RESEARCH PAPER

EMERGING TECHNOLOGIES AND MODERN APPROACHES FOR COLON-SPECIFIC DRUG DELIVERY: A REVIEW

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ABSTRACT- A colon-targeted drug delivery system (CTDDS) has attracted considerable interest for treating inflammatory bowel disease and other diseases of the colon because CTDDS can ensure direct drug delivery to the site of action with minimal side effects. However, the conditions within the colon that include close-to-neutral pH, high residence time, etc., are ideal; nevertheless, some limitations like physiological variations, microbiome, mucus, and poor in vitro-in vivo correlation prevent optimal performance of CTDDS. This review highlights conventional techniques like the prodrug and osmotic approach and advanced techniques such as nanoparticles. In addition, this review presents modern techniques like 3D printing technology, hot melt extrusion, and quality by design. New-age technologies involving artificial intelligence and multiple stimulus-sensitive techniques will also be discussed.

Keywords: colon-targeted drug delivery, inflammatory bowel disease, nanoparticles, 3D printing technology, hot melt extrusion, quality by design, multiple stimulus-sensitive techniques.

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.INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract, most frequently affecting the colon, and its global prevalence is steadily increasing. Targeted delivery of drugs to the colon has gained considerable importance for the management of colonic disorders as well as for improving the systemic absorption of sensitive biomolecules such as peptides and proteins. IBD conditions, including ulcerative colitis (UC) and Crohn's disease, often require site-specific drug delivery to achieve effective therapeutic outcomes. This can be achieved through either rectal or oral administration. Although rectal routes such as enemas and suppositories offer direct access to the colon, their clinical effectiveness is often limited due to inconsistent drug distribution and poor patient compliance.

As a result, the oral route remains the most preferred approach because of its convenience, better patient acceptance, and cost-effectiveness. However, oral delivery to the colon is challenging since drugs must survive the harsh conditions of the stomach and small intestine, including acidic pH, enzymatic degradation, and limited permeability, particularly for biopharmaceuticals that are highly sensitive to hydrolysis.

Despite these limitations, the colon presents a promising site for drug delivery due to its near-neutral pH, prolonged transit time, reduced enzymatic activity, and increased responsiveness to absorption enhancers. These physiological characteristics make it particularly suitable for the delivery of proteins, peptides, and other macromolecular therapeutics.

For successful colon-targeted delivery, drug formulations must ensure minimal release in the upper gastrointestinal tract while enabling rapid and site-specific release upon reaching the colon. Overcoming premature drug release and ensuring stability through the gastrointestinal tract remains a key formulation challenge in developing effective colon-specific systems. [1-6]

The concept of encapsulating nanoparticles into microspheres for site-specific delivery builds upon earlier microsphere-based approaches. Kunchu Kavitha et al. previously demonstrated the successful formulation of Chitosan/Gelatin B microspheres via complex coacervation and chitosan-based microspheres for controlled release, establishing the potential of polymeric microsphere carriers for oral delivery. Further, the development of colonic drug delivery systems for Trimetazidine HCl highlighted the feasibility of targeting drugs to the colon to improve local efficacy. Albumin microspheres were also explored as a unique carrier

system for NSAIDs to reduce systemic exposure. The present study extends this microsphere platform into a nano-in-micro system, where budesonide-loaded Eudragit S100 and Eudragit L100 nanoparticles are further encapsulated into pH-sensitive microspheres to achieve dual protection and colon-specific release for ulcerative colitis, thereby overcoming the limitations of conventional single-unit systems. [7-9]

Building on this, microencapsulation-based colon delivery was reviewed as an overview, while flurbiprofen-loaded Eudragit RL/RS-100 microcapsules prepared by emulsion solvent evaporation demonstrated spherical morphology, 89.5% entrapment and 24-h pulsatile colonic release, supporting the present nano-in-micro approach. [10-11]

The gastrointestinal tract shows major changes in pH and transit time from the stomach to the colon, which complicates drug delivery. (Fig. 1)

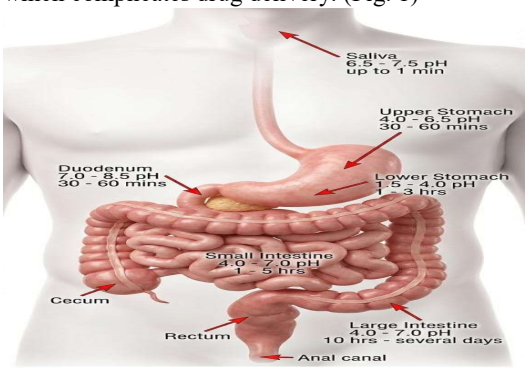


Fig.1 : The average time food spends in each part of the digestive system, along with the average pH.

