The Role of Machine Learning in Enhancing Nanoparticulate Drug Delivery Systems

Sowjanya Pulipati[1], Y. Dinesh[2], K. Vandana[3], K. Sri Ram[4], P. Srinivasa Babu[5]
[1,2,3,4,5] *Department of Pharmaceutics, Vignan Pharmacy College, Vadlamudi, Guntur (Dt) – 522213, Andhra Pradesh, India.*

***Abstract*—Nanoparticulate Drug Delivery Systems (NDDS) have emerged as promising approaches for improving therapeutic efficacy through targeted drug delivery, enhanced solubility and bioavailability, controlled drug release, and reduced systemic toxicity. However, the design and optimization of nanoparticulate systems remain challenging because of the complex interactions among particle size, morphology, surface charge, drug loading, formulation composition, biological barriers, biodistribution, and toxicity. Conventional trial-and-error approaches are often time-consuming and inefficient when dealing with such multidimensional formulation variables. Machine Learning (ML), a key component of artificial intelligence (AI), offers a data-driven strategy to address these limitations by identifying complex relationships within formulation and biological datasets and predicting optimal nanoparticle characteristics. This review highlights the role of ML in the design and optimization of NDDS, including prediction of nanoparticle size, shape, surface properties, encapsulation efficiency, drug loading, release kinetics, stability, pharmacokinetics, biodistribution, and cellular uptake. Different ML approaches, including supervised learning, unsupervised learning, reinforcement learning, neural networks, ensemble methods, and deep learning, are discussed in relation to their applications in nanoparticle development and personalized drug delivery. ML-assisted approaches can reduce experimental iterations, improve formulation optimization, enhance targeting specificity, and facilitate the development of adaptive and stimuli-responsive nanocarriers. Despite these advances, challenges related to data quality and availability, standardization, model interpretability, algorithmic bias, regulatory validation, and clinical translation remain. Future integration of ML with multimodal datasets, physiologically based pharmacokinetic models, Internet of Things (IoT)-enabled healthcare, explainable AI, and in silico trials may further accelerate the development of safer, more effective, and personalized nanomedicines. Overall, the integration of ML with NDDS represents a significant step toward predictive, intelligent, and patient-centric drug delivery systems.**

I. INTRODUCTION TO NANOPARTICULATE DRUG DELIVERY SYSTEMS (NDDS)

1.1. Definition and Fundamental Concepts of Nanoparticles in Drug Delivery:

Nanoparticulate Drug Delivery Systems (NDDS) are a quickly growing area of nanomedicine that use designed technologies to use nanoparticles to deliver therapeutic agents exactly and directly and release them in a regulated way. The main purpose of modern medication delivery is to make treatments far more effective and make patients more likely to follow their treatment plans by lowering the dose, the number of times the medicine needs to be given, and the side effects. Nanoparticles are particles that are usually between 1 and 100 nanometers in size. They have special physical and chemical properties that make them very useful. They are highly useful because they have a high surface-area-to-volume ratio, which lets more ligands bind to the surface of the nanoparticle. This better binding efficiency can lessen the amount of medicine needed and make nanoparticles less hazardous. Also, nanoparticles can be made to work in very specific ways since their chemical and geometric properties can be changed. Advanced computational methods are needed to navigate the huge parameter space of NDDS design since it is so complicated, with many customizable features and the need to fine-tune them to make them more effective and less hazardous to cells. A lot of the time, traditional experimental methods have trouble with this many interacting variables, which shows how important it is to have advanced analytical tools. This complexity solves the "Curse of Dimensionality," which could make

traditional experimental approaches harder to use. It also gives Machine Learning (ML) the basic framework it needs to help people navigate and improve this complex design terrain. [1,20,26]

Table 1: Types of nanoparticles used in NDDS

Nanoparticle Type	Composition	Typical Size	Key Features	Applications
Liposomes	Phospholipid bilayer	50–200 nm	Biocompatible; carry hydrophilic and hydrophobic drugs; surface modification possible	Cancer therapy, vaccine and gene delivery
Solid Lipid Nanoparticles (SLNs)	Solid lipid matrix	50–500 nm	Good stability; controlled release; protects drug from degradation	Poorly soluble drugs, oral and topical delivery
Polymeric Nanoparticles	Biodegradable polymers such as PLGA, PCL	10–300 nm	Tunable size/surface properties; sustained release; high drug-loading potential	Targeted drug, protein, peptide and vaccine delivery
Dendrimers	Highly branched synthetic polymers	2–10 nm	Well-defined structure; high surface functionality; precise size control	Gene delivery, anticancer therapy, imaging
Metallic Nanoparticles	Gold, silver, iron oxide, etc.	5–100 nm	Optical, magnetic and electrical properties; easy surface functionalization	Imaging, photothermal therapy, drug delivery

The table 1 summarizes the major types of nanoparticles used in nanoparticulate drug delivery systems (NDDS) and highlights their composition, size, properties, and pharmaceutical applications. Liposomes are phospholipid-based carriers capable of delivering both hydrophilic and hydrophobic drugs. Solid lipid nanoparticles (SLNs) provide improved stability and controlled release. Polymeric nanoparticles, prepared from biodegradable polymers such as PLGA and PCL, offer sustained and targeted drug delivery. Dendrimers possess highly branched structures with precise surface functionality, making them useful for gene delivery and imaging. Metallic nanoparticles such as gold, silver, and iron oxide provide unique optical and magnetic properties for imaging and therapy.

1.2. Advantages of NDDS over Conventional Drug Delivery:

Nanoparticulate drug delivery systems offer an exciting range of advantages that far outweigh traditional dosage forms. One advantage would be the ability to improve solubility and bioavailability of poorly soluble drugs, which has always posed a challenge in pharmaceutical development. In fact, even in modern drug development, many low solubility drugs continue to limit systemic absorption and negatively affect therapeutic effects. Famotidine and valsartan are poor bioavailability drugs heavily tied to solubility, but after encapsulated in nanoparticulate substance like solid lipid nanoparticles (SLNs), a significant increase in bioavailability and plasmatic absorption occurs, due to improved dissolution rates after encapsulation, providing a possible answer pharmaceuticals have been searching for. A second key advantage is the decrease in toxicity and side effects due to targeted delivery. As stated, currently most drugs are typically delivered in a non-targeted manner, which distributes the drug and causes unwanted effects throughout the entire body. Using a nanocarrier system, drug delivery can be designed to actively release at a precise location. The nanotherapeutic approach relies on nanoparticles being flexible in the manner they can be administered, via oral, intravenous, or topically/dermal routes. Since the method of administration can add to patient compliance by reducing the number of doses and redistributing the physiochemical absorption characteristics of the drug, it may improve the therapeutic experience of the patient. However,

nanoparticle formulations have other advantages apart from offering variable absorption. Nanocarriers enhance stability of encapsulated drugs against chemical or physical degradation, provide sustained drug release for extended periods, improve corrected drug distribution within specific tissues, and ultimately enhance stability and pharmacodynamics of therapeutic agents. Enhanced solubility, preferential drug delivery, reduced toxicity and variable routes of administration are likely to represent complex trade-offs and interactions during the optimization of NDDS. For instance, trying to get the most medicine into the nanoparticles can make them less stable or make the targeted release less accurate. A multi-objective optimization problem is when you try to get all of these benefits at the same time for a certain therapeutic use. ML is great at handling this kind of complexity because its algorithms can weigh and balance competing goals, search through huge parameter spaces to find the best solutions that optimize overall therapeutic value, which is something that is often too hard for humans to figure out or simple linear models to do. [1,20,26]

