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REVIEW ARTICLE

Artificial Intelligence in Predictive Pharmaceutics: From Formulation Optimization to Precision and Smart Drug Delivery

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ABSTRACT

The integration of artificial intelligence, machine learning, and deep learning is transforming pharmaceutical drug delivery systems from empirical trial-and-error paradigms into rational, data-driven platforms. Conventional drug delivery modalities frequently suffer from suboptimal bioavailability, lack of anatomical target specificity, unpredictable burst release, and variable therapeutic outcomes. This critical narrative review provides an in-depth, evaluative examination of artificial intelligence methodologies specifically applied to pharmaceutical drug delivery. We establish clear delineations between computational drug discovery and drug delivery engineering while disambiguating the distinct operational roles of classical machine learning algorithms and deep neural architectures. A structured literature retrieval was conducted across major electronic databases (PubMed/MEDLINE, Scopus, Web of Science, IEEE Xplore, and Google Scholar), covering peer-reviewed studies published from 2015 to 2024. Computational models demonstrate significant capacity to advance formulation optimization, predict nanocarrier critical quality attributes (hydrodynamic diameter, surface charge, and entrapment efficiency), model non-linear dissolution kinetics, and guide the three-dimensional printing of personalized dosage forms. Furthermore, the clinical translation of stimuli-responsive smart therapeutics and active micro-nanorobots is objectively appraised. Finally, we dissect the paramount translational roadblocks, encompassing pharmaceutical data scarcity, algorithmic interpretability, and regulatory harmonization under Good Machine Learning Practice and Predetermined Change Control Plans, providing a publication-standard roadmap for intelligent drug delivery.

Keywords: Drug delivery systems, Machine learning, Formulation optimization, Nanocarriers, Dissolution kinetics, Smart therapeutics

INTRODUCTION

Drug delivery systems (DDS) encompass specialized technologies and engineered formulations designed to transport active pharmaceutical ingredients (APIs) to targeted physiological sites, thereby maximizing therapeutic efficacy while minimizing off-target systemic toxicity[1]. Historically, pharmaceutical delivery relied on conventional dosage forms such as immediate-release tablets, capsules, oral suspensions, and simple ointments, which are inherently constrained by erratic absorption, narrow therapeutic windows, hepatic first-pass degradation, and fluctuating peak-to-trough plasma concentrations[2, 3]. Over recent decades, pharmaceutical engineering has progressed through distinct evolutionary milestones from conventional dosage forms to controlled-release matrices that prolong drug release and reduce dosing frequency, followed by targeted delivery platforms leveraging nanotechnology (e.g.,

liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions) to enhance cellular uptake and bypass biological barriers[4, 5]. Despite these advancements, conventional formulation development remains heavily reliant on empirical trial-and-error experimentation and one-factor-at-a-time (OFAT) methodologies, which are resource-intensive, time-consuming, and frequently fail to capture complex, non-linear interactions among drug molecules, excipients, and biological microenvironments[5, 6].

The evolution of these drug delivery modalities across four technological eras from conventional immediate-release forms to time-controlled matrices, site-specific targeted nanomedicines, and sensor-actuated, AI-driven smart platforms is schematically summarized in Fig. 1.

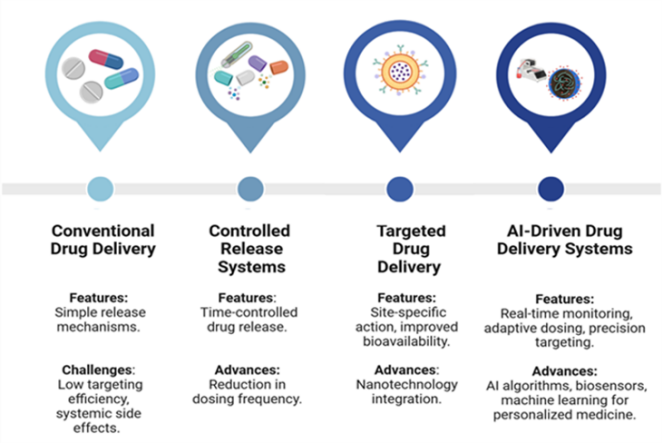


Fig. 1: Evolution of drug delivery systems across four eras: conventional forms, followed by controlled-release for fewer doses, targeted nanomedicines for site-specific action, and real-time adaptive AI systems

