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Artificial Intelligence–Driven Design and Optimization of Lipid Nanocarriers in Pharmaceutics: Opportunities, Challenges, and Future Perspectives

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Abstract:

Lipid nanocarriers, which include solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoparticles (LNPs) have been discovered to be universal platforms that can be used to improve the solubility, stability, and bioavailability of therapeutic agents. Traditional trial-and-error formulation procedures though historically usual, are time-consuming, resource-intensive and often unable to incorporate the rich, nonlinear interactions that exist between formulation and process variables. Artificial intelligence (AI) is introduced in this analytical review as an effective accelerant to formulation design and optimization in pharmaceutics.

The current paper brings together the available literature on AI-based approaches to lipid nanocarrier development, focusing on the recent advances in machine learning, deep learning, artificial neural networks, and hybrid AI-Quality by Design (QbD) approaches. Special emphasis is given to the use of AI in the choice of excipients and prediction of key quality features, such as particle size, poly dispersity, ζ -potential, drug-encapsulation capacity, and stability under long-term conditions. Cases of AI-aided lipid nanocarrier design in oral, ocular, transdermal, parenteral, and gene delivery are explored in detail. Besides, the review covers the relevant challenges associated with data quality, model interpretability, regulatory approvability, and industrial scalability of AI-based formulation development. The emergent trends, including digital twins, autonomous formulation laboratories, and the combination of AI and continuous manufacturing, are also evaluated. Taken together, this review suggests a framework on which formulation scientists and researchers can utilize AI to revolutionize the development of lipid nanocarriers, as well as to close the divide between optimization on the laboratory scale and a pharmaceutical product with the potential to be translated to the clinic.

Keywords

Artificial intelligence, lipid nanocarriers, SLNs, NLCs, LNPs, machine learning, deep learning, formulation optimization, pharmaceutics.

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1. INTRODUCTION

Historically, the pharmaceutical formulation process has been based on empirical, trial-and-error methods of formulation, which entail a lot of experimentation to reach the desired product performance. Even though standard formulation approaches, aided by statistical methods like Design of Experiments (DoE) and Quality by Design (QbD), have enhanced systematic development, they have weak ability to handle complex, nonlinear relationships between formulation components and process variables.[1] This constraint has led to long development times, high material usage and problems with reproducibility and scale-up, especially with complex drug-delivery systems like lipid-based nanocarriers [2.]

Over the past years, lipid nanocarriers, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoparticles (LNPs) have become highly promising drug-delivery platforms due to their biocompatibility and capacity to encapsulate both hydrophilic and lipophilic drugs, in addition to targeted and controlled release.[3] Although these have benefits, formulation development of lipid nanocarriers is still a challenge because there is a high number of formulation and process variables that affect key quality attributes of particle size, polydispersity index, encapsulation efficiency, stability, and in-vivo performance[4,5]

The field of artificial intelligence (AI) is becoming more and more recognized as a disruptive technology in pharmaceutics to provide new solutions to the challenges of the traditional formulation development.[6] By 2025, AI has been used in accelerated pharmaceutical research and development, through machine learning, deep learning, and data-driven modelling, in combination with a greater availability of formulation datasets and computing capabilities, which have enabled rapid prediction and optimization of formulation outcomes with minimum experimental effort.[7] AI-based models have the potential to learn complex, multidimensional relationships between important material properties, important process parameters, and important quality attributes of a product, and therefore, AI-driven design and optimization of lipid nanocarriers is a critical frontier in pharmaceutics.[8]

2. Lipid Nanocarriers.

Lipid nanocarrier is a heterogeneous group of colloidal drug delivery systems developed to overcome the drawbacks of traditional dosage vehicles, especially low aqueous solubility, low bioavailability, and instability of drug molecules. Due to their biocompatibility, biodegradability and ability to entrap both hydrophilic and lipophilic drugs, lipid-based nanocarriers have received considerable attention in pharmaceutical research and clinical practice. Among them, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoparticles (LNPs) are the most thoroughly investigated platforms, which have their own structural features and functional benefits.[9]

2.1 Solid Lipid Nanoparticles (SLNs).

Solid lipid nanoparticles are submicron-sized colloidal carriers that have a diameter of between 50 and 1000nm, which is made of physiologically acceptable solid lipids that are stabilized by surfactants or emulsifiers. Both the room and body temperatures leave the lipid matrix solid,

giving the lipid matrix structural rigidity and allowing controlled drug release [10]. One of the advantages of SLNs is their high biocompatibility, which prevents the degradation of the encapsulated drugs in case of chemical degradation, elimination of using organic solvents, and their ability to be produced on a large scale.[11]

