

# Modified-Release Solid Formulations for Colonic Delivery

Brahma N. Singh\*

Pharmaceutical R & D, Forest Laboratories, Inc., NY 11725, USA

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**Abstract:** Solid formulations intended for targeted drug release into the lower gastrointestinal (GI) tract are beneficial for the localized treatment of several diseases and conditions, mainly inflammatory bowel diseases, irritable bowel syndrome and colon cancer. Also, because of their inherent potential to delay or avoid systemic drug absorption from the small intestine, colonic formulations can be utilized for chronotherapy of diseases which are affected by circadian biorhythms (e.g., asthma, hypertension and arthritis), and to achieve clinically relevant bioavailability of drugs that are poorly absorbed from the upper parts of the GI tract because of their polar nature and/or susceptibility to chemical and enzymatic degradation in the small intestine (e.g., proteins and peptides). The purpose of this review is to summarize the recent patent literature concerning various modified-release (MR) formulation technologies that are claimed to provide colonic delivery for a wide array of therapeutic molecules. These technologies either utilize a single or a combination of two or more physiological characteristics of the colon, which includes pH, microflora (enterobacteria), transit time, and luminal pressure. Accordingly, these technologies may be grouped under four distinct classes: pH-controlled (or delayed-release) system, time-controlled (or time-dependent) system, microbially-controlled system, and pressure-controlled system. Among these, formulations that release drugs in response to colonic pH, enterobacteria, or both are most common and promising.

**Keywords:** Colonic delivery, colonic targeting, colonic delivery system, enteric-coating, delayed-release formulations, time-controlled systems, coated dosage forms, osmotic-controlled systems, timed-release systems, colonic formulations.

## INTRODUCTION

By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e., colon). The site-specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel diseases (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer [1-5]. Other potential applications of colonic delivery include chronotherapy [6], prophylaxis of colon cancer [7] and treatment of nicotine addiction [8].

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 GI tract, in particular, therapeutic proteins and peptides [9-11]. Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systemically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors and antibiotics (e.g., nisin), which are useful in the treatment of inflammatory bowel diseases and GI infections, respectively. Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. Therefore, the uptake of antigens through the colonic mucosa may lead to rapid and local production of antibodies. There is also an increasing interest in the colonic delivery for improving the oral bioavailability of drugs that are substrates of

cytochrome P450 3A class, as the activity of this class of metabolizing enzymes is comparatively lower in the colonic mucosa than in the small intestine [12]. Increasing bioavailability via a colonic formulation approach has also been found to be effective in minimizing unwanted side-effects [13].

Delayed systemic absorption of drugs via colonic delivery is desirable for chronotherapy of diseases such as asthma, hypertension, cardiac arrhythmias, arthritis or inflammation, which are affected by circadian biorhythms. These diseases are characterized by night-time or early morning onset [6]. For treatment of these diseases, it is therefore highly desirable to have a delayed-release delivery system that can provide nocturnal release of a drug, which in turn may provide considerable relief to the patients while they are resting. The purpose of this paper is to briefly review the patented solid formulation technologies that are utilized in the colonic delivery of various therapeutic molecules.

## GENERAL CONSIDERATIONS FOR DESIGN OF COLONIC FORMULATIONS

Formulations for colonic delivery are, in general, delayed-release dosage forms which may be designed either to provide a 'burst release' [14] or a sustained/prolonged release once they reach the colon. The proper selection of a formulation approach is dependent upon several important factors, which are listed below.

- a) pathology and pattern of the disease, especially the affected parts of the lower GI tract

Or, physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.

\*Address correspondence to this author at the Dept of Formulation, Pharmaceutical Research & Development, Forest Laboratories, Inc., 49 Mall Drive, Commack, New York 11725, USA; Tel: 1-631-858-5233; Fax: + 1-631-858-5010; E-mail: brahmasingh@hotmail.com

- b) physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery, and
- c) the desired release profile of the active ingredient.

The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GI tract. In normal healthy subjects, there is a progressive increase in luminal pH from the duodenum (pH =  $6.6 \pm 0.5$ ) to the terminal ileum (pH =  $7.5 \pm 0.4$ ), a decrease in the cecum (pH =  $6.4 \pm 0.4$ ), and then a slow rise from the right to the left colon with a final value of  $7.0 \pm 0.7$  [15]. Some reports suggest that alterations in GI pH profiles may occur in patients with inflammatory bowel disease, which should be considered in the development of delayed release formulations [16].

Formulation of drugs for colonic delivery also requires careful consideration of drug dissolution and/or release rate in the colonic fluids. Generally, the dissolution and release rate from colonic formulations is thought to be decreased in the colon, which is attributed to the fact that less fluid is present in the colon than in the small intestine [17]. The poor dissolution and release rate may in turn lead to lower systemic availability of drugs. These issues could be more problematic when the drug candidate is poorly water-soluble and/or require higher doses for therapy. Consequently, such drugs need to be delivered in a presolubilized form, or formulation should be targeted for proximal colon, which has more fluid than in the distal colon [12]. Likewise, colonic formulations for polar drugs ( $\text{Log } P_{\text{oct/pH } 7.4 \text{ buffer}} < 1.0$ ) including proteins and peptides require use of absorption enhancing agents (also known as absorption promoters). Examples of suitable absorption enhancers include fatty acids [10,18], bile salts [19], and chelating agents [20].