A critical conceptual distinction must be established between artificial intelligence (AI) applications in drug discovery and those in drug delivery systems[7]. While AI in drug discovery predominantly focuses on upstream targets such as genomic target identification, macromolecular protein structure prediction, de novo ligand generation, and virtual screening of chemical libraries, AI in drug delivery addresses the downstream challenges of formulation physics, carrier self-assembly, biopharmaceutical transport, and spatiotemporal release kinetics[6, 8]. Specifically, AI in DDS operates on physical formulation parameters, including excipient compatibilities, polymer-lipid phase behavior, hydrodynamic size distribution, surface charge (zeta potential), encapsulation efficiency, and in vitro-in vivo correlations (IVIVC)[8, 9]. Misattributing upstream discovery capabilities to delivery science obscures the distinct physicochemical and mechanistic principles governing pharmaceutical formulation design.

Therefore, this critical narrative review provides a focused, evaluative analysis of AI, machine learning (ML), and deep learning (DL) technologies strictly within the domain of drug delivery systems. We examine the specific algorithmic architectures applied to formulation optimization, nanocarrier engineering, drug release kinetics, 3D-printed personalized dosage forms, and stimuli-responsive smart delivery platforms. Furthermore, we critically appraise the quality of current empirical evidence, compare model predictive accuracies against experimental benchmarks, provide an objective assessment of the technological maturity of active nanorobotic carriers, and delineate the stringent regulatory and data governance frameworks governing the clinical translation of AI-designed therapeutics.

MATERIALS AND METHODS

To ensure comprehensive coverage, conceptual clarity, and objective rigor, this critical narrative review utilized a structured literature retrieval framework across five major electronic scientific databases: PubMed/MEDLINE, Scopus, Web of Science Core Collection, IEEE Xplore, and Google Scholar. The temporal search window spanned publications from January 2015 to August 2024, capturing the transition from classical empirical statistical modeling to modern machine learning and deep neural network architectures in pharmaceutical technology.

The search strategy employed a combination of Medical Subject Headings (MeSH) and targeted free-text descriptors using Boolean operators: ("artificial intelligence" OR "machine learning" OR "deep learning" OR "artificial neural network*" OR "random forest*" OR "support vector*" OR "genetic algorithm*") AND ("drug delivery system*" OR "nanocarrier*" OR "nanomedicine" OR "controlled release" OR "formulation optimization" OR "smart drug delivery" OR "3D print* pharmaceutical*").

To construct an authoritative critical narrative synthesis, literature was appraised against explicit thematic criteria. Inclusion criteria comprised (a) peer-reviewed original research papers and authoritative review articles published in indexed scientific journals; (b) studies directly investigating AI, ML, or DL computational algorithms applied to pharmaceutical formulation design, nanocarrier characterization (size, polydispersity, surface charge, encapsulation efficiency), dissolution kinetics modeling, 3D printing of patient-tailored dosage forms, or stimuli-responsive delivery platforms; and (c) investigations providing empirical validation data (*in vitro, ex vivo,* or *in vivo*). Exclusion criteria comprised (a) non-peer-reviewed preprints, patents, book chapters, and conference abstracts without complete experimental methodologies; (b) studies focusing exclusively on upstream drug discovery, genomic target identification, de novo small-molecule synthesis, protein folding, or chemical repurposing without delivery vehicle or formulation components; (c) publications lacking

computational or physical experimental validation; and (d) non-English publications. Rather than employing a rigid quantitative meta-analytic aggregation, a critical narrative synthesis approach was adopted to holistically appraise algorithmic strengths, data limitations, physical experimental correlations, and translational feasibility across diverse formulation platforms.

RESULTS

Conceptual hierarchy: disambiguating AI, ML, and DL in drug delivery

In pharmaceutical literature, the terms "artificial intelligence," "machine learning," and "deep learning" are frequently conflated. Establishing a precise hierarchical taxonomy is essential to identify which computational architecture is suited to specific drug delivery challenges[6, 10]. Artificial intelligence (AI) represents the broadest overarching discipline, encompassing any computational technique or system that simulates human intelligence and decision-making logic[6]. Within DDS, classical AI includes rule-based expert systems and heuristic search routines historically used for automated excipient selection.

