

Review

Chitosan-Coated Liposomes: Advances in Synthesis, Modification and Biomedical Applications

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Abstract

Chitosan-coated liposomes (CLPs) have emerged as a multifunctional drug delivery platform that effectively overcomes the key limitations of conventional liposomes, including poor stability, rapid in vivo clearance, weak mucoadhesion, and insufficient targeting specificity. The natural cationic nature of chitosan enables stable coating onto negatively charged liposome surfaces via electrostatic interactions, forming a stable core-shell structure that significantly improves liposomal stability, prolongs circulation time, and enhances mucoadhesive ability. The abundant reactive groups on the chitosan backbone allow further conjugation of targeting ligands, polyethylene glycol chains, and stimuli-responsive moieties, thereby endowing the delivery system with active targeting, long-circulating, and smart drug release properties. Various coating strategies, such as electrostatic deposition, layer-by-layer self-assembly, ionic crosslinking, and microfluidic in-situ coating, provide flexibility and precise controllability for formulation design. These systems have demonstrated considerable therapeutic potential across multiple administration routes, as well as in anti-infective, tumor-targeted, and immunomodulatory applications, by improving drug retention, enabling controlled release, and enhancing bioavailability. Therefore, this review summarizes the synthesis methods, modification strategies, and biomedical applications of CLPs, with the aim of providing a reference for future development in this field.

Keywords: chitosan-coated liposomes; synthesis; modification; biomedical applications

1. Introduction

Liposomes, as biomimetic drug delivery systems, have been extensively studied and clinically applied in the field of drug delivery owing to their favorable biocompatibility, biodegradability, and low immunogenicity [1]. However, traditional liposomes face multiple challenges in clinical applications. First, under physiological conditions, liposomes are susceptible to variations in ionic strength, pH, and serum proteins, leading to markedly impaired stability [2,3]. The stability of liposomal membranes is vigorously affected by their composition, wherein the physical state of the lipid bilayer and the presence of cholesterol play vital roles in determining membrane rigidity and resistance to environmental stressors [4]. Second, the surface of liposomes is readily recognized and opsonized by active plasma proteins, followed by rapid clearance by the reticuloendothelial system, which substantially shortens circulatory half-life [5–7]. The adsorption of serum opsonins to the liposomal surface serves as the determining factor for recognition and subsequent clearance by macrophages in the liver and spleen [7,8]. Third, conventional liposomes are usually



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negatively charged or electrically neutral, lacking the ability to engage in effective electrostatic interactions with negatively charged mucosal surfaces; consequently, they exhibit poor mucoadhesion and cannot efficiently overcome the mucosal barrier [9]. The mucus layer, being negatively charged, repels anionic or neutral liposomes, resulting in poor retention and rapid clearance from mucosal surfaces [10]. Fourth, traditional liposomes lack the capacity to actively recognize specific receptors of target cells, making it difficult to achieve precision drug delivery [11,12]. Passive targeting based solely on the enhanced permeability and retention effect lacks tissue specificity, and without surface-conjugated targeting ligands, liposomes cannot selectively bind to overexpressed receptors on diseased cells [13]. These limitations have substantially hindered both the clinical translation and therapeutic efficacy of conventional liposomal drug delivery systems.

To overcome these limitations, researchers have developed a variety of surface modification strategies, including ligand conjugation and biomimetic coating. Among them, chitosan coating has attracted considerable attention due to its unique physicochemical and biological properties [14–17]. Chitosan is a natural cationic polysaccharide obtained by deacetylation of chitin and possesses excellent biocompatibility and biodegradability and low toxicity [18–20]. The amino groups become protonated and positively charged under acidic conditions, enabling electrostatic adsorption onto the surface of negatively charged liposomes, thereby forming a stable core–shell structure [21]. The chitosan coating significantly enhances liposomal stability, delays clearance by the reticuloendothelial system to prolong circulation time, and owing to its positively charged surface, reinforces adhesion to mucosal layers [22–24]. Moreover, the amino and hydroxyl groups on the chitosan backbone can be further chemically modified to conjugate targeting ligands or polyethylene glycol, thereby conferring active targeting capability or long-circulating properties to the liposomes [25,26]. These advantages make chitosan-coated liposomes (CLPs) a highly promising drug delivery platform [27–29].

In recent years, with the advancement of nanotechnology and materials science, significant progress has been made in the study of CLPs in terms of innovative synthesis methods, improved chemical modification and expansion of drug delivery systems. This review searched PubMed, Web of Science, and Scopus databases using the query (“chitosan-coated liposomes” OR “chitosan-coated nanoliposomes” OR “chitosan-modified liposomes”) to systematically summarize the related research published from 2022 to 2026. Only original research articles and reviews written in English were included. Additional relevant studies were identified by cross-referencing the bibliographies of retrieved articles.

While recent reviews have provided valuable overviews of CLPs, the present review distinguishes itself in several critical aspects. First, a systematic comparison of coating strategies—electrostatic deposition, layer-by-layer assembly, ionic crosslinking, and microfluidic in situ coating—is presented, with emphasis on reproducibility, scalability, and translational potential, rather than on mere methodological description. Second, safety and toxicity considerations (cationic charge-associated cytotoxicity, hemocompatibility, immunogenicity, and protein corona formation) that are crucial for clinical translation are critically discussed. Third, recent advances in stimuli-responsive and enzyme-modified chitosan systems are integrated, providing a forward-looking perspective on this rapidly evolving field.

2. Performance Advantages of Chitosan Coating

As a natural cationic polysaccharide, when chitosan is modified onto the liposome surface via electrostatic interactions, it improves the physicochemical and biological properties of liposomes in multiple respects (shown in Figure 1).

