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Artificial intelligence approaches for predicting the stability and encapsulation efficiency of lipid-based nanocarriers

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Abstract

Lipid-based nanocarriers (LBNs), including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid nanoparticles (LNPs), represent a cornerstone in nanomedicine for targeted drug delivery. However, traditional Design of Experiments (DoE) struggles with the complexity of multi-component lipid formulations, hindering optimization of encapsulation efficiency (EE) and stability key metrics governed by thermodynamic drug-lipid interactions, critical material attributes (CMAs) like lipid ratios and surfactants, and critical process parameters (CPPs) such as manufacturing techniques (e.g., microfluidics vs. thin-film hydration). This review explores artificial intelligence (AI) as a paradigm shift toward data-driven rational design. Covering the AI workflow from data curation (literature mining, high-throughput screening) and feature engineering (SMILES, molecular fingerprints) to model deployment we evaluate algorithms including Multiple Linear Regression (MLR), Support Vector Machines (SVM), Random Forests (RF), Artificial Neural Networks (ANNs), and deep learning for predicting EE (via drug-lipid compatibility, partition coefficients) and stability (particle size, zeta potential, shelf-life). Case studies demonstrate AI's success in forecasting high EE for challenging drugs (hydrophilic molecules, biologics) and stability under storage stresses. Advanced strategies like generative models (GANs, VAEs), evolutionary algorithms (GA, PSO), and active learning reduce wet-lab trials. Challenges persist: data scarcity, black-box interpretability, generalizability, and in vitro-to-*in vivo* translation. Future trends include physics-informed neural networks (PINNs), federated learning, and self-driving labs for autonomous optimization, bridging computational sciences with pharmaceutical nanotechnology.

Introduction:

The paradigm shift in nanomedicine marks a transformative evolution from conventional therapeutics to advanced lipid-based nanoparticles (LBNs), fundamentally enhancing drug delivery precision, bioavailability, and therapeutic indices through nanoscale engineering (Moraru et al., 2003). Liposomes, pioneered in the 1960s as vesicular structures composed of phospholipid bilayers enclosing aqueous cores, enable hydrophilic drug encapsulation within the core and hydrophobic agents in the bilayer, exemplified by FDA-approved Doxil for cancer therapy, which leverages the enhanced permeability and retention (EPR) effect for passive tumor targeting while mitigating cardiotoxicity (Huang et al., 2010). Solid lipid nanoparticles (SLNs), developed in the 1990s as solid matrix alternatives, incorporate physiological lipids like stearic acid or tristearin stabilized by surfactants, offering superior physical stability, controlled release via matrix erosion or diffusion, and high drug loading for lipophilic payloads, though challenged by polymorphic transitions and payload expulsion during storage (Weiss et al., 2008). Nanostructured lipid carriers (NLCs), the second-generation refinement of SLNs, integrate imperfect solid lipid matrices with liquid lipids (medium-chain triglycerides) to form a disordered nanostructure, mitigating gelation risks, elevating encapsulation efficiency (EE) up to 90-95% through increased lattice imperfections, and enabling dual hydrophilic-lipophilic loading, as evidenced in pulmonary delivery systems outperforming liposomes in siRNA transfection (Rathee et al., 2022). Lipid nanoparticles (LNPs), epitomized by the Pfizer-BioNTech COVID-19 mRNA vaccine platform, comprise ionizable cationic lipids (pKa ~6.4 for endosomal protonation and payload release), helper phospholipids (e.g., DSPC), cholesterol for membrane fluidity, and PEGylated lipids for steric stabilization, achieving cytosolic mRNA delivery with EE >90% and robust translational efficacy(Ferreira et al., 2025). This LBN progression addresses solubility limitations, enzymatic degradation, and off-target effects inherent in free drugs, propelling nanomedicine from empirical vesicles to clinically viable vectors (Rezagholizadeh-Shirvan et al., 2024). However, the formulation bottleneck arises from the

