonly used polymers

Polymer	Threshold pH
Eudragit® L100	6.0
Eudragit® S100	7.0
Eudragit® L 30D	5.6
Eudragit® FS 30D	6.8
Eudragit® L100-55PVAP	5.5 5.0 4.5-4.8 5.2

TIME-CONTROLLED OR TIME-DEPENDENT SYSTEMS

Time-controlled systems are useful for synchronous delivery of a drug either at pre-selected times such that patient receives the drug when needed or at a pre-selected site of the GI tract. These systems are therefore particularly useful in the therapy of diseases, which depend on circadian rhythms. Time-controlled formulations for colonic delivery are also delayed-release formulations in which the delay in delivery of the drug is time-based. In these systems, it has been suggested that colonic targeting can be achieved by incorporating a lag time into the formulation equivalent to the mouth to colon transit time [11]. Ideally, formulations are designed such that the site of delivery (i.e. colon) is not affected by the individual differences in the gastric emptying time, pH of the stomach and small intestine or presence of anaerobic bacteria in the colon.

Available technologies based on the time controlled systems are

Codes system - comprises a series of polymers that are combined to protect the drug core until the formulation arrives in the colon.

Colon-Targeted Delivery System - uses lag time to achieve colon delivery. The system is comprised of three parts: an outer enteric coat, an inner semi permeable polymer membrane, and a central core comprising swelling excipients and an active component.

Oros-CT - is a technology developed by Alza Corporation and consists of an enteric coating, a semi permeable membrane, a layer to delay drug release, and a core consisting of two compartments.

Time Clock - delivery device developed by Pozzi and colleagues is a pulsed delivery system based on a coated solid dosage form.

Another formulation approach to achieve time-dependent delivery to the colon is

osmotically controlled system (Figure 1). Theeuwes F described a delayed-release osmotic delivery device that can be used for localized treatment of colonic diseases or for achieving systemic absorption of drugs that are otherwise unattainable. The delivery system, commonly referred as push-pull OROS system, comprises as many five push-pull units encapsulated within a hard gelatin capsule. Each push-pull unit is a bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semi permeable layer (approx. 0.076 mm thickness). In principle, the semi permeable membrane is permeable to the inward entry of water or aqueous GI fluids and is impermeable to the outward exit of the drug. An orifice is drilled through the semi permeable membrane next to the drug layer. The outside surface of the semi permeable membrane is then coated by Eudragit® S-100 (approx. 0.076 mm thickness) to delay the drug release from the device during its transit through the stomach. Upon arrival in the small intestine, the coating dissolves at pH >7. As a result, water enters the unit causing the osmotic push compartment to swell, forcing the drug out of the orifice into the colon. The drug release kinetics is precisely controlled by the rate of influx of water through the semi permeable membrane. For treating the ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the small intestine.

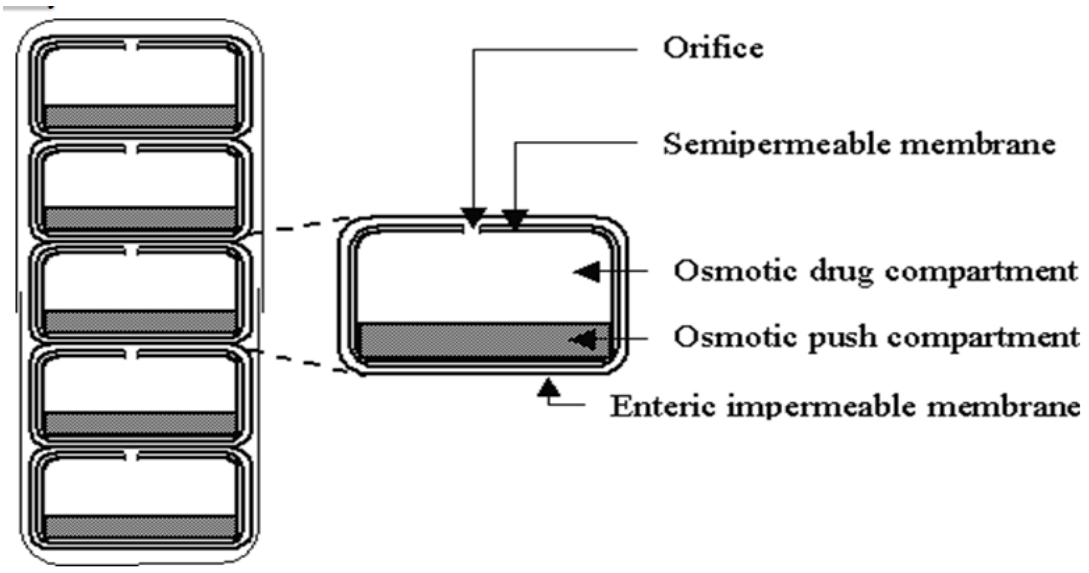

Figure 1: Cross section of the OROS-CT colon targeted drug delivery system

Table 2: Polysaccharide-based materials used to deliver drugs to the lower Intestine