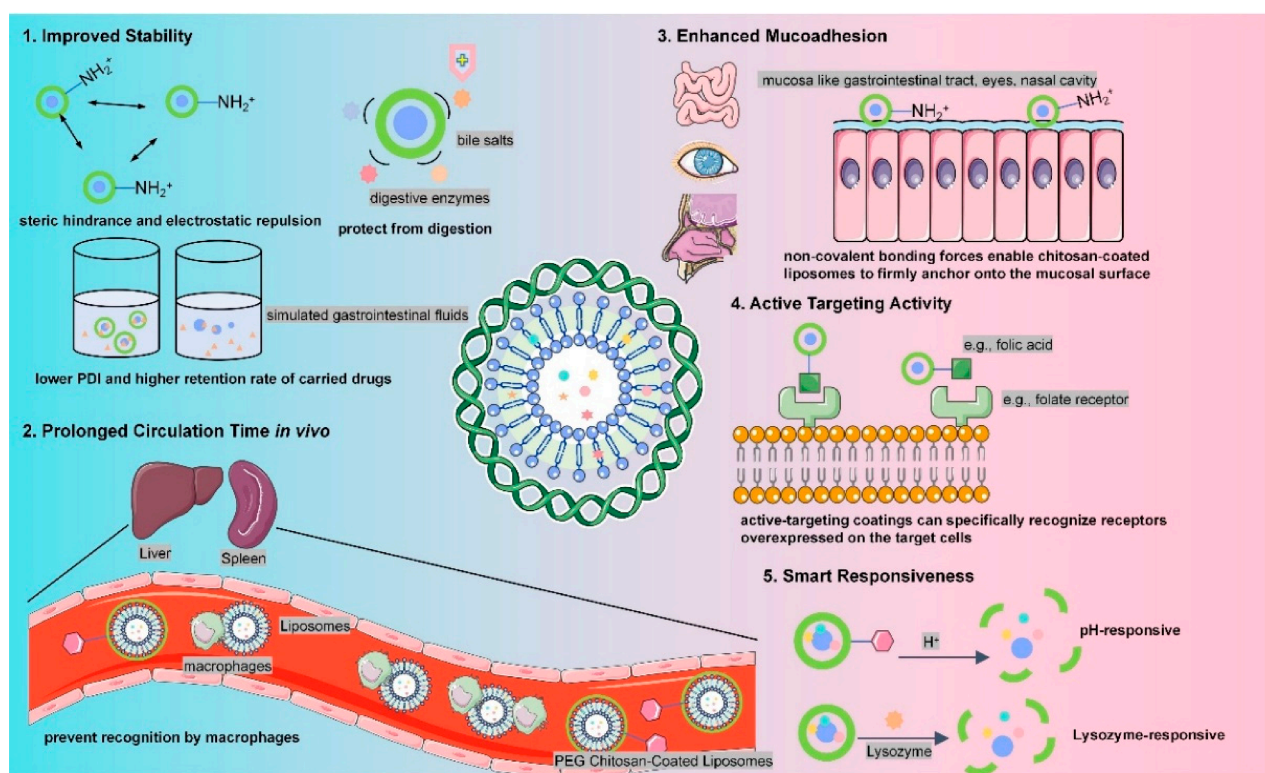


Figure 1. The Advantages of Chitosan Coating.

2.1. Improved Stability

Chitosan deposited on the liposome surface forms a rigid polymeric barrier. On the one hand, it prevents close contact between liposomal particles through steric hindrance; on the other hand, the positive charge arising from its protonated amino groups generates electrostatic repulsion, and this dual mechanism collectively inhibits particle aggregation [30,31]. Studies have shown that the changes in particle size and polydispersity index of CLPs in simulated gastrointestinal fluids, high-salt buffers, or serum are much smaller than those of uncoated liposomes, and the retention rate of encapsulated drugs is significantly increased [3,32]. Moreover, the chitosan coating can protect liposomes from destruction by bile salts and digestive enzymes, which is particularly important for the oral route of administration [33–35].

2.2. Prolonged Circulation Time In Vivo

Traditional liposomes are rapidly recognized and cleared by the reticuloendothelial system (such as macrophages in the liver and spleen) after intravenous injection, with a half-life typically of only minutes to tens of minutes [31]. Although the chitosan coating itself does not possess the “stealth” function of polyethylene glycol (PEG), its positively charged surface can form a dynamic protein corona through interaction with negatively charged plasma proteins, thereby protecting liposomes to some extent and delaying the adsorption of complement proteins [36,37]. Furthermore, by covalently coupling chitosan with PEG, the resulting PEGylated chitosan derivative coating retains the mucoadhesion and positively charged characteristics of chitosan while introducing the long-circulation advantage of PEG, achieving an extended in vivo half-life [38].

2.3. Enhanced Mucoadhesion

Mucosal surfaces such as the gastrointestinal tract, eyes, nasal cavity, oral cavity, and vagina are covered with a layer of mucus, which contains a large number of negatively

charged sialic acid residues in its core. Upon protonation, chitosan becomes positively charged and can engage in strong electrostatic interactions with negatively charged mucin; in addition, the hydroxyl and acetylamino groups on the chitosan molecular chain can form hydrogen bonds with mucin, and chitosan can also undergo hydrophobic interactions with the glycan moieties of mucin [10,23,39]. These multiple non-covalent bonding forces enable CLPs to firmly anchor onto the mucosal surface, significantly prolonging the retention time of the drug delivery system and resisting the flushing action of tears, saliva, or intestinal contents, which is critically important for improving drug bioavailability [40,41].

2.4. Active Targeting Activity

The abundant reactive groups (e.g., amino and hydroxyl groups) on the chitosan molecular chain serve as anchors for chemical modification. Using methods such as carbodiimide-mediated amidation, Schiff base reaction and so on, researchers covalently graft targeting ligands (e.g., folic acid, transferrin, RGD peptide, galactose, aptamers) onto the chitosan backbone, and then coat the resulting conjugate onto liposome surfaces [26,42,43]. Such active-targeting coatings can specifically recognize receptors overexpressed on the surface of diseased cells (e.g., tumor cells), mediate cellular internalization of liposomes, increase drug accumulation at the lesion site, and simultaneously reduce toxicity to normal tissues [24].

2.5. Smart Responsiveness

Chitosan can be used to construct stimuli-responsive release systems by grafting hydrophobic groups (e.g., deoxycholic acid, octanoyl) or pH-sensitive polymers such as poly(ethylene glycol) methyl ether acrylate (PEGA), enabling on-demand drug release in specific microenvironments (e.g., the acidic tumor microenvironment) [44–48]. In addition, chitosan itself exhibits enzyme responsiveness. Lysozyme is a natural antibacterial enzyme present in various body fluids (e.g., tears, saliva, serum), and chitosan can be specifically degraded by lysozyme. Taking advantage of this property, Dong and colleagues developed a chitosan-coated levofloxacin liposome (Lef@Lip@CS) that uses lysozyme in body fluids as the smart “switch”. In vitro antibacterial assays showed that in the presence of lysozyme, the inhibition rate against *Staphylococcus aureus* within 6 h increased from 72.46% to 100%, and the biofilm removal rate increased from 51% to 71% [49]. Therefore, after loading antibiotics into CLPs, the stability and bioavailability of the drug are enhanced, while targeted and on-demand release of the antibiotic is achieved, thereby reducing the risk of bacterial antibiotic resistance.

3. Synthesis Strategies for CLPs

3.1. Ex Vivo Coating Methods

Ex vivo coating is currently the most widely used strategy for chitosan coating, i.e., depositing chitosan onto the surface of preformed liposomes by physical or chemical methods. Depending on the coating mechanism, these methods can be divided into the following categories (Table 1).

Table 1. Studies of Synthesis Strategies of CLPs.