#### **FORMULATION TECHNOLOGIES FOR 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 [6], which are (i) pH-dependent (or delayed-release) system designed to release a drug in response to change in pH, (ii) time-dependent (or timed-release) system designed to release a drug after a predetermined time, (iii) microbially-dependent (or microbially-controlled) system making use of the abundant enterobacteria in the colon, and (iv) pressure-dependent system making use of luminal pressure of the colon. Among these, first three are most widespread formulation technologies being developed for pharmaceutical market [21].

#### **pH-DEPENDENT (OR DELAYED-RELEASE) 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 therefore 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 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 [22]. A detail list of various enteric polymers is given in the Table 1.

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 [23]. In general, the amount of coating required depends upon the solubility characteristics (solubility, dose/solubility ratio) of the drug, desired release profile and surface area of the formulation, and composition of the coating solution/dispersion.

Coating approach is one of the simplest formulation technologies available for colon-specific delivery. It also offers significant advantage in terms of cost and ease of manufacture. From formulation standpoint, coated dosage forms may be either single-unit system or a multi-particulate system, and each of these may be a single-layer product or a multi-layer product. In case of single-layered products, the coating may be composed of a single enteric polymer that has a pH-dependent solubility or a mixture of two polymers one of which is pH-dependent while other is pH-independent. On the other hand, in case of multi-layer products, the coating is applied in successive layers which could be either based on two enteric polymers that have different pH-dependent solubility profiles, or two polymers one of which is enteric while other has a pH-independent solubility but permeable to intestinal fluids. In either case, the coating can be applied to a wide variety of solid core formulations such as tablets, capsules, minitabets, pellets or granules. When coated pellets or granules are filled into a gelatin capsule or compressed together with conventional excipients in the form of tablets, the formulation is regarded as multi-particulate dosage form. The tablets or capsules containing coated pellets or granules can be further coated with a suitable enteric polymer which may be same or different than that used for coating of pellets or granules.

Modified-release formulations that are based on the combination of a pH-dependent and pH-independent polymer are described in a European patent assigned to Aktiebolaget Hässle [24]. The approach involves coating of an active ingredient (e.g., mesalazine) with a mixture of an anionic acrylic polymer soluble just at pH 5.5 (e.g., Eudragit L) and a cationic acrylic polymer insoluble in water (e.g., Eudragit RS or RL). The quantities of anionic acrylic polymers can range from 10 to 85% while that of pH-independent polymers may vary from 15 to 90%. The blending with one or more polymers having a pH-independent solubility thus prevents the active ingredient

**Table 1. Enteric Polymers Utilized in Development of Modified-Release Formulations for Colonic Delivery**

Enteric polymers	Optimum pH for dissolution
Polyvinyl acetate phthalate (PVAP) (Coateric®)**	5.0
Cellulose acetate trimellitate (CAT)	5.5
Hydroxypropyl methylcellulose phthalate (HPMCP)	
HP-50	≥5.0
HP-55 and HP-55S	≥5.5
Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	
*LF Grade	≥5.5
*MF Grade	≥6.0
*HF Grade	≥6.8
Methacrylic acid copolymer, Type C (Eudragit® L100-55*)	5.5
Methacrylic acid copolymer dispersion (Eudragit® L30D-55**)	
Methacrylic acid copolymer, Type A (Eudragit L-100* and Eudragit® L12,5)	6.0
Cellulose acetate phthalate (CAP) (Aquateric®**)	6.0
Methacrylic acid copolymer, Type B (Eudragit S-100* and Eudragit® S12,5)	7.0
Eudragit FS30D**	7.0
Shellac (MarCoat 125*** & 125N***)	7.0

\* Suitable for aqueous dispersion; \*\* Available as aqueous dispersion.

\*\*\* Available as aqueous solution.

from being released too rapidly, once the soluble polymer has reached the optimum pH of solubilization.

Eudragit RS (RS100) and RL (RL100) are copolymers of acrylic and methacrylic acid esters, which contain a low level of quaternary ammonium groups. Eudragit RL is composed of 60% by weight methyl methacrylate, 30% by weight ethyl acrylate and 10% by weight 2-trimethylammonioethyl methacrylate chloride. On the other hand, Eudragit RS is composed of 65% by weight methyl methacrylate, 30% by weight ethyl acrylate and 5% by weight 2-trimethylammonioethyl methacrylate chloride [25]. Both copolymers are insoluble in water but they hydrate in GI fluids independent of pH. Since RS has a lower content of quaternary ammonium groups which are hydrophilic in nature, it displays less water permeability and hydration (or swellability) in comparison with RL.

Eudragit L is an anionic polymer, which dissolves above pH 6.0. It is a copolymer of methacrylic acid and methyl methacrylate in which the ratio of free carboxylic groups to ester groups is approximately 1:1. One of the commercial grades available for an aqueous coating is Eudragit L-100, which comprises 46.0-50.6% methacrylic acid units per g dry substance.

Mesalazine (also known as mesalamine, 5-aminosalicylic acid or 5-ASA) tablets coated with Eudragit L-100 are commercially available as Claversal, Salofalk,

Mesasal and Rowasa. These tablets can effectively deliver mesalazine to the terminal ileum and proximal colon in patients with inflammatory bowel disease. A scintigraphic assessment of Claversal tablets in a group of thirteen patients with Crohn's disease and ulcerative colitis indicated that more than 70% of administered tablets disintegrated with a mean disintegration time of 3.2 h after gastric emptying, resulting in drug dispersion in the distal (lower) small intestine and proximal colon [26]. It is important to recognize that drug release from Eudragit -L coated products may start in the proximal small intestine, which has a luminal pH of 6.6. Consequently, a relatively thick coating may be needed to delay the drug release until the formulation reaches the terminal ileum and proximal colon.

