Colon-Targeted Delivery Systems for Therapeutic Applications: Drug Release from Multiparticulate, Monolithic Matrix, and Capsule-Filled Delivery Systems

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Because of the relatively predictable times in which multiple unit-dosage forms transit the small intestine and arrive at the colon, targeted drug delivery systems are promising and have gained importance as a treatment for inflammatory bowel disease (IBD), as therapy for localized diseases of the colon, and as a potential means for the systemic delivery of drugs, proteins, and peptides. Enteric-coated or sustained-release tablets, capsules, liquid- and dispersion-filled softgel capsules, encapsulated multiparticulates, pellets, beads, mini-tablets, granules, microspheres, and nanoparticle-type formulations have been developed to selectively deliver drugs to the target cells by resisting drug release in the upper intestine, thereby circumventing systemic side effects. Two different colon-targeted delivery systems, each with its own operating release mechanisms, have been designed and evaluated and are discussed in detail in this chapter. Technical aspects in development of each of the delivery systems, their coating composition, their manufacturing steps, and their release...
profiles are revealed. Based on the results, the developed delivery systems can overcome physiological barriers and target the colon for treating IBD. Encapsulation of multiparticulates, including nanoparticles or dispersed systems for colonic delivery, appears to be a promising approach in drug delivery to the colon. Furthermore, this chapter discusses peptide delivery and the use of a capsule device as a tool for research purposes in drug targeting to the gastrointestinal tract.

**Introduction**

For a drug delivery system to be effective and achieve success in pharmacotherapy, the intact drug must reach its target site or receptor to an extent that exceeds the minimum effective required concentration. To achieve this objective, the dynamic relationship between four key biopharmaceutical factors should be considered, as seen in Figure 1. These factors include the drug, the formulation, the route of administration, and the target response, the last of which encompasses both the pharmacokinetics and the pharmacodynamics of the drug.

![Figure 1](image.png)

*Figure 1. The quartet of rational drug delivery system design. The interrelationship and connection between four key factors: the drug, the formulation, biological aspects of the administration route, and the target site and response.*

Gastrointestinal drug targeting offers many key benefits to the successful pharmacotherapy of colonic inflammation and disease (1). In particular, site-specific delivery to the colon offers a means to achieve topical, localized, or systemic therapeutic effects, which is advantageous in addressing the mucosal redox status, persistent state of oxidative stress, and colon cancer (2, 3). For drug delivery to the distal intestine and colon, the utmost concern is how to trigger drug release selectively in the ileocecal region or the colon. Several release mechanisms can be used to accomplish this goal. For example, drug delivery systems based on pH-triggered release, time-triggered release, pressure-induced
shell rupture, and enzymatically triggered release for biodegradable polymers, azo-aromatic polymers, and prodrugs have been investigated (1, 4–6). Likewise, a new perspective on the oral delivery of peptides, proteins, and other labile drugs into the distal gastrointestinal (GI) tract and colon has been demonstrated (7, 8). The success of any delivery system and drug depends on the bioavailability of intact drug molecules at the target site of action, either topically or through systemic circulation. An ideal delivery system must release the drug at a specific rate that matches the real need in vivo. This means that the drug must be released for a certain duration of time and should be present exclusively at the target site of action or within a localized area, such as in certain localized cancers. Various drug delivery system domains and established manipulation techniques that are currently available and in use are presented in Figure 2.

![Figure 2. The domains of drug delivery systems including aspects of dispersed, personalized, biodegradable, microchip-based systems, three-dimensional (3D) printing dosages, sustained-release (SR) and enteric-coated (EC) tablets, capsules, pellets, gels, bioadhesive polymers and manipulated molecular structures and crystal engineered systems currently in use.](image)

**Targeting in the GI Tract, Colon, and Mucosal Surfaces**

Depending on the site in the GI tract where a drug should be released, a variety of approaches and types of delivery systems are currently available and in use. An ideal dosage form for colon targeting should effectively delay or prevent drug release in the stomach and small intestine. However, upon arriving in the ileocecal region, the drug release should begin either rapidly or over an extended time period depending on the in vivo needs. The advantages of delivering a drug to the colon for topical effects include a reduction in the incidence of systemic side effects and
greater localized drug concentrations in the inflamed or diseased tissues \((4, 7–10)\). Furthermore, in many cases, the drug dose can be reduced, as the drug is delivered directly in its intact form to the target site. For example, diseases such as ulcerative colitis, irritable bowel syndrome, and colon cancer can often be more efficiently treated while evading many systemic side effects through the local delivery of low doses of drugs \((11, 12)\).

Some of the drugs and prodrugs commonly used for the treatment of these disorders include mesalazine, budesonide, sulfasalazine, dexamethasone, hydrocortisone, metronidazole, prednisolone, cyclosporine, 5-flourouracil, typhoid vaccines (e.g., enteric-coated oral capsules with live attenuated Ty21a), and peptides such as linaclotide and plecanatide. Moreover, conventional dosage forms such as enemas, rectal foams, and suppositories are used for the topical treatment of IBD, especially in anorectal regions including the sigmoid and descending colon. Prodrugs that are susceptible to reductive enzymes such as nitroreductases, azoreductases, and deaminases have been investigated extensively. For example, azo linkages resist proteolytic breakdown in the stomach and intestine but undergo reduction by azoreductases produced in the colon by indigenous microflora, with estimates indicating the presence of about \(10^{12}\) colony-forming units (CFU) per gram of fecal matter \((13)\). Figure 3 shows examples of commercially marketed prodrugs that are activated into 5-aminosalicylic acid by azoreductases occurring in the colonic environment.

