REVIEW PAPER

Intelligent Drug Delivery: Harnessing Artificial Intelligence and Machine Learning for Precision Formulation, Pharmacokinetic Modeling, and Patient-Centric Therapeutics

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Abstract
The application of artificial intelligence (AI) in drug delivery systems (DDS) is revolutionizing these delivery systems through an innovative, data-driven, and personalized approach to pharmaceutical development. This review provides a critical evaluation of the use of machine learning (ML), deep learning, and generative artificial intelligence in developing and designing state-of-the-art drug delivery techniques, such as nanoparticle manufacturing, biological delivery systems, transdermal delivery, smart implantable delivery, and personalized medicines. Various AI models, such as artificial neural networks, support vector machines, random forest models, convolutional neural networks, recurrent neural networks, graph neural networks, reinforcement learning, and generative adversarial networks, are reviewed for their applicability in DDS development, modeling of pharmacokinetics and pharmacodynamics, drug release, and ADME studies. The article also looks into new emerging technologies like digital twins, AI-powered nanorobots, and 3D/4D bioprinting.
The review demonstrates the role played by the AI-based methods to lower experimental load, speed up drug formulation identification, enhance therapeutic precision, and make possible adaptive drug dosing. Future innovations involving digital twins, AI-powered nanorobotics, and three-dimensional or four-dimensional bioprinting are presented to serve as promising perspectives for autonomous drug delivery devices. Also, several key obstacles to implementation, namely data scarcity, heterogeneous nature of the available datasets, explainability of models, regulatory gaps, privacy-related issues, and absence of appropriate frameworks for evaluation, are considered. Explainable AI, federated learning, the FAIR data approach, and combined mechanical-AI models are presented to overcome these challenges.

Keywords: Artificial Intelligence, Drug Delivery Systems, Machine Learning, Nanomedicine, Personalized Medicine
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Introduction

The main aim of a drug delivery system (DDS) is to deliver a medicine to its target location effectively and efficiently while keeping the medicine concentrations within a certain period of time. This should be done by maintaining the required therapeutic levels of medicine at its site of action without causing systemic toxicity and side effects [1]. Modern drug delivery methods have come a long way compared to the simple conventional methods like tablets and capsules [2]. Yet, there are many problems faced by DDS today in providing high-quality medicine due to poor water solubility, rapid metabolism, poor bioavailability, and wide inter-individual differences [3]. Nearly 40% of new chemical drugs suffer from poor water solubility and hence have limited effectiveness [4]. Also, drug development is a costly and time-consuming process, taking decades to develop and requiring great amounts of financial investment [5].

Traditional methods of designing and optimizing DDS included the use of Design of Experiments (DoE), one-factor-at-a-time (OFAT) experiments, and trial-and-error methodology. These methods were very useful in advancing the field of pharmacy, but they are not sufficient anymore for dealing with the complexities involved with modern DDS because of their interactions and nonlinear behavior [6]. Elements like drug: excipient ratio, polymers used, manufacturing

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procedure, biological effects, and others collectively contribute to the success or failure of a formulation. Experimenting with all these is time-consuming, expensive, and often not efficient [7]. Additionally, traditional mechanistic models tend not to be as effective as biological processes, which are usually complex and dynamic in nature [8].

Against this backdrop, it has become clear that artificial intelligence (AI) and machine learning (ML) can play an important role in solving problems associated with the formulation and development of drug products. These powerful technologies make use of high-dimensional data processing capabilities of computers to uncover patterns and complex interactions that may be impossible to discern using traditional techniques [9]. AI and ML allow for the prediction of important parameters, including particle size, release rate, stability, drug loading efficiency, and other critical attributes, even before conducting experiments [10]. Lastly, AI enables what can be called inverse design, where desired results are predetermined first and then formulation is optimized using computational techniques [11]. This clearly indicates a shift towards pharmaceuticals formulated through rational and predictive processes as opposed to purely empirical experiments. In addition to improving the formulation process, the application of AI in emerging areas like nanomedicines, biologics delivery, 3D printing, and personalized medicines continues to grow rapidly. Application of artificial intelligence to optimize formulations includes designing aerosols, engineering nanoparticles that can cross biological barriers, as well as facilitating the on-demand manufacturing of individualized patient dosage forms. Hence, integration of AI technologies with advanced pharmaceutical technology enables intelligent and adaptive drug delivery systems [12].

This review paper discusses the role of AI in improving drug delivery systems. Specifically, the focus will be on the application of AI and machine learning models to optimize various aspects of drug delivery. The capabilities and predictive power of the existing models used to enhance drug delivery will be examined alongside their applications in emerging areas such as nanomedicines, biologics, etc. Also, issues associated with clinical translation of the various models employed will be addressed, for example, data heterogeneity, validation, interpretation, and regulation, among others. Research gaps and future directions will be pointed out. It further underscores the need for standardized data sets, explainable artificial intelligence, and a validated framework to improve the reliability and usability of AI-based DDS. In essence, the integration of artificial intelligence and precision medicine holds the promise to provide an efficient and predictive treatment system.

2. Artificial Intelligence in Advanced Drug Delivery: Formulation, Targeting, and Personalization

AI-Driven Formulation Design

The advent of artificial intelligence has brought about a revolutionary change in the pharmaceutical formulation development process from the previous conventional process based on trial and error. AI models make use of formulation parameters, physicochemical properties, process conditions, and biological effects to develop an optimal drug formulation while minimizing development costs [13]. The use of AI technologies like neural networks, Bayesian optimization, and genetic algorithms helps optimize critical quality parameters like dissolution, stability, and bioavailability simultaneously. In combination with HTS and DoE, AI enhances the development of drug delivery systems like nanoparticles, co-delivery systems, and stimuli-responsive drug formulations (**Figure 1**).