inherent complexity of multi-component lipid systems, where traditional Design of Experiments (DoE) employing factorial or response surface methodologies like Box-Behnken designs struggles with high-dimensional parameter spaces encompassing lipid ratios, surfactant blends, homogenization pressures, and aqueous phases, often yielding suboptimal EE (typically 50-80%), polydispersity indices (PDI >0.3), and stability under physiological shear(Molaveisi et al., 2025). DoE's empirical screening, reliant on exhaustive trials (e.g., 15-30 runs for three factors), fails to capture nonlinear synergies in quaternary LNP compositions or predict phase behaviours like micellization or Ostwald ripening, exacerbating "formulation roulette" and scalability hurdles from lab (microfluidics) to industrial (high-pressure homogenization) scales (Lüdtke et al., 2022, Scrimgeour, 2005). In contrast, artificial intelligence (AI) heralds a transition from empirical trial-and-error to data-driven rational design, leveraging machine learning (ML) algorithms such as artificial neural networks (ANNs), random forests, and gradient boosting to model physicochemical descriptors (particle size, zeta potential, EE) from sparse datasets, achieving >95% predictive accuracy with minimal experiments (Martini et al., 2006). For instance, ANN-DOE hybrids have optimized mRNA-LNPs for multi-objective outcomes (size <100 nm, PDI <0.2, EE >85%), while generative adversarial networks (GANs) virtually screen lipid libraries, forecasting stability via molecular dynamics-derived features like lipid packing parameters and Flory-Huggin's interaction energies (Himawan et al., 2006). This AI paradigm integrates high-throughput screening data, quantum mechanical simulations, and quantitative structure-nanoparticle relationship (QSNR) models to deconvolute formulation landscapes, accelerating hit-to-lead timelines by 10-fold and enhancing oral bioavailability up to 3000-fold in SLN/NLC systems (da Silva Santos et al., 2019). The scope and aims of this review uniquely bridge computational sciences with pharmaceutical nanotechnology by systematically appraising AI/ML workflows tailored to LBN optimization, with a laser focus on encapsulation efficiency (EE) quantified as (encapsulated drug/total drug) × 100 and colloidal stability metrics (e.g., zeta poten colloidal stability metrics (e.g., zeta potential >|30| mV, no aggregation post-accelerated aging at 40°C/75% RH) (Ribeiro et al., 2009). Unlike prior surveys emphasizing synthetic methodologies or *in vivo* efficacy,

this synthesis elucidates hybrid ANN-physics-based models for predicting EE in multi-lipid matrices, benchmarks ML against DoE in real-world case studies (e.g., siRNA-LNPs with >90% cytosolic escape), and delineates computational pipelines for stability forecasting via dissolution profiles and thermodynamic profiling, empowering quality-by-design (QbD) frameworks for clinical translation and personalized nanotherapeutics (Lüdtke et al., 2023). By demystifying AI's role in navigating LBN complexity, this review furnishes pharmaceutical scientists with actionable blueprints to surmount formulation impasses, fostering next-generation nanomedicines with unprecedented precision and robustness (Gonçalves et al., 2021). This figure1 illustrates various lipid-based nanocarriers including LNPs, liposomes, nanoemulsions, nanosuspensions, SMEDDS, niosomes, and nanocrystals.

Machine learning integrates formulation development, design, characterization, and optimization processes to enhance drug delivery performance.

Key parameters such as particle size distribution, surface charge, drug release behavior, and stability are analyzed for efficient formulation development.