![Figure 3. Sulfasalazine and olsalazine are effective in maintaining remission of ulcerative colitis. Through selective prodrug activation by azoreductases of anaerobic bacteria, 5-aminosalicylic acid is produced and can act to heal the local environment and reduce the number of relapses in colitis.](image)

Additionally, the colon’s neutral pH \((7 \pm 0.3)\), long residence time (>24 h), and relatively low proteolytic enzyme activity can be advantageous for delivering...
drugs that are degraded or poorly absorbed in the upper gastrointestinal tract, such as peptides, protein-based drugs, calcitonin, and vasopressin (7, 14, 15). Moreover, drug delivery with particular release modulation (chronotherapy) for the treatment of certain diseases can be achieved by delivering drugs to the distal gastrointestinal environment (16). The major challenges of colonic drug delivery are related to the physiological constraints, as the gastrointestinal ecosystem is relatively complex (4). The presence of a variety of microorganisms and their enzyme systems, in part, responsible for its metabolic diversity (13, 17, 18). As for many physiological parameters, gastrointestinal pH is influenced by various factors including diet; disease; and the presence of gases, fatty acids, and other fermentation products (19). In addition, gastric residence time is highly variable. Various factors, such as the age, disease state, and emotional status of the patient, as well as the quality and quantity of food present in the stomach, are responsible for causing inter- and intrasubject variability in gastric transit time, which can result in unpredictable outcomes from the dosage form. Nevertheless, under ordinary circumstances, the gastric transit time of nondisintegrating tablets is considered to range from 15 min to a few hours (e.g., 5 h), and the small-intestine transit time is generally about 3–4 h (8, 20–23).

Over the past two decades, considerable effort has been directed toward the design and development of colonic delivery systems, which have been discussed in a number of recent reviews (4, 7, 24–32). Because of the highly unpredictable gastric emptying time, the prediction of the drug release location is not always reliable for single-unit coated tablets or capsules, in contrast to coated multiparticulate systems (e.g., pellets, granules, nanoconstructs), the latter of which more predictably disperses and passes through the various regions of the GI tract. The exploitation of different areas of the GI tract including the colonic environment thus involves not only its pH, but also its microbial population with significant enzymatic activity. For instance, the redox potential is about −65 mV in the stomach, −67 ± 90 mV in the proximal intestine, −196 ± 97 mV in the distal intestine, and −415 ± 72 mV in the colon. Colonic microflora-mediated drug release has been utilized to develop a variety of prodrugs. Simple approaches have been employed in delivering drugs to the colon by using such prodrug molecular manipulations. However, from a regulatory point of view, a prodrug is considered to be a new compound, so its safety, toxicity, and efficacy have to be established in advance. Another method that is based on a pH-triggered release system uses enteric coating materials such as EUDRAGIT L, EUDRAGIT S, and cellulose acetate phthalate, each of which dissolves at a specific pH, depending on where in the GI tract drug release is necessary. Because of inter- and intrasubject variability in gastrointestinal transit time, GI microenvironment, and pH, single unit systems coated with pH-dependent or enzymatically degradable polymers alone often result in unpredictable drug release and transit in the GI tract. Consequently, compressed pellets in tablet, multiparticulate, or liquid- or dispersion-filled systems with diverse formulations are preferred and have demonstrated more predictable transit; once such systems reach the correct location, the coating or shell dissolves, and the pellets or dispersion spread across the GI segment and release the drug. Examples of such systems are presented in Figure 4.
Figure 4. Different delivery systems for drug delivery to the distal intestine (ileum, ileocecal region) or colon: 1, coated beads; 2, encapsulated coated tablets; 3, coated mini-tablets; 4, encapsulated liquid-filled soft gel capsule and mini-tablets; 5, enteric-coated liquid-filled capsule; 6, multicoated tablets with bioadhesion potential; 7, enteric-coated semisolid soft gel dispersion.

GI Physiology and Mucosal Surfaces

The human gastrointestinal tract comprises multiple segments, including the stomach, small intestine, and colon. The GI epithelium is made of a single layer of cells with innumerable folds consisting of crypts and villi, resulting in a large surface area. The function of the GI tract is not only digestive and absorptive, but also immunologic, as it maintains an effective barrier against potentially harmful microorganisms and carcinogens that are present in the intestinal lumen (13, 33). The inner epithelial lining of the small intestine is composed of absorptive enterocytes (about 80% of the intestinal cells), secretory goblet cells (approximately [10 ± 5]% of intestinal cells), immunologically active Paneth cells, and enteroendocrine cells (<1% of intestinal cells). Goblet cells of the intestinal epithelium secrete mucus or mucin, which acts as a protective barrier against chemical and mechanical insult associated with shearing stresses induced by GI motility patterns. Furthermore, antigen-transporting membranous (M) cells, overlying Peyer’s patches of gut-associated lymphoid tissues (GALT), are also present in small regions throughout the intestine. In general, pathogens, toxins, antibodies, and particulate antigens, including nano- and microparticles, are taken up by the M cells of the GALT and presented to dendritic cells at the basolateral surface for further dispensation and response. Enteroendocrine cells are found in gastric glands and produce gastrointestinal hormones or peptides when stimulated. Epithelial cells of the GI tract are some of the most proliferative cells in the human body, as persistent aggravation from luminal content causes a high rate of cell turnover (every 4–5 days). Cell differentiation originates at the base of the intestinal crypts of Lieberkühn, which are populated by stem cells. These stem cells undergo mitosis, with some of the daughter cells remaining in the crypt as stem cells, while others differentiate and migrate towards apical surfaces. These migrating cells include the aforementioned differentiated enterocytes, goblet cells, and enteroendocrine cells, whereas the Paneth cells move toward the basolateral side and protect the stem cells from colonization by potentially pathogenic microbes. Cells at the apical side die after 4–5 days by apoptosis and
shed into the lumen, whereas Paneth cells remain in the crypt for about 23 days before undergoing endocytosis (33). The large intestine (colon) also has glands that are often referred to as colonic crypts and show similar function; notably, however, there are no villi in the colon. The general features of the GI tract in terms of pH variations, transit time, and environmental conditions within each segment of the tract are discussed previously (8). More detailed description is shown in Figure 5 and the real-time changes in pH and transit time in the entire GI tract after oral administration of an electronic capsule are shown in Figure 6.