Modifi- cation	Cargo	Coating Strategy	Lipid Composition	Characteristics of Chitosan		Particle Size (nm)	PDI	Zeta Potential (mV)	Encapsulati- on Efficiencies	Drug Loading Capacity	Advancement	Reference
				Molecu- lar Weight	Degree of Deacetyla- tion							
/	Nadolol	Electrostatic Deposition	Soybean phospholipids, cholesterol, diacetyl phosphate, and cinnamon oil	Low (20–200 cps)	/	160.10 ± 3.17	0.19 ± 0.01	40.77 ± 2.17	56.01 ± 3.70%	61.47 ± 2.03%	1. increased stability in the gastric media; 2. higher drug release at both pH 1.2 and 6.8; 3. improved intestinal permeability	[27]
Fucoidan	Rutin	Electrostatic layer-by-layer self-assembly	Soybean phospholipids	/	≥95%	519	0.15~ 0.25	42.1	71.83%	/	1. excellent physical and chemical stability; 2. sustained drug release; 3. increased cellular uptake	[50]
Tripolyp- hosphate	Vitamin D3	Ionic Cross-Linking	Phospholipon (Lipoid 90 G, 100 mg)	Medium (190–310 kDa)	75–85%	91.3 ± 36	0.29 ± 0.10	35 ± 1	97 ± 1%	/	excellent physical and chemical stability	[51]
Trimethyl chitosan	Anthrax vaccine adsorbed	Microfluidic single step	L-α-phosph- atidyl choline derived from soybean, cholesterol	/	93.8%	101 ± 2	0.42 ± 0.01	12.9 ± 1.8	/	/	1. higher uptake efficiency; 2. stronger in vivo immune responses; 3. lower cytotoxicity	[52]
Methacry- lated	Dexame- thasone sodium phosphate	Microfluidic single step	Dipalmito- ylphospha- tidylcholine, cholesterol	Low (50–190 kDa)	75%	208 ± 1	0.23 ± 0.08	36 ± 2.3	75 ± 1.8%	5.0 ± 0.18%	1. mucoadhesion; 2. controlled drug release; 3. increased drug retention and bioavailability	[40]
TAT and Tet1 peptides	Dexame- thasone	Electrostatic Deposition	Egg yolk phospholipids, cholesterol	/	/	202 ± 1	0.06 ± 0.01	−14 ± 0.4	24 ± 2%	/	1. target specific ear cells; 2. cellular penetration	[53]

Table 1. Cont.

Modifi- cation	Cargo	Coating Strategy	Lipid Composition	Characteristics of Chitosan		Particle Size (nm)	PDI	Zeta Potential (mV)	Encapsulati- on Efficiencies	Drug Loading Capacity	Advancement	Reference
				Molecu- lar Weight	Degree of Deacetyla- tion							
Trastuzu- mab (TZ)-conju- gated chitosan iodoac- etamide	SN-38 (a quinoline alkaloid)	Electrostatic Deposition	Soybean phospholipids, cholesterol	/	/	122.03 ± 4.2	0.3	15–20	84.60%	/	1. sustained drug release; 2. substantial cellular accumulation; 3. enhanced anticancer efficacy	[54]
/	Levetir- acetam	Electrostatic Deposition	L-α-phosph- atidyl choline, cholesterol,	Medium	≥85%	167	/	−35	98.20 ± 0.05%	/	1. pH- sensitive release; 2. enhanced mucoadhesion; 3. intestinal targeting potential; 4. improved biocompatibility; 5. excellent physical and chemical stability	[55]
Tween	Donepezil	Electrostatic Deposition	Soybean phospholipid, cholesterol,	Low- medium	/	74.86 ± 2.3	0.220 ± 0.07	18.61	69.91 ± 4.82%	37.18 ± 2.08%	1. improve stability; 2. increased cellular uptake; 3. cerebral delivery	[56]
Carbox- ymethyl	Magnetic nano- particles and dexam- ethasone phosphate	Electrostatic Deposition	1,2-Dioleo- yloxy-3- trimethyla- mmonium- propane chloride, egg yolk phospholipids	/	/	268.3 ± 5.8	0.32	−20.4 ± 1.6	29.5 ± 1.2%	6.5 ± 0.4	1. excellent physical and chemical stability; 2. sustained drug release; 3. magnetic responsive target	[57]

3.1.1. Electrostatic Deposition

Electrostatic deposition is the simplest and most common method. Unmodified liposomes are usually negatively charged and have a negative zeta potential, whereas chitosan is positively charged under acidic conditions; thus the two can spontaneously achieve surface coating through electrostatic interactions [58]. In the preparation process, a chitosan solution (typically dissolved in 1% acetic acid) is added at a certain ratio to a pre-prepared liposome suspension, and the mixture is incubated under stirring to complete the coating. The concentration and molecular weight of chitosan, as well as the chitosan-to-lipid ratio, are key parameters that affect the coating outcome [59–61]. Studies have shown that as the amount of chitosan added increases, the average particle size and zeta potential of the resulting CLPs increase significantly [59,62].

Despite its simplicity and widespread use, electrostatic deposition has several inherent limitations that have been revealed through these characterization techniques [63]. For example, the process offers limited control over coating uniformity [63]. While particle size and zeta potential can confirm the overall deposition of chitosan onto liposomes, they cannot guarantee that the coating is complete and evenly distributed across all particles. Transmission electron microscopy (TEM) and field-emission TEM (FE-TEM) imaging have revealed that chitosan deposition can result in uneven coverage, with some areas of the liposomal surface remaining uncoated while others exhibit thicker polymer layers [64]. This lack of uniformity may compromise the consistency and performance of the final formulation. Furthermore, the process operates within a narrow critical concentration window [58]. Stable CLPs that resist aggregation could only be achieved when the chitosan concentration was maintained within a narrow range between a minimum (c_{min}) and a maximum (c_{max}) critical value [58]. Below c_{min} , large aggregates formed and underwent phase separation within minutes, which was attributed to the formation of coacervates [58]. Above c_{max} , large flocs sedimented within hours as a result of depletion flocculation. Importantly, both c_{min} and c_{max} varied with liposomal concentration and size [58]. Therefore, while electrostatic deposition remains a widely used and convenient method for preparing CLPs, its limitations—particularly regarding coating uniformity, critical concentration dependence, and aggregation propensity—must be carefully addressed when designing formulations for clinical or industrial applications.

3.1.2. Layer-by-Layer (LbL) Self-Assembly

Layer-by-layer self-assembly is a more refined coating strategy. By alternately depositing oppositely charged polyelectrolytes onto liposomes, a multilayer shell structure is formed [30]. Using chitosan (cationic) and sodium alginate (anionic) as an example, researchers can sequentially coat the two onto the liposome surface to construct multilayer polyelectrolyte vesicles. Cuomo et al. successfully prepared chitosan/alginate multilayer nanoparticles by alternating deposition of alginate and chitosan onto liposomes, and transmission electron microscopy revealed a polyelectrolyte layer thickness of approximately 20 nm. The advantage of multilayer coating lies in the ability to precisely modulate the permeability and mechanical strength of the capsule wall by controlling the number of layers [65]. Moreover, Han et al. employed this strategy using positively charged chitosan and negatively charged fucoidan as biopolymers to coat rutin-loaded nanoliposomes. Under optimized conditions, the particle size was 346 nm, zeta potential was -33.5 mV, and encapsulation efficiency reached 77.01% [50]. Meanwhile, the multilayer chitosan/alginate coating system significantly improves the pH stability, ionic strength tolerance, and storage stability of liposomes [66,67].

Comprehensive characterization has revealed both the structural features and the limitations of LbL-assembled systems. Streaming potential and X-ray photoelectron spec-

troscopy measurements indicated strong interpenetration of chitosan and polyanion layers, while liposomes formed separate layers, which are more promising for sustained release [68]. However, because the diffusion coefficient of nanoparticles larger than 200 nm in tumor tissue decreases as particle size increases, the substantial size increase caused by the multilayer structure may restrict their ability to penetrate deep tissues [69,70]. Indeed, paclitaxel-loaded polyacrylic acid–chitosan multilayered liposomes prepared by LbL assembly reached a particle size of 215 ± 17 nm, exceeding this threshold and potentially limiting their ability to penetrate deeply into tumor [71]. Moreover, the multi-step nature of LbL assembly is labor-intensive and requires numerous purification steps that limit scalability, yield, and potential for clinical translation [72,73]. These limitations make this method more suitable for research applications than industrial-scale production.