1.3. Inherent Challenges in NDDS Development:

Although NDDS offer many advantages, development and translation into the clinic have some major challenges. These challenges are posed by the nanotoxicity of nanoparticles (NPs); biodistribution and accumulation of nanoparticles in the body; and fast clearance due to the human immune system. There is a narrow range of parameters defining the properties of nanoparticles that allow for an adequate efficacy of the drug while minimizing the cytotoxic effects of the nanoparticles. To control this range, many parameters of nanoparticles must be controlled and optimized, anteriorly defined by the surface-area-to-volume ratio and ligand binding efficiency. [3,20,26]

Designing and optimizing NDDS is hard work, and they require an accuracy and complexity that standard approaches often cannot give. The "Curse of Dimensionality" creates a serious problem. It occurs when the issue of materials and pharmaceuticals become complex enough that their non-linear interactions will add up, limiting your understanding of complex structure-function relations. As a result, traditional high-throughput screening, which is often a "brute-force method," is largely ineffective and can fail entirely. The "Curse of Dimensionality" is a major obstacle in the design of NDDS since it limits our ability to get a handle on complex structure function interactions using standard trial-and-error or brute-force high-throughput screening approaches. The ramp up in complexity and non-Linearity in the interactions is made worse in this instance. This clarifies the primary challenge which is especially well suited for ML. ML is about speeding capabilities, but this is also about the ability to understand and enhance NDDS in ways that would be infeasible due to the complexity and dimensionality of the design space. The development of NDDS is also faced with issues of drug resistance, the pivotal requirement of targeted selectivity to differentiate cancerous and healthy cells, and the highly heterogeneous tumor microenvironment that can vary dramatically, even in a single patient. [3,15,20]

In vivo, nanoparticles face biological barriers including the mononuclear phagocytic system (MPS) and the notoriously tough blood-brain barrier (BBB) as nanoparticles are susceptible to rapid clearance by organs including the liver and spleen. Many current mathematical and computational models make oversimplified assumptions and do not accurately represent the complex in vivo conditions and often overestimate the efficacy of a therapeutic strategy. In addition, development and clinical application barriers include substantial regulatory hurdles, high costs of producing nanoparticles, and a poor knowledge of their long-term interactions within the human body. Synthesizing nanomaterials can also be time and labor intensive. There is also generally limited molecular understanding of the cellular or tissue toxicities of nanoparticles and their overall safety profile. Ongoing concerns about nanotoxicity, unpredictable biodistribution, and rapid clearance emphasize important safety and efficacy issues with NDDS. The engagement of regulatory authorities like the FDA in developing guidance on the safety and immunogenicity of nanotherapeutics, as well as the lack of molecular understanding of toxicology, necessitates a focus on safety. With the focus on safety and clinical translation, and the constraints, the ability of ML to estimate toxicity and biodistribution in silico enables not only a gain in efficiency but also the development of safer and more efficacious systems. Not only will this ability significantly de-risk the development of NDDS, but it will expedite

transitioning promising NDDS from the bench to the clinic without the need for considerable reliance on costly and time-consuming in vitro and in vivo experimentation. [3,4,15,20]

II. FOUNDATIONS OF MACHINE LEARNING IN PHARMACEUTICAL SCIENCES

2.1. Overview of Artificial Intelligence and Machine Learning Paradigms:

Overall, artificial intelligence (AI) is a machine-based system that acts, predicts, recommends or decides in accordance with some human-defined goals while making changes to either the real or virtual environment. The AI systems accomplish this activity through machine- and human-based inputs that provide an awareness of the current environment, along with machine-based automation to abstract that awareness into models through analysis. Models can be inferred and further enable action options and information. [6,7,11]

Machine Learning (ML) is an important part of the field of AI and is simply a collection of techniques that can be used to train an AI algorithm to improve its performance on a task based on exposure to more and more data. ML models can look at data, learn from that data, and then make predictions or decisions based on that data, without being programmed to do a step-by-step Teach-and-Tell. ML models borrow heavily from probability as well as linear algebra. Deep Learning (DL) is a more complex subset of ML in which we use artificial neural networks (many layers of layers, hence the term "deep learning") to analyze data, much of the data is complex and often unstructured and to solve complicated problems. DL has had a significant impact in areas where there are huge amounts of data where we need to extract patterns, such as image analysis and natural language processing. The hierarchical relationship of AI, ML, and DL implies a complexity of task and solutions-increasing order. The structure implies as the data and problem on hand increases in complexity, we will see more specific and powerful ML techniques will be required a little like deep learning. Deep learning, through their multi-layer neural networks, excel in identifying nuanced, non-linear relationships from high-dimensional data, which is characteristic of nanomedicine. This has provided an insight into why advanced ML techniques are more widely used and effective in nanomedicine, providing evidence that nanomedicine is employing more advanced computational approaches to deal with the challenges associated with nanoscales and biological interactions, thus enabling breakthroughs that simpler algorithms could not have obtained. [6,7,11]

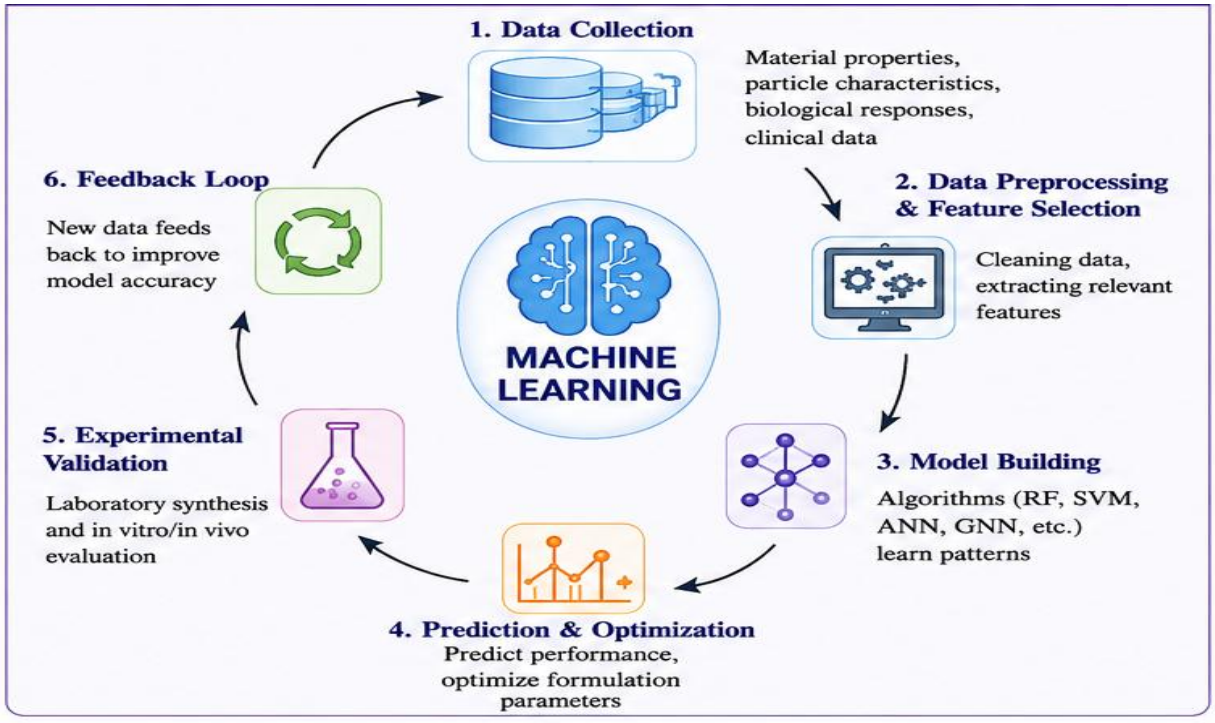

Figure 1: Role of Machine Learning in NDDS

The figure-1 shows how machine learning changes NDDS development from conventional trial-and-error experimentation to a data-driven iterative approach. We first collect nanoparticle and biological data, preprocess the data, and train suitable ML models. The trained model then predicts and optimizes the formulation parameters. These predictions are experimentally validated, and the experimental results are fed back into the model. Thus, each cycle improves prediction accuracy and helps us develop safer, more effective and optimized nanoparticulate drug delivery systems."