A computational framework based on artificial intelligence was established by Wang et al. [14] for the rational design of ionizable lipids used in the LNP-mediated delivery of mRNA. The authors generated a big database of molecular descriptors of lipids together with their experimentally obtained values of transfection efficiencies of mRNA and trained the machine learning algorithms, including XGBoost, random forest (RF), and deep neural networks (DNNs). The main focus of applying XGBoost and RF was the discovery of features and analysis of the impact of lipid structure on nanoparticle stability and transfection. The DNNs found complex nonlinear dependencies between the chemical composition of the lipids and their biological effects. The machine-learning model screened thousands of potential lipids and selected candidates with high delivery properties before their experimental synthesis. The results of this study revealed novel ionizable lipids that had better in vitro and in vivo delivery efficiency of mRNA than the usual lipids.

Nanoparticle Design and Optimization

Drug delivery systems that use nanoparticles provide some of the most exciting research frontiers in pharmaceutical science since they allow for targeted drug delivery and controlled release, yet designing an effective drug carrier requires a complex consideration of factors such as nanoparticle size, surface chemistry, zeta potential, and release profile. Artificial intelligence can help with the creation of intelligent multifunctional nanocarriers by emulating biological phenomena such as target recognition, biodistribution, and intracellular actions. Machine learning models simulate the behavior of nanoparticles, saving costs on experiments during optimization [15]. Intelligent neural networks examine the morphology of nanoparticles and the release pattern of drugs from carriers. Reinforcement learning models optimize formulation through experiment feedback.

Through an artificial intelligence-aided liposomal nanoparticle design platform, Pfizer & BioNTech were able to optimize the physicochemical stability and immunogenicity of their RNA vaccines, thus enabling the development of the world's first approved RNA-based nanomedicine by the FDA. AI-powered design platform tested thousands of lipid compositions in silico, selecting only those formulations that had optimal transfection efficacy, mRNA stabilization potential, and safe toxicity profiles. This example shows the potential of AI to speed up the development process from several years to months, changing the economics of nanomedicine development completely [16].

Personalized Dosing Regimens

The identification of accurate patient-specific skin characteristics represents an essential step before any personalized drug delivery process, whereas the use of AI can become an invaluable tool, particularly in the field of transdermal drug delivery systems, where AI algorithms are applied in skin phenotyping. In particular, deep learning algorithms proved their effectiveness in recognizing relevant skin phenotypes starting from clinical measurements collected from skin images and spectra, as well as their prediction of skin permeability-related parameters such as the stratum corneum thickness and hydration [17]. In addition to the aforementioned skin phenotypes, AI analysis can lead to the development of digital skin maps or "skin fingerprints" able to correlate specific skin properties with drug permeation properties and dose administration requirements. The translation of skin properties to drug delivery parameters through AI-based skin phenotyping makes it possible a personalized design of patches, formulations, and microneedle geometries [18]. A recent work carried out by Yadav et al. [19] investigated predictive models for the permeability of poorly soluble drugs in skin with respect to the penetration enhancers menthol and limonene. ML models were used in virtual screening to predict hydrophobic drugs having better skin permeability when used in the presence of menthol and limonene; in vitro skin penetration experiments later proved the efficiency of the model as it successfully predicted 80% enhancement in permeability in the case of sumatriptan succinate, voriconazole, and pantoprazole sodium. Menthol and limonene improved skin permeation by 4.96-fold and 3.7-fold, respectively, in experiments. The high consistency observed in in silico and in vitro analysis suggests that ML models could be efficiently used to save a lot of experimental effort.

Smart Drug Delivery Devices

The combination of intelligent and miniature drug delivery devices involves the use of artificial intelligence, biosensors, electronics, and Internet of Things technology to administer medicines intelligently and in a programmable manner on a customized basis [20]. AI-based wearables and implants continuously monitor physiological parameters and independently regulate drug release by means of closed-loop treatment systems. Machine learning techniques predict patients' responses, fine-tune infusion doses, promote compliance, and reduce adverse effects on the body from dosing errors and overdose. Sophisticated intelligent drug delivery devices integrate advanced sensing capabilities, wireless data transmission, edge and cloud computing, and other features for adaptive therapies [21]. Nevertheless, problems of dependability, human supervision, regulatory compliance, and ethics are some key factors that should be taken into consideration while designing future intelligent devices for drug administration. The researchers recently fabricated miniature magnetic robots for intelligent targeted drug delivery and combination treatments. The deformable robot was capable of loading and selectively releasing different types of four drugs under the control of applied magnetic fields. It performed stably by moving in six degrees of freedom in biological tissue, and its motion provided precise navigation and drug dispensation at specific locations. Its design allowed controlling drug release rates and minimizing leakage risks [22].

