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Review Article

Liposomes: Bridging the Gap from Lab to Pharmaceutical

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ABSTRACT

Background: Liposomes are highly adaptable and advanced drug delivery systems, capable of encapsulating both hydrophilic and lipophilic drugs, which enhance drug stability, solubility, and targeted delivery. Recent advancements in liposome technology have focused on integrating computational modeling, machine learning, and systems biology to optimize formulations for precision medicine. Main Body of the Abstract: This review highlights the critical parameters influencing liposome behavior, such as lipid composition, encapsulation efficiency, and release kinetics. Sensitivity analysis using tools like PK Solver and Dissolver is discussed to optimize these parameters. The review also explores cutting-edge trends in smart liposomes, including stimuli-responsive and biohybrid liposomes, for their potential in targeted drug delivery applications. The importance of interdisciplinary collaboration, integrating bioinformatics, nanotechnology, and chemistry, is emphasized for advancing liposomal technologies, with applications in personalized medicine, gene editing, and cancer immunotherapy. Through innovative computational techniques and novel formulation strategies, liposomes are revolutionizing drug delivery, particularly in treating complex diseases like cancer. Short Conclusion: Advances in liposome technology, driven by computational modeling and interdisciplinary collaboration, are transforming drug delivery systems. These innovations offer significant potential for treating complex diseases, with future applications in personalized medicine and targeted therapies.

INTRODUCTION

Liposomes are phospholipid bilayer spherical vesicles that contain an aqueous core. It can encapsulate both hydrophilic and hydrophobic drugs to protect them from degradation and to achieve target action with improved drug solubility, enhanced stability, reduced side effects, sustained drug release, and biocompatibility. The development and optimization of liposomal drug formulations remain difficult. The lipid bilayer composition, method of preparation, drug loading, and other factors can affect the physicochemical

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properties, drug release kinetics, and in vivo performance of liposomes. To identify these challenges, sensitivity analysis makes it difficult to understand how variations in formulation and process parameters influence the performance of liposomal drug delivery systems. Sensitivity analysis involves systematically changing one or more input parameters while other parameters are kept constant, to determine the impact on the output variables. By implementing sensitivity analysis, researchers can identify the critical parameters that influence liposome characteristics such as size, zeta potential, encapsulation efficiency, and drug release profile. With this analysis, researchers optimize the formulation and manufacturing process to achieve the desired liposome properties and drug delivery performance [1,2]. Optimizing formulation stability is difficult as liposomes are sensitive to temperature, pH, and ionic strength, impacting their stability and drug release profiles. High encapsulation efficiency for both hydrophilic and hydrophobic drugs is a difficult process and lipid composition, preparation methods, and stabilizers can be influenced. Technology transfer from laboratory to industrial scale faces issues with reproducibility and quality assurance. Adding surface modifications or targeting ligands affects formulations, increasing manufacturing costs and regulatory problems. Biological barriers like cellular uptake and tissue penetration that depend on their physicochemical properties can be overcome by liposomes. Sensitivity analysis helps in understanding liposome behavior by finding critical formulation parameters, and targeted optimization, with predictive models. Key factors in liposome stability include lipid composition, preparation methods, environmental conditions, and storage conditions, all of which affect membrane integrity, size uniformity, and overall stability [3,4].

Table 1: Preparation of liposomes by different method and their characteristics

Method	Conditions of Use	Efficacy	Formulation Benefits	Example Formulation	Key Findings	reference
Thin-Film Hydration + Extrusion	Organic solvent evaporation, hydration, extrusion	High drug loading, uniform size	High reproducibility, dual drug loading, narrow size distribution	Everolimus-loaded liposomes, dual drug-loaded liposomes with resveratrol and 5-fluorouracil	High encapsulation efficiency and homogeneous size distribution	[5]
Reverse Phase Evaporation	Emulsification of organic solvent and aqueous phase	High encapsulation for hydrophilic drugs	Simple, quick, good-size distribution	Hydrophilic drug formulations	Achieved high drug loading and encapsulation efficiency	[5]
Ethanol Injection	Rapid injection of ethanolic lipid solution	Variable drug loading efficiency	Avoids high shear, suitable for both drug types	Various therapeutic agents	Demonstrated versatility in preparing liposomes	[5,6]

Sonication	Ultrasonic disruption of MLVs	Low encapsulation efficiency	Quick, easy, but less suitable for large-scale production	Large Size particles used to reduce size distribution	Size reduction of liposomes	[6]
Supercritical Fluid Techniques	Use of supercritical fluids	High drug loading, narrow size	Environmentally friendly, scalable	Hydrophilic drug formulations	High encapsulation efficiency and environmentally friendly	[5,6]
Dual Asymmetric Centrifugation	Centrifugation with unique rotation	High entrapment efficiency	Small, uniform liposomes, no solvents required	Consistent size and drug-loading liposomes	High reproducibility and scalability, effective for water-soluble drugs	[5,6]

Biological Approach of Liposomes

Liposomes grow into sophisticated systems with complex connections within biological networks, going beyond simple delivery vehicles. Using a systems biology approach to analyze liposomes reveals their significant impacts on a range of biological constituents. Liposomes interact with immune cells, proteins, and lipoproteins that enter the body, which may significantly alter the pharmacokinetics and biodistribution. They can be opsonized, signifying that plasma proteins mark them so macrophages and dendritic cells can take them up and faster clearance with less effective treatment. Drug release and cellular uptake can be affected by liposomes that fuse with or internalize cell membranes, altering the fluidity and membrane permeability. Liposomes have distinct metabolic pathways, which influence overall drug exposure and interactions with the metabolic network. This enables liposomes to modify signaling pathways, which affects downstream gene expression and cellular functioning. Formulation development is facilitated by *in-silico*modeling, which makes it easier to simulate interactions and predicts in vivo performance [1]. Phospholipids are essential for liposome stability. While unsaturated phospholipids like DOPC enhance fluidity and drug release profiles, saturated phospholipids like DSPC and HSPC provide membrane rigidity and stability. By reducing membrane permeability and enhancing resistance to deformation, cholesterol also helps to maintain stability by controlling drug leakage before it happens. The attachment of polyethylene glycol chains, or PEGylation, provides a hydrophilic barrier that reduces interactions with blood constituents and extends the blood circulate duration. Targeted drug delivery using liposomes can maximize efficacy and reduce systemic exposure. Because tumors exhibit leaky vasculature and poor lymphatic drainage, passive targeting makes use of the increased permeability and retention (EPR) effect to allow liposomes to accumulate in the tumors. Using ligands or antibodies to bind specific receptors or antigens on targeted cells is known as active targeting. Lipids specific to certain organs, which those organs detect or process, can improve customized delivery [7]. Liposomes influence variation, prolong circulation times, and regulate release profiles in medication pharmacokinetics.

Biodistribution can be altered by modifying surface, charge, and size properties, enabling enhanced delivery to certain tissues like tumors. Longer circulation results from PEGylation or plasma protein coating, which helps avoid immune recognition. By lowering toxicity and sustaining effective drug levels throughout time, customized lipid composition improves the therapeutic index by controlled drug release [1,7]. Combination therapy with liposomes co-deliver multiple substances to target tumor cells and the immune system, and stimuli-responsive liposomes, release drugs in response to signals like pH or temperature. Additionally, liposomes can target various pathways and improve absorption in cancer cells by incorporating various ligands, such as folate and transferrin. The liposome formulation optimization is assisted by computational modeling, like molecular dynamics simulations and predictive models to predict the influence of changes in lipid content or surface modifications on stability and interactions with biological membranes [1,7].