The overarching taxonomy of artificial intelligence, machine learning, and deep learning applications across drug delivery systems is schematically organized in Fig. 2, establishing the core technical pillars: formulation design, nanocarrier engineering, release kinetics modeling, and smart personalized therapeutics.

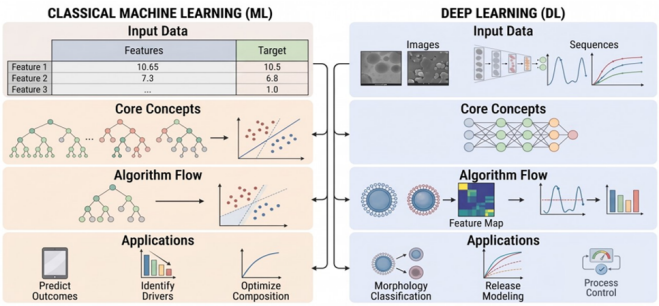


Fig. 2: Schematic comparison of Classical Machine Learning (ML) and Deep Learning (DL) workflows and applications in drug delivery systems

Machine learning (ML) is a specialized subset of AI comprising statistical algorithms that learn mathematical mappings from structured, tabular datasets without being explicitly programmed[8]. In formulation science, ML models operate on tabular feature matrices where input variables include API molecular descriptors (e.g., molecular weight, octanol-water partition coefficient [log P], topological polar surface area [TPSA], hydrogen bond donors/acceptors), excipient concentrations (e.g., polymer-to-lipid ratios, surfactant Hydrophile-Lipophile Balance [HLB] values), and process variables (e.g., homogenization pressure, ultrasonication duration, extrusion temperature)[8, 11]. Prominent classical ML algorithms applied in DDS include:

1. **Random Forests (RF) and Gradient Boosted Decision Trees (e.g., XGBoost, LightGBM):** Ensemble tree-based methods that excel at handling tabular formulation data, ranking feature importance (e.g., identifying whether surfactant ratio or sonication amplitude drives droplet size), and demonstrating robust resistance to overfitting on small sample sizes[11, 12].

2. **Support Vector Machines and Regression (SVM/SVR):** Non-parametric models that utilize kernel functions (e.g., radial basis functions) to map non-linear formulation relationships into high-dimensional hyperplanes, highly effective for predicting continuous response variables such as drug entrapment efficiency and cumulative release percentages from limited experimental batches[13, 14].

3. **Genetic Algorithms (GA) and Bayesian Optimization:** Metaheuristic and probabilistic optimization frameworks frequently coupled with predictive ML models to execute multi-objective Pareto optimization, navigating complex formulation spaces to identify optimal trade-offs between maximum drug loading and minimum particle polydispersity[15-17].

Deep learning (DL) represents an advanced subfield of ML based on multi-layered artificial neural network architectures capable of automated, hierarchical feature extraction from high-dimensional, unstructured, or sequential data[10, 13]. Unlike classical ML models that require manual feature engineering, DL networks learn latent representations directly from raw inputs. Key DL architectures in DDS include:

1. **Multi-Layer Perceptrons (MLP) and Deep Neural Networks (DNN):** Fully connected networks with multiple hidden layers capable of modeling highly complex, non-linear input-output interactions across multi-component formulations[13].

2. **Convolutional Neural Networks (CNN):** Specialized architectures utilizing convolutional kernels to process spatial grid data. In DDS, CNNs are applied to analyze high-resolution microscopy images (cryogenic transmission electron microscopy [cryo-TEM] and scanning electron microscopy [SEM]) for automated morphological classification of nanocarriers, detection of aggregation, and

quantitative tracking of intracellular nanoparticle endocytosis and lysosomal escape[18].

3. **Recurrent Neural Networks (RNN) and Long Short-Term Memory (LSTM) Networks:** Architectures engineered to process sequential, time-series data. LSTMs excel at modeling dynamic, time-dependent drug dissolution curves and non-Fickian anomalous diffusion release kinetics, capturing temporal dependencies that static regression models overlook[14].