An alternate approach to overcome above issues is to use a polymer which is insoluble below pH 7.0. Rhodes and Evans [27] described a non-sustained release solid formulation in the form of a capsule or tablet containing a pharmacologically active agent, for example mesalazine, for the treatment of ulcerative colitis and Crohn's disease. The formulation is coated with a 60 to 150 μ thick layer of an anionic polymer, which is insoluble below pH 7. This anionic polymer is preferably a partly methyl esterified methacrylic acid (i.e., copolymer of methacrylic acid and methacrylic acid methyl ester) in which the ratio of free carboxylic groups to ester groups is approximately 1:2. For aqueous coating, it is commercially available as Eudragit

S-100, which comprises 27.6-30.7% methacrylic acid units per g dry substance.

Delayed-release tablets containing mesalazine and coated with Eudragit S-100 are marketed in a number of countries (Asacol, Proctor & Gamble Pharmaceuticals, USA). These tablets dissolve at pH 7 or greater, releasing mesalazine in the terminal ileum and beyond for topical inflammatory action in the colon. Although this formulation is generally successful in achieving site-specific delivery of mesalazine, failure of the coating to dissolve has been reported, with patients observing intact tablets in their feces [28].

There appears to be an increasing trend toward the development of multiparticulate formulations for colonic delivery. This is primarily attributed to the fact that multiparticulate formulations are less likely to be affected by food, and demonstrate more consistent absorption compared to single unit systems. In addition, these systems have greater potential to provide a uniform spreading (distribution) of the drug particles to the inflamed parts of the GI tract, which is advantageous for the topical therapy of inflammatory bowel disease [29]. Rhodes and Evans [30] developed a multiparticulate formulation which is composed of a plurality of granules of the drug contained in a capsule. Both the granules and the capsule are coated with different enteric polymer such that the coating of capsule dissolves in the small intestine while the coated granules remain intact until they reach the ileum. Thereafter, coated granules provide a sustained release of the drug in the colon. In this way, the possible local irritations due to a too rapid release are avoided. The coating of the granules is composed by polymers that start dissolving at pH 7.

Calanchi *et al.* [31] described a multiparticulate formulation, which consists of a plurality of multidose minitabets each of size less than 5 mm. Each minitabets unit is composed of a core containing the drug and coated with two successive coating layers. The inner coat is composed of a pH-dependent polymer, for example, Eudragit<sup>®</sup> which starts dissolving at pH 7.0. The second (outer) coating polymer is pH-independent and substantially insoluble but permeable to intestinal fluids (e.g., ethylcellulose). The presence of pH-independent layer significantly delays the release of the drug and acts as a rate-controlling membrane. When only pH-dependent polymer was used (i.e., in absence of pH-independent layer), the formulation was able to delay the drug release for 3 hrs only. There was a very low release of the drug in buffered solutions up to pH 6.2 (first 3 hrs) followed by a rapid drug release when the pH increased to 7.2. On the other hand, formulation based on two successive layer coatings released no more than about 10% drug after 3 hrs and no more than about 75% drug after 6 hrs in simulated gastric fluids. Calanchi *et al.* [31] further noted that the drug release characteristics of the formulation, as described above, does not change when the order of successive coating layers are reversed. However, when the polymers constituting these successive layers were mixed, no delaying effect was observed and results were very similar to that of formulation that utilized only pH-dependent polymer.

A recent patent assigned to Roehm GmbH & Co. KH [25] describes a multiparticulate formulation containing two forms of pellets, which comprise a drug in the core and have

different polymer coatings. One type of pellet is coated with an enteric polymer that rapidly dissolves at pH 5.5, while the other form of pellet is coated with an acrylic copolymer (Eudragit FS) that allows less than 20% drug release at pH 6.8 in 6 hrs and releases more than 50% of the drug at pH 7.2 in 6 hrs. The combination of pellets therefore enables a uniform and prolonged-release of the drug throughout the intestinal region (small and large intestines). Such type of formulations are particularly useful for treatment of Crohn's disease, which can affect any part of the GI tract, although lesions occur mainly in the ileum and/or ascending colon.

As noted previously, enteric coating technique offers advantages in terms of cost and ease of manufacturing. However, an important limitation to this formulation approach is the uncertainty of the location and environment in which coat may start to dissolve [22]. It is possible that enteric coating alone may lead to premature drug release in the small intestine depending upon the GI motility patterns which can widely vary in individual patients and in different disease states. Occasionally, failure of the coating to dissolve may also occur particularly when the pH of the colon, and possibly the small intestine drops below normal in patients with ulcerative colitis [16]. These issues have prompted the development of other types of delivery systems.

#### **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 [32]. 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, the site of drug release is decided by the transit time of a formulation in the GI tract, which makes it challenging to develop a formulation in order to achieve a precise drug release in the colon. 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 [33].

On an average, an orally administered dosage form takes about 3 hrs to travel through the length of the small intestine to the beginning of the colon [29]. Compared to gastric emptying rate, the small intestinal transit time is relatively consistent. In principle, time-controlled systems rely on this consistent small intestinal transit time. The drug release from these systems therefore occurs after a predetermined lag phase, which is precisely programmed by selecting a suitable combination of controlled-release mechanisms. In general, time-controlled formulations for colonic delivery include a pH-dependent (enteric coat) component because the transit of a formulation in the GI tract is largely influenced by the gastric emptying time. Enteric coating is also used for preventing the rapid swelling and disintegration in upper GI tract since other controlled-release components based on

mechanism of swelling (gelling), osmosis or a combination of two are often included in the time-release formulations.