Although these benefits exist, SLNs have a shortcoming in terms of their highly ordered crystalline lipid matrix. An ideal crystal lattice often limits drug accommodation resulting in low drug loading capacity.[12] Also, the storage can cause polymorphic transitions that can initiate drug expulsion and reduced formulation stability. All these difficulties have limited the wider clinical implementation of SLNs and triggered the design of the next-generation lipid nanocarriers.[13]

2.2 Nanostructured Lipid Carriers (NLCs)

To address the structural and functional drawbacks of SLNs, nanostructured lipid carriers were developed as improved versions of SLNs. The NLCs are an amalgamation of solid and liquid lipids, which create a less well-organized and imperfect lipid backbone. This flaw or defect in the structure provides more space to accommodate drugs, thus increasing drug loading capacity and minimizing drug expulsion during storage[14].

The NLCs have better physical stability, encapsulation efficiency and formulation flexibility than the SLNs [15] . These characteristics have made them easy to use in various routes of drug delivery such as oral, topical, transdermal, and parenteral routes. Due to their improved performance, NLCs are becoming more appropriate compared to SLNs in the delivery of drugs that are poorly soluble and long-term therapeutic regimens [16].

2.3 Lipid nanoparticles (LNPs) For Nucleic Acid Delivery

Nanoparticles composed of lipids have become a central technology in the delivery of nucleic acid-based therapeutics, in particular, messenger RNA (mRNA), small interfering RNA (siRNA), and plasmid DNA [17]. The reported clinical success of LNP-based mRNA vaccines against COVID-19 has intensely stimulated research and industrial attention towards this delivery system. Ionizable lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-conjugated lipids, which are commonly components of LNPs, serve a specific function in stability, cellular absorption, and endosomal evasion [18,19].

The ionizable lipids assist in efficient encapsulation of nucleic acids and endosomal release in acidic conditions, whereas PEG-lipids are used to increase the colloidal stability and extend the systems circulation in the bloodstream. LNPs provide high transfection efficiency, nucleic acid protection against enzymatic degradation and scale to industrial production [20]. As a result, LNPs have become essential in gene therapy, vaccination and new personalized medicine applications (Table 1).

Table 1: Comparison of Lipid Nanocarriers

Feature	Solid Lipid Nanoparticles (SLNs)	Nanostructured Lipid Carriers (NLCs)	Lipid Nanoparticles (LNPs)
Size Range	50–1000 nm	50–1000 nm	50–200 nm
Lipid Composition	Pure solid lipids	Blend of solid + liquid lipids	Ionizable lipids, phospholipids, cholesterol, PEG-lipids
Matrix Structure	Highly ordered crystalline	Imperfect / less ordered crystalline	Amorphous / flexible lipid matrix
Drug Loading Capacity	Moderate to low	Higher than SLNs	High for nucleic acids
Encapsulation Efficiency	Moderate	High	Very high (esp. for nucleic acids)
Stability	Susceptible to polymorphic transitions & drug expulsion	Improved over SLNs	Good physical & chemical stability
Applications	Oral, topical, parenteral	Oral, topical, transdermal, parenteral	Gene therapy, mRNA/siRNA vaccines, parenteral drug delivery
Advantages	Biocompatible, controlled release, solvent-free	High drug loading, enhanced stability, versatile	Efficient nucleic acid delivery, endosomal escape, scalable
Limitations	Low drug loading, drug expulsion, limited stability	Slightly more complex production	Requires precise lipid formulation, costlier

2.4 Critical Formulation and Process Parameters.

Formulation/process parameters interaction is a complicated system which determines the performance, stability and therapeutic efficacy of lipid nanocarriers. The major formulation variables include nature and concentration of solid and liquid lipids, surfactant and co-surfactant choice, lipid to drug ratio and physicochemical characteristics of the encapsulated drug [21]. These aspects have a direct effect on internal architecture of the lipid matrix, ability to take in drugs as well as the interfacial stability of the nanocarrier system.[22]

Homogenization pressure, homogenization cycles, sonication time, emulsification temperature, cooling rate and mixing speed are process parameters with significant influence

on the final particle properties.[23,24] The changes in these parameters may significantly affect the droplet break up, lipid crystallization behaviour and aggregation of particles, thus affecting the reproducibility and scalability of the formulation [25].The combination of the formulation and processing variables control the critical quality attributes (CQA), such as the particle size, polydispersity index (PDI), zeta potential, drug encapsulation efficiency, in-vitro release behaviour, and long-term physical and chemical stability(Table 2). The interdependence of these variables is nonlinear, which makes the traditional optimization strategies rather difficult, and the use of advanced, data-driven and artificial-intelligence-based techniques is highly recommended to obtain stable and reproducible lipid nanocarrier formulations [26].