Polysaccharide	Dosage formsinvestigated
Pectin Calcium salt Methoxylated Derivatives Mixed films Of pectin	Matrices, compression Coated tablets, Compression coatingFilm coating for tablets And beads
Chitosan Chitosan Chitosan derivatives	Coated capsules andMicrospheres Matrices
Guar gum Guar gum Guar gum –derivatives	Matrix tablets, Compression coatedTablets Coatings or matrixTablets
Chondroitin sulfateCross-linked Chondroitin	Matrix tablets
Alginates Calcium salt	Swellable beads
Inulin Mixed films	Tablet and bead coatings
Dextran Diisocyanate cross-linked dextran	Hydrogels

ENZYME-BASED SYSTEMS - PRODRUG

A successful prodrug-based delivery system is one in which the promoiety (i.e, inactive portion of the prodrug) minimizes absorption until the active moiety is released (usually by enzymatic action) near the target site. Thus, the promoiety is used to increase the hydrophilicity of the parent drug, increase molecular size, or both, thus minimizing absorption of the drug prior to reaching the target site.

This principle has been exploited commercially to deliver 5-aminosalicylic acids to the colon by way of a prodrug carrier. The prodrug sulphasalazine consists 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 is cleave by the host bacteria, liberating the carrier molecule sulphapyridine and the pharmacologically active agent 5-aminosalicylic acid [13]. This concept has led to the development of novel azo-bond-based polymers (azo-polymers) for the purpose of obtaining universal carrier systems. However, issues with regard to the safety and toxicity of these synthetic polymers have yet to be addressed.

Cyclodextrins (CyDs) have been proposed as inert carriers for targeting in the GIT. Since CyDs are poorly absorbed from the GIT due to their size and hydrophilicity and degraded in the large intestine, it is possible to use them as carriers for delivery of drugs in the lower intestine. α, β, and γ-CyD-drug conjugates of prednisolone were prepared and tested as potential colon-specific prodrugs .

It has been proved through a study in healthy human volunteers that β-CyDs are meagerly digested in small intestine but are completely degraded by the microflora of the colon. The anti-inflammatory effect and systemic side effect of the prednisolone succinate/alpha-cyclodextrin ester conjugate after oral administration were studied using IBD model rats. The systemic side effect of the conjugate was much lower than that of prednisolone alone when administered orally.

The lower side effect of the conjugate was attributable to passage of the conjugate through the stomach and small intestine without significant degradation or absorption, followed by the degradation of the conjugate site-specifically in the large intestine.

EVALUATION OF COLON-SPECIFIC DRUG DELIVEY SYSTEMS

Various in vitro and in vivo evaluation techniques have been developed and proposed to test the performance and stability of colon-specific drug delivery systems.

In vitro dissolution testing

Currently, four dissolution apparatus are recommended in the USP to accommodate different actives and dosage forms: basket method, paddle method, Bio-Dis method and flow-through cell method.

A. Conventional dissolution testing

Dissolution testing of colon delivery systems with the conventional basket

method has usually been conducted in different buffers for different periods of time to simulate the GI tract pH and transit time that the colon-specific delivery system might encounter in vivo. For example, Takeuchi et al., assessed the dissolution of spray-dried lactose composite particles containing alginate-chitosan complex as a compression coating in pH 1.2 and 6.8 buffers. Results indicated that such dry coating showed excellent acid-resistance and prolonged induction periods for drug release.

USP Dissolution Apparatus III (reciprocating cylinder) was employed to assess in vitro performance of guar-based colonic formulations. Because of the unique setup of dissolution apparatus III (i.e. the dissolution tubes can be programmed to move along successive rows of vessels), drug release can be evaluated in different medium successively. Wong et al. evaluated several guar-based colonic formulations using apparatus III in simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 7.5) and simulated colonic fluids containing galactomannanase.