AI in drug formulation design and nanocarrier engineering

Solid dosage forms, including tablets, capsules, and controlled-release pellets, constitute over 60% of commercial pharmaceuticals but present multifaceted formulation challenges involving powder flowability, compressibility, tablet hardness, friability, and disintegration[19]. Traditional formulation development utilizes Design of Experiments (DoE), such as Box-Behnken or central composite designs. While DoE provides statistical estimation of linear and quadratic effects, it struggles when formulation spaces exhibit high-order non-linear interactions or discontinuities[19, 20]. Artificial neural networks coupled with genetic algorithms (ANN-GA) have emerged as superior alternatives, establishing non-linear response surfaces that accurately predict tablet mechanical strength and dissolution profiles[19]. Furthermore, in liquid dispersions and self-nanoemulsifying drug delivery systems (SNEDDS), machine learning models such as Random Forest and Extreme Gradient Boosting (XGBoost) accurately predict pseudo-ternary phase boundaries, emulsification efficiency, and spontaneous droplet size from oil, surfactant, and co-surfactant physicochemical descriptors[12].

Nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and polymeric nanoparticles, are governed by critical quality attributes (CQAs) that dictate biological fate: hydrodynamic particle size, polydispersity index (PDI), surface zeta potential, and encapsulation efficiency (%EE)[5, 21]. Hydrodynamic size determines systemic circulation half-life and passive extravasation via the enhanced permeability and retention (EPR) effect, while zeta potential influences colloidal stability and opsonization by serum proteins[21]. Recent investigations have demonstrated that multi-task deep neural networks and ensemble regressors can predict nanocarrier CQAs prior to physical synthesis[8, 22]. By training on datasets incorporating lipid melting points, acyl chain lengths, surfactant concentrations, and homogenization parameters, ML models achieve coefficients of determination (R^2) exceeding 0.90 for particle size and %EE prediction[11, 22, 23]. This in silico screening reduces laboratory formulation iterations by more than 70%, conserving costly APIs and excipients.

Integrating AI with Process Analytical Technology (PAT) represents a cornerstone of modern pharmaceutical manufacturing and Quality by Design (QbD) initiatives (Fig. 3)[6, 19]. During continuous manufacturing processes such as high-shear wet granulation, fluid-bed drying, and twin-screw hot-melt extrusion, in-line near-infrared (NIR) and Raman spectroscopy probes capture real-time spectral data reflecting blend uniformity, moisture content, and solid-state polymorphic transitions[19, 24]. Deep learning chemometric models, including 1D-CNNs and partial least squares regression (PLSR) integrated with artificial neural networks, process raw spectral feeds in real time, automatically detecting deviations and modulating feed rates, screw speeds, or drying temperatures[24]. This closed-loop process control ensures consistent batch-to-batch quality and prevents batch rejection.

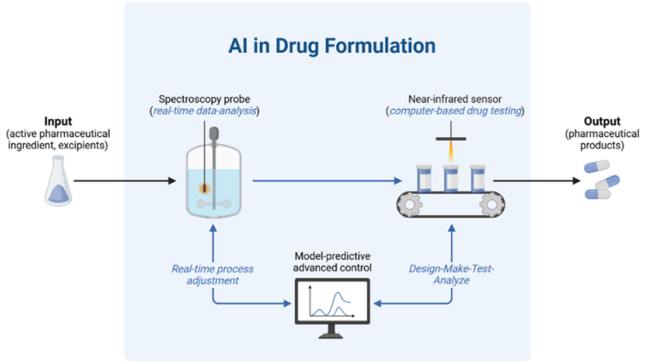


Fig. 3: AI-integrated Process Analytical Technology (PAT) and closed-loop process control in continuous pharmaceutical manufacturing. In-line near-infrared (NIR) probes capture real-time spectral data, which are processed by neural chemometric models to autonomously modulate processing parameters and ensure batch-to-batch critical quality attributes

Predictive modeling of drug dissolution and release kinetics

Mathematical characterization of drug release from polymeric matrices, liposomes, and hydrogels has historically relied on classical semi-empirical equations, such as the zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models[1, 14]. While these equations offer basic mechanistic insights into diffusion-controlled or erosion-controlled release, they operate under rigid assumptions: perfect sink conditions, constant diffusion coefficients, uniform drug dispersion, and invariant matrix geometry[14]. Consequently, empirical models fail to predict complex, multi-phasic release behaviors such as initial burst

release followed by slow anomalous (non-Fickian) relaxation diffusion and terminal matrix degradation[14, 25].