Table 2: Critical Formulation and Process Parameters Influencing Lipid Nanocarrier Performance

Parameter Type	Specific Variables	Impact on Nanocarrier Attributes (CQAs)	Notes / Comments
Formulation Variables	Lipid type (solid/liquid)	Influences particle size, drug loading, matrix rigidity	Determines crystallinity and drug accommodation
	Lipid–drug ratio	Affects encapsulation efficiency, release profile	High drug loading may destabilize formulation
	Surfactant type & concentration	Modulates particle stability, zeta potential	Too low → aggregation; too high → toxicity risk
	Co-surfactant type	Impacts surface charge, PDI, and stability	Helps reduce polydispersity
	Drug physicochemical properties	Solubility, lipophilicity	Determines encapsulation efficiency and release behavior
Process Variables	Homogenization pressure	Affects particle size, PDI, and reproducibility	Higher pressure → smaller particles but risk of degradation
	Number of homogenization cycles	Influences uniformity and size distribution	Excess cycles → instability

	Sonication time / energy	Reduces particle size, affects encapsulation	Over-sonication → heat generation and drug degradation
	Emulsification temperature	Modulates lipid crystallization and encapsulation	Critical for thermolabile drugs
	Cooling rate	Determines lipid polymorphism, particle stability	Rapid cooling → amorphous state, better drug retention
	Mixing / stirring speed	Influences droplet breakup and size distribution	Key for scale-up reproducibility
Critical Quality Attributes (CQAs)	Particle size, PDI, zeta potential, encapsulation efficiency, in vitro release, stability	Directly linked to formulation & process parameters	Nonlinear relationships often require AI or QbD optimization

3. Pharmaceutical Artificial Intelligence.

Artificial intelligence (AI) is now a primary methodology in pharmaceutical research, allowing the use of data to make decisions and predictive modelling in drug discovery, formulation development, and manufacturing [27]. The complexity of systems, including lipid nanocarriers, is where the application of AI techniques is especially beneficial as most of the formulation and process variables interact in nonlinear and interdependent ways [28]. Through the combination of experimental and historical data, AI models help detect the underlying trends, forecast the success of the formulation, and optimize the key parameters, eliminating the necessity to perform a lot of experimentation [29].

3.1 Machine Learning

Predictive modelling and Optimisation are supported by machine learning (ML) algorithms that formulate relationships between the input variables and the formulation outcomes that are observed based on an experimental dataset. Traditional ML techniques, such as linear regression, decision trees, random forests, k -nearest neighbors, and support vector machine (SVM), have been widely utilized in the pharmaceutical field.[30] The methods have proven to be useful in a significant capacity to predict formulation properties including particle size, encapsulation efficiency and drug release behaviours. The benefits of ML methods are that they can be implemented easily, explained by simpler models, and 3139-2733 too small to medium-sized data that is regularly produced during formulation research [31,32].

3.2 Deep Learning

Deep learning (DL), a branch of machine learning, uses multilayered neural networks that are able to represent the complex non-linear relationships in large datasets [33.] CNNs and RNNs have become more and more popular in pharmaceutical formulation development. DL models are especially useful when being used to process high-dimensional data that is collected in high-throughput experiments, imaging modalities, and continuous manufacturing processes. Empirically, the findings have shown that DL methods can be utilized to forecast the formulation performance and stability profiles, especially in the lipid nanocarrier research [34,35].

3.3 Artificial Neural Networks

Artificial neural networks (ANNs) are based on the architecture and working mechanisms of biological neural networks and are made up of interconnected input, hidden and output layers. The common use of ANNs in pharmaceutical sciences is driven by the strong ability to simulate non-linear interaction between formulation variables and quality properties [36]. ANN models have been successfully 3139-2733 in predicting the size of lipid nanocarriers, polydispersity index, drug loading, encapsulation efficiency, and in-vitro release profiles of nanoparticles in the particular case of lipid nanocarriers. In turn, ANNs are among the most popular AI tools in the optimisation of nanocarrier formulations, which is explained by their flexibility and excellent predictive capabilities [37,38.]

