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AI-Enabled Colon-Targeted Drug Delivery Systems: Revolutionizing Personalized Gastrointestinal Therapeutics

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Abstract: Colon-targeted drug delivery has emerged as a promising strategy for the management of lower gastrointestinal diseases, including inflammatory bowel disease (IBD) and colorectal cancer, as well as for improving the bioavailability of drugs susceptible to gastric degradation or hepatic first-pass metabolism [1–4]. Conventional colonic delivery systems — relying on time-controlled release, pH-sensitive polymer coatings, or microbiota-triggered polysaccharide degradation — are limited by significant inter-individual variability in gastrointestinal physiology, restricting their therapeutic precision and scalability. To overcome these issues, pharmaceutical research is increasingly incorporating machine learning (ML) and artificial intelligence (AI) . The relevance of AI-enhanced physiologically based pharmacokinetic (PBPK) modeling for patient-specific digital twin dosing and reactive oxygen species (ROS)-responsive smart nanoplatforms for site-selective IBD therapy is thoroughly examined in this review. Additionally examined are the implications for customized colonic therapy design and the incorporation of AI into diagnostic techniques. AI-driven optimization is examined in relation to advanced formulation technologies, such as hot-melt extrusion (HME), three-dimensional (3D) printing, computer-aided molecular simulation, and electronic drug delivery devices like IntelliCap®. Despite notable progress, challenges remain regarding model interpretability, data scarcity, lack of standardized protocols, and incomplete integration between AI-based diagnostics and therapeutic formulation pipelines [33–35]. This review concludes that the convergence of AI with colonic drug delivery science offers a transformative path toward precision, efficiency, and patient-individualized therapeutic outcomes.

Keywords: *Artificial Intelligence; Machine Learning; Colon-Targeted Drug Delivery; Inflammatory Bowel Disease; Colorectal Cancer; Physiologically Based Pharmacokinetic Modeling; Graph Neural Networks; Hot-Melt Extrusion; 3D Printing; Drug-Microbiota Interactions.*

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I. INTRODUCTION

Targeted drug delivery to the colon represents a notable advancement over traditional oral pharmaceutical approaches [1,2]. This methodology is particularly beneficial for managing localized diseases of the lower gastrointestinal tract, such as inflammatory bowel disease (IBD) and colorectal cancer [3]. Beyond localized conditions, colonic delivery is also advantageous for compounds prone to gastric irritation, those subject to extensive hepatic first-pass metabolism, or drugs that lose stability in the acidic gastric environment [4]. Various modified-release strategies have been developed to achieve reliable colonic targeting, including transit time-based systems, pH-responsive polymer coatings, and formulations activated by gut microbiota [1,4].

These approaches collectively aim to improve drug stability, reduce required dosing, and limit unwanted systemic exposure, thereby improving therapeutic outcomes. Despite these benefits, traditional colon-targeted formulations often involve lengthy, resource-intensive development processes. The growing complexity of modern delivery systems adds further implementation hurdles. In this context, artificial intelligence (AI) and machine learning (ML) have emerged as powerful tools capable of accelerating formulation development, fine-tuning drug release behavior, and predicting delivery outcomes with greater accuracy [5, 6]. The pharmaceutical sector is increasingly adopting AI across numerous development stages, from early target identification and excipient selection to supply chain management and continuous manufacturing optimization. [6].

➢ *Conventional Approaches in Colonic Drug Delivery*

Traditional strategies for delivering drugs to the colon rely on physiological triggers such as intestinal transit time, luminal pH gradients, and microbial enzymatic activity [1, 4]. Time-controlled systems release drugs after a pre-set lag phase, while pH-sensitive coatings dissolve only when the luminal pH reaches the colonic range [4]. Microbiota-triggered systems exploit the enzymatic capabilities of colonic bacteria to degrade specific polysaccharide coatings, releasing the drug payload [1]. Each of these strategies has limitations rooted in inter-individual variability in GI physiology, dietary habits, disease states, and concomitant drug use, all of which can compromise targeting precision [2, 3].