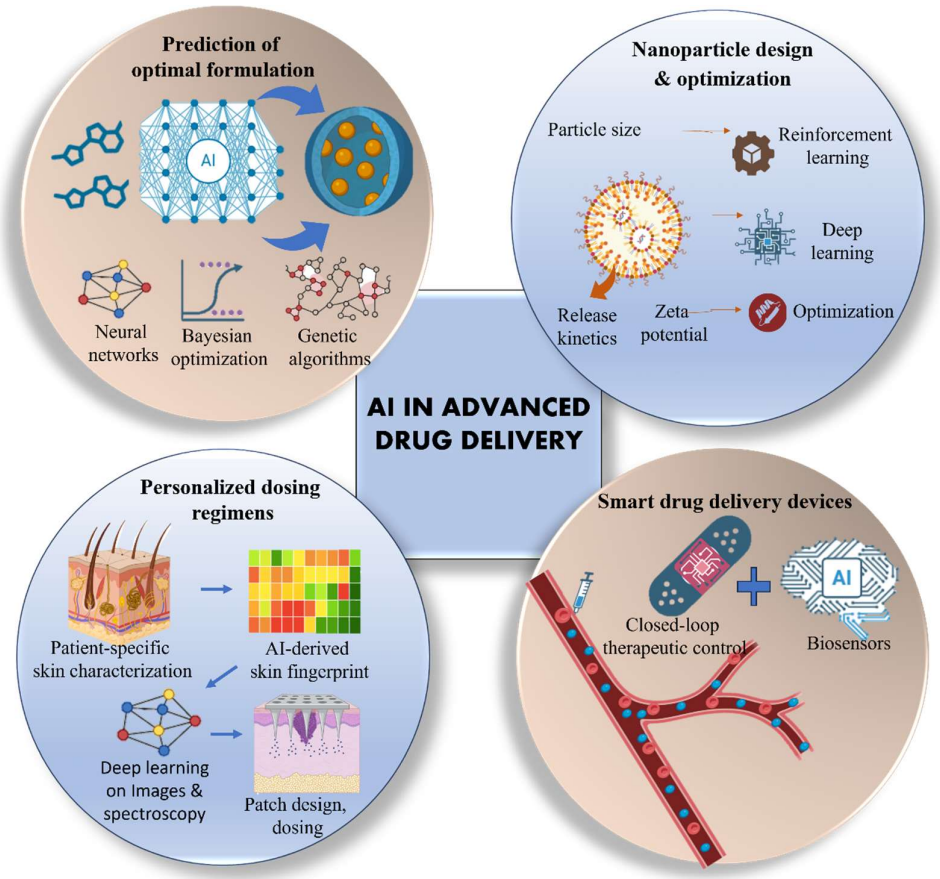

Figure 1: Artificial Intelligence in Advanced Drug Delivery: Formulation, Targeting, and Personalization

3. Deep Learning and Machine Learning Models in Drug Delivery Systems

Artificial Intelligence (AI) algorithms are being implemented for Drug Delivery Systems (DDS) in order to analyze the complexity and nonlinearity of interactions between formulation parameters and biological responses. AI models can be classified as follows: Generative & Adaptive, Deep Learning, and Supervised Learning (**Table 1**).

Artificial Neural Networks (ANNs)

Artificial neural networks (ANNs), which are computational systems mimicking biological brain systems, consist of various layers (such as input, hidden, and output layers) that operate on data using an activation function and weighted connection processes [23]. Backpropagation algorithms allow weights to be updated during training in order to reduce the prediction error.

ANNs are quite beneficial for use in DDS in modeling the non-linear correlation of formulation factors such as drug loading, polymer concentration, and environmental factors [24]. Formulation factors are generally considered as the input variable, while important quality attributes such as drug release rate, encapsulation efficiency, and particle size are considered as the output variable. For example, ANN models exhibit predicted accuracy of about 73% for disintegration time and up to 99% for tablet hardness. Furthermore, in vitro-in vivo correlation construction and dissolution profile prediction are among the other successful applications of these models [25]. Due to difficulty in understanding the model internally, the predictive power of the ANN is much higher than its interpretability.

Maderuelo et al. [26] applied Artificial Neural Networks (ANNs) to predict and optimize the drug release from sustained-release metronidazole hydrophilic matrices (**Figure 2**). This ANN approach was effective in evaluating the complicated correlation of drug release kinetics with various parameters of the formulations, including the composition of the coating layer, weight gain ratio, and viscosity of HPMC. The results proved that ANN technology is an effective method for the QbD-approach driven design of drugs.

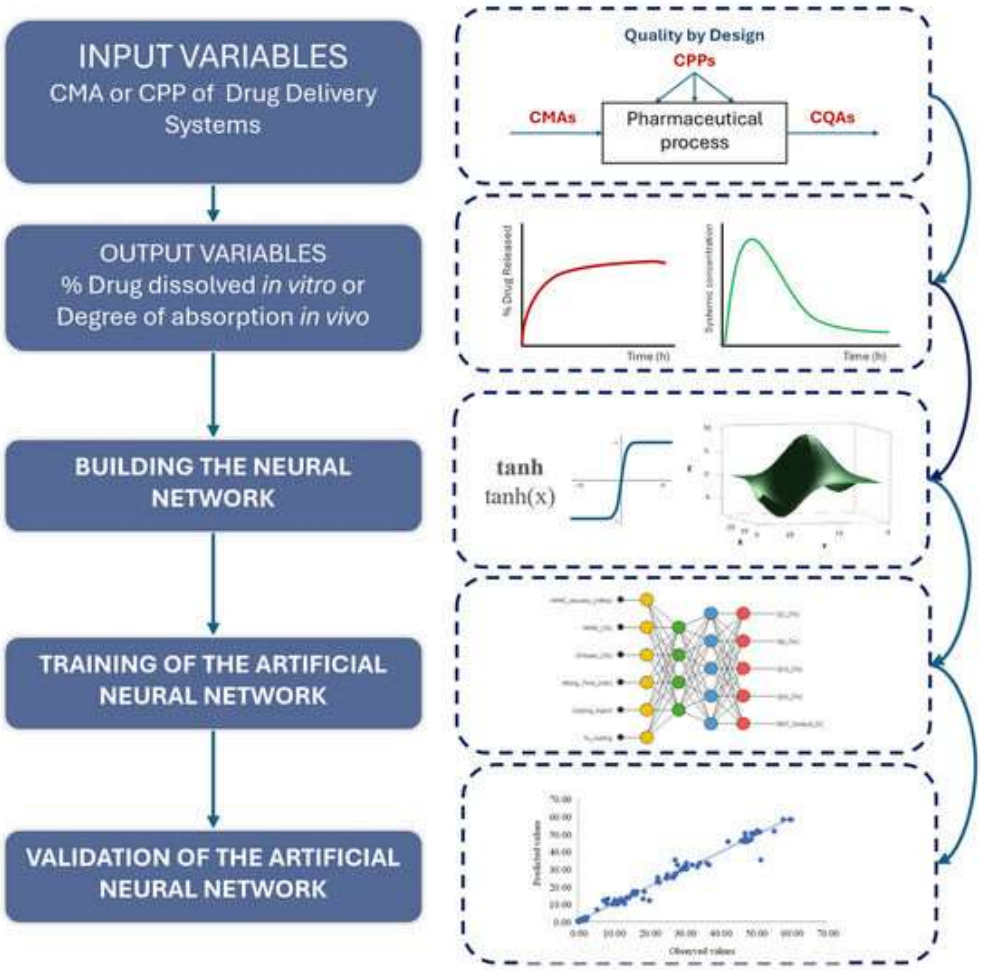

Figure 2: Flowchart for building and implementing a neural network for drug delivery systems. Reprinted with permission from [26].

