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Review Article

Chrono-Colonic Delivery in Engineering Time-Responsive Systems for Site-Specific Therapy

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Abstract

Background: Chrono-colonic drug delivery represents a novel pharmaceutical engineering strategy that combines the principles of circadian rhythm-based chronotherapy with colon-targeted the drug delivery. This approach seeks to optimize therapeutic efficacy by synchronizing drug release with the body's biological clock while ensuring precise site-specific delivery.

Objective: The primary aim of chrono-colonic delivery is to achieve controlled drug release after a predetermined lag time, ensuring that the therapeutic effect coincides with peak disease activity and that the drug reaches the colon for localized or systemic action.

Methods: This strategy integrates time-dependent and site-specific technologies, employing pH-sensitive polymers, biodegradable coatings, osmotic systems, and microbially triggered release platforms. These delivery systems are designed to withstand the upper gastrointestinal tract environment and to release the active agent in the colon, where favorable physiological conditions such as near-neutral pH, slower motility, and microbial activity can be exploited.

Results: Chrono-colonic delivery systems offer significant therapeutic benefits, including improved precision of drug action, reduced systemic side effects, and enhanced patient compliance. They are particularly beneficial in managing diseases with circadian variability, such as asthma, hypertension, arthritis, ulcerative colitis, and inflammatory bowel disease.

Conclusion: By integrating chrono-therapeutic principles with colon-targeted technologies, chrono-colonic drug delivery holds promise as a next-generation approach for achieving site- and time-specific therapy. It represents a forward-looking strategy for addressing both local and systemic diseases with enhanced safety and efficacy.

Keywords: Chrono-Colonic Delivery, Circadian Rhythm, Colon-Targeted Drug Delivery, Time-Responsive Systems, Site-Specific Therapy, Chronotherapy

1. Introduction to Chrono-Colonic Drug Delivery

Chrono-colonic drug delivery is an advanced pharmaceutical engineering approach that combines the principles of time-dependent (chrono) drug release and colon-targeted drug delivery. Chronotherapy refers to the administration of medication at specific times of the day to synchronize drug delivery with the body's natural biological rhythms (circadian rhythms)[1]. This alignment ensures that the drug's therapeutic effect coincides with the period when the disease symptoms are most pronounced, thereby maximizing efficacy while minimizing side effects. For example, certain diseases such as asthma, hypertension, arthritis, and ulcerative colitis exhibit time-dependent variations in their severity, and a drug given at the right time can provide significantly better outcomes[2].

Colon-targeted drug delivery, on the other hand, focuses on transporting the drug specifically to the large intestine (colon), either for local treatment or for systemic absorption in cases where the colon offers pharmacokinetic advantages[3]. The colon is a unique site in the gastrointestinal tract because it has a near-neutral pH (6.0–7.0), slower motility, reduced enzymatic activity compared to the small intestine, and a large population

of anaerobic bacteria[4]. These physiological conditions make the colon an attractive target for treating localized conditions such as inflammatory bowel disease (IBD), colorectal cancer, and amoebiasis, as well as for systemic delivery of drugs that may be degraded or poorly absorbed in the upper gastrointestinal tract[5].

By integrating these two concepts, chrono-colonic drug delivery systems can be designed to release the drug after a pre-determined lag time (matching the circadian rhythm of the disease) and at the exact site of action (colon)[6]. This dual targeting improves therapeutic precision, reduces dosing frequency, and minimizes systemic toxicity, making it a promising strategy in modern drug delivery research. Various formulation technologies such as pH-sensitive polymers, biodegradable coatings, osmotic systems, and microbially triggered release systems are utilized to achieve the desired release profile in chrono-colonic delivery[7].

1.1 Anatomical and Physiological Considerations

The gastrointestinal (GI) tract is a highly complex and constantly changing environment which, therefore, creates special problems and opportunities in drug delivery. One of the most notable features is the extreme change of the pH along its way; it has a highly acidic pH because the stomach is highly acidic, ranging between 1.5 and 3.5, and finally a highly neutral or even slightly alkaline environment as the pH progresses in the small intestine of 6.0 to 7 Table 1 and Figure 1 illustrates the significant variability in pH and transit time across the different segments of the gastrointestinal tract[8]. This pH gradient has a big impact on both stability and solubility of drugs. Moreover, when it comes to substances, such as drugs, the rate of passage through the GI system varies a lot with each sector[9]. A drug thus would pass through the stomach and then into the small intestine spending a further 3-4 hours, giving a total Oro-cecal transit time of say 4-6 hours. In addition to the small bowel the colon is vital which provides a much greater transit time, which could be as long as 24 hours[10]. The long residence time, combined with a large area over which absorption can be possible, makes the colon a highly desirable place to achieve extended systemic absorption of drugs, or as a site of localized action of drugs in the lower GI tract[11].

Table 1: Physiological Challenges of the GI Tract for Drug Delivery

GI Segment	pH Range	Transit Time	Key Characteristics & Challenges	Ref
Stomach	1–4	1-2 hours	Highly acidic; drug degradation, especially for acid-labile compounds like proteins and peptides.	12
Small Intestine	6.0 -7.4	3-4 hours	Neutral to slightly alkaline; primary site of drug absorption, but fast transit time limits sustained release.	13
Colon	6.0 -7.4	Up to 24 hours	Neutral to slightly alkaline; large surface area, long residence time, and unique microbial environment.	14

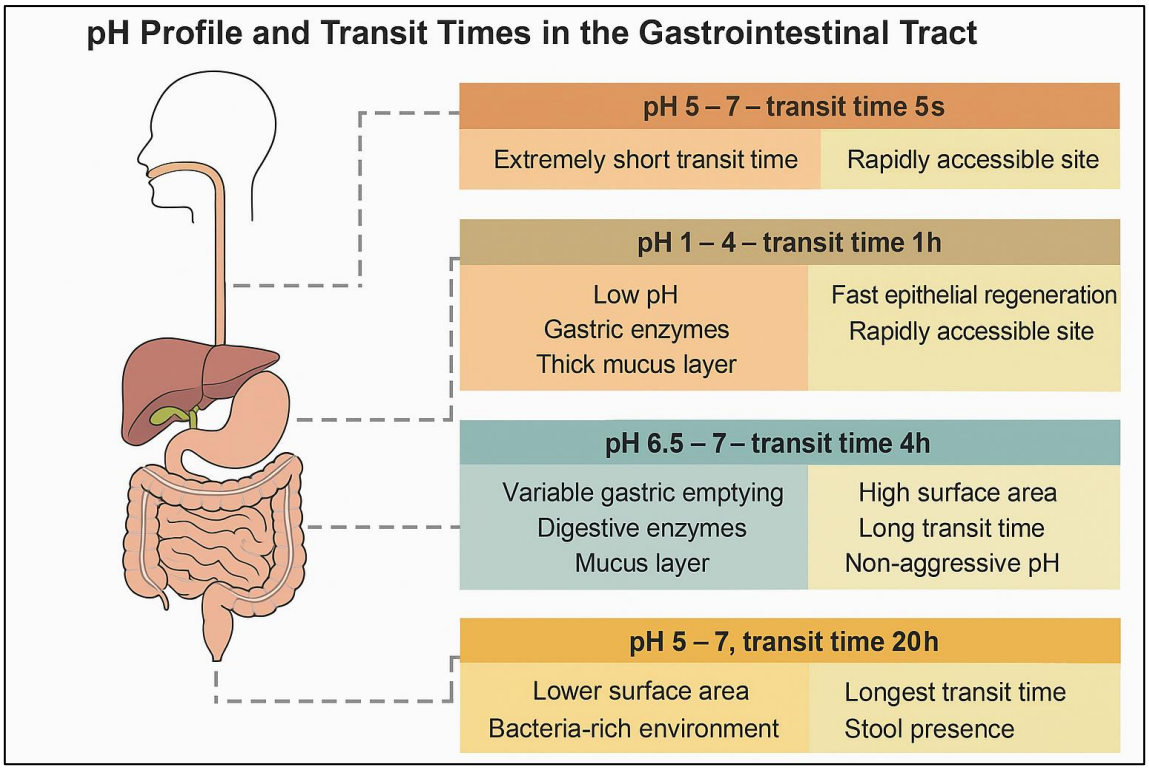

Figure 1: pH Profile and Transit Times in the Human Gastrointestinal Tract

The diagram illustrates the pH range and average transit times across different regions of the gastrointestinal tract. The esophagus has a neutral pH (5–7) with a very short transit time (~5 seconds). The stomach exhibits an acidic pH (1–4) with an average transit time of ~1 hour, aided by gastric enzymes and a thick mucus layer. The small intestine maintains a pH of 6.5–7, with a transit time of ~4 hours, providing high surface area and enzymatic digestion. The large intestine has a neutral pH (5–7) with the longest transit time (~20 hours), influenced by bacterial activity and stool presence.

1.2 Rationale for Chronotherapy in Colon Delivery

Numerous human illnesses such as nocturnal asthma, the severe morning stiffness that occurs with rheumatoid arthritis and some inflammatory bowel diseases (IBD) also have a definite time course as their symptoms are seen to intensify or reach a peak during certain times of the day or night, and this is primarily dependent on the inherent circadian rhythm of the human body[15]. Realizing the complexity of the physiological processes in relation to disease manifestations, chronotherapy comes as a complex treatment method that attempts to coordinate drugs administration with inherent biological features. Timing of the medication is the main essence of chronotherapy as it aims to maximize the therapeutic effect and reduce the side effect by timing the dose to coincide with the best possible timing[16]. To illustrate, in morning stiffness with rheumatoid arthritis, in which the severity of the condition is reported in the morning, a chronotherapeutic approach may include the nighttime administration of the drug. This drug would be developed with an inbuilt time delay system such that it is released and acts in the colon just before the patient opens his/her eyes and thus relieves just when it is due the most[17]. **Table 2** sums up the main treatment arguments of creating these advanced delivery systems. Such a personalized delivery not only has the potential to improve therapeutic outcomes but also has the possibility to at least potentially reduce overall drug dosage and side effects, a breakthrough in personalized medicine[18].

Table 2: Rationales for Colon-Targeted Drug Delivery

Rationale	Description	Example Disease/Drug Class	Ref
Chronotherapy	Aligning drug release with the body's circadian rhythm to treat diseases with time-dependent symptoms.	Nocturnal asthma, morning stiffness in rheumatoid arthritis.	15
Local Drug Action	Delivering high concentrations of a drug directly to the site of action to treat localized diseases.	Ulcerative colitis, Crohn's disease, colon cancer.	19
Systemic Absorption	Enhancing the bioavailability of drugs that are poorly absorbed or extensively metabolized in the upper GI tract.	Proteins, peptides (e.g., insulin), drugs with extensive first-pass metabolism.	20
Reduced Side Effects	Minimizing drug exposure to healthy tissues and organs by targeting delivery to the disease site.	Chemotherapeutic agents, potent anti-inflammatory drugs.	21

1.3 Targeted Diseases

1.3.1 Inflammatory Bowel Disease (IBD)

In cases of diseases such as ulcerative colitis and Crohns disease, collectively referred to as inflammatory bowel disease (IBD) mainly affecting the colon, delivery of the drug with precision is of great benefit. The major aim is to attain high dose of the therapeutic agent at the target area at the inflammatory site keeping global exposure with side effects to minimum[22]. Such local delivery reduces not only increases efficacy of the drug where it is required but also avoids the risk of undesirable effects that may follow in the event that the medication circulates in the whole body[23]. Typical drugs to be employed under such circumstances are mesalazine also referred to as 5-ASA and corticosteroids such as budesonide. Such medications are designed to dissolve in the colon, either by dissolving pH-sensitive coatings in the more alkaline colon, or by uses a time-released mechanism so that the drug arrives in the colon before it is released. There is the possibility of a powerful anti-inflammatory effect exactly in the area of the disease, which manifests itself in greater control of symptoms and better patient outcomes[24].