3.1.3. Ionic Crosslinking

Ionic crosslinking uses multivalent anions to crosslink chitosan molecules, forming stable coating layers. The most common crosslinker is sodium tripolyphosphate, which forms a nanoscale crosslinked network with the amino groups of chitosan through electrostatic interactions. This method can be carried out under mild conditions without the use of organic solvents, making it suitable for drugs that are sensitive to temperature or organic solvents. It is also simple to operate, offers controllable particle size, and exhibits good reproducibility. The TPP-CLP system shows excellent drug-loading capacity for various types of drugs. For hydrophobic drugs, the system can achieve a drug loading of 41–56%, while for bioactive compounds such as polyphenols and flavonoids, the optimized TPP-CLPs can achieve an encapsulation efficiency as high as 95–99%. And for lipophilic micronutrients like vitamin D₃, the encapsulation efficiency can reach 97% [51,74,75]. At the same time, the crosslinked network of chitosan and TPP can significantly slow the drug release rate and achieve concentration-dependent controlled release behavior, which is especially beneficial for drugs requiring sustained release.

To confirm the formation of the TPP–chitosan crosslinked network and to evaluate the quality of the resulting coating, a comprehensive characterization approach is essential. High-resolution transmission electron microscopy (HRTEM) provides direct visualization of the coating layer, revealing the spherical shape and smooth surface of peptide-loaded CS-TPP/liposomes [76]. Fourier transform infrared (FT-IR) spectroscopy can confirm the cross-linking between chitosan and TPP [76]. Differential scanning calorimetry (DSC) provides additional insights into the thermal stability of the system; DSC findings have indicated enhanced electrostatic interactions among CS and lecithin molecules, leading to an increase in the melting (T_m) and decomposition temperature (T_d) in peptide-loaded TPP-CLPs [76].

However, several limitations of this method must be carefully considered. The crosslinking process is highly sensitive to formulation parameters, which significantly affects colloidal stability and aggregation behavior. Studies have shown that the initial chitosan concentration and the TPP solution concentration are critical variables that promote the aggregation of nanoparticles over time [77]. Insufficient TPP mass ratios result in inadequate crosslinking of the chitosan chains, producing an unstable nanoparticle structure prone to rupture [77]. Conversely, increasing the TPP concentration beyond the optimal level leads to excessive cross-linking, causing nanoparticles to become overly dense or aggregate, which reduces encapsulation efficiency due to limited space for drug loading and possible particle instability [77]. Therefore, although ionic crosslinking with TPP offers a mild, solvent-free approach for preparing CLPs with excellent drug loading capacity, its limitations—particularly regarding formulation parameters and aggregation propensity—must be carefully addressed when designing formulations for specific therapeutic applications.

3.2. *In Situ* Coating Methods

Although conventional *ex vivo* coating methods are simple to perform, they are often time-consuming and suffer from poor batch-to-batch reproducibility [78]. In recent years, *in situ* coating methods, in which chitosan coating is performed simultaneously with liposome formation, have been developed. These methods can yield a more uniform and tighter coating while reducing the final particle size [52,79]. Microfluidic technology is the most representative *in situ* coating method. Bochicchio et al. proposed a continuous preparation method based on microfluidic principles that enables uniform chitosan coating during liposome formation [78]. Compared with the traditional drop-wise addition method, this microfluidic approach exhibits significant advantages in three dimensions: time efficiency, product homogeneity, and equipment requirements [78]. In terms of time efficiency, the microfluidic method requires only 20 min to prepare 1 L of CLPs suspension, whereas the traditional method can only produce 20 mL of product in the same time, representing a 50-fold difference in yield [78]. Structurally, the traditional method tends to produce aggregated precipitates between liposomes and cationic chitosan rather than an ideal encapsulating structure; in contrast, the microfluidic method allows continuous and uniform interaction between the liposome suspension and the chitosan solution, ensuring complete and uniform coverage of chitosan [78]. As a result, the polydispersity index decreases from 0.30 (traditional method) to 0.19, the zeta potential increases significantly from -20.0 mV to $+47.8$ mV, and no aggregation or precipitation is observed. Moreover, this method operates in a continuous production mode, where the feed solutions mix and react at fixed flow rates in microchannels; it does not require large, expensive equipment and can be run under ambient laboratory conditions, thereby overcoming the disadvantages of traditional methods (time-consuming, large equipment, high cost) [78]. Microfluidic technology has also advanced the clinical application research of CLPs. For example, Mirkani et al. used microfluidic technology to synthesize methacrylated chitosan (CSMA)-coated liposomes for ocular drug delivery [40]. Owing to the precise control over fluid mixing offered by microfluidics, this platform achieved excellent control over particle size and surface charge: the uncoated liposomes had a size of 154 nm, which increased to only 208 nm after CSMA coating, and the zeta potential shifted from -8.3 mV to $+36$ mV, fully confirming effective functionalization [40]. TEM imaging further confirmed the successful coating, revealing nearly spherical, unilamellar vesicles with uniform distribution, indicative of superior colloidal stability conferred by the CSMA layer [40]. Through dual electrostatic and covalent interactions, the CSMA coating specifically binds to mucin; after 4 h of incubation with mucin, the particle size significantly increased to 369 nm and the zeta potential decreased to $+2.4$ mV, demonstrating efficient mucin-anchoring and mucoadhesive ability [40]. Dexamethasone sodium phosphate exhibited a sustained biphasic release profile from the CSMA-coated liposomes, achieving more efficient ocular drug bioavailability and therapeutic outcomes [40]. This study fully demonstrates the advantages of microfluidic technology for preparing functionalized liposomes.

Despite these notable advantages, the application of microfluidic technology in production of CLPs still faces several significant limitations. Limited throughput remains a major obstacle for industrial integration, as current platforms typically operate at milliliter-scale flow rates and require parallelization to achieve meaningful production volumes, which introduces challenges in flow distribution uniformity and channel-to-channel reproducibility [80]. Material compatibility is another critical concern: PDMS, the most common chip material, exhibits inherent hydrophobicity that causes nonspecific adsorption of hydrophobic drugs and lipids, leading to deviations in drug concentration and batch inconsistency [81]. Moreover, organic solvents used in liposome preparation are incompatible with PDMS, while glass or silicon alternatives are costly and complex to fabri-

cate [82]. Device fouling during prolonged operation may reduce particle homogeneity and encapsulation efficiency. Solvent removal from the final formulation adds further safety concerns [80]. Additionally, chip design variability complicates the establishment of standardized manufacturing protocols [83]. Collectively, these challenges confine microfluidic CLPs production predominantly to laboratory settings, and overcoming them is essential for successful translation to industrial-scale manufacturing.

Table 2 provides a comparative overview of the four chitosan coating strategies discussed in this section, highlighting their respective strengths and limitations across multiple parameters relevant to formulation development and clinical translation.

Table 2. Comparative Analysis of Synthesis Strategies for CLPs.