Support Vector Machines (SVMs)

The supervised learning technique Support Vector Machine (SVM), on the other hand, searches for the best hyperplane separating data points in high-dimensional feature spaces. The support vector machines are able to handle non-linear relationships efficiently because of kernel functions [27]. Support vector machines can be used for classification and regression applications, such as predicting the solubility and release profile of medicines under different conditions. Examples of inputs are physicochemical properties and formulation parameters, while output examples include classification results and quantifiable prediction values. Accuracy levels between 85% and 90% have been shown by the Support vector machine techniques in classifying drug release experiments. These machine learning techniques are used in predicting the solubility of medicines in supercritical environments, including busulfan [28]. However, SVM performance is sensitive to kernel selection and parameter tuning, and scalability can be an issue for large datasets.

Random Forests (RF)

In order to improve predictive capability and reduce overfitting, the Random Forest (RF) ensemble method involves constructing multiple decision trees whose results are then combined. In order to build a robust model, each of the trees involved is trained using random samples of data. Parameters such as particle size, polydispersity index (PDI), and bioavailability, among others, about nanoparticles are common targets for selection and prediction by RF models in the case of DDS [29]. Inputs and outputs include formulation or molecular descriptors and performance metrics, among other things. RF models have helped to identify critical formulation factors that affect nanoparticle stability and have an accuracy of more than 80 percent in predicting oral bioavailability. Despite being easier to interpret compared to NN, RF models are not totally transparent due to their ensemble nature and large volume of data [30].

A comparative study: Shomope et al. [31] present a comparison of the Random Forest (RF) algorithm and the Support Vector Machine (SVM) for calcein release prediction using ultrasound-induced liposomes. With the use of more than 300,000 data points from experiments, RF was able to perform significantly better than SVM. Specifically, the RF algorithm had higher accuracy and less prediction error, particularly at higher ultrasound power densities, where the calcein release was stable and thus more predictable. RF was a superior algorithm since

it could handle large datasets, noise, and interactions among variables with ensemble averaging. On the other hand, the SVM algorithm, which used an RBF kernel, had a higher performance when it came to modeling complex nonlinear calcein release behaviors for intermediate and irregular conditions like those with Herceptin and hyaluronic acid liposomes. Nevertheless, the SVM algorithm had sensitivity problems in parameter tuning and computation.

Convolutional Neural Networks (CNNs)

A Convolutional Neural Network (CNN) is an advanced type of deep learning model, which is utilized in the field of drug delivery systems due to its high precision, efficiency, and customization capabilities. This algorithm is particularly good at analyzing medical and pharmaceutical images, including MRI images, CT scans, microscope images, and nanoparticle shapes [32]. When applied to drug delivery purposes, convolutional networks can be used to find diseased regions like tumor cells for delivering medication precisely in the affected area while limiting the destruction of neighboring healthy cells [33]. Furthermore, the machine learning algorithms play a key role in the analysis of nanoparticles with the help of a 3D CNN model, which helped to analyze the hyperspectral images and recognize the spatial and spectral characteristics for precise liposome identification. Synthetic Minority Oversampling Technique (SMOTE) helped balance the data set to improve the performance of the model, while Principal Component Analysis (PCA) helped simplify the data set to preserve valuable information. The AI framework achieved 99.16% accuracy, highlighting the potential of ML for rapid and reliable pharmaceutical quality control (**Figure 3**) [34].

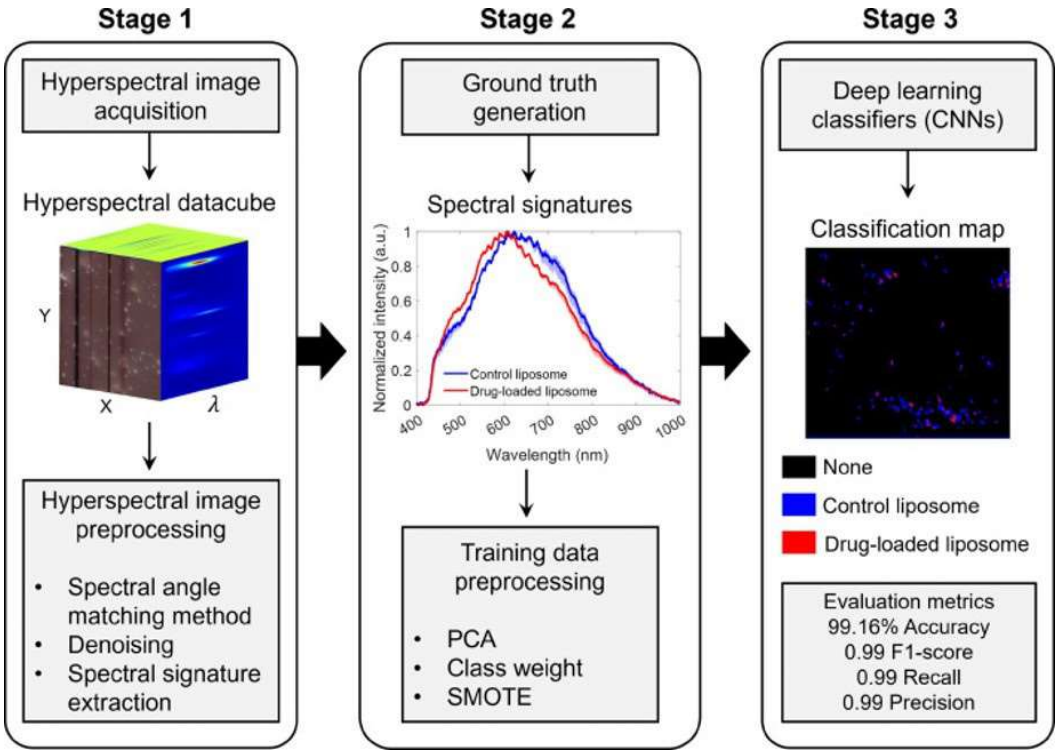

Figure 3: Schematic overview of deep learning-based hyperspectral image classification framework. (Stage 1) Hyperspectral image preprocessing including spectral angle matching, denoising, and spectral signature extraction. (Stage 2) Ground truth generation and training data preprocessing using extracted spectral signatures. (Stage 3) Classification using a convolutional neural network (CNN). Reprinted with permission from [34].

