

Machine Learning & Artificial Intelligence in the Development of Gastro-Retentive Drug Delivery Systems: Current Advances & Future Prospectives

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Publication Date: 2026/10/16

Abstract: The integration of machine learning (ML) and artificial intelligence (AI) into pharmaceutical sciences is reshaping the development of advanced drug delivery systems. Traditional gastroprotective drug delivery systems (GRDDS) are designed to prolong the residence time of oral dosage forms in the stomach to enhance bioavailability and therapeutic efficacy for drugs with narrow absorption windows. However, conventional formulation development often relies on empirical optimization, which is time-consuming and resource-intensive. AI and ML bring a data-driven paradigm to this complex landscape by enabling computational modeling, predictive analytics, and intelligent optimization of formulation parameters. These technologies can analyze multidimensional datasets to identify patterns and relationships between formulation components, physiological variables, and release kinetics that would be challenging to discern using traditional methods. AI-assisted models such as artificial neural networks, support vector machines, and Bayesian optimization have demonstrated significant potential in predicting drug release profiles, selecting optimal polymer systems, and simulating gastric behavior. Moreover, AI can streamline experimental design, reduce trial-and-error iterations, and accelerate the development timeline, thus improving formulation robustness and performance. The convergence of AI with gastroprotective systems also promises personalized approaches that account for patient-specific gastric motility and physiological factors, fostering tailored therapies. Although challenges remain—such as the need for high-quality datasets, interpretability of complex models, and integration with regulatory frameworks—the current advances provide a compelling foundation for future research. Embracing these intelligent tools in GRDDS development is likely to expand the frontiers of oral drug delivery by enhancing design precision, improving therapeutic outcomes, and reducing developmental costs. Continued innovation and interdisciplinary collaboration will be essential to fully harness the transformative potential of AI and ML in pharmaceutics.

Keywords: Artificial Intelligence in Pharmaceutics, Machine Learning–Based Formulation Design, Gastroprotective Drug Delivery Systems, Predictive Modeling of Drug Release, Intelligent Formulation Optimization, Floating and Mucoadhesive Delivery Systems, Data-Driven Pharmaceutical Development.

How to Cite: Sahil Sanjay Nantekar; Madan D. Pomaje; Avadhut Nitin Hande; Sanika Mahesh Gangan; Ashwini B. Patil (2026) Machine Learning & Artificial Intelligence in the Development of Gastro-Retentive Drug Delivery Systems: Current Advances & Future Prospectives . *International Journal of Innovative Science and Research Technology*, 11(10), 695-703.
<https://doi.org/10.38124/ijisrt/26oct553>

I. INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, patient compliance, and cost-effectiveness. However, conventional oral dosage forms often face limitations such as short gastric residence time and variable drug absorption, particularly for drugs that

are primarily absorbed in the upper part of the gastrointestinal tract.[1] Rapid gastric emptying can significantly reduce bioavailability for drugs with a narrow absorption window or those that act locally in the stomach.

Gastroretentive drug delivery systems (GRDDS) were developed to overcome these limitations by prolonging the

residence time of dosage forms in the stomach. These systems are designed to remain in the gastric region for extended periods, thereby enhancing drug absorption, improving therapeutic efficacy, and reducing dosing frequency [1,3]. Various approaches such as floating systems, expandable systems, high-density systems, bioadhesive systems, and superporous hydrogels have been investigated to achieve effective gastric retention [3–8]. Over the past two decades, GRDDS have gained significant research attention due to their potential in improving the performance of drugs with poor intestinal stability, low solubility at higher pH, or site-specific absorption requirements[2–4]

Despite promising advancements, the formulation of gastroretentive systems remains complex. The performance of GRDDS depends on multiple interrelated factors including polymer type and concentration, swelling behavior, density, drug release kinetics, and gastric motility conditions. Traditional formulation development typically relies on trial-and-error experimentation and statistical optimization methods such as Design of Experiments (DoE). Although effective, these approaches can be time-consuming, resource-intensive, and sometimes insufficient to model highly nonlinear relationships among formulation variables.

In recent years, artificial intelligence (AI) and machine learning (ML) have emerged as transformative tools in pharmaceutical research and drug delivery design [4,5]. AI techniques such as artificial neural networks (ANN), deep learning (DL), genetic algorithms, and predictive modeling enable the analysis of complex datasets and identification of hidden relationships between formulation variables and performance outcomes [14,17]. These computational approaches can improve prediction accuracy, accelerate optimization processes, and reduce experimental burden.