2.2. Key Machine Learning Algorithms and Their Relevance:

In the disciplines of precision medicine and medication delivery, choosing the right ML models is particularly important. Different paradigms offer different benefits that are best suited to different problems: [6,7,11]

- Supervised Learning: In supervised learning, the input data (features/ 'x') and their relevant output (labels/ 'y') are completely known. 15 From this labeled data, models learn to provide 'y' that predicts 'y' for a new value of 'x'. This includes classification tasks, where data is assigned to separate categories (e.g., the best and worst drug release profiles), or regression tasks predicting a value (e.g., the drug release over time). Algorithms that use supervised learning for predicting drug release profiles include Random Forests, Support Vector Machines (SVM), and Gradient Boosted Machines.
- Unsupervised Learning: Used when we have access to unlabeled data. The primary purpose of unsupervised learning is to extract the inherent patterns, structures, or groups of unlabeled data in a dataset on our own. Clustering algorithms (for instance, k-means clustering and hierarchical clustering) will group similar data points which can be useful for detecting anomalies, or for creating new categories of nanoparticles according to their functionality. Some dimension reduction methods (including Principal Component Analysis, PCA) will primarily help us simplify our complex collection of data, and visualize it.
- Reinforcement Learning (RL): RL models learn as the result of repeated interactions with an environment, rewarded for desirable actions in that environment and punished for undesirable actions. Because of this, RL models are well suited for decision-making, where a sequence of actions can yield an outcome that is better in terms of wider outcomes. In the NDDS domain, RL agents offer an opportunity to dynamically optimize the design of nanoparticles at the preclinical stage by adjusting each of the characteristics that contribute to therapeutic efficacy (e.g., size, coating, drug loading), while minimizing off-target effects. The specification of the reward function in RL models typically takes account of critical clinical criteria (e.g., bioavailability, lower toxicity).
- Neural Networks (NN): This category including Artificial Neural Networks (ANNs) and Convolutional Neural Networks (CNN). Neural networks are particularly useful for characterizing complex, non-linear relationships between aspects of nanoparticles and resulting performance parameters. They are especially useful for the prediction of complex drug release profiles, nanoparticles formulation optimization, and identifying different patterns in complex data, such as images related to drug distribution or molecular interactions.
- Ensemble Methods: These methods aggregate the predictions from several different individual models when simultaneously attempting to be more predictive than any one of their models alone. Algorithms like XGBoost, LightGBM, and CatBoost conjunction of ensemble algorithms have been shown to outperform every other supervised algorithm in a personalized drug delivery setting while utilizing numerous patient data factors for predictive modeling, often times achieving high accuracy and recall rates due to their ability to correctly identify complex patient behavioural change patterns in real-time. The extensive uncluttered detail on the supervised, unsupervised, reinforcement and deep learning algorithms outlines that there is not a single ML approach that is 'best'. All paradigms are intended to deal with different kinds of data structures, or problem formulations, and this indicates that ML

for NDDS is starting to grow-up. As researchers we can effectively choose the best computational modeling tool for a particular problem and apply more than one of them to the same problem to see which performs best. Ensemble methods are a great demonstration of the concept of using the diversity of approaches to combine algorithms to obtain a more robust, accurate solution for complex nanomedicine book, capstone, research problem(s).

2.3. General Applications of AI/ML in Drug Discovery and Development:

Artificial Intelligence (AI) and Machine Learning (ML) are having a major impact on the pharmaceutical industry, providing efficiency and efficacy improvements throughout the drug product lifecycle. The change allows for the realization of precision medicine, enhances therapeutic outcomes, and greatly decreases the time it typically takes to develop drugs. [6,7,11,25]

Key applications of AI and ML in this domain include:

- Drug Discovery and Target Identification: AI/ML methods evaluate large biological and chemical data sets, which could comprise proteomics and genomics which give a detailed understanding of disease mechanisms at the molecular level. This can lead to better-suited proteins for therapeutic design and the ability to accurately predict drug-target interactions, new drug candidates, as well as to improve a molecular compound. An example of advancements made using AI in drug discovery employs deep learning models such as graph neural networks, which have drastically decreased the time from drug discovery to drug production, largely because it allows broad prediction of protein-ligand binding affinities. [7,11,25]
- Clinical Trials Optimization: AI/ML improve patient recruitment through the identification of appropriate candidates by analyzing genetic profiles and clinical characteristics. Furthermore, it allows for prediction of trial outcomes and monitoring of trials in real-time, consigning adaptive trial designs that limit costs and time. [11,25]
- Pharmacovigilance and Safety Surveillance: AI/ML algorithms are critical for drug safety risk monitoring to support post market surveillance. They analyze adverse drug event reporting systems, electronic health records and the social media landscape to proactively identify safety signals and detect low prevalence adverse events. [6,11,25]
- Pharmaceutical Manufacturing and Quality Control: AI/ML technologies can improve manufacturing processes for consistent drug quality. Predictive maintenance models represent a type of AI model that you can use to prevent equipment failures. Image analysis is also driven by AI and can be used to detect defects in drug formulations, packaging, and labeling). The pharmaceutical industry must ensure commercial goods conform to standards, guidelines, or regulations. [6,11]
- Precision Medicine and Personalized Treatment: AI-based technologies are changing the delivery of healthcare by individualizing medical treatments to incorporate the individual characteristics of patients. This includes studying large-scale genomic data; the individual patient's response to treatment; and resulting clinical outcomes so that a healthcare provider can select the best therapies, anticipate the patient's individual response to drugs, and avoid the occurrence of adverse events. [6,11,25]
- Optimization of Processes and Cost Saving: The possibility for AI to save money in development is vast if it helps improve the research and development process. AI processes can help to streamline the research process, through the reduction of lengthy trial and error experimentation, and carrying out many in silico scenarios, thereby lowering the overall development time. The application of ML can impact the whole pharmaceutical value chain creating an opportunity for all-round optimization. Not only can efficiencies gained through ML in one stage, such as in nanoparticle design, then have positive spill-over effects to the next stage, for example, in success rates for trial protocols, manufacturing costs, and patient safety benefits, and this can combine to help multiply the acceleration of the drug delivery process into one strong synergistic loop, leading to more effective and lesser cost therapies.

