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Time-Controlled Polymers for Colon-Targeted Drug Delivery Systems

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ABSTRACT
Colon-targeted drug delivery systems (CTDDS) are a very promising approach in the treatment of any colonic disease, such as ulcerative colitis (UC), Crohn's disease, irritable bowel syndrome (IBS), and colorectal cancer (CRC). One of the several methods devised to release drug at the site of the colon is the time-controlled release system (TCRS), which has attracted significant scientific and clinical interest because it takes advantage of the small intestinal transit time that is relatively constant (3 ± 1 hours) to deliver a drug release precisely at the ileocecal junction and beyond. This review will cover all of the polymers used in the time-controlled CTDDS: swellable hydrophilic cellulose ethers like hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC), enteric polymers like the Eudragit® series and natural polysaccharides like guar gum, pectin, chitosan, and high amylose starch. The mechanisms underlying the duration of the lag phase, erosion-controlled drug delivery and dual drug delivery (time- and pH-triggered) or triple drug delivery (time-, pH- and microbial-triggered) are discussed critically. The latest technologies such as injection molding, fused deposition modeling (FDM) 3D printing and hot-melt extrusion (HME) are summarized and discussed in relation to the fabrication of next generation CTDDS. Clinical benchmarks are discussed for commercial formulations of mesalamine including Pentasa®, Asacol® and MMX mesalamine. Inter-individual differences in gastrointestinal transit, disease-induced changes in the colonic microbiomes and regulatory obstacles are addressed. This review highlights the versatility of polymers that are responsive to time in the design of precision oral colon drug delivery platforms.

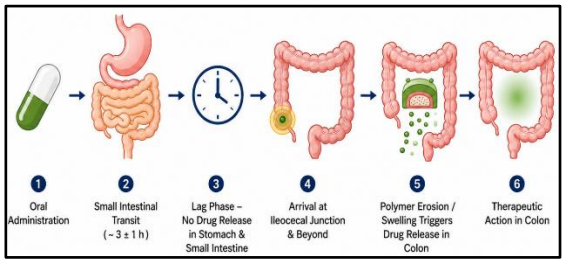

Figure 1: Schematic Representation of Colon-Targeted Drug Release

1. INTRODUCTION

The human colon is about 150 cm long, and is involved in important functions such as water absorption, electrolyte balance, and fermentation of undigested food substrates by a diverse microbial population. These physiological properties combined with a different pH gradient within the lumen of the ascending colon (around 5.7 – 6.0) and the transverse and descending colon (around 6.6 – 7.0) can be used to achieve targeted drug delivery [1]. Colon diseases such as ulcerative colitis (UC),

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Crohn's disease (CD), irritable bowel syndrome (IBS), and colorectal cancer (CRC) are on the rise and are major health issues worldwide, causing morbidity and poor quality of life [2].

The intestinal absorption or degradation of the drug in the upper gastrointestinal tract (GIT) is the main reason why conventional oral drug delivery systems are unable to provide a therapeutic concentration of the drug at the colonic mucosa. To overcome these limitations, colon targeted drug delivery systems (CTDDS) have been developed, which promote the development of a higher concentration of the drug in the colon and therefore lower side effects in the rest of the body, and better therapeutic results [3].

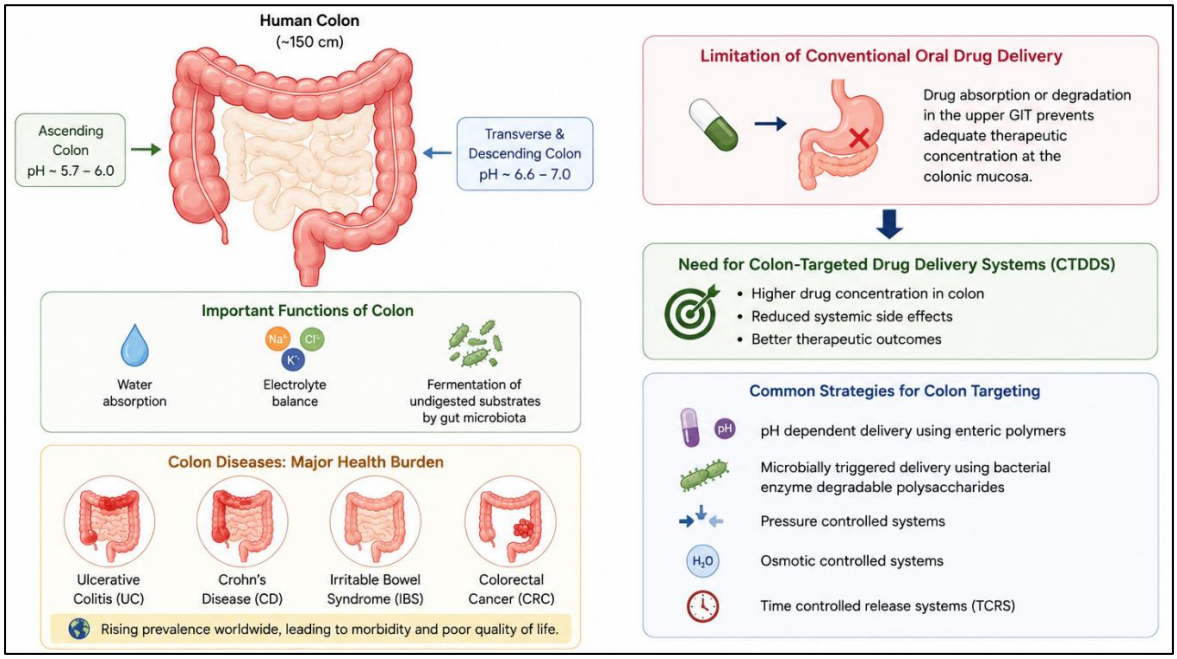

Figure 2: Basic Concepts of Colon Drug Targeting

The most common strategies used for colon targeting are:

- pH dependent delivery using enteric polymers
- Microbially triggered delivery using bacterial enzyme degradable polysaccharides
- Pressure controlled systems
- Osmotic controlled systems
- Time controlled release systems (TCRS) [4].

