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# AI-driven design and optimization of nanoparticle-based drug delivery systems

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## ABSTRACT

Nanoparticle-based drug delivery systems represent a transformative advancement in targeted therapeutics, providing meticulous drug delivery, enhanced bioavailability, and diminished side effects. However, designing nanoparticles (NPs) optimal for specific drugs and diseases remains a complex challenge. The advancements in artificial intelligence (AI) have provided innovative approaches to design and optimize these systems, improving their efficacy and adaptability. This review encompasses the integration of AI in the conceptualization and development of NP drug delivery systems, signifying its potential to revolutionize the field. The review discusses the different AI methods such as machine learning, neural networks, and optimization algorithms that simplify the fabrication of NPs with tailored characteristics such as size, surface chemistry, and drug release profiles. AI can also standardize these characteristics to enhance drug loading capacity, targeting specificity, and controlled release at the chosen site of action. AI-based predictive modeling enables the quick screening of numerous parameters, thus quickening the discovery of optimal NP configurations tailored to specific therapeutic needs. Furthermore, the review also discusses the case studies where AI has efficaciously forecasted NP behavior in biological environments, crucial for enhanced targeting and diminished off-target effects. The amalgamation of AI and nanotechnology not only streamlines the drug development process but also paves the way for personalized medicine. The review also entails the different challenges associated with implementing AI in this field, such as data quality, algorithm transparency, and regulatory specifications. By utilizing AI, researchers and healthcare providers can unlock new potentials in novel drug delivery systems, ultimately advancing the precision and effectiveness of treatments for various diseases. Finally, the review discusses the future directions of AI-based NP design, highlighting its benefits to transform drug delivery and augment patient outcomes.

**Keywords:** nanoparticles; artificial intelligence; machine learning; algorithms; drug delivery

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# 1. INTRODUCTION

## 1.1 Importance of nanoparticle drug delivery systems

Nanotechnology has introduced a new era in drug delivery. A variety of drawbacks are associated with conventional dosage forms that lead to the development of NPs. They include less absorption, random distribution, long disease cure time, systemic side effects, and early excretion. Nanocarriers as drug delivery systems have various advantages over conventional treatments, such as improved bioavailability, absorption time, and drug solubility in the blood, with reduced side effects and drug aggregation (Afzal et al., 2022; Manchun et al., 2012; Prajapati et al., 2023). Drug delivery is critical for the development of new molecules for specific delivery to the target site and patient compliance with improved efficacy and safety. Novel approaches for drug delivery include gel, microparticles, NPs, and liposomes (Dalwadi et al., 2025; Huanbutta et al., 2023; Patel et al., 2015). These approaches have opened the door for the development of new pharmaceutical products (May, 2022). The term nanotechnology was first introduced by Richard Feynman in 1959. His idea was further explored in 1980, with applications of nanotechnology in almost all disciplines like molecular biology, physics, engineering, material sciences, chemistry, information technology, and the diagnosis and treatment of various ailments (Prasad et al., 2021). Numerous nanomaterials, such as polymeric, lipid, metallic, and silica-based NPs, dendrimers, liposomes, micelles, and nanogels, are utilized for therapeutic applications. They can be used for the delivery of therapeutic agents in almost all disorders, such as cancer, cardiovascular, ocular, skin, neurodegenerative, pulmonary, autoimmune diseases, etc. for prevention and treatment as well as diagnosis. NPs have been used for vaccine and drug delivery as they enhance immunogenicity, improve stability, and possess targeted delivery. Nanovaccines developed for the co-delivery of tumor antigens and immune adjuvants in cancer represent an innovative therapeutic approach.

## 1.2 Role of AI in enhancing NP drug delivery systems

Reduced efficiency and high cost are the biggest hurdles in the development of new drugs. The utilization of AI technology coupled with computational power can be used to revolutionize the process of drug development. In this context, pharmaceutical giants collaborate with AI-powered drug discovery firms (Mak and Pichika, 2019). Human intelligence is simulated by computers using AI for the betterment of society (Sriamornsak and Waijanya, 2021, 2022). AI includes processes like self-correction, obtaining information, estimated drawing, etc. It is categorized into three parts: artificial general, narrow, and super intelligence, including the subfields of machine learning (ML), deep learning (DL), and artificial neural networks (ANNs).