	Electrostatic Deposition	Layer-by-Layer Assembly	Ionic Crosslinking	Microfluidic In Situ Coating
Coating Efficiency	Low	Moderate	High	High
Reproducibility	Moderate	Low	Moderate	High
Particle Size Control	Poor	Poor	Moderate	Excellent
Scalability	High	Low	Moderate	Moderate
Manufacturing Feasibility	Simple	Complex	Simple	Complex
Clinical Translation Potential	Low	Low	Moderate	High
Key Limitations	prone to coacervation and depletion flocculation; limited coating uniformity	Significant particle enlargement; time-consuming; aggregation at higher layer numbers	TPP concentration sensitivity; aggregation; particle enlargement	Low throughput; PDMS nonspecific adsorption; solvent removal; chip fouling; high equipment cost

4. Modification Strategies for CLPs

Although chitosan itself possesses excellent mucoadhesive properties and biocompatibility, its functionality is limited in specific application scenarios, such as lack of enough long circulatory half-life, insufficient active targeting, and decreased solubility under neutral pH conditions [26,84]. To expand the application scope of CLPs, researchers have chemically modified the chitosan to prepare a variety of functional chitosan derivatives and have used them for liposome surface coating. These modification strategies not only retain the inherent positive charge and mucoadhesive advantages of chitosan but also endow the liposomes with additional features such as smart responsiveness, longer half-life and active targeting [44,85,86].

4.1. Polymer Modification

By grafting hydrophilic polymers onto the chitosan backbone, hybrid coatings can be constructed that combine mucoadhesive and stealth functions. PEG is the most commonly used hydrophilic modification molecule; it is covalently linked to the amino or hydroxyl groups of chitosan to form PEG–chitosan copolymers. Liposomes coated with this copolymer exhibit a unique “dual-function” property: the chitosan provides mucoadhesion through positive-charge adsorption, while the extended PEG chains form a hydration layer on the liposome surface that effectively resists plasma protein adsorption, thereby delaying clearance by the reticuloendothelial system [87,88]. For example, Deygen et al. provided a classic and representative example of this dual-function coating strategy. They applied

a branched PEG–chitosan copolymer as a stabilizing additive to anionic liposomes [89]. The study demonstrated that anionic liposomes complex with PEG–chitosan through electrostatic interactions, leading to surface charge neutralization. Notably, the PEG–chitosan copolymer generated two protective shields for the liposomes: on one hand, the PEG chains formed a hydration layer that effectively reduced plasma protein adsorption; on the other hand, complex formation increased the liposome size and enhanced surface steric hindrance, thereby significantly improving storage stability of the liposomes. This work directly demonstrated that the PEG–chitosan copolymer serves as an effective liposomal stabilizer, providing both electrostatic and steric stabilization. Moreover, polymer modification can increase the mucoadhesion of CLPs. For instance, the CSMA-coated liposomes prepared by Mirkani et al. showed significantly longer fluorescence retention time in an ex vivo bovine conjunctival tissue retention assay compared with uncoated liposomes and CLPs [40]. In another study, PEG–chitosan was used to coat oral insulin liposomes; the results showed that the formulation significantly prolonged intestinal mucosal retention time while resisting degradation by pepsin and trypsin [90,91].

4.2. Targeting Modification

Conjugation of small targeting ligand molecules onto chitosan can confer active targeting ability to liposomes toward specific cells or tissues. Folic acid has a low molecular weight and low immunogenicity; the folate receptor is highly overexpressed on the surface of various tumor cells but expressed at very low levels on normal cells, making it one of the most commonly used ligands for tumor-targeted drug delivery systems. For example, Le et al. reported the synthesis of a chitosan–polyethylene glycol–folic acid (CTS-PEG-FA) conjugate and its application as a functional coating for liposomes [38]. CTS-PEG-FA-coated liposomes served as carriers for quercetin, exerted active targeting functions in vivo, specifically recognized the folate receptor overexpressed on tumor, promoted receptor-mediated drug endocytosis, significantly increased drug accumulation at the lesion, and exhibited promising cytotoxic effects [38]. This study provided strong evidence for the application of multifunctional chitosan coatings in targeted drug delivery. In addition, galactose, RGD peptide, and aptamers have been successfully conjugated to chitosan for targeting the asialoglycoprotein receptor on hepatocyte surfaces, integrin $\alpha v \beta 3$, and various biomarkers, respectively. Wei et al. developed galactosylated chitosan-modified liposomes (GC@Lipo) that selectively bind to the ASGPR highly expressed on the membrane of hepatocellular carcinoma cells, delivering oleanolic acid to the lesion and significantly enhancing the antitumor efficacy of the drug [92]. Notably, the multiple active sites on the chitosan backbone allow covalent conjugation of multiple ligands, enabling multi-target synergistic targeting or dual-function design. Iftode et al. constructed dual-peptide-functionalized carboxymethyl CLPs loaded with dexamethasone for active targeted therapy of inner ear diseases. Carboxymethyl chitosan (CMCS) was co-functionalized with Tet1 peptide (targeting specific inner ear cells) and TAT peptide (promoting cell penetration). Infrared spectroscopy confirmed successful functionalization of CMCS with both peptides [53].

4.3. Smart Responsive Modification

The introduction of crosslinkable or responsive chemical groups, or the loading of responsive particles, enables the chitosan coating to respond to different physiological conditions [85]. In recent years, a diverse array of stimuli-responsive CLPs has been developed, responding to endogenous stimuli (such as redox gradients, pH changes, and enzyme) or exogenous stimuli (including temperature, light, and magnetic fields) [93]. These smart systems enable spatiotemporally controlled drug release, improved therapeutic efficacy, and reduced systemic toxicity.

4.3.1. pH-Responsive Modification

pH-responsive CLPs have attracted considerable interest. Chitosan itself loses its positive charge and becomes less soluble when $\text{pH} > 6.5$. Researchers have introduced pH-sensitive groups so that the chitosan coating remains stable at neutral pH but undergoes conformational change or degradation in an acidic microenvironment, thereby triggering rapid drug release. Dong et al. firstly used chitosan quaternary ammonium salt to coat luteolin-loaded liposomes, constructing an acid-responsive targeted drug delivery system (H-L-NPs) [94]. In vitro and in vivo experiments demonstrated that the system had higher solubility, could target and adsorb negatively charged *Helicobacter pylori*, released drugs earlier and faster in an acidic environment, and exhibited stronger gastric mucoadhesion than intestinal adhesion. In addition, the system increased the permeability of the bacterial cell membrane, facilitating drug entry into cells [94].

4.3.2. Redox-Responsive Modification

Redox-responsive systems exploit the notable differences in redox potential between healthy physiological conditions and pathological sites, such as tumors or inflamed tissues [95]. Introducing thiol groups onto chitosan (thiolated chitosan) allows the formation of a disulfide crosslinked network on the liposome surface, significantly enhancing mechanical stability and dilution resistance [96]. Thiolated CLPs exhibit far better stability in digestive fluid than ordinary CLPs [97]. Mazzotta et al. synthesized a novel folic acid-cysteine-thiolated chitosan (FTC) dual-functional derivative with active targeting capability and redox responsiveness, and used it to coat liposomes [98]. The disulfide bonds of the thiol groups provided a tight physical barrier until the complex reaches the target site, while the cysteine moiety served as an effector group for different redox potentials [98]. Meanwhile, Arshad et al. developed cholic acid-grafted thiolated chitosan-coated nanoliposomes (CA-CS-TGA-NLs) for loading azathioprine. The coating enhanced mucoadhesive potential, with a mucoadhesion time of 180 ± 13 min, increased intestinal penetration by 2.84-fold, and improved the oral bioavailability of azathioprine [99].

