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Current Opinion in Biomedical Engineering

Intelligent nanoparticle design: Unlocking the potential of AI for transformative drug delivery

Sepinoud Azimi

Artificial intelligence (AI) is revolutionizing nanoparticle (NP)-based drug delivery by tackling design, synthesis, and optimization challenges. Traditional approaches to NP development often rely on trial-and-error methods, leading to scalability, biocompatibility, and targeted drug release inefficiencies. This review explores how AI-driven models are transforming the landscape of NP formulation, from enhancing drug encapsulation and optimizing release kinetics to improving targeted delivery and overcoming physiological barriers. Additionally, we examine the challenges associated with AI integration, including data limitations and model interpretability, and discuss strategies for bridging these gaps. By leveraging AI, the field of nanomedicine can accelerate the transition from laboratory research to clinical applications, ultimately improving treatment outcomes for complex diseases.

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Introduction

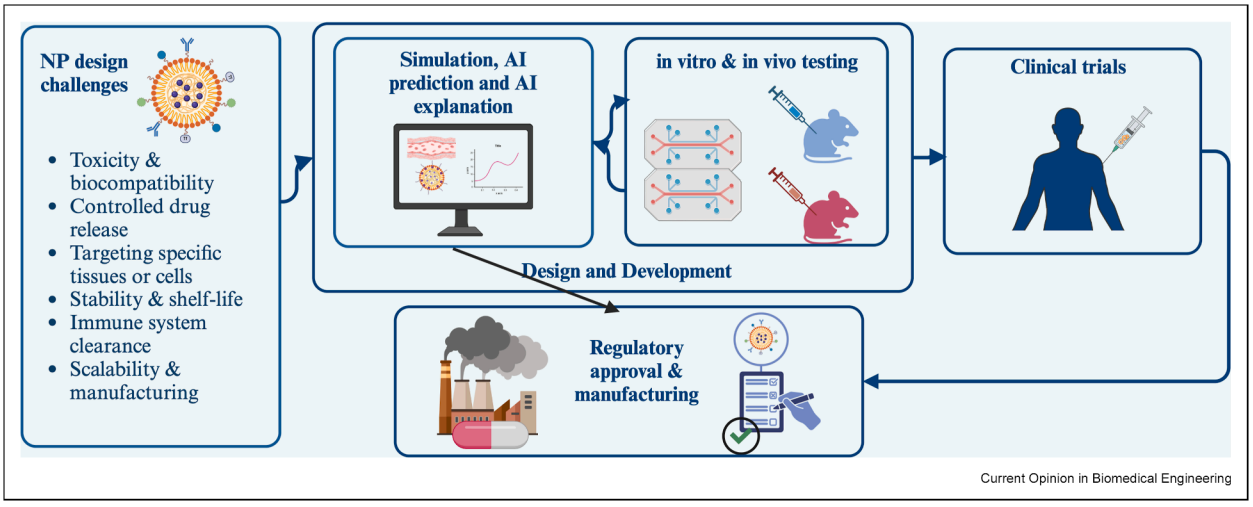
Nanoparticles (NPs) have emerged as a transformative approach in drug delivery, offering the potential to enhance therapeutic efficacy while minimizing adverse effects, [1]. Their nanoscale dimensions enable them to navigate biological barriers, facilitating targeted delivery to specific tissues or cells. This precision reduces systemic toxicity and improves the bioavailability of drugs, making NPs particularly valuable in treating complex diseases such as cancer and neurodegenerative disorders.