Of these, special interest has been shown to be time-controlled release systems which have a consistent transit time (3 ± 1 h) from the small intestine and which are not affected by food intake or pathological condition. The predictability offers the possibility of a physiological time clock for drug release programming. Typically, the polymers used in TCRS are hydrophilic and swell, dissolve or erode over a specified time after gastric emptying to create a programmed lag time before release of the drug begins at the ileocecal junction [5]. Lag time can be carefully controlled and matched by choosing the right polymer type and grades, as well as coating thickness.

The objective of this review is to critically analyse the polymeric materials used for the manufacturing of the time-controlled CTDDS, the mechanism of drug release, the important formulation platforms with the incorporation of time-controlled components, clinical applications, recent technological development such as 3D printing and injection moulding, and challenges and future perspectives.

Table 1. Overview of Colon-Targeted Drug Delivery Systems (CTDDS)

Topic	Key Information
Human Colon	About 150 cm long; involved in water absorption, electrolyte balance, and microbial fermentation.
Colon pH	Ascending colon: pH 5.7–6.0; transverse/descending colon: pH 6.6–7.0.
Colon Diseases	UC, Crohn's disease, IBS, and colorectal cancer (CRC).
Problem with Conventional Delivery	Drug absorption/degradation in upper GIT reduces drug reaching the colon.
CTDDS Purpose	Delivers drug specifically to the colon with fewer side effects.
Colon Targeting Strategies	pH-dependent, microbial-triggered, pressure-controlled, osmotic-controlled, and time-controlled systems.
Time-Controlled Release Systems (TCRS)	Use small intestinal transit time (3 ± 1 h) for programmed drug release in the colon.
Mechanism of TCRS	Polymers swell, dissolve, or erode to create a lag time before drug release.

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Objective of Review	Discuss polymers, mechanisms, technologies, applications, and future prospects of CTDDS.

2. Gastrointestinal Physiology Pertaining to Colon Targeting:

The rational design of CTDDS requires a good knowledge of gastrointestinal physiology. The GIT comprises of compartments that have different pH, enzyme activities, microbial flora and transit times which in turn have a significant role in the drug release behavior [6].

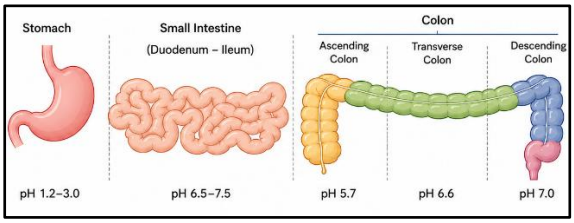

Figure 3: Regional pH Distribution in the Gastrointestinal Tract

2.1 pH Profile of the GIT:

The gastric pH is extremely low (1.2-3.0) in the fasted state. The pH gradually rises through the small intestine reaching about 6.5–7.5 in the ileum. Within the colon, the luminal pH can be even as low as 5.7 in the ascending colon, increasing to about 6.6 in the transverse colon and 7.0 in the descending colon [3]. The reason for this pH change is due to bacterial fermentation of polysaccharides forming short-chain fatty acids (SCFAs) in the proximal colon which tend to lower the pH, while the distal colon is more alkaline. Colonic pH can also be further modified by inflammatory bowel disease (IBD) and thus increase the complexity of the design of pH-dependent systems. These pH changes illustrate both the possibilities and restrictions of pH dependent delivery, and underscore the importance of the time-controlled approaches as a complementary mechanism [7].

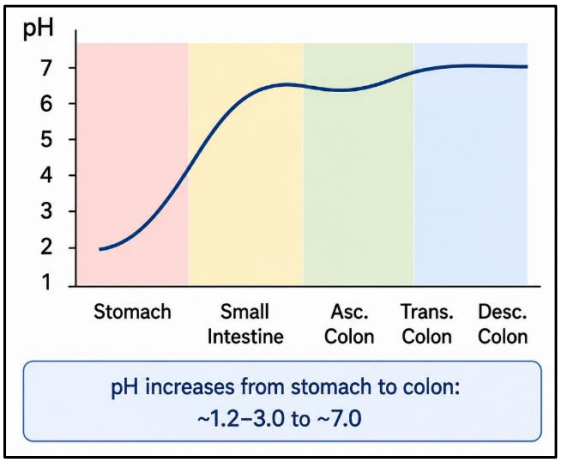

Figure 4: Variation in pH Across the Gastrointestinal Tract

2.2 Gastrointestinal Transit Time

The time required for stomach emptying is very variable, from 30 minutes to several hours, and varies with fed/fasted state, composition of the meal and pathological conditions. Contrastingly, the transit time of the small intestine is relatively constant, with an average of 3 ± 1 hours in healthy adults. The uniformity of this provides a desirable physiological marker for the development of timed drug release devices in the small intestine [5]. The total colonic transit time is more variable, ranging from 6-72 hours and can be lengthened or shortened in disease states like constipation, diarrhoea, short bowel syndrome and UC. The transit changes associated with these diseases are able to impact the timing and/or the microbial-induced systems as well [1].