Explore Liposomes in Precision Medicine

Liposomal formulations can be modified for the specific genetic and molecular properties of a patient's tumor through genetic and molecular studies. Effective treatments with fewer adverse reactions are made feasible by using liposome engineering to deliver medications that specifically target mutations or overexpressed receptors in cancer cells. Targeting the overexpressed HER2 receptor in some subtypes of breast cancer could be done with modified liposomes. Therapeutic efficacy can be improved by improving trastuzumab delivery to tumor cells through the encapsulation of the drug within HER2-targeted liposomes [8]. Functionalizing liposome surfaces with ligands that attach to target cell receptors or proteins. Treatment results are improved by active targeting, which increases liposome accumulation at target action. For example, folate-modified cationic liposomes can target folate receptors specifically, those that overexpressed in cancer. By using this strategy to improve the anticancer medications that target tumor cells with better efficacy [9]. Liposomal co-deliver with therapeutic drugs for distinct targets for their pathways or modes of action. This multi-target strategy reduces the probability of resistance and improves treatment efficacy. For example, liposomes co-deliver siRNA that targets anti-apoptotic proteins in cancer cells with doxorubicin. This combination not only changes doxorubicin's cytotoxic effect but also makes treatment-resistant cancer cells more sensitive to it [10]. To improve the administration of immunotherapeutic drugs like checkpoint inhibitors and cancer vaccines, liposomes are used in cancer immunotherapy. Liposomes encoding antigens linked to tumors can act as vaccines to elicit an immune response against cancerous cells and also adding adjuvants to the liposomes may enhance the immune response substantially to improve clinical results [11]. Liposomes with carrier gene editing tools, such as CRISPR/Cas9 systems, to specific tissues or cells with specificity. For example, CRISPR/Cas9 components are delivered using liposomes for in vivo gene editing. Researchers may efficiently deliver these gene editing tools to specific tissues by altering the liposomes' surface, enabling customized gene therapies. Modifications in formulation, such as lipid composition, size, and surface charge, might impact drug delivery and therapeutic outcomes through the use of in silico modeling, which utilizes computational simulations to estimate the interactions between liposomes and biological systems. For example, molecular dynamics simulations can offer valuable insights into the stability and behavior of liposomes under

physiological conditions, guiding the design of formulations that optimize drug encapsulation and release profiles [12]. In identifying biomarkers for liposomal therapy responses, predictive models are necessary. Clinicians can successfully select individuals who benefit from particular liposomal formulations by establishing a relationship between treatment outcomes and genetic or molecular profiles. The effectiveness of liposomal drug delivery systems in cancer treatment can be estimated based on the expression of specific proteins by customizing strategies for each patient by incorporating biomarker data into predictive models [8-12]. Cationic liposomes with positive surface charge, improvegene delivery by facilitating electrostatic interactions with negatively charged cell membranes that increase uptake efficiency, encapsulate and protect nucleic acids, such as siRNA, from degradation in the bloodstream, and also cationic liposomes promote endosomal escape through the "proton sponge" effect, leading to the rupture of endosomal membranes and release contents into the cytoplasm [12].

Challenges In Genetically Controlling Liposome Membrane Synthesis

The expression of several enzymes and regulatory components within the liposome is required for the effective genetic control of membrane production in liposomes. The existing techniques frequently depend on complicated synthetic pathways, which makes it difficult to customize for sustainable lipid synthesis. Phospholipid-producing enzymes inside liposome compartments by using a synthetic minigenome. It is still difficult to produce multiple types of lipids, like phosphatidylethanolamine and phosphatidylglycerol, because accurate transcriptional regulation and metabolic feedback mechanisms are needed [7,13]. Efficiency may be affected by the low-yield lipids that are produced inside liposomes. For example, the yield of acyl-CoA conversion to phospholipids was approximately 40%, which wouldn't be adequate for large-scale applications. For genetically modified liposomes, their stability must be maintained. Proper development and formulation of liposomes is necessary, but it is difficult to achieve due to internal membrane manufacturing. For liposomes to function as synthetic cells, they must integrate various functional modules, such as DNA replication and membrane remodeling. Achieving this integration to maintain the stability and functionality of the liposomes is still challenging in the field of synthetic biology [13,14].

Focus On Advanced Computational Modelling & Machine Learning

Based on physicochemical properties such as size, surface charge, and lipid composition, machine-learning models can be created to predict the circulation time and biodistribution of liposomes. Research has demonstrated, for example, that artificial neural networks (ANNs) can reliably predict the stability and dispersity of liposome formulations derived from microfluidic synthesis parameters, with an accuracy of up to 93% in predicting formulation outcomes. Moreover, artificial intelligence can be used to predict the therapeutic efficacy of liposomes by modeling their interactions with biological targets. By combining data on target receptor expression and liposome composition, predictive models can determine the probability of obtaining desired therapeutic outcomes [15,16]. By determining the best combinations of formulation factors to increase performance, machine learning can be used to improve liposome formulations. The optimal lipid ratios and processing parameters for liposome formulations can be determined by data-driven formulation design analysis. For example,

depending on the physicochemical characteristics of the pharmaceuticals and the lipids, machine learning techniques are employed to estimate the drug loading efficiency in liposomes. Moreover, adaptive learning makes machine learning models possible that are used to quickly identify effective formulations and continuously refine predictions, which facilitates the development of customized liposomal therapies [17,18]. Liposome interactions with biomolecules can be predicted at the molecular level by using advanced computational models, such as coarse-grained modeling and molecular dynamics simulations. Using visual representations of liposome interactions with proteins, nucleic acids, and cell membranes, molecular dynamics simulations reveal the mechanisms underlying drug release and cellular absorption. For example, liposome production and stability have been investigated via coarse-grained molecular dynamics simulations, which have provided significant knowledge of lipid content and environmental factors. By predicting the results of interactions between liposomes and biomolecules, AI may enhance those simulations. The liposome formulation development that efficiently transfers genetic material or therapeutic compounds is made easier by machine learning algorithms that can assess the stability of liposome formulations based on their interactions with particular proteins or nucleic acids [17,18].

Personalized Drug Delivery Strategies

Customized liposomal medication delivery systems can be made possible by the combination of cutting-edge simulation techniques and machine learning. Predictive models can help with the liposome that is customized for individual patient features by investigating the genetic and molecular profile of a patient. To increase the effectiveness of the drug administered, liposomes can be designed, to target receptors that are overexpressed in a patient's tumor. Furthermore, machine learning models can adapt in real-time to liposome compositions and dosage approaches based on current information regarding patient reactions as treatment progresses. To maximize therapeutic benefits while preventing negative side effects, this dynamic adaptation is necessary [18].

Optimizing Liposome Formulations Using Machine Learning for Specific Diseases

Using machine learning (ML) to optimize liposome formulations with the design and effectiveness of liposomal drug delivery systems can be greatly improved by ML models via significant dataset analysis and the identification of patterns that affect liposome action. Previous information on liposome formulations, including their stability, physicochemical characteristics, and therapeutic results, can be analyzed by machine learning algorithms. ML models may predict liposome stability and encapsulation efficiency based on preparation techniques and lipid content. With this, identify the most effective formulations for cancer or genetic abnormalities, where targeted distribution is essential, due to this predictive capability [18]. By integrating patient-specific data, such as genetic profiles or biomarker expression, ML modelshelpin designing liposomes that target specific cellular receptors or pathways associated with a patient's disease. For example, liposomes can be engineered to deliver drugs specifically to tumors with unique genetic mutations by enhancing therapeutic efficacy and reducing side effects [19].

Latest Advancements in AI-Driven Liposome Synthesis

The synthesis of liposomes is being changed by recent developments in liposome synthesis. Artificial intelligence (AI) techniques have been

used in microfluidic platforms to improve liposome synthesis by adjusting parameters including reagent concentrations and flow rates. This enabled AI algorithms to forecast the final liposome features, including size and dispersity. For example, using microfluidic synthesis parameters, support vector machines, and artificial neural networks was able to predict liposome stability and dispersity with over 90% accuracy. High-throughput screening of formulations is made simpler by the use of robots and artificial intelligence in the synthesis and characterization of liposomes. This speeds up the development process and makes it possible to quickly identify the best formulations for specific therapeutic applications [16]. Artificial intelligence is used in predicting liposome stability over time, a crucial component in ensuring the efficacy of drug delivery systems. Machine learning models can estimate the efficacy of different formulations under varied storage conditions by analyzing previous stability data. Researchers can now create liposome formulations with more stability since studies have used artificial intelligence (AI) to determine the shelf life of liposomal formulations based on their composition and environmental conditions. Real-time monitoring of liposome stability through AI integration with sensor technologies enables dynamic formulation parameter modifications during manufacture or storage [16,17]. Drug delivery optimization requires an accurate prediction of liposome pharmacokinetic parameters with the help of machine learning. To determine the primary variables affecting the absorption, distribution, metabolism, and excretion (ADME) of liposomes, ML algorithms can evaluate data from pharmacokinetic investigations to improve therapeutic outcomes with more precise dosage regimens and predictions of liposome behavior in vivo. Moreover, multi-omics data (genomics, proteomics, metabolomics) can be integrated into machine learning models to provide an in-depth understanding of the interactions between liposomes and biological systems that can help create customized liposomal treatments and increase the precision of pharmacokinetic estimates [15,16].