**Inflammatory Bowel Disease (IBD)**

Both Crohn’s disease and ulcerative colitis are forms of inflammatory bowel disease (IBD), with the former classically affecting the distal small intestine (ileum) and colon, whereas the latter usually affects the colon alone. Crohn’s disease is characteristically transmural and can cause tissue breakdown, ulceration, bleeding, abdominal pain, diarrhea, and significant loss of quality of life. The Crohn’s and Colitis Foundation estimates that approximately 1.6 million Americans currently suffer from IBD, with new cases diagnosed each year in both adults and children (34). The Crohn’s and Colitis Foundation also reports that about 160 genes are associated with IBD. Future research investigating genetic susceptibility and the role of the gut microbiome in the onset and progression of IBD could transform our understanding of the disease process and allow for the development of new drugs for disease management. Although the precise cause of IBD is not completely understood, it is known to develop as a consequence of a complex interaction between genetics, the immune system, age, race/ethnicity, family history, cigarette smoking, excessive use of nonsteroidal anti-inflammatory
medications, and other environmental factors. Figure 7 identifies potential regions of the GI tract where Crohn’s disease and ulcerative colitis disease can occur.

Figure 6. Real-time GI profiling after oral administration of an electronic capsule IntelliCap device, where pH values and transit times in different regions of the GI tract were recorded simultaneously. Adapted with permission from Medimetrics.

Figure 7. Schematic of the human GI tract with highlights showing potential regions of inflammation (Crohn’s disease and ulcerative colitis) and disorders in the gastrointestinal tract. Crohn’s disease is more widespread in the entire GI tract, whereas ulcerative colitis primarily affects the colon and rectum.
Delivery System Design and Formulation Development
Considerations in Drug Delivery System Design for Colon Targeting

The physicochemical properties of a new chemical entity dictate its success or failure during drug development phases, as unfavorable properties can result in undesirable toxicity or a lack of efficacy resulting from poor solubility, permeability, stability, or bioavailability (35). Because of the introduction of the Biopharmaceutics Classification System (BCS) and its adoption by the U.S. Food and Drug Administration (FDA) in 1995 “as a prognostic tool to facilitate product development” (36), it is now easier to predict oral drug absorption. Use of the BCS improves the ability to predict absorption and be able to relate the physicochemical properties of a drug, such as aqueous solubility and membrane permeability, to formulation variables, including drug dissolution rate, transit time, regional differences in drug absorption along the GI tract, food effects, dosing regimen, disease state, metabolism, and bile salts. It is now well established that the fraction of drug absorbed is closely related to the effective permeability. If the effective permeability of a drug is less than $2 \times 10^{-4}$ cm/s, then absorption is incomplete, whereas greater values indicate more complete absorption. Expressed differently, drugs with a dissolution number ($D_n$) greater than 1 or an absorption number ($A_n$) equal to 1.15 have high solubilities and high permeabilities (>90% absorption); such drugs have been grouped into BCS Class I (37).

Based on the above discussion, it is evident that many factors and GI physiological constraints, including contraction forces, can impact drug bioavailability. In an effort to enable predictions of drug bioavailability, a number of mechanistic models based on the original compartmental absorption and transit model have been published. These models provide a greater and more systematic understanding of the events that occur in the GI lumen with respect to the dose, particle size, dissolution-limited absorption, and transit time of the dosage form or drug solution–dispersion within the GI tract (38–40). Moreover, the BCS has been used as a tool to predict the in vitro dissolution of drug substances, to optimize dissolution conditions by using the appropriate apparatus, to develop biorelevant media, and to introduce new parameters for closely simulating GI conditions and transit times within different parts of the GI tract (including the colonic environment) (40–42). For example, knowledge of the relationship among a drug’s solubility, permeability, absorption, bioavailability, and dissolution characteristics will allow researchers to define a situation in which in vitro dissolution conditions can be used as a surrogate for in vivo bioequivalence assessments, thereby facilitating product development process. With respect to the development of modified-release drug delivery systems (including EC dosage forms), an understanding of their in vivo behavior is critical and is generally based on in vitro tests. These in vitro tests generally consist of dissolution tests in a series of biorelevant media or simulated GI conditions that are used to predict drug product performance in vivo, especially when combined with actual human bioavailability data (42). It should be noted that, to date, most of the in vivo permeability data available within the BCS are derived from human jejunal studies, with little information on distal intestinal permeability, including
in the colon. This is particularly important when the intent is to deliver drugs in modified-release and EC forms specifically for colon targeting. Accordingly, it is imperative to recognize that drugs intended for site-specific absorption or distal intestinal delivery having low permeability (BCS Classes III and IV) or poor solubility (BCS Classes II and IV) will have direct implications for the product development process. Moreover, based on the physiology of the GI tract and the conditions present in each region of the GI tract (Figure 5), the ratio of epithelial area/luminal volume is higher in the distal small intestine than in the colon, so that the transport rates (diffusion and convection), motility pattern, mixing level and activities of various absorptive or efflux carrier proteins, are also higher in the former region.

Consequently, a more in-depth understanding of the performance of the delivery system both in vitro and in vivo, coupled with an improved grasp of mechanisms of drug release via simulations, could pave the way for improved dissolution methods and a better understanding of the critical quality attributes and factors in quality by design during the product development process (40, 43), particularly with respect to colon targeting of drugs.