APPROACHES

1. Colonic Pressure-Controlled Drug Delivery Systems

Pressure-controlled colon-targeted drug delivery systems are designed by taking advantage of a key physiological feature of the large intestine: its relatively high intraluminal pressure. In the colon, water absorption leads to increased viscosity of luminal contents, and strong peristaltic movements further contribute to elevated pressure levels compared to the small intestine. In healthy individuals, colonic intraluminal pressure is reported to average around 100–110 mm Hg.

To exploit this condition, pressure-responsive delivery devices have been developed. A notable example is the Pressure-Controlled Colon Delivery Capsule (PCDC). This system is typically coated with a thick layer of water-insoluble polymer such as ethyl cellulose. The coating protects the drug from premature release in the stomach and small intestine. However, once the formulation reaches the colon, the higher pressure causes the capsule to rupture, enabling drug release at the target site. Drugs such as 5-aminosalicylic acid and tegafur have been successfully incorporated into such systems. The release behaviour is influenced by factors like capsule size and coating thickness.

Further investigations using gastrointestinal transit studies, including biomagnetic tracking, and clinical evaluations have demonstrated the site-specific performance of PCDC systems. In human studies involving healthy volunteers, caffeine-loaded capsules showed no drug release in saliva until approximately 3–4.5 hours after administration, corresponding to transit into the colon, where rupture occurred due to colonic pressure.

Despite these promising findings, pressure-controlled systems still face limitations. The variability in colonic pressure due to circadian rhythms, as well as physiological factors such as high viscosity of colonic contents, can affect consistent capsule rupture and drug release. These challenges highlight the need for improved design strategies to ensure more reliable and reproducible colon-specific delivery. [12-15]

2. Prodrug Approach for Colon Targeting

Prodrug-based colon targeting involves administering an inactive drug that is selectively converted into its active form only in the colon. This helps protect the drug from premature degradation in the upper gastrointestinal tract, improves stability, enhances absorption, and reduces systemic side effects. A key strategy is the use of azo-based prodrugs, which are cleaved by colonic bacterial azo-reductase enzymes, ensuring site-specific drug release in the large intestine. Another important approach includes enzyme-triggered systems, such as phospholipase A2 (PLA2)-responsive phospholipid–drug conjugates, which release the drug selectively at inflamed colonic sites.

Recent advancements also include antibody or protease-activated prodrugs (e.g., CI-107), which are specifically activated in tumour microenvironments, enabling targeted therapy for colon cancer with reduced toxicity. [16-20]

3. Cyclodextrin-Based Conjugates for Colon-Targeted Drug Delivery

Cyclodextrins (CDs) are naturally derived cyclic oligosaccharides composed of α-, β-, and γ-forms containing 6, 7, and 8 glucose units, respectively. Their unique structure consists of a hydrophilic outer surface and a hydrophobic internal cavity, allowing them to form inclusion complexes with a wide range of drug molecules. This property enhances the solubility, stability, and bioavailability of poorly soluble drugs.

Recent advances have expanded their use in advanced drug delivery platforms such as nanofiber-based systems. For example, niclosamide, a poorly water-soluble antiparasitic drug, has been incorporated into electrospun nanofibers using Eudragit L100 with hydroxypropyl-β-cyclodextrin (HPβCD). Formulations containing the CD inclusion complex showed strong protection against premature drug release in acidic conditions,

releasing only about 8% of the drug in simulated gastric fluid over 2 hours, compared to higher release from non-complexed systems. In contrast, under colonic pH conditions, nearly complete drug release was observed, confirming effective site-specific delivery.