Although years of research and numerous reports exist, fewer than 5 % of nanoparticle (NP) systems progress to clinical trials, [2,3]. Alarmingly, nearly 75 % of these investments do not lead to successful drug approvals, [4]. Developing new medicines remains a slow and costly process, taking 10−15 years and exceeding $2 billion in costs, with nearly 75 % of this investment failing, [5]. A key contributor to this inefficiency is the costly and time-consuming trial-and-error approach in NP development with preclinical testing on animals, particularly rodents. Furthermore, animal models lack critical physiological features, such as the human blood−brain barrier (BBB), [6]. This results in poor translation from animal models to humans and ineffective or toxic therapeutics advancing to clinical trials. Artificial Intelligence (AI) approaches, especially those based on machine learning (ML), have shown promising potential to revolutionize the field of drug delivery, [7−9], offering innovative solutions to longstanding challenges. Predictive models have been employed to design self-assembling nanomedicines from drug pairs, mitigating challenges such as toxicity and instability [10,11]. AI has also been used to streamline the clinical translation of nanomedicines by addressing barriers such as manufacturing scalability, regulatory hurdles, and reproducibility. By fostering early-stage planning and collaboration among researchers, industry stakeholders, and regulatory bodies, AI-driven frameworks help efficiently transition nanomedicines from the lab to the clinic, [12]. In parallel, experimental advancements such as high-throughput screening and fragment-based drug discovery have deepened our understanding of molecular self-assembly, offering new directions for designing stable, efficient nanocarriers for targeted delivery, [13].

Current status of NP drug delivery

Despite its promises, the development of nanomedicines in general and NPs for drug delivery is still in its early stages. This slow process and unrealized promise are partly due to the complex and demanding process that every newly developed medicine needs to go through, i.e., the design and development phase that also includes in vitro and in vivo testing, the clinical trial phase, and then regulatory approval, and manufacturing and scaling up. This process is more complicated for nanomedicine due to the challenges in the design and development stage. As shown in Figure 1, several critical challenges must be addressed to develop efficient nanoparticles. An NP must be non-toxic and biocompatible to advance to clinical trials, as those that trigger adverse immune responses or show cytotoxicity should

Figure 1



The AI-driven NP drug delivery pipeline integrates simulation-generated data with laboratory experiments to build robust datasets. AI models trained on these datasets optimize NP design by improving drug release kinetics, targeting efficiency, and stability while reducing reliance on extensive experimental testing. XAI techniques enhance transparency, facilitating regulatory approval and accelerating clinical translation.

be avoided. To have impactful therapeutics, NPs need precise control over the release kinetics of the drug from the NP. At the same time, it is crucial to design NPs that have batch-to-batch consistency, maintain sterility, adhere to Good Manufacturing Practices (GMP)[1], and have long-term stability without aggregation or degradation. Finally, an efficient NP design should facilitate reaching its predefined target region (tissue or cell) without being rapidly cleared by the immune system. Thus, these design requirements can be categorized into six key aspects: **(1) toxicity and biocompatibility**, **(2) controlled drug release**, **(3) targeting specific tissues or cells**, **(4) stability and shelf-life**, **(5) immune system clearance**, and **(6) scalability and manufacturing**.

AI-driven NP design

In this section, AI is used as an umbrella term that includes both ML and deep learning (DL) methods. ML refers to algorithms that improve performance by learning patterns from data, while DL is a subset of ML that uses multi-layered neural networks to capture complex, non-linear relationships. In the rest of this section, we refer specifically to the method used, whether ML or DL, while using "AI" more broadly when discussing overarching trends or implications.

AI-driven nanoparticle: controlled drug release

Precise timing of drug release is crucial. Rapid release can cause toxicity, whereas slow or inconsistent release may reduce treatment efficacy. NP-based drug delivery offers a promising approach to addressing these challenges by enabling precise drug targeting. However, fine-tuning drug release is a complex problem, requiring tight control over nanoparticle composition, synthesis, and characterization. Traditional trial-and-error approaches are valuable but resource-intensive and do not capture the intricate relationships between nanoparticle properties and drug behavior. This is where AI comes in. AI models have been used to support nanoparticle design by reducing experimental workload and identifying relationships that are not easily captured through traditional methods.