The integration of AI into drug delivery research has already demonstrated promising results in formulation optimization, drug release modeling, stability prediction, and material selection[4,6,7]. Applying AI-driven methodologies to gastroretentive drug delivery systems offers an opportunity to enhance formulation precision, improve gastric retention performance, and facilitate data-driven pharmaceutical development. Therefore, this review aims to comprehensively discuss the role of machine learning and artificial intelligence in the development of gastroretentive drug delivery systems, highlighting current advances, practical applications, challenges, and future perspectives in this rapidly evolving interdisciplinary field.

II. OVERVIEW OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Gastroretentive drug delivery systems (GRDDS) are specialized oral formulations designed to prolong the residence time of a dosage form in the stomach. These systems are particularly beneficial for drugs that exhibit a narrow absorption window in the upper gastrointestinal tract, are unstable in the intestinal environment, or require localized action in the stomach. By extending gastric

retention, GRDDS enhance drug bioavailability, improve therapeutic efficacy, and reduce dosing frequency. However, the successful design of such systems requires careful consideration of gastric physiology, including motility patterns, pH variability, gastric emptying time, and fed or fasted states.[8,9] GRDDS are broadly classified into several categories based on their mechanism of gastric retention.

➤ Types of Gastroretentive Drug Delivery Systems

• Floating Drug Delivery Systems

Floating systems, also known as low-density systems, are designed to remain buoyant in gastric fluids for prolonged periods. These systems possess a density lower than that of gastric contents, allowing them to float on the stomach's surface without affecting gastric emptying significantly. Floating systems are generally categorized into effervescent and non-effervescent types. Effervescent systems generate carbon dioxide through chemical reactions, which reduces density and promotes buoyancy, while non-effervescent systems rely on swellable polymers to maintain flotation. These systems are widely used due to their relative simplicity and effectiveness in sustaining drug release.[10,11]

• Mucoadhesive Systems

Mucoadhesive gastroprotective systems adhere to the gastric mucosal lining through bio adhesive polymers. The adhesion prolongs the residence time of the formulation at the absorption site. Polymers such as Carbopol, Chitosan, and Hydroxypropyl methylcellulose (HPMC) are commonly used to promote adhesion. These systems are particularly advantageous for localized gastric therapy. However, mucus turnover and continuous gastric motility may reduce adhesion time, limiting their effectiveness.[12]

• Expandable Systems

Expandable or swelling systems are designed to increase in size after administration, preventing their passage through the pyloric sphincter. Upon contact with gastric fluids, these systems swell or unfold to achieve dimensions larger than the pyloric opening. After drug release, they gradually reduce in size to allow safe elimination. Expandable systems provide prolonged retention but require precise control of swelling behavior to avoid obstruction risks.[13]

• High-Density Systems

High-density systems are formulated to possess a density greater than gastric fluids, enabling them to sink and remain at the bottom of the stomach. These systems resist peristaltic movements and maintain gastric retention for extended durations. Although theoretically promising, their clinical application is limited due to challenges in achieving uniform high density without compromising drug release characteristics.[14]

• Super Porous Hydrogels

Super porous hydrogels are three-dimensional polymeric networks capable of rapid swelling due to interconnected pores. These systems can absorb gastric fluids

quickly and expand to large sizes within minutes. Their fast-swelling rate and mechanical strength make them suitable candidates for prolonged gastric retention. However, maintaining structural integrity during peristaltic contractions remains a significant formulation challenge.[15]

➤ *Advantages and Limitations of GRDDS*

• *Advantages:*

Gastroretentive systems offer several therapeutic and pharmacokinetic benefits. They enhance bioavailability of drugs with a narrow absorption window and improve drug solubility in acidic environments. These systems also allow for sustained drug release, leading to reduced dosing frequency and improved patient compliance. Furthermore, GRDDS are valuable for drugs intended for local action in the stomach, such as those used in *Helicobacter pylori* eradication therapy.