1.3.2 Colorectal Cancer (CRC)

Systemic chemotherapy, either intravenous or orally, allows effective distribution of drugs throughout the whole body to reach widespread cancer cells, but it can also result in serious side effects; in particular, systemic chemotherapy may lead to systemic toxicity caused by the destruction of proliferating nonmalignant cells along with cancerous ones[25]. The main disadvantage is that systemic activation of chemotherapeutic agents seems to cause serious systemic toxicity via the indiscriminate destruction of healthy and fast-proliferating cells as well as cancerous cells. In contrast to systemic drug distribution, loading This targeted methodology has multiple prominent benefits: first, it lowers the overall exposure of the system to the potent chemotherapy chemicals, thereby decreasing the side effects on the healthy tissue of the whole body[26]. Second, it enables obtaining a considerably higher concentration of the medicine at the immediate location of the tumor mass, maximizing their cytotoxic effect on the cancerous cells. Such precision of delivery can be possible with several approaches, direct injection into the tumor, the implanting of drug-eluting devices or delivery via special catheters into blood direct to tumor[26]. Local

chemotherapy enables a more direct application of the therapeutic punch where it is most needed and, by doing so, increases the efficacy of chemotherapy treatment, but also reduces the burdensome effects that patients undergoing conventional systemic chemotherapy generally experience[27].

1.3.3 Systemic Diseases

Therapeutics, whether they are proteins and peptides (e.g., insulin) or drugs that have an intrinsically low oral bioavailability, are frequently administered through an oral route but are plagued by a series of roadblocks upon delivery through the upper gastrointestinal (GI) tract packed with digestive enzymes and subject to extreme pH conditions that can quickly destroy even the most robust proteins and peptides. Moreover, these molecules also suffer very low permeability of the intestinal lining that only contributes to their drug exposure. The colon is usually less hostile in general containing lower levels of enzymes and more neutral ph as compared to the stomach and small intestine and therefore provides a more stable environment to these fragile compounds. Furthermore, drugs have more time to be released and absorbed as they spend a long time in the colon, this may result in high bioavailability of the drugs that are poorly absorbed in other parts of the body. With the ability to tailor areas that deliver drugs to be within the colon itself, sensitive molecules may not be destroyed before absorption and therefore allow maximum absorption and therefore increased effectiveness of their work in treating many conditions[28].

1.4 Advantages of Site-Specific Colon Delivery

1.4.1 Targeted Therapy

In localized diseases, one of the prime objectives is to achieve high concentration of the drug where the pathology occurs since it is directly related to the increased therapeutic effect with a reduction of the systemic side effects. In the case when the pathology is localized in a certain body or problems with specific organs and tissues, such as in inflammatory bowel disease of the colon, in a tumor located in a specific organ or in an infection in a joint, the therapeutic agent is brought into the target site and ensures concentration of a high dose at the point of required action. A localized treatment would maximize drug interaction with the diseased tissue or pathogen resulting in a more successful therapeutic effect. Alternatively, when locally unsuited disease treated drug is given systemically (e.g., orally or intravenously), the drug spreads throughout the whole body and therefore only a small portion is actually delivered to the target location. This frequently requires the use of higher total doses to attain the desired level at the action point which, subsequently, considerably raises the threat of the systemic concentration, as well as the probability of the seeming half-toxicity in healthy tissues. Hence, methods of facilitating high drug concentration at the locus of response play a vital role in maximizing effectiveness, reducing side effects, and eventually leading to patient safety and welfare[29].

1.4.2 Reduced Systemic Side Effects

The potential to reduce exposure of the healthy tissues and organs to the drug is one of the main benefits of advanced drug delivery systems and, in particular, of localized strategies of delivering drugs and drug delivery. In the case of the traditional systemic administration of a drug, when the medicine enters the bloodstream and flows in all organs of an organism, some of it is inevitably exposed to the healthy tissues. Such a wide dispersion might result in unfavorable side outcomes and in a toxic effect, with the drug being able to deliver both therapeutic and negative results in a random manner. Localized delivery by comparison seeks to directly deliver the drug to the site of disease, e.g. administering the drug to a tumor, an inflamed joint, or infected area. The targeted delivery means that the systemic concentration of the drug is reduced significantly, effectively sparing healthy organs the exposure of unnecessary drug. As an example, during cancer treatment, administration of chemotherapy to a tumor can greatly enhance the concentration of the drug in the cancerous tissue with minimal drug distribution in the bloodstream and other important organs, resulting in a smaller number of systemic complications (nausea, hair loss, and bone marrow suppression). Such selective targeting does not only increase the therapeutic index of the drug but also ensures a better safety and life quality of patients through the prevention of the ubiquitous adverse effects that accompany the extensive use of drugs[30].

1.4.3 Improved Efficacy

Various diseases show their symptoms and pathological activity vary regularly over a period of 24 hours by matching the natural circadian rhythm of the whole body. This has led to the adoption of the concept of chronotherapy which is a more advanced method of drug delivery timing which is aimed to maximize therapeutic benefits and minimize adverse effects by ensuring that the drug is provided at the site of action in the right dose at the right time. Diseases that are the focus of chronotherapeutic intervention would be diseases such nocturnal asthma, whereby the asthma symptoms would increase during early Such exact timing of the drug not only increases its effectiveness (by aligning the peak level with the physiological need of the body) but also making it possible to administer lower doses overall, reducing the risk of side effects and increasing patient compliance as well. The current state of research in chronobiology merely continues to demonstrate how rhythmic some physiological processes are, as well as how certain diseases can be as well, in turn opening up the possibility to implement even more specific and effective chronotherapeutic approaches[31].

1.4.4 Protection of Sensitive Drugs

This stomach greatly acidic environment, with an average pH between 1.5-3.5, presents a great challenge to oral delivery of any drug especially the so-called acid labile drugs which include certain proteins and peptides (e.g. insulin), and even some small molecule drugs. Such

degradation may undergo significant loss of therapeutic activity, which makes the medication useless and in the end resorts to poor oral bioavailability. To circumvent this obstacle, advanced measures regarding drug delivery have been used to protect these fragile compounds by the brutal stomach environment. One of the most direct and successful of these methods is the incorporation of enteric coatings.3 These specialized polymeric coatings are made to guard against the acidic stomach environment without triggering the release of drugs prior to reaching the small intestines where the environment is much more neutral or even slightly alkaline (6.0-7.4 pH). The enteric coating is also the most popular protective mechanism because it is the most beneficial in safeguard[32] .

1.4.5 Bypassing First-Pass Metabolism

In several orally administered drugs, the key challenge to attaining effective therapeutic concentrations is first-pass metabolism wherein a large part of the drug is metabolized, mainly by the enzymes in the liver and gut wall, before it can even enter the systemic circulation. The extensive metabolism not only severely limits the bioavailability of the drug that is available to achieve its intended effect but also wastes much of the dose. To circumvent this, there exist numerous strategies. One such strategy is through alternative routes of administration, as some routes bypass the portal vein and liver. A third approach is the development of the drug as a prodrug, which is an inactive substance, effective when metabolized after first passing the first-pass effect, or in a manner in which by damaging it the first-pass metabolism leads to activation. Also important are the advances in formulation and nanotechnology. Physical means, such as micronation or nanosizing of drug particles, expose more surface area to improve dissolution and absorption. Formulations such as self-emulsifying drug delivery systems or solid lipid nanoparticles can enhance the solubility of some hydrophobic drugs and thus their absorption through the lymphatic system, which avoids much of the portal circulation and two-pass effect in the liver. There are also the co-administration of drugs with so-called bioenhancing agents, substances that inactivate drug-metabolizing enzymes or efflux[33].

2. Mechanistic Approaches in Colon-Specific Drug Delivery

The magic of any chrono-colonic delivery system is that it releases the drugs upon arriving in the colon, rather than immediately. provides an overview of the primary ways in which this is ensured, namely by pH-dependent or microbially controlled releases. All this is via different trigger mechanisms:

2.1 pH-Dependent Systems

pH-dependent drug delivery systems employ polymers that remain insoluble in the acidic pH of the stomach (pH 1.5–3.5) but dissolve when exposed to higher pH values in the small intestine or colon[34]. This property enables targeted release of drugs, minimizing degradation in the stomach and allowing site-specific delivery . Commonly used polymers include Eudragit® L (soluble above pH 6.0), Eudragit® S (soluble above pH 7.0), Hydroxypropyl Methylcellulose Phthalate (HPMCP), Cellulose Acetate Phthalate (CAP), and Polyvinyl Acetate Phthalate (PVAP) each selected for its distinct dissolution threshold and film-forming properties[35]. As illustrated in Figure 2, pH-dependent systems can be broadly categorized into (i) colon-targeted formulations using enteric coatings, (ii) nanoparticle-based carriers with pH-responsive polymer shells, and (iii) smart-release mechanisms that activate drug discharge in response to environmental pH changes[36]. These approaches collectively enhance therapeutic precision, reduce systemic exposure, and improve patient outcomes[37].

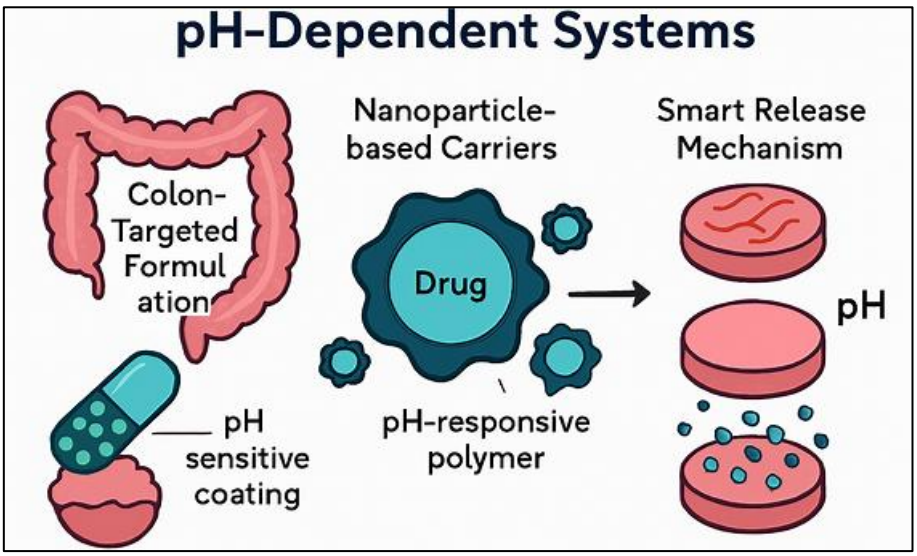

Figure 2 : pH-Dependent Drug Delivery Systems illustration depicting three major strategies in pH-responsive drug delivery: (i) colon-targeted formulations utilizing pH-sensitive coatings to ensure site-specific release in the lower gastrointestinal tract; (ii) nanoparticle-based carriers encapsulating drugs within pH-responsive polymers for controlled release; and (iii) smart release mechanisms that activate drug discharge in response to environmental pH changes. These systems enhance therapeutic precision and minimize off-target effects.

2.1.1 Eudragit® L

Eudragit® L is a methacrylic acid copolymer designed to dissolve at pH above 6.0. It is commonly used in enteric coatings for drugs that require protection from gastric acid and need release in the upper to mid-small intestine. For example, acid-sensitive drugs such as proton pump inhibitors (omeprazole) and certain antibiotics can be protected until they reach the optimal absorption site. The pH range of 6.0–7.4 in the small intestine ensures rapid dissolution of the Eudragit® L coating once the dosage form passes the stomach. In addition to protecting unstable drugs, this system also prevents gastric irritation caused by drugs such as aspirin and NSAIDs. The flexibility in formulation allows combining Eudragit® L with other grades for tailored dissolution profiles, making it a versatile choice for both local and systemic drug delivery targeting the upper GI tract.

2.1.2 Eudragit® S

Eudragit® S dissolves only at pH values above 7.0, making it highly suitable for distal small intestine and colon-specific drug release. This property is particularly useful for the treatment of local colonic diseases like ulcerative colitis and Crohn's disease, where high local concentrations of the drug are required with minimal systemic exposure. Drugs such as mesalamine are often coated with Eudragit® S to achieve targeted delivery directly to the inflamed colon. Moreover, it is valuable for delivering proteins and peptides that are prone to enzymatic degradation in the upper GI tract. The longer transit time in the colon offers the potential for sustained drug absorption. Eudragit® S can also be blended with Eudragit® L to create coatings that dissolve at intermediate pH levels, providing flexibility in designing delayed-release formulations tailored to specific therapeutic needs[38].