3.4 Hybrid AI Approaches

Hybrid AI approaches combine artificial intelligence approaches with traditional pharmaceutical design tools, such as Quality by Design (QbD) and Design of Experiments (DoE). These combined models utilize the predictive power of AI and combine mechanistic findings of the classical experimental designs to provide an integrated approach to the formulation development [39]**.** Hybrid AI-QbD methods enable a systematic evaluation of risk, determination of the material attributes and key process parameters that are critical and creation of strong design spaces. This type of integration makes models more interpretable and helps to accept AI-based formulation development by regulators [40.]

4. Artificial Intelligence-Based Design and Optimization of Lipid Nanocarriers

Lipid nanocarrier formulation and optimisation has been shown to be a multivariate process where various formulation and process parameters are optimised simultaneously to define the quality of the product, stability and therapeutic functionality. Traditional trial-and-error methods and classical statistical methods tend to be inefficient to search this multidimensional design space, especially in cases of nonlinear and synergistic interactions [41]. Artificial intelligence (AI) has been a strong solution to overcome these challenges through the ability to formulate design using data by its predictive and systematic nature.

Combining the formulation composition, processing conditions and performance data, AI-based models allow gaining profound understanding of the intricate relationships determining

the behaviour of lipid nanocarriers [42,43]. These models aid in quick screening of formulation variables, decimation of experimental workload, increase in reproducibility and faster translation between laboratory level development and industrial production. In turn, there is a tendency to use AI-based formulation strategies in order to obtain robust, scalable and regulatory-compliant lipid nanocarriers products [44].

4.1 AI-Based Excipient Selection

The choice of excipients is an important factor that defines the stability of lipid nanocarriers in physicochemical and biological performance. Lipids and surfactants should be selected to guarantee maximum drug solubility, compatibility and stability. Rational selection of excipients AI-based models is used to select excipients rationally through the analysis of large datasets of physicochemical properties, including melting point, hydrophobicity, molecular weight, solubility parameters and lipid drug compatibility indices.[45]

Machine-learning models and AI neural networks can quickly filter through viable solid and liquid lipids, surfactants and co-surfactants, eliminating the need to use large-scale screening in the experiment [46]. This information-driven strategy allows the early discovery of the most effective excipient combinations, reduces the risk of formulation failure and hastens the development of the formulation at its initial stages [47,48.]

4.2 Prediction of Particle Size, Polydispersity Index, and Zeta Potential

Some of the most vital quality properties that have an impact on the stability, biodistribution, cellular uptake and therapeutic efficacy of lipid nanocarriers include particle size distribution, polydispersity index (PDI) and zeta potential. Formulation composition and processing conditions including homogenisation pressure, surfactant concentration and temperature, have a strong influence on these parameters [45].

Machine-learning algorithms and artificial neural networks are AI-based predictive models that have proven to be highly accurate in predicting particle size, PDI and surface charge due to being trained on complex nonlinear relationships between formulation and process variables. The prediction with the help of AI enables the rapid optimisation of nanocarrier properties, facilitates batch-to-batch consistency and enables the formulation scientist to attain target specifications with the minimum of experimental iterations [49].

4.3 Optimization of Drug Encapsulation Efficiency

The dosage accuracy, therapeutic efficacy and cost-effectiveness of lipid nanocarrier formulations are important determinants of encapsulation efficiency. Generally, a complicated drug-lipid interaction and lipid matrix behaviour make it difficult to achieve high drug loading and retain physical stability.

The optimisation models based on AI combine variables of the formulation (lipid composition, drug-to-lipid ratio, surfactant concentration, and processing parameters) to find the best conditions in order to maximize encapsulation efficiency [50]. Such models allow the

simultaneous analysis of various variables and their interactions which are not always feasible with traditional methods of experiments. Therefore, the use of AI-based optimisation facilitates the rationale formulation design, which has superior drug loading and stable performance [51].

4.4 Prediction of Critical Quality Attributes

Multiple input variables can be modelled by AI to make predictions on critical quality attributes (CQAs) together, which allows the comprehensive interpretation of the effects of the formulation composition and process parameters on the nanocarrier performance. In contrast to classical methods that make use of one attribute of optimisation at a time, AI-based multivariate prediction offers a complete understanding of formulation behavior [52,53].

This integrated predictive capability facilitates strong formulation design, risk-based optimisation plans and decision-making in the formulation development. AI models can help to enhance the formulation robustness and regulatory preparedness by determining the important formulation and process variables that control the quality of the products [54].