Overall, cyclodextrin-based systems provide a promising approach for protecting drugs during upper gastrointestinal transit while enabling controlled, microbiota-triggered release in the colon, making them valuable tools for targeted therapy. [21-25]

4. Osmotic Pressure-Controlled Colon-Targeted Drug Delivery

Osmotic pressure-controlled drug delivery systems are designed based on the pressure differences that exist throughout the gastrointestinal tract. In the colon, slower motility combined with extensive water and electrolyte absorption leads to increased viscosity of luminal contents and relatively higher intraluminal pressure compared to the upper GI tract. These physiological conditions are exploited to achieve controlled and site-specific drug release. These systems typically consist of a drug core along with an osmotic agent enclosed within a semipermeable membrane. In more advanced designs, such as push–pull osmotic systems, a drug layer and a swelling (push) layer are separated inside a coated capsule with a small delivery orifice. After the outer coating dissolves in the intestine, gastrointestinal fluids enter the system, causing the push layer to swell and gradually expel the drug through the orifice at a controlled rate. The rate of water influx primarily governs the drug release profile.

To prevent premature drug release in the upper gastrointestinal tract, these systems are often designed with a lag time, ensuring that drug delivery begins only after reaching the colon. Osmotic pressure is generated using agents such as salts or sugars, while pore-forming additives help improve the release of poorly soluble drugs.

More recently, microbially activated osmotic drug systems (MAODS) have been developed, combining osmotic technology with microbial responsiveness. In such systems, drug release can be influenced by colonic bacterial activity and membrane properties, offering more precise colon targeting. Studies using drugs like metronidazole have shown that membrane characteristics significantly affect release behavior, highlighting the potential of these systems for controlled and site-specific therapy with reduced systemic side effects. [26-27]

5. Inulin-based colon-targeted drug delivery

Inulin is a naturally occurring fructan polysaccharide widely explored as a carrier for colon-targeted drug delivery systems. It can withstand acidic gastric conditions and enzymatic digestion in the upper gastrointestinal tract, allowing it to reach the colon largely intact. In the colon, inulin is selectively metabolized by the resident microbiota, which triggers site-specific drug release. Apart from its role as a carrier, inulin possesses excellent biocompatibility, biodegradability, and prebiotic activity that supports the growth of beneficial intestinal bacteria. These characteristics make it highly suitable for colon-specific delivery systems. It has been formulated in various forms, including hydrogels, solid dispersions, nanoparticles, microparticles, and conjugates, depending on the therapeutic requirement.

Inulin-based nanoparticles, in particular, have shown promising results by protecting drugs during gastrointestinal transit and enabling microbiota- or pH-triggered release in the colon, thereby improving local therapeutic action while minimising systemic side effects. [28]

6. 3D-Printed Colon-Targeted Drug Delivery and Hot Melt Extrusion

Conventional oral dosage forms are generally mass-produced and may not provide patient-specific therapy, especially in conditions like inflammatory bowel disease (IBD), where disease location and severity vary between individuals. Additive manufacturing, particularly 3D printing, offers a solution by enabling the fabrication of personalised dosage forms with controlled dose strength, geometry, and drug release behaviour.

In colon-targeted delivery, 3D printing has been successfully used to develop pH-responsive tablets, such as budesonide formulations, designed to release the drug specifically in the colon. By modifying internal structure and layer thickness, drug release can be precisely directed to different gastrointestinal regions, including the ileum or specific segments of the colon. This enables localized and patient-specific therapy. Additionally, 3D printing supports complex systems such as liquid-loaded capsules and microbiota-based therapies like faecal microbiota transplantation, ensuring protection in the upper GI tract and controlled release in the colon.

Hot melt extrusion (HME) is a solvent-free manufacturing technique widely used to improve the solubility and bioavailability of poorly water-soluble drugs. Its importance has increased with several FDA-approved formulations. HME can also be integrated with technologies such as 3D printing, nanotechnology, and process analytical technology (PAT), making it highly versatile for advanced colon-targeted drug delivery systems. [29-31]

7. Design of experiments (DOE) and quality by design (QbD)

The application of Design of Experiments (DoE) and Quality by Design (QbD) has become increasingly important in developing colon-targeted drug delivery systems. These approaches allow systematic, statistically guided optimization of

formulation and process variables, replacing traditional trial-and-error methods.