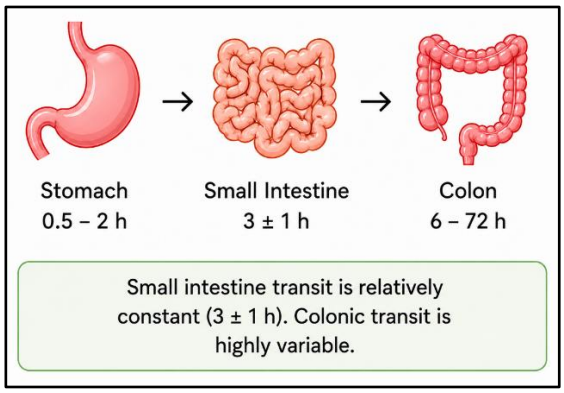

Figure 5: Gastrointestinal Transit Time Across Different GIT Regions

2.3 Colonic Microbiota:

The human colon has by far the most varied and abundant microbial community of any part of the body, with over 10^11 colony forming units (cfu) per milliliter. The microbiota has the ability to selectively degrade specific polymers and prodrug conjugates thanks to enzymes such as azoreductases, glycosidases and polysaccharidases that are present in the colon [4]. This microbial enzymatic activity is being utilized in microbially-triggered drug delivery, as well as being used increasingly as a secondary trigger in combined time-pH-microbial systems. In IBD however, a decrease in microbial diversity and species composition (e.g. dysbiosis) may make it less reliable to rely on purely microbially-triggered approaches, further emphasizing the importance of the time-based components [8].

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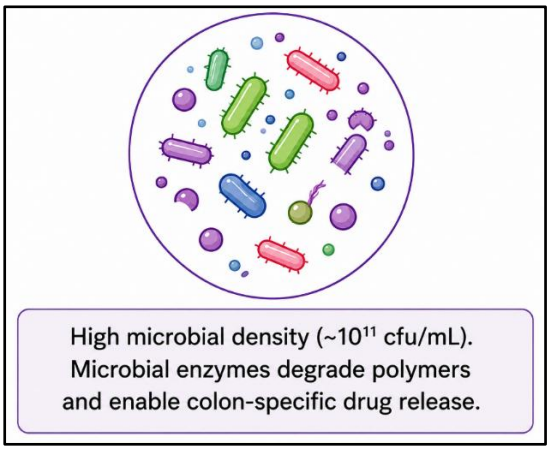

Figure 6: Role of Colonic Microbiota in Colon-Targeted Drug Delivery

3. Concepts of Time-Controlled Release Systems (TCRS):

The idea of time-controlled release systems (TCRS) is based on the fact that the oral dosage forms have predictable small intestinal transit and the formulation scientists can program a lag time of about 3-5 hours after gastric emptying to start the drug release [5]. A functional polymer layer is incorporated which is resistant to stomach and proximal small intestine erosion/dissolution, then slowly swells, erodes or dissolves over a predetermined period of time, releasing the drug core after the polymer layer has completely eroded or ruptured.

3.1 Swelling and Erosion Mechanisms:

Most common TCRS polymers are hydrophilic cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC). These polymers, on contact with aqueous media, rapidly hydrate to create a viscous layer of gel, which inhibits the diffusion of water into the polymer and the diffusion of drug molecules out of the polymer [5]. The outer gel gradually dissolves in time, thus gradually decreasing the thickness of the polymer barrier. When the erosion front reaches the core tablet or the drug reservoir, the drug release begins. The thickest polymer coat and the highest molecular weight grades of cellulose polymer are those that result in the longest lag times [18].

In enteric-coated TCRS, a layer of swellable cellulose will be protected in the gastric environment by an acid-resistant layer (usually Eudragit® L (pH > 6.0) or Eudragit® S (pH > 7.0)). After emptying into the small intestine, the enteric coat decomposes quickly in the presence of intestinal fluid, leaving the HPMC or HPC layer to come into contact with the intestinal fluid. The cellulose layer then starts to decay, creating the lag period. The dual-layer concept developed is an outer enteric layer and an inner hydrophilic cellulose layer, which is the mechanistic principle of the commercial TCRS products Pentasa® and the Chronotopic™ system [21].

3.2 Membrane Rupture Mechanisms:

The other TCRS mechanism is the breaking of a semi-permeable polymer membrane. These designs involve an increase in osmotic pressure inside the core surrounded by water permeable coating as water enters the core containing the drug. If the osmotic pressure is greater than the mechanical resistance of the coating, the membrane breaks and the drug is released in a quick burst, called a pulsatile bolus. This mechanism is the basis for time-controlled explosion systems (TCES) and has been modified for colon targeting by the use of an enteric outer coat which prevents water penetration in the acidic gastric environment [8].