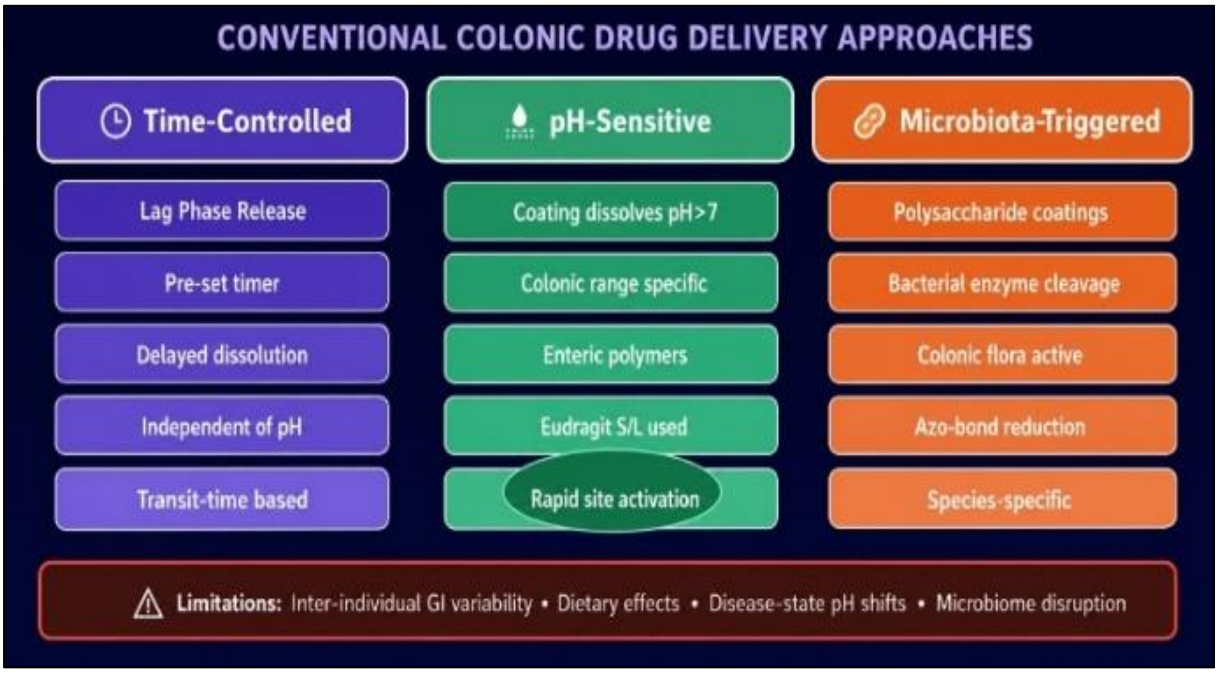

Fig 1 The Three Principal Conventional Trigger Mechanisms for Colonic Drug Delivery are Time-Controlled Hase Release, pH-Sensitive Polymer Dissolution, and Microbiota-Activated Polysaccharide Coating Degradation, Alongside their Shared Physiological Limitation.

II. ARTIFICIAL INTELLIGENCE TECHNIQUES IN DRUG DELIVERY

➢ *Machine Learning*

Machine learning encompasses two broad paradigms: supervised and unsupervised learning [7]. Supervised algorithms are trained on labeled datasets to generate predictions — for instance, forecasting compound activity against a biological target or anticipating adverse drug reactions from historical safety data [8]. Unsupervised approaches, in contrast, operate on unlabeled data to detect inherent patterns, such as grouping genes with similar expression signatures or categorizing compounds by structural similarity [9].

Widely used ML algorithms in pharmaceutical research include random forests, which handle high-dimensional data effectively while revealing feature importance [10]; support vector machines (SVMs), suited to classification and boundary optimization tasks [11]; and gradient boosting machines, which aggregate multiple weak learners into a highly predictive composite model [12]. Together, these tools enable faster identification of promising drug candidates and efficient processing of large, complex datasets [13].