**Encapsulated Enteric-Coated Pellets and Enteric-Coated Mini-Tablets for Delayed Release and Delayed-Extended Release**

Two techniques frequently used to produce pellets that contain drugs include drug layering onto spherical substrates or sugar spheres and direct pelletization by wet extrusion of a drug/excipient mixture followed by spheroidization and drying. Such pellets can be directly enteric-coated with pH-sensitive polymers, or they can be coated for the controlled-release delivery of a drug over a prolonged time period. The coating process can be accomplished using an air-suspension coating approach. In this case, a solution of polymers or a suspension of the drug in a polymer solution is sprayed by nozzle atomization onto the pellets in a fluidized-bed apparatus under controlled conditions of air pressure and temperature to achieve a target percentage weight gain (i.e., desired coat thickness) for a specific delivery rate or release location in the GI tract. The core materials could also be formulated mini-tablets or filled capsules, for which both the fluidization and pan-coating approaches can be used. The coating of solid substrates in the forms of drug layered beads, spheroidized drug pellets or tablets, and capsules is one of the most commonly used operations in the pharmaceutical industry for the purposes of masking taste, addressing aesthetic and trademarking issues, improving stability, generating a particular release rate, and imparting a function. The functional coating option allows formulators to develop pH-triggered-release dosage forms of the drug that can resist gastric dissolution or induce delayed release kinetics as part of modified-release drug delivery systems (8).

An enteric coating is typically and successfully employed when

- drug targeting in the GI tract is desired, particularly in the colon, for topical effects or systemic absorption (for example, delayed release at pH ≥7.0 in the ileum and colon) for distal GI delivery is particularly
advantageous in the treatment of ulcerative colitis and Crohn’s disease [i.e., dosage forms containing mesalamine, polypeptide linaclotide, plecanatide, and budesonide]);

- a drug substance is acid-labile or otherwise destroyed by gastric acid or enzymes and should therefore be protected;
- a drug causes irritation and damage to the gastric mucosa, so that tolerability can be improved by controlling the release rate or delaying release until the drug reaches the small intestine;
- absorption and bioavailability are considerably improved in the intestine by time-based and pH-dependent dissolution and release; and
- delivery of a drug should occur after a lag time or time delay (i.e., controlled-onset delivery), particularly when pulsatile delivery in different GI locations is the goal.

Frequently used materials for enteric coatings include polymeric acids with free carboxyl groups that confer gastric resistance, such as anionic polymethacrylates (copolymers of methacrylic acid with methyl methacrylate or ethyl acrylate, e.g., EUDRAGIT L 30 D-55, EUDRAGIT FS 30 D, and EUDRAGIT L 100, which form aqueous dispersions with pH values of ~3.0), cellulose-based polymers (e.g., hydroxypropyl methylcellulose acetate succinate [with a pH of ~3.85], hydroxypropyl methylcellulose phthalate, and aqueous cellulose acetate phthalate [Aquateric]), and polyvinyl derivatives such as poly(vinyl acetate phthalate) (Coateric). Because aqueous dispersions of EUDRAGIT L 100 have high film-forming temperatures of about 85°C, mixing EUDRAGIT L 100 with the softer EUDRAGIT L 30 D-55 makes it possible to reduce the film-forming temperature to about 40°C, which is a more acceptable range, especially when hard gelatin capsules and hydroxypropyl methylcellulose (HPMC) capsules are coated. To modulate drug release in the range of pH 5.5–7.0, further mixing with EUDRAGIT NE 30 D and FS 30 D is an acceptable option (44, 45). Aqueous dispersions of HPMC and hard-shell gelatin capsules have been investigated specifically for enteric coating (EUDRAGIT L 30 D-55) and colonic coating (EUDRAGIT FS 30 D). Apart from enteric film formers, other components of enteric film coatings include plasticizers (e.g., diethyl phthalate, triacetin), anti-adhesion agents, colorants, pigments, solubilizers, and dispersing agents. Viscosity-enhancing suspension stabilizers might also be added, as they are designed to retard the sedimentation of undissolved excipients or dispersed film formers.

Mention must be made of the fact that acid-labile drugs or proteins can also be degraded as a consequence of contact with acidic of enteric coating polymers during formulation development and manufacturing (46, 47). Thus, it is essential not only to protect the drug from acid exposure in the acidic environment of the stomach but also to employ protective measures during formulation development to prevent degradation and enhance the drug’s storage stability for predictive bioavailability and therapeutic efficacy after oral administration (47–51). Figure 8 shows a cross section of fractured pancreatic enzyme pellets or mini-tablets to demonstrate the significance of the stepwise coating process and evaluation of various coating layers.
Various coating layers on an extruded and spheronized pellet of acid-labile pancreatic enzyme when fractured and viewed by confocal laser scanning microscopy. The presence of enzyme in the core and a protective subcoat between the core interface and acidic enteric coating layer is highlighted in the image. The scale bar is 50 μm.

**Drug-Coated Pellets for Inclusion into a Compressed Coated Tablet or Coated Capsule**

Pellets containing drugs can be produced in combination with microcrystalline cellulose and sodium carboxymethylcellulose (using Avicel PH 101 and Avicel CL 611) in different ratios by an extrusion spheronization process. Alternatively, sugar spheres can be coated with drug solution as drug-coated pellets (52). The pellets can be either enteric-coated or designed for sustained drug delivery with a mixture of various polymers and components in a fluidized-bed coater using the Wurster technique. A typical enteric coating dispersion is composed of mixtures of EUDRAGIT L 30 D-55, EUDRAGIT FS 30 D or RS, glyceryl monostearate, triethyl citrate, Polysorbate 80, and deionized water. The film coating materials should display some degree of malleability to be able to withstand compression forces while also being able to dissolve at a particular pH (typically ranging from 5.5 to >7.0). The elasticity, plasticity, and deformation properties of the excipients as well as coating layers are determined by observing consolidation mechanisms and the amount and type of plasticizers used, the elongation of the polymer at break, and the thickness of the coating or polymer film (51, 52). Compression testing of the pellets to determine their viscoelastic behavior and resistance to fracture or deformation can be conducted using a texture analyzer as shown in Figure 9 (51).
Figure 9. Typical force–displacement profiles for individual pellets subjected to compression forces that they can encounter during tableting operations. Coated pellets show greater mechanical strengths than uncoated pellets.