3.3 Dissolution and Erosion of Polysaccharide Components:

Natural polysaccharides like guar gum, pectin, inulin and high-amylose starch are used as accessories to the time-controlled delivery system (CTDDS) that deliver an enzymatic or timed release. For instance, guar gum has been shown to be a time-controlled retardant and will be broken down by microbial enzymes once it reaches the proximal colon, but will not affect drug release in the small intestine [3]. Complementary targeting mechanisms are offered by high amylose starch (Amylo N460®) added to Eudragit® S coatings, which are pH-dissolved and then under enzymatic attack in the colon. These polysaccharides possess unique physicochemical properties, which can be exploited to make them useful components in multi-trigger CTDDS architectures [24].

4. Polymers used in time controlled CTDDS.

Various synthetic and natural polymers have been studied for the purpose of time-controlled colon drug delivery. These materials can be grouped into two categories: hydrophilic cellulose ethers, enteric polymethacrylates, water-insoluble ethylcellulose, and natural polysaccharides. Two or more types of polymers are often used in combination to achieve optimal TCRS performance with protection in the upper GIT and time triggered release in the colon.

4.1 Hydroxypropyl Methylcellulose (HPMC):

The most widely studied time-controlled colon drug delivery polymer is hydroxypropyl methylcellulose (HPMC) which is commercially available as Methocel® in different viscosity grades. HPMC is a cellulose polymer which is soluble in water and non-ionic. It however quickly absorbs water and will produce a viscous gel layer upon contact with any aqueous fluids. The molecular weight (viscosity grade) of HPMC and the coating weight applied to

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the dosage form are the main factors which affect the rate of erosion of the gel and hence the lag time before the drug is released [18].

The concept of time-controlled colon targeting with HPMC has been confirmed by gamma scintigraphy studies which have shown consistent disintegration in the ascending colon of fasted healthy volunteers for HPMC-coated tablets with Eudragit® L outer enteric films [21]. Low viscosity viscosity grades of HPMC (e.g., Methocel® E5, E50) are especially useful in applications with controlled lag times because they have faster erosion rates, resulting in a shorter lag time and more controlled lag phases. In addition, HPMC has been used in time-controlled capsule shells, using the technique of injection molding and 3D printing using hot-melt extrusion as detailed in Section 6.

A study with a pH-, microbiota-, and time-based triple-triggered oral delivery platform employed an inner swellable HPMC layer and outer coating of a mixture of pH-responsive Eudragit® S and microbially-degradable high-methoxyl pectin [22]. In vivo testing in transgenic mice allowed the release of mesalamine to be restricted to the colon, and yielded better anti-inflammatory effects than commercial mesalamine products. The triple triggering system is the current trend in colon-targeting using polymers.

4.2 Hydroxypropyl Cellulose (HPC):
Hydroxypropyl cellulose (HPC) is a thermoplastic cellulose ether with water-soluble properties, which is especially suitable for injection molding (IM) and hot-melt extrusion (HME) processes and has a low glass transition temperature. IM has extensively studied the HPC capsule shell as an appropriate time-controlled colon delivery device [23]. The HPC shell starts to swell and dissolve in the small intestinal fluid leading to a programmable period without any drug release, with the shell thickness and composition as the major design variables that determine the lag time.

A combined HPC capsule formulation which is based on the presence of a second component (high amylose starch) which is degraded by colonic bacterial enzymes, resulting in a time-controlled drug release, has been developed [11]. The versatility of this approach was confirmed by in vitro data showing pulsatile release of drug was obtained with lag times of 2 to 5 hours depending on the blend ratio and the molecular weight of HPC. In particular, the enzyme-mediated release was highly enhanced in the presence of patient faecal samples, thus confirming the enzyme triggered release under clinically relevant conditions [23].

4.3 Eudragit® Series Polymers:
Currently, the series of polymethacrylate copolymers marketed under the name “Eudragit®” (Evonik Industries) are the most popular synthetic polymers for colon targeting. They are pH dependent soluble and are ideal for enteric coating of the drug to protect the drug from premature release occurring in the acidic gastric condition. The use of Eudragit® polymers in the context of time-controlled CTDDS is mainly as outer protective enteric layers which will dissolve in the small intestine, releasing the underlying time-controlled cellulose layer [5].

Eudragit® L100 and L100-55 are soluble at pH > 6.0 and pH > 5.5 respectively, thus providing protection in the stomach and proximal small intestine. The solubility of Eudragit® S 100 is only at pH>7.0 and is therefore suitable as an outer enteric barrier in combination with HPMC as inner layers. Eudragit® FS30D is an aqueous dispersion soluble at pH >6.8, specially developed for colon targeting and used in commercial formulations for colon targeting for mesalamine [6]. Eudragit® RL and RS100 are polymers that are neither soluble nor swellable and are employed for sustained release matrix system in time dependent formulations, as shown in indomethacin liquisolid tablet formulations with polysaccharide carriers [17].

A time-dependent layer (HPMC K4M) and an outer enteric barrier (Eudragit® L100) were optimized by simplex lattice design considering a combined pH and time-dependent delivery of the ingredient [19]. From the results, it could be seen that the lag time and t50 increased with the increase in content of HPMC and decreased with the increase in the content of dextrose and PVP as diluents, giving a rational reason for optimizing the lag time.