Recurrent Neural Networks (RNNs) and Long Short-Term Memory (LSTM) Networks

Recurrent Neural Networks (RNNs) are deep neural network architectures specifically created to handle time-series and sequence data through the use of historical data from past inputs to influence present predictions. RNNs differ from conventional neural networks in their capacity to employ a feedback loop that gives them the ability to remember past experiences, allowing them to analyze biological and pharmaceutical processes that change with time [35]. Nevertheless, recurrent neural networks have the challenge of vanishing gradients that restrict their capacity to learn long-term relationships in the data. Consequently, LSTM networks are created as a more sophisticated variant of RNNs that allow for the analysis of long-term dependencies. In other words, LSTMs have memory cells and gating mechanisms that control information flow.

Between the two models, LSTMs are usually considered better than RNNs when applied in drug delivery systems since they enable efficient learning of long-term relationships and accurate predictions in complex biological systems. RNNs are computationally less complex but useful in predicting short sequential patterns, yet their performance becomes poor with long-

duration biomedical data due to memory losses in training. LSTM is considered computationally more intensive and demands large amounts of data, but is more dependable in capturing complex physiological phenomena and nonlinear drug delivery processes [36]. In addition to being beneficial in personalized medicine and real-time monitoring in drug delivery, LSTM-based neural networks have become indispensable in smart and intelligent drug delivery systems. The use of RNNs and LSTMs is not without limitations as far as overfitting, intensive computations, and demand for large quality datasets are concerned. However, other than in drug delivery, its application has spread across many fields. It has found applicability in drug discovery, where LSTM-based recurrent neural networks have been employed in generating antiviral drugs against SARS-CoV-2 variants using over 2.5 million SMILES sequences from ChEMBL 29 and MOSES databases. LSTM models successfully captured the dependencies in the molecular sequences and synthesized chemicals that were highly valid (98%), novel (94.1%), and unique (97.9%). It was clearly demonstrated in the research that LSTM models have the capability to speed up the process of drug development through the fast prediction and synthesis of potential molecules of pharmaceutical interest [37].

Generative Models

Generative adversarial networks (GANs) and variational autoencoders (VAEs) constitute one of the most exciting paradigms of progress in computational drug delivery because they shift from predicting to actually generating molecules and formulations. In DDS research, it is not just enough to find efficient drug carriers; rather, there is an added burden of optimizing several interconnected attributes at once, including particle size, encapsulation capacity, biodegradation rate, delivery kinetics, and so on [38]. The process of experimentation is time-consuming, expensive, and largely empirical, while generative methods are capable of rapidly exploring massive formulation spaces and designing new drug carriers.

Between the two models, VAEs are especially beneficial in learning a latent space representation of molecules and materials that can be smooth, making them extremely useful for optimization and interpolation of molecular structures that are already known. The application of VAEs would be useful for designing biodegradable polymers and liposomal nanoparticles where the fine-tuning of physicochemical properties is required [39]. GANs, on the other hand, stand out in the creation of very realistic and structurally varied compounds using an adversarial learning method, which promotes innovation in the design of nanoparticles and carriers.

Their actual usefulness will rely not as much on the complexity of the network architecture but rather on the quality of the data available for pharmaceutical datasets and validation processes. Indeed, drug delivery datasets have the particularity to be scarce, complex and sometimes even noisy, making training difficult and potentially leading to mode collapsing or unrealistic generation of formulations by GANs. Furthermore, most of the generated formulations will indeed be chemically valid but will fail when tested in practice. It seems that GANs and VAEs will have a bright future in DDS by merging with other methodologies.

Reinforcement Learning (RL)

Reinforcement Learning (RL) is a state-of-the-art machine learning approach that allows systems to learn their best actions by interacting with the environment continuously. In drug delivery, reinforcement learning can be applied to enhance the process of optimizing dosing, timing, and target delivery depending on patient responses and physiological parameters. It can respond and adapt to dynamic processes of disease progression and metabolism. Reinforcement learning has promising applications in personalized medicine, chemotherapy schedules, smart insulin administration, and nanoparticle drug delivery systems. The algorithms utilized in reinforcement learning include the use of Q-learning, Deep Q-Networks (DQN), and Actor–Critic. These have great potential in improving the efficacy of therapies and minimizing adverse events and toxicities. In nanomedicine, reinforcement learning can be used to optimize parameters, including the size, surface chemistry, and release kinetics of nanoparticles for enhanced targeting of tumors [40]. RL is also being explored in intelligent nanorobots and controlled drug release implant devices. However, issues associated with the application of RL include a lack of clinical data and safety concerns.

Doxorubicin release optimization from the nanoparticles for the treatment of cancer patients was done using Deep Q-Learning by considering the process as an MDP. Release of drugs is done dynamically based on the environment, like the acidic environment of tumors (pH~6.5) and the healthy environment (pH~7.4), ensuring that the release process targets the tumors effectively. The optimized system resulted in dual-phase drug release, where 35% of drugs are released within six hours, after which there is a sustained 60% release of drugs in 48 hours, hence minimizing the drug's off-target by 18.7%. The model exhibited accurate prediction results with an RMSE value of 1.4% and an MAE value of 1.1%. The results were more favorable compared to those of GA, PSO, SARSA, and Q-learning since RL exhibited faster adaptation and convergence [41].