Machine learning approaches, including Support Vector Regression (SVR), Artificial Neural Networks (ANN), and Long Short-Term Memory (LSTM) recurrent networks, model dissolution kinetics with high accuracy by capturing dynamic time-series interactions without imposing predefined kinetic constraints[14, 26]. Feature inputs typically include dissolution medium pH, ionic strength, hydrodynamics (paddle rotation speed), matrix polymer molecular weight, polymer blend ratios, and drug solubility profiles[25]. In comparative benchmarking studies, ensemble tree models and neural architectures consistently achieve lower root mean square error (RMSE < 0.04) and higher similarity factors ($f_2 > 75$) when matching predicted release curves against experimental USP dissolution profiles, significantly outperforming classical Korsmeyer-Peppas regression ($R^2 = 0.82$ vs. 0.97 for AI models)[14, 26].

Personalized drug delivery systems: 3D printing and tailored formulations

Personalized medicine in drug delivery focuses on engineering customized pharmaceutical dosage forms tailored to an individual patient's physiological needs, anatomical dimensions, and release profile requirements, distinct from general pharmacotherapy response prediction[27, 28]. Three-dimensional (3D) printing has emerged as the premier manufacturing technology for personalized drug delivery, enabling the fabrication of complex geometries, multi-drug polypills with segregated release compartments, and personalized transdermal microneedle arrays[28, 29]. However, 3D printing techniques such as Fused Deposition Modeling (FDM), Semi-Solid Extrusion (SSE), Selective Laser Sintering (SLS), and Stereolithography (SLA) are plagued by empirical trial-and-error optimization of critical processing and formulation parameters[29, 30].

Machine learning has advanced 3D pharmaceutical printing by predicting 'printability' and optimizing fabrication parameters[30, 31]. For instance, the M3DISEEN machine learning framework demonstrated that ensemble models (Random Forest, XGBoost) trained on chemical structures, polymer glass transition temperatures (Tg), melt flow indices, and printing temperatures can predict printability, filament feedability, and final dosage form dimensions with an accuracy exceeding 85%[30]. Furthermore, genetic algorithms have been applied to compute optimal multi-layer capsule wall thicknesses and porous architectures to achieve custom zero-order or pulsed chronotherapeutic release profiles matching circadian disease rhythms[31]. By automating parameter selection, AI eliminates costly print failures and ensures the rapid, on-demand fabrication of tailored oral delivery systems.

Smart and stimuli-responsive drug delivery systems

Smart drug delivery systems (SDDS) are engineered to release therapeutic payloads selectively in response to specific endogenous or exogenous physiological stimuli[32]. Endogenous triggers include acidic extracellular tumor pH (pH 6.5–6.8), endosomal acidic environments (pH 5.0–5.5), elevated intracellular glutathione (GSH) concentrations driving disulfide cleavage, and upregulated matrix metalloproteinases (MMPs)[32, 33]. Exogenous stimuli encompass externally applied alternating magnetic fields, near-infrared light, and focused ultrasound[33]. AI algorithms, specifically classification models and deep neural networks, predict the triggering threshold, swelling ratios, and payload release rates of stimuli-responsive polymers and lipid-polymer hybrids based on crosslinking density, polymer pKa, and cleavage kinetics[32, 33].

In closed-loop drug delivery platforms, AI algorithms are coupled with continuous biosensors to establish self-regulating therapeutic systems[34]. The most clinically advanced paradigm is the automated artificial pancreas, wherein a machine learning controller (model predictive control or reinforcement learning) processes continuous subcutaneous glucose sensor streams to dynamically adjust micro-pump basal and bolus insulin delivery, effectively buffering against glycemic excursions while preventing life-threatening hypoglycemia[34, 35].

Architectural paradigms of closed-loop smart drug delivery systems (SDDS) and predictive formulation optimization are systematically illustrated in Fig. 4.

