RESEARCH PAPER

Evolution of Artificial Intelligence in Drug Delivery System Design: Applications, Challenges and Future Perspectives

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ABSTRACT

Background: Conventional drug formulation strategies are constrained by empirical experimentation, protracted development timelines, and limited capacity for patient-specific optimization. The emergence of artificial intelligence (AI) as a transformative computational framework has begun to redefine these limitations across pharmaceutical sciences.

Objective: This review examines the progressive integration of AI methodologies — encompassing machine learning (ML), deep learning (DL), and generative models — into drug delivery system (DDS) design, with emphasis on practical applications, translational barriers, and future directions.

Methods: A comprehensive narrative review was conducted using Scopus and Google Scholar databases, covering publications between 2015 and 2025. Studies examining AI, ML, and computational intelligence techniques applied to DDS formulation, optimization, pharmacokinetics, and nanomedicine were identified and selectively reviewed.

Results: AI technologies have demonstrated measurable efficacy across multiple DDS domains including nanoparticle engineering, lipid nanoparticle formulation, pharmacokinetic modeling, stimuli-responsive systems, and tumor-targeted delivery.

Conclusion: AI represents a paradigm-shifting convergence for drug delivery science. Despite challenges related to data governance, model interpretability, and regulatory acceptance, the trajectory of AI-integrated DDS development points toward highly personalized, adaptive, and precision-guided therapeutics.

Keywords: artificial intelligence, drug delivery systems, machine learning, deep learning, nanoparticles, formulation optimisation, personalized medicine, computational pharmaceutics.

Key Insights:

• AI improves efficiency and accuracy in drug delivery system design, reducing dependence on trial-and-error experimentation.

• Machine learning enables robust prediction of drug release profiles, pharmacokinetics, and nanoparticle characteristics.

• AI-integrated nanotechnology supports targeted drug delivery, improved bioavailability, and site-specific delivery.

• Data fragmentation, model interpretability, and evolving regulatory frameworks remain key translational challenges.

• Future adaptive DDS may incorporate real-time AI-controlled release mechanisms guided by biosensor inputs.

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1. INTRODUCTION

Drug delivery systems (DDS) are one of the most important factors that affect how well a treatment works. Their function beyond mere vehicle design; an optimally constructed DDS regulates the spatiotemporal dynamics of drug release, establishes the level of site-specificity attained, and significantly impacts both the intensity and duration of the pharmacological response. Even though formulation science has come a long way, traditional methods still have some well-known problems, such as the fact that active pharmaceutical ingredients (APIs) don't dissolve well, bioavailability isn't great, cellular targeting isn't very precise, and there aren't any adaptive mechanisms that can respond to changing pathophysiological signals [1,2].

Nanotechnology and new biomaterials have made these problems a lot easier to deal with. This has led to the creation of liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, and hydrogels that respond to stimuli. Still, most of the work that goes into building these advanced platforms comes from expensive trial and error [3,4].

Artificial intelligence has developed into a revolutionary computational framework that could change this paradigm in a big way. In the field of pharmaceutical sciences, the most pertinent AI subdomains encompass supervised machine learning for property prediction and classification, deep learning for intricate feature extraction, reinforcement learning for sequential decision optimization, and generative models for novel molecular and formulation design [5,6]. Hassanzadeh et al. (2019) in Advanced Drug Delivery Reviews [7] fully understood how important AI is to the design of drug delivery systems.

This merging of AI with DDS design has been going on since the 1990s, when early artificial neural network (ANN) applications showed that nonlinear formulation relationships may be modeled more precisely than traditional regression methods. The next few decades saw more different algorithms, more powerful computers, and more pharmacological datasets [8,9]. Wang et al. (2021) characterized this integration as 'computational pharmaceutics'—a novel data-driven paradigm for drug delivery design, published in the Journal of Controlled Release [10].

This review offers a thorough narrative analysis of the progression of AI in DDS design. We look at the history of AI-pharmaceutical integration, the main areas where it is used, the challenges to translation, and the most promising new directions.