Graph Neural Networks (GNNs)

Graph-based data comprises nodes representing entities (e.g., atoms) and edges depicting relations (e.g., chemical bonds). Graph Neural Networks (GNNs) analyze this type of data. In DDS, GNNs are used for predicting molecule properties, facilitating accurate predictions of drug-carrier interactions and delivery efficiency [42]. Models based on this technique have proven to be more advanced than traditional deep learning methods, achieving an R2 score of about 0.86 for delivering-related properties' predictions. Nonetheless, GNNs are computationally expensive and require specialized expertise. Lu et al. [43] proposed a multi-layered Graph Attention Neural Network (MLGANN) model for improving drug-target interaction predictions. The researchers incorporated heterogeneous data in the form of biological data, such

as drug similarity, protein-protein interactions, disease links, and drug side effects, in a graph network. Through graph convolution and attention techniques, the system could learn intricate relations between drugs and targets. The results indicate that their approach offered superior predictive capability compared to previous studies on the DrugBank database.

Table 1: AI-Based Predictive and Generative Models in Drug Delivery Research

AI Model Category	Primary Application in Drug Delivery	Quantitative Results & Deep Impact	Key References
Artificial Neural Networks (ANN)	Modelling non-linear release kinetics; predicting tablet attributes.	99% accuracy in tablet hardness; 73% in disintegration time; RMSE of 0.04 in dissolution.	[44]
Support Vector Machines (SVM)	Drug solubility prediction in supercritical drug delivery systems	Achieved R^2 up to 0.993 for busulfan solubility prediction	[45]
Random Forest (RF)	Prediction of protein corona formation and nanoparticle–cell interactions	Successfully predicted protein binding and cellular recognition using nanoparticle physicochemical properties, improving targeted nanoparticle drug delivery design and safety	[46]
Convolutional Neural Networks (CNN)	Label-free classification and quality control of liposomal drug delivery nanoparticles using hyperspectral imaging	Achieved 99.16% classification accuracy with near-perfect F1-scores, enabling rapid, non-destructive, and automated nanoparticle characterization for drug delivery systems	[47]
Generative Adversarial Networks (GAN)	De novo molecular generation and optimization for drug delivery candidates	Generated 4,831 novel molecules with 93% novelty and 95% uniqueness using MedGAN	[48]
Bayesian Optimization (BO)	Optimization of polymeric nanoparticle synthesis and formulation parameters	Successfully optimized PLGA particle fabrication for target sizes of 300 nm and 3.0 µm with minimal experiments, reducing experimental workload and improving formulation precision	[49]
Reinforcement Learning (RL)	Adaptive optimization of nanoparticle drug release for targeted cancer therapy	Reduced simulated off-target drug exposure by 18.7% and achieved optimized dual-phase doxorubicin release using Deep Q-Learning	[41]
Graph Neural Networks (GNN)	Prediction of drug-target interactions and molecular relationship modeling for targeted drug delivery	Achieved higher prediction accuracy than existing DTI models by integrating heterogeneous biological networks using graph attention mechanisms	[50]
XGBoost / LightGBM	Prediction of personalized drug dosage, treatment response, and adaptive drug administration using patient clinical data	The models analyzed patterns in patient demographics, disease progression, prior medication history, and treatment outcomes to predict optimal dosing adjustments, administration frequency, and individualized therapeutic strategies for safer and more effective drug delivery	[51]

4. Computational AI Models in Pharmacokinetics, Drug Release, and ADME Prediction

Pharmacokinetic and Pharmacodynamic Modeling

The advent of artificial intelligence and machine learning (AI/ML) has revolutionized PK and PD modeling through the accurate predictions of the absorption, distribution, metabolism, excretion, and toxicity of drugs (ADMET) (**Table 2**). Traditional compartmental models, limited by linearity, have increasingly become supplemented or replaced by ML methods that can accommodate nonlinearity and high-dimensional biological data. ML methods such as deep neural networks and Gaussian process regression have been successfully implemented in predicting plasma concentration-time curves of drugs, thus diminishing dependence on in vivo tests [52]. Notably, Pfizer used ML PK modeling in optimizing the Paxlovid doses [53]. In addition, PBPK models combined with the random forest algorithm have been applied in predicting pediatric and geriatric doses in populations that are usually underrepresented in clinical trials [54]. For instance, RNNs have shown better performance in

modeling the time-dependent interaction between drug receptors compared to traditional models. This is illustrated by RNN's application in predicting appropriate insulin doses for patients suffering from Type 1 diabetes [55].

Prediction of Drug Release Profiles

Proper prediction of drug release kinetics is vital for rational design of drug delivery systems, and there is a rapid growth in the application of AI/ML techniques in this field. Conventional mathematical models like zero order, first order, Higuchi, and Korsmeyer–Peppas models frequently lack adequate description of the complex and non-linear correlations that exist in multi-component formulations. Machine Learning models, such as artificial neural networks (ANNs), support vector regressions (SVR), and gradient boosting models, are known to provide better predictions owing to their ability to learn complex structure property relationships from experimental data [56]. Interestingly, in vitro release kinetics of prednisone pellets fabricated using extrusion–spheronization technique were modeled by an MLP Artificial Neural Network trained via backpropagation and BFGS algorithm [57]. In particular, the ANN model considered the effects of microcrystalline cellulose concentration, sodium starch glycolate concentration, spheronization time, and extrusion speed on dissolution rate.

Likewise, accurate prediction of two important nanoparticle properties, particle size and zeta potential, was made using Gaussian Process Regression (GPR), Kernel Ridge Regression (KRR), and Adaptive Neuro-Fuzzy Inference System (ANFIS) models in PLGA-based drug delivery systems. The models predicted nanoparticle properties with great accuracy, with test R^2 coefficients of 0.9427 and 0.9841, respectively. The study also involved the use of pre-processing methods such as Leave-One-Out encoding, outlier detection, and Min–Max normalization. Of importance is the fact that the AI model was able to identify optimum synthesis parameters that could generate nanoparticles with sizes less than 150 nm and zeta potential values smaller than −30 mV, which is desirable in drug delivery systems [58]. These approaches have been instrumental in optimizing in silico formulations, reducing costs associated with experimental approaches, and moving towards in vitro–in vivo correlation (IVIVC).