4.3.3. Enzyme-Responsive Modification

Enzyme-responsive modification represents another emerging strategy. Since chitosan can be specifically degraded by lysozyme—a natural enzyme present in various body fluids—the Lef@Lip@CS uses lysozyme in body fluids as its smart “switch” [49]. In vitro bacteriostatic experiments showed significant differences before and after enzyme addition, with 6-h inhibition rates of 72.46% and 100%, and biofilm removal rates of 51% and 71%, respectively [49].

4.3.4. Thermo-Responsive and Photo-Responsive Modification

Thermo-responsive groups have also been integrated with CLPs. And photo-responsive and near-infrared (NIR)-responsive components have been designed for spatiotemporally controlled drug release. Wang et al. developed a photothermal responsive drug carrier by loading resveratrol in CLPs and coating them with gold nanoshells (GNS@CTS@Res-lips) [100]. The GNS@CTS@Res-lips function as effective photothermal agents under NIR irradiation, enabling localized temperature elevation for combined chemo-photothermal therapy [100].

4.3.5. Magnetic-Responsive Modification

CLPs can acquire magnetic responsiveness by incorporating magnetic nanoparticles (MNPs) into the liposomal system. The carboxymethyl chitosan-coated magnetic cationic liposomes serve as smart nanocarriers for targeted corticosteroid delivery to auditory hair

cells [57]. The magnetic nanoparticles and dexamethasone phosphate are loaded in the aqueous core [57]. This system has demonstrated efficacy in preserving mitochondrial function in an in vitro model of hearing loss, thereby preventing gentamicin- and cisplatin-induced cellular senescence and cytotoxicity [57]. Future studies should focus on in vivo investigations to evaluate the targeting ability of magnetic CLPs toward lesions under an external magnetic field, enabling spatiotemporally controlled drug release and enhanced therapeutic efficacy.

The development of these diverse smart-responsive CLPs represents a significant advancement toward precision medicine, offering spatiotemporally controlled drug release, improved therapeutic efficacy, and reduced systemic toxicity.

4.4. Enzyme Modification

Conjugation of active biological enzymes can endow the chitosan coating with unique bioactivities. Park et al. designed bromelain-modified CLPs. They first prepared highly mucoadhesive CLPs using 0.1% chitosan solution, and then covalently coupled bromelain (a protease complex extracted from pineapple stems) onto the chitosan surface to generate Bro-CS-Lip. When the enzyme density reached 9.2 nmol/mg lipid, Bro-CS-Lip showed a 6.50-fold increase in apparent permeability in a Caco-2 monolayer model compared to CLPs and a 2.53-fold increase in a Caco-2/HT29 co-culture model (simulating a mucus-secreting environment). Confocal Z-stack imaging confirmed that Bro-CS-Lip could penetrate deeply into the cell layer, whereas CLPs were largely trapped in the mucus matrix. Based on the above evidence, Bro-CS-Lip exhibit significant advantages in oral drug delivery: their positively charged surface achieves mucoadhesion and formulation protection through electrostatic interactions, and bromelain conjugation can effectively balance and overcome the mucus barrier, markedly enhancing the transmembrane transport efficiency and bioavailability of drugs [101].

5. Biomedical Applications of CLPs

CLPs, owing to their excellent stability, mucoadhesive properties and functionalizable surface characteristics, have been extensively investigated for drug delivery via various administration routes. This system has achieved significant progress in anti-infective therapy, tumor-targeted therapy and immunomodulation research (shown in Figure 2 and Table 3).

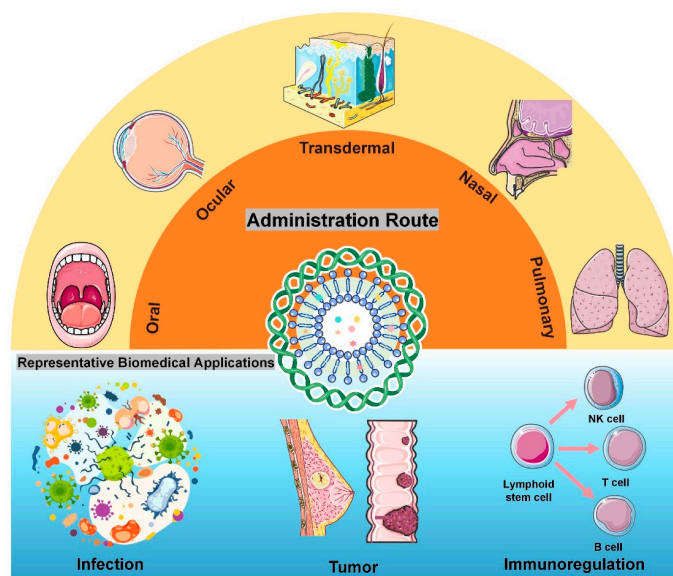


Figure 2. The Various Administration Routes and Representative Biomedical Applications of CLPs.

Table 3. Applications of CLPs in Biomedicine.

Modification	Cargo	Encapsulation Efficiencies	Administration	Type of Experiment	Disease Model	Advancement	Reference
/	Exemestane (EXM) and genistein (GNS)	70–80%	Oral	in vivo	Breast Cancer	1. synergistic effect of EXM and GNS; 2. excellent physical and chemical stability; 3. controlled drug release	[102]
Bile salt	Ganciclovir and resveratrol	Ganciclovir: $68.4 \pm 5.9\%$; resveratrol: $88.5 \pm 6.1\%$	Ocular	in vivo	Ocular viral infection	1. higher transcorneal flux and permeability coefficient; 2. non-irritant properties; 3. anti-inflammatory	[103]
/	Exemestane (EXM) and genistein (GNS)	70–80%	Oral	in vivo	Breast Cancer	1. synergistic effect of EXM and GNS; 2. excellent physical and chemical stability; 3. controlled drug release	[102]
Bile salt	Ganciclovir and resveratrol	Ganciclovir: $68.4 \pm 5.9\%$; resveratrol: $88.5 \pm 6.1\%$	Ocular	in vivo	Ocular viral infection	1. higher transcorneal flux and permeability coefficient; 2. non-irritant properties; 3. anti-inflammatory	[103]
/	Ciprofloxacin and 5-fluorouracil	/	Oral	in vitro	Colorectal cancer and bacterial infections	1. gastrointestinal stability; 2. mucoadhesion; 3. low hemato-toxicity; 4. antibacterial activity	[104]
D-tocopherol polyethylene glycol, cholesteryl hemisuccinate	Temozolomide	$78.85 \pm 2.62\%$	Nasal mucosal	in vitro	Glioblastoma	1. pH-sensitive release; 2. superior mucoadhesion; 3. optimized CNS accumulation with minimal systemic exposure	[105]
/	Usnic acid	/	/	in vitro	Multidrug-resistant	1. antimicrobial efficacy; 2. biofilm control	[106]
Lactose-leucine based microspheres	Ambrisentan	/	Pulmonary inhalation	in vitro	Pulmonary arterial hypertension	1. prevent fusion during drying and reconstitution; 2. sustained drug release; 3. optimal targeted lung deposition; 4. minimized systemic distribution.	[107]

Table 3. Cont.