2. EVOLUTION OF ARTIFICIAL INTELLIGENCE IN DRUG DELIVERY

2.1 Early Computational Approaches (1990s–2005)

The intellectual roots of AI in pharmaceutical formulation trace to QSAR (quantitative structure–activity relationship) modeling in the 1980s and 1990s. The incorporation of ANN architectures during the early 1990s introduced the capacity to model nonlinear structure–property relationships of greater complexity than classical regression could accommodate [11,12].

The first ANN applications in pharmaceutical formulation demonstrated that feed-forward backpropagation networks could predict tablet hardness, disintegration time, and dissolution profiles with performance exceeding polynomial response surface models. These investigations established a foundational proof-of-concept: that ML architectures could meaningfully represent the nonlinear, multivariate space of pharmaceutical formulation [12].

2.2 Algorithmic Expansion and Big Data Integration (2005–2015)

The decade from 2005 to 2015 was characterized by substantial expansion in the variety of ML algorithms applied in pharmaceutical sciences. Ensemble methods including random forests and gradient boosting, kernel-based approaches such as support vector machines, and evolutionary computation methods including genetic algorithms all found application in pharmaceutical development [13,14].

Genetic algorithms proved particularly valuable for multi-objective formulation optimization, where competing design criteria — such as maximizing encapsulation efficiency while minimizing particle size and controlling release rate — must be simultaneously balanced. The proliferation of open-source ML frameworks substantially lowered technical barriers to pharmaceutical ML adoption [15].

2.3 The Deep Learning Era and Generative AI (2015–Present)

The current era began around 2015, catalyzed by the broader deep learning revolution documented by LeCun, Bengio, and Hinton in Nature [6]. Convolutional neural networks (CNNs) brought new capabilities to nanoparticle characterization, enabling automated

morphology classification from electron microscopy images [16,17].

Among the most significant recent developments has been the emergence of generative AI models — variational autoencoders (VAEs), generative adversarial networks (GANs), and transformer-based architectures — capable of proposing entirely novel molecular structures with user-specified property targets. Zhavoronkov et al. (2019) demonstrated that a deep learning-generated molecule could be validated in preclinical models within 46 days — a landmark in Nature Biotechnology [16]. Serov and Vinogradov (2022) further documented how AI can bring nanomedicine to life in Advanced Drug Delivery Reviews [18].

Table 1.Key Published Studies on AI Applications in Drug Delivery Systems

Author(s)	Year	Research Focus	Key Findings
Hassanzadeh et al.	2019	AI significance in DDS design	Established AI's role; identified key ML applications.
Vamathevan et al.	2019	ML in drug discovery	AI accelerates compound identification.
Zhavoronkov et al.	2019	Deep learning in drug design	DL-generated DDR1 inhibitor validated in 46 days.
Brown et al.	2019	Molecular generative models	GANs improved de novo compound screening.
Wang et al.	2021	Computational pharmaceutics	Defined 'computational pharmaceutics' as new DDS paradigm.
Bannigan et al.	2021/2023	Automated nanomedicine design	ML-directed closed-loop LNP formulation optimization.
Lu et al.	2021	Neural-ODE PK modeling	Neural-ODE outperformed LSTM for temporal PK prediction.
Keutzer et al.	2022	ML vs pharmacometrics	Compared ML and classical PK modeling. Pharmaceutics.
Mitchell et al.	2021	Precision nanoparticles	Engineering precision nanoparticles for drug delivery.
Serrano et al.	2024	AI in drug discovery & delivery	Comprehensive review; personalized medicine applications. Pharmaceutics.
Gholap et al.	2024	AI in drug delivery	Extensive review of AI advances in pharmaceutical development.
Huang et al.	2025	ML for drug concentrations	Tree-based algorithms most applied for PK

			prediction.
Serov & Vinogradov	2022	AI in nanomedicine	AI-guided design of stimuli-responsive nanocarrier systems. A
Topol	2019	AI in medicine	Landmark analysis of AI convergence with human medicine.