4.4 Ethylcellulose:
Cellulose ether, ethyl cellulose (EC) is a cellulose ether, which is generally water-insoluble and is used as the coating polymer for sustained-release pharmaceuticals. In CTDDS applications, EC is used to create a diffusion barrier that is not soluble in water around the drug cores, which allows the system to control the release of the drug over a period of time. Drug release from EC films takes place via pores filled with water or pores created via the inclusion of a pore forming excipient in the film. EC alone is a sustained release but not colon specific and is used in combination with pH dependent polymers and polysaccharides. Optimization of colon targeting pellet formulations containing EC and combination with Eudragit® S and Eudragit® L have resulted in release of less than 10% of the drug in pH 1.2 medium and more than 60% of the drug in the medium of pH 6.8 within 10 h [29].

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4.5 Natural Polysaccharides:

Natural polysaccharides have a special role in colon targeted drug delivery as they are both biocompatible and selectively degraded by colonic bacteria. They use their resistance to the action of enzymes in the stomach and small intestine (where they do not exist or may only be present in very small amounts) and their sensitivity to action by the strong microbial population of the proximal colon (where enzymes exist) [3].

Guar gum has been shown to work as a time-controlled retardant coating material, a galactomannan polysaccharide. It was found that pellets coated with guar gum were not prone to drug release in the upper GIT and were broken down by bacterial enzymes in the proximal colon [3]. In triple-trigger systems, pH-dependent and microbially-triggered release are achieved by incorporating pectin, especially high methoxyl pectin, in the outer coating made of Eudragit® S [22]. Chitosan is a deacetylated derivative of chitin, which is pH and enzyme sensitive and has been employed as a carrier polymer in liquisolid tablet formulations for colon delivery of indomethacin [17]. High amylose starch (Amylo N460®) which is poorly digested by pancreatic amylase in the small intestine but easily digested by amylases in the colon is especially useful as an enzyme-sensitive ingredient in time-controlled platforms [24].

The use of inulin as matrix former in colon targeted nanoparticulate and micronized systems has been investigated. Mechanically stable tablet matrices that release drug only in the colon when exposed to enzymes have been developed using cross-linked guar gum matrices, cross-linked pectin and cross-linked amylose [4].

Table 2. Common Polymers Used in Time-Controlled Colon-Targeted Drug Delivery Systems (CTDDS)

Polymer	Main Role in CTDDS	Key Feature
HPMC	Time-controlled release	Swells and erodes to create lag time
HPC	Capsule shell polymer	Suitable for injection molding and HME
Eudragit®	Enteric coating	pH-dependent drug release
Ethyl cellulose	Sustained-release coating	Forms water-insoluble diffusion barrier
Guar Gum	Microbial-triggered release	Degraded by colonic bacteria
Pectin	Triple-trigger systems	pH and microbial responsive
Chitosan	Colon delivery carrier	pH and enzyme sensitive
High Amylose Starch	Enzyme-sensitive release	Digested by colonic enzymes only

5. Key Formulation Platforms for Time-Controlled CTDDS:

5.1 ETP (Enteric-coated Timed-release Press-coated) Tablet Syste:

The ETP tablet is a three-component platform that is designed specifically for time-controlled colon drug delivery. This system is that it has a drug inside a rapid release core tablet, a press coated outer swellable hydrophobic polymer layer (usually HPC), and an outer enteric coated layer. Following oral administration, enteric coat will prevent dissolution and release of the drug in acidic gastric environment. Following gastric emptying the enteric coat is quickly dissolved in small intestinal fluids, revealing the HPC press-coat layer [7]. The HPC layers erode gradually over time with the fluid present in the intestine and once the erosion front reaches the core tablet, the drug is released rapidly. The length of the lag phase can be programmed by the weight and composition of the HPC layer. The ability of ETP tablets to target the colon with various drugs has been validated, including 5-fluorouracil, prednisolone and mesalamine; scintigraphic studies have shown consistent ileal/cecal release of all three in healthy volunteers [10].

5.2 Chronotopic™ System:

Formenti Farmaceutici (Italy) has developed a reservoir system called Chronotopic™ which is used for pulsatile drug release. The system is composed of a drug loaded core surrounded by a hydrophilic HPMC coating and an enteric film. After gastric transit the enteric film dissolves and the HPMC coating starts to break down, resulting in a drug release as a pulse after a programmable delay. The Chronotopic™ system has been clinically assessed by scintigraphy indicating a constant release of the drug in the ascending colon. The lag phase can be adjusted by changing the viscosity grade and coat weight of HPMC [21]. Recently, dual-nozzle FDM 3D printing has been used to produce structures with complex geometry similar to that of Chronotopic™ with fine tuning of lag time control [40].

5.3 CTDC (Colon-Targeted Delivery Capsule) System:

The CTDC system is a reservoir device which consists of a gelatin capsule filled with a drug-acid mixture, an inner acid soluble permeable Eudragit® E layer, a hydrophilic HPMC separation layer and an outer HPMCAS enteric coat. After passing through the stomach (protected by HPMCAS), both the HPMCAS and HPMC layers dissolve in the small intestine. Water then diffuses through the permeable Eudragit® E layer, the enclosed organic acid progressively decreases the pH within the capsule causing the intracapsular Eudragit® E coat to dissolve and hence release the drug. In human volunteers, gamma scintigraphy showed that the

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disintegration process of CTDC capsules is constant in the ascending part of the colon, which validates this dual-mechanism time-pH approach [21].