➢ *Gene Expression Learning*

In colorectal cancer (CRC) research, ML models are applied to gene expression (GE) datasets to advance biomarker discovery, refine drug response prediction, and enable individualized treatment approaches [14]. Preprocessing pipelines such as Microarray Suite (MAS) and Robust Multi-array Average (RMA) are employed to normalize data, followed by functional enrichment analysis using tools like Cluster Profiler [15, 16]. The functional links between differentially expressed genes (DEGs) are further revealed by protein–protein interaction (PPI) networks, which are then confirmed by survival analysis [14]. Advanced ensemble classifiers, such as ABF-Cat Boost, considerably boost prediction accuracy in these operations [14].

Machine learning has also been used to anticipate drug-induced disruption of intestinal microbial communities [17, 18]. Using a large-scale dataset encompassing over 18,600 drug-bacteria interaction records, researchers have trained thirteen distinct algorithms—spanning tree-based models, artificial neural networks, and ensemble techniques—to predict how specific drugs affect gut microbiota [18]. Following hyperparameter tuning and multi-metric evaluation, optimal models were identified that can reliably forecast previously unknown pharmacological effects on microbial populations [18, 19].

➢ *Deep Learning and Neural Network Architectures*

Drug design increasingly relies on deep neural networks (DNNs), especially Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs) [20]. CNNs are useful for virtual screening, target validation, and drug optimization because they can handle spatially structured molecular data, such as 2D or 3D point cloud representations of chemical structures [21]. By independently extracting pertinent molecular features instead of depending on manually created descriptors, deep learning is greatly improving structure–activity relationship (SAR) modeling [20, 22]. This makes it possible to anticipate characteristics like binding affinity, water solubility, and metabolic stability with greater accuracy [23].

Early toxicity prediction is another benefit of deep learning [24]. DL models may detect subtle structural correlates of harm by analyzing massive chemical datasets in conjunction with known toxicity profiles, allowing researchers to identify potentially hazardous chemicals before they move forward with clinical investigation [25]. This proactive screening enhances overall medication safety and lowers attrition risk.

➢ *Graph Neural Networks*

A specific class of deep learning architectures called "Graph Neural Networks (GNNs)" is made to handle graph-structured data, which consists of nodes that represent entities and edges that represent relationships [26, 27]. They differ from traditional neural networks intended for grid-like inputs in that they can model dependencies in non-Euclidean environments [27]. In order to create meaningful representations of both local and global graph structure, GNNs use a message-passing mechanism in which each node iteratively integrates data from its neighbors [26].

Prominent GNN architectures include Graph Convolutional Networks (GCNs), Graph Attention Networks (GATs), and Graph SAGE, each offering distinct strengths in scalability, attention weighting, and inductive learning [27]. These architectures hold significant promise for modeling complex microbiome interaction networks relevant to colonic drug delivery [26].

III. AI APPLICATIONS IN COLON-TARGETED DRUG DELIVERY SYSTEMS

➢ *Drug Release Forecasting*

The colonic epithelium offers distinct pharmacological advantages for drug delivery, including reduced cytochrome P450 enzyme concentrations and a unique efflux transporter profile that can enhance drug bioavailability [1, 2]. However, current development workflows for colon-targeted formulations remain largely dependent on slow, low-throughput in vitro and in vivo screening, impeding rapid material selection [5]. Polysaccharides are attractive candidates for colonic coating due to their selective breakdown by resident microbial enzymes [28].

To streamline material screening, ML models have been applied using publicly available experimental data to forecast the release of 5-aminosalicylic acid from polysaccharide-based coatings in simulated colonic environments representing human, rat, and canine physiology [28]. Polysaccharide features were encoded exclusively from Raman spectral data, and models were validated against eight previously unseen drug release datasets from novel coatings [28]. This approach not only demonstrated robust predictive reliability but also provided mechanistic insight into which chemical properties determine a polysaccharide's suitability for colonic drug delivery, laying a foundation for spectral data-driven formulation pre-screening [28].