Modification	Cargo	Encapsulation Efficiencies	Administration	Type of Experiment	Disease Model	Advancement	Reference
Glucose oxidase	Copper sulfide	/	Nasal mucosal	in vivo	Glioblastoma	1. Cu ²⁺ -mediated Fenton-like reaction; 2. lipid peroxidation and the onset of ferroptosis; 3. immunogenic cell	[108]
Bile salt	Olmesartan	87.36 ± 1.07%	Nasal mucosal	in vivo	Alzheimer's disease	1. sustained drug release; 2. increased flux and permeability; 3. improved brain bioavailability	[109]
Fucoidan	Rutin	/	Oral	in vivo	Hyperuricemia	Enhanced bioavailability and targeting function of rutin	[110]
Microneedle capsules	Insulin	/	Oral	in vitro	Diabetes	1. sustained drug release; 2. decreased gastric degradation; 3. facilitated delivery to the intestine	[111]
Quaternized	Mometasone furoate	/	Nasal mucosal	in vivo	Allergic rhinitis	mucoadhesion and mucosal retention	[112]
/	Ghrelin	53.2 ± 0.7%	Nasal mucosal	in vivo	/	1. excellent physical and chemical stability; 2. mucoadhesion; 3. increased permeability; 4. cerebral delivery	[113]
Tween	MMK-1931	81.66%	Oral	in vivo	Ehrlich ascites tumour	1. sustained and controlled drug release; 2. better anti-tumor efficacy	[114]
Catechol	Resveratrol (RES) and carnosine (CAR)	82.39 ± 1.54%	Cutaneous	in vivo	Skin aging	1. increase the transdermal penetration; 2. sustained drug release; 3. skin anti-aging	[115]

5.1. Oral Delivery

Oral administration is the most convenient route of drug delivery; however, drugs face multiple barriers in the gastrointestinal tract, including gastric acid degradation, enzymatic breakdown, the mucus barrier and hepatic first-pass metabolism [116,117]. Due to the electrostatic interaction between the positive charge of chitosan and the negatively charged proteins of the mucus layer, CLPs can prolong their retention time on the gastrointestinal mucosa. In addition, chitosan possesses a certain penetration-enhancing effect and can promote drug absorption by opening intercellular tight junctions. İpekci et al. developed a CLP system loaded with Nadolol for the treatment of hypertension. They coated liposomes at different chitosan-to-lipid ratios (0.1–0.4 *w/w*). The optimized coated liposomes (L1C-NDL) showed a particle size of approximately 160.10 ± 3.17 nm, a PDI of 0.19 ± 0.01 , an encapsulation efficiency of $56.01 \pm 3.70\%$, and a drug loading capacity as high as $61.47 \pm 2.03\%$. Enzymatic degradation studies demonstrated that the chitosan coating significantly improved the stability of liposomes in gastric medium, and higher *in vitro* release rates were observed under pH 6.8 conditions. More importantly, the Caco-2 cell monolayer model confirmed that the transport of CLPs from the apical to the basolateral side was markedly enhanced, with cell viability exceeding 95%, showing good oral absorption potential [27].

5.2. Ocular Delivery

The main challenges for ocular drug delivery include rapid tear washout, the corneal barrier, and the limited surface area for drug absorption [118,119]. Due to the strong electrostatic interaction between chitosan and the negatively charged mucin on the ocular surface, CLPs can significantly prolong the retention time of drugs on the ocular surface [120]. Badran et al. combined CLPs with thermosensitive *in situ* gels (ISG) to construct a novel ophthalmic delivery system loaded with metoprolol (MT-CLPs) for glaucoma treatment. The zeta potential of the system changed from negative to positive after chitosan coating, enhancing electrostatic adhesion to the mucosa. The CLPs-loaded ISG underwent rapid sol–gel transition at physiological temperature. *In vivo* experiments showed that this system enhanced corneal permeability of the drug, significantly reduced intraocular pressure without irritative reactions [121]. Furthermore, bile salt-modified liposomes (bilosomes) have also shown unique advantages in ocular drug delivery in recent years. Shalaby et al. co-loaded the antiviral drug ganciclovir (GCV) and the natural anti-inflammatory and antioxidant resveratrol (RES) into bilosomes, and further introduced a chitosan coating to enhance ocular adhesion. The results showed that the optimized formulation achieved the best ocular delivery of both GCV and RES, with transcorneal fluxes reaching 2.31 ± 0.17 $\mu\text{g}/\text{cm}^2\cdot\text{h}$ and 3.27 ± 0.28 $\mu\text{g}/\text{cm}^2\cdot\text{h}$, respectively. The chitosan coating not only improved the ocular surface retention but also acted synergistically with the bile acid components of the bilosomes: the bile acids in the bilosomes effectively regulated tight junctions between corneal epithelial cells to increase corneal permeability, while chitosan provided long-lasting mucoadhesion. Together, they enabled precise, efficient and synergistic delivery of antiviral and anti-inflammatory drugs [103].

5.3. Transdermal Delivery

Transdermal administration can avoid the first-pass effect associated with oral delivery and provide stable plasma drug concentrations; however, the stratum corneum barrier of the skin restricts the transdermal absorption [122]. The positive charge of chitosan facilitates electrostatic interactions with the negatively charged skin surface, promoting adhesion of liposomes to the stratum corneum, while the deformability of liposomes helps them to penetrate the skin barrier [123]. Lee et al. employed CLPs to deliver the photosensitizer

indocyanine green (ICG) for topical photodynamic therapy (PDT) of melanoma. Their study not only demonstrated that the chitosan coating significantly improved the stability and transdermal permeability of ICG, but also effectively enhanced its accumulation in target cells and the photodynamic killing effect, thereby providing a feasible transdermal delivery strategy for non-invasive treatment of melanoma and offering strong evidence for the application potential of CLPs in transdermal drug delivery [124]. Eid et al. further extended the application scenario of CLPs in transdermal therapy to diabetic skin wound repair. They constructed citicoline-loaded CLPs (CT-CS-LPs) with an average particle size of 211.6 nm, encapsulation efficiency of 50.7%, and surface potential of +32.1 mV; the carrier exhibited significant sustained-release behavior in vitro. In a diabetic rat skin wound model, the wounds treated with CT-CS-LPs healed significantly faster than those in the untreated group and the CLP group. The mechanism involved effective regulation of the inflammatory response, promotion of re-epithelialization, neovascularization, fibroblast proliferation and connective tissue remodeling, which acted synergistically to achieve faster wound healing [125]. Owing to their deformability and positive-charge-mediated skin penetration, CLPs show excellent prospects for the local treatment of chronic wounds, including diabetic ulcers.