Pharmacokinetics And Pharmacodynamics: Sensitivity Analysis Via Pk Solver

Reducing the clearance rate through changes like PEGylation leads to prolonged circulation times and increased accumulation in target tissues that enhance therapeutic efficacy and also changes in the clearance rate of liposomal formulations can significantly alter a drug's bioavailability [17]. Sensitivity analysis reveals that liposomes with a higher volume of distribution (Vd) exhibit better tissue penetration and distribution, which is essential for achieving effective drug concentrations at the target site. Also, liposome pharmacokinetic profile is highly influenced by their rate of absorption; formulations that increase absorption using particular lipid compositions to improve therapeutic effects in preclinical animals [20]. The ratio of phospholipids to cholesterol affects the efficacy of encapsulation and the release kinetics of the drug, so changing the lipid composition of liposomes can result in significant variations in drug release rates and stability. The significance of achieving an ideal ligand density on liposome surfaces has been emphasized by sensitivity analysis. Therapeutic efficacy can be enhanced and cellular uptake can be improved, but densities that are too high or too low may have the opposite impact. Sensitivity analysis has also been used in formulations designed for hyperthermia applications to determine how temperature variations impact liposome stability and drug release. This helps to design liposomes to thermal stimuli effectively to maximize drug delivery to tumor sites during hyperthermia treatment [21,22].

A study using a Box-Behnken design found that the molar ratio of phosphatidylcholine to diolylphosphatidylethanolamine significantly affected the vesicle size and drug entrapment efficiency in paclitaxel-containing liposomes. It enables researchers to optimize the formulations to improve therapeutic efficacy. Machine learning (ML) with PK Solver to improve liposome formulation simulation and optimization by creating accurate predictive models that take into account the complex interactions between liposomes and biological systems. For example, ML can analyze past pharmacokinetic data to increase the accuracy of estimates regarding the changes in formulation parameters that affect in vivo drug behavior and also determine the optimal formulation parameters based on simulation results from PK Solver, and machine learning algorithms in the optimization process. This allows for rapid testing and modification of liposomal formulations, which eventually results in more efficient drug delivery systems [22,23]. In certain studies, paclitaxel-loaded liposomes with sensitivity analysis revealed that the amount of drug and the lipid molar ratio were significant variables affecting drug entrapment and release, that improved therapeutic efficacy [24]. In a different study, machine learning was utilized to optimize the synthesis of liposomes loaded with curcumin. The results showed that differences in the lipid composition had a significant impact on the stability of the liposomes as well as the efficiency of drug loading. Machine learning additionally assisted in identifying the best synthesis conditions to enhance performance [25]. Also, liposomal formulations for gene delivery were subjected to sensitivity analysis to investigate how variations in surface charge and lipid composition influence transfection efficiency and cellular intake. This allowed formulations to be optimized for use in mRNA vaccine administration [26].

Sensitivity Analysis of Liposome Drug Release Using DDSOLVER

The diffusion coefficient (D), which controls the drug's release rate within the liposome bilayer and the surrounding medium, is also a key variable that may be altered in DDSolver to evaluate its effect on liposomal drug release. This allows for simulations of changes in lipid composition, drug physicochemical properties, or diffusion-affecting environmental conditions. Another significant variable is degradation rate (k), which indicates how oxidation, hydrolysis, or enzymatic degradation affect liposome stability and drug release. It is possible to manipulate matrix features like porosity, tortuosity, and swelling behavior to mimic the ways that affect drug release. Modeling of burst release, or the initial rapid release of a drug from liposomes, by altering variables such as the percentage of drug adsorbed to the liposome surface or the rate at which the drug separates from the bilayer and enters into the surrounding media. To achieve the desired therapeutic effects, variables influencing the sustained release phase, such as the rate of drug diffusion from the liposome core or the degree of drug binding to the bilayer, can be optimized [27,29]. To use DDSolver to maximize liposomal medication release: First, decide which mathematical model best fits the drug release data like Korsmeyer-Peppas, Weibull, or Michaelis-Menten equations. The choice will rely on the model that finds the best liposomal formulation's release kinetics. Enter the experimental release data next, which will be utilized as the starting point for the sensitivity analysis. This data should include time points and the associated drug release percentages. Next, within a suitable range, gradually change significant parameters, like the diffusion coefficient or degradation rate, and then DDsolver determines the release profiles that arise for each set of parameters [28,29]. Next,

determine the parameters that have prominent effects on the release kinetics by evaluating the changes in each parameter that affect the release rate, burst release, and sustained release. To attain the intended drug release profilemake some alterations in liposome formulation based on the sensitivity analysis. For example, if the diffusion coefficient is shown to be critical, then change the lipid composition to improve drug diffusion. Moreover, DDSolver uses several nonlinear optimization methods. By minimizing the sum of squares (SS) or weighted sum of squares (WSS) between observed and anticipated values, it provides a nonlinear least-squares curve fitting to match dissolution models with experimental data and find the ideal parameter values for drug release models. The Nelder-Mead simplex technique is used to determine the best-fit parameters because it can handle complex models and is also useful for nonlinear optimization without the need for derivative computations. Lastly, since accurate beginning estimates are essential for rapid results and units by avoiding local minima, DDSolver offers techniques for initial parameter estimation, such as trial-and-error methods and simple linear regression [27-30].

Sensitivity Analysis in Experimental Design Using Design Expert

A complex statistical software program called Design Expert was created to make sensitivity analysis and design of experiments (DOE) easier, particularly when it comes to the formulation and administration of drugs like liposomes. With this program, scientists may systematically examine the numerous ways in which modifications to formulation parameters impact drug release patterns, stability, bioavailability, and encapsulation efficiency. Several important factors that affect liposome formulations can be analyzed with a Design Expert. These factors include drug loading, where the type and quantity of drug utilized can affect the release profile and therapeutic efficacy, and also lipid composition, which significantly impacts the physical properties of liposomes. Particle size has an impact on biodistribution, cellular uptake, and release rates [31]. Design Expert uses Response Surface Methodology and Factorial Design, two potent statistical techniques. In a factorial design, several parameters are systematically varied at the same time to assess their respective and combined impacts on response variables, including the rate at which drugs are released from the body. For example, a 2^3 factorial design can investigate the impact of three factors at two levels each (high and low): lipid type, drug loading, and particle size.This allows researchers to identify significant variables and their interactions that affect liposomal behavior. By fitting a polynomial equation to experimental data, RSM improves on factorial design by providing suggestions for the most suitable conditions for targeted results. To enhance encapsulation efficiency while minimizing burst release, the optimal lipid composition and drug loading can be determined with this approach for formulation optimization [32]. A study that liposomes loaded with doxorubicin by using a factorial design reveals optimization of encapsulation efficiency. Lipid and cholesterol ratios have been used to find significant variables that influence encapsulation. Researchers found ideal conditions that significantly increased encapsulation efficiency from 30% to 85% by altering lipid composition and drug loading parameters. Response Surface Methodology (RSM) was applied in a different study to examine the stability of liposomal formulations under various storage conditions. Researchers analyze the kinetics of liposome disintegrating by varying pH and temperature. They discovered that temperature had a greater impact on stability than pH. Sensitivity analysis

was also used in curcumin-loaded liposomes to evaluate the effect of lipid composition and particle size on bioavailability. The results suggested that particular lipid combinations and smaller particle sizes improved curcumin absorption in vivo, leading to better therapeutic effects [31,32].

Factorial Design: Impact Of Parameter Variation

A study using a Box-Behnken design with three parameters at three levels to optimize pH-sensitive liposomes carrying paclitaxel. A 15-run experimental design matrix with three center points was generated by Box-Behnken design and analyzing such variables as lipid composition, drug loading, and stirring speed at three different levels. Particle size, polydispersity index, zeta potential, and entrapment efficiency were evaluated and analyzed during the liposome characterization [33]. Low PDI values and particle sizes suggested a limited size distribution. Moderate stability was indicated by zeta potential values, and entrapment efficiency was higher than 91%. High R^2 values show a well-fitting model that was found by statistical analysis using ANOVA to determine the component's relevance and their interactions with responses. Optimum formulation with specific lipid composition, drug loading, and stirring speed was identified by numerical optimization. The responses were validated using checkpoint batches that confirm the optimization accuracy. To improve drug delivery systems, the technique used in specific formulation parameters affects drug entrapment efficiency and provides a framework for improving optimal liposomal formulations [33,34].

Response Surface Methodology (RSM) For Liposome Sensitivity Analysis

Response Surface Methodology (RSM) analyzes the formulation and process variables that affect liposome parameters including particle size and polydispersity index (PDI) that have been used in some studies to optimize sirolimus liposomes. Lipid composition (molar ratios of cholesterol to dipalmitoylphosphatidylcholine), drug loading, and stirring speed are important independent variables. Particle size, PDI, and encapsulation efficiency (EE%) are used to represent the proportion of sirolimus encapsulated which are the primary variables to be measured [35]. To elaborate the relationships between the independent and dependent variables, a second-order polynomial equation is created. And these correlations are practically demonstrated via contour and response surface plots, which emphasize optimal and suboptimal conditions for the desirable characteristics of the liposomes. The use of RSM revealed important information on how lipid composition affects particle size and encapsulation efficiency. Additional work on doxorubicin- and curcumin-loaded liposomes shows the efficacy of RSM in formulation optimization and improving drug delivery efficiency [36].