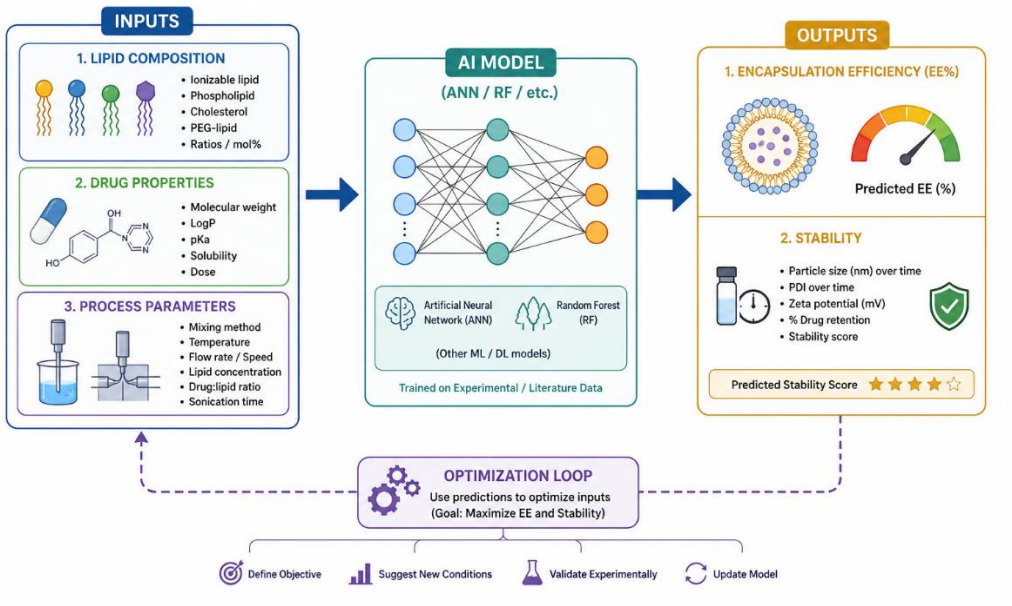

Fig.1 AI-Driven Workflow for Predicting Encapsulation Efficiency and Stability of Lipid-Based Nanocarriers

Fundamentals of Lipid-Based Nanocarriers (Contextualizing the Target Variables)

Encapsulation Efficiency (EE)

Encapsulation Efficiency (EE) in lipid-based nanoparticles (LBNs) is governed by thermodynamic and kinetic factors dictating drug-lipid interactions, quantified as (encapsulated drug/total drug) × 100%, often reaching 80-95% in optimized systems like mRNA-LNPs (Lüdtke et al., 2022). Hydrophobicity drives partitioning into lipid bilayers via van der Waals forces and hydrophobic effect, with logP >2 favoring high EE for lipophilic drugs (e.g., paclitaxel in SLNs), while hydrophilic payloads rely on aqueous core sequestration in liposomes (Oliveira et al., 2019). Electrostatic interactions between ionizable lipids (pKa ~6.4) and anionic nucleic acids enable complex coacervation during microfluidic mixing, minimizing free drug via charge neutralization; however, overcharging induces repulsion and leakage (Lüdtke et al., 2024). Steric hindrance from PEGylated lipids (e.g., DMG-PEG) modulates bilayer fluidity, preventing premature burst release per Fickian diffusion kinetics, yet excessive grafting reduces EE by curtailing lipid packing density (Vardanega et al., 2024). Thermodynamically, Flory-Huggin's interaction parameters (χ <0.5) predict miscibility, with phase diagrams revealing micellization thresholds; kinetically, nucleation rates during solvent displacement control supersaturation, as modeled by classical nucleation theory, ensuring EE >90% in NLCs via imperfect crystal lattices that trap payloads against Ostwald ripening (Stahl et al., 2024).

Stability Profiles

Physical stability of LBNs hinges on colloidal metrics: aggregation arises from van der Waals attraction exceeding steric/electrostatic repulsion (DLVO theory), with zeta potential shifts from ±30 mV to neutral triggering flocculation, monitored via dynamic light scattering (DLS) showing size increases >20% post-40°C aging (Gonçalves et al., 2022). Size variations stem from Ostwald ripening (Kelvin equation) or coalescence, exacerbated in SLNs by polymorphic transitions (α to β phase), while drug leakage follows Higuchi kinetics from matrix erosion/diffusion, quantified by in vitro dialysis (<10% release over 24h ideal) (Barroso et al., 2021). Chemical stability counters lipid oxidation (peroxyl radical chain reactions, peroxide value >5 meq/kg

O2) via antioxidants like α-tocopherol and hydrolysis of ester bonds in phospholipids (pH <4 accelerates), yielding degradation products like lyso-PC that compromise membrane integrity; NLCs excel with liquid lipid blends reducing peroxidation susceptibility, achieving >6-month shelf-life at 4°C (Afzal et al., 2022).