The drug-coated pellets are then mixed with cushioning excipients or blank pellets of the same size, made of viscoelastic cushioning materials, to achieve a homogeneous mixture for reproducible size, weight, and eventual content uniformity. Blends of the lubricated drug-coated pellets and cushioning excipients are fed into a tableting machine fitted with the desired punch and dies and compressed at an optimized compaction pressure (10–30 kN) to ensure the integrity of the intact coated pellets within the matrix of the entire tablet after consolidation. A general description of a final tablet with schematics and an actual cross section of a tablet are shown in Figure 10. Dissolution results confirmed that, regardless of the type of pellets and the amount of coating, the integrity of the drug-coated pellets was maintained during compression. Apparently, the viscoelasticity of the coated pellets, together with the excipients used, provided excellent cushioning properties and protected the integrity of the coating during compaction.

Figure 10. Typical design of an enteric-coated compressed tablet containing multiparticulate drug-coated beads for more predictable drug delivery to the distal intestine and colon.
Using laser scanning microscopy, one can view the integrity of the spherical coated pellets in the fractured compressed tablet. One such example is shown in Figure 11.

*Figure 11. Cross-sectional image (viewed by laser scanning microscopy) of intact drug-coated pellets after compression into a tablet with cushioning excipients.*

**In Vitro Dissolution Studies of the Above-Described Coated Drug Delivery System under GI Simulation Conditions**

In vitro dissolution tests were performed according to the USP 34 dissolution method, apparatus II (paddle), thermostatically controlled at 37°C, with stirring rates of 50 and 75 rpm. The dissolution medium was a buffer including a phosphate/acetate buffer (0.05 M), in the pH range of 1.5–7.5, containing 0.05% (w/w) Polysorbate 80. The dissolution tests were conducted according to a pH-gradient procedure anticipated to simulate the pH variations and transit time of the coated tablets and pellets in the GI tract. Tablets were placed in the dissolution medium and drug release was measured by UV spectrophotometry with an automated dissolution machine (n = 3 replicate tests), giving the dissolution profile shown in Figure 12.
Development of a pH- and Time-Dependent Sustained-Release Colonic Delivery System Using pH-Sensitive Polymer Coating and Enzymatically Degradable Low Methoxylated Pectin

The objective of this research was to develop a colonic drug delivery system with a controlled onset and release rate satisfying both temporal and spatial constraints using 5-aminosalicylic acid (5-ASA) as the model drug. In this context, dual-coated matrix tablets were developed with the aim that drug release should begin at least 6–8 h after ingestion of the dosage form and that the drug release should take place in a controlled-release manner with complete delivery (4). The pH solubility profile for 5-aminosalicylic acid based on calculations and experimental data is shown in Figure 13.
Figure 13. pH solubility profile of 5-aminosalicylic acid.

Preparation of Core Tablets

Six different formulations of 5-amino salicylic acid were evaluated initially with the aim of selecting the most suitable one for further development (Table 1). A 500-g batch was processed by the wet granulating method using a 5% aqueous solution of HPMC (METHOCEL E15LVP) as the granulating agent. Tablets were manufactured in a Stokes 16-punch rotary tablet machine (Stokes Inc., Philadelphia, PA) and had an average weight of 410 mg (±6 mg) using an 11-mm concave-shaped die and punches.

Table 1. Core Formulations and Their Dissolution Data at pH 6.8 without Enzymes (n = 6)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>5-ASA</th>
<th>Pectin</th>
<th>Avicel</th>
<th>HPMC</th>
<th>Hardness (kPa)</th>
<th>t_{80%} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>200</td>
<td>0</td>
<td>100</td>
<td>8.6 (±3.2)</td>
<td>17.6</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>0</td>
<td>200</td>
<td>100</td>
<td>16.6 (±1.4)</td>
<td>11.2</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>11.6 (±2.1)</td>
<td>15.3</td>
</tr>
<tr>
<td>D</td>
<td>100</td>
<td>100</td>
<td>150</td>
<td>50</td>
<td>10.8 (±2.3)</td>
<td>6.3</td>
</tr>
<tr>
<td>E</td>
<td>100</td>
<td>50</td>
<td>200</td>
<td>50</td>
<td>15.3 (±2.2)</td>
<td>6.1</td>
</tr>
<tr>
<td>F</td>
<td>100</td>
<td>50</td>
<td>225</td>
<td>25</td>
<td>14.8 (±1.8)</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Note: All quantities are in milligrams, and the total tablet weight was 400 mg for each formulation.
Core Composition and Coating of the Core Tablets

To target the colon for sustained delivery, two layers of coating were applied to the core tablets. The inner enteric coating was cellulose acetate phthalate (CPD), and the outer coating was a semipermeable film of ethylcellulose dispersion with a pore former included. The CPD was plasticized with triethyl citrate. Ethylcellulose (Surelease E-7-7050) was plasticized with dibutyl sebacate. To include pore-forming agents in the Surelease dispersion, poly(ethylene glycol) with an average molecular weight of 1450 (PEG-1450), referred to as Carbowax, was mixed with deionized water and slowly added to the Surelease with moderate mixing. The PEG concentrations in the final coating compositions were 15%, 20%, and 25% (w/w) in relation to the solid contents. A 12-in. Erweka AR-400 (Heusenstamm, Germany) coating pan was used for coating the tablets. A Preval spray gun was calibrated to deliver 2–3 g min$^{-1}$ of the formulation with manual sequential actuations of the device. The inlet temperature was maintained at 60–70 °C, the bed temperature was about 35–45 °C, and pan speed was set at 15 rpm to avoid sticking of the tablets. The tablet bed was prewarmed for about 10 min, and the tablets were coated to different percentage weight gains (e.g., 2.5%, 5%, 7.5% and 10%) with respect to the initial tablet weight. For multiple coats, Aquacoat CPD was applied first, and Surelease alone or with a channeling agent was applied on top of the first coat. After the tablets had gained the desired amount of weight, they were left in the warm rotating pan for about 10 min for further drying. The coated 5-ASA tablets were placed in glass vials and allowed to equilibrate to the ambient environment for 14 days before in vitro evaluations were conducted.