AI is a broad field of computer science focused on creating systems that can perform tasks typically requiring human intelligence, such as problem-solving, understanding language, and recognizing patterns. AI is an umbrella term that encompasses various subfields, including machine learning and deep learning. ML is a subset of AI that enables systems to learn from data and improve their performance over time without being explicitly programmed for each specific task. Instead of hard-coded rules, ML algorithms use statistical methods to identify patterns in data and make predictions or decisions based on that information. DL is a specialized subset of ML that focuses on neural networks with many layers, often referred to as deep neural networks. These networks can automatically discover intricate patterns in large amounts of data, making DL particularly effective for tasks like image recognition, natural language processing, and autonomous driving.

AI is the overarching concept that includes ML and DL as methods to achieve intelligent behavior. ML uses various algorithms to learn from data, while DL uses more complex, layered neural networks to handle even larger and more complex datasets.

These approaches are widely used in medical science. ML and DL are primarily utilized for the development of nano-based drug delivery systems (DDSs). As the term NPs indicates, these particles are as small as atoms and molecules. Hence, AI assists in executing data analytics and mining related to NPs. The combination of nanotechnology and AI is growing rapidly. AI is an essential tool to combine different therapies into one nanocarrier, and various types of nanocarriers can be utilized simultaneously for varied medical conditions in different patients (Aumklad et al., 2024; Zohuri and Behgounia, 2023). Improved molecular profile, early disease diagnosis, and optimized NP design by fine-tuning their properties are possible through nanotechnology. It works on achieving a higher synergistic effect of drugs with reduced toxicity, further improving the dosing, targetability, and potency of NPs (Tan et al., 2023; Saikia et al., 2022).

AI can help in the targeted delivery of anticancer drug nanoparticulate systems. Diagnostic NPs are used for biomarker identification at cancerous sites. Further, AI-associated systems can help determine the complexity and types of cancer. Its advanced algorithm can be used for biomarker detection, drug efficacy evaluation, and interaction between NPs with different drugs (Das and J, 2022). Lipid NPs have several applications in the development of vaccines, gene therapy, and protein replacement but may demonstrate toxicity, less efficient delivery, and immune activation. AI can help in designing ionizable lipids and optimize the designing and targeted conjugations of lipid NPs for better performance. Their combination is used for enhanced efficiency and safety of the delivered drugs. DL models of AI help in the representation of molecular data and the modeling of antibodies for the targeted conjugation of NPs (Yuan et al., 2024).

A patient disease profile is generated using diagnostic NPs, based on which specific therapeutic nanocarriers are employed. Analyzing their output could be a difficult task due to patient and intra-tumor heterogeneities. AI can overcome these limitations by applying classification algorithms, pattern analysis, and optimizing the nanocarrier design using predicted interaction with drugs, the immune system, cell membranes, and biological fluids to enhance diagnostic and therapeutic efficiency. Thus, the integration of AI

with NPs contributes to precise cancer medicine by improving the design of nanomaterials and patient data acquisition. ML finds an optimal solution by generating an algorithm employing previous large datasets from existing examples as input. Single biomarker nanosensors used for diagnostic screening of liquid biopsies of patients can detect specific biomarkers with high specificity and sensitivity to provide information about the presence or absence of the disease (Adir et al., 2020). AI using an ANN for the data analysis of multiplex nanosensors can detect several targeting molecules and identify biomarker patterns involved in disease to provide information on the health status of a patient along with subtypes and staging. It is challenging to develop an effective cancer treatment strategy with inorganic NPs due to the unavailability of a comprehensive database. In this context, ML as a transformative tool, by data mining an assembled database of inorganic NPs with experimental datasets in cancer nanomedicine from 745 preclinical studies, suggested that inorganic NPs may improve patient outcomes in cancer treatment (Mendes et al., 2024). Figure 1 depicts the role of AI in NPs.