APPLICATION OF ARTIFICIAL INTELLIGENCE IN DRUG DELIVERY SYSTEMS

3.1 Improving the formulation of nanoparticles

Nanoparticle-based medicine delivery platforms are among the most dynamic areas for AI utilization. The pharmaceutical efficacy of nanoparticles—encompassing drug loading capacity, encapsulation efficiency, particle size distribution, zeta potential, and in vitro drug release kinetics—is influenced by a complex network of interrelated formulation and process variables that traditional experimental design methodologies inadequately represent [21,22].

Bannigan et al. (2021, 2023) illustrated that AI-assisted closed-loop development for lipid nanoparticles (LNPs), utilizing Bayesian optimization to steer an automated synthesis platform, could meet target specifications in a fraction of the experimental runs needed by traditional methods [19,23]. Rebollo et al. (2024) created Gaussian process models to forecast drug encapsulation efficiency and therapeutic efficacy for polymeric nanoparticles [25]. Combining machine learning with molecular dynamics simulations has been proven to make it easier to forecast the properties of nanoparticles that are important for their effectiveness as drugs [26,27].

3.2 Predicting Drug Release and Pharmacokinetics

It has long been a challenge in drug development to accurately estimate the kinetics of drug release and pharmacokinetic characteristics. Traditional methods use empirical dissolution testing, classical compartmental modeling, and semi-empirical in vitro–in vivo correlation methods, which make a lot of assumptions and aren't very generalizable [28,29].

Lu et al. (2021) suggested using neural ordinary differential equations (Neural-ODE) for pharmacokinetic modeling. They showed that this method worked better than LSTM and LightGBM for predicting the time course of trastuzumab emtansine, which was reported in Nature Machine Intelligence [30]. Huang et al. (2025) performed an extensive analysis in Clinical Pharmacology and Therapeutics, revealing that tree-based algorithms and neural networks attained performance on par with or surpassing population pharmacokinetic models [31,32].

3.3 Smart Drug Delivery Systems That Respond to Stimuli

Smart drug delivery systems can detect physiological signals and change how much medicine is released based on changes in the environment, such pH, temperature, redox potential, or enzyme activity. AI helps with the development of smart DDS in many ways. For example, ML models can anticipate how candidate materials will respond to different stimuli, and reinforcement learning algorithms can improve the control logic that governs adaptive release systems [33,34].

Serov and Vinogradov (2022) examined the potential of AI to actualize nanomedicine, focusing on the creation of stimuli-responsive systems in Advanced Drug Delivery Reviews [18]. Combining AI with control theory for controlled release systems has been discovered to have a bigger impact on the design of DDS than either field could have on its own [35].

3.4 Personalized Medicine and Custom Formulation Design for Patients

A primary constraint of traditional pharmaceutical development is its emphasis on population-average performance indicators. The nascent paradigm of precision medicine necessitates therapeutic approaches customized to the unique biological attributes of each patient, encompassing their genetic profiles, illness status, comorbidities, and drug-metabolizing enzyme phenotypes [36,37].

In Clinical and Translational Science, Johnson et al. (2021) wrote that AI and precision medicine would work together to make personalized healthcare better in the future [37]. Sahu et al. (2022) examined ML and AI in precision medicine, illustrating how large data

analysis facilitates understanding of molecular effects of medication exposure unattainable by traditional methods [38]. Serrano et al. (2024) presented a thorough review in Pharmaceutics (DOI: 10.3390/pharmaceutics16101328 — verified) about how AI is changing customized medicine through drug discovery and delivery [39].

3.5 Nanomedicine and Targeted Drug Delivery

Site-specific drug delivery, which means that a therapeutic agent builds up at the target tissue while reducing exposure to the rest of the body, is still one of the most important goals of DDS research. AI speeds up the logical design of targeted nanocarrier systems by anticipating how changes in the size, shape, surface charge, and ligand identity of nanoparticles affect how they spread through the body and how cells take them up [40,41].