2.1.3 Hydroxypropyl Methylcellulose Phthalate (HPMCP)

HPMCP is a cellulose derivative that dissolves at pH 5.0–5.5, making it suitable for protecting acid-sensitive drugs until they reach the duodenum. This polymer is widely used for enteric coatings, ensuring that drugs like omeprazole and pancreatic enzyme supplements remain stable in the stomach's acidic environment. Once the dosage form moves into the duodenum and the pH rises, the HPMCP coating swells and dissolves, releasing the drug where it can be absorbed effectively. HPMCP coatings also reduce gastric irritation caused by certain drugs and prevent premature degradation, thus improving bioavailability. Due to its good film-forming properties and compatibility with various plasticizers, HPMCP is a preferred material for tablets and capsule coatings in oral drug delivery systems[39].

2.1.4 Cellulose Acetate Phthalate (CAP)

CAP is one of the earliest and most widely used enteric coating agents, dissolving at pH values above 5.0. It is particularly useful for protecting drugs that are unstable in acidic conditions, such as erythromycin, aspirin, and certain probiotics. CAP coating ensures that the drug remains intact in the stomach and releases only upon entering the more alkaline small intestine. This property helps maximize absorption, minimize drug degradation, and reduce gastric side effects. CAP has been extensively used in both pharmaceutical and nutraceutical formulations, thanks to its relatively low cost and ease of application. However, its moisture sensitivity and brittleness require careful formulation with plasticizers to ensure stable coatings during storage[40].

2.1.5 Polyvinyl Acetate Phthalate (PVAP)

PVAP is a synthetic polymer that dissolves at pH values above 5.0, making it effective for targeted delivery to the upper small intestine. It is often used for coating NSAIDs such as diclofenac sodium, preventing gastric irritation and ensuring drug release after the dosage form leaves the stomach. PVAP has better stability and lower permeability to moisture compared to CAP, which enhances the shelf life of coated products. Its film-forming properties make it compatible with aqueous and organic coating systems, allowing flexible manufacturing options. PVAP is also used in combination with other polymers to fine-tune drug release timing and achieve desired therapeutic outcomes, especially in cases where partial protection from the upper GI environment is required before drug release[37].

2.2 Time-Dependent Systems (Chronotropic Pulsatile Release)

These systems are designed to release the drug after a specific lag time, independent of the GI tract's pH.

2.2.1 Pulsatile Release:

Pulsatile release systems are specifically engineered to produce a distinct lag phase followed by a rapid and concentrated drug release, closely resembling the body's natural biological rhythms or meeting the therapeutic need for time-specific dosing shown in Figure 3 [41]. These systems are particularly effective for diseases that exhibit circadian variation in symptoms or for drugs that must bypass the stomach and upper intestine before release[42]. The principle involves physically preventing drug release until a controlled trigger point is reached. This is often achieved using dosage forms with an erodible, swellable, or biodegradable plug made from polymers such as hydroxypropyl methylcellulose (HPMC), polyethylene oxide, guar gum, or xanthan gum. Upon ingestion, gastrointestinal fluids begin to erode or hydrate the plug, and swelling generates internal pressure until the plug is expelled or ruptured, releasing the drug in a burst. The lag time can be fine-tuned by modifying the plug's thickness, hardness, polymer type, or by incorporating hydrophobic excipients to slow fluid ingress. Examples of such systems include Pulsincap®, which employs a hydrogel plug to control release timing; the Port® System, where a swellable plug seals a drug-filled capsule; and the Time Clock® System, which uses a wax or lipid coating that gradually dissolves[43]. Other designs, like press-coated tablets and three-pulse systems, layer the drug with time-delay barriers to create sequential bursts. These approaches are valuable in chronotherapy, for instance, enabling anti-asthmatic drugs to be released just before early morning bronchospasm or anti-inflammatory agents to act before

morning stiffness in arthritis. They are also widely used for colon-targeted drug delivery where high localized concentrations or protection from enzymatic degradation in the upper gastrointestinal tract is required[44].

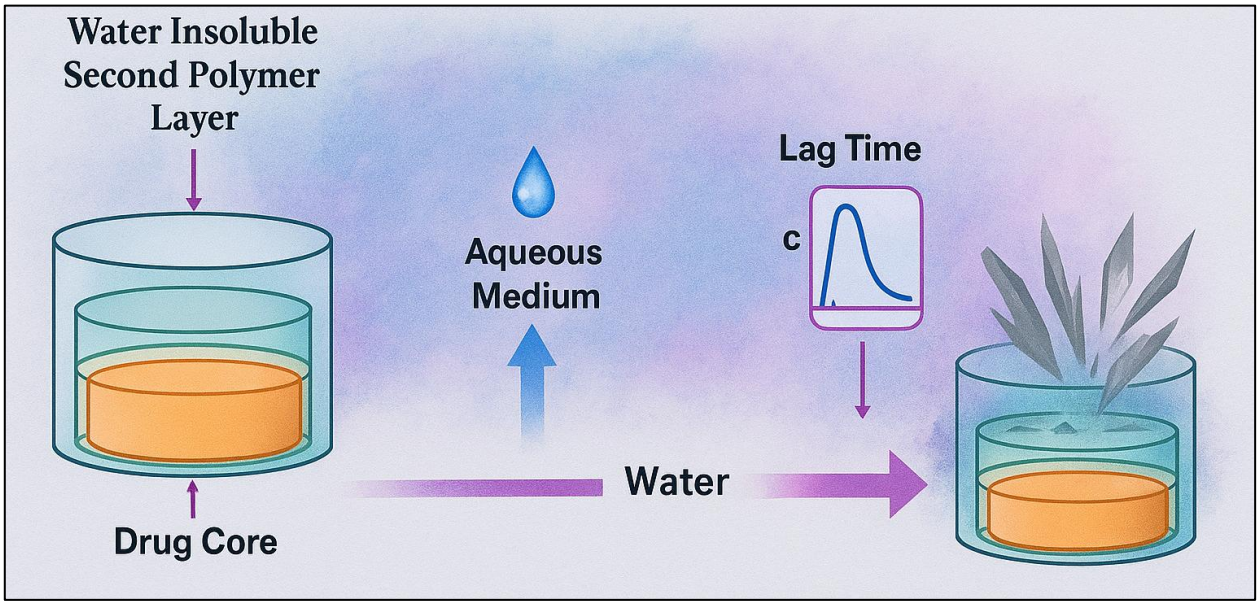

Figure 3: Chronotropic Pulsatile Release. This schematic illustrates a chronotherapeutic drug delivery approach where release timing aligns with the body's circadian rhythm. A press-coated tablet design enables lag-time-based release, optimizing treatment for conditions like asthma, arthritis, and hypertension that exhibit time-dependent symptom patterns.

2.1.2 Coated Systems

Coated systems for time-dependent drug delivery achieve delayed release by surrounding the drug core with specially designed polymer coatings that erode, dissolve, or rupture after a predetermined period in Figure 4. In contrast to pH-dependent coatings, these rely solely on the physical properties of the coating such as thickness, permeability, and erosion rate rather than the chemical environment of the gastrointestinal tract. Typically, the core is covered by an inner hydrophilic swellable layer and an outer water-insoluble layer made from materials such as ethylcellulose, cellulose acetate, or polyvinyl acetate[45]. As the dosage form travels through the GI tract, the outer layer slowly becomes permeable due to fluid penetration or mechanical abrasion. Once the outer coat is compromised, the inner hydrophilic layer swells or erodes, initiating drug release. The lag time before release can be precisely controlled by adjusting coating thickness, polymer blend ratios, the addition of plasticizers, and the use of pore-forming agents. Systems like the Chronotropic® design employ a swellable inner layer beneath an insoluble coating to program a fixed delay; GeoClock® tablets apply partial barrier layers to specific regions of a tablet surface to control release onset; and time-delay tablets use cellulose acetate films with pore formers to regulate water entry. Multi-particulate pellet systems coat each pellet individually to provide uniform release, while advanced designs such as sigmoidal release and dual-coating approaches allow for complex, multi-phase drug delivery profiles. These coated systems are highly versatile, enabling not only colon-specific drug release but also sophisticated chronotherapeutic schedules and combination therapies within a single dosage form, ultimately improving patient compliance, therapeutic efficacy, and safety[46].

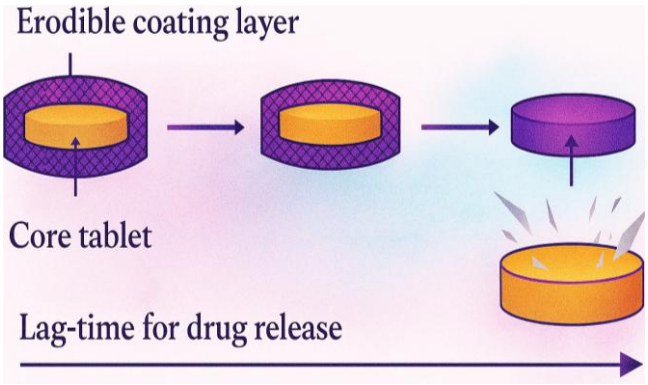

Figure 4: Coating-Based Drug Delivery System. The schematic illustrates a drug delivery system where an erodible coating layer surrounds the core tablet. During administration, the coating gradually erodes over a defined period, creating a lag time before the drug is released. This design enables controlled and delayed drug release, useful for chronotherapy and time-specific therapeutic applications.

2.3 Microbially Triggered Systems (Polysaccharide-Based Carriers)

The colon being a distinctive and highly complex ecosystem, with its enormous and diversified population of anaerobic bacteria, the so-called gut microbiota, the complex of microbial communities, is the focus of many physiological processes, such as fermentation of undigestible food substances and production of key vitamins.Notably, these colonic anaerobes have a formidable repertoire of enzymes, including several specialized enzymes not or scarcely found elsewhere in the GI tract[47]. These special enzymes include azoreduct Azoreductases are capable of creating azo bond cleavage, typically utilized in the manufacturing of creating products to be inert until contacting colon. This confers the advantage of selective arrival in the lower GI aside the activation. Similarly, glycosidases can break glycosidic bonds in a variety of compounds, including in some polymers used in drug coats or as conjugates in drugs. The ability to design drugs that cleavage at these specific enzyme substrates, in turn, enables the researchers in creating advanced delivery technologies that will not only endure in the quagmire of the upper GI tract but also be activated or released immediately they encounter these specific bacterial enzymes in the colon. The potential of the phenomenon is that it offers a dynamic method of effecting very localized drug delivery, a form that is invaluably useful in treating colonic disease, like inflammatory bowel disease, or to further increase the extent of uptake and absorption of a drug that would otherwise be degraded or decreasingly absorbed further along the digestive tract as indicated in Figure 5[48].