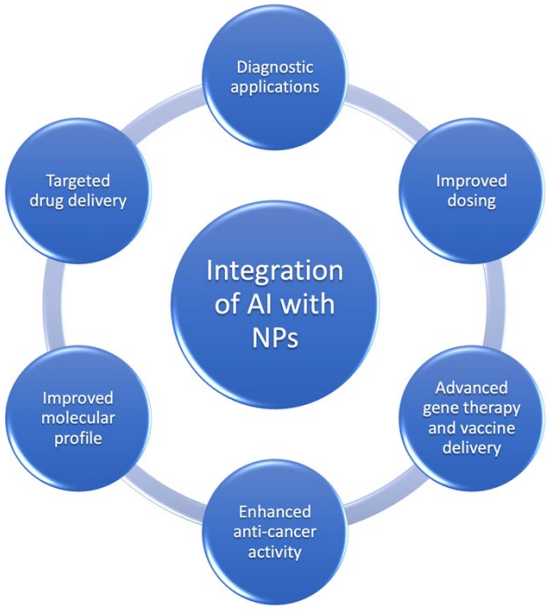


**Figure 1.** Benefits of the integration of AI with NPs

## 2. OVERVIEW OF NP-BASED DRUG DELIVERY SYSTEM

### 2.1 Types of NPs used in drug delivery

Various types of NPs have been developed by researchers to overcome drug degradation and other drawbacks associated with conventional treatment. Several biodegradable and non-biodegradable polymers are used for targeted drug delivery, its controlled release profile, and to avoid its enzymatic degradation by developing polymeric NPs (Rizvi and Saleh, 2018). Different polymeric NPs include polymersomes, polymer micelles, dendrimers, and nanospheres.

A central nucleus consisting of dendritic-like branches is called a dendrimer. These particles can carry different molecules in their branches and protect them from the environment. They release the molecules only in a controlled environment and can be used for the delivery of hydrophobic as well as hydrophilic drugs. Polyamidoamine (PAMAM) and poly (propylene imine) (PPI) dendrimers are frequently used. The spherical particles composed of polymeric matrices are called nanospheres. These are used for the controlled release of drugs with poor water solubility. Nanoprecipitation and emulsification-evaporation are the methods generally used for nanosphere preparation (Hsu et al., 2023). Polymeric micelles are obtained by the self-assembly of amphiphilic polymers when their concentration is above the critical micelle concentration. These are available in various shapes, such as tubules, spheres, bottle-brush-shaped, inverse micelles, etc., based on the hydrophilic and hydrophobic units and solvent conditions. They are used for targeted drug delivery, imaging, and skin and ocular treatment (Perumal et al., 2022). Inorganic NPs are categorized into gold, silica, and iron oxide NPs, as well as quantum dots. These are applied for imaging and drug delivery. They possess unique optical, magnetic, and electrical properties due to their base material and are utilized for diagnostic and photothermal therapy. Those specially prepared with heavy metals may possess toxicity and low solubility, which limits their clinical use. Iron oxide NPs with magnetic properties are employed as contrast agents in drug delivery and thermal-based therapeutics. Silica NPs are suitable for gene delivery. Silicon quantum dots are used for diagnostic purposes in in vivo and in vitro studies (Mitchell et al., 2021). Medical imaging techniques have emerged as new approaches to cancer treatment. Different types of gold NPs, such as nanoshells, nanostars, nanorods, nanocages, and nanospheres, are used as agents

for the photothermal therapy of cancer. Gold NPs have been developed to achieve enhanced photothermal efficiency and scattering properties for imaging, reduced cytotoxicity, and adequate body clearance (Yang et al., 2019).

Lipid-based NPs are FDA-approved and comprise at least one aqueous core surrounded by a lipid bilayer. Subclasses of lipid-based NPs are liposomes and lipid NPs. Liposomes are the earliest generation and have successfully proceeded from concept to clinical use. They are uni or multilamellar vesicles composed of phospholipids. They can entrap hydrophilic and lipophilic compounds together in a single system. Clinical trials have been conducted on various liposomal formulations for the delivery of anti-inflammatory, anticancer, anesthetic, and anti-fungal drugs, gene therapies, and vaccines. Lipid NPs such as solid lipid NPs (SLNPs) and nano lipid carriers (NLCs) are gaining more attention over liposomes due to their associated drawbacks, such as the use of organic solvents (Chamsai et al., 2020; Tenchov et al., 2021; Hirun et al., 2024). SLNPs are composed of a solid lipid core stabilized by an aqueous shell. These systems are used to enhance the solubility and bioavailability of lipophilic drugs utilizing biodegradable lipids. The lipids employed in SLNPs belong to the generally recognized as safe (GRAS) category. They offer controlled and targeted delivery of drugs due to features like small size, potential to cross the blood–brain barrier, and protection against enzymatic degradation (Bhatt et al., 2018; Suwanpitak et al., 2024). NLCs are prepared by modification into SLNPs by using a small amount of liquid lipids to reduce crystallinity at the lipid core. Biocompatible solid and liquid lipids are utilized in NLC preparation. These provide higher stability by retaining the drug within the lipid matrix (Bhatt et al., 2021).