➢ *Prediction of Microbiota Interactions*

Given the colon's dense microbial population and its substantial enzymatic capacity to metabolize drugs, predicting drug-microbiota interactions is critically important [17]. Such metabolism can substantially alter drug stability and toxicity, especially when compounds are administered directly to the colon [29]. Recent ML advances have enabled bidirectional prediction of these interactions, elucidating both how gut bacteria biotransform medications and how non-antibiotic drugs modulate microbial growth [18, 19].

In two complementary studies, McCoubrey et al. used ML to investigate these relationships [18, 19]. The first, drawing on a 455-drug dataset, classified compounds as susceptible or resistant to microbial metabolism based on physicochemical descriptors and molecular fingerprints—providing a rapid in silico tool to anticipate pharmacokinetic variability arising from gut-mediated drug depletion [19]. The second study analyzed over 18,000 drug-bacteria interaction records to model the effects of drugs on gut flora development, offering a systematic framework for assessing microbiome impact [18].

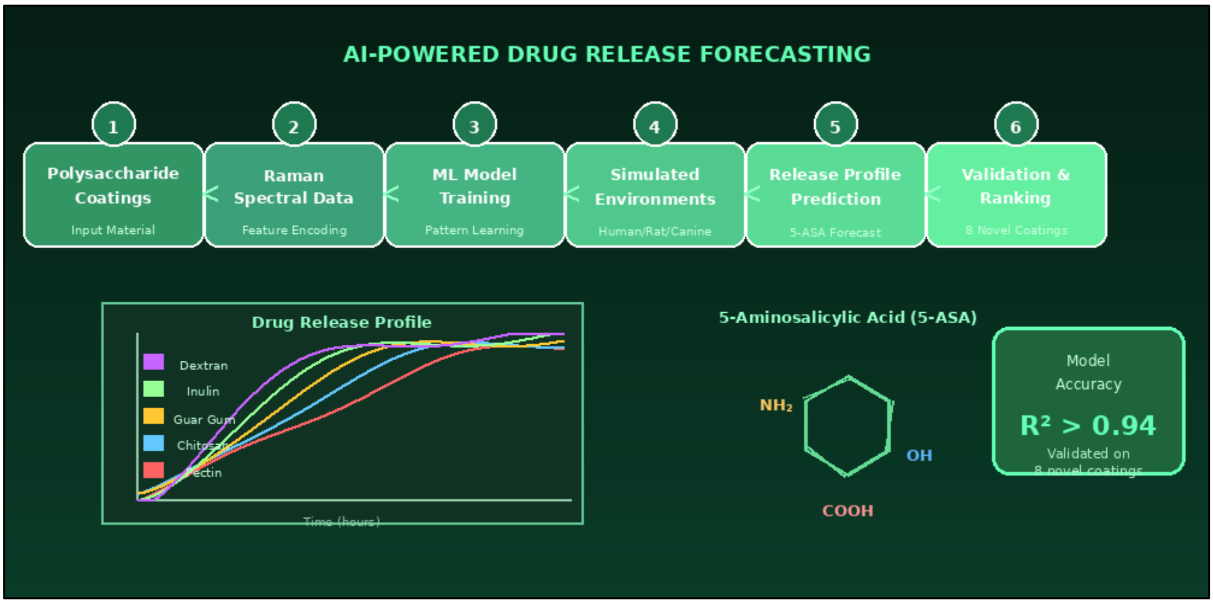

Fig 2 The AI-Powered Drug Release Forecasting Pipeline: from Polysaccharide Coating Input and Raman Spectral Encoding Through ML Model Training and Simulated Colonic Environments to Validated Release Profile Predictions for 5-Aminosalicylic Acid (5-ASA) from Novel Coatings

➢ *Mechanistic and Pharmacokinetic Modeling*

Pharmaceutical development relies heavily on accurate prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) [30]. By enabling parameter optimization and patient-level customization, artificial intelligence (AI) is improving conventional pharmacokinetic/pharmacodynamic (PK/PD) modeling, especially physiologically based pharmacokinetic (PBPK) models [30,31]. AI generates patient-specific pharmacokinetic simulations that function as a digital twin for therapeutic dosing by incorporating individual patient data—such as genetic profiles, organ function metrics, and comorbidities—instead of depending on population-averaged physiological values [30, 31].