In Vitro Release Studies

For preliminary screening purposes, dissolution studies of core tablets were carried out in USP apparatus I (basket) at 50 rpm, using 900 mL of USP phosphate buffer at pH 6.8 and 37 (±0.5) °C in a Vankel (VK7000) dissolution apparatus (Varian, Cary, NC) equipped with fully automated seven-channel peristaltic pump and HP-8453 diode-array spectrophotometer. To evaluate the effects of pectinolytic enzymes on the matrix containing pectin, separate dissolutions were carried out with 3 mL of enzymes in the media. Once the most promising coated formulation had been identified (onset of drug release in about 6 h and more than 80% release taking place in about 18 h), media with a sequential pH gradient containing pectinolytic enzymes were employed for further dissolution studies. For the first 2 h, dissolution was carried out in 900 mL of medium at pH 1.5. The tablets were then transferred to a medium having a pH of 5.5 for an additional 2 h, followed by a medium of pH 6.8 with 3 mL of pectinolytic enzymes. In addition, dissolutions were carried out in media of pH 1.5 and 5.5 to investigate the effect of low pH on drug release.
From the dissolution data for the core tablets (Table 1), it appears that formulation F is the most promising composition to achieve the goals of this project. The time of 80% drug release ($t_{80\%}$) was about 4 h in pH 6.8 buffer. Moreover, the mean dissolution times for 10%, 50%, and 90% dissolution for that formulation were calculated to be 1.1, 3.1, and 5.3 h, respectively. The rationale for using that formulation for further development was that the combined transit time in the ascending and transverse colon was about 7 h for patients with ulcerative colitis and 17 h in a nondiseased colon (21). Because the tablets would be subjected to a double coating, it was expected that the overall release time would be longer and would satisfy the objectives of this work. Coated cores were also subjected to dissolution studies at different pH values, and release profiles for different coating levels and optimized dissolution profiles are shown in Figures 14 and 15, respectively.

![Figure 14](image)

**Figure 14.** Influence of coating composition on the release rate of 5-ASA. SR, Surelease; PEG, poly(ethylene glycol); CPD, aqueous cellulose acetate phthalate dispersion.
A successful colonic delivery system based on a pH- and time-dependent triggered release mechanism was developed by application of an outer semipermeable functional coating with pore-forming agents on top of an enteric coating on the tablet core. It is well recognized that the usual transit time to the colon is about 6 h, and ideally, a delivery system should not begin releasing drug until it reaches the ileocecal junction. When in vitro evaluations were carried out, the dual-coated formulation effectively prevented drug release in the upper intestine in a medium of pH 1.5 or 5.5 for 12 h. However, it provided reproducible and controlled drug release at pH > 6.8 with an initial lag time of about 6 h. The coating shells were generally ruptured at about 15 ± 2 h as a result of the swelling of the matrix and hydrodynamic conditions. The developed delivery system, therefore, offers potential for a predictable onset of release with extended delivery in a controlled manner in the distal intestine and colon.

**Oral Micro- and Nanostructured Drug Delivery to the Colon**

Apart from the conventional drug delivery systems described above (Figure 4), micro- and nanodelivery systems as new pharmaceutical strategies have proven to be promising in improving the delivery of drugs to inflamed regions both passively and by active targeting of the site of inflammation. The particle size and surface characteristics of the nanostructured carrier strongly influence the adhesion and interaction with the epithelial cells and tissues (53). For example, particles ranging in size from <500 nm to many micrometers are undeniably taken up by intestinal enterocytes and GALT, including M cells of Peyer’s patches (54). Among various nanostructured drug delivery carriers, lipid-based systems and colloidal dispersions of various compositions are particularly promising because of their favorable biopharmaceutical properties, biocompatibility, biodegradability, permeability across the GI epithelium, safety, diversity, and commercial availability (55). For example, solid lipid nanoparticles,
microparticles, hybrid lipid nanocapsules with or without surface charges having the ability to improve mucoadhesion, bioadhesion, and penetration into inflamed tissues play a vital role in targeting mucosal surfaces and interacting with epithelial cells (1, 56, 57). Furthermore size-dependent nano- or microparticle delivery systems with the potential to deliver drugs to the mucosal surfaces or facilitating translocation to the serosal regions of inflamed tissues and blood is a stimulating direction in drug targeting with promising applications in nanomedicine (58–60). In general, the fate of nanosized drug carriers in the human GI tract varies depending on size, surface charges, and the composition of the carrier system (e.g., polymers, lipids), together with all of the GI constraints, in a highly complicated and thus far incompletely understood manner. Other limitations encountered in the development of micro- and nanostructured systems, particularly in nanotechnology innovation and nanomedicine, include inadequate information on the toxicology of such carriers, stability during GI transit, premature delivery of drugs, and bioadhesion in regions unrelated to the desired target site or location. Likewise, from a commercial point of view and in terms of large-scale manufacturing, it is essential to have design simplification and validation of the process for reliability. Colonic drug delivery, especially in the area of nanotechnology, is also associated with new regulatory challenges, particularly from the point of view of safety for both short- and long-term use. The development of micro- and nanostructured systems based on appropriate formulation design, optimization, process validation, and suitable in vitro and in vivo evaluation based on accurate simulations and scientifically sound models is nonetheless promising.