The first attempt to develop a time-dependent system for colon delivery was made by Ueda *et al.* [34]. These inventors developed a time-controlled explosion system in which drug release is caused by the explosion of a membrane after a definite time period (defined as "lag times"), which is precisely programmed. The system could be in the form of a bead or granule with a four-layered spherical structure, which consists of a core, a drug, swelling agent (e.g., sodium starch glycolate, carboxymethylcellulose sodium) and an outer membrane of water-insoluble polymer (e.g., ethyl cellulose, Eudragit RL). The penetration of GI fluids through the outer membrane causes the expansion of the swelling agent. The resulting stress due to swelling force leads to destruction of the membrane and subsequent rapid drug release. There are several advantages of this system: (i) the release rate or pattern is minimally influenced by the solubility or dissolution rate of the drug, (ii) the release pattern is independent of pH of the dissolution medium, and (iii) the drug is completely released.

Takada [35] described a similar time-controlled formulation in the form of capsules and bilayered tablets. The release time of the drug from formulations is controlled by disintegration lag-time which depends on the balance between the tolerability and thickness of a water-insoluble membrane and the amount of a swellable excipient such as low substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate. The shell of the capsule formulation is made up of ethyl cellulose (EC), approximately 120  $\mu\text{m}$  in thickness, which contains micropores at the bottom of body. The fill material is composed of a solid dispersion formulation of the drug filled into a capsule body also made of EC, and a tablet containing L-HPC made by direct compression. Finally, a cap made up of EC is attached to the body of outer EC capsule (Fig. 1). After oral administration, GI fluid permeates through the micropores and causes swelling of swellable excipients. This causes an inner pressure, which pushes the drug container. Then the

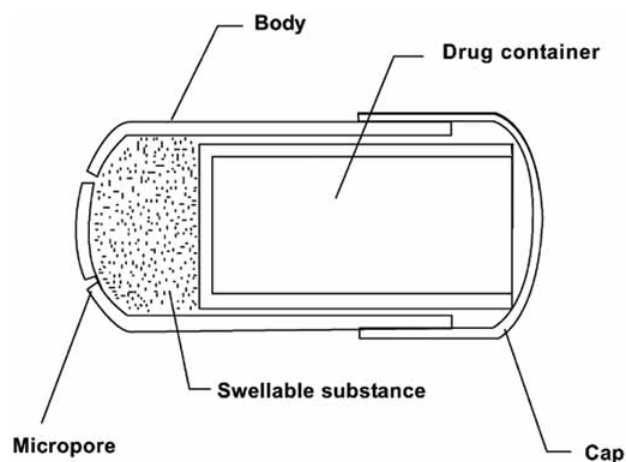


Fig. (1). Time-controlled capsule for colonic delivery (adapted from ref. 35).

disintegration of the capsules occurs with the breakdown of the capsule cap. In this regard, the disintegration of time-controlled capsule is dependent on the balance between the swelling pressure of formulated L-HPC and the strength or tolerability of the EC cap [17].

The bilayered tablets are formulated in four steps. First a tablet is made by compression of L-HPC and lactose or stearic acid (first layer), which is then compressed along with mixture of the drug and crystalline cellulose (second layer). The bilayered tablet is then coated with solution of EC and micropores are formed either mechanically or by laser ray on the first layer. Finally, tablets are sugar coated.

Shah *et al.* [33] described a system in the form of a tablet formulation (patent assigned to Hoffman-La Roche Inc.), which could release the drug consistently in the colon via a time-dependent explosion mechanism. The formulation is comprised of three parts: (i) a central core containing the drug and swelling excipients (ii) an inner semi-permeable polymer membrane containing a plasticizer which allows water influx but prevents the outward diffusion of drug and (iii) an outer enteric-coating which dissolves at or above pH 5.5. The outer enteric coat keeps the tablet intact until it reaches the small intestine. Upon arrival in the small intestine, the enteric coat dissolves allowing for GI fluid to diffuse through the semi-permeable membrane into the core. As a result, the core swells during the transit of the tablet through the small intestine. Finally, after a consistent period of 4-6 hrs transit in the small intestine, the swollen core burst the semi-permeable membrane releasing the drug in the colon.

Lerner *et al.* [22] described a time-dependent system in which the core is surrounded by two coating layers. The formulation consists of (a) core containing a drug and a suitable core material which is preferably a swellable material for water-soluble drugs or a non-swellable material for water-insoluble drugs, (b) coating surrounding the core made up of water-insoluble or relatively water-insoluble materials in which a hydrophilic, water-insoluble, particulate is embedded, and (c) an outer enteric coating surrounding the middle coating layer. This design allows the slow entry of water or aqueous GI fluids into the device. When the delivery device enters the GI tract, the embedded particulate matter takes up the liquid and swells. The particles eventually form channels interconnecting the outer part of the device to the core containing the drug. The drug is released through these channels.

A similar formulation approach has been described by Iamartino *et al.* [36]. The formulation consists of a core of an active ingredient surrounded by three layers: an outer enteric coating, a middle gelling layer which swells when exposed to the intestinal fluid, and an inner layer of an anionic copolymer that dissolves at a pH above 7. After enteric coat dissolves in the small intestine, the middle layer swells and forms a protective layer for the inner layer and the core for about 2-4 hrs while the dosage form transits through the small intestine. After 2-4 hrs, the protective layer disintegrates followed by complete disintegration of the inner layer. Subsequently, the core dissolves and drug release occurs at about the time formulation reaches the colon.