AI-driven formulation design: drug encapsulation and release prediction

Designing nanoparticles for controlled release requires understanding how different formulations affect encapsulation efficiency and release kinetics. AI has proven very effective, moving beyond empirical testing to predictive modeling. For example, Noorain et al. [14] used Gaussian Process (GP) modeling to predict drug loading and encapsulation efficiency in poly(lactic-co-glycolic acid) (PLGA) nanoparticles, reducing the need for expensive and time-consuming experimental iterations. In Ref. [15], Huang et al. employed convolutional neural networks (CNNs) and artificial neural networks (ANNs) to analyze the chemical composition of polymeric nanoparticles and to design formulations that improve drug stability and targeted release. These models allowed researchers to quickly find the optimal nanoparticle formulation by processing large datasets that describe particle properties and drug interactions. Ensemble learning methods have taken formulation design to the next level by improving the accuracy of nanoparticle property prediction. For example [16], utilized Least-

[1] https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards/gmp

Squares Boosting (LSBoost) to fine-tune the size and polydispersity index of liposomal nanoparticles—both key to drug release rates. In another example, Dong et al. [17] used GP modeling to predict encapsulation efficiency and therapeutic efficacy to make more informed decisions in nanoparticle formulation.

Optimizing synthesis for precise drug release

Even the best-designed nanoparticle formulations must undergo synthesis, a process that determines their final properties and, ultimately, their ability to control drug release. The challenge is to ensure consistency—slight variations in particle size, surface charge, or structure can lead to significant differences in drug behavior. AI has proven valuable for refining synthesis processes to make them more predictable and reproducible. One approach is to combine Extreme Gradient Boosting (XGBoost) with Design of Experiments (DoE) to optimize nanoprecipitation methods. This has allowed researchers to precisely control nanoparticle size and surface properties, both critical for drug release kinetics, [18]. In cases where multiple drugs are encapsulated in one nanoparticle, Support Vector Machines (SVMs) and Decision Trees have been used to ensure synchronized drug release to maximize therapeutic outcomes, [19]. Microfluidic systems that provide a controlled nanoparticle synthesis environment have also benefited from AI-based optimization. Kouhkord et al. [20] utilized Differential Evolution (DE) algorithms to tune design parameters to ensure uniform drug release properties in nanoparticles. Tabular Generative Adversarial Networks (TGANs) have also proven successful in generating synthetic datasets to improve nanoparticle size prediction in microfluidic synthesis, [21,22]. Since the size is one of the most critical factors for drug release behavior, this data generation translates to a more reliable therapeutic outcome. Besides these, researchers have used central composite design (CCD) within a DoE framework to optimize polymeric nanoparticle formulations. This allows fine-tuning parameters such as particle size, surface charge, and polymer composition and ultimately controls drug release, [18]. LGBM models have also been used to predict drug release from long-acting injectable formulations, speed up nanoparticle design, and reduce experimentation, [7].

Characterization and monitoring: ensuring consistency in drug release

Even with optimized formulations and synthesis methods, batch-to-batch consistency is still challenging. Variations in nanoparticle properties can lead to fluctuations in drug release and affect treatment outcomes. AI improved characterization techniques, making monitoring NP properties easier and predicting their behavior in biological environments more feasible. In Ref. [23] Lopez et al. used molecular dynamics (MD) simulations and clustering algorithms to study how therapeutic peptides interact with PEG−PLGA NPs to understand drug storage and release mechanisms. In another study Mancoo et al. applied PCA and supervised classification models to light scattering data to characterize polydisperse nanoparticle mixtures and ensure uniformity in drug release [24]. Deep learning took nanoparticle characterization to the next level. Molecular MD simulations combined with deep neural networks (DNNs) were used to predict nanoparticle behavior in biological environments to ensure drugs are released in a controlled and sustained manner, [25]. In Ref. [22], Kibria et al. used many-body tensor representation (MBTR) descriptors and time-series models to predict the solvent-accessible surface area of nanoparticles—a critical factor for drug bioavailability and release. Deep learning-based image analysis was also used to analyze nanoparticle distribution to ensure consistent drug release across formulations [26].

While many of these models show promising results, they are often tested on specific datasets and under controlled conditions. This raises questions about how well they would perform in more diverse or less regulated environments. Biological systems inherently introduce uncertainty that is challenging to model, and validating these models outside their original settings is seldom addressed.