**Oral Delivery of Proteins and Peptides**

To be therapeutically effective, proteins and biopharmaceuticals are generally administrated subcutaneously or parenterally by an intramuscular or intravenous route. If given orally, they must be protected, as they tend to undergo acidic degradation and enzymatic digestion. Furthermore, they have low permeability through the intestinal epithelial cells in the gastrointestinal tract. Nevertheless, multiple oral products with specialized formulations are currently available and FDA-approved with many therapeutic applications, including tablets and capsules of pancreatic enzymes (pancrelipase, indicated for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions) and peptides such as linaclotide and plecanatide, both approved for the treatment of chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). Also, the bioavailability of many macromolecules by the oral route is often suboptimal, but site-specific targeting of the mucosal surfaces in different regions, including the colon, is promising. For example, a variety of penetration enhancers including ethylenediaminetetraacetic acid; citric acid; sodium lauryl sulfate; poly(oxyethylene lauryl ether); and fatty acids such as sodium caprate, sodium laurate, and oleic acid have been used to promote the bioavailability of macromolecules.
Encapsulated Beads of a Polypeptide Linaclotide for Once-a-Day Oral Administration

Linaclotide (brand name Linzess) is a 14-amino-acid peptide agonist of guanylate cyclase-C. Both linaclotide and its active metabolite bind to guanylate cyclase-C and act locally on the luminal surface of the intestinal epithelium in order to treat chronic idiopathic constipation CIC and IBS-C in adults. The drug reduces the activation of colonic sensory neurons, thereby reducing pain. In addition, linaclotide activates colonic motor neurons, which increases smooth muscle contraction and promotes bowel movements. The product is a hard gelatin capsule (145- and 290-μg strengths) containing the linaclotide drug coated onto microcrystalline cellulose beads along with HPMC and stabilizing agents such as calcium chloride dihydrate and L-leucine, and it is intended for once-a-day administration. The molecular formula of linaclotide is C_{50}H_{79}N_{15}O_{21}S_{6}, and its molecular weight is 1526.8. It is a 14-amino-acid synthetic peptide with three disulfide bridges (Scheme 1). All amino acids have the L configuration in the following order: L-tyrosine, L-cysteiny1-L-cysteiny1-L-α-glutamyl-L-tyrosyl-L-cysteiny1-L-cysteiny1-L-asparaginyl-L-proly1-L-alanyl-L-cysteiny1-L-threony1glycyl-L-cysteiny1-. cyclic (1 ↔ 6),(2 ↔ 10),(5 ↔ 13)-tris(disulfide).

![Scheme 1. Synthetic peptide sequence of linaclotide](image)

It is an amorphous, white powder with no X-ray powder diffraction pattern that is soluble in water and has a pH (2.4 mg/mL) of 3.4, an isoelectric point of 4.0; specific optical rotation from −235° to −261° (589 nm, c = 0.1 in 1% acetic acid). Linaclotide is minimally absorbed with low systemic availability following oral administration (i.e., plasma levels are below the limit of quantitation after oral doses of 145 or 290 μg). Its solubility in aqueous solution over a pH range from 1.0 to 7.5 is >100 μg/mL. Therefore, linaclotide is considered to be a BCS Class III (high-solubility, low-permeability) compound. A hard-shell capsule appears to be an ideal carrier for this compound. Because it is a polypeptide, it is likely to lose its structural features if subjected to the compression forces used in tableting. This is due to mechanical shearing, which will ultimately result in a loss of its therapeutic value. It is known that mechanical perturbation and shearing forces of impaction and compression during tableting consolidation are high enough to kill bacterial cells and mold spores (52). Consequently, if proteins and polypeptides are subjected to similar conditions, they might not maintain their molecular stability and folded state, potentially resulting in conformational changes and a loss of biological function.
Formulation of Plecanatide, a 16-Amino-Acid Peptide in Tablet Dosage Form

Plecanatide (brand name Trulance) is available as a 3-mg tablet and is FDA-approved for the treatment of CIC and IBS-C (Scheme 2). It is a 16-amino-acid peptide with the following chemical name: L-leucine, L-asparaginyl-L-α-aspartyl-L-α-glutamyl-L-cysteinyl-L-α-glutamyl-L-leucyl-L-cysteinyl-L-valyl-L-asparaginyl-L-valyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-, cyclic (4 → 12), (7 → 15)-bis(disulfide).

Scheme 2. Synthetic peptide sequence of plecanatid.

The tablet formulation is possible due to the small (3-mg) dose, and it uses a viscoelastic cushioning excipient (spray-dried microcrystalline cellulose) that protects the drug against the mechanical shearing of compression forces.

As mentioned previously, protein availability following oral administration can be limited due to acid degradation, enzymatic digestion, and poor permeability across the GI mucosa. Nevertheless, treatments for intestinal diseases such as Clostridium difficile infection (CDI), ulcerative colitis, and Crohn’s disease would benefit greatly from an oral delivery system that can target proteins and peptides to the colon. To that end, epithelial cell penetration and subsequent absorption might not be required for these conditions.

Additionally, even for the systemic delivery of protein therapeutics through the colon, site-specific delivery of proteins to the colon is a prerequisite. Spray layering of bovine serum albumin as a model protein onto beads followed by application of an enteric coating polymer (EUDRAGIT FS 30 D at 20% and 30% weight gain) demonstrated an in vitro release of stable and intact protein (7). Others have shown that the in vitro release of bovine serum albumin from chitosan-coated pectin beads in a simulated colonic medium is achievable (61).