5.4 CODES™ System:
The CODES™ (Colon-targeted Delivery System) is an innovative technology that is a combination of pH-dependent and microbially-triggered delivery mechanisms and time-controlled delivery system. The system is composed of a tablet core including lactulose (the microbial trigger) which is first overcoated with acid-soluble Eudragit® E and then with enteric Eudragit® L. Eudragit® L disintegrates in the small intestine, leaving Eudragit® E in the intestinal fluid; in the colon, the enteric coat disintegrates. The lactulose is subsequently broken down by the bacteria in the colon to release organic acids which decrease the local pH and help to dissolve the remaining Eudragit® E coating, thereby releasing the drug. The system cleverly takes advantage of the pH lowering effect of the colonic microbiota as a site-specific trigger, and includes gastric protection throughout the time in the stomach [4].

5.5 Multimatrix (MMX) System:
The Multimatrix (MMX) system is an advanced formulation system where the lipophilic solid matrix of stearic acid and carnauba wax is dispersed in a hydrophilic core of HPMC. The Eudragit® S on the outside is designed to dissolve in the colon, allowing the matrix to be exposed to the contents of the colon. This hydrophilic and lipophilic matrix forms a special architecture for the drug which facilitates drug retention and thus extended and prolonged drug release at the entire colon. In mild to moderate UC, the clinical efficacy of MMX mesalamine (Lialda®/Mezavant®) has been shown to be greater than other formulations, and it has been proven to be more convenient for patients to take once a day because of extended colonic residence and prolonged mucosal drug exposure [27].

6. Advanced Technologies in Time Controlled CTDDS Fabrication:
6.1 Injection Molding (IM):
Injection molding (IM) is a thermoplastic processing method used to produce complex geometries for the capsule shell that have precise dimensional control, demanded for time-controlled drug delivery systems where shell thickness is the key factor determining the lag time. The thermoplastic nature of HPC and its safe characteristics have made it the polymer of choice for IM capsule shell manufacturing [23]. The ideal capsule formulations are referred to as IM capsules and consist of a blend of HPC and high-amylose starch, which ensures time-controlled swelling/erosion and a further degradation of the starch in the colon due to enzymes in the colon lumen. In both in vitro and in vivo study, the lag time has been demonstrated to be tunable by changing the grade of HPC molecular weight and wall thickness of the shell, and in the presence of colonic fecal microbiota, the lag time can be significantly shortened compared to the small intestine [11].

In healthy volunteers' gamma scintigraphic studies on the capsule disintegration of radiolabeled IM HPC capsules coated with an outer layer of Eudragit® S/Amylo N460 film showed consistent capsule disintegration at the JI, confirming the triple-trigger (time, pH and enzyme) concept in human subjects [24]. This synergy between IM fabrication technology and polymer science provides a scalable, precise and regulatory friendly route to next-generation CTDDS.

6.2 Fused Deposition Modeling (FDM) 3D Printing:
In the field of colon-targeted drug delivery devices, fused deposition modeling (FDM) 3D printing has proven to be a game-changer technology for the creation of personalised devices with complex geometries. The thermoplastic polymer-drug filament can be deposited in a precise control of the layer-by-layer architecture to control shell thickness, infill density, surface area and geometry, which play crucial roles in drug release kinetics with FDM [36]. The versatility of FDM is especially important for CTDDS, where the geometry of the shell and the thickness of the shell can be designed to achieve certain lag times without the need for extra processing, like coating pan applications.

A dual-nozzle FDM printer is used to fabricate capsules for the delivery of 5-ASA, with an outer compartment composed of a polymer with pH-dependent dissolution properties (HPMCAS) and an inner compartment composed of water-soluble polymer (PVA). In vitro dissolution testing showed a biphasic release profile, releasing less than 6% of the drug at pH 1.2 and 6.8, and the majority of the drug payload was released after 5 h that corresponded to ileocecal arrival time [39]. The optimized ratio of Eudragit® FS100 and polylactic acid (PLA) filaments for FDM printing of colon-targeted mesalamine tablets was found to be 80:20 (Eudragit® FS100: PLA) in a study in 2024 [35].

DrugCoat S 12.5 polymer was used to coat the three-dimensionally printed fractal-like structures, which were designed to have high drug loading percentages to maximize surface area for enhanced colonic drug release and to provide zero-order colonic release profiles [37]. A tailored biopolymer capsule system (HME-3D printing and FDM processing with low G-T HPMC – Affinisol™ HPMC HME 15LV) showed a dual time- and

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microbiota-triggered release mechanism, which was validated in healthy volunteers by gamma scintigraphy and in vivo tracking and was a landmark study that linked 3D printing technology to colon targeting performance in vivo [38].

6.3 Hot-Melt Extrusion (HME):

Hot melt extrusion (HME) is a continuous, solvent-free method of fabrication, which involves melting a blend of drug and polymer to extrude it into a shaped dosage form, such as filaments used for FDM 3D printing, pellets, and matrix tablets. HME allows for intimate mixing of drug and polymer at the molecular level, thus enhancing drug solubility and homogeneity. HME has been used to prepare solid dispersions of poorly water-soluble drugs, for delivering these drugs specifically to the colon. The colon targeting of niclosamide from solid dispersions was achieved using HME by incorporating Eudragit® FS30D as a pH-dependent carrier, which showed great efficacy in suppressing UC in a murine model and resulted in higher mucosal concentration of the drug than was found with the unformulated drug [35]. The HME technology allows for the production, on a large scale, of colon-targeted formulations continuously and with process analytical technology (PAT) tools, quality is monitored in real-time.