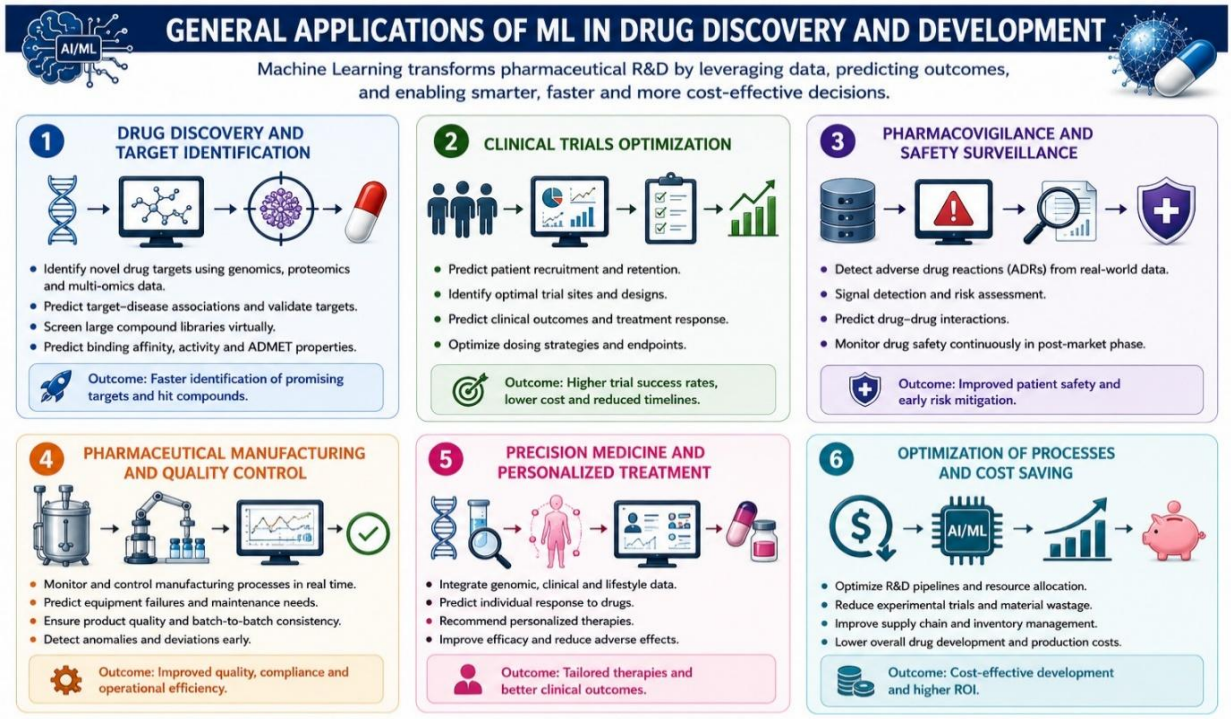

Figure-2: General Applications of AI/ML in Drug Discovery and Development

III. MACHINE LEARNING'S TRANSFORMATIVE ROLE IN ENHANCING NDDS

3.1. AI/ML-Guided Design and Optimization of Nanoparticles:

Artificial Intelligence (AI) and Machine Learning (ML) are changing the game in the design of smart multifunctional nanocarriers (SMNs) for drug and gene delivery purposes. AI methodology speeds up the design process, optimizes loading and release kinetics, increases biocompatibility, and predicts interactions with complex biological barriers more reliably. ML models provide an important resource by assessing historical data to predict potential outcomes for new designs of nanoparticles while minimizing time and effort from traditional trial-and-error experimentation processes. [8,9,12,26]

Many different AI methods, including traditional machine learning algorithms, neural networks, and combinatorial optimization algorithms will simplify the fabrication of nanoparticles by allowing accurate shaping of their properties when designed, including size, surface chemistry, and drug release profiles that are optimized for therapeutic performance. AI-based predictive modeling of parameters also means rapid screening of lots of design parameters using little computational resources can occur and that optimized nanoparticle designs can be quickly discovered for specific therapeutic intentions. [8,9,12]

An innovative, high-throughput nanoparticle design strategy combines microfluidic-based formulation, high content imaging (HCI), and active machine learning into an iterative workflow. This combination allows one to effectively traverse the vast combinatorial design space of nanoparticle formulations. Active machine learning is leveraged to intelligently select new samples for screening based on predictions from the model, which allows scientists to reach desired responses more quickly with fewer experimental iterations. The ML facilitates the transformation of nanoparticle design from empirical guessing to data-driven engineering. Designing nanoparticles with the best possible properties (e.g. size, shape, surface charge, drug loading, release kinetics) has historically been an extremely difficult undertaking as a result of the hyper-dimensional combinatorial space surrounding the formulations and their long and complex structure – function relationships. This has created the necessity for lengthy and tedious “trial-and-error experimentation”. ML fundamentally changes this landscape by revealing relationships in the past data and predicting

the outcomes of new designs and therefore reducing trial-and-error experimentation. The PLGA-PEG case study offers real examples of this process, and shows a staggering three times improvement in uptake with just two experiments. This represents a transition from an originally slow, linear, and often intuitively driven process of optimization, to a rapid, exponential, and engineered process which more effectively and predictably promotes the advancement of nanomedicine. Active learning is an important part of making ML work in nanomedicine, since there isn't a lot of data. One of the biggest problems with using ML in nanomedicine is the "lack of high-quality, standardized datasets," especially since comprehensive in vivo pharmacokinetics investigations take a long time to complete. Active machine learning focuses on the problem of not having enough training data. With active learning, "an ML model can intelligently select which new samples (nanoparticle formulations) should be screened" − based on either the model's prediction uncertainty or by quantifying information content in future predictions − and learn "more efficiently with fewer samples ... by screening these fewer samples and getting to these responses more quickly". ML may be used well without having large datasets if you use an adaptive technique to get data. Active machine learning can speed up research in domains where it takes a long time and costs a lot of money to collect data.

3.2. Enhancing Targeting Specificity and Overcoming Biological Barriers:

AI and ML are powerful tools that improve targeting specificity for nanoparticle-based drug delivery systems by improving designed strategies and delivering drugs specifically to targeted tissues or cells while minimizing off target effects and systemic exposure. AI algorithms, on their own, can analyze much larger datasets of all biologically-related interactions and chemistries than can humans alone. The ability of the algorithm to assimilate into more complex biological systems and recognize nuanced trends, gives massive benefits to the ultimate direction of design. Design is key to drug delivery and moving ai and ml into drug delivery allows for greater confidence in design selection. [4,9,16]

Deep learning models also have the ability to precisely predict molecular behaviour and ligand-receptor binding affinity, as well as toxicity properties, which is valuable in designing nanoparticles to target for example cell surface receptors or tumor markers over expressed on cells targeted for delivery, such as cancer cells. The algorithm becomes more directly useful by providing insights regarding the ability to design nanoparticles to trigger release of therapeutic payload in relation to biological cues within the environments of the body or with particle triggers to address specific cues, such as pH change or temperature increase, or enzymatic formats for increasing specificity. AI models will play a significant role in optimizing strategies for those designs and confirming triggered release is achieved. [4,9,15]

Machine learning (ML) models are crucial in improving targeted delivery by identifying and optimizing successful nanocarriers that may breach serious biological barriers such as the blood-brain barrier (BBB), which is very important for the treatment of central nervous system (CNS) disease. ML and deep learning models are used to optimize drug formulations to create better bioavailability in the brain and better penetrate the BBB for treatment of brain disorders, which include but are not limited to brain cancer, Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis. An example of ML technology in the development of an SGH-loaded cubosomal thermos reversible mucoadhesive gel to facilitate nose-to-brain drug delivery using ML was established. The students involved were able to create formulations with optimized nanoparticle size and controlled drug release, which not only significantly improved pharmacokinetic performance in the CNS compared to the drug solution alone, but also resulted in a drug formulation that could achieve nose to brain delivery. AI-based nanomedicine is accelerating the treatment of brain tumors by identifying specific molecular targets for therapeutic intervention. Long-term treatment of brain tumors using nanoparticles will persist and is advancing the identification of novel and effective antitumor complex. Deep learning models applied with molecular docking techniques have been used to predict the presence of nanoparticles with high binding affinity and high inhibitory potential against these unfortunately named targets, such as the EGFR-iRGD protein, which will lead to the identification of even more effective antitumor complexes. [4,9]