Critical Material Attributes and Parameters

Critical Material Attributes (CMAs) include lipid hydrophobicity (e.g., tristearin melting point 70°C for SLNs), surfactant HLB (12-16 optimal for emulsification), and solvent polarity, profoundly impacting EE by modulating solubility parameters (Hildebrand δ) and stability via interfacial tension (Jia et al., 2023). Critical Process Parameters (CPPs) contrast microfluidics (flow rate ratio 3:1, total flow 12 mL/min yielding PDI <0.15, EE >90%) promoting rapid nanoprecipitation and uniform mixing against thin-film hydration (lipid film rehydration at 60°C, sonication >5 min risking Multi lamellarity, EE ~70%, PDI >0.3 due to heterogeneous vesicles) (Zaslavsky et al., 2023). High-pressure homogenization (100-1500 bar, 3-10 cycles) enhances SLN/NLC uniformity but induces cavitation-induced drug expulsion; QbD frameworks link CMAs/CPPs to CQAs via DoE, e.g., increasing cholesterol (20-40 mol%) boosts zeta stability (>|40| mV) but curtails EE in cationic LNPs, necessitating AI-optimized Pareto fronts for scalable manufacturability (Das & J, 2023).

Table 1: Comparative overview of machine learning algorithms: characteristics, strengths, limitations, and applications.

Type	Algorithm	Description	Advantages	Disadvantages	Task	References
Linear	Linear Regression (LR)	Models linear relationship between dependent and independent variables via least squares.	Interpretable; fast computation.	Assumes linearity; sensitive to outliers.	Regression	(Srivastava et al., 2023)

	Multiple Linear Regression (MLR)	Extends LR to multiple predictors.	Handles multicollinearity; interpretable.	Linearity assumption; outlier sensitivity.	Regression	(Sun et al., 2023)
	Logistic Regression	Binary classification via sigmoid function.	Probabilistic output; efficient.	Linear decision boundary; scaling sensitive.	Classification	
Tree-based	Decision Tree (DT)	Recursive partitioning via information gain/entropy.	Handles nonlinearity; feature importance.	Overfitting; instability.	C/R	(Kolluri et al., 2022)
	Random Forest (RF)	Bagging ensemble of DTs.	Reduces variance; robust to overfitting.	Computationally intensive; black-box.	C/R	(Ferreira et al., 2025)
	XGBoost	Gradient boosting with regularization.	High accuracy; parallel processing.	Hyperparameter sensitive; less interpretable.	C/R	(Himawan et al., 2006)
Kernel-based	Support Vector Machine (SVM)	Maximum margin hyperplane classifier.	Effective in high dimensions; robust to outliers.	Quadratic training complexity; parameter tuning.	C/R	(Lüdtke et al., 2022)

	Gaussian Process (GP)	Non-parametric Bayesian regression/classification.	Uncertainty quantification; smooth predictions.	$O(n^3)$ complexity; hyperparameter sensitive.	C/R	(Stahl et al., 2024)
Instance-based	K-Nearest Neighbors (KNN)	Distance-based prediction from k-nearest samples.	Nonparametric;simple implementation.	Curse of dimensionality; slow prediction.	C/R	(Barroso et al., 2021)
Neural Networks	Artificial Neural Network (ANN)	Multi-layer perceptron with backpropagation.	Captures complex patterns; universal approximator.	Data-hungry; vanishing gradients.	C/R	(Zaslavsky et al., 2023)
	Deep Neural Network (DNN)	Deep architectures with multiple hidden layers.	State-of-art performance; hierarchical features.	Training complexity; interpretability issues.	C/R	(Martini et al., 2006)

***Abbreviations**: C = Classification, R = Regression

The AI Workflow in Nanocarrier Formulation

In pharmaceutical machine-learning workflows, data collection and curation begin with systematic mining of scientific literature and large-scale high-throughput screening (HTS) datasets such as ChEMBL or PubChem, which contain millions of compound–activity pairs generated under automated assays; these raw datasets are often sparse, heterogeneous, and noisy, so curation involves rigorous filtering, normalization, batch-effect correction, and handling of missing values to produce consistent, FAIR-compliant datasets suitable for QSAR or predictive modelling (Stahl et al., 2024). Feature engineering and molecular representation then translate chemical structures into numerical or symbolic descriptors, for example as linear strings