### 2.2 Challenges in designing effective NPs

Liposomes can be taken up by the reticuloendothelial system. Their production is a complex procedure involving the use of organic solvents. Particle size, lamellae numbers, composition of lipids, and surface charge may alter the in vitro and in vivo stability of liposomes. Surface modification is required for the enhanced delivery of liposomes (Mitchell et al., 2021).

Nanotechnology is a rapidly budding area for targeted drug delivery toward improving human health. However, it still faces some challenges, such as the unavailability of standard synthesis protocols, in vivo monitoring systems, toxicity uniformity, standardized safety guidelines, and a complete understanding of the impact of NPs on biological systems (Das and J, 2022).

Somehow, NPs are unable to conquer all the biological barriers to targeted drug delivery. A complete understanding of the nature, size, shape, biological interaction, and surface properties of NPs is vital for their development. Liposomes can be taken up by the reticuloendothelial system. Their production is a complex procedure involving the use of organic solvents. Particle size, lamellae numbers, lipid composition, and surface charge may alter the in vitro and in vivo stability of liposomes. Surface modification is required for their enhanced delivery (Mitchell et al., 2021). Achieving the control characteristics of NPs for diagnostic, pharmaceutical, and catalysis purposes is a time-consuming process due to the involvement of a variety of reagents and experimental conditions (Tao et al., 2021). Metal NPs are prepared under harsh chemical and high-temperature conditions; their shape and size control are a big concern for researchers. Silver NPs become toxic to aquatic life due to specific environmental conditions. More research is required for the determination of environmental factors that affect metal NPs (Altammar, 2023). Over time, NPs are more likely to agglomerate and separate from the dispersion medium; stability is a major concern and should be accounted for while designing NPs (Selmani et al., 2022). The use of ionizable lipids in the development of lipid NPs can activate the immune system, and thus, designing them is also a complicated task for researchers. Major concerns associated with lipid nanocarriers are low delivery efficiency and their high doses may produce toxicity. AI-based screening and designing approaches are required for the development of lipid NPs (Yuan et al., 2024). Lipid nanoparticles (LNPs) encounter crucial obstacles due to their ionic lipid components, which can exacerbate adverse reactions. These include triggering the immune system, activating the complement system, and inducing anti-PEG antibodies (Yuan et al., 2024). A major challenge in the realm of cancer nanomedicine is the insufficient transportation of NPs to the tumor site, hampering treatment effectiveness (Lin et al., 2022).

Designing effective NPs for therapeutic applications presents several challenges. First, achieving the desired size and shape is crucial for optimal drug delivery and cellular uptake. Moreover, ensuring biocompatibility while minimizing toxicity is essential to avoid adverse effects in patients. The stability of NPs in biological environments can also be problematic, as they may aggregate or degrade before reaching their target. Additionally, controlling the release of therapeutic agents from NPs is necessary to maintain efficacy while minimizing side effects. Finally, regulatory hurdles and scalability in manufacturing further complicate the development of safe and effective nanoparticle-based therapies.

## 3. AI TECHNIQUES IN NP DESIGN

AI methodologies, such as ML, neural networks, and optimization algorithms, aid in designing NPs with ideal characteristics, including size, shape, surface charge, and drug release profiles. Different AI approaches are employed to represent LNPs in different dimensions by applying DL methods like convolutional neural networks (CNNs), recurrent neural networks (RNNs), and transformers to forecast their characteristics.

ML was used to guide the design of LNPs for delivering mRNA. By employing a curated dataset of 622 published LNPs, the capability of the model to accurately predict the transfection efficiency of novel LNPs was demonstrated; the multilayer perceptron model attained a classification accuracy of 97% on the test set; this method considerably improves the screening efficiency by employing computational methods to prioritize LNP candidates for experimental testing, thus speeding up the development of effective mRNA delivery systems (Ding et al., 2023).