ML converts passive targeting to smart, actively delivered targeting. Traditional NDDS often rely on "passive targeting" mechanisms (eg, the Enhanced Permeability and Retention (EPR) effect in tumors). Although there is some level of preferential accumulation present, it "does not target tumor cells directly". However, ML creates opportunities for a more advanced model. Nanoparticles can be "engineered to release their payload in response to specific biological signals" and "AI models can be used to optimize the designs of the nanoparticles to respond to specific triggers". This is a fundamental change from "allowing a drug to passively accumulate" to designing "smart multifunctional nanocarriers" capable of actively and intelligently responding to real time physiological changes. This capacity increases the likelihood and precision of drug delivery; achieving desired therapeutic effect at the target site, while limiting systemic exposure and harmful side effects. [9,16]

It should also be noted that ML is essential in addressing the most challenging biological barriers and thus creating new therapeutic paths. For instance, the blood-brain barrier (BBB) is known to be a major physiological barrier that may prevent "large molecule biologics or therapeutic drugs from reaching affected areas in the brain" and is recognized as a substantial "treatment gap" in the treatment of neurological disorders. ML is able to "predict the BBB permeability of small molecules" helping us to "enhance targeted delivery". This is not simply an improvement in drug delivery; it is a significant unrighted breakthrough that enables us to help treat previously untreatable or difficult to treat diseases which include: Alzheimer's, Parkinson's, and brain cancers. This suggests that ML is not simply elevating current NDDS but is creating a new therapeutic landscape by successfully enabling access to sites of disease that were previously targeted only by limited modes of nanomedicine.

3.3. Optimizing Drug Loading Capacity and Controlled Release Kinetics:

AI/ML techniques vastly improve the engineering of nanocarriers by improving several critical aspects, such as drug loading capacity and release profiles, which increase efficiency and effectiveness for therapeutics. If needed, AI could normalize and transform nanoparticle characteristics to achieve an optimal drug loading capacity, and allow for a maximal amount of therapeutic agent to be loaded into the nanocarrier. AI also allows for optimization to obtain controlled release at the site of action, to ensure when and where the therapeutic is released. [8,9,26]

Deep learning models can also predict the complex effects of shape, size, surface charge, or material composition properties of nanoparticles on drug loading capacity, release rates, and cellular uptake. These predictive models support the design of nanoparticles to achieve these properties for therapeutic applications. Models developed with AI were able to optimize drug release profiles to ensure therapeutic agents are released in the body at the correct time and dose. A more stringent control can substantially improve therapeutic outcomes and patient compliance because of the ability to enhance dose frequency. [8,9,15]

ML changes medication release from static profiles to dynamic, adaptive control. As was said before, classic controlled release systems are made to get a pre-defined release profile, which is usually static (such sustained or pulsatile). Biological settings are always changing and aren't always the same, thus ML, especially deep learning, can help us get more accurate drug release profiles, even if we don't know what they are ahead of time. For instance, we may use ML to reliably forecast medication release "under a range of conditions, including low- or high-frequency ultrasound, microwave exposure, ultraviolet light exposure, and different pH levels." These prediction skills can help create "true" stimuli-responsive nanocarriers that let the drug out when they come into contact with pH, temperature, enzymes, or other outside signals. This big step forward means that the NDDS can now adjust to changes in physiology in real time, moving from a rigid, programmed release profile to an adaptive, intelligent release profile. In general, this method might make therapy much more accurate, such that the right amount of medicine is at the right place at the right time, which would increase effectiveness and decrease adverse effects. [8,9]

Additionally, ML provides multi-objective optimization for complex nanoparticle properties. Nanoparticle property optimization for drug delivery involves a complicated task with many often-interrelated and competing objectives in properties such as size, morphology, composition, surface functionalization, and dosaging. Conventionally, optimization methods assess several or even all of the

aforementioned properties in optimization models one-by-one. However, ML, and in particular reinforcement learning, can also assess competing objectives simultaneously: for example, an anti-microbial efficacy and a critique on safety, stability and production feasibility. This would represent a fundamental development toward moving existing NDDS toward the clinic, by enabling researchers to investigate formulations that represent the best trade-off across a range of properties. This represents a shift from finding an optimal characteristic, to more effectively finding a multi-object formulation. Find a holistic solution to the problem of designing an NDDS in a vast, multi-dimensional design space, whereas optimally reducing a single feature is manageable using classic or traditional methods. [8,9,12]

3.4. Improving Nanoparticle Stability and Drug Bioavailability:

AI algorithms are central to helping researchers interpret large datasets and to identify patterns and relationships between drugs. The data-driven analysis allows researchers to improve drug delivery systems for higher efficacy, safety and importantly stability. AI machine learning algorithms can predict drug stability, solubility and drug release kinetics by looking at the available experimental or computational dataset, and determining the complex relationships between the material structure, the formulator components in the formulation and relevant environmental conditions. [8,11,26]

ML models can determine the complex relations and non-linear dependencies allowing the prediction of drug stability under different conditions as storage conditions, and the solubility of a drug with different formulations. The accuracies achieved become valuable in driving the direction for robust formulation development. AI may be able to recommend formulations, and intelligently recommend excipients, or carriers, which may be more suited to maximise drug solubility improve stabilisation, or control release profiles. [8,11]

AI and ML are changing the game for increasing drug bioavailability by improving drug formulation, accurately predicting pharmacokinetics, and reducing the length of drug development. AI models can predict solubility and permeability, and ascertain the polymers, surfactants, and lipids needed to improve bioavailability. Advanced deep-learning models are also used to predict nano formulation parameters that influence drug absorption in biological systems. [8,11,26]

Furthermore, ML's predictive ability for stability improves shelf-life and decreases development costs. Drug stability is a "critical determinant in the action and efficacy of drug delivery systems" and is a significant factor in achieving a "long shelf-life". In the past, drug stability was evaluated by tedious and expensive empirical studies done empirically under multiple storage conditions. The fact that ML can "fast evaluate drug stability under various storage conditions" implies that researchers can efficiently screen in silico their potentials for long-term viability of drug formulation. This significantly mitigates the requirement for overwhelming amounts of physical experimentation, allowing advanced development timelines, and drastically reduces R&D costs. Ultimately, ML makes developing stable NDDS financially smart and fiscally responsible for more efficient commercialization and availability.

ML also improves bioavailability by getting rid of basic physiological obstacles. Poor bioavailability is a "important aspect in determining the therapeutic efficiency of orally taken medications, generally coming from difficulties including poor solubility, limited permeability, substantial first-pass metabolism, and enzymatic degradation. NDDS already have benefits because they change the size of particles and how they are released. ML makes these benefits even better by optimizing drug formulation and predicting pharmacokinetics. AI models can guess how soluble and permeable a substance is and suggest certain lipids, surfactants, and polymers that will make it easier for the body to use. Deep learning methods are utilized to guess the parameters of nano formulations that would help drugs get absorbed better. This shows how ML improves the natural benefits of NDDS by using data to get around basic physiological obstacles, which makes drug administration more effective and reliable.