4.5 Processing Parameters Optimization.

The processing conditions, including homogenization pressure, sonication time, emulsification temperature, mixing speed and cooling rate have a considerable effect on the physicochemical properties of lipid nanocarriers. Even small changes in these parameters can give rise to significant differences in particle size, encapsulation effectiveness and stability.

The artificial intelligence algorithms are used to optimize these processing parameters systematically, as they can be used to create correlation between the inputs to the process and the formulation outcomes. Predictive AI models allow determining the most suitable operating conditions that lead to reproducible product quality and assist in the scale-up processes. The ability can be especially useful in case of industrial production, where the robustness and consistency of the processes are a necessity to comply with the regulations [53,54].

4.6 Stability and Shelf -Life Prediction.

The challenge of lipid polymorphism, aggregation, and expulsion of drugs during storage are significant to the development of lipid nanocarriers and ensure long-term physical and chemical stability. The conventional stability investigations are time consuming and resource consuming [55].

The use of predictive AI models is getting popular to assess long-term stability through the analysis of formulation composition, storage, and accelerated stability data. These models assist in the early identification of risks of instability, prediction of shelf-life, and rational formulation optimization, which shortens the development cycles and eliminates failures at the late stages [56].

4.7 AI and Quality by Design.

AI-based Quality by Design (QbD) paradigms is a paradigm of synergy that combines systematic pharmaceutical development concepts with artificial intelligence predictive

capabilities. AI can be used to improve the implementation of QbD by improving risk assessment, design space exploration, and control strategy establishment [57].

Combining AI with QbD facilitates lifelong learning on the basis of formulation data, allows design space to be refined in an adaptive manner, and guarantees the ability to have uniform product quality across the formulation lifecycle. Notably, this hybrid strategy is in line with regulatory requirements since it maintains scientific transparency but uses advanced predictive modelling, which is specifically appropriate in complex lipid nanocarrier systems[58].

5. AI-Assisted QbD and DoE Approaches in Lipid Nanocarrier Development

The Quality by Design (QbD) and Design of Experiments (DoE) models have played a crucial role in the systematic formulation of pharmaceutical formulations allowing the structured analysis of variables of formulation and process. However, the growing sophistication of more complicated drug delivery platforms, especially lipid nanocarriers, has highlighted natural constraints of the traditional QbD and DoE approaches. In this regard, artificial intelligence (AI)-based solutions tend to be implemented as auxiliary technologies to improve the formulation efficiency, predictive quality, and process insights [59].

5.1 Classical DoE shortcomings.

Classical DoE methods are based on fixed experimental designs and statistical assumptions that are usually focused on linear or low-order interactions between variables. Although these techniques work well with relatively simple formulations, they are less useful in the case of complex lipid nanocarrier systems that have more than one formulation component and processing parameter. The number of required runs increases exponentially with the number of variables, which consumes more material, increases the duration of development, and increases cost[60]. Additionally, the conventional DoE models often do not have strong predictive power outside the design space explored and might not be able to sufficiently describe nonlinear and synergistic interactions which have a critical impact on nanocarrier performance [61].

5.2 Hybrid AI-QbD Models

Hybrid AI -QbD models combine the principles of QbD, which are structured and regulatory-compliant, and the powerful predictive abilities of AI algorithms. In these frameworks, AI models are used to analyze experimental data produced according to QbD-guided designs to enhance risk assessment, optimize design space, and predict the key quality attributes. The model used in machine learning and artificial neural network is a dynamically learned model that relies on the formulation data and can then be continually improved as the new information in the experiment is released. Notably, hybrid AI -QbD methods maintain regulatory transparency by ensuring scientifically reasonable design spaces with significant lessening of experimental load and better formulation robustness [62].

5.3 Recent Case Studies (2023-2025)

The most recent research (2023-2025) has yielded successful results in the application of AI-assisted methodologies in the development of lipid nanocarriers. Artificial neural networks and

Random Forests models have shown better performance in the prediction of particle size, encapsulation efficiency and stability than traditional DoE-based models. The Bayesian optimization methods have also facilitated quick determination of optimal formulation compositions at significantly reduced number of experiments run. All these studies point at the fact that AI-based QbD models are significantly more predictive, and they also have a better scalability and reproducibility, thus enabling easier scaling of laboratory-scale development to industrial production [63,64.]