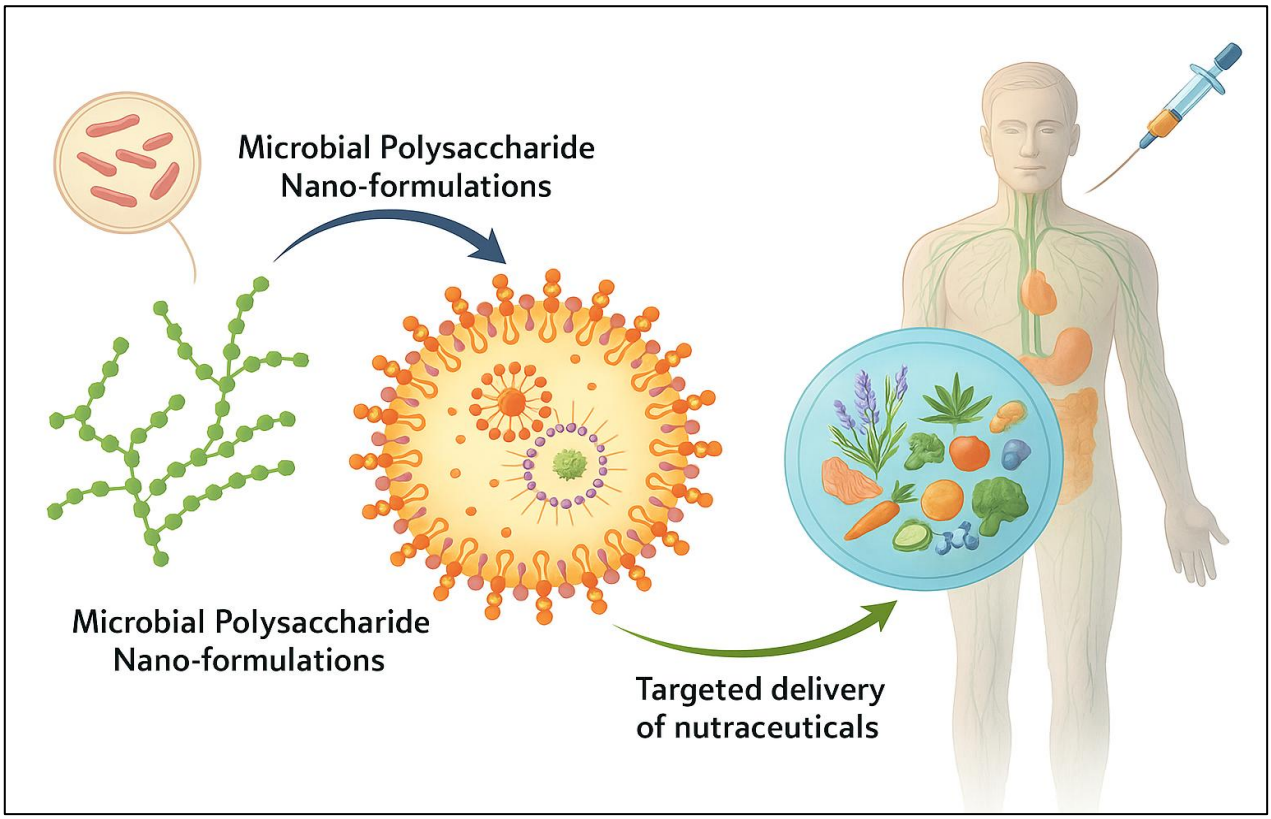

Figure 5: Microbially Triggered Systems (Polysaccharide-Based Carriers) Microbial polysaccharides are engineered into nano-formulations that encapsulate nutraceuticals, enabling their controlled and targeted delivery within the human body to enhance bioavailability and therapeutic efficacy.

2.3.1 Polysaccharides

Certain natural polymers, including pectin, chitosan, dextran and guar gum have recently become the hot targets of colon specific drug-delivery due to their ability to utilize the special colonic environment by exploiting colon specific targets to administer drugs. One major benefit of such biopolymers is the natural resistance to digestion and absorption in the upper gastrointestinal (GI) tract such as the stomach and the small intestine. This safeguards that drug delivery formulations embedded in these carriers will be stable as they enter the first, usually hostile, portions of the digestive tract, thus preventing premature drug release or degradation.Once they enter the colon however, these natural polymers are exposed to the massively diverse and anaerobic bacterial population that characterizes the colonic section of the GI tract. As discussed earlier, these colonic bacteria have a distinct and characteristic set of enzymes such as glycosidases, and other fermentative enzymes that can degrade a complex polysaccharide form of pectin, Dextran and Guar gum as also the chitin-based biopolymer chitosan. This process actually causes the erosion, or degradation of the polymer of the carrier by enzymatic processes used by the body or fermentation of the polymer carrier, which results in liberation of the drug directly into the lumen of the colon. This is a site specific delivery method to reduce the need of frequent administration in the treatment of colonic diseases, in this case, by directing high amounts of

therapeutic agent locally to sites of inflammation/disease. It also presents an excellent approach towards increasing the bioavailability of drugs that otherwise are unabsorbed or destroyed in the upper GI tract, since the relatively stable conditions of the colon, along with the increased durability are an ideal period in which the drug can be absorbed after being released by the enzymes.

2.3.2 Azo Polymers

Of the newer approaches of highly selective drug delivery to the colon, those involving the use of synthetic polymers in conjunction with azo bond (-N=N-) are notably a clean and highly workable prospect. The targeted polymers are able to withstand acidic conditions within the stomach and the working environment of the small intestine, where there are enzymes. Such inherent stability insures that the drug being encapsulated in or conjugated to such polymers would not be prematurely released or degraded during its transit through these early segments[49].It is in the sheer brilliance of this means to take advantage of a very distinctive capability of the colonic microbiota. Anaerobic bacteria which are profusely present in colon have a particular group of enzymes known as azoreductases. The enzymes are essentially excluded in the upper GI tract and human tissues; thus, they are a highly specific colonic biomarker. Upon arrival of a drug delivery system comprising of an azo-bond polymer in the colon, these azoreductase enzyme selectively cleaves the azo-bond.1 This enzyme-mediated degradation in turn initiates the breakdown or degradation of the polymer itself, resulting in a highly specific, local release of an entrapped or conjugated drug. This rapid targeted release process is invaluable toward treating localized diseases of the colon (i.e., inflammatory bowel disease) by getting the therapeutic agent up to high levels in the vicinity of an inflamed area with little systemic exposure and resultant side effects. Moreover, it also provides a controllable approach to the enhancement of the bioavailability of drugs which are better absorbed in the colon or need protection against degradation within the upper size of the intestines[50].

2.4 Enzyme-Specific Prodrugs

To obtain a very specific drug delivery into the colon and reduce systemic exposure, one can complicate the tactic by altering an active drug to an inactive prodrug using a chemical process shown in Figure 6[51]. Such transformation is accomplished by means of the covalent binding of therapeutic agent and carrier molecule through a specific chemical bond that can only be resolvable by the distinctive enzymatic condition of the colonic microbiota. The fundamental concept here applies the fact that a system could be designed whereby the active drug is Masked or inert until it reaches the lower GI tract where it is planned to work. Nevertheless, when the prodrug enters the colon, it encounters the abundant and heterogeneous population of anaerobic bacteria that contains unique enzymes that other parts of the human body cannot be found in large amounts. These colonic bacterial enzymes have the ability of breaking the well-designed bond between the active drug and the carrier molecule[52]. One prominent example of recent-acting analog-based decomposition mechanism is that of a anti-drug known as balsalazide, applied in the therapeutics of inflammatory bowel disease. Balsalazide is connected chemically through an azo bond to a inert carrier. The azoreductase enzymes colon produced by colonic bacteria specifically cleave this azo link and in so doing releases the potential anti-inflammatory substance, 5-aminosalicylic acid (5-ASA), directly to the inflamed spot. Correspondingly, by virtue of this strategy, local drug levels are very high, from which, at the same time, the maximum therapeutic index on colonic disease can be achieved, together with the minimum dose-related systemic absorption and the accompanying risk of the undesirable sequelae, presenting a highly optimum and specific form of colon-directed therapy[53].

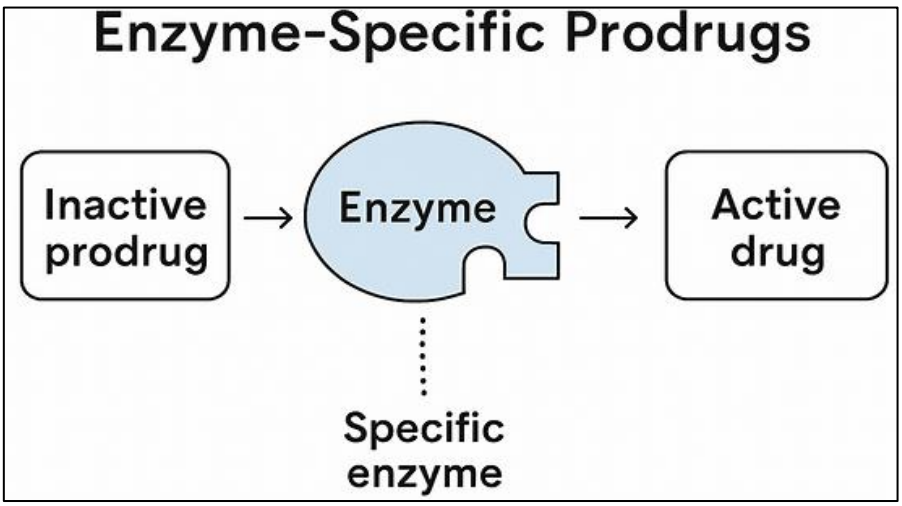

Figure 6: Mechanism of Enzyme-Specific Prodrug Activation. This diagram illustrates how an inactive prodrug is selectively converted into its active form by a specific enzyme. The process enhances drug targeting, minimizes systemic toxicity, and is commonly used in precision medicine strategies such as cancer therapy. The enzyme acts as a biological trigger, ensuring activation only in desired tissues or cellular environments.

2.5 Membrane Transporter-Targeted Prodrugs

Further than merely the liberation of a drug in the colon another improved method of the absorption of a drug exploits the availability of certain types of transporters on the colonic mucosal cells. Such systems of drug delivery are called "carrier-mediated drug delivery" and are developed to take advantage of the machinery of the intestine already adapted to absorb nutrients (through transporters) more efficiently.The colon mucosa, and other regions of the intestine, express a number of transporter proteins, which may include, e.g., oligopeptide transporters (e.g., PepT1)[54]. Such transporters are naturally implicated in digestive absorption of small peptides (the di- and tri-peptides) of the dietary protein. Through chemical conversion of a drug to a prodrug, which shares a structural similarity with these natural substrates, it is possible to be recognised and actively transported across the colonic epithelial cells. Such a mimicry of the substrate enables the prodrug to avoid the slower diffusion mechanism of passive absorption, resulting in greatly increased absorption in the colon[55]. After getting inside the cells, the prodrug gets converted to its active form, generally with those enzymes within the cells and then gets released into the bloodstream. It is especially useful with those drugs in which there is poor permeability intrinsically or low bioavailability when orally administrated because of low passive absorption. This approach can combine exploiting these particular transporters to increase the drug absorption as well as providing a degree of targeting since these transporters may be more concentrated or active in one region of the colon, or their expression may vary in certain disease, increasing the control of the added specificity to drug delivery in Figure 7[56].