This AI-enhanced PBPK framework has been applied to guide the development of colon-selective therapies by informing molecular design, formulation selection, and clinical trial planning [31]. Sensitivity analyses within these models have identified key compound and formulation attributes required to achieve favorable colon-to-systemic drug exposure ratios, demonstrating utility in first-in-human and late-stage trial design [31]. The approach marks a shift from population-based to truly individualized dosing strategies [32].

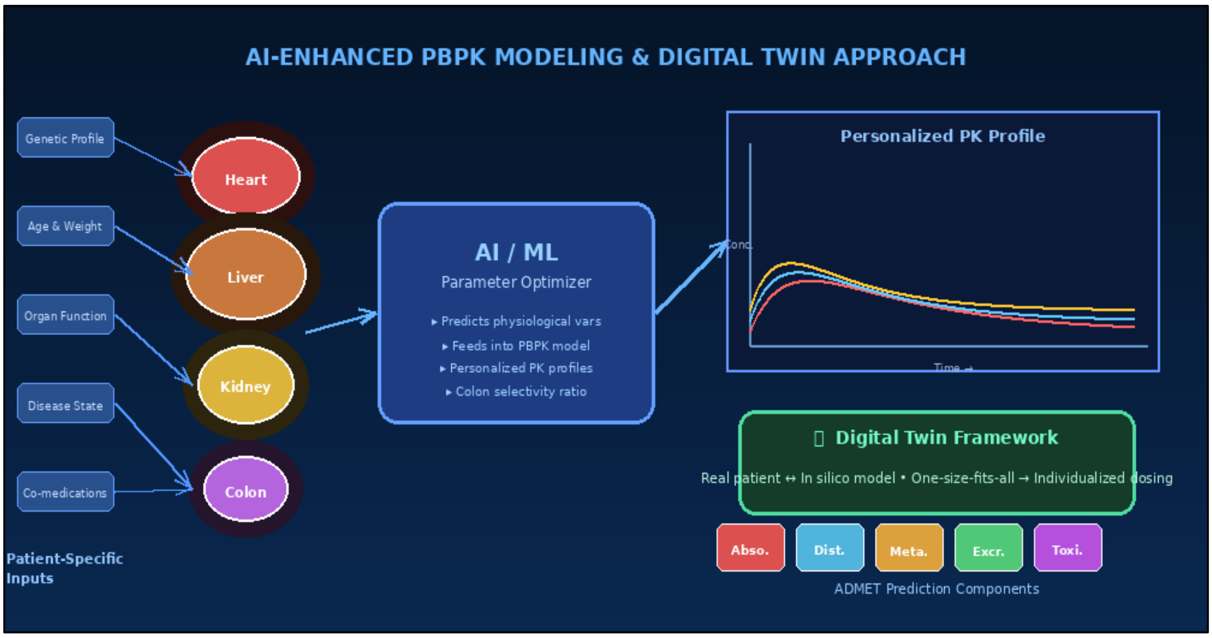

Fig 3 AI-Enhanced PBPK (Physiologically Based Pharmacokinetic) Modeling Framework: Patient-Specific Genetic, Organ Function, and Disease Data Feed an AI Optimizer that Personalizes PBPK Parameters, Generating Individual Drug Concentration-Time Profiles—the 'Digital Twin' Approach to Precision Dosing.

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➢ *Smart AI-Driven Delivery Platforms*

Pharmacological treatment of gastrointestinal inflammatory conditions, such as IBD, remains challenging due to difficulties in achieving adequate local drug concentrations at inflamed sites [1, 3]. Smart nanomaterials engineered to respond to reactive oxygen species (ROS) — which are overproduced in inflamed GI tissue — represent an emerging strategy for site-specific drug release [36]. ROS-responsive nanoplatforms can be engineered to release therapeutic payloads selectively at disease sites, minimizing systemic absorption and off-target effects [36, 37]. Recent innovations have further enhanced these systems through surface modifications that improve cellular uptake, tissue targeting, and integration into multi-stimulus-responsive architectures [36, 37].