Application of Devices for Drug Targeting in the GI Tract during Drug Development Phases and Research To Assess Local Delivery of the Drug in Selected GI Segments

Multiple delivery systems with potential use in chronotherapeutics, in accord with the circadian rhythms of disease, have been developed with specific time-dependent trigger mechanisms for the delivery of drug(s) at a particular rate to a specific region of the GI tract. (For more details, see reference (8).) One such delivery system that couples a remote activation port (for drug delivery to the region of interest) with the capability of continuously monitoring the pH of the GI tract (via a sensing chip) is discussed below.
IntelliCap System for Targeted Drug Delivery to the GI Tract and Colon

Medimetrics’ IntelliCap is a wirelessly controlled electronic capsule system that delivers drugs to the region of interest in the gastrointestinal tract for regional absorption studies. The 11 mm × 26 mm (approximately 000 size capsule) is composed of a microprocessor, battery, pH sensor, temperature sensor, wireless transceiver, fluid pump, and drug reservoir capable of storing up to 275 µL of test compound (Figure 16). It communicates via its wireless transceiver to an external control unit worn by the subject.

![IntelliCap system and its components](image)

*Figure 16. IntelliCap system and its components. Adapted with permission from Medimetrics.*

Radiolabeling and scintigraphic monitoring of the IntelliCap allows one to determine its position within the GI tract (Figure 17). This assures that the drug is released at the desired site, thus increasing its value in animal and clinical studies during product development phases.

![Scintigraphic study showing the location of an IntelliCap device after oral administration](image)

*Figure 17. Scintigraphic study showing the location of an IntelliCap device after oral administration. Adapted with permission from Medimetrics.*
The IntelliCap system allows for more predictable drug release within the target region. At the same time, the transit time from the stomach to the colon can be easily monitored with a wireless pH sensor. Figure 18 shows representative data collected from an IntelliCap study in a dog model. The capsule was programmed to release atenolol at a constant rate for 6 h starting at arrival in the duodenum. The zero-order release strategy allowed for examination of the entire intestinal tract with a single experiment. Regional transit and location are clearly described, along with the pH data, drug release duration, and concurrent plasma concentrations of the drug.

![Figure 18](image-url)

**Figure 18.** (A) Concurrent determination of drug absorption and transit time, together with changes in pH as a capsule transits through the GI tract. (B) Regional drug absorption based on deconvolution and in vitro in vivo correlation. Data collected from an IntelliCap study in a dog model. Adapted with permission from Medimetrics.
Conclusion

Adequate information and knowledge about drugs, including colon-targeted oral drug delivery systems, is a prerequisite at all healthcare levels to ensure proper application and promote rational prescribing. It is recognized today that scientific research in drug development and advances in delivery system design can contribute to health standards only if the patients themselves become full partners with healthcare providers in safeguarding and promoting health and wellness. Because of the vast scope of this topic, a comprehensive review of all mechanisms and delivery innovations is not feasible. However, this chapter highlights the more commonly used colonic delivery systems that are FDA-approved and currently marketed.

As discussed herein, colon-specific drug delivery systems offer major therapeutic benefits to patients in terms of safety and efficacy. Many side effects are reduced, lower drug doses are necessitated, and the drug is released in close proximity to its target region. Although these benefits are of great value, successful delivery of drugs to the colon presents many unique formulation challenges. In addition to accounting for the physicochemical characteristics of the drug and the nature of the delivery system, one must also overcome pH variations, avoid drug release in the proximal intestine, acknowledge the GI microenvironment, and account for GI transit time and motility patterns. Multiple formulation approaches have been exploited to overcome these issues, primarily by employing pH-triggered release (via enteric coatings); enzyme-triggered release; time-triggered release; and multiparticulate systems, small tablets, capsules, and mini-tablets, each with its own operating release mechanisms, to more predictably deliver intact drug to the colon and mucosal surfaces. The capsule shell can be enteric-coated for drug delivery to the distal intestine, especially for the delivery of acid-labile drugs, peptides, proteins, biotechnology-derived drugs, and macromolecules that are destroyed by mechanical shearing or manufacturing processes. Also, controlled or extended release of a drug from a capsule delivery system and osmotic pump systems with the potential for pulsatile and targeted delivery to the GI tract and colon are easily attainable. Furthermore, a variety of innovations in the design of new capsule shells (e.g., microbiologically triggered systems and biodegradable, ruptureable, or pressure-sensitive shells) and delivery types for targeting various regions of the gastrointestinal tract are under investigation.

In addition, future prospects for three-dimensional (3D) printing technology in colonic drug delivery, including its role in personalized medicine, are promising and already being implemented in other areas such as tissue engineering to produce artificial heart valves, skin grafts, ears, bones, and joints (62). In terms of drug delivery, the first FDA-approved (2015), 3D-printed tablet, Spritam (levetiracetam), which utilizes 3D printing tablet technology to treat myoclonic seizures, is now commercially available (63). The 3D printing technology can be employed to address individual needs of patients suffering from IBD and other colonic diseases for personalized drug delivery and therapy. The process of 3D printing involves the layer-by-layer accumulation of drug(s) and excipients to create a particular geometry to optimally release drug while reaching the colonic...
mucosa by overcoming aforementioned GI tract constraints (63, 64). Although there are benefits for patients, challenges remain regarding manufacturing and regulatory hurdles. Prospects for the application of 3D printing in the area of dosage form design including colonic drug targeting and personalized medicine are highly promising. The future of colonic drug delivery and the accuracy of colon targeting, along with the development of new in vitro methods relevant to more complex in vivo conditions, will stimulate the creation of more innovative delivery system designs.

Finally, the exploration of nanotechnology, self-emulsified lipid-filled, colloidal and dispersed systems for inclusion into soft-shell coated capsules, and compressed multiparticulate systems in the form of small tablets can facilitate drug distribution in the target region, and enhance the dissolution and efficacy of drug action within the low water content of the colonic environment.

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