AI-driven nanoparticle: drug delivery to specific tissues or cells

One of the biggest challenges in NP-based drug delivery systems is targeting specific tissues or cells. Traditional formulations do not efficiently reach their intended targets, resulting in systemic toxicity and reduced therapeutic outcomes. Several studies have applied machine learning techniques to model biological and physicochemical factors influencing delivery, with the aim of improving formulation outcomes.

Machine learning for personalized nanoparticle targeting

AI-based predictive models have enabled personalized NP targeting by combining patient-specific biological data. The XGBoost-SHAP model, for example, combines tumor genomic mutations with NP properties to predict delivery efficiency and improve precision in cancer treatment, [27]. Similarly, in Ref. [28] Islam et al. used Levenberg−Marquardt neural networks (LM-NN) to optimize drug transport in cancerous tissues, especially in cases involving foamy structures associated with cardiovascular diseases. This has improved chemotherapy targeting.

AI has also optimized lipid nanoparticle (LNP) formulations for mRNA delivery. XGBoost, a gradient-boosting AI model, screened large combinatorial libraries to identify highly efficient ionisable cationic lipids that enhance nanoparticle uptake and intracellular delivery and improve the efficacy of RNA-based therapies, [29].

In another study [30], Chou et al. integrated machine learning-driven Quantitative Structure—Activity Relationship (QSAR) with traditional Physiologically Based Pharmacokinetic (PBPK) modeling to predict nanoparticle tumor delivery. This innovative combination of data-driven and mechanistic approaches enhances predictive accuracy while minimizing reliance on animal data.

Physiological barrier penetration

Many AI-driven approaches focus on overcoming physiological barriers that impede nanoparticle transport to target tissues. In vascular applications, the Radial Basis Kernel Artificial Intelligence Model has been used to model nanofluidic gold nanoparticle flow in stenotic arteries to ensure optimal drug delivery, [31]. Similarly, Harrison et al. combined CNNs with long short-term memory (LSTM) to predict the success of lipid NPs in delivering mRNA to liver cells, which is critical for RNA-based therapies [32].

For neurodegenerative diseases, an ANN with Linear Discriminant Analysis (LDA) has been developed to identify nanoparticle formulations that can cross the blood—brain barrier (BBB), a crucial step in central nervous system drug delivery, [33]. Kleandrova et al. proposed a new AI architecture, i.e., Information Fusion + Perturbation Theory + Machine Learning (IFPTML) to improve neuronal drug delivery by combining multiple datasets, including drug assays and cytotoxicity studies. Combined with Decision Tree algorithms, this model achieved 96.4 % specificity and 79.3 % sensitivity in predicting NPs that can cross the BBB and advance treatment for neurodegenerative disorders [34].

Yousfan et al. [35] followed another approach, employing machine learning-driven statistical models and mechanistic pharmacokinetic analysis to predict nanoparticle permeability across the BBB.

AI screening and optimization of nanoparticles

AI has been used for large-scale screening and optimization to improve nanoparticle targeting. The perturbation theory machine learning (PTML) model predicts the likelihood of drug—nanoparticle complexes hitting glioblastoma cells, improving tumor penetration strategies, [36]. Random Forest algorithms have been successful in analyzing the physicochemical properties that affect nanoparticle uptake in tumour tissue to develop better therapeutic strategies, [37]. AI has also improved drug delivery through mucus barriers. A machine learning-assist single-vessel analysis model has been used to study nanoparticle movement in the mucus environment so that drug carriers reach their target without premature clearance, [38]. In Ref. [39], Akhtar et al. optimized magnetic field-assisted nanoparticle targeting using AI, where machine learning models predict nanoparticle movement in response to external magnetic forces to accumulate drugs in tumor tissue.

Deep learning for imaging and spatio-temporal drug delivery

Deep learning has further improved nanoparticle tracking and targeted delivery by using imaging-based functional assays. The LungVis 1.0 framework, a DL-based imaging system using CNNs, maps nanoparticle deposition in lung tissue. This system enables profiling nanoparticle behavior in the bronchial and alveolar regions to optimize the delivery route for respiratory diseases like pulmonary infections and lung cancer, [40]. In Ref. [29], Lin et al. used to predict nanoparticle biodistribution in tumors based on physicochemical properties, tumor models, and cancer types, outperforming traditional regression models in accuracy. AI-driven image-based functional assays and advanced cellular profiling improve nanoparticle precision, so treatments are more effective and personalized, [41].

