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# *An Analysis of the Colon-Targeting Drug Delivery System in its Totality*

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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 methods of colonic delivery and significant uses of colonic medication delivery systems.*

***Keywords: -*** *Colon, Drug Delivery System, upper gastrointestinal tract (GIT).*

## INTRODUCTION

Oral medication administration to the colon is becoming popular for the treatment of big intestine disorders and 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 [4]. IBDs such


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as ulcerative colitis and Crohn's disease necessitate targeted local delivery of medications to the colon. The most commonly 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-fluorouracil, 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 [5, 6], and oxprenolol [7] 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 [7].

## 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.


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**PH-DEPENDENT SYSTEMS**

Solid formulations for colonic administration based on a pH-dependent drug release mechanism are comparable to typical enteric-coated formulations, but the target location for delivery and enteric polymer type differ. In contrast to typical enteric-coated formulations, colonic formulations are intended to transport medications to the distal (terminal) ileum and colon, and they use enteric polymers with a higher solubility threshold pH. 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 [8].

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.


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***Table 1. Threshold pH of commonly used polymers***

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

**TIME-CONTROLLED OR TIME-DEPENDENT SYSTEMS**

Time-controlled systems are beneficial for synchronising medication administration at pre-determined periods so that the patient receives the medicine only when needed or at a pre-determined place in the GI tract. As a result, these devices are particularly beneficial in the treatment of disorders that rely on circadian rhythms. Time-controlled formulations for colonic administration are also delayed-release formulations with a time-based delay in medication delivery. It has been proposed that colonic targeting in these systems can be accomplished by inserting a lag period into the formulation equal to the mouth-to-colon transit duration [11]. Ideally, formulations are formulated so that individual variations in gastric emptying time, pH of the stomach and small intestine, or the presence of anaerobic bacteria in the colon have no effect on the location of delivery (i.e., the colon).

**Available technologies based on the time controlled systems are**

1. **Codes system -** comprises a series of polymers that are combined to protect the drug core until the formulation arrives in the colon.
2. **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.
3. **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.


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4. **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 [12]. 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.

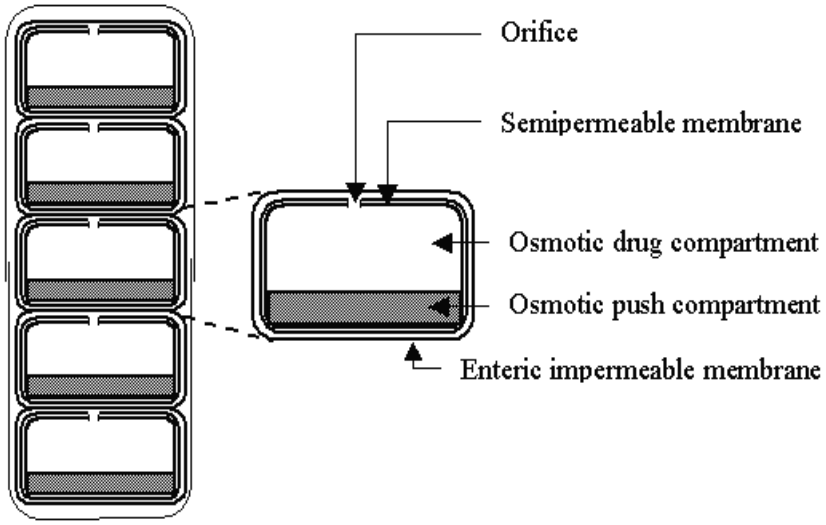


***Figure 1: Cross section of the OROS-CT colon targeted drug delivery system***


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

| **Polysaccharide** | **Dosage forms investigated** |
|---|---|
| *Pectin* Calcium salt Methoxylated Derivatives Mixed films Of pectin | Matrices, compression Coated tablets, Compression coating Film coating for tabletsAnd beads |
| *Chitosan*Chitosan Chitosan derivatives | Coated capsules and Microspheres Matrices |
| Guar gum Guar gum Guar gum –derivatives | Matrix tablets, Compression coatedTablets Coatings or matrixTablets |
| Chondroitin sulfate Cross-linked Chondroitin | Matrix tablets |
| Alginates Calcium salt | Swellable beads |
| Inulin Mixed films | Tablet and bead coatings |
| Dextran Diisocyanatecross-linked dextran | Hydrogels |

**ENZYME-BASED SYSTEMS - PRODRUG**

A successful prodrug-based delivery system is one in which the promoiety (the inactive component of the prodrug) reduces absorption until the active moiety (typically through enzymatic activity) is released at the target site. Thus, the promotive agent is employed to raise the parent drug's hydrophilicity, molecular size, or both, thereby limiting drug absorption before it reaches the target site.

This approach has been commercially utilised to transport 5-aminosalicylic acids to the colon through a prodrug carrier. Sulphasalazine is a prodrug composed of two distinct moieties, sulphapyridine and 5-aminosalicylic acid, connected by an azo-bond.

The prodrug passes through the upper intestine intact, but once in the colon, the host bacteria sever the azo-bond, releasing the carrier molecule sulphapyridine and the pharmacologically active compound 5-aminosalicylic acid [13]. This notion has resulted in the development of innovative azo-bond-based polymers (azo-polymers) for the creation of universal carrier systems. However, questions about the safety and toxicity of these synthetic polymers remain unanswered.


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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 [14, 5, 16] .

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 has traditionally been done in different buffers for varying durations of time to imitate the GI tract pH and transit time that the colon-specific delivery system could face in vivo. Takeuchi et al. [17], for example, investigated the dissolution of spray-dried lactose composite particles with an alginate-chitosan complex as a compression coating in pH 1.2 and 6.8 buffers. The results demonstrated that this type of dry coating had good acid resistance and lengthy induction times for drug release.


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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. [18] 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.

When compared to drug release in simulated stomach and intestinal fluids, data revealed that drug release in the colonic fluid was increased due to the presence of galactomannanase, which 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 [20]. 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).


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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**

Rats, pigs, and dogs have all been used to investigate the effectiveness of colon-specific drug delivery systems. The selection of an appropriate animal model for evaluating a colon-specific delivery system is dependent on its triggering mechanism and system design in order to precisely imitate the human physiological milieu of the colon. Guinea pigs, for example, have comparable glycosidase and glucuronidase activity in the colon, as well as digestive architecture and physiology to humans. As a result, they are more suited to assessing glucoside and glucuronate conjugated prodrugs intended for colon administration.

**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 withinhuman 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 incorporation of a radio-opaque substance into a solid dosage form allows for X-ray visualisation. By integrating barium sulphate into a pharmaceutical dosage form, it is feasible to track the movement, position, and integrity of the dosage form following oral administration using a fluoroscope and a series of X-rays at various time periods. Using barium sulphate as a radio-opaque substance, Dew et al. evaluated a capsule dosage form coated with Eudragit S to transfer orally consumed medicines to the colon.


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***Table 3. Marketed colon specific drug delivery systems***

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

**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 [2].
- Colon delivery also a mean of achieving chronotherapy of disease that is sensitive to circadian rhythm such as asthma & arthritis [3].
- Targeted delivery ensures the direct treatment at the disease site, lower dosing, & reduction in side effects.

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