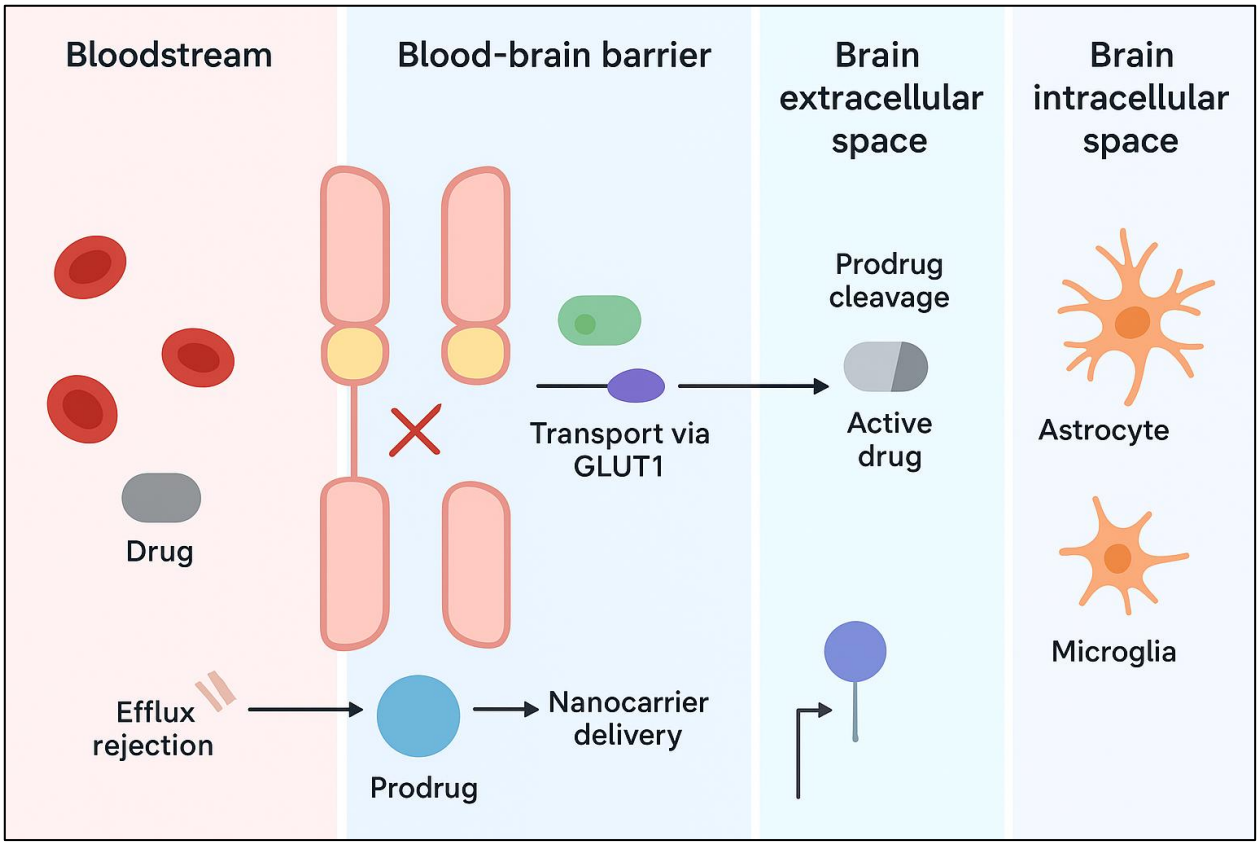

Figure 7: Membrane Transporter Targeted Prodrug Delivery Across the Blood–Brain Barrier Schematic representation of a prodrug strategy designed to enhance central nervous system (CNS) drug delivery. The bloodstream contains both conventional drug molecules and a transporter-targeted prodrug. Conventional drugs are unable to cross the blood brain barrier (BBB) and are rejected at the endothelial tight junctions. In contrast, the prodrug is recognized by specific influx transporters within the BBB endothelium, enabling its translocation into the brain extracellular space. The prodrug then traverses the parenchymal barrier via additional influx transporters to reach the brain intracellular compartment. Within target cells — including microglia, astrocytes, and neurons enzymatic activation cleaves the promoiety, releasing the active drug. Efflux transporters at the BBB are also depicted, illustrating their role in limiting brain penetration of non-targeted compounds.

2.6 Pressure-Triggered Capsule Systems

Other interesting areas of application may include the relatively high intraluminal pressure of the colon, which could be exploited by making a system that works on pressure stimulation or is activated mechanically. Although there is some variability of pressures over time in the small intestine, rhythmic contractions of the small intestine, the muscular activity of the colon during mass movements and defecation can produce much greater and more prolonged changes in intraluminal pressure[57]. This difference in pressure can be cleverly utilized to formulate oral dosage forms that have specificity to the

colon. Consider a capsule or a tablet that is designed, with a seal that is sensitive to pressure, or a plug. Such a seal is carefully adjusted withstand the reduced pressures in the stomach and small bowel and avoid the early release of the drug. But when the capsule moves to the colon and when influences of the high intraluminal pressure are encountered this force applied on the sensitive seal or plug becomes enough to cause them to rupture. The resulting mechanism of a mechanical breach results in a swift burst release of the encapsulated drug directly into the colonic lumen shown in Figure 8[58]. This type of system has the following benefits linked to the colon-specific delivery of drugs. It offers a highly localized release making sure that the medication reaches the same area where the drugs are needed to address colonic disorders such as inflammatory bowel disease or colorectal cancer. It also avoids system wide exposure and hence minimizes chances of side effects[59]. Additionally, in case of pressure activated systems as compared to pH-dependent, time-dependent systems, individual differences in GI pH levels or transit time may cause some variability in drug release; however, pressure-activated systems are less prone to these effects. These pressure-sensitive systems provide a strong and efficient way of target drug delivery by capitalizing on the different biomechanical forces in the colon[60].

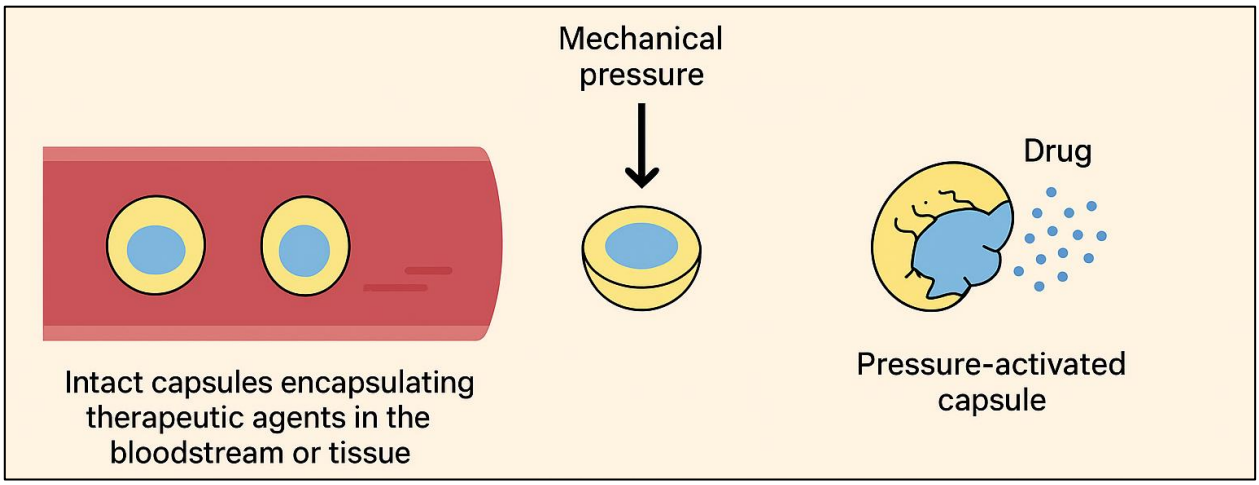

Figure 8: Pressure-Triggered Capsule Systems for Targeted Drug Delivery Schematic representation of pressure-responsive capsule technology designed to achieve site-specific and controlled drug release. The bloodstream or tissue environment contains intact capsules encapsulating therapeutic agents. Under normal physiological conditions, the capsule shell remains stable, preventing premature release. When the capsule encounters regions of altered mechanical pressure such as tumor microenvironments, inflamed tissues, or vascular constrictions, the applied force disrupts the capsule membrane. This mechanical trigger causes rupture or pore formation, leading to the rapid and localized release of the encapsulated drug. Such systems minimize systemic exposure, enhance local drug concentration, and improve therapeutic efficacy while reducing side effects.

2.7 Osmotically-Controlled Systems (e.g., OROS-CT)

The Oral Osmotic Release System for Colon Targeting (OROS-CT) is a vintage and an effective example of an ideal complex drug delivery platform to achieve a definite drug release requirement specifically in the lower gastrointestinal tract in Figure 9[61]. It is based on the principles of osmosis which offers a highly controlled and reproducible drug release profile, conveniently following a specific lag period.It is constructed in a way that it has a solid formulation of drugs coated with a semipermeable membrane of which water could pass through and remain impermeable to the drug. In The Oral Osmotic Release System for Colon Targeting (OROS-CT) is a vintage and an effective example of an ideal complex drug delivery platform to achieve a definite drug release requirement specifically in the lower gastrointestinal tract[62]. It is based on the principles of osmosis which offers a highly controlled and reproducible drug release profile, conveniently following a specific lag period. It is constructed in a way that it has a solid formulation of drugs coated with a semipermeable membrane of which water could pass through and remain impermeable to the drug. After this pH-sensitive coating dissolves, the semipermeable membrane is exposed to the aqueous environment of the GI tract and water then comes to permeate selectively into the core, driven by the high-osmotic pressure formed by the soluble osmotic agent. As more water enters, it builds up to an increasing internal hydrostatic pressure within the core. The resultant pressure forces the drug along with the osmotic agent, out a carefully fabricated, laser-drilled opening in the semipermeable membrane. There is a significant lag time. This delay is exactly designed in such a way that, the drug is only released into the body when the system has undergone a sequence of releases all the way up to the colon shown in Figure 9. This is what makes OROS-CT the drug therapy of choice in chronotherapeutic, when the release of the drug must be linked with the particular time of the day or delivering the drug directly to the colon to act locally or granting better absorption, and also give a consistent and controlled release rate[61].

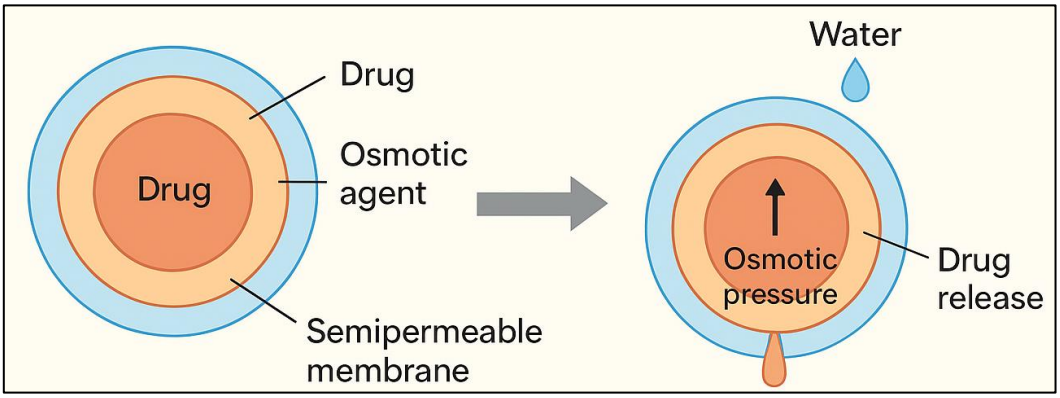

Figure 9: Osmotically Controlled Systems for Sustained Drug Delivery Schematic representation of an osmotically controlled oral drug delivery system designed to provide precise and prolonged release. The system consists of a core containing drug and osmotic agents, surrounded by a semipermeable membrane. When exposed to gastrointestinal fluids, water enters the core through the semipermeable wall due to osmotic pressure. This influx of water dissolves the drug and increases internal pressure, which forces the drug solution or suspension out through a pre-formed delivery orifice at a controlled rate. The release mechanism is independent of pH or gastrointestinal motility, allowing for predictable and sustained plasma drug concentrations. These systems enhance patient compliance, reduce dosing frequency, and improve therapeutic outcomes.

2.8 CODESSM (Combined Approach)

The CODES(TM) (Colon-Targeted Delivery System) is an extremely advanced and synergistic site-specific drug delivery system which shown in Figure 10 , a clever system utilizing two different mechanisms of drug release, one pH-dependent dissolution and the other microbial biodegradation[63]. The application of this dual-trigger system allows an extremely accurate and predictable delivery of the drug to areas of the colon, bypassing preceding sections of the gastrointestinal (GI) tract. The aforementioned CODESTM apparatus is generally comprised of a capsule containing the drug that is then encircled by two protective coatings. It is made up of an outer layer of a pH-sensitive polymer, in most cases Eudragit R S. Such essential coating is designed to stay alive under the low pH condition of the stomach (pH 1.5-3.5) and also in the less acids, yet relatively low pH conditions in the small intestine (pH 6.0-7.4)[64]. Its stability in their transport through these upper GI segments protects the drug against premature liberation and degradation. The Eudragit S coating only dissolves in the more alkaline conditions of the distal small intestine (pH > 7.0) and consequently in the colon, (pH 7.0-7.4).Once in its alkaline environment, the dissolved Eudragit S coating exposes an inner layer made of a naturally occurring polysaccharide, like dextran[65]. This polysaccharide layer which has passed through the upper G.I. now faces the colonic microbiota with its distinctive enzyme machinery. The resulting high numbers of anaerobic bacteria that inhabit the colon have certain enzymes (e.g. glycosidases) that are able to ferment and breakdown these complex polysaccharides. The dissolution of the dextran gel layer which occurs as a result of the enzymatic attack then causes the encapsulated drug to be released.The CODES™ system therefore provides increased specificity and reliability in colon targeting by combining both a pH-dependent lock (in this case Eudragit S) and a microbe-activated release mechanism (in this case dextran digestion)[66]. Such multiple coatings creates a strong platform of localized delivery of drugs to the colon, which is highly beneficial in treating localized colonic diseases such as inflammatory bowel disease, increasing the bioavailability of drugs that are ideally absorbed in the colon, or creates the possibility of chronotherapeutic applications where precise temporal and spatial release of drugs is essential[67].