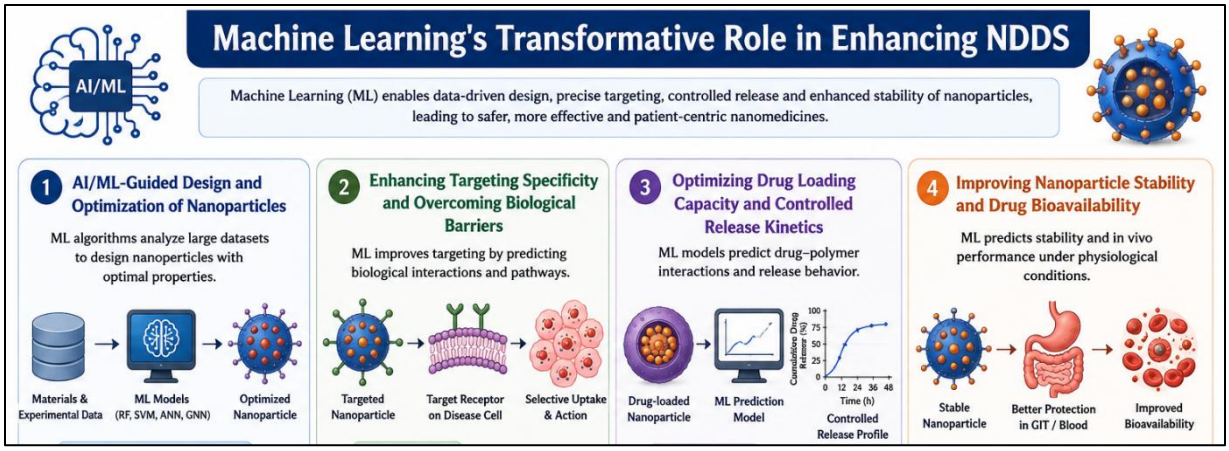

Figure-3: Machine Learning's Transformative Role in Enhancing NDDS

IV. MACHINE LEARNING APPLICATIONS IN NDDS DESIGN AND OPTIMIZATION

4.1. Predictive Modeling of Nanoparticle Properties (Size, Shape, Surface Charge, Encapsulation Efficiency):

A lot of the time, machine learning models are utilized to predict and improve crucial nanoparticle properties that are important for their safety and effectiveness as medications. Research has indicated that particle size is the most critical element, making up 35.2% of the ability to forecast. Second and third are surface charge (25.8%) and encapsulation efficiency (20.5%), respectively. Deep learning models can figure out how the size and shape of nanoparticles affect how much medicine they can carry, how quickly they release it, and how well they go into cells. AI algorithms are being used to find the ideal shape and size of nanoparticles to get them as deep into tumors as feasible. For instance, AI-designed rod-shaped nanoparticles have been shown to be better at finding cancers than spherical nanoparticles. Genetic algorithms also assist medications build up in the proper tissues by finding the ideal size for polymeric nanoparticles. Deep learning-based methods for making nanocrystals can accurately predict the size and shape of nanoparticles solely from the recipes used to manufacture them. ML models are also highly useful for determining out how nanoparticles reach inside cells. Research demonstrates that the lipophilicity of chemicals that are connected to nanoparticles is a key factor that impacts how quickly they penetrate into cells. ML can anticipate and improve multiple properties of nanoparticles at once, which is a substantial improvement above typical single-factor optimization. Some of these features are size, shape, surface charge, and how well they can be encapsulated. 7 Finding the particle size as the most essential attribute based on data offers future design efforts a clear, actionable aim. With this expertise, you may make nanoparticles that have all the right qualities for various medical uses in a rational and complete method. ML speeds up the research cycle, makes it more likely that drugs will work, and may even get rid of the requirement for numerous rounds of testing. All of these things lead to more effective and efficient nanomedicines. Also, the fact that AI can figure out the ideal shape for nanoparticles, like rod-shaped particles, to go into tumors better is a direct answer to a huge challenge in vivo. This is a little but powerful ability since it means that ML can identify links between the shape (morphology) of a nanoparticle and its complex biological function and how it interacts with a living system that aren't obvious. This means that nanoparticles can be engineered to perform effectively in a controlled lab setting, but they can also be made to work even better in the body's complex and dynamic biological environment. This is a huge step toward NDDS that works for therapy since it makes sure that the medicine is better targeted, builds up, and functions better at the site of the sickness. [9,15,20]

4.2. Optimizing Formulation Parameters and Drug Release Kinetics:

Machine learning algorithms are very helpful for improving NDDS formulation parameters and forecasting how quickly a medicine will be released. This is a big step forward from the old trial-and-error

methods. 20 AI can figure out how well drugs and polymers will work together and make small changes to different formulation parameters to get the results you want.

Artificial Neural Networks (ANNs), which are typically used with Genetic Algorithms (GAs), have been able to improve the formulation of polymer-lipid hybrid nanoparticles (PLN). This combined method has led to very high drug loading efficiency (92.4%) and very small mean particle sizes (approximately 100 nm). ANNs are better at recognizing and generalizing than standard Response Surface Methodology (RSM). Algorithms like gradient boosting have done a great job at forecasting drug release kinetics for nanostructured materials like aerogels, with R2 values over 0.9. In these systems, the K-index was used to measure morphology, and the ratio of macropores to mesopores was found to be a very important component in determining drug release. In the same way, supervised ML models like Gaussian process regression have accurately predicted drug release from acetylated dextran nanofibers (R2 = 0.931). ML, especially ANNs with GAs, may optimize interdependent factors like medication loading and particle size. This has a direct effect on how pharmaceuticals are released in a regulated way. Gradient boosting and Gaussian process regression are exceptionally good at predicting how drugs will be released over time. This means that ML can accurately manage the timing of drug administration. Also, finding that scaffold-specific factors are more important than drug-specific properties give formulation scientists a valuable, data-driven understanding of where to focus their optimization efforts. 31 This means that NDDS can be designed to have very particular release profiles, such sustained, pulsatile, or adaptive, which makes the therapeutic windows as wide as possible, reduces side effects, and makes patients more likely to follow their treatment. This changes the focus from just putting pharmaceuticals in capsules to carefully designing how they are released in the body's complicated environment. This opens the door to drug delivery systems that are truly smart.

4.3. Predicting Pharmacokinetics, Biodistribution, and Cellular Uptake:

The *in vivo* behaviour of nanoparticles, essentially their pharmacokinetics (PK), biodistribution, and cellular uptake, is rather difficult to predict in NDDS development on account of the complex biological interactions and difficulty in assembling good-quality sets of experimental data. Machine-learning-driven approaches have thus appeared to address this, taking advantage of large datasets to uncover difficult relationships amongst nanoparticulate properties and their biological fate. [3,4,15]

Advanced AI-driven approaches incorporate prior nanoparticle property knowledge—such as particle size, charge, and shape—into multi-view deep learning frameworks. This type of innovative integration aids pharmacokinetic prediction in instances where little or no experimental data exist, by selecting features on a context-aware basis. Also, ensemble learning paradigms that mix deep learning with classical machine learning methods, such as XGBoost and Random Forest, greatly enhance the robustness and predictive capabilities of these models. Physiologically Based Pharmacokinetic (PBPK) models are then seamlessly integrated into ML-based pipelines to quantify time-averaged nanoparticle concentration within individual organs. This mechanistic plane offers physiologically relevant dosimetry, thus linking the in vitro assessments with in vivo toxicity and making improved predictions of organ-specific toxicity. Models based on ML techniques are also indispensable for assessing the biodistribution of nanoparticles in different organs (e.g., brain), which is extremely difficult to predict, because of the penetrative action of blood-brain barrier (BBB). Using Linear Mixed-Effect Models (LMEMs) some recent work has shown that they help in capturing hidden patterns as well as explain the variations in brain targeting. These models show that things like how fast a drug is released and its molecular weight can hurt brain targeting. Being a P-glycoprotein substrate might help a little bit. For cancer treatment, AI makes a big difference in getting drugs where they need to go. It predicts how nanoparticles interact, checks how well drugs work, and helps cells take in more of the drug. This means processing complex tumor data making nanomedicine better, and giving extra info on how drugs are wrapped up and let go. It's hard to predict how nanoparticles move in the body, which makes it tough to use them in real treatments. [4,9]