As expected, when compared with drug release in simulated gastric and intestinal fluids, results showed that drug release was accelerated in the colonic fluid due to the presence of the galactomannanase that could hydrolyze the guar gum.

B. Alternative method for evaluation of colon-specific delivery system in vitro

To overcome the limitation of conventional dissolution testing for evaluating the performance of colon-specific delivery systems triggered by colon-specific bacteria, animal caecal contents including rats, rabbits, and pigs have been utilized as alternative dissolution medium. Because of the similarity of human and rodent colonic microflora, predominantly comprising bifid bacterium, Bacteroides and Lactobacillus, rat caecal contents were more commonly used in the dissolution studies. Rat caecal contents were usually prepared immediately prior to the initiation of drug release study due to the anaerobic nature of the cecum.

Rats were anaesthetized and the cecum was exteriorized for collection of the contents. The caecal contents were diluted with phosphate-buffered saline (PBS, pH 7) to obtain an appropriate concentration for release study. This step was conducted under CO2 or nitrogen to maintain an anaerobic environment.

The drug release studies were generally carried out in sealed glass vials at 37 0C for a defined period of time. Samples were withdrawn at different intervals for analysis [21]. In the present in vitro study, the volume of dissolution fluid, containing rat caecal contents, was only 100 ml in order to simulate the fluid volume of the colon. Apparatus 2 is not suitable since the wider paddle blade (diameter 75 mm) cannot be dipped in the dissolution fluid contained in the beaker
(diameter 55 mm).

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 with visualization techniques such as γ-scintigraphy imaging.

Animal studies

Different animals have been used to evaluate the performance of colon-specific drug delivery systems, such as rats pigs and dogs .To closely simulate the human physiological environment of the colon, the selection of an appropriate animal model for evaluating a colon-specific delivery system depends on its triggering mechanism and system design. For instance, guinea pigs have comparable glycosidase and glucuronidase activities in the colon and similar digestive anatomy and physiology to that of human. So they are more suitable in evaluating glucoside and glucuronate conjugated prodrugs intended for colon delivery.

Gamma-Scintigraphy

In most cases, conventional pharmacokinetic evaluation may not generate sufficient information to elucidate the intended rationale of system design. γ-Scintigraphy is an imaging modality, which enables the in vivo performance of drug delivery systems to be visualized under normal physiological conditions in a non-invasive manner.

Through γ-scintigraphy imaging, the following information regarding the performance of a colon-specific delivery system within human GI tract can be obtained: the location as a function of time, the time and location of both initial and complete system disintegration, the extent of dispersion, the colon arrival time, stomach residence and small intestine transit times.

Roentgenography

The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by the use of X-rays. By incorporating barium sulphate into a

pharmaceutical dosage form, it is possible to follow the movement, location and the integrity of the dosage form after oral administration by placing the subject under fluoroscope and taking series of X-rays at various time points. Dew et al. used this technique to evaluate a capsule dosage form coated with Eudragit S to deliver orally ingested drugs to the colon using barium sulphate as a radio- opaque material.

Applications of colon targeting drug delivery

- Colon targeting can be used to treat Inflammatory bowel disease and colon carcinoma which is two third cause of cancer in both man & women.
- Colon can be utilized as portal for the entry of drugs into the blood stream for the systemic therapy.
- Colon having very few luminal & mucosal digestive enzymes as compared with the small intestine reduces the chances of drug degradation. e.g., to facilitate absorption of acid and enzymatically labile materials, especially proteins and peptides.
- Colon delivery also a mean of achieving chronotherapy of disease that is sensitive to circadian rhythm such as asthma & arthritis.
- Targeted delivery ensures the direct treatment at the disease site, lower dosing, & reduction in side effects.

Table 3. Marketed colon specific drug delivery systems

Drug	Trade Name	Coating Polymers
Mesalazine	claversa® Asacolitin Mesazal Asacol	Eudragit® L100 Eudragit® S Eudragit® L100 Eudragit® S
Budesonide	Entrocort® Budenofalk® Targit®	Eudragit® L100-55 Eudragit® S Coated Starch Capsule
Sulfasalazine	Azulfidine Colo-Pleon	Cellulose acetate phthalate Eudragit® L100-55

CONCLUSION

The colon is increasingly recognised as a significant location for medication delivery. Because of the absence of digestive enzymes, the colon is thought to be a good place for medication absorption. This review concentrated on various ways to colonic delivery and significant uses of colonic medication delivery systems.

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