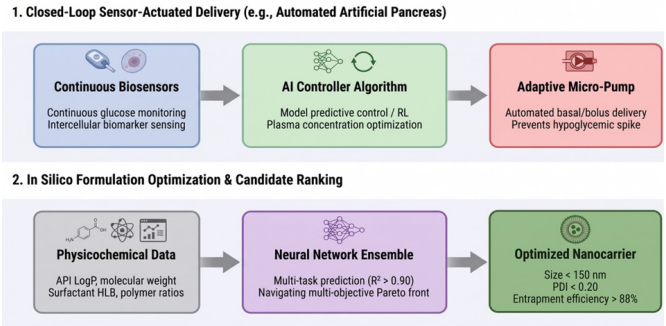


Fig. 4: Architectural paradigms of AI-driven smart drug delivery systems (SDDS): (1) Closed-loop sensor-actuated delivery platforms utilizing model predictive control to optimize plasma concentration; (2) In silico formulation optimization loop navigating multi-objective Pareto trade-offs

Critical literature synthesis of AI architectures in DDS

To provide a structured comparative analysis of the empirical literature, Table. 1 synthesizes representative studies applying AI, machine learning, and deep learning

models across diverse drug delivery systems, highlighting their specific inputs, key findings, computational limitations, and experimental validation levels.

Table 1: Critical comparative synthesis of AI, machine learning, and deep learning architectures implemented in drug delivery systems

AI / Model Architecture	Application in DDS	Input Data / Features	Carrier / System Studied	Main Results / Performance	Limitations / Bottlenecks	Validation Level
Artificial Neural Network + Genetic Algorithm (ANN-GA)	Multi-objective formulation optimization (size, PDI, %EE)	Lipid concentrations, surfactant types, ultrasonication amplitude, homogenization cycles	Solid Lipid Nanoparticles (SLNs) / NLCs	Predicted optimal composition: size < 150 nm, PDI < 0.20, EE > 88% (R^2 > 0.94)	Susceptible to local minima; requires extensive experimental calibration datasets (N > 30 batches)	*In vitro & ex vivo*
Random Forest (RF) & XGBoost	Self-emulsification efficiency and droplet size prediction	Excipient HLB, oil-surfactant-cosurfactant ratios, API log P, molecular weight	Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)	Predictive accuracy > 88% for spontaneous nanoemulsion formation; droplet size RMSE < 12.5 nm	Inability to extrapolate outside defined excipient chemical space; empirical feature dependency	*In vitro*
Support Vector Regression (SVR)	Non-linear drug dissolution kinetics & burst release prediction	Polymer molecular weight, matrix porosity, drug loading %, dissolution medium pH	Hydrophilic polymeric matrix tablets (HPMC / Carbopol)	Achieved R^2 = 0.96 and similarity factor f_2 > 78 against experimental USP dissolution profiles	Computationally intensive quadratic programming for large time-series datasets; kernel sensitivity	*In vitro*
Long Short-Term Memory (LSTM) Networks	Dynamic time-series release profiling under variable pH conditions	Time-step release percentages, gastrointestinal transit pH gradients, degradation rates	pH-responsive enteric-coated nanoparticles & microgels	Captured biphasic and anomalous non-Fickian diffusion kinetics with RMSE < 0.035; outperformed Korsmeyer–Peppas equation	High data requirement for training; black-box architecture lacks direct physical transport interpretability	*In vitro & in silico*
Ensemble Machine Learning (M3DISEEN framework)	Predicting printability & dimensional fidelity in 3D-printed medicines	Polymer glass transition temp (Tg), melt flow index, extrusion temp, printing speed, infill density	FDM 3D-printed personalized tablets	Classification accuracy > 85% for filament feedability and printability; minimized nozzle clogging failures	Limited to thermoplastic polymer filament formulations; requires physical filament preparation data	*In vitro*
Convolutional Neural Networks (CNN)	High-throughput nanocarrier morphological profiling & cellular uptake quantification	Cryo-TEM micrographs, confocal fluorescence imaging z-stacks of endocytosed particles	Tumor-targeted polymeric nanoparticles & functionalized liposomes	Automated detection of particle shape, agglomeration state, and intracellular distribution with > 92% accuracy	Requires thousands of annotated microscopy images; sensitive to focal plane artifacts and background noise	*In vitro* (cellular)
Model Predictive Control with Deep Q-Learning	Real-time closed-loop adaptive dosing & glycemic regulation	Continuous subcutaneous glucose sensor feeds, meal carbohydrate inputs, physical activity telemetry	Automated Artificial Pancreas (closed-loop subcutaneous insulin delivery)	Maintained patient time in range (70–180 mg/dL) > 80% without clinical hypoglycemic events	Sensor lag time (~10–15 min); sensor biofouling and patient physiological variability over time	Clinical (*in vivo*)