6.4 Liquisolid Technology:

Liquisolid (LS) technology is a process that turns liquid or dissolved drugs into free flowing, compressible powder systems with the aid of carrier-coating agents, which allows poorly soluble drugs to be formulated into solid dosage forms. Indomethacin was evaluated as a CTDDS carrier in LS systems using natural polysaccharides (guar gum, pectin and chitosan) as carriers together with Eudragit® RL 100 as a time-dependent polymer for compression of matrix tablets [17]. The sustained drug release obtained with LS formulations with high drug loading efficiency was found useful for the preparation of colon targeted matrix tablets.

Table 3. Advanced Technologies Used in Time-Controlled Colon-Targeted Drug Delivery Systems (CTDDS)

Technology	Application in CTDDS	Key Advantage
Injection Molding (IM)	Fabrication of capsule shells	Precise lag time control
FDM 3D Printing	Personalized colon delivery devices	Custom geometry and release profile
Hot-Melt Extrusion (HME)	Preparation of solid dispersions and filaments	Continuous solvent-free process
Liquisolid Technology	Colon-targeted matrix tablets	Improves drug solubility and sustained release

7. Clinical Applications and Commercial Formulations:

7.1 Ulcerative Colitis and Crohn's Disease:

The most significant therapeutic implication of CTDDS is inflammatory bowel disease (IBD) which consists of the two forms of inflammatory bowel disease, ulcerative colitis (UC) and Crohn's disease (CD). 5-aminosalicylic acid (5-ASA/mesalamine) is the first-line drug treatment for mild-to-moderate UC, and efficacy is dependent upon achieving high drug concentrations in the inflamed colonic epithelium [33]. Several oral mesalamine preparations using different colonic targeting systems are commercially available.

The release of Pentasa® (Ferring Pharmaceuticals) is controlled by a time independent and pH independent erosive mechanism that releases drug continuously in the duodenum and colon – but, is not truly a colon targeted formulation. Asacol® (Warner Chilcott) contains mesalamine that is coated with Eudragit® S which allows the release of the drug in the terminal ileum and ascending colon at a pH > 7.0. In Japan the approved formulation is Lialda® (Shire) which uses the MMX multimatrix technology as described in Section 5.5 [27]. A detailed 2024 narrative review of clinical trial data up to October 2023 suggested that MMX mesalamine has acceptable clinical and endoscopic remission rates and is easy to administer (once a day) when compared with other UC treatments. In the last years, mesalamine formulations have also been investigated for delivering combination systems that are delayed-release and enzyme-sensitive for selective delivery to the colon [28].

7.2 Colorectal Cancer:

Colorectal cancer (CRC) is the third leading cause of cancer in the world and a leading cause of cancer death. Colon targeted drug delivery (CTDD) of chemotherapeutic agents has the potential of high intratumoral drug concentration with low systemic drug exposure and low systemic toxicity. Polymethacrylate polymers such as Eudragit® series, natural polysaccharide chitosan and synthetic polymer based smart delivery materials can take advantage of the pH gradient in CRC tissue microenvironment (pH 6.5-7.2) [6]. For CRC treatment, various targeted nano-drug delivery systems such as polymeric nanoparticles, dendrimers, lipid-based nanoparticles, and polymer-drug conjugates are being investigated which are made of pH-responsive and enzyme-responsive elements and time-controlled elements [2]. In the case of CRC, CTDDS should be stimuli-responsive to deliver the cytotoxic drug to the specific site and not absorb into the system too early to negate the colon-targeting benefit.

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7.3 Irritable Bowel Syndrome and Other Colonic Conditions:
The clinical features of IBS are changes in bowel function, abdominal pain, and bloating, in the absence of any structural or biochemical disease. There has been an investigation of the use of time-controlled systems to control symptoms and minimize systemic side effects by using colon targeted delivery of antispasmodics, probiotics, and pain modulators. Patients with IBS experience variable colonic transit, which is further evidence for the need to use multiple time-based methods (microbial or pH trigger) for increased redundancy [1]. Circadian drug delivery also is being assessed in other disease areas, such as nocturnal asthma and rheumatoid arthritis, where symptom timing is known to be important, with the hypothesis that timed targeted delivery of drug to the gastrointestinal tract would yield the highest drug levels in the early morning [7].

8. Challenges and Limitations:
Although much progress has been made, there are several important challenges which must be addressed before the time-controlled CTDDS can be widely adopted in the clinical setting.

8.2 Disorders of GI transit:
In healthy adult patients, the transit time through the small intestine is 3 ± 1 hours, and is relatively constant; however, it varies significantly between and within individuals in patients. Fixed-lag-time TCRS may not be applicable to disease states such as Crohn's disease, short bowel syndrome, post-surgical anatomical changes, and autonomic neuropathy, which can have significant effects on intestinal transit [1]. Gastric emptying is especially unpredictable, and it is the most common source of unpredictability in clinical settings with TCRS. The time of dosage form leaving the stomach is highly dependent on feeding state, meal composition, posture, and pathological gastroparesis, and the programmed lag phases are not necessarily accurate when compared to the time of dosage form arrival in the colon.

8.2 Disease-Related Alterations:
Colonic pH is altered, colonic microbiota is dysbiotic and contains decreased numbers of bacteria, colonic transit is accelerated or slowed, and colonic mucosa barrier is dysfunctional. These disease-induced alterations may affect at the same time pH dependent, microbially triggered and time-controlled delivery systems [8]. The higher pH of the colon lumen in active UC could paradoxically promote the premature dissolution of Eudragit® S coatings in the small intestine and reduced bacterial colonization in CD could reduce the degradation of polysaccharide coatings. A key unmet need is the design of effective CTDDS which will be effective over the entire range of IBD disease activity.