Critical Parameters for Liposomal Optimization

Drug delivery methods depend on liposomal formulations, and optimizing their properties is essential for enhancing therapeutic efficacy. Lipid type, cholesterol ratio, drug-lipid ratio, and hydration time are significant variables that can affect liposomal characteristics. Sensitivities related to stability, drug encapsulation efficiency, and release patterns have been detected in each parameter. External variables also have prominent effects on liposomal stability, lipid oxidation, aggregation, and drug leakage. These variables include temperature, pH, and exposure to light

[37]. Structural integrity and fluidity are influenced by the type of lipid used; phosphatidylcholine is used mainly due to its stable bilayer formation and biocompatibility. Changes in lipid chain length and saturation alter the fluidity and permeability of membranes affecting the rates of drug release. Optimum ratios typically range between 30 and 50 percent by weight. Higher cholesterol content increases rigidity and reduces drug leakage but can hinder release [38]. The cholesterol ratio is also essential to maintain membrane stability. To achieve estimated loading and release characteristics, the drug-lipid ratio is essential, involving practical adjusting for particular formulations. Longer hydration can improve loading but the risk of aggregation is also high. Hydration time affects liposome size and encapsulation efficiency. Storage conditions are also important: lower temperatures are recommended for stability, whereas higher temperatures might speed up lipid oxidation and destabilize liposomes. Because liposomal integrity and drug stability are impacted by the pH of the storage medium, buffering to physiological values (about 7.4) is required. To stop the photodegradation of encapsulated lipids and drugs, liposomal formulations must be protected from light [37,38].

Table 2: Liposomal Challenges and its optimization

Liposome Type	Challenges	Optimized Parameters	Optimized Results	Reference
Salbutamol-loaded Liposomes	Vesicle size, zeta potential, drug entrapment efficiency, long sonication times	Cholesterol concentration, phospholipid concentration, hydration time	Optimized vesicle size, zeta potential, and drug entrapment efficiency	[39]
Doxorubicin-Curcumin Co-loaded	Decreasing doxorubicin toxicity, enhancing curcumin solubility, and improving stability	Buffer pH, temperature, phospholipid concentration, phospholipid-to-cholesterol ratio, extrusion temperature	Optimized size, surface charge, drug loading, encapsulation efficiency, and zeta potential	[40]
Antibody-loaded Liposomes	Optimizing antibody-to-lipid ratio	Antibody-to-lipid ratio, supercritical fluid-assisted process	Optimized mean diameter, polydispersity index, zeta potential, and encapsulation efficiency	[41]
Continuous Manufacturing Liposomes	Predicting the hydrodynamic diameter of monodispersed liposomes	Continuous processing models	Accelerated development and flexible operating conditions	[42]
Docetaxel-loaded Liposomes	Inconsistent sizes and low encapsulation efficiency	Incubation time, cholesterol concentration, drug-to-lipid ratio	Optimized liposome size and encapsulation efficiency, favorable for tumor targeting	[43]
Paclitaxel-loaded Liposomes	Investigating the impact of lipid composition,	Lipid composition, cholesterol content, drug-to-lipid ratio	Optimized liposome size, zeta potential, drug loading, and in vitro	[27]

	cholesterol content, and drug-to-lipid ratio		release for effective tumor targeting and drug delivery	
Gemcitabine-loaded Liposomes	Challenges with drug stability and encapsulation efficiency	Lipid composition, cholesterol content, drug-to-lipid ratio	Stable formulation with high drug loading, suitable for cancer therapy	[44]
Irinotecan-loaded Liposomes	Enhancing size, zeta potential, drug loading, and in vitro release	Lipid composition, cholesterol content, drug-to-lipid ratio	Improved drug delivery and therapeutic efficacy	[45]
Vincristine-loaded Liposomes	Low encapsulation efficiency and high drug leakage	Lipid composition, drug-to-lipid ratio	Increased encapsulation efficiency, reduced drug leakage, enhanced stability, and therapeutic efficacy in vitro	[46]
Cisplatin-loaded Liposomes	Low antitumor activity due to rapid drug release	Phospholipid content, cholesterol incorporation	Optimized balance between drug retention and release, improved antitumor efficacy in vivo	[47]
Methotrexate-loaded Liposomes	Optimizing lipid composition, cholesterol content, and drug-to-lipid ratio	Lipid composition, cholesterol content, drug-to-lipid ratio	Enhanced drug delivery and therapeutic potential	[48]
Dexamethasone-loaded Liposomes	Challenges with drug stability and release profiles	Lipid composition, hydration conditions	Improved encapsulation efficiency and controlled release, enhancing therapeutic potential for inflammatory diseases	[49]
Amphotericin B-loaded Liposomes	High toxicity and poor stability	Lipid ratio, hydration time	Reduced toxicity, improved encapsulation efficiency, and stability under various storage conditions	[50]
Insulin-loaded Liposomes	Enhancing drug stability and release kinetics, preventing rapid degradation	Stabilizers, adjusted storage conditions	Stable formulation with high insulin retention over time	[51]
Curcumin-loaded Liposomes	Poor drug loading due to suboptimal phospholipid concentration and hydration time	Phospholipid concentration, hydration time	High encapsulation efficiency and sustained release	[52]

Incorporate Emerging Trends in Smart and Stimuli-Responsive Liposomes

pH-responsive liposomes are novel drug delivery systems that release their drug content only under acidic conditions, likely in tumor tissues. These

liposomes have been coated with pH-sensitive polymers, which allow conformational changes that enhance drug release at lower pH values.Research has indicated that polymers such as polyacrylic acid are useful in enhancing the release of drugs in acidic conditions. When the pH falls, these polymers expand and disintegrate, increasing the drug's availability in particular areas, reducing systemic toxicity, increasing the therapeutic efficacy, and improving the liposomal formulations' ability to target targets [53]. The permeability of temperature-responsive liposomes is modified at particular temperatures through the use of thermosensitive components. These liposomes are especially useful for treating localized hyperthermia because they can efficiently release their contents when heated. Studies have shown that temperature-sensitive liposomes that are modified with polymers like poly(N-isopropylacrylamide) (PNIPAAm) are effective. When these liposomes are subjected to temperatures higher than 37°C, they undergo a phase transition at a lower critical solution temperature (LCST), which causes membrane disintegration and improved drug release. This method increases tumor vascular permeability and promotes increased drug retention in specified locations, which helps with site-specific drug delivery and enhances the effectiveness of hyperthermia treatments [54]. Light-responsive liposomes enable accurate regional control over drug release by releasing their drug content in response to particular light wavelengths. For applications like photodynamic therapy, where localized treatment is essential. Studies show that the creation of photosensitizer-containing light-sensitive liposomes that trigger the release of drugs when exposed to light. With minimal adverse impact on nearby healthy tissues, these liposomes can efficiently transport medications to the desired sites. With fewer systemic adverse effects and increased treatment success, this focused method shows great promise in cancer therapy [55]. By utilizing external magnetic fields, magnetic field-responsive liposomes are used to improve targeted drug delivery. These liposomes often contain magnetic nanoparticles, which enable accurate delivery to particular target areas, such as tumor spots. The efficacy of liposomes modified with magnetic nanoparticles that can targeted to tumor areas with the use of an external magnetic field. Temperature-responsive polymer integration is used to release drugs under controlled heating conditions, resulting in a dual process that improves targeting and therapeutic efficacy [56].

Biohybrid Liposomes: Integrating Living Cells with Artificial Nanocarriers

Lipid-hybrid cell-derived biomimetic functional materials combine liposomes with biological components obtained from cells, like bacterial outer membrane vesicles, extracellular vesicles, or cell membranes, providing an innovative approach in drug delivery systems. These hybrid materials make use of the inherent targeting abilities and immune evasion characteristics of cell-derived components, in addition to the high drug-loading capacity and flexibility of liposomes. Thin-film hydration is also used to make liposomes, and lipid compositions can be tuned for stability, targeted distribution, and controlled drug release. For example, lipids such as 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine combined with polyethylene glycol to create temperature-sensitive liposomes that have improved functioning. Liposome hybridization with EVs, OMVs, or cell membranes produces biomimetic materials with enhanced immune-modulating, targeting capabilities and improving medication delivery efficiency [57].