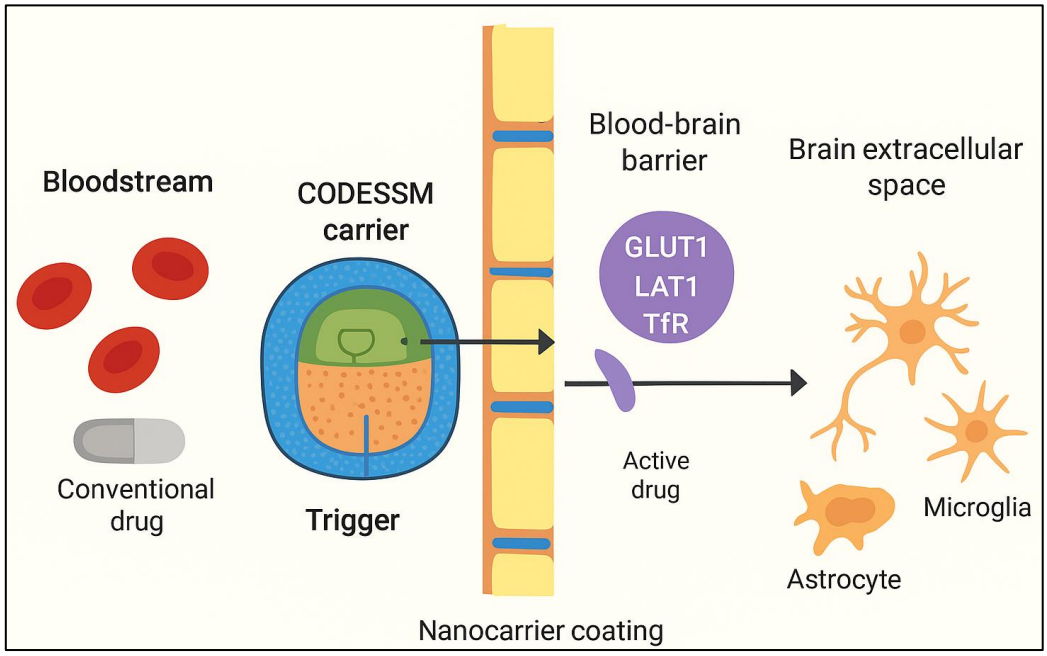

Figure 10: CODESSM (Combined Approach) for Targeted Drug Delivery Across the Blood–Brain Barrier Schematic representation of the CODESSM carrier system designed to overcome the restrictive nature of the blood–brain barrier (BBB). Conventional drugs in the bloodstream are unable to cross the BBB and are rejected at endothelial tight junctions. In contrast, the CODESSM carrier integrates a nanocarrier coating, a prodrug promoiety, and an osmotic/trigger-based release core. This multi-layered system is recognized by specific influx transporters (GLUT1, LAT1, TfR) within the BBB endothelium, enabling translocation into the brain extracellular space. Once inside, the trigger mechanism ensures controlled release of the active drug, which subsequently reaches target cells including neurons, astrocytes, and microglia. This combined approach maximizes brain penetration, enhances therapeutic efficacy, and minimizes systemic side effects.

3. Polymers and materials in CDDS

When it comes to designing Colon-Targeted Drug Delivery Systems (CDDS), the choice of polymers and materials matter strategically because their physiochemical properties determine the time and the place where the release of drugs occurs. Such materials can be broadly classified according to their behaviour under the different conditions of the gastrointestinal (GI) tract, especially under pH, and critical activities.

3.1 Enteric Coating Polymers and Their Dissolution pH (pH-Dependent Synthetic Polymers)

Enteric coating polymers are synthetic materials designed to protect drugs from the acidic gastric environment and release them at specific alkaline pH levels in the intestine or colon in Table no 3 . This mechanism is essential for delivering acid-labile drugs, preventing gastric irritation, and targeting drug release to specific intestinal regions.

Table 3: pH-Dependent Synthetic Enteric Coating Polymers

Polymer	Dissolution pH	Mechanism	Applications	Ref
Eudragit® L Series	> 6.0	Methacrylic acid copolymer; dissolves in upper/mid-small intestine.	Protects acid-labile drugs; improves absorption in small intestine.	38
Eudragit® S Series	> 7.0	Dissolves in distal small intestine and colon.	Local colonic delivery for IBD, CRC.	68
Cellulose Acetate Phthalate (CAP)	> 6.0	Acid-resistant cellulose ester; dissolves in small intestine.	Enteric tablets for delayed small intestinal release.	69
Polyvinyl Acetate Phthalate (PVAP)	> 5.5–6.0	Flexible, acid-resistant coating; dissolves in intestine.	Protects acid-sensitive drugs; enhances bioavailability.	70
Hydroxypropyl Methylcellulose Phthalate (HPMCP)	> 5.0	Dissolves earlier in small intestine; dissolution varies by grade.	Flexible targeting for upper small intestine drugs.	71

3.2 Natural Polymers for Microbial Degradation (Microbially-Triggered Polymers)

These polymers are of natural origin and remain intact through the stomach and small intestine but undergo enzymatic degradation in the colon by specific bacterial enzymes Table no 4 . This approach exploits the high density of anaerobic microflora in the large intestine, allowing localized or systemic delivery of drugs that are unstable or poorly absorbed in the upper GI tract.

Table 4: Natural Microbially-Degradable Polymers

Polymer	Source	Degrading Enzyme(s)	Mechanism	Applications	Ref
Pectin	Fruit cell walls	Pectinolytic enzymes (glycosidases)	Passes undigested to colon; degraded by bacterial enzymes.	Local colonic delivery for IBD, CRC.	50
Chitosan	Chitin from crustacean shells	Chitosanases	Unabsorbed in upper GI; degraded in colon.	Controlled colon-specific release.	72
Guar Gum	Guar bean endosperm	β-Mannanases, galactosidases	Fermented by colonic bacteria after upper GI transit.	Sustained colon release for anti-inflammatory drugs.	72
Dextran	Bacterial fermentation of sugars	Dextranases	Stable in upper GI; degraded by colonic enzymes.	Reliable colon-specific drug release.	50
Inulin	Chicory root, Jerusalem artichoke	Inulinases	Fermented by bifidobacteria in colon.	Prebiotic-linked targeted delivery systems.	50

3.3 Synthetic Carriers for Chrono-Release (Time-Dependent Synthetic Polymers)

These synthetic carriers are engineered to release drugs after a predetermined lag period, independent of pH or enzymatic environment in Table 5. They are crucial in chronotherapy, where drug release is synchronized with the body's circadian rhythms or disease symptom patterns.

Table 5: Synthetic Time-Controlled Carriers

Polymer / Carrier	Chemical Type	Mechanism of Lag Time Control	Applications	Ref
Ethylcellulose	Water-insoluble cellulose ether	Semi-permeable barrier slows water ingress; controls delay.	Press-coated tablets, pellet coatings for colon release.	73
Cellulose Acetate	Cellulose ester	Low permeability; maintains lag time across pH range.	Osmotic pump systems, time-delay coatings.	74
Polyvinyl Acetate (PVAc)	Synthetic vinyl polymer	pH-independent barrier; slows fluid penetration.	Multiparticulate pellet coatings.	75
Polyethylene Oxide (PEO)	Synthetic polyether	Swells to expel plug or rupture coating after hydration.	Pulsatile-release capsules (e.g., Pulsincap®).	76
Eudragit® RS	Methacrylate copolymer (low permeability)	Controls long lag times by slow water uptake.	Chronotherapeutic coatings.	38
Eudragit® RL	Methacrylate copolymer (high permeability)	Blended with RS to adjust permeability and release time.	Multi-layer chrono-release systems.	38
Cellulose Acetate Butyrate (CAB)	Cellulose ester	Slowly erodes in intestinal fluid to initiate release.	Hybrid time- and pH-independent systems.	74

3.4 Role of Plasticizers and Layering Techniques

The use of polymer coatings is an important step in the art and science of formulating pharmaceuticals, especially the manufacture of controlled-release dosage forms. To further make these coatings perform optimally, not only regarding their physical characteristics but also regarding the drug release regulation by the coating, certain additives and exact application methods cannot be overlooked[77]. One of the main groups of additives that are used in polymer coating is called plasticizers, and it includes triethyl citrate and dibutyl phthalate. Although polymers contain the material of desired barrier or release modulating properties, processed as-is the material may be brittle or challenging to work with. Plasticizers are organic organic or inorganic molecules, of low molecular weight, which are used to supplement the flexibility of the polymer, its brittleness and vice versa its general processability[78]. Their action is to weaken the intermolecular forces that hold polymer chains together to enable greater mobility between them such that a coating can become less brittle and less likely to undergo cracking or peeling. This heightened malleability is of vital importance towards the integrity of the coating during the manufacturing process (e.g. during compression or handling) as well as during its passage through the dynamic, mechanically stressed nature of the gastrointestinal tract. Many advanced polymer-coated systems would not be possible without plasticizers[79]. Polymer-coating applications are extremely delicate and precise processes and must be very well controlled and reproducible to enhance consistent drug release profiles. This is mostly done through the layering, where spray coating is an excellent example. During spray coating, a solution or suspension of the polymer, typically with plasticizers and other excipients, are atomized into droplets and subsequently uniformly sprayed onto the surface of pills or other drug-holding cores (e.g., tablets or pellets or granules) which tumble in a coating pan or fluid bed[79]. The thin film on the substrate is left by the solvent in the spray and remains uniform in a thin layer. This is done thoroughly under control with such parameters as spraying rate, atomization air pressure, dry air temperature, and pan speed meticulously monitored and maintained. The fact that multiple and distinct layers may be implemented each with a defined polymer or thickness enables the possibility of creating complex release profile as needed in pulsatile or time-delay controlled drug delivery. The stability of the dosage form allowed by spraying makes it such that individual units of the dosage all have the same and predictable release profile, a parameter that is essential to therapeutic reach and to the safety of the patients[80].

4. Formulation and Design Considerations

The development of colon-targeted drug delivery system (CDDS) has been a complicated task, not without various physiological and formulation complexities, which need to be given much thought. The complex and extremely variable design of the gastrointestinal (GI) tract requires strong and versatile design solutions.

4.1 GI Transit Time and pH Variability

One of the major impediments to oral drug delivery (at least in the context of colon targeting) is the natural variation of GI transit time and pH across the digestive tract. These parameters are not wholly fixed, and they can take a significant variation according to the influence of various factors. These parameters include the state of food (fasting or fed status), the patient age (infants and elderly will differentially have variable GI motility), gender and the disease condition that that specific individual has (i.e. irritable bowel syndrome, or diabetes gastroparesis or inflammatory bowel disease) are all factors that can make a significant contribution to the rate of passage of a dosage form across the GI tract and pH of the various regions. This difference is one of the greatest problems due to the fact that it can lead to release of drugs that cannot be controlled. In an example of a colonic-release system that may encounter an abnormally high transit time it may exit the body before performing its business. Conversely, such a delayed passage can lead to premature discharge into the small bowel in the event that the system is constituted of time machine. Similarly, change in pH may pre-dispersely or overly disperse pH-sensitive coating and render it unable to be precisely targeted[81].

4.2 Role of Colonic Microbiota and Enzymes

Even though the colonic microbiota creates a unique enzymatic environment to favorable drug interactions (e.g., intestinal polysaccharides digestion or azo bond cleavage), its inherent variability introduces an additional dimension of complexity. The composition of gut microbiota is dramatically different in people due to such factors as diet, genetics, geographical location, use of antibiotics, and disease[48]. Inter-individual differences like these suggest that enzyme activities (e.g., azoreductases or glycosidase levels), capable of dissolving polysaccharide-based carriers, can be vastly different. Consequently, a drug release profile that might be optimal in one subject taking a drug based on microbial degradation may not be the same in the second subject resulting in unpredictable drug release rate and bioavailability[82].