Bioavailability Prediction

The bioavailability is defined as the percentage of the drug that reaches systemic circulation in its active form. The latter factor defines the efficacy of drugs and represents one of the most important reasons for their failure in later phases of clinical trials. Machine learning algorithms like Random Forest, Support Vector Machine, and neural networks have been extensively used to predict oral bioavailability based on descriptors like lipophilicity (LogP), molecular weight, polar surface area, and number of hydrogen bond acceptor/donor with great accuracy [59]. The application of graph neural networks (GNN) provided even greater advancements within this domain through the learning of structural properties beyond common fingerprint-based models. The tools pkCSM, SwissADME, and DeepPK utilize artificial intelligence to provide fast and multi-parameter evaluation of bioavailability. In addition, the incorporation of machine learning into PBPK models allowed for patient-specific prediction of bioavailability, taking into account individual variation in terms of gastrointestinal physiology, transporters, and metabolic enzymes expression, and thus enabling precision dosage strategies. Support Vector Machine was additionally applied by Jamshidi et al. [60] to solve formulation-related problems by predicting the drug solubility in $SCCO_2$ as a result of interaction between process variables and molecular descriptors. Lovric et al. [61] have shown that Random Forest achieves excellent performance (competitive R2/RMSE) with an economical descriptor representation, making Random Forest a good choice for predicting intrinsic aqueous solubility, where descriptor construction plays a vital role. Random Forest, by virtue of its tree-based nature, intrinsically captures non-linear interactions (e.g., threshold interaction between the effect of pKas). It is also able to accommodate complicated partition behavior pertinent to poorly soluble compounds. In addition, Random Forest works well with relatively small data sets commonly found in drug discovery.

Absorption, Distribution, Metabolism, and Excretion (ADME) Modeling

The accurate prediction of ADME properties is crucial during early-stage drug discovery because pharmacokinetics failures make up a substantial percentage of phase failures. AI and machine learning algorithms including deep neural networks, graph convolutional network, and ensemble learning techniques have made significant improvements to in-silico ADME prediction through the learning of complicated and nonlinear structure-property relationships through chemical data analysis. For the prediction of absorption properties, models like Optibrium's StarDrop platform have been successfully implemented to predict intestinal permeability and oral bioavailability with excellent accuracy [62]; similarly, the application of GCNs to predict permeation from Caco-2 and PAMPA datasets has produced better results compared to the application of physicochemical rules. Models that model distribution predict plasma protein binding, volume of distribution, and BBB penetration through various ML and deep learning approaches. The BBBpredict and DeepBBB models apply deep learning to fingerprint information to predict BBB permeability to facilitate CNS drug discovery [64]. Recurrent neural networks and transformer-based models like MetaSite and P450-BERT predict CYP450 metabolic sites and metabolic stability [65]. Excretion/renal clearance prediction also has been aided by ML models built using data from human pharmacokinetics studies, which include the pkCSM and ADMETlab 2.0 platforms providing a combination of end-to-end ADME predictions [66]. Together, these AI-enabled approaches shorten the time needed to make ADME evaluations, selecting lead compounds based on pharmacokinetics and reducing attrition rates.

Table 2: AI-Assisted Prediction of Pharmacokinetic Parameters, Drug Release Profiles, and ADME Profiling

AI/ML Model	Primary Application in PK, Drug Release & ADME	Functions	References
Deep Neural Networks (DNNs)	Pharmacokinetic (PK) modeling	Predicted plasma concentration–time profiles and nonlinear ADMET relationships	[52]
Gaussian Process Regression (GPR) & Kernel Ridge Regression (KRR)	PK prediction; nanoparticle optimization	Modeled nonlinear pharmacokinetic trends and predicted PLGA nanoparticle size/zeta potential	[58]
Random Forest (RF)	Bioavailability and ADME prediction	Achieving strong performance (competitive R^2/RMSE) for intrinsic aqueous solubility	[61]
Support Vector Machines (SVM)	Drug release and solubility prediction	Modeled nonlinear dissolution and $SCCO_2$ solubility relationships	[60]
Recurrent Neural Networks (RNNs)	Pharmacodynamic (PD) modeling	Predicted time-dependent drug–receptor interactions and adaptive insulin dosing optimization	[55]
Multilayer Perceptron ANN (MLP-ANN)	Drug release profile prediction	Predicted dissolution behavior of prednisone pellets using formulation variables	[57]
Graph Neural Networks (GNNs) / Graph Convolutional Networks (GCNs)	Bioavailability and ADME modeling	Learned molecular graph relationships for permeability, BBB penetration, and bioavailability prediction	[64]
Transformer-based Models (P450-BERT)	Metabolism prediction	Predicted CYP450-mediated metabolic sites and metabolic stability	[65]
Gradient Boosting Models	Drug release and bioavailability prediction	Demonstrated superior predictive accuracy by learning intricate structure property relationships from experimental datasets	[56]
pkCSM / SwissADME / ADMETlab 2.0	Integrated ADME profiling	Predicted bioavailability, toxicity, clearance, and pharmacokinetic properties	[66]

5. Current Challenges and Future Directions of AI-Driven Drug Delivery Systems

Data Scarcity, Heterogeneity, and Standardization

The first limitation of AI-assisted DDS lies in the fact that large, standard, and quality pharmaceutical datasets are simply not available. Experimental data from various institutions were acquired under different experimental conditions and using different vocabularies and data structures, which affects the generalizability of models [67]. In addition, the limited sample size of nanomedicines and biologics makes machine learning models susceptible to overfitting. The deficiency of carefully curated and openly accessible data resources devoted to formulations poses serious challenges for AI model development and validation. Recently, federated learning has been identified as an emerging approach for dealing with this problem, in which the privacy-preserved AI-based algorithms can be trained through collaboration among multiple non-centralized institutions. Standardized vocabularies, adherence to the FAIR principles, and creation of open pharmaceutical datasets will facilitate the development of the much-needed data infrastructure for AI-assisted formulations [68].