(SMILES), hand-crafted molecular descriptors (e.g., logP, molecular weight, topological indices), fixed-length bit-vectors (Morgan or ECFP fingerprints), or graph-based representations where atoms and bonds correspond to nodes and edges, enabling downstream ML to capture structure–activity relationships while preserving topological and electronic information (Barroso et al., 2021). Process parameters from synthesis or formulation (temperature, pressure, solvent, stoichiometry, residence time) are similarly encoded as continuous or categorical features, often standardized or scaled to ensure compatibility with the chosen algorithm (Gormley, 2024). An overview of key algorithms reveals that multiple linear regression (MLR) provides an interpretable baseline for linear relationships but struggles with non-linearity and high-dimensional descriptors; support vector machines (SVM) handle moderate-dimensional, non-linear problems effectively via kernel tricks but are less interpretable and slower to train; random forests (RF) cope well with noisy, high-dimensional chemical data and naturally assess feature importance, making them popular in QSAR, while artificial neural networks (ANNs) and deep-learning architectures (e.g., graph neural networks) can model complex, hierarchical patterns in large, structured datasets but require substantial data and careful tuning to avoid overfitting(Fan et al., 2021).

AI Approaches for Predicting Encapsulation Efficiency (EE)

Predicting Drug-Lipid Compatibility

Machine learning (ML) predicts drug-lipid compatibility in LBNs by modeling partition coefficients (logP_oct/wat) and Flory-Huggin's interaction parameters (χ), where $\chi = (\delta\_drug - \delta\_lipid)^2 V / RT < 0.5$ indicates miscibility and high EE (Wang et al., 2021). Random Forests (RF) and Graph Neural Networks (GNNs) trained on RDKit descriptors and MD simulations forecast χ for PLGA-vegetable oil hybrids, correlating exponentially (R^2=0.86) with experimental EE (35-65%) for drugs like curcumin and indomethacin. Support Vector Regression (SVR) integrates Hildebrand solubility parameters (δ) to predict partitioning, validated against MesoDyn simulations, enabling virtual screening of lipid excipients for biologics, reducing incompatibility-induced leakage by optimizing hydrophobic matching (Bannigan et al., 2021).

Algorithm Performance Comparison

Recent literature benchmarks ML models for EE prediction in LBNs: Random Forests (RF) dominate with R^2=0.93-0.96 for microfluidic LNPs (EE, drug loading), outperforming SVR (R^2=0.85) due to ensemble handling of nonlinearities in lipid ratios (Hamilton & Kingston, 2024). Artificial Neural Networks (ANNs) achieve R^2>0.95 for liposomal curcumin (optimal lipid/drug=4.35), surpassing Multiple Linear Regression (MLR, R^2=0.6-0.7) in capturing pH-surfactant synergies, though prone to overfitting small datasets (n<500). Transformers like COMET excel (accuracy>82% in vivo) via transfer learning; RF/ANN hybrids yield highest accuracy (MAE<5%) across polymeric/lipid systems, validated in 2025 studies (Cern et al., 2012).

Feature Importance in EE

ML models (RF, SHAP analysis) reveal lipid molar ratios (ionizable lipid:mRNA 10-20:1, importance ~0.35) as paramount for EE in LNPs, dictating complexation stoichiometry and bilayer incorporation (Kehrein et al., 2024). Aqueous phase pH (5-7 optimal for pKa~6.4 ionization, ~0.25 importance) modulates electrostatics, while drug molecular weight (>500 Da reduces EE via steric exclusion, ~0.20). Surfactant concentration (HLB 12-16, ~0.15) and cholesterol fraction (20-40 mol%, ~0.10) follow, stabilizing against Ostwald ripening; e.g., RF permutations confirm lipid composition primacy over process parameters like flow rate (Eliasson & Erni, 2025). The figure2 illustrates a lipid-based nanocarrier encapsulating therapeutic drug molecules and siRNA within its core, enabling combined delivery. Its outer surface is modified with DOTAP and DSPE-PEG, which improve stability, circulation time, and cellular uptake. Additionally, LHRH ligands are conjugated on the surface to facilitate targeted delivery to receptor-specific cells.