AI-driven solutions for stability, self-assembly, and toxicity in nanoparticle design

Most AI research in NP drug delivery has focused on controlled drug release and targeting specific tissues or cells. However, AI has also played a role in addressing other fundamental NP design challenges. Structural stability, self-assembly efficiency and toxicity reduction are important but underexplored compared to drug release kinetics and targeting. One of the challenges in NP design is structural stability, which directly impacts drug delivery efficacy and shelf life. NPs must remain intact under physiological conditions to prevent premature degradation, aggregation or loss of therapeutic function. Ataei et al. tackled this issue using machine learning-assisted segmentation to analyze the microstructural evolution of oil-shell microbubbles coated with gold nanoparticles, [42]. They could track morphological changes and optimize NP formulations for increased stability. This study introduced a scalable method for developing structurally stable NP carriers using AI-driven image analysis in theranostic applications. Pink et al. used self-organizing maps (SOMs) to analyze the internal morphology of liquid lipid nanoparticles (LLNs), [43]. The study showed how lipid and surfactant distribution affects NP stability by clustering molecular conformations within the NPs. These AI-driven methods can design NPs that remain structurally intact during storage and therapeutic application. Besides stability, another important design aspect in NP-based drug delivery is self-assembly efficiency, to ensure uniform nanoparticle properties. The formation of NPs with consistent size, shape and molecular arrangement is key to a reproducible therapeutic effect. Zanganeh et al. tackled this challenge by using quantitative structure—property relationship (QSPR) models combined with SVMs to predict the critical aggregation concentration (CAC) of amphiphilic peptides, [44].

CAC is key in determining how well self-assembling peptides form stable NP carriers. Using AI-driven predictions, researchers could design peptides with higher aggregation efficiency, reducing the need for costly and time-consuming experimental iterations. Azagury et al. used decision tree-based machine learning models to predict how small-molecule drug pairs self-assemble into stable NPs, [11]. Their AI-driven approach allowed for rapid identification of synergistic drug combinations that form highly stable NPs, improving drug loading and minimizing formulation failures. Toxicity, while maintaining therapeutic efficacy, is one of the biggest challenges in biomedical applications. While nanoparticles offer precise drug delivery, some formulations can be cytotoxic, immunogenic or off-target. Basso et al. addressed this issue using hierarchical clustering (HCA), principal component analysis (PCA) and neural networks to analyze the effect of cationic lipid properties on NP toxicity in glioblastoma treatment, [45]. They found that specific lipid structures could enhance NP uptake by tumor cells while minimizing toxic effects on healthy tissues. Using unsupervised AI methods, they identified safer lipid formulations, reducing cytotoxicity concerns associated with traditional cationic nanoparticles.

Although AI approaches offer promise for improving delivery precision, many rely on assumptions that are difficult to justify in biological systems. Variables such as immune response, tissue variability, and unintended distribution are hard to model reliably. These aspects are often under-reported, and model outputs are rarely interpreted in light of such limitations.

Challenges in AI-driven design

Despite AI's promises and advancements in overcoming several NP design-related challenges over the past few years, some limitations remain. Data quality and availability are two such issues. AI-driven solutions are data-hungry by design. However, the available data is most of the time scarce, unbalanced, or of low quality. The main reason is the cost of data collection, which requires expensive and extensive in vitro and in vivo experiments. In addition to limited availability, another concern is the bias present in the training data. Many datasets used to train AI models in nanoparticle research are derived from narrow experimental settings or restricted chemical libraries. As a result, models may perform well on specific tasks but fail to generalize to new compounds, delivery routes, or patient groups. These biases are often implicit and not systematically assessed, which complicates both model evaluation and future deployment. Adoption of these AI-based solutions is also a significant challenge. Although lab experiments test some of these approaches, there is no report of a clinical trial involving an NP designed using AI. Besides all the usual bottlenecks in moving from research design to lab experiments to clinical trials, one important reason is the interpretability challenges of AI-driven solutions. Most of the studies investigated in this research either skipped the interpretation/explanation of their models, opted for using basic models that are inherently explainable but incapable of fully capturing complex systems or used basic interpretable models that do not offer actionable explanations.