➢ *AI in Diagnosis and Disease Monitoring*

AI is increasingly applied to diagnostic and imaging workflows for colon-related diseases, with direct implications for optimizing colonic drug delivery systems [38, 39]. ML and deep learning algorithms can analyze patient records, histopathological data, and medical imaging to facilitate early detection of conditions such as ulcerative colitis and colorectal cancer [38]. These tools not only reduce diagnostic error but also enable stratification of patients by disease severity—a critical input for designing individualized colonic therapies [15, 16].

In imaging, AI has demonstrated value across CT, MRI, and colonoscopy modalities [38, 39]. AI-assisted colonoscopy systems autonomously identify polyps, categorize lesions, and support real-time biopsy decisions, improving early lesion detection rates [39]. Enhanced CT and MRI analysis yields precise characterization of tumor location, inflammatory extent, and mucosal integrity — all of which inform decisions about where and how to deliver colon-targeted drugs [38, 39]. Despite these advances, integration of imaging-based AI with formulation development pipelines remains largely incomplete, with most systems operating independently in diagnostic rather than therapeutic contexts [33].

IV. COMPUTATIONAL AND ADVANCED FORMULATION TECHNOLOGIES

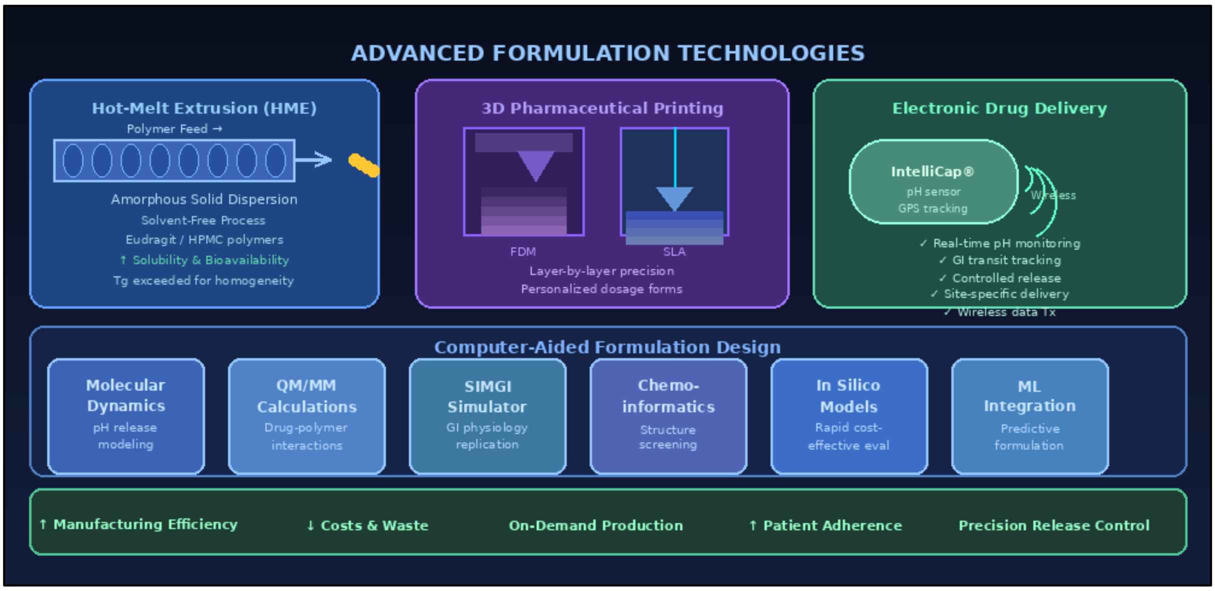

Fig 4 Advanced Pharmaceutical Formulation Technologies: Hot-Melt Extrusion (HME) for Amorphous Solid Dispersions, FDM, and SLA 3D Printing for Precision Dosage Forms; IntelliCap® Electronic Delivery; and Computer-Aided Design Methods Including Molecular Dynamics, QM/MM, and SIMGI Simulation.