Another formulation approach to achieve time-dependent delivery to the colon is osmotically controlled system. Theeuwes *et al.* [37] 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 5 push-pull units encapsulated within a hard gelatin capsule (size 2). Each push-pull unit is a bilayered laminated structure containing an osmotic push layer and a drug layer, both surrounded by a semipermeable layer (approx. 0.076 mm thickness). In principle, the semipermeable 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 laser drilled in the semipermeable membrane to the drug layer. The outside surface of the semipermeable 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 semipermeable membrane.

The osmotic system as described above has several shortcomings [32]. First, the system is able to delay the onset of delivery in the intestinal fluid for a period of about two hrs, which is too short. Secondly, the delivery rate of the system is too slow and therefore the bulk of drug is not delivered to the colon. Recent formulation developments in this area have therefore addressed both issues by improving the composition of delayed release coatings as well as rate of drug release in the colon. For instance, Wright and Guittard [23] modified the composition of the exterior enteric coat by incorporating a hydrophobic compound in excess of its solubility. This modification was done to prevent the influx of fluids through the coat, particularly during the transit of dosage form through the stomach. Lack of such composition may cause the early hydration of the osmotic device, leading to premature and rapid drug release in the small intestine.

Savastano *et al.* [32] described an osmotically controlled device for colonic delivery, which is designed such that it resists dissolution in the gastric fluids for at least two hrs, releases approximately 10% or less for at least three hours in the intestinal fluids, and about 70 to 80% of its drug to the colon. The formulation has four components. A solid core comprising the drug is coated with a delay-release coat, then coated with a semipermeable membrane, which could be optionally drilled to provide a release orifice, then further optionally coated with an enteric material.

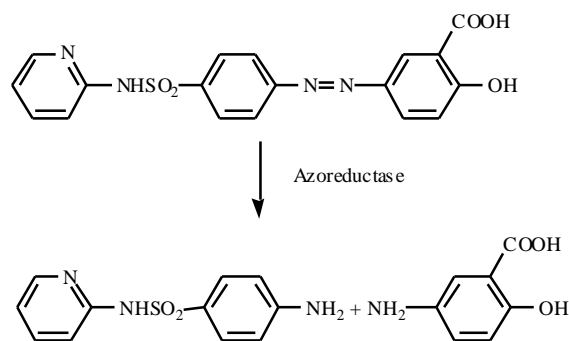
Ritschel and Agrawal [38] described a controlled release system, which delivers a drug in a sustained manner to the upper portion of the GI tract followed by a burst release in the colon. The accelerated rate of drug release occurs because of the self-destructive nature of the semipermeable membrane. This particular system also represents an improvement in the manufacturability of the osmotically-controlled systems. The semipermeable membrane is constructed by press-coating instead of spray or dip coating process while a stylus in the upper punch of the compression

tools provides the release orifice for drug. Thus, both critical elements needed for controlled delivery are created in a single step on a compression coating machine.

### MICROBIALY-CONTROLLED (OR MICROBIALY-DEPENDENT) SYSTEMS

These systems are based on the exploitation of the specific enzymatic activity of the microflora (enterobacteria) present in the colon. The colonic bacteria are predominately anaerobic in nature and secrete enzymes that are capable of metabolizing substrates such as carbohydrates and proteins that escape the digestion in the upper GI tract [12]. Most common mechanisms of microbial activation in the colon are azo-reduction and glycosidic-bond hydrolysis.

The first commercial product that is based on the principle of microbial activation in the colon is salicylazo-sulfapyridine, also known as sulfasalazine. This product is marketed for the therapeutic treatment of ulcerative colitis. It is a prodrug in which 5-aminosalicylic acid (the active moiety) is linked by an azo bond to sulfapyridine (the carrier molecule). The prodrug passes through the upper parts of GI tract intact, but once in the colon, the azo bond is cleaved by azo reductase, liberating the active moiety 5-aminosalicylic acid at the site of inflammation [39]. A schematic presentation of this mechanism is provided in Fig. 2. There are several other commercial examples of prodrug-based formulations that depend on this mechanism of activation in the colon. Examples include olsalazine sodium or azodisal sodium (Dipentum capsules), balsalazide disodium (Colazide and Colazal capsules), and Intestinol (bensalazine or bensalazide) [6]. Other prodrugs that are useful in delivering drugs to the colon include glycosides, dextran derivatives, amino acids, polyamino acids and cyclodextrins [40].



**Fig. (2).** Mechanism of microbial activation of sulfasalazine in the colon

The concept of bioactivation of prodrugs via azo reduction in the colon has led to the development of several novel azopolymers. Parkinson *et al.* [41,42] described polymers in which 5-aminosalicylic acid was linked to a polymer backbone via an aromatic azo linkage. This concept further evolved into development of drug delivery systems based on polymers that can be used for site-specific drug release in the colon. Saffran and Neckers [43] were the first to demonstrate the usefulness of azo polymers for

development of a colonic delivery system. The delivery system consists of a pellet formulation containing a peptide drug (e.g., insulin, vasopressin) and is coated by azo-containing crosslinked polymers. Apparently, the release of the enclosed drug occurs due to enzymatic degradation of the polymeric coating in the colon.

Kopecek *et al.* [44] developed a colonic delivery system based on crosslinked hydrogels, which contains azo bonds and exhibit pH-dependent swelling. The drug release occurs in the colon by a combination of pH-dependent swelling and microbial degradation of the hydrogels by enzymatic cleavage of the azobonds by azoreductases. In addition to azo-polymers, disulfide bond containing polymers have been utilized as carriers for colon-specific delivery [45]. These polymers are also sensitive to redox potential (reduction mechanism) of the colon, like azo-polymers.