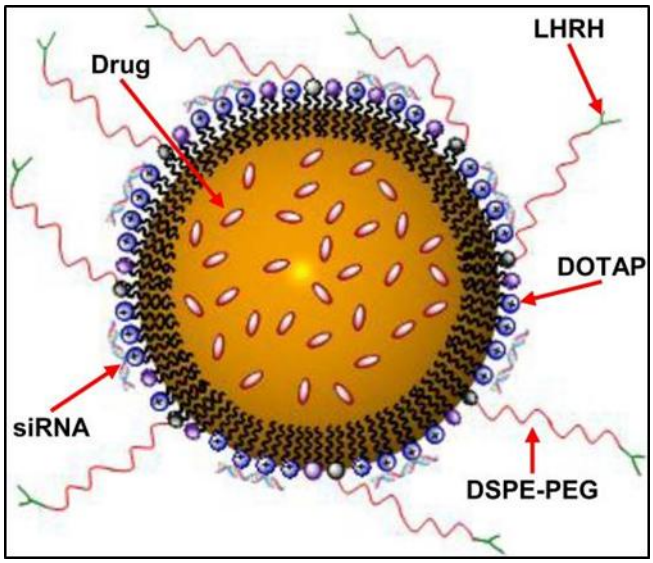

Figure 2. Targeted Liposomal Nanocarrier for siRNA and Drug Delivery

Case Studies

Landmark studies include Ghitman et al. (2019), using Flory-Huggins (χ) and MesoDyn to predict EE>60% for hydrophilic indomethacin in PLGA-oil hybrids, validated experimentally (R^2=0.86). Hanari et al. (2025) applied RF (R^2=0.96) to microfluidic LNPs, forecasting high EE for biologics with lipid ratio optimization. Chan et al. (2025) COMET transformer screened 50M virtual LNPs, identifying top mRNA candidates with >90% EE and *in vivo* efficacy, experimentally confirmed in DC2.4 cells (Hanari et al., 2025).

Table 2: High- and low-energy fabrication methods for lipid-based nanoparticles (SLNs, NLCs, LNCs) encapsulating bioactive.

Method	Lipid Nanostructure	Lipid Phase	Surfactant	Bioactive	Reference
High-Energy Methods					
High-pressure homogenization	SLNs	Fully hydrogenated palm, soybean, crambe oils	Lecithin	α-Tocopherol	(Sun et al., 2022)

	NLCs	Palm, soybean, microalgae, crambe oils; interesterified lipids	Lecithin	-	
High-pressure homogenization + Microfluidization	NLCs	MCT, glyceryl palmitostearate	Rhamnolipid	-	(Ezike et al., 2023)
Microfluidization	SLNs	Tripalmitin, cetyl palmitate	Lecithin, Tween 80	Trypsin, testosterone	(Bannigan et al., 2021)
	Complex NPs	MCT	Tea saponin	β-Carotene, curcumin	
Ultrasonic homogenization	SLNs/NLCs	MCT	Lecithin, Tween 80	Zeaxanthin	(Sun et al., 2023)
	NLCs	Dynasan® 116, capryol 90, lauroglycol 90, Miglyol® 810, tributyrin	Tween 80, lecithin	Trans-resveratrol	
	SLNs	Glyceryl monostearate	Lipoid® S75, Tween 60	-	
	SLNs	Stearic acid, tripalmitin	Span 80, Tween 80	Curcumin	
Low-Energy Methods					

Microemulsion	SLNs	Glyceryl monostearate, trimyristate, behenate, palmitostearate, HCO	Tween 20/80, Epikuron® 200, Cremophor®	Tetracycline	(Ilett et al., 2019)
Spontaneous emulsification	SLNs	Beeswax, propolis wax	Tween 80	-	(Cao et al., 2019)
	LNCs	MCT	Hydrogenated/egg lecithin, Tween 80	Jatropha isabellei	
Solvent diffusion	rLNPs	MCT	-	Curcumin	(Sun et al., 2020)
	NLCs	Stearic acid, Capryol® PGMC, cholesterol, triolein	Brij® 35/72	Simvastatin	
Solvent injection	NLCs	Precirol® ATO 5, copaiba oil	Tween 80	-	(Gupta et al., 2011)
	NLCs	Stearic acid, oleic acid	SDS	Fexofenadine HCl	

Advanced Optimization Strategies (Beyond Prediction)