### 3.1 ML models for predicting NP properties

The evaluation of LNPs presents significant challenges. Traditional electron microscopy often yields highly qualitative results due to the manual analysis of conservatively sized sample populations. Non-image-based

methods including dynamic light scattering offer average readouts across an aggregated particle population, which can be limiting. ATEM structural discovery (ATEM) has led the way in employing AI to overcome the challenges associated with cryogenic electron microscopy (cryo-EM). By applying AI, ATEM has effectively resolved the issue of low signal–noise ratios in cryo-EM data.

Stillman et al. (2021) have explored an evolutionary computational platform aimed at the automatic discovery of nanocarriers specifically designed for cancer treatment. The researchers developed EVONANO, an open-source platform that integrates multiscale and modular simulations with advanced ML techniques. This allows for the assessment of the properties of both nanocarriers and treatments within biologically pertinent tissue models, which are fabricated employing a virtual tumor generated in silico. EVONANO features a simulator capable of developing tumors, extracting representative scenarios, and modeling the transport of NPs through these scenarios to forecast their distribution. They showed in this first such study that ML can be used to recognize NP configurations capable of efficiently targeting and eradicating evident portions of tumor tissue while maintaining minimal dosages. The outcome exhibited that NPs with high diffusion rates (smaller radius) and low binding affinities (higher KD values) are most effective for drug delivery.

Additionally, a lower concentration of NPs, numbering in the tens of thousands, is adequate, as long as each NP carries a substantial drug payload consisting of thousands of molecules. The researchers showed that EVONANO has the potential to identify NP treatments that attain a 95% success rate in eradicating cancer cells within a virtual tumor with a minimum dosage. In another example, in the case of a heterogeneous tumor containing cancerous stem cells, the investigators identified NP designs that achieve high efficacy even at low dosages. A treatment regimen was developed that efficiently eliminated 99% of cancerous cells and >80% of cancerous stem cells within tumor tissues. They observed that the solutions typically favored designs characterized by a high diffusion coefficient, signifying smaller NPs. These designs also showed a low binding affinity, corresponding to higher dissociation constants. In addition, the preferred solutions feature a high concentration of NPs and a low count of drug-laden molecules. In conclusion, the ML method is employed to optimize NP designs and efficiently identify the most effective cancer treatments.

A study predicted the delivery of NPs to tumors by employing ML methodologies (Lin et al., 2022). This research presented a novel DL neural network model grounded in PBPK principles that precisely predicts the efficacy of NP delivery to tumor sites in mice. The effectiveness of different NPs in delivering drugs to dissimilar tumor types was precisely forecasted by a deep neural network model, surpassing the performance of alternative ML approaches such as random forest, support vector machine, linear regression, and bagged model methods. The revised coefficients of determination ($R^2$) in the complete training set were 0.93, 0.78, 0.79, and 0.77 for the maximum delivery efficiency (DEmax), delivery efficiency after 24 h (DE24), after 168 h (DE168), and at the final sampling time (DETlast). The $R^2$ values for the test dataset were 0.71, 0.47, 0.34, and 0.64, respectively. This research showed that the type of cancer considerably influenced the accuracy of the deep neural network model in predicting the effectiveness of tumor delivery across different measures, with improvements ranging from 20% to 30%.

### 3.2 AI algorithms for optimizing NP size, shape, and surface characteristics

In recent times, AI tools have been proposed for the progressive development of improved predictive models, which the pharmaceutical and biomedical sectors are eager to apply (Moussa et al., 2020). ANNs excel in analyzing intricate data, detecting patterns, and fabricating predictive models that outperform the design of experiments, which typically employ polynomial bases limited to degrees 1 or 2. Additionally, the model can predict multiple results simultaneously (Minphimai et al., 2015; Piriyaprasarth et al., 2011; Sarker, 2021).

Otitis media is most commonly diagnosed and treated in children, but its accurate identification using otoscopy can be challenging. To address this issue, Li et al. (2024) have employed ANN to enhance the effectiveness of NPs in the automated detection of otitis media. Employing ANNs can support investigators in designing, developing, and delivering medications more competently. ANNs can learn and self-adjust, making them useful in managing the complexities linked to otitis media (Vora et al., 2023).