Table 3: Various biohybrid liposomes and their purpose

Liposome Type	Cell Type	Purpose	Reason	Reference
Cell-Membrane-Coated Liposomes	Cancer cell membranes	Enhance targeted drug delivery	Evades the immune system and improves targeting to tumor sites.	[58]
Liposomes with Immune Cell Membranes	Macrophages	Improve delivery of Immuno-therapeutics	Enhances targeting and activation of the immune response against tumors.	[59]
Liposomal Systems with Stem Cells	Mesenchymal stem cells (MSCs)	Deliver therapeutic agents for tissue regeneration	Enhances homing to damaged tissues, improving regenerative therapy efficacy.	[60]
Liposomes with Bacterial Membranes	Bacterial cells	Enhance drug delivery and target bacterial infections	Improves targeting and penetration of bacterial biofilms.	[61]
Liposomes with Neuronal Membranes	Neuronal cells	Deliver drugs for neurological disorders	Enhances delivery of therapeutics across the blood-brain barrier.	[62]
Hybrid Liposomes with Erythrocyte Membranes	Red blood cells (erythrocytes)	Improve circulation time and drug delivery	Prolongs circulation time, enhancing delivery to target tissues.	[63]
Liposomes with Platelet Membranes	Platelets	Enhance targeting to inflamed tissues	Targets sites of inflammation, promoting localized drug delivery.	[64]
Liposomes with Fibroblast Membranes	Fibroblasts	Improve delivery for wound healing	Enhances targeting to sites of tissue injury, promoting healing.	[65]
Liposomes with Dendritic Cell Membranes	Dendritic cells	Enhance vaccine delivery and immune activation	Improves immunogenicity, making liposomes effective for vaccine delivery.	[66]
Liposomes with Tumor Cell Membranes	Tumor cells	Enhance targeted cancer therapy	Targets and delivers drugs specifically to cancer cells, improving efficacy and reducing off-target effects.	[67]

Table 4: Advancement in liposome formulation

Liposome Type	Mechanism of Action	Purpose	Example	Reference
Long-Circulating Liposomes	Engineered to evade the RES by surface modification (e.g., PEGylation) to reduce opsonization and prolong circulation time.	Enhance bioavailability by increasing circulation time, particularly in cancer therapy.	PEGylated liposomes improved the pharmacokinetics of doxorubicin, increasing drug concentration in tumor tissues.	[68]
Stimuli-Responsive Liposomes	Designed to release drugs in response to stimuli such as pH, temperature, light, or	Achieve site-specific drug delivery and enhance	pH-responsive liposomes released camptothecin in tumor tissues, improving	[69,70]

	redox conditions, causing membrane destabilization.	therapeutic efficacy at the desired site (e.g., tumors).	targeting while sparing healthy tissues.	
Nebulized Liposomes	Aerosolized liposomal formulations for inhalation, allowing drug delivery to the lungs.	Treat respiratory diseases by enhancing drug deposition in the lungs.	Nebulized liposomes containing corticosteroids improved drug delivery in asthma models.	[71]
Elastic Liposomes	Flexible lipid bilayers allow enhanced penetration through biological barriers.	Improve drug absorption and bioavailability for transdermal, oral, or topical applications.	Elastic liposomes enhanced the transdermal delivery of NSAIDs, improving skin permeation.	[72,73]
Covalent Lipid-Drug Complexes	Therapeutic agents are chemically linked to lipids, enhancing membrane penetration and bioavailability.	Improve bioavailability of poorly soluble drugs.	Paclitaxel-lipid conjugates increased cellular uptake and cytotoxicity in cancer cells.	[74,75]
Combination Therapies	Co-delivery of multiple therapeutic agents, enhancing synergistic effects for better treatment outcomes.	Target multiple disease pathways, particularly in cancer therapy.	Liposome co-encapsulated alendronate and doxorubicin (PLAD) on the tumor immunologic milieu in a mouse fibrosarcoma model.	[76]
Photosensitizer-Doped Liposomes	Release drug contents upon exposure to light, allowing controlled release during photodynamic therapy.	Enhance localized drug release for improved therapeutic effects with minimal systemic exposure.	Photosensitizer-doped Indocyanine Greenliposomes enhanced photodynamic therapy by increasing tumor cell death upon light activation.	[77]
Enzyme-Triggered Release Systems	Release drug contents in response to specific enzymes overexpressed in pathological conditions, altering liposome structure.	Targeted drug delivery with reduced side effects.	Liposomes released drugs in the presence of MMP-2, effectively delivering chemotherapeutics to cancer cells.	[78]

Emphasize Multi-Disciplinary Collaborations and Future Directions

Multidisciplinary teams working in the fields of chemistry, engineering, bioinformatics, and nanotechnology are needed to develop liposomal drug delivery methods. By utilizing modern technologies like microfluidics and 3D printing, engineers improve the design and manufacturing of liposomes and provide reliable, reproducible formulations with regulated drug release profiles. Future initiatives will concentrate on adaptable, scalable procedures that guarantee clinical application and quality control [79].Large datasets on liposome formulations, interactions, and

biological reactions are analyzed with outstanding results by bioinformatics, and machine learning can be used to optimize formulations and predict their behavior in biological systems, improving the safety and efficacy of drug administration. Materials like graphene and gold nanoparticles to improve stability, drug loading capacity, and targeting abilities specifically in cancer therapies by nanotechnology that makes it possible to control liposomal characteristics at the nanoscale. The field of chemistry and its usefulness in the biocompatibility of liposomes will be improved by the creation of new lipids and conjugation methods of attaching pharmaceuticals and targeting ligands to liposomal surfaces. The novel potential of these multidisciplinary efforts is demonstrated by innovations such as the use of cationic lipids for siRNA transport in gene therapy and the combination of liposomes with gold nanoparticles to enhance photothermal effects in cancer treatments. Future liposomal technologies could lead to enhanced therapeutic applications for a large number of diseases [80].

CONCLUSION

Liposome progression from simple drug carriers to complex with customizable delivery systems demonstrates their transformative potential in modern treatment. This review demonstrates that by employing advanced computational modeling, machine learning, and sensitivity analysis, researchers can significantly improve the liposome formulations thereby enabling them to target action and patient profiles. Recent advances particularly smart and biohybrid liposomes can be used to enhance the sensitivity and effectiveness, particularly in cancer and gene therapy. In the future, some interdisciplinary collaboration of engineering, bioinformatics, and nanotechnology may be happening that will overcome challenges in large-scale production of liposomes, regulatory compliance, and clinical application. With progressive innovation and technological integration, liposomes also playa major role in personalized medicine that provides more effective, safer, and targeted treatment options for wide diseases.

REFERENCES

1. Liu P, Chen G, Zhang J. A Review of Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives. Molecules. 2022 Feb 17;27(4):1372. doi: 10.3390/molecules27041372. PMID: 35209162; PMCID: PMC8879473.
2. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: structure, composition, types, and clinical applications. Heliyon. 2022 May 13;8(5):e09394. doi: 10.1016/j.heliyon.2022.e09394. PMID: 35600452; PMCID: PMC9118483.
3. Pande, S. (2023). Liposomes for drug delivery: review of vesicular composition, factors affecting drug release and drug loading in liposomes. Artificial Cells, Nanomedicine, and Biotechnology, 51(1), 428–440. https://doi.org/10.1080/21691401.2023.2247036
4. Peng T, Xu W, Li Q, Ding Y, Huang Y. Pharmaceutical liposomal delivery—specific considerations of innovation and challenges. 2023 Jan 1;11(1):62–75.
5. Šturm L, PoklarUlrih N. Basic Methods for Preparation of Liposomes and Studying Their Interactions with Different Compounds, with the Emphasis on Polyphenols. Int J Mol Sci. 2021 Jun 18;22(12):6547. doi: 10.3390/ijms22126547. PMID: 34207189; PMCID: PMC8234105.
6. Lombardo D, Kiselev MA. Methods of Liposomes Preparation: Formation and

Control Factors of Versatile Nanocarriers for Biomedical and Nanomedicine Application. Pharmaceutics. 2022 Feb 28;14(3):543. doi: 10.3390/pharmaceutics14030543. PMID: 35335920; PMCID: PMC8955843.