4.3 Drug Solubility and Stability Issues in GI Tract

In addition to the delivery system, the drug substance should also be of certain criteria. Once the protective formulation is removed in the GI environment, the drug should have enough stability in the environment. Although effective delivery to the colon is achieved, provided that the drug can be degraded by residual enzymes in the colon or other microbial activity it may suffer, its effectiveness will be reduced[80]. Besides, the drug should provide excellent solubility so that it can be absorbed once it becomes free. Although the colon provides a long residence time, there is less volume of fluid and surface area of passive absorption than that of the small intestine. Hence, low inherently soluble drugs may also not easily achieve absorption despite their accurate colon release[83].

4.4 Criteria for Drug and Polymer Selection

Given these challenges, the selection of both the drug candidate and the polymers for the CDDS is critical and follows stringent criteria shown in Figure 11

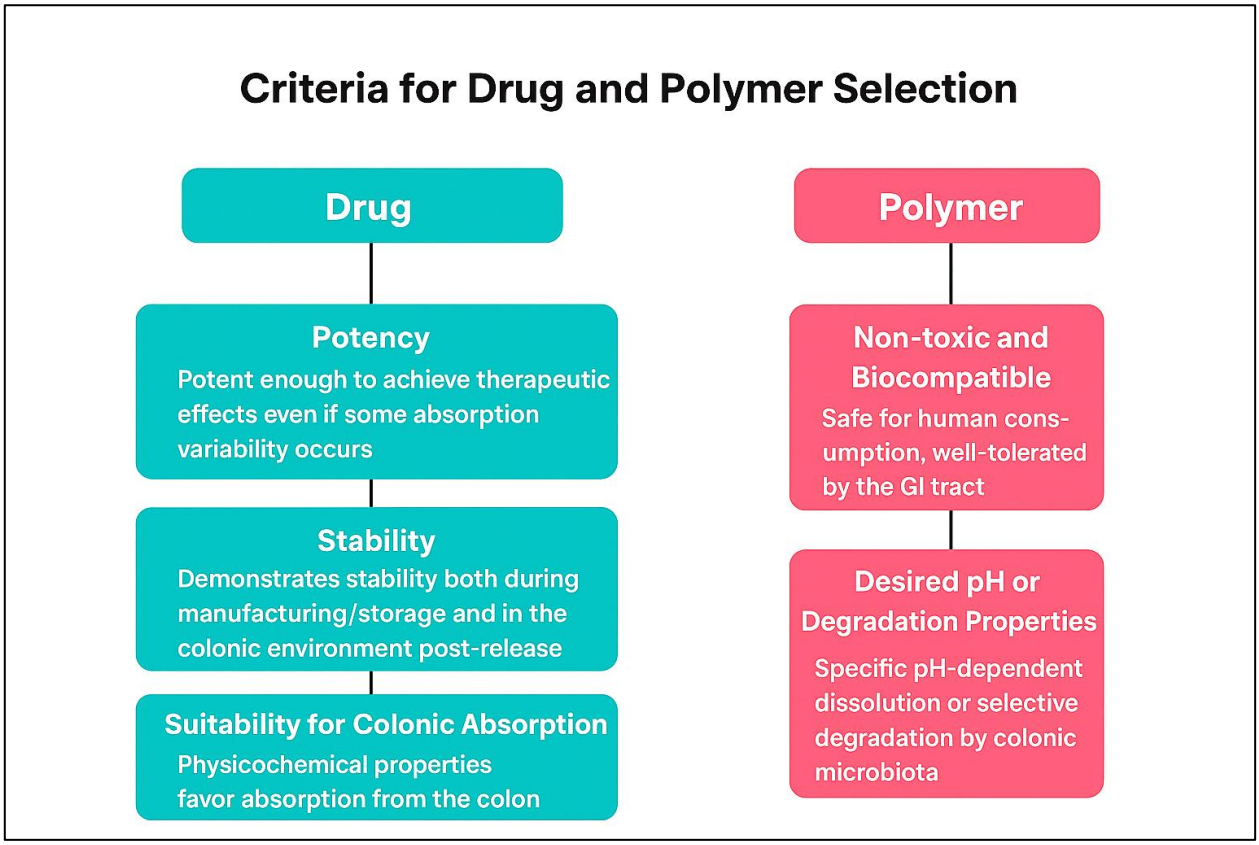

Figure 11: Criteria for Drug and Polymer Selection in Colon-Targeted Drug Delivery Systems The flowchart shows the criteria for drug and polymer selection in colon-targeted drug delivery systems (CDDS). The diagram highlights essential drug factors such as potency, stability, and suitability for colonic absorption, along with critical polymer attributes including biocompatibility, non-toxicity, and pH-sensitive or microbially degradable properties. Together, these ensure precise spatial and temporal release of drugs in the colon for effective therapeutic outcomes[72].

5. Evaluation of Colon-Targeted Systems

In the development of a colon targeted drug delivery system (CDDS) as a pharmaceutical formulation, effective in vitro evaluation plans are required to inform and assess anticipated formulation behavior before advancing to the more complex and costly in vivo testing. Among the most significant tests is the dissolution testing which is more so when it is designed to be dynamic and variable as it is in the gastrointestinal (GI) track.A sequential pH dissolution test is one of the most informative tests that aims at mesmingling passage of an orally formulated drug through the different parts of the GI track. It is performed under special equipment of dissolution (e.g. USP dissolution apparatus 1, 2 or 3) and is a sequence of sequential passage to the pH of the transition in time, consistent with the pH transition in the human body as exchanged in the stomach to the colon. characterizes the key methods of the working quality of such delivery systems[3].

5.1 *In Vitro* Evaluation Methods:

5.1.1 Gastric Phase Simulation:

Drug formulation is first treated with an acidic medium, the pH of which is generally 1.2 (which is the gastric fluid mimic) and is subjected to drug exposure as an acidic environment (taking around 2 hours). This stage is important in determining the integrity of PH sensitive coating or stability of the drugs in the stomach. A well-designed colon-targeted system would result in minimal to no drug release during this acidic exposure thus, symbolizing an effective prevention of the drug degradation in the gastrointestinal[84].

5.1.2 Small Intestine Phase Simulation:

After the gastric phase, the medium is next transferred to some neutral or slightly alkaline medium (usually at pH 6.8, similar to intestinal fluid), and kept there about 3 hours. This is the transition that represents the movement of the drug to the small intestine. Under such a phase, the release of drugs should be minimal or at best very minimum in case the system is designed in such a way that they are released colonially (e.g., the use of Eudragit S or a time-delay delivery). Nevertheless, in case that the system is programmed to be released in the small intestine (e.g., by Eudragit L or polymer with pH > 5.0), drug release would be considerable at this point[85].

5.1.3 Colonic Phase Simulation:

Lastly to determine colon-specific release, the medium is switched once again to a colonic medium which in most cases is pH 7.4. Requests to include more advanced simulations at this stage can be carried out (such as inclusion of microbial enzymes (e.g., azoreductase, glycosidases), or even fecal slurries of healthy donors). Deliberately adding enzymes or fecal material can be useful when assessing systems based on microbial degradation (e.g. systems based on polysaccharide carriers or azo-bond prodrugs). The controlled and substantial drug release of the well-designed colon directed formulation in this final stage will demonstrate that it is indeed the drug released in the desired target area, and it verifies the planning of a protective coating. Subsequently designed colon-directed tests, such as the sequential pH dissolution test, allow investigators to reference the regulatory conduct of their CDDS formulations, the safety of protective coatings, and the anticipation of premature or targeted drug discharge in different parts of the GI tract. The method is an important screening tool that saves costly time on large-scale in vivo tests. Although these in vitro dissolution procedures give invaluable initial information, final confirmation of a colon-targeted drug delivery system (CDDS) requires in vivo experimentation to acknowledge the complicated physiology of bodily systems of a living being. These kinds of experiments usually include animal models and modern methods of imaging[86].

5.2 *In Vivo* Animal Models

Various animal species serve as valuable surrogates for human gastrointestinal physiology in CDDS research.

5.2.1 Rats and Rabbits:

Smaller animals have been used often in initial stages of research because they are relatively cheaper, easy to handle and have pre-determined protocols. They are advantageous at initial studies of drug release profiles, absorption features, and the integrity of the delivery system, as a whole, in a biological environment. Their GI physiology however, specifically their transit times and the microbial composition thereof can vary considerably with a human being and hence their direct translatability of result is restricted in predicting human efficacy[87].

5.2.2 Dogs:

Similar to human GI tract anatomy and physiology, in particular, gastric emptying and small bowel transit times are more similar in dogs than in smaller animal models, such as rats. This renders them very useful in evaluating time-and pH- dependent discretionary releases[88]v. Later-stage preclinical development usually incorporates the use of dogs where data on the release kinetics and absorption of drugs is more robust and within a system that better predicts the human response. In spite of the strong points, inter-species difference in colonic microbial flora and information on general GI motility also needs close attention when inference to human beings is made[89].

5.3 Gamma Scintigraphy:

Gamma Scintigraphy is a strong and most commonly used method to non-invasively monitor passage of an oral dosage form through the GI tract in real-time in these animal models and subsequently in human studies.

5.3.1 Mechanism:

Such an approach includes the introduction of a small, non-toxic dose of a radiolabel (ex: Technetium-99m) directly into drug formulation or inert core of the delivery system. The radiolabel is capable of generating gamma rays that can be measured exteriorly, with a gamma camera[90].

5.3.2 Real-Time Data:

The gamma camera acquires images at intervals that have been predetermined as radiolabeled formulation passes through the GI tract. Such images present quantitative real-time data on the exact location of the dosage form at any time. Its progress can be traced by scientists through the small intestine and most importantly through the colon having started in the stomach[91].

5.3.3 Insights into Release Site:

With the observance of loss of the radiolabel into the dosage form (denoting drug release) and its position, gamma scintigraphy allows specifying the specific point of drug release. In another example, should a colon-specific system be created that should release its contents in the large intestine, the method can check whether the radiolabel disperses out of the formulation only once it reaches the colon[92].

5.3.4 Assessment of Integrity and Lag Time:

Gamma scintigraphy plays an incalculable role in the verification of integrity of coatings and accuracy of programmed lag times. It is able to pick up early release of drug in the upper GI tract or verify that the system has not disintegrated until desirable colonic localization site. This optical, non-invasive evidence is imperative in supporting the work in proving the postulates of the design of CDDS, as well as correlating in vitro actions with in vivo behavior.

5.4 Evaluation of Coating Integrity and Lag Time

One such method of invaluable use in characterization and quality control of the polymer-coated drug delivery system is the electron microscopy especially Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). The fact it gives high resolution images enables researchers to carefully analyze the physical parameters of these vital coatings before and after exposure to several environmental challenges, which in this case, is in vitro dissolution.Electron microscopy is employed to accurately determine the integrity and thickness of the polymer coating. SEM, as an example, may easily give you sufficient topographical data on the surface of the coating and allow you to identify any surface features such as imperfections, cracks, pores or non-uniformity that may be interfering with the protective aspect of the coating, or add or

remove any drug release characteristics[93]. Replica of the coated dosage form is also easily prepared, and as such, SEM can be utilized to measure the polymer layer thickness directly. This is vital since in most of the controlled-release systems (such as those that depend on erosion or swelling), the lag time (or the rate of drug release) simply depends on the thickness of the coating[94]. Reproducible results require accurate coating consistency batch to batch. The use of electron microscopies can be even more essential after an in vitro dissolution test as it is possible to view drug release mechanism and the action of a polymer coating in terms of a simulated physiological environment. Provided there are samples removed at each stage of a sequential pH dissolution test over time (e.g., after the gastric phase, the small intestinal phase, and the colonic phase), a researcher can observe the time-based transformation that occurs in the polymer coating[95]. In clear cases, SEM may indicate whether the coatings have survived or crashed in the acidic media, followed by their eventual swelling, crumbling or breaking, in the specified pH of interest. In systems that utilize microbial degradation, electron microscopy may be used to document the morphological changes (e.g., pitting, erosion, or total disintegration) in the polymer structure in response to enzymatic activity thus visually demonstrating polymer degradation. In other words, electron microscopy provides concrete evidence to supplement dissolution data. It assists in validating that a coating performed as expected e.g. staying in place where needed and breaking down or degrading in exactly the target environment. Such a microscopic study is crucial in the aspects of the most efficient design of the formulation, root cause troubleshooting of problems, and consistent robustness and predictability of the new drug delivery systems with advanced targeting[96].