Model Interpretability and the Black-Box Problem

Many highly performing AI models, like deep neural networks, CNNs, and GANs, function as black boxes with low levels of mechanistic transparency. In the realm of pharmaceutical science, which necessitates a clear understanding of causality between the variables in the formulation process and its clinical efficacy, any prediction made by an AI model with no explainability capability becomes scientifically and legally indefensible. Lack of the capability to examine decision-making processes lowers scientific credibility and hinders model optimization as well as its incorporation into the QbD paradigm [69].

Regulatory Frameworks and Clinical Translation Barriers

Current regulation processes, set by regulatory authorities like FDA and EMA, were not designed for assessing AI/ML-based pharmaceutical products. The inherent dynamics of adaptive machine learning

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algorithms, where a prediction model may continuously evolve when receiving novel data points, has created several open issues around validation, liability, and post-market monitoring [70]. In addition, at present, there is no consensus around minimal size of datasets, performance indicators, and validation protocols for AI-driven DDS, hence the presence of an important regulatory gap hampering clinical implementation and marketing authorization of these novel systems [71]. Collaborative consortia among pharmaceutical companies, academia, and regulatory authorities are required to develop together regulatory frameworks for validation, qualification, and post-market monitoring of AI-enabled drug delivery systems. Harmonized regulations worldwide will be crucial to avoid market fragmentation.

Integration of Multi-Modal and Real-World Data

AI for drug delivery is mostly based on single-modality data from the lab. But incorporating multiple modalities like genomic, proteomics, metabolomics, imaging, EHR, wearables, and patient outcomes can help in predicting a more accurate treatment that will be beneficial at the biological level as well [72]. Digital twins can play a key role in AI-assisted drug delivery by simulating personalized drug responses using patient-specific computational modeling [73]. Challenges like reducing the dimensionality, handling missing values, computational burden, and complying with GDPR/HIPAA are also worth mentioning (**Figure 4**). Improvements in self-supervised learning, transfer learning, and pharmaceutical LMs can pave the way forward.

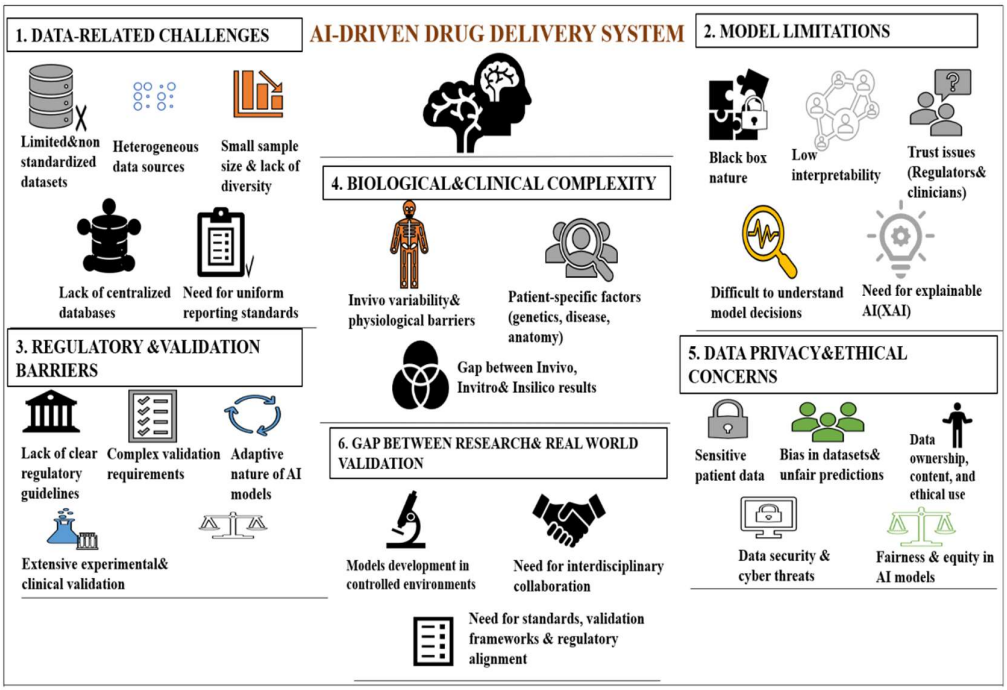

Figure 4: Key challenges in AI-driven drug delivery systems.

Convergence between AI technology, nanotechnology, synthetic biology, and manufacturing technologies is making possible the invention of smart drug delivery vehicles, which are able to sense and react in real-time. The integration of closed-loop systems, which allow real-time biomarker tracking and stimulation of AI-controlled stimuli-responsive carriers, has been proven effective in insulin release and cancer immunotherapy applications. Implementation of reinforcement learning algorithms into implantable devices and nanorobots will allow for dynamic adaptation of treatment methods, particularly those used to treat chronic diseases such as diabetes and heart disease. Moreover, the emergence of novel diffusion and transformer-based generative AI approaches will facilitate the discovery of new lipid nanoparticles, biodegradable polymers, and targeting ligands far beyond the capabilities of conventional screening approaches. Lastly, AI-driven 3D and 4D bioprinting technologies will allow patient-specific production of dosage forms featuring programmable release kinetics. The development of this vision will require effective AI governance policies and ethical standards regarding autonomous therapeutic systems, as well as a globally collaborative data ecosystem.

Conclusion

The advent of artificial intelligence has been completely revolutionizing the design and development process of drug delivery systems, changing the face of pharmaceutics from a trial-and-error-based approach to a rationale-oriented one. The use of artificial intelligence-based models has helped in the effective prediction of formulation variables, pharmacokinetics, release profile, and ADME properties, thus saving time and making the therapy much more precise. Though there continue to be some limitations in data

standardization, model transparency, and regulation of the technology, approaches like explainable AI, federated learning, and generative modeling provide very promising solutions.

Declarations

Conflict of interest statement: All authors declare no conflict of interest.

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