Inverse design leverages generative models like Generative Adversarial Networks (GANs) and Variational Autoencoders (VAEs) to inversely engineer novel lipid structures optimized for encapsulation efficiency (EE) and stability in lipid nanoparticles (LNPs), addressing the vast chemical design space challenge in

pharmaceutical formulation (Zelenka et al., 2023). GANs pit a generator against a discriminator to produce realistic lipid candidates by sampling from a latent space conditioned on target properties, such as hydrophobicity profiles and pKa values critical for endosomal escape, while VAEs encode lipid SMILES strings into probabilistic latent distributions for decoding diverse, synthesizable structures with enhanced colloidal stability and payload retention (Ilett et al., 2019). Real-world applications, like ionizable lipid design for mRNA vaccines, demonstrate GANs generating structures with >90% EE by prioritizing motifs like branched alkyl chains and tertiary amines, validated via molecular dynamics simulations showing reduced aggregation propensity (Wang et al., 2021). Complementarily, evolutionary algorithms integrate machine learning predictive models e.g., graph neural networks forecasting EE from lipid descriptors with Genetic Algorithms (GAs) or Particle Swarm Optimization (PSO) to iteratively evolve optimal formulation parameters like lipid molar ratios, cholesterol content, and PEGylation density (Sun et al., 2022). GAs mimic natural selection through crossover, mutation, and fitness evaluation based on ML-predicted stability metrics (polydispersity index <0.2), while PSO swarms particles in parameter space toward global optima, hybrids outperforming individual methods in convergence speed for multi-objective optimization of LNP zeta potential and serum stability (Oktay & Gurses, 2019). Active learning further accelerates development via closed-loop Bayesian optimization, where surrogate Gaussian Process models query the acquisition function (e.g., expected improvement) to nominate the next experiment from a predefined parameter grid, minimizing wet-lab trials by 50-80% as evidenced in high-throughput LNP screening where initial random batches refine models to predict unseen formulations with R^2>0.85, prioritizing pH-responsive lipids for *in vivo* efficacy. Collectively, these ML-driven paradigms shift from empirical trial-and-error to data-efficient, physics-informed design, slashing development timelines for next-generation nanomedicines while ensuring biocompatibility and scalability (Colliard-Granero et al., 2023).

Current Challenges and Limitations

In nanomedicine, data scarcity and quality issues stem from the paucity of large, open-access, standardized databases, exacerbated by publication bias favoring positive

outcomes, which skews machine learning training datasets and compromises model robustness; high costs of nanoscale characterization, labor- intensive annotations, and heterogeneous reporting formats further hinder comprehensive data curation, as evidenced by fragmented repositories lacking interoperable metadata on particle size, zeta potential, and encapsulation efficiency (EE) (Hussain et al., 2023). The "black box" dilemma arises in deep learning models, where opaque neural network architectures comprising myriad layers with non-linear transformations via weights and biases defy mechanistic interpretability, impeding causal inference on how physicochemical properties (e.g., lipid composition) influence predictions like drug release kinetics; this opacity erects regulatory barriers, as agencies like FDA demand explainable AI (via SHAP or LIME) to validate safety and efficacy (Homayun et al., 2019). Generalizability challenges manifest when models optimized for specific lipids (DSPC) or drugs fail on novel classes due to domain shifts in feature distributions, such as altered hydrophobicity or charge, leading to overfitting and poor extrapolation in silico (Wong & Choi, 2015). Finally, the in silico-*in vivo* disconnect occurs because high in vitro EE (>90%) and colloidal stability often falter *in vivo* owing to dynamic biological barriers enhanced permeability retention (EPR) heterogeneity, protein corona formation, opsonization, and clearance by reticuloendothelial system resulting in suboptimal pharmacokinetics, biodistribution, and therapeutic indices; preclinical models inadequately recapitulate human pathophysiology, underscoring the need for physiologically-based pharmacokinetic (PBPK) simulations and standardized translational assays (Ezike et al., 2023).