Formulations based on azo-polymers have an important advantage that they are relatively stable in the upper GI tract, which is attributed to the resistance of azo bonds to chemical and enzymatic degradation in the stomach and small intestine. However, it has been reported that degradation of the azo polymers by enterobacteria is slow. This is attributed to the hydrophobic nature of the azo-polymers, which renders it difficult for azoreductase to approach the azo bond of these polymers [46]. Another critical disadvantage of azo-polymer based systems is that there is always a risk of producing a harmful substance originated in an azo linkage so that the system may be unsuitable for long-term use. To overcome these limitations and toxicity concerns of these synthetic polymers, natural polymers especially glycosidic-bond containing materials offer a viable alternative for colonic drug delivery. The glycosidic bond-containing polymers include disaccharides, oligosaccharides, and polysaccharides [47].

Polysaccharide-based formulations are very common since they can be selectively degraded by a colonic enzyme and are natural polymers with proven final toxicity. These formulations are considered safe because they utilize materials that are taken as dietary fiber. Examples of various polysaccharide carriers are given in the Table 2. Various enzymes that are involved in the degradation of some of these polymers are amylase, chitosanase, pectinase, inulinase, xylanase, dextranase, and galactomannanase.

It is important to note that there are also certain limitations associated with use of polysaccharides as drug carriers for colonic delivery. These materials are hydrophilic in nature, which renders them either soluble or prone to swelling in the aqueous environment of the GI tract [12]. An illustrative example is that of calcium pectinate. Edman *et al.* [51] disclosed a pharmaceutical composition containing calcium pectinate as a major component and a filler such as pectin, dextran, microcrystalline cellulose, or mixture thereof. In this formulation, the calcium pectinate composition is used in the form of a coacervate pellet but it has the disadvantage that pellets disintegrate and release the drug in the upper GI tract. It is believed that calcium pectinate, which is insoluble in water, is readily converted to a water-soluble matrix (sodium or potassium pectinate) by exchanging calcium ions with sodium or potassium ions

**Table 2. Microbially Degradable Materials Used for Colonic Delivery [40, 48-50]**

Class	Examples
Disaccharides	Lactose Maltose
Oligosaccharides	Cellobiose Cyclodextrins Lactulose Raffinose Stachyose
Polysaccharides	Alginates Amylose Arabinogalactan Arabinoxylan Cellulose Chitosan Chondroitin sulfate Dextran Galactomannan (guar gum, locust bean gum) Inulin Karaya gum (Kadaya gum) Laminarin Pectins and pectates Starch Tragacanth gum Xanthan gum Xylan

present in the digestive fluid of the upper GI tract. This renders the formulation containing calcium pectinate susceptible to premature disintegration and drug release before it reaches the colon. To overcome these inherent limitations of polysaccharide carriers, several approaches have been suggested which may be either based on the chemical modification of the carrier itself or a suitable strategy in which formulation compositions are modified.

Sintov and Rubinstein [48] suggested a compressed tablet formulation to solve this problem. The matrix tablet is prepared by pulverizing and compressing a pharmaceutical composition containing a drug and calcium pectinate. However, this method has certain limitations because the composition is difficult to pulverize and the disintegration of tablets in the GI tract is largely affected by the strength of compression force. The weakly compressed tablets disintegrated easily in the upper GI tract by converting to a water-soluble matrix, whereas tablets compressed with strong pressure hardly disintegrated in the colon. It is obvious that the compositions disclosed by Edman *et al.* [51] and Sintov and Rubinstein [48] are highly dependent on the swelling of the delivery systems, thus on the transit time

through the upper GI tract, and not on unique characteristics of the formulation composition.