Shabanzadeh et al. (2015) illustrated the biosynthesis of silver nanoparticles (AgNPs). The process involved using Muller Hinton agar, $AgNO_3$, methanol, and nutrient agar as additional reagents. Researchers employed an ANN model to forecast the size of the NPs. The investigation employed 30 samples derived from experimental datasets. Key variables influencing the size of AgNPs included the molar concentration of $AgNO_3$, the weight of *Vitex negundo* L. extract (%), the reaction temperature, and the stirring duration. By employing experimental data for training, the ANN model precisely forecasted the size of NPs across different conditions. This model proved to be a critical asset in fabricating a sustainable and effective method for producing AgNPs. Specifically, higher $AgNO_3$ concentrations, elevated temperatures, and longer stirring times resulted in larger NPs, while increasing the amount of V. negundo extracts led to smaller NPs.

Shabanzadeh et al. (2013) applied an ANN model to forecast the size of AgNPs synthesized within the interlayer space of montmorillonite. The model helped optimize design parameters and reduce the need for expensive experimental research. A multilayer perceptron feed-forward ANN using a Levenberg Marquardt back-propagation learning method was employed to forecast the size of AgNPs. The results indicated that temperature and $AgNO_3$ concentration were the primary factors affecting NPs size.

A hybrid method amalgamating ANN and particle swarm optimization was employed to forecast the size of AgNPs synthesized through a green approach (Khayati, 2020). The researchers also emphasized refining the practical approach to achieve the smallest size of AgNPs. $AgNO_3$ as the source of silver and opium syrup as both a reducing agent and stabilizer were used to fabricate AgNPs. With operational factors serving as the inputs for the optimization procedure, the diameter of the AgNPs was the result.

### 3.3 Characterization of NPs using AI

AI can revolutionize the NP characterization process by streamlining and enhancing the analysis of key parameters such as particle size, distribution, and structure. Machine

learning algorithms can analyze vast datasets from particle size distribution measurements with greater precision than traditional methods, enabling a more accurate understanding of NP populations. This can help identify subtle variations that may impact the performance and safety of the nanoparticles in applications like drug delivery or diagnostics. AI can play a critical role in detecting impurities within nanoparticle formulations. By employing advanced pattern recognition and anomaly detection techniques, AI can identify contaminants that may not be easily detectable by conventional analytical methods. This improves the reliability and safety of NP-based products (Li et al., 2024).

AI's predictive capabilities can also assist in forecasting nanoparticle stability across various environments, including biological systems. By training models on historical data, AI can predict how particles will behave under different conditions, such as varying pH or temperature, aiding in the design of more robust formulations. Moreover, AI can enhance imaging techniques, such as electron microscopy, by automating the analysis of complex NP structures. AI-driven image processing can provide more detailed insights into the morphology, composition, and surface characteristics of nanoparticles, improving both the accuracy and speed of the characterization process (Rajendra Kumar et al., 2024).

## 4. CLINICAL APPLICATIONS OF AI-DRIVEN NP DESIGNS

AI techniques are utilized to model lipid NPs at various dimensional levels, employing DL methods such as CNN and RNN to predict their properties (Yuan et al., 2024).

Suriyaamporn et al. (2024) investigated the physical and chemical properties of SLNPs encapsulated with progesterone (PG), which were fabricated employing an emulsification ultrasonication approach. They employed an experimental design and ANN to enhance predictive accuracy. Ideally, the particle size should be between 20 and 100 nm, the polydispersity index should be <0.2, and the zeta potential should be above±30. The ANN model demonstrated excellent superior predictive accuracy compared to the response surface methodology. The ANN model reduced resource and time requirements, speeding up production. The chosen PG-SLNPs formulation (5% stearic acid + 1.75% medium-chain triglycerides + 0.32% Pluronic F-127 + 0.5% PG) showed remarkable delivery of drugs through the skin compared to the PG suspension, especially when loaded with limonene.

The optimization methods employing computational approaches were applied to enhance the synthesis of chitosan NPs produced by *Streptomyces microflavus*. These NPs were investigated for their effectiveness in inhibiting *Pectobacterium carotovorum*, a common plant pathogen. The maximum yield of chitosan NPs, amounting to 8.59 mg/mL, occurred during experiment number 27, applying an initial pH of 5.4, 1% chitosan concentration, operation at 40°C, and incubation for 12 h. The ANN was employed to confirm and predict the biosynthesis of chitosan NPs using experimental data derived from a face-centered central composite design. This approach demonstrated enhanced predictive accuracy and minimized errors in the prediction process (Lin et al., 2022).