Abbreviations: ANN: Artificial Neural Network; GA: Genetic Algorithm; SLN: Solid Lipid Nanoparticle; NLC: Nanostructured Lipid Carrier; PDI: Polydispersity Index; EE: Entrapment Efficiency; RF: Random Forest; XGBoost: Extreme Gradient Boosting; SNEDDS: Self-Nanoemulsifying Drug Delivery System; HLB: Hydrophile-Lipophile Balance; SVR: Support Vector Regression; HPMC: Hydroxypropyl Methylcellulose; LSTM: Long Short-Term Memory; FDM: Fused Deposition Modeling; CNN: Convolutional Neural Network; Cryo-TEM: Cryogenic Transmission Electron Microscopy; TEM: Transmission Electron Microscopy; MPC: Model Predictive Control.

DISCUSSION

Quality of evidence and model benchmark discrepancies

A critical evaluation of the published literature reveals significant disparities in the quality of evidence supporting AI in drug delivery. While numerous studies claim exceptional predictive performance, few rigorously benchmark novel machine learning models against simpler, established baseline methods such as multiple linear regression or classical response surface methodology. In many formulation instances, simple ensemble trees (e.g., Random Forest) perform comparably to complex deep neural networks while exhibiting markedly less susceptibility to overfitting and requiring far fewer training instances[8, 11]. Furthermore, true external validation on independent experimental batches synthesized under distinct laboratory conditions remains rare. Most published models rely exclusively on internal k-fold or leave-one-out cross-validation, which often inflates predictive accuracy ($R^2 > 0.95$) by failing to capture batch-to-batch raw material variability and operator bias[14, 36].

Regulatory standards, GMLP, and predetermined change control plans

Transitioning AI-designed drug delivery systems from computational benchwork to regulatory approval requires meeting stringent international validation standards. Vaguely classifying AI regulations as 'unclear' overlooks substantial policy frameworks established by global health authorities. The United States Food and Drug Administration (US FDA), Health Canada, and the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) jointly published ten guiding principles for Good Machine Learning Practice (GMLP) for Medical Device Development[37, 38]. In pharmaceutical formulation and delivery, GMLP dictates that computational models must demonstrate: (a) rigorous data representativeness, ensuring training data encompasses formulation diversity and edge-case excipient behaviors; (b) separation of training, tuning, and independent testing datasets to avoid data leakage; and (c) statistically sound validation across pre-specified acceptance criteria[38, 39].

A profound regulatory challenge in AI-driven smart therapeutics is the fundamental dichotomy between 'locked' algorithms and 'adaptive' (continuous learning) models[37, 40]. Conventional pharmaceutical regulatory approvals (e.g., FDA Investigational New Drug [IND] and New Drug Application [NDA] pathways) mandate immutable formulation specifications and validated manufacturing tolerances. A locked AI model, wherein weights, hyperparameters, and decision thresholds remain static post-validation, fits readily into existing regulatory schemas[37]. However, smart drug delivery devices (e.g., adaptive closed-loop insulin pumps and sensor-actuated implants) benefit significantly from continuous learning models that adaptively refine dosing algorithms based on real-time patient physiological changes[34, 40].

To reconcile continuous algorithm evolution with patient safety, regulatory agencies have introduced the concept of Predetermined Change Control Plans (PCCP) under Software as a Medical Device (SaMD) and Software in a Medical Device (SiMD) guidelines[37, 41]. Under a PCCP, manufacturers must prospectively delineate: (1) what aspects of the delivery algorithm will be updated (e.g., basal rate scaling factors), (2) the computational methodology governing re-training, and (3) verification and validation protocols that automatically constrain model drift within safe therapeutic boundaries without necessitating de novo regulatory submissions for every iteration[41].