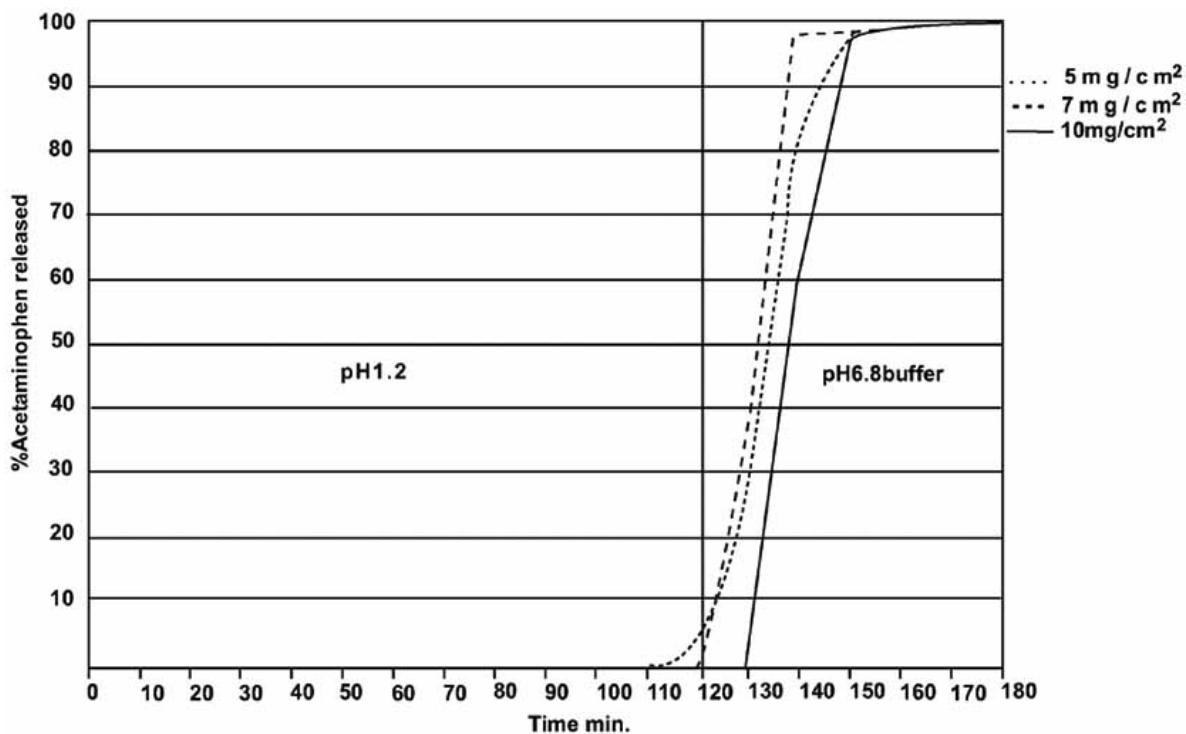
Enteric coating is another formulation approach used to prevent the rapid swelling and/or disintegration of polysaccharide-based formulations in the upper GI tract. Zeitoun and Brisard [52] described the preparation of coated tablets, which disintegrate in the colon. The tablet consists of a compressed core, which is coated with two layers. The first layer is made up of a pH-independent polymer, which is resistant to neutral or alkaline aqueous medium (preferably ethylcellulose) and microcrystalline cellulose (MCC). The presence of MCC together with the pH-independent polymer is essential to ensure the disintegration of tablets in the colon since MCC is digested by specific enzymes present in the colon. The second layer is made up of an enteric polymer (e.g., cellulose acetate phthalate). Sekigawa and Onda [53] described a similar approach in which formulation is prepared by coating a solid core first with chitosan and then top-coated with an enteric polymer such as hydroxypropyl methyl cellulose acetate succinate (HPMCAS) or hydroxypropyl methyl cellulose hexahydrophthalate.

Watts [54] described an approach in which a starch capsule containing the drug is coated with a suitable material such that capsule will not release the drug until it is in the colon and/or terminal ileum. The coating material may be a pH-sensitive polymer, a redox sensitive polymer (e.g., azopolymers), or fermentable sugars that are only degradable in the colon. The approach is commonly known as TARGIT technology (West Pharmaceutical Services, UK). Recently, a hydroxypropyl methyl cellulose (HPMC) capsule coated with acrylic polymers has also been invented [55]. These HPMC capsules had much higher resistance in acidic

media, and variation in coating levels had little influence on the dissolution profiles, which is illustrated in Figure 3. Formulations based on starch and HPMC capsules also have some manufacturing advantages, besides their propensity to microbial and/or pH-dependent degradation in the colon. Conventional enteric-coated capsules based on gelatin are very sensitive to aqueous coating process, and have smooth surface which causes poor adhesion of the enteric coat [55].

Most recent approaches to overcome the limitations of polysaccharides for colonic delivery include development of polysaccharide-based film coated dosage forms. These approaches are capable of controlling the swelling of polysaccharides as well provide mechanical strength to the dosage forms. The film coating composition is generally made up of a polysaccharide in combination with a suitable film forming material. Lee *et al.* [49] described a composition in which tablets containing the drug were coated with a crosslinked gelatin/pectinate film. Alternatively, a gelatin/pectinate soft capsule filled with a drug is also suggested. The gelatin was employed to enhance the mechanical strength of the formulation. Gelatin forms a complex with calcium pectinate by intermolecular forces including ionic bonding, hydrogen bonding and steric forces [49].

Lehmann *et al.* [56] developed a composition comprising guar gum or locust bean gum blended with a film forming material. Ring *et al.* [57] and Allwood *et al.* [58] described the compositions of delayed release formulations comprising a drug coated with an inner coating of amorphous amylose and an outer coating of a film forming material (e.g., ethylcellulose or an acrylate/methacrylate copolymer). Alternatively, the formulation may consist of an admixture of the drug and amorphous amylose coated with a film



**Fig. (3).** Dissolution profiles of acetaminophen from HPMC capsules coated with various quantities of Eudragit L30D-50 (adapted from ref. 55).