6. Applications Across Drug Delivery Routes

Optimization of lipid nanocarriers by artificial intelligence has shown a wide range of applications in different drug administration routes. Allowing to make rational choices on the formulation components and allowing to strictly regulate the characteristics of nanocarriers, AI-based technologies will assist in achieving route-specific performance requirements and improve therapeutic outcomes.

6.1 Oral Delivery

The use of poorly water-soluble drugs via oral route is still a significant problem because of the low dissolution, erratic absorption, and first-pass metabolism. The design of lipid nanoparticles with the assistance of AI allows to optimize the lipid composition, surfactants, and size to enhance solubilization and gastrointestinal protection. The in vivo bioavailability using machine learning models with formulation variables has been used to develop lipid nanocarriers that increase the permeability of the intestines and controlled release of the drug. Such methods cut down on the screening of the experimental trials but enhance the performance of the oral drugs and reproducibility [22,23.]

6.2 Ocular Delivery

Drug delivery to the eye needs a very tight regulation of particle size, surface charge, and residence time in order to overcome the rapid turnover of tears and low permeability of the corneas. Optimization of lipid nanocarriers by AI assists in the rational design of lipid nanocarrier systems that are more likely to be absorbed into the skin, release drugs in a controlled manner, and reach the ocular cavity in their original state. The application of artificial neural networks and deep learning models has been implemented on the optimization of nanostructured lipid carriers and lipid nanoparticles as ophthalmic delivery systems, such as in situ gelling systems, capable of long-acting therapeutic effect and high patient adherence [65,66].

6.3 Transdermal Delivery

In the case of transdermal drug delivery, lipid nanocarriers should be designed in a way that they can traverse stratum corneum without causing skin incompatibility. Intelligence-based predictive models are used to optimize the lipid fluidity, concentration of surfactants, and drug partitioning behavior in order to improve dermal and transdermal permeation. With the assistance of correlating the variables of formulations with the permeation profiles and the data of skin retention, AI-based solutions allow developing lipid nanocarriers that enhance drug flux and reduce irritation and variability [67].

6.4 Parenteral and Gene Delivery.

The design of lipid nanocarriers with the help of AI has been instrumental in the parenteral and gene delivery of nucleic acid therapeutics, in particular. Predictive modeling assists in optimization of lipid nanoparticle composition, ionizable lipid pK a and particle size to optimize encapsulation efficiency, circulation stability, and cellular uptake. These methods have played a crucial role in making it much faster to develop lipid nanoparticle-based mRNA and siRNA formulations, improving the transfection efficiency and safety profiles [5,17,18].

6.5 CNS Targeting

The blood brain barrier restricts the delivery of therapeutic agents to the central nervous system, which requires a specific design of nanocarriers. AI-assisted formulation plans combine physicochemical and biological data to maximize the characteristics of lipid nanocarriers to CNS targeting, such as the size of the particle, the surface modification, and the lipid composition. Machine learning models can be used to predict the uptake and biodistribution of the brain to develop lipid nanocarriers that can help enhance therapeutic delivery of neurological diseases [68,69.]

7. Artificial Intelligence Tool limitations in Pharmaceutical Formulation.

Although artificial intelligence (AI) has great benefits to pharmaceutical formulation, there are a number of limitations that should be taken into consideration to have safe, reliable, and interpretable results. The quality and availability of data is critical to the functionality of AI-based models, and they might not perform correctly when exposed to biased, incomplete, or unrepresentative data. Therefore, AI should be implemented in cooperation with the conventional methods of experimentation instead of a single decision-making mechanism [70].

A significant drawback of AI models is that they do not have transparency in decision-making. Most sophisticated algorithms are what are referred to as black-box models, and one may not even know how certain predictions are made. This interpretability may decrease the confidence of formulation scientists and clinicians, especially when model results do not agree with known experimental or clinical predictions [71,72].

AI algorithms are also largely statistical in nature and might not have a domain-specific clinical or formulation knowledge. This could cause them to have reduced capability to capture the biological importance and practical implications of specific formulation parameters [73.] Biological systems are also intrinsically complex, with dynamic interactions or feedback, molecular variability, and further complicate AI models, which are based on simplified models of these processes [74.]

The use of artificial intelligence tools also presents other complexities on ethical matters. Protection of patient data confidentiality, informed consent, and the definition of proper data ownership are critical, especially in the case of datasets that are based on clinical or patient-related data [75]. Standardisation of ambiguity over ownership and entitlement to use data might give rise to ethical dilemmas among patients, researchers and pharmaceutical stakeholders [76,77.]