• *Limitations:*

Despite their advantages, GRDDS are not universally applicable. Drugs that are unstable in acidic environments or extensively absorbed throughout the gastrointestinal tract may not benefit from gastric retention. Additionally, variability in gastric emptying time among individuals can result in inconsistent performance. Food intake, disease state, and physiological differences further influence system behavior. The complexity of gastric physiology makes it challenging to achieve predictable in vivo outcomes.[8,13]

➤ *Challenges in Formulation Development*

The development of gastroretentive drug delivery systems presents multiple formulation and physiological challenges. One major difficulty lies in achieving consistent gastric retention despite dynamic and unpredictable gastric motility patterns. The migrating motor complex, particularly during the fasted state, can expel dosage forms prematurely.

Another challenge involves balancing buoyancy, swelling, mechanical strength, and controlled drug release within a single formulation. Optimizing polymer concentration and excipient combinations requires careful experimentation to ensure both retention and therapeutic performance. Over-swelling may cause discomfort or obstruction risks, whereas insufficient swelling may result in early gastric emptying.

Reproducibility and scalability also pose challenges during manufacturing. Minor variations in polymer grade, compression force, or formulation parameters can significantly impact floating behavior and release kinetics. Furthermore, in vitro evaluation methods often fail to fully replicate complex gastric conditions, leading to discrepancies between laboratory results and in vivo performance.

These challenges highlight the need for advanced predictive and optimization tools, such as artificial intelligence and machine learning approaches, to model complex interactions and accelerate the rational design of gastroretentive systems.[11]

III. FUNDAMENTALS OF ARTIFICIAL INTELLIGENCE IN PHARMACEUTICS

The rapid digital transformation of pharmaceutical research has introduced computational intelligence as a powerful support system for formulation design and optimization. Artificial intelligence (AI) and its associated techniques enable researchers to analyze complex datasets, recognize nonlinear relationships, and generate predictive models that enhance decision-making. In pharmaceuticals, where formulation variables, process parameters, and biological interactions are highly interconnected, AI provides a systematic and data-driven alternative to traditional empirical approaches [4,6].

➤ *Definition of Artificial Intelligence (AI)*

Artificial intelligence refers to computational systems capable of performing tasks that typically require human intelligence, such as learning from data, recognizing patterns, reasoning, and making predictions. In pharmaceutical sciences, AI is used to simulate formulation behavior, predict drug release kinetics, optimize excipient selection, and assist in quality control processes. Unlike conventional statistical tools, AI systems can handle multidimensional datasets and adapt as new data become available, thereby improving predictive performance over time [4,5].

➤ *Machine Learning (ML)*

Machine learning is a subset of AI that enables algorithms to learn from historical data without being explicitly programmed. ML models identify hidden relationships between input variables (e.g., polymer concentration, compression force, excipient ratio) and output responses (e.g., drug release rate, buoyancy lag time). Supervised learning methods such as support vector machines, decision trees, and random forests are widely used in pharmaceuticals for predicting formulation performance. ML has demonstrated significant potential in reducing experimental workload and accelerating product development cycles [6,16].

➤ *Deep Learning (DL)*

Deep learning is an advanced branch of machine learning that uses multi-layered neural networks to model highly complex and nonlinear patterns. These models are particularly useful when handling large datasets, imaging data, or intricate biological interactions. In pharmaceutical development, deep learning techniques have been explored for predicting dissolution behavior, identifying critical quality attributes, and simulating drug-excipient interactions. Although computationally intensive, DL models often provide superior predictive accuracy compared to traditional regression approaches [5,17].

➤ *Artificial Neural Networks (ANN)*

Artificial neural networks are computational models inspired by the structure and functioning of the human brain. ANNs consist of interconnected layers of nodes (neurons) that process information and adjust internal weights during training to minimize prediction error. In drug delivery research, ANNs have been successfully applied to model

sustained drug release, optimize polymer blends, and predict pharmacokinetic parameters. Their ability to capture nonlinear relationships makes them particularly valuable in complex systems such as gastroretentive formulations[16,18].

➤ Genetic Algorithms (GA)

Genetic algorithms are optimization techniques inspired by the principles of natural selection and evolution. These algorithms iteratively search for optimal solutions by applying processes analogous to selection, crossover, and mutation. In pharmaceuticals, genetic algorithms are often combined with ANN models to optimize formulation variables and process conditions. By exploring a wide solution space efficiently, GA-based optimization can identify ideal combinations of excipients and manufacturing parameters with fewer experimental trials compared to traditional approaches [6,7].