Initial screening often uses factorial designs, while optimisation is performed using response surface methodologies such as Box–Behnken, Central Composite, and D-optimal designs. These methods help optimise critical factors, including polymer ratios, coating thickness, drug-to-polymer ratio, and process parameters like spray drying and hot melt extrusion.

This approach helps define a robust design space that ensures minimal drug release in the upper gastrointestinal tract and controlled release in the colon. Studies have shown that combinations of pH-sensitive polymers like Eudragit S100/L100 with biodegradable polysaccharides can be optimised to achieve minimal release in gastric and intestinal pH, followed by rapid release under colonic conditions.

For example, Eudragit-coated systems developed via hot melt extrusion have been optimized using the Box-Behnken design to achieve a lag phase with minimal early release and more than 90% drug release in simulated colonic conditions. Similarly, nanoparticle and microparticle systems have been optimised using response surface methods to control particle size, drug loading, and release behaviour. [32-36]

CHALLENGES IN COLON-TARGETED DRUG DELIVERY SYSTEMS

Colon-targeted drug delivery systems are designed to provide localised treatment in the colon while reducing systemic side effects. Although the concept is highly promising, translating these systems from laboratory research into reliable clinical products remains difficult due to several biological and technical limitations.

1. Physiological variability of the gastrointestinal tract

One of the major challenges is the natural variation in gastrointestinal physiology between individuals and even within the same person. Factors such as gastric emptying time, intestinal transit speed, colonic movement, pH levels, and fluid volume can change significantly. Because of this variability, systems that depend only on pH or time triggers may not always release the drug at the correct site, leading to either early or incomplete drug release.

2. Variability in gut microbiota

Many colon-targeted systems rely on bacterial enzymes present in the colon to activate drug release. However, the composition and activity of gut microbiota differ widely among individuals due to diet, age, disease conditions like IBD, and antibiotic use. These differences can affect enzyme levels and result in inconsistent drug release from microbiota-responsive systems.

3. Mucus barrier limitations

The colon is covered by a thick mucus layer that protects the intestinal wall but also acts as a barrier to drug delivery. This layer can prevent drug carriers from reaching the epithelial surface or trap mucoadhesive particles before they reach the target site. In inflammatory diseases, mucus properties may change further, making it even more difficult to design systems that can both penetrate and remain stable in the mucus environment.

4. Poor *in vitro in vivo* correlation

Another key issue is that laboratory tests often fail to accurately reflect what happens inside the human body. In vitro models cannot fully replicate the complex conditions of the gastrointestinal tract, such as movement, enzyme activity, microbial interaction, and mucus dynamics. As a result, formulations that perform well in the lab may behave differently in real biological systems.

5. Stability of sensitive drugs

Delivering biologically active molecules such as peptides, proteins, nucleic acids, and probiotics to the colon is challenging. These compounds are easily degraded in acidic and enzymatic conditions of the stomach and small intestine. Therefore, it is difficult to design systems that can protect these molecules during transit and still release them effectively in the colon without losing activity.

6. Scale-up and manufacturing challenges

Although many advanced drug delivery systems work well at a laboratory scale, reproducing them on an industrial scale is often difficult. Issues such as batch-to-batch variation, coating uniformity, particle size control, and process reproducibility can affect product quality and limit commercialization.

7. Safety and long-term toxicity concerns

New delivery systems, especially those involving nanoparticles or novel materials, may behave unpredictably inside the body. There is a risk of accumulation in tissues or immune reactions. Long-term safety data is still limited, which makes regulatory approval more challenging.

8. Regulatory challenges

Regulations for advanced systems such as nanomedicines, 3D-printed dosage forms, and microbiota-responsive formulations are still evolving. The lack of clear guidelines for testing, safety evaluation, and clinical endpoints slows down their development and approval process.

9. Patient-specific variability

Effective colon targeting often requires personalised treatment because disease location, severity, and microbiome composition differ between patients. However, there are currently limited clinical tools to customise formulations based on individual patient profiles.