8.3 In Vitro–In Vivo Correlation:
The technical difficulty of creating suitable in vitro dissolution models that accurately predict colonic in vivo drug release behavior is a challenge. The colonic environment is complex and consists of a viscous mucus layer, a small fluid volume (~10-20 mL in the proximal colon), the presence of fecal microbiota, motility patterns and the pH which changes over time.The colonic environment is complex, with a viscous mucus layer, a very limited amount of fluid (10-20 mL in the proximal colon), presence of fecal microbiota, motility patterns and a time varying pH [4]. Biorelevant dissolution media with fecal matter and mucin and defined bacterial communities are being developed to better simulate colonic conditions and enhance in vitro-in vivo correlation (IVIVC) for CTDDS. The validation of IVIVC is essential to get approval of new colon-targeted formulations.

8.4 Regulatory Challenges:
To date, there are no regulatory approvals for a major regulatory agency (such as the FDA or EMA) for any CTDDS. At the present time, pH-controlled mesalamine preparations are available under the label of delayed-release preparations and are not specifically labelled as colon-targeting. Regulatory challenges include the absence of bioequivalence guidelines for colon targeted formulations, ability to characterize the location of release in vivo, and the need for the use of expensive, complex scintigraphy studies of human volunteers [14]. There is a need for harmonized regulatory guidance on the approval pathways for CTDDS, standardized in vitro testing methods, and biomarkers of colonic drug exposure.

9. Future Perspectives:
The field of time-controlled CTDDS has experienced rapid growth in recent years, with an increasing number of innovations in the polymer science, digital manufacturing and GI physiology/ microbiome fields. A number of new trends have great potential for the future within the next decade and beyond.

Multi-trigger systems that use a combination of time, pH and microbial triggers have been shown to offer superior and reliable colon targeting in different physiological conditions as compared to single trigger systems [22]. A triple-trigger platform, in which a time-triggered HPMC swellable inner layer is surrounded by a pH-responsive/enzyme-degradable outer bilayer, is especially promising and has been tested in animal models and is now in the process of being evaluated in humans. Optimization of polymer blend ratios, coating weights, and drug

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loading will continue to be key elements for translation of these systems to clinical practice.

3D printing for personalized medicine is a game-changing opportunity for CTDDS. In one 3D print, patient specific dose customization and geometry-driven lag time programming can be achieved [36]. Eventually, personalization of formulations for targeted delivery to the colon could be possible in point of care or in hospitals, as the manufacturing of pharmaceutical grade thermoplastic polymer filaments is developed and regulatory standards for 3D-printed pharmaceuticals are advanced, for those with rare or complex transit patterns or those with refractory disease. The Center for Drug Evaluation and Research within the FDA has already published guidance on 3D printing in the pharmaceutical industry, outlining a path forward for such innovations [40].

New generation CTDDS in CRC and IBD are being investigated by stimuli-responsive smart polymers that contain other triggers like redox potential, temperature, reactive oxygen species (ROS) and inflammatory mediators [12]. Because of the high oxidative stress in inflamed colonic tissue, ROS-responsive polymers are especially interesting for the treatment of IBD: if the drug is released in response to the presence of ROS in the tissue, it will actually provide a disease-activity-responsive drug release profile, releasing more drug where and when inflammation is greatest.

The performance of CTDDS has been assessed under physiologically relevant conditions and such advances in gut-on-chip microfluidic systems and organoid-based models of the colon are opening up unprecedented opportunities without the ethics and logistics of human scintigraphy studies. The incorporation of these advanced in vitro tools with computational pharmacokinetic/pharmacodynamic (PK/PD) modeling will speed up the rational design and optimization of time-controlled polymeric systems for colon drug delivery [1].

10. CONCLUSION:

The time-controlled polymers are a scientifically proven and clinically approved platform for colon targeted drug delivery. The small intestinal transit time which is about 3 ± 1 hours is relatively constant and can be used as a physiological basis for the programming of drug release at the ileocecal junction via swellable, erodible, or membrane-rupture polymer systems. The backbone polymers of TCRS are the hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and Eudragit® series of polymethacrylates, whilst natural polysaccharides such as guar gum, pectin, high amylose starch and chitosan are used to complement the microbially triggered components for the development of reliable multi-trigger systems.

Examples of commercially available formulations that have been developed through polymer targeting for the colon include Pentasa®, Asacol® and MMX mesalamine, which have revolutionized the treatment of inflammatory bowel disease (IBD). Advanced manufacturing technologies such as injection molding, FDM 3D printing, and hot-melt extrusion are making next-generation CTDDS more precisely, more complexly, and more personally.

However, there are still a number of persistent issues to address: inter-individual GI transit variability, disease-related physiological changes, lack of validation of in vitro models and lack of understanding of the regulatory pathways for colon-targeted formulations. To achieve the therapeutic potential of time-controlled CTDDS, interdisciplinary collaboration between polymer scientists, pharmaceutical technologists, gastroenterologists and regulatory scientists will be necessary to tackle these challenges. A future filled with promises awaits the realm of precision colon drug delivery with the combination of triple-trigger polymer architectures, digital 3D manufacturing, and the innovative stimuli-responsive materials.

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