➤ QSAR Modeling

Quantitative Structure–Activity Relationship (QSAR) modeling involves the use of mathematical and statistical methods to correlate chemical structure with biological activity. AI-enhanced QSAR models utilize machine learning algorithms to improve prediction accuracy and handle complex descriptor datasets. In drug delivery research, QSAR approaches assist in predicting solubility, permeability, and stability characteristics, which are critical for designing effective formulations. Modern ML-based QSAR models offer greater robustness compared to conventional linear regression techniques [3,5].

➤ DoE versus AI-Based Optimization

Design of Experiments (DoE) has long been employed in pharmaceutical formulation to systematically evaluate the influence of multiple variables. While DoE is effective for structured experimental design and regulatory compliance, it is often limited to predefined factor ranges and linear or moderately nonlinear interactions. In contrast, AI-based optimization methods can process large, multidimensional datasets and identify complex nonlinear relationships without rigid experimental constraints. AI models continuously improve as additional data are incorporated, enabling adaptive optimization and enhanced predictive accuracy. However, AI approaches require high-quality datasets and careful validation to ensure reliability and regulatory acceptance [4,16].

A. Applications of Artificial Intelligence in Gastroretentive Drug Delivery Systems

The integration of artificial intelligence (AI) and machine learning (ML) into gastroretentive drug delivery system (GRDDS) development represents a transformative shift from empirical experimentation to predictive, data-driven formulation science. Gastroretentive systems involve complex interactions between formulation variables, physiological conditions, and drug release mechanisms. AI tools are particularly valuable in this context because they can model nonlinear relationships, analyze multidimensional datasets, and generate accurate predictions that support rational formulation design [4,6].

➤ AI in Formulation Optimization

Formulation optimization in GRDDS traditionally requires extensive experimental trials to determine ideal polymer concentrations, excipient ratios, and processing parameters. AI models significantly reduce this experimental burden by learning from historical datasets and predicting optimal conditions with high precision [4,5].

• Polymer Concentration Prediction

Polymer concentration plays a critical role in determining swelling behavior, buoyancy, matrix integrity, and drug release rate in gastroretentive systems. Machine learning algorithms such as artificial neural networks (ANN), support vector machines (SVM), and random forest models can identify complex relationships between polymer levels and formulation responses. These models enable prediction of optimal polymer concentrations required to achieve desired floating duration and sustained release profiles, minimizing trial-and-error experimentation [6,16]

• Floating Lag Time Prediction

Floating lag time is a key parameter in floating gastroretentive systems, reflecting the time required for a dosage form to become buoyant in gastric fluid. This parameter is influenced by effervescent agents, polymer hydration rate, tablet density, and compression force. AI-based predictive modeling can analyze these interacting variables simultaneously and accurately estimate floating lag time under different formulation scenarios. Such predictive capability enhances formulation robustness and ensures reproducible gastric retention performance [5,17].

• Drug Release Modeling

Drug release behavior from gastroretentive matrices is governed by diffusion, erosion, swelling, and polymer relaxation mechanisms. These processes are often nonlinear and difficult to predict using conventional regression models. AI-driven approaches, particularly ANN and deep learning models, can successfully model complex release kinetics and predict dissolution profiles across different time intervals. This facilitates optimization of sustained-release behavior while reducing experimental dissolution studies [16,18].

➤ AI in Predicting Drug Release Kinetics

Understanding drug release kinetics is essential for ensuring therapeutic efficacy and regulatory compliance. Machine learning models can be trained using dissolution datasets to classify release mechanisms (e.g., diffusion-controlled, erosion-controlled) and predict long-term release behavior. Compared to traditional kinetic models such as zero-order, first-order, or Higuchi equations, AI algorithms can accommodate nonlinear and multifactorial influences simultaneously. This allows for more accurate prediction of in vitro and potentially in vivo drug release patterns in gastroretentive systems [4,18]

➤ AI in Polymer Selection

Selection of appropriate polymers is fundamental to the success of GRDDS. Factors such as viscosity grade, swelling capacity, mucoadhesive strength, and compatibility with the drug significantly influence system performance. AI tools

can analyze large formulation databases and identify correlations between polymer properties and desired outcomes. Predictive algorithms assist in screening suitable polymers based on target characteristics such as prolonged gastric retention, controlled swelling, and optimized drug diffusion. This data-driven polymer selection approach enhances efficiency and reduces formulation development timelines [6,7].