Chou et al. (2023) developed an AI-driven physiology-based pharmacokinetic (PBPK) model by amalgamating an AI-based quantitative structure–activity relationship (QSAR) model with a PBPK framework to forecast the effectivity of tumor-targeted delivery and the biodistribution of different NPs using ML and deep neural network algorithms. These algorithms were trained on datasets from the publicly available "Nano-Tumor Database" to predict important input parameters for the PBPK model. The predictions of the AI-PBPK model exhibited a strong correlation with experimentally measured pharmacokinetic profiles of various NPs in tumors following intravenous administration, with an $R^2$ of ≤0.70 in 133 out of the 288 datasets. This model provided a swift and significant screening tool to predict the delivery efficiency of NPs by considering their physicochemical properties, eliminating the need for an animal-based training dataset.

The researchers focused on optimizing pullulan production by the fungus *Aureobasidium pullulans* through semi-solid-state fermentation, employing ANN. The researchers also characterized the pullulan and evaluated its antibacterial properties when impregnated with silver/titanium dioxide ($Ag/TiO_2$) NPs. This approach resulted in an unprecedented pullulan yield of 37.25 mg/g in just 10.82 days, surpassing all previous values. The research exhibited the effective incorporation of pullulan with $Ag/TiO_2$ NPs during the synthesis process utilizing *Fusarium oxysporum*. This advanced technique markedly improved the stability and effectiveness of NPs by altering their surface characteristics, resulting in considerably enhanced antibacterial activity against a range of human pathogens. The ANN model surpassed the one variable at a time technique in attaining higher pullulan yield and desirability. It anticipated a maximum pullulan yield of 37.25 mg/g of faba bean biomass, which closely matched the actual yield of 36.81±3.43 mg/g FBB, leading to an impressive desirability score of 0.998 (Eldadamony et al., 2024).

Dawoud et al. (2023) explored the integration of AI with quality-by-design (QbD) principles in the formulation of lecithin/chitosan NPs for delivering a poorly water-soluble drug in carcinoma treatment. Silymarin is employed as a model drug due to its potential efficacy in liver cancer. A design framework was developed, yielding an optimized formulation with a lecithin-to-chitosan molar ratio of 18.33:1 and 39.25 mg of silymarin. This produced NPs with a size of 162 nm, a polydispersity index of 0.3, and an entrapment efficiency of 98%. The optimized formulation exhibited a zeta potential of +38 mV and well-defined spherical particles. AI demonstrated strong predictive accuracy for the drug's release rate. The optimized formulation enhanced the cytotoxic effect of silymarin, resulting in a lower $IC_{50}$ compared to standard silymarin (Dawoud et al., 2023).

AI has been applied to augment the efficacy of drug delivery employing NPs. For instance, AI-driven in situ forming piroxicam NPs were developed for treating arthritis via intra-articular delivery; in addition, AI has been employed to design experiments, thereby conserving time and resources during experimental procedures (Yacoub et al., 2022). In another study, Lin et al. (2022) explored the use of advanced computational methods to predict the delivery of NPs to cancerous tumors. They employed a specialized database called Nano-Tumor,

containing 376 datasets derived from a model that simulates the movement of drugs through the body. The study involved numerous analytical methods, including random forest, support vector machine, linear regression, and a sophisticated neural network approach. Among these procedures, the DL model exhibited promising outcomes for this specific use. Nuhn (2023) explored the application of advanced computational methods in analyzing individual blood vessels, and the recognition of varied levels of vascular permeability within diverse tumor types when employing protein NPs DDS. This method also displayed the potential to enhance active transport across tumor endothelial barriers. Table 1 summaries the applications of AI with different NPs formulations.