10. Cost and real-world applicability

Even if these systems are scientifically effective, their complexity often makes them expensive to manufacture. For chronic diseases like inflammatory bowel disease, high production costs and supply limitations can restrict accessibility, especially in low-resource settings.

Overall Insight

To overcome these challenges, future research must focus on better physiological models, improved scale-up techniques, stronger safety evaluations, and patient-specific treatment strategies. Only by integrating pharmaceutical science, biology, engineering, and regulatory science can colon-targeted drug delivery systems become reliable and widely used in clinical practice. [37- 42]

ROLE OF ARTIFICIAL INTELLIGENCE AND ADVANCED TECHNOLOGIES IN OVERCOMING CTDDS CHALLENGES

Recent developments show that artificial intelligence (AI) and related digital technologies are becoming important tools in improving colon-targeted drug delivery systems (CTDDS). These approaches help overcome many long-standing limitations related to variability in human physiology, formulation design, and clinical predictability.

AI and machine learning are now being used to support formulation design and optimisation by linking formulation variables with biological and physiological data. These models can predict drug release patterns, coating performance, and how variability in gastrointestinal conditions may affect drug behaviour. This reduces trial-and-error experimentation and improves formulation efficiency.

Another important advancement is the use of AI-based physiologically based pharmacokinetic (PBPK) modelling and digital twin technology, which allows simulation of patient-specific conditions such as colonic pH, transit time, and disease variability. This helps improve the prediction of in vivo performance and strengthens in vitro–in vivo correlation (IVIVC), which has traditionally been a major challenge in CTDDS development.

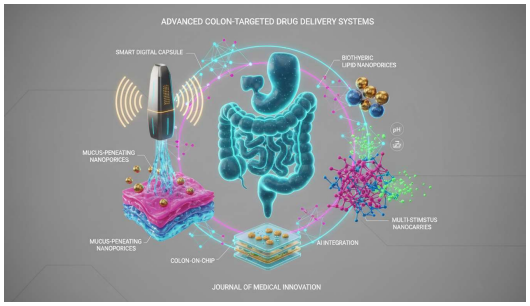
In parallel, organ-on-chip and colon-on-chip systems have emerged as highly relevant experimental platforms. When combined with AI-based data analysis, these microfluidic models can closely mimic real intestinal conditions, including mucus secretion, peristaltic movement, microbial interaction, and inflammatory responses. This provides a more realistic environment compared to conventional laboratory dissolution tests.

At the material level, smart and multi-stimuli-responsive drug carriers such as pH-, enzyme-, and oxidative stress (ROS)-responsive systems are being developed to improve site-specific drug release. Additionally, mucus-penetrating nanoparticles and bioresponsive carriers are helping improve drug transport and epithelial targeting in the colon.

Furthermore, advanced manufacturing techniques like 3D and 4D printing enable precise control over dosage form design, including geometry, internal structure, and release behaviour. These technologies also support personalised medicine by allowing patient-specific formulation design and improving reproducibility during scale-up.

Overall, the combination of AI-driven modelling, advanced biomimetic testing platforms, and intelligent drug delivery materials offers a powerful integrated strategy. Together, these innovations can address major challenges such as physiological variability, microbiome differences, poor IVIVC, and manufacturing limitations, ultimately accelerating the clinical translation of colon-targeted drug delivery systems. [43-49]

ADVANCED TECHNOLOGIES FOR COLON-TARGETED DRUG DELIVERY SYSTEMS



Recent advancements in colon-targeted drug delivery are increasingly driven by the integration of smart technologies, computational tools, and bioengineered systems. These innovations aim to overcome major limitations such as physiological variability, poor predictability, and scale-up challenges, while improving precision and patient-specific therapy.

1. Artificial Intelligence (AI) and Machine Learning (ML)

AI and ML are being widely used to improve formulation design and predict drug release behaviour in colon-targeted systems. By combining formulation variables (such as polymer type, coating thickness, and particle size) with biological factors like GI transit time, pH variation, and disease conditions, these models help reduce experimental uncertainty. AI-assisted PBPK modelling and digital twin approaches also support simulation of patient variability, improving prediction accuracy and enabling more personalised therapy.