➤ *AI for Stability Prediction*

Stability is a critical quality attribute for gastroretentive formulations, particularly those containing moisture-sensitive polymers or effervescent components. AI models can analyze accelerated stability data and predict long-term shelf-life under various storage conditions. Machine learning techniques help identify degradation patterns and assess the impact of temperature, humidity, and packaging variables. Early prediction of instability reduces development risks and supports proactive formulation adjustments [3,5].

➤ *AI versus Traditional Design of Experiments (DoE)*

Design of Experiments (DoE) remains a cornerstone of pharmaceutical optimization, offering structured evaluation of factor interactions within defined experimental ranges. However, DoE models are often limited to predetermined experimental spaces and may struggle to capture highly nonlinear relationships. AI-based optimization techniques extend beyond these limitations by processing large datasets and continuously refining predictions as new data become available. While DoE provides regulatory transparency and structured statistical validation, AI offers adaptability, enhanced predictive accuracy, and reduced experimental workload. The integration of both approaches may represent the most effective strategy for advanced GRDDS development [4,16].

IV. CASE STUDIES AND REPORTED RESEARCH ON AI APPLICATIONS IN DRUG DELIVERY

The application of artificial intelligence (AI) and machine learning (ML) in pharmaceutical formulation has been increasingly reported in recent years. Although specific studies focusing exclusively on gastroretentive drug delivery systems (GRDDS) remain limited, several published investigations demonstrate how AI-based modeling can be successfully applied to sustained-release matrices, floating systems, and polymer-based drug delivery platforms. These studies collectively highlight the feasibility of integrating intelligent algorithms into GRDDS development for predictive modeling and optimization [4,6].

➤ *Summary of Published Studies*

Several researchers have applied artificial neural networks (ANN) to predict drug release from hydrophilic matrix systems. Agatonovic-Kustrin and Beresford demonstrated that ANN models outperformed traditional regression approaches in predicting dissolution behavior across different formulation compositions, confirming the suitability of neural networks for complex pharmaceutical systems [16].

In another study, ML algorithms such as random forest and support vector machines were used to predict formulation performance based on excipient composition and processing parameters. These models successfully identified nonlinear interactions between polymer concentration and drug release kinetics, reducing the number of experimental trials required for optimization [6].

Recent research has also explored AI-assisted optimization of sustained-release tablets, where ANN models were combined with genetic algorithms (GA) to determine optimal excipient ratios. The hybrid ANN-GA approach improved prediction accuracy and identified optimal formulations with fewer experimental iterations compared to conventional design of experiments (DoE) methods [19].

Deep learning techniques have further been applied to large dissolution datasets to classify drug release mechanisms and predict long-term release profiles. These models demonstrated enhanced predictive reliability when handling multidimensional variables, indicating their potential application in gastroretentive floating and swelling systems [3].

Additionally, AI-driven predictive tools have been used to forecast stability outcomes under accelerated conditions. ML models successfully predicted degradation trends based on environmental factors such as temperature and humidity, offering early insight into formulation robustness [5].

Although direct AI-based case studies specific to floating GRDDS are still emerging, the existing evidence from sustained-release and matrix systems provides a strong foundation for extending these intelligent approaches to gastroretentive formulations.

➤ *Comparative Analysis of Reported Studies*

The following table summarizes representative studies demonstrating the application of AI techniques in drug delivery system optimization.

Table 1 Comparative Analysis of Reported Studies

Study	AI Technique Used	System Type	Key Objective	Major Outcome
Agatonovic-Kustrin et al. [16]	ANN	Hydrophilic matrix tablets	Predict drug release	ANN showed superior prediction accuracy over linear regression
Gormley et al. [6]	Random Forest, SVM	Controlled-release systems	Model nonlinear formulation interaction	Reduced experimental workload with high predictive reliability

ANN-GA Hybrid Study [19]	ANN + Genetic Algorithm	Sustained-release tablets	Optimize excipient ratios	Identified optimal formulation with fewer trials than DoE
Deep Learning Study [3]	Deep Neural Networks	Dissolution datasets	Classify release mechanisms	Improved prediction of long-term release profiles
Stability Modeling Study [5]	ML Regression Models	Solid dosage forms	Predict degradation trends	Accurate shelf-life prediction under accelerated conditions

• *The Reviewed Studies Collectively Demonstrate Several Important Outcomes:*

✓ *Improved Predictive Accuracy:*

AI models consistently outperform traditional statistical regression models in capturing nonlinear relationships between formulation variables and drug release behavior [3,16].