Dorsey et al. (2024) published a comprehensive review in the Journal of Pharmaceutical Sciences covering the state of ML applications for lipid nanoparticle formulation and process development — a domain where ML has proven particularly valuable for predicting critical quality attributes [42]. Light-triggered smart delivery systems represent another active area; Tao et al. (2020) demonstrated sophisticated light-controlled drug release mechanisms in Advanced Functional Materials [43]. Gholap et al. (2024) published a comprehensive review in Computers in Biology and Medicine covering the broad spectrum of AI tools being applied to nanomedicine design [44].

Table 2. Summary of AI Application Domains in Drug Delivery System Design

Application Domain	AI Techniques	Key Outcomes	References
Nanoparticle Optimization	ANN, Random Forest, Bayesian Optimization, Gaussian Process	Accurate CQA prediction; reduced experimental screening burden	[21–27]
Drug Release / PK Prediction	LSTM, Neural-ODE, Gradient Boosting, PBPK-ML	High-accuracy release kinetics and individualized PK modeling	[28–32]
Smart/Stimuli-Responsive DDS	Reinforcement Learning, ANN, Control Theory AI	Optimized responsive material design; adaptive release control	[18,33–35]
Personalized Medicine	DNN, PBPK-ML, Random Forest, Transfer Learning	Patient-specific dosing and formulation recommendations	[36–39]
Targeted Nanomedicine	CNN, GNN, GAN, Reinforcement Learning	Improved tumor accumulation; rational ligand and surface design	[40–44]
de novo Molecular Design	VAE, GAN, Transformer, AlphaFold	Novel molecules with optimized ADMET profiles generated in silico	[16–20]

ANN = artificial neural network; CNN = convolutional neural network; LSTM = long short-term memory; Neural-ODE = neural ordinary differential equation; VAE = variational autoencoder; GAN = generative adversarial network; PBPK = physiologically based pharmacokinetic; CQA = critical quality attribute.

4. CHALLENGES IN AI-DRIVEN DRUG DELIVERY DEVELOPMENT

4.1 Quality, availability, and standardization of data

The creation of strong, generalizable AI models for DDS applications is fundamentally limited by the amount, quality, and availability of training data. Pharmaceutical formulation databases are usually small, private, and use different methods of assessment [45,46]. This is different from image recognition or natural language domains, where there are millions of training examples available. To solve these problems, we need to work together to put money into standardized data reporting frameworks, open-access pharmaceutical databases, and federated learning systems.

4.2 Understanding and Explaining Models

One big drawback with many high-performance AI models is that they are hard to understand, which is known as the "black-box" problem. This makes it hard to create new drugs, because understanding how things work is important and regulatory transparency is needed [47]. Explainable AI (XAI) is a new discipline that offers post-hoc interpretation approaches that help with this problem. SHAP (SHapley Additive exPlanations) values give us a mathematically sound way to link prediction results to specific input features [48]. LIME (Local Interpretable Model-Agnostic Explanations) uses locally linear approximations to model how things work around each unique prediction [49]. König and Vellido (2024) conducted a focused study of explainable machine learning techniques for elucidating drug profile predictions in BioData Mining [50].

4.3 Rules and regulations, as well as requirements for validation

Adding AI to the process of making pharmaceutical products creates new regulatory problems. From 2016 to 2023, the FDA received more than 500 regulatory submissions that included AI components. This shows that the technology is being used quickly in the industry. However, complete guidance specifically for AI in medication formulation is still being developed [51]. The European Commission's AI Regulation (EU) 2024/1689, which was passed on May 21, 2024 and went into effect on August 1, 2024, sets up a risk-based framework that will gradually control the use of AI in the pharmaceutical industry across Europe [52].

4.4 Data Privacy and Ethical Issues

The creation of AI systems for tailored DDS design is fundamentally reliant on patient-specific data, encompassing clinical records, genomic profiles, and treatment response histories, which raises significant issues regarding patient privacy, informed consent, and data security [53]. Privacy-preserving computational frameworks, such as federated learning, differential privacy, and secure multi-party computation, provide technical methodologies for facilitating collaborative AI research while safeguarding patient privacy [54].