➢ *Computer-Aided Formulation Design*

Computational methods, including molecular dynamics simulation, quantum mechanics/molecular mechanics (QM/MM) calculations, and cheminformatics, are widely employed in colonic drug delivery system (CDDS) design to rationalize formulation development and reduce empirical workload [40, 41]. These techniques support prediction of formulation behavior under varied physiological conditions—including changes in pH, temperature, ionic strength, and biological interactions [41, 42]. For example, computational models of glycogen-based hydrogels have successfully predicted pH-dependent drug release patterns and characterized polymer-drug binding interactions [43]. In silico gastrointestinal simulators, such as SIMGI, can replicate colonic microenvironments and microbial activity, enabling rapid and cost-effective evaluation of formulation performance before resource-intensive in vivo studies [44].

➢ *Electronic Device-Assisted Formulation*

Electronic drug delivery devices represent a sophisticated approach to colon-targeted therapy by enabling real-time in vivo assessment of drug release and gastrointestinal transit [45, 46]. Devices such as the IntelliCap system integrate drug release control, physiological monitoring, and wireless data transmission in a single capsule platform [45]. By continuously measuring luminal pH and tracking capsule position, these systems provide valuable in vivo data to guide formulation design and

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confirm site-specific delivery—including ileocolonic administration in human subjects [46]. While offering precision and real-time data acquisition, challenges include high manufacturing costs, biocompatibility requirements, and the potential for technical malfunction [45].

➤ *Hot-Melt Extrusion*

A common solvent-free manufacturing method for creating amorphous solid dispersions that improve the solubility and bioavailability of poorly water-soluble medications is hot-melt extrusion (HME) [47]. Its adoption has grown substantially following regulatory approval of multiple commercial products prepared by this method [47, 48]. HME is compatible with a range of enabling technologies, including process analytical tools (PATs), nanotechnology, and 3D printing [49, 50]. Processing temperature must exceed the polymer glass transition temperature and drug melting point to achieve molecular-level homogeneity [51]. Polymers such as Eudragit and HPMC are frequently used due to their favorable thermal stability and pH-responsive release properties [50, 51].

➤ *Three-Dimensional Printing*

Expanded capabilities to create customized dosage forms with precise control over drug release kinetics are provided by combining HME with 3D printing technology; this is particularly beneficial for colon-specific delivery. Expanded capabilities to develop customized dosage forms with exact control over drug release kinetics are provided by combining HME with 3D printing technology; this is particularly valuable for colon-specific delivery. [47, 48]. Three-dimensional printing enables fabrication of complex geometries with multiple drug-loaded compartments, personalized dose strengths, and tailored release profiles that are difficult or impossible to achieve through conventional manufacturing processes [47].