6. Marketed CDDS Products and Commercial Insight

Several marketed Chronotherapeutic Drug Delivery Systems (CDDS) are designed to improve site-specific delivery and therapeutic outcomes, particularly for gastrointestinal disorders. These systems utilize different mechanisms such as pH-dependent polymers, time-dependent release coatings, or microbially triggered prodrugs to ensure the drug is released at the desired site in the gastrointestinal tract shown in Table 6.

Table 6: Mechanism-Based Comparison Table

Product	Drug	Mechanism	Target Site	Ref
Asacol®	Mesalamine	pH-Dependent (Eudragit S)	Colon	97
Lialda®	Mesalamine	pH- and Time-Dependent	Colon	98
Budenofalk®	Budesonide	pH-Dependent	Ileum, Colon	99
Entocort® EC	Budesonide	pH-Dependent	Small Intestine, Colon	100
Balsalazide	Mesalamine Prodrug	Microbially Triggered	Colon	101

7 Challenges in Translation from Lab to Market

The process of making any new pharmaceutical product to the market, regardless of its complexity, such as a colon-targeted drug delivery system (CDDS) is a long, hard trail with many major obstacles that go well beyond the initial scientific discovery and formulation process. The main challenges here include the fact that it is very expensive to carry out clinical trials, there are complex regulations, and that there is an element of unpredictability in the human body.

7.1 The High Cost of Clinical Trials

The costly and long part of drug development is clinical trials. In the case of CDDS, these trials have to reveal not only the drug safety and efficacy but also unambiguously prove that the system indeed delivers drug to the colon as designed and that it is released in an unpredictable manner. This usually requires special, non-invasive imaging tools such as gamma scintigraphy on humans and further complicates and increases the cost. Research should include large enough patient cohorts to factor in the inter-individual variation in GI transit, pH and microbiome composition each of which may impact drug release and absorption. Unexpected outcomes whether it is release too early or lack of sufficient delivery to the colon may result in costly delays, further studies or failure of the product[102].

7.2 Regulatory Hurdles

Regulatory agencies in the different parts of the world (eg, FDA in the US, EMA in Europe, or CDSCO in India) adopt very high criteria as regards the approval of new drugs and new drug delivery systems. In the case of CDDS, the regulatory attentiveness is even stronger as targeting is specialized. Producers will have to give comprehensive data that proves[103].

7.3 Safety and Biocompatibility

Both of the active pharmaceutical ingredient (API) and of all excipients and polymers composing the delivery system and, in particular, those intended to be degraded or long-exposed to the GI mucosa[104].

7.4 Predictable Release Profile

This is one of the necessities of regulatory approval. Regulators ask that there be solid evidence starting with in vitro tests of dissolution, following to in vivo pharmacokinetics that the drug is releasing in a consistent rate and at the desired site, in a variety of physiological conditions that may model the human GI tract. Released variation can cause a material deviation in efficacy or safety[105].

7.5 Batch-to-Batch Consistency

A crucial regulation point is the necessity to guarantee that every single batch of the drug product produced by the company is identical to its quality, its performance features, and the drug release properties. It means that it will be necessary to demonstrate that the manufacturing process is safe and repeatable, the dosage forms with the same physical properties, drug content, and release profile will be obtained. Even a slight variation in raw materials, processing parameters or relative coating thickness, etc. could alter the desired release profile and the product would be rejected. This consistency demands that firms utilize the strict Quality Management Systems and Good Manufacturing Practices (GMP) which will involve mass of in-process controls, testing the finished products, and stability research[106].

7.6 Variability in Human Physiology

The variability established in the field of human physiology is an ongoing issue even with systems perfectly manufactured. Various sources of inter-individual variation in the performance of a CDDS were described above: different individuals may vary in GI transit times, pH levels (which vary with diet, illness, and medication), and the large and changing population of the gut microbiome. Although enhanced designs are designed to lessen such variations, they cannot get rid of it. This physiological diversity means that predictable release profile may not be universal to all patients and huge amounts of clinical data will be needed to define the expected performance spread and which subsets of patients would most likely respond. there are some formidable challenges yet to be overcome but also promising advances that lay ahead in CDDS development. In brief, successful market approval of CDDS requires not only scientific advancement in the development of formulations, but also the ability to understand complex biological systems, to control their manufacturing, and to produce sufficiently extensive evidence of consistency and predictability of effect within highly variable human population to meet the rigorous requirements of regulatory agencies[107].

8. Recent Advances and Future Trends

Colon-targeted drug delivery systems (CDDS) have a bright future that can undergo a revolutionary change due to the evolution of material science, engineering, and data-driven methods. Such emerging trends can take over existing constraints and result in accurate, specific and efficacious therapeutic interventions.

8.1 Chronotherapeutic Drug Design

One of the most significant future activities, which can be pursued, is the chronotherapeutic design of drugs, i.e. beyond the state of delayed release into the design of drugs with highly specific pharmacokinetics to the natural circadian rhythms[2]. This is not just limited to the timely administration of such a drug within the day but also to the body profiles of drug absorption and elimination in order to fit the physiological alterations of a disease[108]. As an illustration: An antihypertensive medication can be tailored so that its maximum plasma concentration occurs at the moment of the day when blood pressure tends to increase and definitively not a uniform steady discharge during the 24 hours. Through such a level of synchronization, one is attempting not only to achieve optimal efficacy during the optimal period of disease activity but also to minimize the side effects at the time when the body is most susceptible to the drug and hence to, in reality, maximize the therapeutic window of the drug[43].

8.2 Role of Smart Polymers, Nanocarriers, and 3D Printing:

8.2.1 Smart Polymers

The latter form of CDDS shall also utilize smart polymers, that is, polymer which reacts to stimuli. These novel resources would be utilized to respond to diverse physiological environmental conditions found in the GI tract, such as a combination of pH and temperature, or in fact, specific enzyme activities[38]. A smart coating, in extremum, could be designed, in which it is not only dissolvable on attaining a pH of over 7.0, but also at a range of temperatures that conveys to a colon still a greater and much more specific targeting mechanism than its counterpart that reacts to a single stimulus. This is multi-responsive and increases drug release specificity and reduces variability and off-target effects[34].

8.2.2 Nanocarriers

The development of nanocarriers including nanoparticle, liposome, and micelles, provides an unprecedented control of drug release and increased bioavailability. Their nano size and ability to encapsulate drugs makes it easy to control the size, surface load and loading of the drugs and this affects the way drugs travel or interact with the intestine mucosa and became stable as well[109]. Nanocarriers have the potential to protect delicate medications, help them get across the bowel of the intestine, and include extended or pulse-controlled launch properties. The size of the particles is also small and could therefore offer the potential for increased uptake into pathological sites of the colon resulting in an increase in local concentrations of drug[30].

8.2.3 3D Printing

Additive manufacturing (3D printing) is transforming the formulation of pharmaceuticals because it is possible to fabricate novel and highly complex systems of drug delivery so it is possible to deliver drugs with precision as never before. This technology enables one to develop geometries of great complexity, multi-layered tablets at

different drug loads and even tailored dosage forms. Using 3D printing, the internal architecture of a tablet can be fine-tuned in order to regulate the rate and pattern of drug release, and thus tailor a drug release profile (e.g., immediate, sustained, delayed, or pulsatile release of a single dose). Such high degree of customization presents new opportunities to personalized medicine, where forms of dosage may be tailored to suit the needs of a particular patient, time of transit, or disease condition[45].

8.3 AI and QbD in CDDS Development:

8.3.1 Artificial Intelligence (AI)

Independent of CDDS development, Artificial Intelligence (AI) algorithms integration will achieve a highly dramatic increase in acceleration and optimization of CDDS development. AI can also process large preclinical or clinical datasets, optimise drug release profiles based on highly complex physiological data (such as inter-individual variations in pH or transit time), and even optimise polymer mixtures[110]. Machine learning models can help find weak correlations between variables in the formulation and performance outcomes, which means more efficient exploring of the design space and less trial-and-error in the development phase. It is this predictive potential which is likely to simplify the development procedure and make the CDDS more successful[111].

8.3.2 Quality by Design (QbD)

Quality by Design (QbD) is a rational and proactive Quality pharmaceutical development can be described in a rational but proactive approach to pharmaceutical development that has its focus on understanding and controlling the manufacturing process in order to address consistency of the products quality. With respect to CDDS, QbD entails defining such attributes of the material of concern (e.g. polymer molecular weight, particle size), and such parameters of the process of concern (e.g. spray rate of coating solution, the drying temperature) as may influence drug release, and drug stability. QbD guards against this by defining a clear, specific design space and establishing batch-to-batch consistency and a well understood release profile as intrinsic to the product, not just something tested at the end. This is essential proactive quality assurance not only in gaining regulatory approval, but also in uniform therapeutic benefit[112].

8.4 Personalized and Microbiome-Based Targeting:

The final CDDS frontier is the creation of targeting approaches that are personalized and microbiome-based. This includes tailoring drug delivery systems to precisely suit the physiological peculiarities of the person including the unique GI transit time of the patient and most importantly the unique microbial composition of the patient[113]. Recent developments in genomics and metabolomics are enabling the mapping of a patient gut microbiome to define which enzymatic activities exist. Such information could then be applied to choose or formulate polymers that are selectively biodegraded by the bacteria flora of that particular individual making the drug release very efficient and specific. These most effective personalized therapeutic options have the potential of maximizing treatment efficacy, reducing side effects and changing patient care when colon-specific intervention is needed[114].

9. Conclusion:

The concept of chrono-colonic drug delivery is a work of art, which is a well-intelligent and interesting method of administering various disorders using modern pharmaceutical science in the most efficient manner. This approach has the potential to crucially alleviate the drawbacks of conventional delivery strategies because it has the attributes of both time-responsive and site-specific constructs; therefore, it is important to note that such resourceful combination of spatial and temporal release of drugs was a smart approach to overcome the limitation of a fixed-time schedule from conventional oral drug administration. It also deals with the problems of drug degradation in the hostile upper gastrointestinal (GI) tract, variable absorption profiles and unwanted systemic side effects which are commonly caused by non-specific delivery head-on. The advantages are numerous: better therapeutic efficacy of the drug because it is administered in the place and the right time of day and hence the disease is managed better. Simultaneously, specificity of such systems considerably limits systemic exposure to drugs, thus, reducing unwanted effects and enhancing the entire safety of a given drug. Moreover, since most drug delivery strategies are aimed at patient convenience (e.g., once-daily dosing at bedtime to treat morning symptoms), compliance rates tend to increase leading to improved long-term health statuses.Although it is an area that has made impressive advances in recent years, some recognized challenges remain; most of these challenges are attributed to the basic physiological differences existing among individuals regarding GI transit time, pH, and heavily diverse composition of the gut microbiota. Such changes may bring in uncertainties in drug release. Nonetheless, the outlook on the future chrono-colonic drug delivery is remarkably good due to the ceaseless investigations and technical achievements in time. Even greater precision will be achieved by use of innovations in smart materials, which would react to various low-intensity physiological triggers. This will allow production of very high customized and complicated dosage forms manufactured through advanced manufacturing methods such as 3D printing. In addition, individualized medicine is becoming a new and exciting area, and a better comprehension of the microbiome could hold the cure to the potential therapies based on a specific biological profile of an individual. Such combined efforts will continue to transform drug delivery and usher into a new era of extremely targeted, very effective and highly efficient therapies, which have the potential to limitlessly transform the quality of life of patients and clinical outcomes.

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