Machine learning can predict where nanoparticles go and how cells take them in, which tackles this problem

head-on. Using multi-view deep learning that brings in what we already know about key nanoparticle features is a smart way to deal with the lack of data from live studies. Also, combining this with mechanistic PBPK models grounds these predictions in how bodies work making them more trustworthy. This ability plays a key role in speeding up clinical translation. It helps researchers predict how nanoparticles will act inside the body (where they go, build up, and leave organs). This allows them to create safer and better systems cutting down on expensive and lengthy animal and human tests. As a result, the field moves towards computer-based clinical trial simulations. This makes the development process less risky and gets new treatments to patients quicker. [4,15]

V. CHALLENGES AND FUTURE DIRECTIONS

5.1. Data Quality, Availability, and Integration:

The extensive application of AI in nanomedicine, and NDDSs in particular, will be limited by the ubiquitous issues of data quality, availability, and integration. One big problem is that much of the important nanomedicine data is spread out among several sources, such journals, patents, and databases. This means that there aren't frequently any complete, centralized databases. This makes it hard to build strong data mining tools that can gather, process, and evaluate the data that is already out there. The discipline is further limited by a lack of sample size (data sparsity), as many research only employ a small number of samples or simulated data that may not be physiologically different in real life. since of this, the performance of the models may suffer since AI models don't always operate well with data that is different from the data they were trained on. Also, the fact that there are no standard ways to report data and that research journals publish data in different ways makes it hard to share and reuse data. Most of the nanomedicine data that is out there is in the form of unstructured language in journal articles. AI can't interpret this data at all without Natural Language Processing (NLP) capabilities, or it can only process it partly without unifying or reformatting it. The fact that there are no standard definitions for terms makes it extra harder to handle data. [12,15,26]

Large gaps exist among chemical, physical, and biological data sets owing to a void of characterization of nanomaterials and a lack of minimum information standards for reporting data. This has resulted in issues of irreproducibility, which is a fundamental challenge of nanomedicine coming from a lack of standardized methods for nanoparticle preparation, characterization and reporting data. [12,15,26]

In the future, our efforts must focus on establishing large, high-quality, complete, and balanced datasets, including both physicochemical and toxicological data on nanomaterials. This will require sophisticated data collection methodologies, possibly involving high-throughput experimental data generation and automated data mining techniques. We will also need to establish innovative data integration strategies, such as multimodal AI and knowledge graphs, to better unify datasets that include genomic, clinical and molecular measurements and answer the questions of nanoparticle-based therapy. [12,15,26]

5.2. Regulatory Hurdles and Clinical Translation:

The rapid and steady uptake of artificial intelligence (AI) and machine learning (ML) into medicine across the drug development paradigm, including new drug delivery systems (NDDS) now makes clinical validation and regulatory process more essential than ever to meet the demand of patient safety and efficacy. Compared to traditional medical intervention, the use of AI and ML systems have added challenges. They are fundamentally more complex than traditional approaches, and are continuously developed over time, in the context of rapidly changing and expanding health data. Therefore, determining the clinical validity and reliability of AI/ML for drug delivery applications is more challenging than traditional drug delivery.

On the other hand, today for new formulated nanomedicines, they must still undergo strict regulatory path before used in people and those constructs are restrictive and can slow development and distribution. The FDA and other regulators have acknowledged the high usage of AI in the lifecycle of drug products and recently issued a draft guidance - Considerations for the Use of Artificial Intelligence (AI) To Support Regulatory Decision-Making for Drug and Biological Products - offering recommendations for industry. This guidance does provide recommendations to industry and suggest the use of a risk-based credibility assessment framework for the AI models, focusing on the effect and consequences of wrong decisions. Additionally, the

need for "human in the loop" was also considered as a method of risk mitigation, to ensure that human judgement towards serious decisions is still the focus of any critical decision making.

Considerable challenges remain over the reliability of findings and possible biases associated with the variable datasets used to train AI models. As there is also the possibility of AI model performance changing over time (known as "data drift") there requires ongoing life cycle maintenance and review. Additionally, nanoparticles can be costly to manufacture which may limit accessibility and clinical translation. [11,19,25]

There remains considerable opportunity in the regulatory space to streamline translation of promising nanoparticle technologies from research to clinical practice. Significant engagement with regulatory entities, such as the FDA, very early in the translational process is needed to set mutual expectations and highlight potential challenges. There is a need for standardized frameworks and methods to validate AI/ML algorithms in healthcare settings that include well-defined testing protocols and guidance on data collection and model building. We also envision industry-wide collaborations and sharing of expertise will advance validity and regulation to further transparency and accountability. [6,11]

5.3. Ethical Considerations:

The integration of Artificial Intelligence (AI) and Machine Learning (ML) in healthcare, including NDDS, presents several multifaceted ethical considerations that demand careful attention. [19,25]

•Privacy and Security of Data: The implementation of AI and ML technologies undoubtedly processes sensitive amounts of patient data including but not limited to electronic health records (EHRs), genomic data, and imaging studies. With such sensitive data being processed there are issues regarding privacy and the need for the data to remain secure. The ethical concerns are also more expansive than security as we need to consider how this sensitive data is handled as well as used. If there are unauthorized inquiries into a patient's information, there may be a breach of confidentiality, theft of identity and/or misuse of their medical information. This could further hinder the patient's autonomy and trust.

•Algorithmic Bias and Fairness: With AI and ML, we know the algorithms can be biased (racial, sex, socioeconomic) due to the training datasets being skewed by not representing patients equally based on diversity or flawed algorithm design. In healthcare, bias can lead to inequities in diagnosis, treatment, and outcomes which denies the values of fairness, justice and equity.

•Transparency and Explainability: The opaque nature of certain AI and ML models creates challenges to transparency and explainability, which are essential for trust and accountability in a healthcare context. When healthcare providers and patients are unable to understand how AI algorithms produce predictions, or recommendations, they may view the technology with skepticism and refrain from utilizing it.

•Professional Responsibility and Accountability: Healthcare professionals are ethically compelled to critically evaluate and implement the AI and ML technology within their clinical practice while continuing to provide high standards of patient care and safety. They also have to be diligent to assess the proven validity and reliability of AI-based recommendations because AI and ML technology can make errors. Accountability for who has responsibility for any errors is also a significant concern because the legal and ethical ramifications for AI use in the healthcare setting are not yet known.

Future directions roll with the direction of developing strong ethical frameworks and regulatory guidelines. With some specific action provided, that continues with to improve data safety, this direction maps the way forward and reduces/mitigate bias through diverse and representative data are necessary for algorithm decision trees (so additional importance). At the same time, building explainable AI (XAI) to better model interpretability is the next challenge, as is better defining accountability for each party in the AI/ML development and deployment chain. Also, robust training for clinicians on AI understanding relative to function, limitations and bias is needed.

5.4. Emerging Trends and Future Prospects:

The synergy between AI and nanomedicine is poised to revolutionize healthcare, with several emerging trends shaping the future of NDDS. [12,18,21]

• Personalized Nanomedicine: AI can manipulate huge amounts of patient specific information, such as genomics and clinical information, to facilitate the personalization of nanomedical therapy targeted specifically at the individual. In this way, drug delivery

systems will truly be personalized to the patient as it would be able to adjust in real time, in order to optimize the therapeutic outcomes and decrease side effects.

• Integration with IoT and Smart Health Systems: The integration of AI and nanotechnology with the IoT, will be able to develop the next generation of drug delivery systems that will have real time reporting features. IoT devices can monitor patient vital signs or drug levels in real-time and will be combined with an AI system to automatically adjust the dosages, creating closed-loop systems for diseases such as diabetes. Traditional patient care will now become remote, while also increasing medication adherence.