✓ *Reduced Experimental Burden:*

ML-assisted optimization significantly minimizes the number of laboratory trials required, accelerating development timelines and reducing material costs [6,19].

✓ *Enhanced Optimization Capability:*

Hybrid approaches, such as ANN combined with genetic algorithms, enable efficient exploration of complex formulation spaces beyond predefined experimental limits [19]

✓ *Potential for Application in GRDDS:*

Although direct AI-based gastroretentive studies remain limited, the success observed in matrix and sustained-release systems strongly supports the extension of these methodologies to floating, mucoadhesive, and expandable gastroretentive formulations.

A. Advantages of Artificial Intelligence in Gastroretentive Drug Delivery System (GRDDS) Development

The incorporation of artificial intelligence (AI) into the development of gastroretentive drug delivery systems represents a significant advancement in pharmaceutical formulation science. GRDDS design involves multiple interacting variables, including polymer characteristics, swelling behavior, buoyancy parameters, and drug release kinetics. Traditional development approaches often rely on extensive empirical experimentation, which can be time-consuming and resource-intensive. AI-driven methodologies provide a data-centric alternative that enhances efficiency, precision, and innovation in formulation development [4,6].

➤ *Reduced Experimentation*

One of the most prominent advantages of AI in GRDDS development is the substantial reduction in experimental workload. Conventional formulation strategies require multiple iterative trials to optimize polymer concentration, excipient ratios, and processing parameters. AI models, particularly artificial neural networks and machine learning algorithms, can analyze existing datasets to predict formulation outcomes with high reliability. By identifying critical formulation variables and their interactions, AI minimizes unnecessary laboratory experiments while maintaining formulation robustness. This

not only conserves materials but also reduces human effort and development time [4,16].

➤ *Cost-Effectiveness*

Pharmaceutical formulation research often involves high costs associated with raw materials, analytical testing, stability studies, and manpower. AI-based optimization reduces these expenses by streamlining the development process and decreasing the number of failed or suboptimal batches. Predictive modeling allows early identification of promising formulations, thereby limiting resource expenditure on ineffective designs. Additionally, AI-assisted stability prediction can forecast degradation trends, reducing the need for prolonged real-time studies during the early stages of development [5,6].

➤ *Faster Optimization*

Speed is a critical factor in pharmaceutical product development, particularly in competitive therapeutic markets. AI algorithms can process large datasets rapidly and identify optimal formulation conditions within a shorter timeframe compared to traditional design of experiments (DoE). Hybrid models, such as artificial neural networks combined with genetic algorithms, efficiently explore complex formulation spaces and generate optimized solutions. This accelerated optimization process shortens development cycles and supports quicker progression toward scale-up and commercialization [16,19].

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➤ *Improved Prediction Accuracy*

GRDDS performance is influenced by nonlinear interactions among formulation variables and physiological factors. Conventional statistical models may struggle to capture such complexity. AI-based models excel in identifying nonlinear patterns and multidimensional relationships, resulting in enhanced predictive accuracy. Accurate prediction of floating lag time, swelling behavior, drug release kinetics, and stability profiles strengthens formulation reliability and reproducibility. Improved prediction also supports better in vitro–in vivo correlation, contributing to more robust product performance [4,5].

V. LIMITATIONS AND CHALLENGES OF ARTIFICIAL INTELLIGENCE IN GRDDS DEVELOPMENT

Although artificial intelligence (AI) offers transformative potential in the development of gastroretentive drug delivery systems (GRDDS), its implementation is not without limitations. The effectiveness of AI-based models depends heavily on data quality, model design, interpretability, and regulatory acceptance. While AI can enhance prediction accuracy and reduce experimental workload, certain technical and practical challenges must be addressed to ensure reliable and reproducible outcomes in pharmaceutical research [4,6].

➤ Data Dependency

AI models are fundamentally data-driven, meaning their performance is directly influenced by the quality, accuracy, and completeness of the input datasets. In GRDDS development, experimental data may vary due to differences in laboratory conditions, equipment calibration, raw material variability, and human error. If inconsistent or biased data are used for training, the predictive model may generate unreliable outputs. Furthermore, incomplete datasets may fail to capture critical interactions among formulation variables, leading to inaccurate predictions. Therefore, robust data preprocessing, validation, and standardization are essential before implementing AI-based modeling approaches [4,16].