**Table 1.** Applications of AI with different NPs formulations

| Type of AI | Type of NPs | Application of AI, key findings | References |
|---|---|---|---|
| ANN | Fucoidan and polyethyleneimine-based sorafenib-loaded NPs | The ANN-DoE model demonstrated superior accuracy and predictability, surpassing all the other models. | Chaurawal et al. (2024) |
| ML | Silver NPs | The AI-assisted multiparameter approach demonstrated outstanding capability in rapidly achieving highly accurate size differentiation of NPs at the individual particle level. | Xu et al. (2024) |
| ANN C4.5, Adaboost, decision tree, support vector machine | Engineered NPs | The assessment of model performance revealed that the internal validation accuracy for all classification models varied between 71.4% and 100%, while the determination coefficients for regression models ranged from 0.702 to 0.999. These results suggest that the developed models exhibited strong performance. | Qi and Wang (2024) |
| ML | Polystyrene NPs | By employing ML techniques, particularly genetic algorithms, researchers effectively forecast the progression of cancer stem cells. | Ramović Hamzagić et al. (2024) |
| RNN-CNN | NPs | The combination of ML and NPs enhance; precision detection of gastric cancer. | Wu et al. (2024) |

## 5. CURRENT LIMITATIONS, CHALLENGES, AND FUTURE DIRECTIONS OF AI IN NP DESIGN

Despite its transformative potential, AI in NP design encounters numerous critical obstacles. One of the main challenges is the quality and availability of data. Robust AI models need high-quality, annotated datasets for effective training, yet such datasets are often limited in nanotechnology (Oviedo et al., 2022). In addition, the absence of standardized methods for data collection and reporting intensifies this problem, resulting in models that may not perform consistently across several experimental settings or types of NPs.

Another challenge is the lack of transparency in AI models. Several AI methods, mainly DL models such as CNN and RNN, function as "black boxes," offering minimal understanding of how they reach specific outcomes. This opacity can hinder the acceptance and trust of AI-based methods in the scientific community and regulatory authorities, where comprehending the underlying processes is vital (Jariwala et al., 2023). Additionally, AI-generated forecasts and designs regularly entail substantial experimental validation, which can be both time-consuming and expensive. The iterative nature of refining AI models with experimental feedback can obstruct the speed of innovation. Furthermore, while AI can pinpoint potential NP configurations, it may overlook practical aspects such as manufacturability, scalability, and cost-effectiveness, all of which are essential for clinical applicability and commercial viability (Javanmard, 2024). Lastly, ethical and regulatory concerns present further obstacles. AI-based methods in NP design must comply with ethical standards and regulatory requirements to mitigate potential risks posed by nanomaterials.

The main obstacle to the clinical application of cancer nanomedicine is the poor delivery efficiency of NPs to solid tumors. Increasing computational power and the advent of new ML and AI methods offer innovative solutions to tackle this issue (Chou et al., 2023). Overcoming these challenges requires a cooperative effort to augment data quality, improve the transparency of models, safeguard adequate computational resources, and encourage collaboration across disciplines, all while prioritizing ethical and regulatory adherence (Vora et al., 2023).

Future directions for AI in NP design hold immense promise, particularly in enhancing precision and efficiency. AI can facilitate the development of tailored NPs by predicting optimal formulations, surface modifications, and physicochemical properties for specific applications, such as targeted drug delivery or diagnostics. Machine learning algorithms can analyze vast datasets to identify patterns that may not be apparent through traditional methods, enabling the rapid screening of NP candidates with improved stability, biocompatibility, and therapeutic efficacy.

AI-driven simulations and optimization techniques could reduce the need for extensive trial-and-error experiments, accelerating the design process (Sriamornsak and Waijanya, 2021). Additionally, integrating AI with high-throughput experimental techniques and real-time feedback systems may allow for dynamic adjustments in NP design. Future AI advancements could also focus on enhancing safety profiles, minimizing off-target effects, and predicting long-term biological interactions of NPs. Collaborations between AI researchers and

nanotechnology experts will be crucial for harnessing AI's full potential in NP design (Hamilton and Kingston, 2024; Ortiz-Perez et al., 2024).

## 6. CONCLUSION

The amalgamation of AI in the design and optimization of NP DDS marks a notable advancement in medical science, offering enhanced accuracy and effectiveness in drug delivery. AI techniques offer noteworthy opportunities for analyzing large volumes of multivariate data and addressing the complex challenges involved in designing NPs DDS. The application of automated workflows and wide-ranging databases simplifies the swift analysis of large datasets. The utilization of ANNs facilitates the formulation of new hypotheses and treatment approaches, predicting disease progression, and evaluating the pharmacological properties of candidate drugs. By utilizing the capabilities of AI in ML, predictive modeling, and optimization of algorithms, investigators can now fabricate highly specialized NPs tailored to specific therapeutic needs, enhancing drug targeting and diminishing adverse effects.

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