In addition, artificial intelligence models are often faced with challenges when trying to explain biological and population-wide heterogeneity, since they are typically trained on data that represents mean responses. Retraining and validation of such models to maintain predictive accuracy can be resource-intensive, particularly when new experimental or clinical data is to be used to update the model [78]. All these constraints highlight the need to implement AI responsibly that is supported by solid experimental and professional supervision [79].

8. Data, Ethical, and Regulatory Problems.

Although the application of artificial intelligence in the pharmaceutical formulation development continues to increase, numerous regulatory, ethical, and data-related challenges need to be overcome to make the practice widespread and sustainable. All of these issues are especially relevant to the cases of complex delivery systems like lipid nanocarriers, the formulation performance of which is dictated by multifactorial interactions and fluctuating responses at different developmental stages [80,81.]

8.1 Data Quality and Bias

The quality of AI-based models, their diversity, and representativeness of training datasets are the conditions under which their reliability is determined. Formulation data in pharmaceutics are frequently small, heterogeneous and obtained under different experimental conditions. These inconsistencies may result in bias, which causes overfitting and reduced model generalizability. Biased datasets can lead to poor predictions of important quality characteristics or stability behaviour when 3139-2733 to lipid nanocarrier development, and hence the importance of standardized data generation, curation and sharing practices [82.]

8.2 Model Interpretability

Most AI models, especially deep learning models, do not give much information about how they make decisions internally. This interpretability is a problem to scientific understanding, formulation risk assessment and regulatory review. Transparency between the variables of the formulation and the quality features of the products is required in pharmaceutical development. The explainable AI methods are thus crucial to achieve the model interpretability and develop regulatory and scientific trust in AI-aided formulation strategies [83].

8.3 The Regulatory Acceptance of AI-Assisted Formulation.

Even though regulatory bodies are actively supporting model-based development of drugs, formal rules on the use of AI in formulation design are still under development. To be accepted by the regulatory authorities, AI-assisted methods require detailed records of model development, validation and lifecycle control. It is necessary to show strong performance and reproducibility and adherence to the Quality by Design principles to enable approval of AI-optimised lipid nanocarrier products by the regulatory authorities [84].

8.4 Reproducibility and Validation Problems.

The problem of ensuring reproducibility of AI-based predictions across laboratories, developmental stages, and manufacturing conditions is still a major issue. The differences in the experimental protocols, data preprocessing, and instrumentation may affect the model

performance and restrict transferability. Strong verification plans such as external and prospective experimental verification are consequently invaluable [85]. Long-term reliability and acceptance by the regulatory bodies are also aided by constant monitoring and updating of the model over the product lifecycle [86].

9. Clinical Translation and Industrial Adoption

The future of AI-optimised lipid nanocarriers as a promising platform of clinical translation depends on the successful incorporation of the predictive modelling tools into the pharmaceutical production and quality assurance processes [87]. With the increasing uptake of data-driven development approaches and continuous manufacturing paradigms by the pharmaceutical industry, artificial intelligence has become a key facilitator in the process of closing the gap between laboratory level formulation optimisation and commercial level production [88].

9.1 Integration of Scale-Up and Manufacturing.

The most common challenges associated with scaling lipid nanocarrier formulations have included changing particle size distribution, decreased encapsulation efficiency and increased batch-to-batch variability [89]. Predictive models that are based on AI can be used to evaluate scale-dependent effects through correlating laboratory-scale formulation, process parameters with pilot- and industrial-scale results [90]. AI tools enable a rational process transfer by simulating the effect of critical processing variables, such as pressure of homogenisation, mixing speed and temperature and reduce the risks of scale-up. Integrating AI into the factory processes increases the resilience of the processes, leads to a higher reproducibility rate, and reduces the timeframes of developing products [91,92.]

9.2 Process Analytical Technology and Real-Time Release Testing.

The emerging fusion of artificial intelligence and Process Analytical Technology (PAT) has facilitated the high-tech real-time monitoring and control of the process of lipid nanocarrier manufacturing. The use of AI in the interpretation of inline and at-line data of PAT allows the early identification of process deviations and facilitates adaptive control measures [89]. This statistical method corresponds to real-time release testing models, which minimize the reliance on end-product testing and maintains a stable quality of the products. Continuous manufacturing platforms are especially benefiting in the context of such integration since quick and informed decision-making is necessary to ensure the stability of the processes.