➤ Need for Large Datasets

Advanced machine learning and deep learning models generally require substantial datasets to achieve optimal performance. However, in pharmaceutical formulation research, especially in specialized areas such as gastroretentive systems, datasets are often limited due to the cost and time required for experimental studies. Small datasets may restrict model generalizability and reduce predictive robustness. Although certain algorithms can function with limited data, the overall reliability of AI-driven optimization improves significantly with larger and more diverse datasets. Generating and curating high-quality pharmaceutical datasets therefore remains a critical challenge [5,6].

➤ Overfitting Issues

Overfitting is a common challenge in AI modeling, particularly when complex models are trained on limited datasets. An overfitted model performs EXCEPTIONALLY well on training data but fails to predict new or unseen data accurately. In the context of GRDDS, this could result in misleading optimization outcomes and poor real-world performance. Proper model validation techniques, including cross-validation, external validation datasets, and regularization methods, are necessary to minimize overfitting risks. Ensuring balanced model complexity is essential to achieve reliable and reproducible predictions [16,19].

➤ Regulatory Concerns

Regulatory acceptance remains one of the most significant barriers to widespread AI adoption in pharmaceutical development. Regulatory agencies emphasize

transparency, reproducibility, and validation of formulation development processes. AI models, particularly deep learning systems, are sometimes perceived as “black box” models due to limited interpretability of internal decision-making processes. This lack of transparency may complicate regulatory review and approval. Clear documentation, robust validation strategies, and explainable AI approaches are necessary to align AI-driven formulation development with regulatory expectations and quality-by-design (QbD) principles [4,5].

VI. REGULATORY AND ETHICAL CONSIDERATIONS IN THE USE OF AI FOR GRDDS DEVELOPMENT

The growing integration of artificial intelligence (AI) into pharmaceutical formulation, including gastroretentive drug delivery systems (GRDDS), necessitates careful evaluation of regulatory and ethical frameworks. While AI offers substantial advantages in predictive modeling and optimization, its adoption must align with established quality, safety, and transparency standards. Regulatory authorities emphasize reliability, traceability, and scientific justification of all development processes, including computational methodologies [4,5].

➤ FDA Perspective on Artificial Intelligence

The United States Food and Drug Administration (FDA) has increasingly recognized the role of AI and machine learning in pharmaceutical development and medical product lifecycle management. Regulatory discussions emphasize the importance of transparency, risk-based assessment, and lifecycle management of AI models. Rather than discouraging innovation, regulatory bodies advocate for responsible AI integration supported by robust validation and documentation practices [4,20].

From a formulation development perspective, AI models used for predicting drug release, optimizing polymer concentrations, or simulating gastric retention behavior must demonstrate reproducibility and reliability comparable to conventional statistical tools. Regulatory authorities expect clear documentation of model training procedures, dataset sources, algorithm selection, and performance evaluation metrics. In addition, explainability of AI systems is gaining importance, particularly when complex models influence critical quality attributes (CQAs) of pharmaceutical products [5,20].

➤ Validation Requirements

Validation is a fundamental requirement in pharmaceutical development. AI-based models applied in GRDDS optimization must undergo systematic validation to ensure accuracy, consistency, and generalizability. This includes internal validation techniques such as cross-validation, as well as external validation using independent datasets. Performance indicators such as prediction error, sensitivity, specificity, and robustness must be clearly reported [5,16].

In alignment with Quality by Design (QbD) principles, AI tools should be integrated within a structured risk management framework. Model assumptions, limitations, and decision boundaries must be explicitly defined. Continuous monitoring and periodic revalidation may also be necessary, particularly when AI systems are updated with new datasets over time. Such lifecycle management ensures that predictive performance remains reliable throughout product development and commercialization [4,20].

➤ *Data Integrity*

Data integrity is central to ethical and regulatory compliance in AI-driven pharmaceutical research. Since AI systems are highly dependent on data quality, incomplete, biased, or manipulated datasets can lead to inaccurate predictions and compromised product safety. Regulatory authorities emphasize adherence to ALCOA principles (Attributable, Legible, Contemporaneous, Original, and Accurate) to maintain trustworthy datasets [5,21].

In the context of GRDDS development, experimental data related to floating lag time, dissolution profiles, swelling behavior, and stability must be accurately recorded and securely stored. Proper documentation ensures traceability and reproducibility of AI-generated predictions. Ethical considerations also extend to responsible data sharing, protection of proprietary information, and prevention of algorithmic bias.