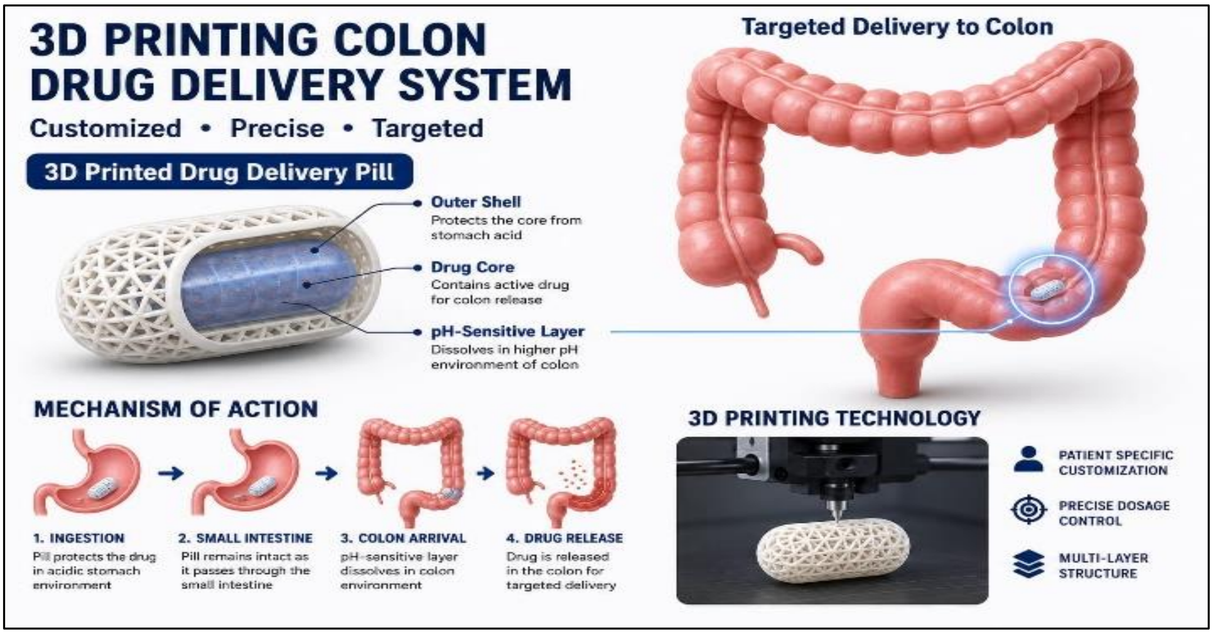

Fig 5 Schematic Representation of 3D-Printed Colon-Specific Drug Delivery Systems: Design, Mechanisms, and Applications”

V. LIMITATIONS AND CHALLENGES

The practical performance of AI-driven pharmaceutical models is constrained by several interrelated factors, including algorithmic transparency, reproducibility, data quality, and accessibility [33, 34, 35]. Pharmaceutical datasets are often limited in size and heterogeneous in collection methodology, making standardization of ML research protocols challenging [35]. Scarcity of negative data — instances where a drug or formulation fails — can bias models toward overly optimistic predictions that fail to generalize to real-world conditions [34].

Many ML models function as "black boxes," offering limited interpretability that reduces clinician and researcher confidence [33]. Furthermore, models seldom quantify prediction uncertainty, limiting their practical utility in clinical decision-making [35]. Addressing these gaps requires establishing clear guidelines for AI use in oral drug delivery, promoting data-sharing norms, and improving model transparency through explainability tools [33, 34]. Inter-patient physiological variability and imprecise anatomical targeting prior to drug release remain persistent challenges that computational approaches alone cannot fully resolve [33].

VI. CONCLUSION

The convergence of artificial intelligence with colonic drug delivery science offers a meaningful path forward in addressing the longstanding challenges of the field [1, 5, 6]. The complexity of the GI microenvironment, pronounced inter-individual physiological differences, and intricate drug-microbiome interactions have historically limited the reliability and scalability of colon-targeted therapies [2, 4]. AI provides robust predictive tools that reduce dependence on trial-and-error experimentation and foster more systematic, data-driven formulation development [5, 6].

Realizing this potential, however, requires coordinated efforts to promote research openness, data sharing, and interdisciplinary collaboration between pharmaceutical scientists and data engineers [33, 34]. Existing AI research, while primarily focused on controlled and sustained-release systems, is already enhancing drug release profile optimization and enabling more precise colonic targeting [28]. As GI physiology varies considerably across patients, AI-driven personalization—incorporating microbiome-triggered release mechanisms and patient-specific physiological data—represents a particularly promising frontier [18, 19, 31]. Integration of AI with big data analytics and personalized medicine principles can ultimately support a shift toward therapy individualized to each patient's pathology, colonic anatomy, and microbial profile [5, 6, 33]. While substantial opportunities for further research and development remain, the trajectory of AI in colon-targeted drug delivery is clearly toward greater precision, efficiency, and therapeutic impact.

➢ *Conflict of Interest:*

It is hereby declared that there is no conflict of interest among authors.

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