7. Parchekani, J., Allahverdi, A., Taghdir, M. et al. Design and simulation of the liposomal model by using a coarse-grained molecular dynamics approach towards drug delivery goals. Sci Rep 12, 2371 (2022). https://doi.org/10.1038/s41598-022-06380-8
8. Kim B, Shin J, Wu J, Omstead DT, Kiziltepe T, Littlepage LE, Bilgicer B. Engineering peptide-targeted liposomal nanoparticles optimized for improved selectivity for HER2-positive breast cancer cells to achieve enhanced in vivo efficacy. J Control Release. 2020 Jun 10;322:530-541. doi: 10.1016/j.jconrel.2020.04.010. Epub 2020 Apr 8. PMID: 32276005; PMCID: PMC7932755.
9. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK and Hua S (2015) Advances and Challenges of Liposome Assisted Drug Delivery. Front. Pharmacol. 6:286. doi: 10.3389/fphar.2015.00286
10. Naik H, Sonju JJ, Singh S, Chatzistamou I, Shrestha L, Gauthier T, Jois S. Lipidated Peptidomimetic Ligand-Functionalized HER2 Targeted Liposome as Nano-Carrier Designed for Doxorubicin Delivery in Cancer Therapy. Pharmaceuticals (Basel). 2021 Mar 6;14(3):221. doi: 10.3390/ph14030221. PMID: 33800723; PMCID: PMC8002094.
11. Canato E, Grigoletto A, Zanotto I, Tedeschini T, Campara B, Quaglio G, et al. Anti-HER2 Super Stealth Immunoliposomes for Targeted-Chemotherapy. Advanced Healthcare Materials [Internet]. 2023 Aug 17 [cited 2023 Sep 18];e2301650.
12. Elamir, A., Ajith, S., Sawaftah, N.A. et al. Ultrasound-triggered herceptin liposomes for breast cancer therapy. Sci Rep 11, 7545 (2021). https://doi.org/10.1038/s41598-021-86860-5
13. Pasarin D, Ghizdareanu AI, Enascuta CE, Matei CB, Bilbie C, Paraschiv-Palada L, Veres PA. Coating Materials to Increase the Stability of Liposomes. Polymers (Basel). 2023 Feb 3;15(3):782. doi: 10.3390/polym15030782. PMID: 36772080; PMCID: PMC10004256.
14. Izumi K, Ji J, Keiichiro Koiwai, Kawano R. Long-Term Stable Liposome Modified by PEG-Lipid in Natural Seawater. ACS Omega. 2024 Feb 22;9(9):10958–66.
15. Meaney, C., Stapleton, S. &Kohandel, M. Predicting intratumoral fluid pressure and liposome accumulation using physics informed deep learning. Sci Rep 13, 20548 (2023). https://doi.org/10.1038/s41598-023-47988-8
16. Di Francesco, V., Boso, D.P., Moore, T.L. et al. Machine learning instructed microfluidic synthesis of curcumin-loaded liposomes. Biomed Microdevices 25, 29 (2023). https://doi.org/10.1007/s10544-023-00671-1
17. Hoseini B, Jaafari MR, Golabpour A, Momtazi-Borojeni AA, Karimi M, Eslami S. Application of ensemble machine learning approach to assess the factors affecting size and polydispersity index of liposomal nanoparticles. Sci Rep. 2023 Oct 21;13(1):18012. doi: 10.1038/s41598-023-43689-4. PMID: 37865639; PMCID: PMC10590434.
18. Hashemzadeh, H., Javadi, H. & Darvishi, M.H. Study of Structural stability and formation mechanisms in DSPC and DPSM liposomes: A coarse-grained molecular dynamics simulation. Sci Rep 10, 1837 (2020). https://doi.org/10.1038/s41598-020-58730-z
19. Dimov, N., Kastner, E., Hussain, M. et al. Formation and purification of tailored liposomes for drug delivery using a module-based micro continuous-flow system. Sci Rep

7, 12045 (2017). https://doi.org/10.1038/s41598-017-11533-1

20. Luo D, Carter KA, Molins EAG, Straubinger NL, Geng J, Shao S, Jusko WJ, Straubinger RM, Lovell JF. Pharmacokinetics and pharmacodynamics of liposomal chemophototherapy with short drug-light intervals. J Control Release. 2019 Mar 10;297:39-47. doi: 10.1016/j.jconrel.2019.01.030. Epub 2019 Jan 23. PMID: 30684512; PMCID: PMC6399029.
21. Zhang Y, Huo M, Zhou J, Xie S. PKSolver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. Computer Methods and Programs in Biomedicine. 2010 Sep;99(3):306–14.
22. Hoseini B, Jaafari MR, Golabpour A, Rahmatinejad Z, Karimi M, Eslami S. Machine Learning-Driven Advancements in Liposomal Formulations for Targeted Drug Delivery: A Narrative Literature Review. Curr Drug Deliv. 2024 Jun 27. doi: 10.2174/0115672018302321240620072039. Epub ahead of print. PMID: 38939987
23. Li, Y., Ji, T., Torre, M. et al. Aromatized liposomes for sustained drug delivery. Nat Commun 14, 6659 (2023). https://doi.org/10.1038/s41467-023-41946-8
24. Jaradat E, Weaver E, Meziane A, Lamprou DA. Synthesis and Characterization of Paclitaxel-Loaded PEGylated Liposomes by the Microfluidics Method. Mol Pharm. 2023 Dec 4;20(12):6184-6196. doi: 10.1021/acs.molpharmaceut.3c00596. Epub 2023 Nov 6. PMID: 37931072; PMCID: PMC10698720.
25. Chen Y, Wu Q, Zhang Z, Yuan L, Liu X, Zhou L. Preparation of curcumin-loaded liposomes and evaluation of their skin permeation and pharmacodynamics. Molecules. 2012 May 18;17(5):5972-87. doi: 10.3390/molecules17055972. PMID: 22609787; PMCID: PMC6268695.
26. Tseu, G.Y.W.; Kamaruzaman, K.A. A Review of Different Types of Liposomes and Their Advancements as a Form of Gene Therapy Treatment for Breast Cancer. Molecules 2023, 28, 1498. https://doi.org/10.3390/molecules28031498
27. Zhang, Y., Huo, M., Zhou, J. et al. DDSolver: An Add-In Program for Modeling and Comparison of Drug Dissolution Profiles. AAPS J 12, 263–271 (2010). https://doi.org/10.1208/s12248-010-9185-1
28. Rahim MA, Madni A, Tahir N, Jan N, Shah H, Khan S, Ullah R, Bari A, Khan MS. Mild Hyperthermia Responsive Liposomes for Enhanced In Vitro and In Vivo Anticancer Efficacy of Doxorubicin against Hepatocellular Carcinoma. Pharmaceutics. 2021 Aug 21;13(8):1310. doi: 10.3390/pharmaceutics13081310. PMID: 34452271; PMCID: PMC8400916.
29. Shah H, Madni A, Rahim MA, Jan N, Khan A, Khan S, Jabar A, Ali A. Fabrication, in vitro and ex vivo evaluation of proliposomes and liposomal derived gel for enhanced solubility and permeability of diacerein. PLoS One. 2021 Oct 19;16(10):e0258141. doi: 10.1371/journal.pone.0258141. PMID: 34665836; PMCID: PMC8525764.
30. Smits EAW, Soetekouw JA, Pieters EHE, Smits CJP, de Wijs-Rot N, Vromans H. The availability of drug by liposomal drug delivery : Individual kinetics and tissue distribution of encapsulated and released drug in mice after administration of PEGylated liposomal prednisolone phosphate. Invest New Drugs. 2019 Oct;37(5):890-901. doi: 10.1007/s10637-018-0708-4. Epub 2018 Dec 13. PMID: 30547315; PMCID: PMC6736927.
31. Barros C, Aranha N, Severino P, Souto EB, Zielińska A, Lopes A, Rios A, Batain F,

Crescencio K, Chaud M, Alves T. Quality by Design Approach for the Development of Liposome Carrying Ghrelin for Intranasal Administration. Pharmaceutics. 2021 May 10;13(5):686. doi: 10.3390/pharmaceutics13050686. PMID: 34068793; PMCID: PMC8151022.