4.5 Technical and Computational Problems

Training large-scale DL models requires a lot of computing power. Creating and keeping AI-driven DDS pipelines up and running needs knowledge from several fields, such as pharmaceutical sciences, computational biology, and ML engineering. This kind of knowledge is not often found in one research group [55,56].

FUTURE PERSPECTIVES

5.1 Biosensors and adaptive delivery systems that work with AI

One of the most exciting short-term uses of AI in medication administration is the creation of closed-loop adaptive delivery systems that constantly monitor physiological biomarker data and change the release of drugs in real time. Wearable and implantable biosensor technologies have come a long way, and it is now possible to continuously monitor glucose, electrolytes, and medication concentrations in the blood with clinical-grade precision [57,58].

5.2 Foundation Models and Generative AI in Pharmaceutical Science

The rise of large language models (LLMs) and foundation models has made it possible for AI to help with drug development in new ways. The AlphaFold protein structure prediction method, which was published in Nature in 2021 [59], has opened up the proteome to AI-guided drug design, allowing for better modeling of drug-target interactions that were not possible before. These methods, along with generative architectures like VAEs and diffusion models, are making it possible to suggest new nanoparticle formulations that have been tested in the lab [60,61].

5.3 Precision Nanomedicine with AI Help

The combination of AI and precision nanomedicine may be the most important long-term goal for AI in DDS. The current development of nanomedicine yields platforms tailored for typical tumor biology and standard pharmacokinetic parameters. In actuality,

tumor heterogeneity and differences between patients in how proteins form a corona, how phagocytes clean them, and how receptors are expressed indicate that nanoformulation works quite differently for each patient [63,64]. AI systems that can combine omics data, imaging biomarkers, and clinical factors for each patient to create personalized nanoformulations are a long-term aim that can be reached [64,65].

5.4 Bringing together and translating ideas from different fields

To get AI-driven DDS advances into clinical practice, pharmaceutical scientists, data scientists, ML engineers, clinicians, regulatory scientists, bioethicists, and patient advocates will need to work together in an organized way over a long period of time. Dedicated translational pharmaceutical AI centers, industry-academic-regulatory alliances, and open-access data and model sharing programs are all examples of institutional frameworks that will help this convergence happen. These will be important ways to speed up the field [62].

6. CONCLUSION

The advancement of artificial intelligence in the design of drug delivery systems signifies one of the most crucial technological transformations in modern pharmaceutical science. Over the course of more than thirty years, starting with simple early applications of ANNs for modeling tablet formulations, the field has moved forward with new waves of algorithmic innovation. These include ensemble methods, deep learning, generative models, and foundation architectures. Each of these has made it possible for formulation researchers to make better predictions, generate new ideas, and optimize their work.

The evidence examined herein indicates that AI-driven methodologies routinely surpass traditional empirical and statistical formulation techniques on critical performance indicators, including predictive accuracy, experimental efficiency, and the ability to traverse high-dimensional formulation spaces. ML and DL models can now accurately predict important drug delivery characteristics such encapsulation efficiency, particle size, drug release kinetics, and individual pharmacokinetic profiles in a way that is useful in a clinical setting.

There are still some big problems to solve. The speed of clinical translation is slowed down by things like data fragmentation, model opacity, regulatory frameworks that aren't fully developed, and ethical considerations about how to handle patient data. None of these problems are impossible to solve, but they all need careful, coordinated investment in standardized data infrastructure, explainable AI methodologies, regulatory science, and privacy-preserving collaborative computing architectures.

The combination of AI with closed-loop biosensor systems, wearable delivery devices, precision omics profiling, and sophisticated nanofabrication technologies suggests that treatment systems will become more individualized and adaptable in the future. To make this future happen, we will need not only further technology progress but also the ongoing collaboration between different fields that has led to the most important pharmacological breakthroughs of the previous hundred years.

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