• AI Driven Nanobots and Advanced Interventions: Looking futuristic, the potential of AI driven nanobots that will have the ability to look for early disease detection, targeted intervention, and possibly micro-surgery, is exciting. These intelligent nano-devices will be able to specifically target damaged cells or tissues, and provide a level of precision that has never before been achieved.

•Multimodal Data Integration and Predictive Modeling: Future developments will depend largely on the integration of multiple data sources, e.g., genomics, proteomics, imaging, clinical data, into multimodal AI models that offer improved predictive ability for disease development, treatment response, and drug-nanoparticle interactions, through a more rigorous and accurate nanomedicine design.

•Resolving Technical Limitations: It will be imperative to ameliorate some of the current technical limitations that are standards when designing nanomedicines, e.g., lengthy synthesis times, lack of molecular specificity on toxicity, barriers in scaling up manufacturing. AI will be integral to fine-tuning the synthesis process, predicting stability, ensuring quality control in the same time frame at stake.

•Explainable AI (XAI) and Trust: With the complexity of AI models, the focus on Explainable AI (XAI) will only increase in importance. Fostering in-depth interpretability in an AI model is pivotal to improve clinical trust, gain regulatory approval, and ease translational journey into practice. Similar to the gap between technological capability and patient acceptance, improving trust is imperative to improve uptake and scale.

•Computational Pharmaceutics and In Silico Trials: The pathway towards computational pharmaceutics driven by big data and AI is likely to develop multi scale modelling techniques that can change pharmaceutical sciences through this virtual construction while minimising physical experimentation. This will enable *in silico* clinical trials, significantly accelerating drug development and reducing costs.

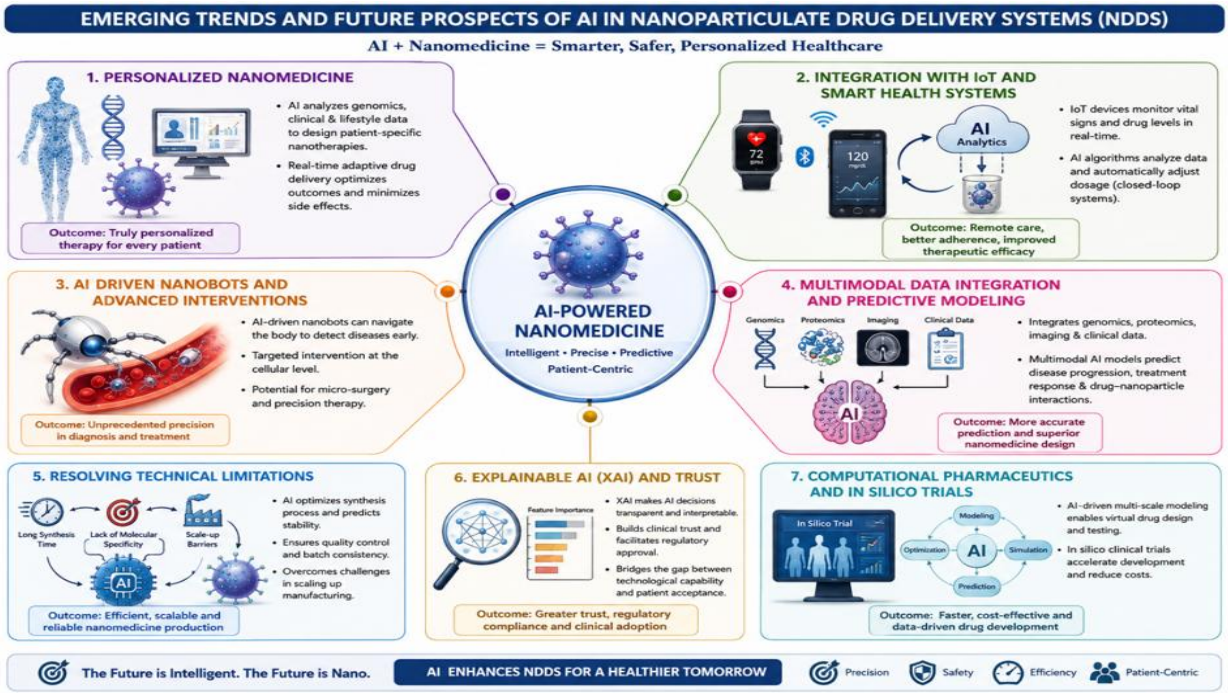

Figure-4: Emerging Trends and Future Prospects of AI in Nanoparticulate Drug Delivery Systems

VI. CONCLUSION

The confluence of Machine Learning (ML) and Nanoparticulate Drug Delivery Systems (NDDS) represents a new paradigm in pharmaceutical sciences with the potential to dramatically transform drug development, delivery, and patient care. NDDS face a number of challenges, as advantages such as targeted delivery, better solubility, and lower toxicity are offset by challenges of the "Curse of Dimensionality" and the unknown complexity of actual biological, in vivo, interactions. Traditional empirical approaches are rapidly becoming inadequate, as the combinatorial design space becomes too vast to sort through and ensure safety and efficacy. [8,9,12,26]

ML presents a revolutionary opportunity to transform NDDS development from empirical guesswork to a predictive engineering discipline. There are many different types of ML algorithms to suit specific NDDS problems that can be utilized in research and development, so that developing NDDS becomes tractable, as we can hone in on precise, multi-parameter control of nanoparticle (NP) attributes of interest such as size, shape, surface charge, and encapsulation efficiency, and systematically develop nanoparticles with optimized morphology for improved NP performance in vivo. Importantly, ML allows us to develop highly controlled release kinetics from mechanistically static NP release profiles to kinetic profiles that are dynamic, optimized and robust as it pertains to delivering therapeutically effective amounts to the intended patient and improving compliance. [8,9,15]

ML is particularly useful because it can be used with prior knowledge and physiologically based pharmacokinetic (PBPK) models to provide in vivo predictive capacity for nanomedicine behaviour, a major translational gap. This is essential for de-risking NDDS development, accelerating regulatory approvals, and lowering the dependency on expensive and lengthy preclinical studies. And toxicity prediction using ML is fundamental to the design of safer nanoparticles and development of more robust safety assessment processes. Evaluating nanoparticles with AI instance-based learning for characterization and quality control using sophisticated microscopy and/or spectroscopy analysis is a way to ensure the batch-to-batch consistency and that the nanoparticles manufactured are compliant biomedical devices, which will ultimately accelerate pipeline development. [4,9,15]

Despite the exciting advances, challenges remain. Issues related to data quality, availability, and interoperability remain a significant hurdle, and cannot be understated; an industry build means standardized reporting and data storage, and merging the data into a suitably comprehensive database. The inherent opacity of ML complexity requires advanced attention to algorithmic transparency and Explainable AI (XAI) to support trust in clinicians and regulators. Engaging with regulators and developing robust validation methodologies is important to avoid regulatory obstacles on the pathway to effectively translating to clinical services. Considerations related to citizens' equitable access to AI-driven health care, privacy related to data, algorithmic bias, and healthcare professionals' responsibility as stewards of research and society, are important to be consistently considered to bear responsible use of AI in health care. [12,19,26]

As we look to the future, NDDS will depend on the trajectory of ML. Future indications are to achieve genuinely personalized nanomedicine, moving to interventions that change through IoT and smart health system integration, and even AI-driven nanobots to assist in fully targeted precision medicine. Ongoing research and collaborative efforts across multiple disciplines need to overcome limitations and improve predictive models, and to ensure ethical and responsible use of powerful ML techniques, and fully realize the potential of ML-informed NDDS for the benefit of patients. [11,12,18,21]

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