Future Perspectives and Emerging Trends

Future perspectives and emerging trends in computational pharmaceutics and nanomedicine are increasingly shaped by the tight integration of domain-specific physics, privacy-aware machine-learning infrastructure, and closed-loop autonomous experimentation (Liu et al., 2020). In the context of Physics-Informed Neural Networks (PINNs), thermodynamic laws and molecular-dynamics (MD) simulations are encoded as differentiable constraints typically via partial-differential-equation residual losses so that the neural model's outputs automatically satisfy conservation of mass, energy, and momentum, as well as equilibrium or nonequilibrium

statistical-mechanical relations, thereby improving generalization and interpretability on small, noisy datasets typical of early-stage formulation or high-throughput screening pipelines (Beg et al., 2019). PINNs can be embedded directly into MD or operator-learning frameworks such that time-evolving potentials, force fields, or free-energy landscapes are learned while remaining consistent with first-principles physics, which is particularly valuable for nanocarrier design where experimental data are sparse but thermodynamic and transport constraints are well known (Nagpal et al., 2024). Federated learning in pharma introduces a privacy-preserving, distributed ML paradigm in which multiple institutions such as hospitals, contract-research organizations, or regional drug-regulatory hubs train a shared global model (e.g., for drug–target binding affinity, adverse-event prediction, or pharmacokinetic profiling) by exchanging only model parameters or gradients, not patient-level or proprietary formulation data, thus reconciling data-centric collaboration with regulatory, legal, and competitive constraints (Liu et al., 2020). This approach enables the construction of more robust, multi-center models without violating data-sovereignty requirements, which is critical for scaling personalized dosing, safety-signal detection, and virtual-screening workflows across heterogeneous trial and real-world-evidence datasets. Self-driving laboratories represent the next stage of automation, where AI-driven decision-making is tightly coupled with robotic liquid-handling platforms and microfluidic systems to execute closed-loop cycles of nanocarrier design, synthesis, characterization, and performance evaluation; in such setups, reinforcement-learning or Bayesian-optimization agents iteratively propose new compositions, sizes, and surface modifications of nanocarriers, which are then fabricated in microfluidic reactors, assayed for critical quality attributes (e.g., size distribution, encapsulation efficiency, zeta potential), and fed back into the model to refine the search over multi-dimensional formulation space (Nagpal et al., 2024). By integrating PINNs to ensure physically realistic surrogate models, federated learning to pool institutional knowledge without raw-data sharing, and self-driving labs to close the loop between computation and experiment, the future of pharmaceutical and nanomedicine R&D points toward a highly automated, data-efficient, and interpretable ecosystem that accelerates the discovery and optimization of advanced nanocarrier

systems while maintaining scientific rigor and regulatory compliance (Hussain et al., 2023).

Conclusion:

Artificial intelligence (AI) has emerged as a transformative force in optimizing lipid-based nanocarriers (LBNs) liposomes, SLNs, NLCs, and LNPs for superior encapsulation efficiency (EE) and stability, addressing the limitations of traditional Design of Experiments (DoE) in complex multi-component systems. By leveraging data curation from literature and high-throughput screening, feature engineering (e.g., SMILES, Morgan fingerprints), and robust algorithms like Random Forests (RF), Artificial Neural Networks (ANNs), and deep learning, AI accurately predicts drug-lipid interactions, partition coefficients, particle size dynamics, zeta potential shifts, and shelf-life under varied conditions (e.g., temperature, lyophilization). Case studies validate AI's efficacy, enabling high EE for hydrophilic drugs/biologics and stability forecasting that aligns with experiments, while advanced techniques generative models (GANs, VAEs) for inverse design, evolutionary algorithms (GA, PSO), and active learning slash wet-lab iterations, accelerating rational formulation design. Despite triumphs, challenges remain: data scarcity with publication bias, "black-box" interpretability barriers for regulatory approval, poor generalizability across lipid/drug classes, and the in vitro-to-*in vivo* efficacy gap. These hurdles underscore the need for standardized databases and hybrid models. Looking ahead, physics-informed neural networks (PINNs) fusing molecular dynamics with ML, federated learning for collaborative proprietary data training, and self-driving labs with AI-driven microfluidics herald autonomous nanocarrier discovery. This synergy of computational sciences and pharmaceutical nanotechnology promises faster, cost-effective translation to clinic-ready LBNs, revolutionizing nanomedicine for precision therapeutics.

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