Algorithmic explainability (XAI), accountability, and liability

The pervasive 'black-box' nature of deep learning neural networks represents a major barrier to regulatory approval and clinical acceptance [42, 43]. Regulatory reviewers and clinical toxicologists require mechanistic interpretability to comprehend why an algorithm selected a particular excipient ratio, predicted anomalous dissolution kinetics, or modulated an in vivo delivery rate. Consequently, the adoption of Explainable AI (XAI) frameworks such as SHapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME) has become essential[42, 43]. SHAP values assign game-theoretic contribution weights to each formulation parameter, enabling formulation scientists to verify whether AI predictions align with established physicochemical laws (e.g., confirming that higher surfactant concentrations reduce interfacial tension and droplet size)[42, 43].

Furthermore, legal liability frameworks surrounding algorithm-induced adverse events remain intensely contested. When an AI-optimized nanocarrier causes unexpected in vivo toxicity, or a smart closed-loop delivery device administers a toxic over-infusion, accountability must be legally apportioned across the formulation scientist, software developer, medical device manufacturer, and prescribing clinician[39, 44]. Establishing comprehensive audit trails documenting raw training data, model versions, hyperparameter sets, and pre-release validation data is mandatory to ensure legal compliance and patient safety[44].

Pharmaceutical data scarcity, FAIR stewardship, and translational maturity of micro-nanorobots

Underlying algorithmic bottlenecks is the acute challenge of pharmaceutical data scarcity. Unlike small-molecule discovery databases containing millions of screening readouts, pharmaceutical formulation datasets remain fragmented, proprietary, and heavily biased toward positive results. Establishing findable, accessible, interoperable, and reusable (FAIR) data stewardship principles is essential to generate open-access formulation repositories capable of sustaining robust machine learning workflows in modern

pharmacy practice[45, 46]. Beyond stationary nanocarriers, magnetically, acoustically, and chemically propelled micro- and nanorobots represent the emerging frontier of active, precision drug delivery[47, 48]. These active micro-nanoscale motors can overcome physiological transport barriers, navigate complex rheological biological fluids, and actively penetrate dense extracellular matrices or tumor microenvironments[48, 49]. Utilizing machine learning algorithms for real-time trajectory optimization, autonomous swarm navigation, and remote actuation enables target-specific localization and triggerable drug release[49, 50]. Nevertheless, their translational maturity remains predominantly restricted to pre-clinical proof-of-concept models due to persistent hurdles in biocompatibility, in vivo clearance, real-time deep-tissue tracking, and scalable cGMP fabrication[47, 50].

CONCLUSION

In this critical narrative review, we demonstrated how artificial intelligence, machine learning, and deep learning are fundamentally reshaping the landscape of pharmaceutical drug delivery systems, driving a paradigm shift from empirical trial-and-error formulation to predictive, rational, and patient-specific therapeutics. By establishing a clear separation from upstream drug discovery, delivery-focused AI models provide precise quantitative solutions for optimizing solid and liquid dosage forms, engineering nanocarriers with tailored critical quality attributes, predicting multi-phasic dissolution kinetics, and automating the 3D printing of personalized polypills. Furthermore, stimuli-responsive systems and closed-loop biosensor platforms exemplify the potential of intelligent therapeutics to dynamically control drug release in real time.

Scope for future research should focus on three transformative frontiers: First, overcoming data scarcity by developing physics-informed neural networks (PINNs) and transfer learning frameworks that embed fundamental physicochemical equations directly into algorithm loss functions[6, 51]. Second, establishing automated high-throughput robotic formulation workstations ('self-driving pharmaceutical laboratories') that integrate Bayesian active learning loops to compress formulation development from years to days[8, 52]. Third, bridging the gap between in vitro dissolution and in vivo clinical pharmacokinetics by integrating formulation CQAs with physiologically based pharmacokinetic (PBPK) models to accurately forecast human plasma concentration-time profiles and tissue biodistribution[9, 53]. Through rigorous interdisciplinary collaboration among pharmaceutical scientists, computational engineers, clinicians, and regulatory authorities, AI-driven drug delivery systems will pave the way toward safer, more effective, and truly personalized healthcare.

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