9.3. Industrial Adoption and Case Studies.

There has been a growing adoption of AI-aided platforms in pharmaceutical and biotechnology industries in formulation development and process optimisation of lipid-based drug delivery systems. In the industrial applications reported, these results include shortening development cycles, increased consistency in batches and a better understanding of processes by making data-driven decisions. It is worth noting that AI-based optimisation of lipid-nanoparticles

formulations to address parenteral and gene delivery based biomedical uses have shown to be highly beneficial in speeding up clinical translation as well as meeting high regulatory and quality standards [93]. The above developments highlight increasing industrial confidence in AI-assisted formulation strategies and their ability to revolutionize modern pharmaceutical manufacturing [94].

10. Future Perspectives

The integration of artificial intelligence with developed pharmaceutical technologies will have a significant impact on the future design, development, and production of lipid nanocarriers. Continued development of digitalization, automation, and personalized medicine is expected to keep accelerating innovation in pharmaceutics and make it more efficient, predictive, and patient-centered.

10.1 Pharmaceutical Analytics Digital Twins.

Digital twins, which can be described as a digital model of physical systems, are also being used more and more in the pharmaceutical development and production. In the framework of lipid nanocarrier formulation, digital twins can be used to simulate the impact of formulation composition and processing parameters on important quality attributes in real time [95]. This allows predictive process control, quick troubleshooting, and proactive risk mitigation and, therefore, lessens the need to utilize extensive physical experimentation [96]. Also, digital twins enable virtual scale-up research, which lies between laboratory-scale development and commercial production and enhances process knowledge and regulatory trust [97].

10.2 Autonomous Formulation Laboratories

Combination of artificial intelligence and robotics and high throughput experimental platforms is driving the development of autonomous formulation laboratories [98]. These self-optimising systems can design, execute and analyse formulation experiments with little human intervention and significantly fast track the development cycle. Autonomous laboratories can be used in lipid nanocarrier studies to quickly map multidimensional formulation spaces, discover the most effective formulations, and dynamically optimize formulation approaches, reducing the number of experiments and material use [99,100.]

10.3 Integration with Continuous Manufacturing

Continuous manufacturing is closely related to this concept, and both ideas should be combined in the project. Continuous manufacturing relates closely to the concept, and both notions need to be integrated in the project [101]. The concept of continuous manufacturing has become a new paradigm shift in pharmaceutical engineering that offers better process control, scalable production, or high product consistency. Optimization of lipid nanocarrier formulation and processing parameters with the use of artificial intelligence can be easily integrated into continuous manufacturing platforms, allowing real-time monitoring, adaptive control and automated quality assurance [102.] This convergence enables an easy scale-up process, maintains the same quality of the product and is compatible with real time release testing models, which eventually leads to effectiveness in manufacturing and compliance with regulations [103].

10.4. Individualized Lipid Nanomedicines.

Artificial intelligence demonstrates significant opportunities to create individual lipid nanomedicines based on patient-specific factors, such as genetic, disease, and pharmacokinetic heterogeneity [104]. Combining patient-related information with forecasting formulation algorithms, AI can be used to design personalized lipid nanocarriers to maximize therapeutic efficacy, safety and dosing regimens. Lipid nanomedicines which are patient-specific are thus a historic breakthrough in precision medicine, and an example of how AI can improve clinical outcomes by providing customized treatment plans [105,106].

11. Conclusion

AI has developed as an influential and revolutionary tool in the design, Optimisation and clinical translation of lipid nanocarriers. The AI-designed methods overcome the constraints of traditional trial-and-error methods and traditional Design of Experiments methods, because they enable effective exploration of multidimensional formulation and process design spaces. The forecasting of key quality features, rational choice of excipients and stability are all part of the effort to make development schedules more predictable and enhance the reproducibility of formulation.

Scalability, process knowledge and regulation further increase with the combination of AI and Quality by Design models and Process Analytical Technology and continuous manufacturing. Despite the problematic issues associated with data quality, the readability of models, and regulatory approval, the use of AI-driven lipid nanocarrier development is gaining momentum both in academia and industry.

It is expected that the emerging technologies such as digital twins, autonomous formulation laboratories, and tailored lipid nanomedicines will further transform the way pharmaceuticals are developed, allowing them to produce predictive and efficient formulation approaches, as well as patient-centric ones. Overall, AI-assisted design and optimisation of lipid nanocarriers represents a breakthrough in the pharmaceutical science domain that bridges the gap between the laboratory development and clinically translatable, scalable, and personalised therapeutic approaches and has a significant role in the development of precision medicine.

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