2. Colon-on-Chip and Advanced In Vitro Models

Colon-on-chip systems replicate key features of the human colon, including epithelial lining, mucus secretion, microbial environment, and peristaltic motion. These platforms provide a more realistic biological environment compared to conventional dissolution tests. Disease-specific models, such as IBD-on-chip, are especially useful for evaluating drug performance under inflammatory conditions and improving IVIVC.

3. Multi-Stimulus-Responsive Polymers

Modern polymer systems are designed to respond to multiple biological triggers such as pH changes, bacterial enzymes, and oxidative stress. These dual- or triple-responsive materials ensure that drug release occurs specifically in the colon while

minimising premature release in the upper GI tract. They are particularly useful for targeted delivery of anti-inflammatory drugs and biologics.

4. Mucus-Penetrating Nanoparticles

Unlike traditional mucoadhesive systems, mucus-penetrating nanoparticles are engineered with hydrophilic or zwitterionic coatings (such as PEG) that allow them to pass through the mucus layer rather than becoming trapped. This improves drug diffusion to the epithelial surface, enhancing absorption and therapeutic effectiveness, especially in inflammatory bowel disease.

5. Microbiome-Responsive and Synthetic Biology Systems

These systems use colonic bacteria or engineered microorganisms to trigger drug release. Advances in synthetic biology have enabled the development of engineered probiotics that can sense inflammatory signals and release therapeutic agents locally. This approach allows more controlled and potentially personalised therapy based on an individual's microbiome profile.

6. Digital Pills and Smart Capsule Systems

Smart capsules equipped with sensors can monitor gastrointestinal parameters such as pH, temperature, and transit time in real time. This provides valuable in vivo data on how colon-targeted formulations behave, helping improve IVIVC and supporting regulatory evaluation.

7. Advanced Manufacturing and PAT Tools

Process Analytical Technology (PAT) tools such as NIR and Raman spectroscopy allow real-time monitoring of manufacturing parameters like coating thickness, particle size, and drug distribution. This improves consistency, reduces batch variability, and supports smooth scale-up from lab to industry.

8. Nano-Biohybrid and Biomimetic Systems

Nano-biohybrid systems such as polymer lipid hybrids, exosome-inspired nanoparticles, and metal organic frameworks (MOFs) improve drug stability and targeted delivery. These systems are especially useful for delivering sensitive molecules like peptides, proteins, and nucleic acids to the colon.

9. AI-Based Toxicity and Biodistribution Prediction

AI-driven toxicology platforms are being used to predict long-term safety, immune response, and biodistribution of nanocarriers. These tools help identify potential risks early in development, reducing reliance on animal studies and accelerating regulatory approval. [50-59]

Future Aspects of Colon-Targeted Drug Delivery Systems.

Colon-targeted drug delivery systems (CTDDS) continue to evolve rapidly, but several existing limitations also open new opportunities for future innovation. The next generation of CTDDS is expected to be more intelligent, patient-specific, and clinically reliable through the integration of advanced materials, nanotechnology, and digital health tools.

1. Smart and Multi-Responsive Polymer Systems

Traditional systems mainly depend on pH or time-dependent release mechanisms, which often show variability in real conditions. Future research is moving toward smart polymer systems that respond to multiple biological signals, such as pH, microbial enzymes, redox conditions, and mucus environment. These multi-trigger systems can significantly improve site-specific drug release and reduce premature drug loss in the upper gastrointestinal tract. Development of safer, biodegradable, and biocompatible polymers will also be important, especially for long-term treatment of chronic diseases like IBD.

2. Nanotechnology and Hybrid Carrier Systems

Nanocarriers such as liposomes, solid lipid nanoparticles, and nanoemulsions are gaining attention for colon targeting due to their ability to improve drug solubility, permeability, and controlled release. Future work is expected to focus on surface engineering of nanoparticles for improved mucus penetration, receptor targeting, and colon retention. Hybrid systems combining polymeric stability with lipid-based permeability advantages are also promising, especially for poorly soluble drugs and biologics.

3. Advanced Manufacturing and Personalised Dosage Forms

Technologies like 3D printing and hot-melt extrusion are expected to transform CTDDS development. These methods allow precise control over dosage form structure, drug distribution, and release behaviour. In the future, they may enable fully personalised therapies, where drug dose, release site, and combination therapies are tailored to individual patients based on disease severity and colon transit time. However, challenges such as large-scale manufacturing, material standardisation, and regulatory approval still need to be addressed.