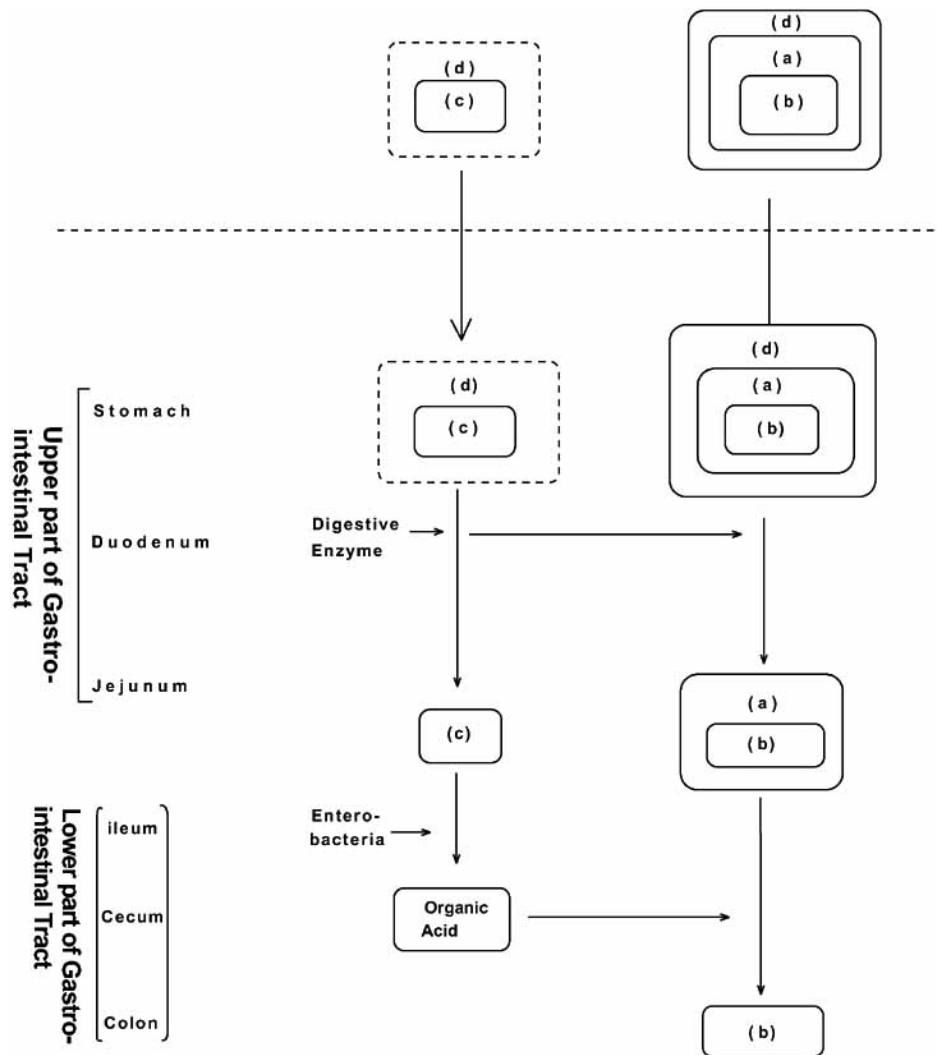
forming material or a drug coated with a mixed coating composition comprising amorphous amylose and a film forming material. Amylose as such is normally resistant to environment of the stomach and the small intestine, but in its amorphous (“glassy”) state, it is also resistant to degradation by salivary and pancreatic alpha amylases. However, it is susceptible to degradation by microbial amylases found in the colon. Newton and Siew [59] have also explored the combination of amorphous amylose and water-insoluble film forming polymer for development of colon-specific controlled release formulations. In these compositions, use of a water-insoluble polymer such as ethylcellulose or an acrylic polymer is necessary to control the swelling of amylose. The film coating system based on combination of amorphous amylose and ethylcellulose has recently been commercialized as COLAL technology (Alizyme plc, Cambridge, UK).

Another interesting approach to achieve rapid degradation and higher specificity in the colon has been described by Watanabe *et al.* [50]. The details of this approach are

given in Fig. 4, which is commercially known as CODES technology (Yamanouchi Pharmaceutical Co., Ltd., Japan). In this approach, a core tablet is coated with three layers of polymeric coatings. The first coating (next to the core tablet) is an acid-soluble polymer (e.g., Eudragit E), the middle layer is a barrier coat of HPMC and the outer coat is an enteric coating. The core tablet is comprised of a drug, one or more saccharides and other excipients. The saccharides rapidly generate an organic acid by the action of enterobacteria in the colon. Examples of such saccharides include mannitol, maltose, stachyose, lactulose, etc. Upon arrival in the colon, the saccharide inside the core tablet dissolves and diffuses out through the inner coating of Eudragit E. The colonic bacteria then degrade the saccharide into organic acid. This lowers the microclimate pH surrounding the formulation, leading to dissolution of acid-soluble coating and subsequent drug release.

### PRESSURE-CONTROLLED SYSTEMS

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements



**Fig. (4).** Schematics of the design of CODES technology (adapted from ref. 50).

[a = organic acid soluble polymer; b = drug; c = saccharide; d = enteric coating polymer]

for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis [60]. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day. However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems.

The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces [18].

To author's knowledge, there is only one invention related to the development of pressure-controlled system for colonic delivery [18,35]. This particular delivery system is in the form of a capsule, which is resistant to the pressures of the upper GI tract but is collapsed in the large intestine due to increased pressure. The capsule shells are fabricated from ethylcellulose and the collapse time of the capsule in the large intestine can be controlled by adjusting the thickness of the capsule shell wall [18]. The preferred thickness of the capsule wall is about 35-60  $\mu\text{m}$  [35].

#### CURRENT & FUTURE DEVELOPMENTS

Currently, there are several MR solid formulation technologies available for colonic delivery. These technologies rely on GI pH, transit times, enterobacteria and luminal pressure for site-specific delivery. Each of these technologies represents a unique system in terms of design but has certain shortcomings, which are often related to degree of site-specificity, toxicity, cost and ease of scale up/manufacturing. It appears that microbially-controlled systems based on natural polymers have the greatest potential for colonic delivery, particularly in terms of site-specificity and safety. In this regard, formulations that employ a film coating system based on the combination of a polysaccharide and a suitable film forming polymer represents a significant technological advancement. Further developments in this area require means to improve the co-processing of the polymeric blend of a polysaccharide(s) and a film forming material while maintaining the propensity of the composition to microbial degradation in the colon.

#### DISCLAIMER STATEMENTS

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