➤ *Future Perspectives*

The integration of artificial intelligence (AI) into gastroretentive drug delivery systems (GRDDS) is still evolving, yet its potential to redefine oral drug delivery is substantial. As computational capabilities expand and pharmaceutical datasets become more structured and accessible, AI-driven methodologies are expected to move beyond predictive modeling toward fully integrated intelligent drug delivery ecosystems. Future advancements are likely to focus on smart delivery platforms, digital twin technology, and personalized gastroretentive therapies that align with precision medicine principles [4,6].

- *AI-Integrated Smart Delivery Systems*

Next-generation gastroretentive systems may incorporate AI-assisted design with real-time monitoring technologies to create intelligent drug delivery platforms. Smart systems could integrate sensor-based feedback mechanisms capable of responding to physiological signals such as gastric pH, motility, or fluid volume. AI algorithms may analyze these signals and dynamically adjust drug release behavior to maintain optimal therapeutic levels. The convergence of AI with nanotechnology, advanced polymers, and microelectronic components could lead to adaptive gastroretentive systems that optimize retention time and release kinetics under varying gastric conditions. Such innovations would enhance therapeutic precision and reduce variability associated with conventional static formulations [4,5].

- *Digital Twins in Pharmaceuticals*

Digital twin technology represents an emerging frontier in pharmaceutical sciences. A digital twin is a virtual replica of a physical system that simulates its behavior under different conditions. In the context of GRDDS, digital twins could model formulation characteristics, gastric physiology, and drug release dynamics simultaneously. By integrating experimental data, physiological parameters, and machine learning models, digital twins may enable real-time simulation of formulation performance before actual manufacturing or clinical testing. This approach has the potential to reduce development timelines, optimize scale-up processes, and enhance regulatory transparency through predictive validation frameworks. As computational power and data integration strategies improve, digital twins may become a cornerstone of intelligent pharmaceutical development [3,6].

- *Personalized Gastroretentive Systems*

Personalized medicine aims to tailor therapeutic strategies according to individual patient characteristics. AI-driven analytics can process patient-specific data such as gastric motility patterns, age, disease condition, metabolic rate, and dietary habits to design customized gastroretentive formulations. Personalized GRDDS could optimize drug release rates and gastric retention time based on individual physiological variability. Such an approach may be particularly valuable for drugs with narrow therapeutic windows or those requiring localized gastric action. Although significant technical and regulatory challenges remain, the integration of AI with patient data analytics represents a promising step toward individualized oral drug delivery systems [4,22].

VII. CONCLUSION

The integration of artificial intelligence (AI) and machine learning (ML) into the development of gastroretentive drug delivery systems (GRDDS) represents a transformative shift in pharmaceutical formulation science. Throughout this review, it has been highlighted that AI-based tools can significantly enhance formulation optimization, predict floating behavior and drug release kinetics, assist in polymer selection, and support stability assessment. Compared to traditional trial-and-error approaches and classical Design of Experiments (DoE), AI-driven methodologies offer improved predictive accuracy, faster development timelines, and more efficient utilization of experimental data.

The application of artificial neural networks, deep learning models, genetic algorithms, and other computational techniques has demonstrated strong potential in modeling complex, nonlinear relationships inherent in gastroretentive systems. These technologies are particularly valuable in optimizing critical parameters such as polymer concentration, floating lag time, swelling behavior, and sustained drug release profiles. Furthermore, emerging concepts such as AI-integrated smart delivery systems and digital twins suggest that future GRDDS development may

move toward adaptive, data-driven, and potentially personalized therapeutic platforms.

Despite these promising advancements, several research gaps remain. A major limitation is the dependency of AI models on large, high-quality datasets, which are not always readily available in pharmaceutical research. Overfitting, lack of model interpretability, and challenges in regulatory acceptance also restrict broader industrial implementation. Additionally, standardized validation frameworks for AI-generated predictions in formulation development are still evolving.

In conclusion, AI has the potential to revolutionize gastroretentive drug delivery by improving efficiency, precision, and innovation in formulation design. However, sustained interdisciplinary collaboration, robust data infrastructure, and clear regulatory guidance are essential to fully harness its capabilities. Future research should focus on generating high-quality datasets, developing explainable AI models, and establishing standardized validation pathways to ensure safe and reliable integration of AI into pharmaceutical development.

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