Although many studies report high model performance, few extend their validation beyond the original datasets or computational settings. External testing, particularly in biological or clinical contexts, is rarely carried out. This is a critical weakness, especially in drug delivery, where variability between physiological systems can undermine predictive accuracy. Models trained and tested in silico often show promising results, but this does not guarantee comparable performance under experimental or clinical conditions. Follow-up studies involving wet-lab validation have been relatively rare, and examples of clinical progression remain even more limited. As a result, the gap between computational output and practical application continues to raise concerns in the field.

Conclusion

Nanoparticles (NPs) are promising tools for targeted and personalized treatments, primarily because they can address biological barriers, decrease systemic toxicity, and enhance drug bioavailability—qualities especially advantageous in treating complex diseases. Designing such NPs remains challenging, requiring careful consideration of toxicity, biocompatibility, controlled drug release, targeted delivery, stability, immune system clearance, and scalability. Emerging AI-based solutions have shown significant capabilities in addressing several of these challenges. However, they are not challenge-free themselves; as mentioned earlier, data and interpretability challenges are two critical bottlenecks in the AI-based design reaching to clinical trials and being adopted. To address these bottlenecks, there are a few avenues to explore. One promising direction is the use of in-silico simulations. Simulations are increasingly used in nanoparticle design, yet their role is not always clearly defined. Some studies treat them as stand-alone tools, overlooking experimental variability, while others exclude them entirely. Integrating simulations with laboratory data, rather than relying on either in isolation, could offer a more dependable foundation for AI model development. Such integration ensures realistic representation while supplying sufficient data volume for effective AI model training. Iterative updates through continuous experimental validation would further improve dataset quality and AI model accuracy.

One potential solution for the challenge of interpretability is shifting away from traditional black-box models and focusing on inherently explainable AI models. Recent reports indicate promising advancements in this field [46]. Current high-performing black-box models

are often too complex for explainable AI (XAI) techniques to effectively interpret. Studies have shown that many of these models contain substantial architectural redundancies [47], making them overly intricate and difficult to analyze. Developing AI models with reduced redundancy could be a promising direction to enhance interpretability.

Reducing architectural redundancy may help clarify how models reach their conclusions. Still, even well-structured models can fall short when applied outside controlled settings. In many studies, the focus remains on model accuracy or predictive performance, while downstream considerations—such as how these nanoparticle designs behave in manufacturing or clinical contexts—receive less attention. These aspects, though less explored, often determine whether an approach can be carried forward.

Looking ahead, several developments in AI may shape the next phase of nanoparticle design. Foundation models, large-scale pretrained architectures initially developed for other domains, are beginning to find applications in chemistry and materials science, offering the potential to generalize across different molecular and formulation tasks with minimal fine-tuning. Transfer learning and active learning approaches are also gaining traction, as they reduce the need for large annotated datasets by selectively focusing on the most informative data points. Physics-informed models, which integrate basic biophysical knowledge into the learning process, are also gaining interest. By combining data-driven learning with established principles, these approaches may help improve model reliability in biological contexts.

Figure 1 suggests a practical route for improving nanoparticle (NP) design. It starts with combining simulation results and lab-based data, allowing the strengths of each to inform a more representative dataset. AI models trained on this composite dataset may reduce the dependence on extensive experimental screening. In parallel, the use of explainable AI methods and interpretable model structures can help clarify how design decisions affect NP behavior, an important step toward clinical testing and regulatory acceptance. However, most existing models remain confined to controlled settings, with limited validation in real biological systems. To advance toward clinical relevance, it is essential that computational tools are developed in close coordination with experimental workflows and tested across diverse, clinically meaningful scenarios.

Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Sepinoud Azimi reports financial support was provided by Horizon Europe research and innovation program. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Data availability

No data was used for the research described in the article.

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