32. Dehariya P, Soni R, Paswan SK, Soni PK. Design of experiment based formulation optimization of chitosan-coated nano-liposomes of progesterone for effective oral delivery. Journal of Applied Pharmaceutical Science [Internet]. 2023 [cited 2024 Sep 9];
33. Rane S, Prabhakar B. Optimization of Paclitaxel Containing pH-Sensitive Liposomes By 3 Factor, 3 Level Box-Behnken Design. Indian J Pharm Sci. 2013 Jul;75(4):420-6. doi: 10.4103/0250-474X.119820. PMID: 24302796; PMCID: PMC3831723.
34. Tatode, A. A., Patil, A. T., &Umekar, M. J. (2018). APPLICATION OF RESPONSE SURFACE METHODOLOGY IN OPTIMIZATION OF PACLITAXEL LIPOSOMES PREPARED BY THIN FILM HYDRATION TECHNIQUE. International Journal of Applied Pharmaceutics, 10(2), 62–69. https://doi.org/10.22159/ijap.2018v10i2.24238
35. Ghanbarzadeh S, Valizadeh H, Zakeri-Milani P. Application of response surface methodology in development of sirolimus liposomes prepared by thin film hydration technique. Bioimpacts. 2013;3(2):75-81. doi: 10.5681/bi.2013.016. Epub 2013 Apr 30. PMID: 23878790; PMCID: PMC3713873.
36. López, R.R.; Ocampo, I.; Sánchez, L.-M.; Alazzam, A.; Bergeron, K.-F.; Camacho-León, S.; Mounier, C.; Stiharu, I.; Nerguizian, V. Surface Response Based Modeling of Liposome Characteristics in a Periodic Disturbance Mixer. Micromachines 2020, 11, 235. https://doi.org/10.3390/mi11030235
37. Ramana, L.N., Sethuraman, S., Ranga, U. et al. Development of a liposomal nanodelivery system for nevirapine. J Biomed Sci 17, 57 (2010). https://doi.org/10.1186/1423-0127-17-57
38. Hsu TW, Yang CH, Su CJ, Huang YT, Yeh YQ, Liao KF, et al. Revealing cholesterol effects on PEGylated HSPC liposomes using AF4–MALS and simultaneous small- and wide-angle X-ray scattering. Journal of Applied Crystallography [Internet]. 2023 Jul 25 [cited 2024 Sep 9];56(4):988–93.
39. Bonde S, Tambe K. Lectin coupled liposomes for pulmonary delivery of salbutamol sulphate for better management of asthma: Formulation development using QbD approach. Journal of Drug Delivery Science and Technology. 2019 Dec;54:101336.
40. Lu, X., Zhang, P., Li, J. et al. The effect of doxorubicin curcumin co-loaded lipid nanoparticles and doxorubicin on osteosarcoma before surgery. Cancer Nano 15, 11 (2024). https://doi.org/10.1186/s12645-024-00247-5
41. Sela M, Poley M, Mora-Raimundo P, Kagan S, Aviram Avital, Kaduri M, et al. Brain‐Targeted Liposomes Loaded with Monoclonal Antibodies Reduce Alpha‐Synuclein Aggregation and Improve Behavioral Symptoms of Parkinson's Disease. Advanced Materials. 2023 Sep 27;
42. Sheybanifard M, Guerzoni LPB, Omidinia-Anarkoli A, Laporte LD, Buyel J, Besseling R, et al. Liposome manufacturing under continuous flow conditions: towards a fully integrated set-up with in-line control of critical quality attributes. Lab on a Chip [Internet]. 2022 Dec 20 [cited 2023 Nov 8];23(1):182–94.
43. Vakili-Ghartavol, R., Rezayat, S.M., Faridi-Majidi, R. et al. Optimization of Docetaxel

Loading Conditions in Liposomes: proposing potential products for metastatic breast carcinoma chemotherapy. Sci Rep 10, 5569 (2020). https://doi.org/10.1038/s41598-020-62501-1

44. Tamam H, Park J, Gadalla HH, Masters AR, Abdel-Aleem JA, Abdelrahman SI, Abdelrahman AA, Lyle LT, Yeo Y. Development of Liposomal Gemcitabine with High Drug Loading Capacity. Mol Pharm. 2019 Jul 1;16(7):2858-2871. doi: 10.1021/acs.molpharmaceut.8b01284. Epub 2019 Jun 14. PMID: 31136710; PMCID: PMC6662591.
45. Li, Z., Liu, C., Li, C. et al. Irinotecan/scFv co-loaded liposomes coaction on tumor cells and CAFs for enhanced colorectal cancer therapy. J Nanobiotechnol 19, 421 (2021). https://doi.org/10.1186/s12951-021-01172-0
46. Yang Y, Guo Y, Tan X, He H, Zhang Y, Yin T, Xu H, Tang X. Vincristine-loaded liposomes prepared by ion-paring techniques: Effect of lipid, pH and antioxidant on chemical stability. Eur J Pharm Sci. 2018 Jan 1;111:104-112. doi: 10.1016/j.ejps.2017.09.045. Epub 2017 Sep 28. PMID: 28964951.
47. Gomes IP, Silva JO, Cassali GD, De Barros ALB, Leite EA. Cisplatin-Loaded Thermosensitive Liposomes Functionalized with Hyaluronic Acid: Cytotoxicity and In Vivo Acute Toxicity Evaluation. Pharmaceutics. 2023 Feb 9;15(2):583. doi: 10.3390/pharmaceutics15020583. PMID: 36839905; PMCID: PMC9961010.
48. Guimarães D, Noro J, Loureiro A, Lager F, Renault G, Cavaco-Paulo A, Nogueira E. Increased Encapsulation Efficiency of Methotrexate in Liposomes for Rheumatoid Arthritis Therapy. Biomedicines. 2020 Dec 18;8(12):630. doi: 10.3390/biomedicines8120630. PMID: 33353028; PMCID: PMC7766404.
49. Benne N, Daniëlle terBraake, Porenta D, Yin C, Mastrobattista E, Broere F. Autoantigen‐dexamethasone Conjugate‐Loaded Liposomes Halt Arthritis Development in Mice. Advanced Healthcare Materials. 2024 Feb 11;
50. Santoso P, Komada T, Ishimine Y, Taniguchi H, Minamihata K, Goto M, Taira T, Kamiya N. Preparation of amphotericin B-loaded hybrid liposomes and the integration of chitin-binding proteins for enhanced antifungal activity. J BiosciBioeng. 2022 Sep;134(3):259-263. doi: 10.1016/j.jbiosc.2022.06.005. Epub 2022 Jun 30. PMID: 35781189.
51. Liu, G.; He, S.; Ding, Y.; Chen, C.; Cai, Q.; Zhou, W. Multivesicular Liposomes for Glucose-Responsive Insulin Delivery. Pharmaceutics 2022, 14, 21. https://doi.org/10.3390/pharmaceutics14010021
52. De Leo V, Milano F, Mancini E, Comparelli R, Giotta L, Nacci A, Longobardi F, Garbetta A, Agostiano A, Catucci L. Encapsulation of Curcumin-Loaded Liposomes for Colonic Drug Delivery in a pH-Responsive Polymer Cluster Using a pH-Driven and Organic Solvent-Free Process. Molecules. 2018 Mar 23;23(4):739. doi: 10.3390/molecules23040739. PMID: 29570636; PMCID: PMC6017095.
53. Zangabad PS, Mirkiani S, Shahsavari S, Masoudi B, Masroor M, Hamed H, Jafari Z, Taghipour YD, Hashemi H, Karimi M, Hamblin MR. Stimulus-responsive liposomes as smart nanoplatforms for drug delivery applications. Nanotechnol Rev. 2018 Feb;7(1):95-122. doi: 10.1515/ntrev-2017-0154. Epub 2017 Dec 12. PMID: 29404233; PMCID: PMC5796673.
54. Ta T, Porter TM. Thermosensitive liposomes for localized delivery and triggered release of

chemotherapy. J Control Release. 2013 Jul 10;169(1-2):112-25. doi: 10.1016/j.jconrel.2013.03.036. Epub 2013 Apr 11. PMID: 23583706; PMCID: PMC5127786.