4. Improved Clinical Translation and Safety Evaluation

Despite strong laboratory evidence, clinical translation of CTDDS remains limited. Future progress will depend on better in vivo predictive models, long-term safety studies, and improved understanding of biodistribution and immunogenicity, especially for nanocarriers. Development of physiologically relevant models and regulatory frameworks specific to advanced drug delivery systems will be essential for successful commercialisation.

5. Personalized and Targeted Therapies

Future CTDDS are expected to move away from a "one-size-fits-all" approach toward personalized medicine. Systems may be designed to respond to specific disease markers, such as inflamed tissue receptors or tumour-associated antigens. Additionally, microbiome-responsive drug delivery

systems are emerging, where drug release is triggered by disease-associated bacterial enzymes or metabolites. Patient-specific factors such as microbiome profile, mucus thickness, and transit time may eventually guide individualised therapy design.

6. Overcoming the Mucus Barrier

The mucus layer of the colon remains a major obstacle for drug penetration. Future strategies include mucus-penetrating nanoparticles, smart surface-modified carriers, and mucoadhesive systems that improve retention without hindering drug diffusion. A deeper understanding of mucus changes in healthy versus diseased conditions will help in designing more effective delivery systems.

7. Expansion to Biologics and Advanced Therapies

CTDDS is no longer limited to small molecules. Future systems are expected to deliver biologics, vaccines, nucleic acids, and combination therapies such as anti-inflammatory agents with probiotics or chemotherapy with immunotherapy. These advanced systems will require highly protective carriers that ensure stability, targeted release, and safe mucosal interaction. [60-69]

DISCUSSION: Colon-targeted drug delivery has evolved from conventional delivery strategies to sophisticated and smart delivery platforms. This review underscores the role of traditional approaches such as prodrug strategies, osmotic systems, and polysaccharides as excipients for site-specific delivery and how variability in gastrointestinal physiology, such as different pH, transit time, and microbial population, affects their performance (1-5,19-21).

Nanoparticle-based delivery systems have revolutionised this field with their unique characteristics: higher drug stability, enhanced drug protection, and the flexibility to tailor a myriad of system parameters like particle size, surface properties, and drug load, providing control over release and absorption (4, 15, 16). Mucus-penetrating nanoparticles, an example of an intelligent system, have overcome a critical barrier in colon-targeted delivery- poor mucin interaction (12, 34).

New technologies such as 3D printing and hot melt extrusion have introduced greater control and individuality to this field (22-24, 25-26). These methods allow for modification of dosage form structure, drug incorporation, and release kinetics with excellent precision, reproducibility, and scalability (22-27). Furthermore, application of quality by design (QbD) principles ensures optimisation of formulation variables, which results in robust and reliable delivery systems (27).

However, there are still barriers to the translation of such advanced technologies to clinical applications. Variability of GI physiology, microbial species diversity, poor interaction with the mucin layer, and lack of reliable in vitro-in vivo correlation of systems remain limitations for colon-specific drug delivery. Moreover, the scaling of production, the regulation of nanocarriers, and the long-term effects of nanocarriers are still issues that need to be addressed.

In general, colon-targeted drug delivery is transitioning toward a combination of nanomedicine, modern manufacturing processes, and computational modelling. The key to the clinical translation of colon-targeted delivery systems lies in research and innovation toward improving interaction with biological barriers and in vitro-in vivo correlation.

CONCLUSION: Targeted drug delivery to the colon offers a novel strategy for delivering drugs for treating colonic diseases with increased efficacy and lower systemic toxicity. Based on the foundation of the earlier approaches, recent progress in the areas of nanotechnology, smart polymers, and modern manufacturing processes has enabled more precise targeting of colonic diseases. Nevertheless, physiological variations, the mucus barrier, and regulatory barriers still need to be overcome for their successful clinical application. The future efforts are expected to make these more resilient, personalised, clinically translatable systems by integrating more cutting-edge technologies and better in vivo evaluation methods.

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