55. Ashrafizadeh M, Delfi M, Zarrabi A, Bigham A, Sharifi E, Rabiee N, Paiva-Santos AC, Kumar AP, Tan SC, Hushmandi K, Ren J, Zare EN, Makvandi P. Stimuli-responsive liposomal nanoformulations in cancer therapy: Pre-clinical & clinical approaches. J Control Release. 2022 Nov;351:50-80. doi: 10.1016/j.jconrel.2022.08.001. Epub 2022 Sep 20. PMID: 35934254.
56. Nemoto R, Fujieda K, Hiruta Y, Hishida M, Ayano E, Maitani Y, Nagase K, Kanazawa H. Liposomes with temperature-responsive reversible surface properties. Colloids Surf B Biointerfaces. 2019 Apr 1;176:309-316. doi: 10.1016/j.colsurfb.2019.01.007. Epub 2019 Jan 3. PMID: 30641302.
57. Liu WS, Wu LL, Chen CM, Zheng H, Gao J, Lu ZM, Li M. Lipid-hybrid cell-derived biomimetic functional materials: A state-of-the-art multifunctional weapon against tumors. Mater Today Bio. 2023 Aug 3;22:100751. doi: 10.1016/j.mtbio.2023.100751. PMID: 37636983; PMCID: PMC10448342.
58. Liu Z, Wang F, Liu X, Sang Y, Zhang L, Ren J, Qu X. Cell membrane-camouflaged liposomes for tumor cell-selective glycans engineering and imaging in vivo. Proc Natl Acad Sci U S A. 2021 Jul 27;118(30):e2022769118. doi: 10.1073/pnas.2022769118. PMID: 34301864; PMCID: PMC8325163.
59. Besançon H, Larpin Y, Babiychuk VS, Köffel R, Babiychuk EB. Engineered Liposomes Protect Immortalized Immune Cells from Cytolysins Secreted by Group A and Group G Streptococci. Cells. 2022 Jan 5;11(1):166. doi: 10.3390/cells11010166. PMID: 35011729; PMCID: PMC8749993.
60. Mandpe P, Prabhakar B, Shende P. Role of Liposomes-Based Stem Cell for Multimodal Cancer Therapy. Stem Cell Rev Rep. 2020 Feb;16(1):103-117. doi: 10.1007/s12015-019-09933-z. PMID: 31786749.
61. Scheeder A, Brockhoff M, Ward EN, Kaminski GS, Mela I, Kaminski CF. Molecular Mechanisms of Cationic Fusogenic Liposome Interactions with Bacterial Envelopes. Journal of the American Chemical Society. 2023 Dec 12;145(51):28240–50.
62. Eckert GP, Chang S, Eckmann J, Copanaki E, Hagl S, Hener U, Müller WE, Kögel D. Liposome-incorporated DHA increases neuronal survival by enhancing non-amyloidogenic APP processing. BiochimBiophys Acta. 2011 Jan;1808(1):236-43. doi: 10.1016/j.bbamem.2010.10.014. Epub 2010 Oct 29. PMID: 21036142.
63. Himbert S, Blacker MJ, Kihm A, Pauli Q, Khondker A, Yang K, Sinjari S, Johnson M, Juhasz J, Wagner C, Stöver HDH, Rheinstädter MC. Hybrid Erythrocyte Liposomes: Functionalized Red Blood Cell Membranes for Molecule Encapsulation. Adv Biosyst. 2020 Mar;4(3):e1900185. doi: 10.1002/adbi.201900185. Epub 2020 Jan 7. PMID: 32293142.
64. Wan S, Fan Q, Wu Y, Zhang J, Qiao G, Jiang N, Yang J, Liu Y, Li J, Chiampanichayakul S, Tima S, Tong F, Anuchapreeda S, Wu J. Curcumin-Loaded Platelet Membrane Bioinspired Chitosan-Modified Liposome for Effective Cancer Therapy. Pharmaceutics. 2023 Feb 13;15(2):631. doi: 10.3390/pharmaceutics15020631. PMID: 36839952; PMCID: PMC9965064.
65. You C, Zu J, Liu X, Kong P, Song C, Wei R, Zhou C, Wang Y, Yan J. Synovial fibroblast-targeting liposomes encapsulating an NF-κB-blocking peptide ameliorates zymosan-induced synovial inflammation. J Cell Mol

Med. 2018 Apr;22(4):2449-2457. doi: 10.1111/jcmm.13549. Epub 2018 Jan 30. PMID: 29383874; PMCID: PMC5867099.

66. Nagy NA, de Haas AM, Geijtenbeek TBH, van Ree R, Tas SW, van Kooyk Y, de Jong EC. Therapeutic Liposomal Vaccines for Dendritic Cell Activation or Tolerance. Front Immunol. 2021 May 13;12:674048. doi: 10.3389/fimmu.2021.674048. PMID: 34054859; PMCID: PMC8155586.
67. Zhang, W., Gong, C., Chen, Z. et al. Tumor microenvironment-activated cancer cell membrane-liposome hybrid nanoparticle-mediated synergistic metabolic therapy and chemotherapy for non-small cell lung cancer. J Nanobiotechnol 19, 339 (2021). https://doi.org/10.1186/s12951-021-01085-y
68. Wei XQ, Ba K. Construction a Long-Circulating Delivery System of Liposomal Curcumin by Coating Albumin. ACS Omega. 2020 Jul 2;5(27):16502–9.
69. Yuba E. Development of functional liposomes by modification of stimuli-responsive materials and their biomedical applications. Journal of Materials Chemistry B. 2020;8(6):1093–107.
70. Lin CH, Al-Suwayeh SA, Hung CF, Chen CC, Fang JY. Camptothecin-Loaded Liposomes with α-Melanocyte-Stimulating Hormone Enhance Cytotoxicity Toward and Cellular Uptake by Melanomas: An Application of Nanomedicine on Natural Product. J Tradit Complement Med. 2013 Apr;3(2):102-9. doi: 10.4103/2225-4110.110423. PMID: 24716164; PMCID: PMC3924967.
71. Rudokas M, Najlah M, Alhnan MA, Elhissi A. Liposome Delivery Systems for Inhalation: A Critical Review Highlighting Formulation Issues and Anticancer Applications. Med Princ Pract. 2016;25 Suppl 2(Suppl 2):60-72. doi: 10.1159/000445116. Epub 2016 Mar 2. PMID: 26938856; PMCID: PMC5588529.
72. Kuznetsova DA, Vasilieva EA, Kuznetsov DM, Lenina OA, Filippov SK, Petrov KA, et al. Enhancement of the Transdermal Delivery of Nonsteroidal Anti-inflammatory Drugs Using Liposomes Containing Cationic Surfactants. ACS omega. 2022 Jul 12;7(29):25741–50.
73. Hussain A, Singh S, Sharma D, Webster TJ, Shafaat K, Faruk A. Elastic liposomes as novel carriers: recent advances in drug delivery. Int J Nanomedicine. 2017 Jul 17;12:5087-5108. doi: 10.2147/IJN.S138267. PMID: 28761343; PMCID: PMC5522681.
74. Wu, X., Chen, X., Wang, X., He, H., Chen, J., & Wu, W. (2023). Paclitaxel-lipid prodrug liposomes for improved drug delivery and breast carcinoma therapy. Chinese Chemical Letters.
75. Yuan H, Miao J, Du YZ, You J, Hu FQ, Zeng S. Cellular uptake of solid lipid nanoparticles and cytotoxicity of encapsulated paclitaxel in A549 cancer cells. Int J Pharm. 2008 Feb 4;348(1-2):137-45. doi: 10.1016/j.ijpharm.2007.07.012. Epub 2007 Jul 18. PMID: 17714896.
76. Islam MR, Patel J, Back PI, Shmeeda H, Adamsky K, Yang H, Alvarez C, Gabizon AA, La-Beck NM. Comparative effects of free doxorubicin, liposome encapsulated doxorubicin and liposome co-encapsulated alendronate and doxorubicin (PLAD) on the tumor immunologic milieu in a mouse fibrosarcoma model. Nanotheranostics. 2022 Sep 1;6(4):451-464. doi: 10.7150/ntno.75045. PMID: 36105861; PMCID: PMC9461478.
77. Liao WT, Chang DM, Lin MX, Lee JW, Tung YC, Hsiao JK. Indocyanine-Green-Loaded Liposomes for Photodynamic and Photothermal Therapies: Inducing Apoptosis and Ferroptosis in Cancer Cells with Implications beyond Oral Cancer. Pharmaceutics. 2024 Feb 4;16(2):224. doi:

10.3390/pharmaceutics16020224. PMID: 38399278; PMCID: PMC10891763.

78. Penate Medina O, Haikola M, Tahtinen M, Simpura I, Kaukinen S, Valtanen H, Zhu Y, Kuosmanen S, Cao W, Reunanen J, Nurminen T, Saris PE, Smith-Jones P, Bradbury M, Larson S, Kairemo K. Liposomal Tumor Targeting in Drug Delivery Utilizing MMP-2- and MMP-9-Binding Ligands. J Drug Deliv. 2011;2011:160515. doi: 10.1155/2011/160515. Epub 2010 Dec 29. PMID: 21490745; PMCID: PMC3066593.
79. Sun, L., Liu, H., Ye, Y. et al. Smart nanoparticles for cancer therapy. Sig Transduct Target Ther 8, 418 (2023). https://doi.org/10.1038/s41392-023-01642-x
80. Andra, V.V.S.N. ., Pammi, S.V.N., Bhatraju, L.V.K.P. et al. A Comprehensive Review on Novel Liposomal Methodologies, Commercial Formulations, Clinical Trials and Patents. BioNanoSci. 12, 274–291 (2022). https://doi.org/10.1007/s12668-022-00941-x.

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