5.4. Nasal Delivery

Intranasal administration can deliver drugs directly to the brain via the olfactory and trigeminal nerves, bypassing the blood–brain barrier, and thus represents an important strategy for the treatment of central nervous system diseases. However, the mucociliary clearance mechanism of the nasal mucosa severely limits the residence time of drugs in the nasal cavity [126,127]. Chitosan coating can overcome this obstacle by enhancing the adhesiveness of formulations to the nasal mucosa. Kapoor et al. prepared CLPs of amantadine for nose-to-brain delivery to treat Parkinson's disease. The chitosan coating significantly enhanced the retention time of the formulation in the nasal cavity. In vitro drug release showed a sustained release profile, with a cumulative release of 71.01% over 24 h. Ex vivo goat nasal mucosa experiments demonstrated that the permeability of CLPs of amantadine was 3.22-fold higher than that of the drug solution [128]. For the treatment of glioblastoma (GBM), Jain et al. further combined chitosan coating with pH-responsive liposomes to develop a temozolomide nasal delivery system (SpH-TMZ-CS-LIPO) [105]. This system employed cholesterol hemisuccinate to construct a pH-sensitive lipid bilayer that triggered rapid drug release (cumulative release 92–94%) in the acidic GBM microenvironment (pH 4.5–5.5) while remaining stable at a physiological pH. The chitosan coating significantly enhanced the nasal adhesiveness of the liposomes, increasing the ex vivo goat nasal mucosal permeation flux by 1.39-fold compared with free drug. Cellular uptake experiments showed that the uptake of SpH-TMZ-CS-LIPO in U87MG glioma cells was 4.6-fold higher than that of free temozolomide, and the IC_{50} value was reduced to $0.396 \pm 0.105 \mu\text{g/mL}$, representing a more than 33-fold improvement in efficacy. After nasal administration in rats, this liposomal formulation achieved a peak concentration of $260.82 \mu\text{g/mL}$ in the brain, and the brain AUC was more than 22-fold higher than that of free temozolomide. The drug targeting efficiency reached 177.2%, and the direct nose-to-brain transport percentage was 94.3%, confirming that the drug was delivered to the brain mainly via the direct nose-to-brain pathway rather than through systemic circulation. Therefore, by tailoring the chitosan coating technology and liposomal bilayer composition, it is possible to further integrate intelligent responsiveness and precise targeting control on the basis of enhanced nasal mucoadhesion, thereby markedly increasing intracerebral drug accumulation and therapeutic efficacy, and providing a safe and highly efficient new approach for the non-invasive administration of drugs against brain diseases.

5.5. Pulmonary Delivery

Pulmonary administration can deliver drugs directly to the lungs, achieving higher local drug accumulation and lower systemic exposure, and is particularly suitable for lung tissue targeting [129]. However, conventional liposomes are prone to structural disruption and drug loss due to fusion and leakage during the spray-drying process for preparing dry powder inhalers [130]. Chitosan coating, by virtue of its cationic nature wrapping around the liposome surface, can effectively maintain the structural integrity of liposomes during drying and reconstitution. At the same time, electrostatic interactions between chitosan and the pulmonary mucosa enhance drug retention and targeting in the lungs [131]. Ali et al. developed a breath-activated, ambrisentan (AMB)-loaded CLPs dry powder inhaler (Ambri-Chitosomes) for the treatment of pulmonary arterial hypertension (PAH) [107]. Given that the therapeutic target of AMB—the pulmonary arterioles—is in direct contact with the alveoli, pulmonary delivery is expected to improve local efficacy while significantly reducing systemic toxicity. They encapsulated AMB in liposomes, then surface-coated them with chitosan to protect the liposomes during drying. The Ambri-Chitosomes were subsequently encapsulated in lactose-leucine carrier microspheres and finally processed into an inhalable dry powder formulation using nano-spray drying technology. After reconstitution, the Ambri-Chitosomes had a particle size of approximately 190 nm and a mass median aerodynamic diameter (MMAD) of about 1.9 μm , indicating good pulmonary inhalability. In vitro release studies showed sustained drug release for up to 48 h and good biocompatibility with A549 lung epithelial cells. In vivo pharmacokinetic results in rats demonstrated that, compared with oral AMB, the inhaled Ambri-Chitosomes significantly increased drug accumulation and retention time in the lungs while markedly reducing systemic exposure. These findings prove that CLPs can achieve sustained drug release and optimized pulmonary delivery after inhalation administration. Therefore, as a lung-targeted delivery system, they hold promise for the local treatment of pulmonary arterial hypertension, pulmonary infections, and lung cancer.

5.6. Anti-Infective Therapy

CLPs can be used to deliver antibiotics or other antibacterial active ingredients against bacterial and fungal infections. Conventional anti-infective therapy faces multiple challenges, including poor drug stability, low oral bioavailability, difficulty in penetrating bacterial biofilms, and rising antibiotic resistance [132]. Chitosan coating, by virtue of its positively charged surface, mucoadhesive properties and controlled-release characteristics, offers a promising formulation strategy to overcome these difficulties [133]. Wen et al. prepared moringin-loaded CLPs (MR-CS-LPs) to inhibit *Staphylococcus aureus*. In vitro antibacterial assays showed that the minimum inhibitory concentration (MIC) of MR-CS-LPs was as low as 0.125 mg/mL, demonstrating potent antibacterial activity. Further mechanistic studies revealed that this liposomal system destroyed the cellular wall and membrane integrity of *S. aureus*, causing leakage of cellular contents, while inducing oxidative stress-mediated apoptosis and effectively inhibiting biofilm formation [134]. To address the treatment dilemma of multidrug-resistant (MDR) infections, Coriolano et al. developed usnic acid (UA)-loaded CLPs (Lipo-UA-Chi) and systematically evaluated their antibacterial, anti-biofilm and hemocompatibility properties, both alone and in combination with polymyxin B (PMB). The chitosan coating not only solved the problems of poor UA solubility and high toxicity, but also, through strong electrostatic interactions between its positively charged surface and bacterial lipopolysaccharides, enhanced the affinity of the liposomes towards drug-resistant bacteria, thereby significantly improving the antibacterial activity of UA. In checkerboard microdilution assays against clinical MDR isolates of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, the combination of

Lipo-UA-Chi and PMB showed additive or synergistic interactions for all tested strains. The combination reduced the MIC of PMB by up to 128-fold and that of Lipo-UA-Chi by up to 4-fold, successfully reversing the initial tolerance of the resistant strains. Notably, for a particular *P. aeruginosa* strain, the combination of Lipo-UA-Chi and PMB achieved up to 100% inhibition of biofilm formation and up to 81.3% eradication of preformed mature biofilms. Moreover, all tested concentrations exhibited non-hemolytic behavior, indicating good safety [106]. In addition, nystatin is a highly effective antifungal drug, but its poor solubility and low permeability severely limit its clinical efficacy. Sulastri et al. used chitosan and sodium alginate to coat nystatin liposomes via layer-by-layer self-assembly technology, successfully constructing a multilayer polyelectrolyte delivery system against *Candida albicans*. By optimizing the chitosan/alginate ratio, the optimal formulation NA7-Ch3-Nys-Lip showed a significant increase in encapsulation efficiency from $61.61 \pm 1.60\%$ to $83.77 \pm 2.00\%$, with a particle size between 200–300 nm, a positive zeta potential, and a well-defined spherical morphology confirmed by transmission electron microscopy. Compared with uncoated nystatin liposomes (MIC $1.456 \mu\text{g/mL}$), NA7-Ch3-Nys-Lip exhibited a much lower MIC of $0.732 \mu\text{g/mL}$, demonstrating the strongest antifungal activity. In vitro release studies showed that the multilayer coating achieved controlled and sustained drug release, with only $64.17 \pm 4.00\%$ released within 24 h, markedly superior to the rapid release of uncoated liposomes ($89.28 \pm 2.67\%$ within 12 h). Furthermore, after 28 days of storage at 4°C , the particle size, zeta potential and encapsulation efficiency of the multilayer coated system showed no significant changes ($p > 0.05$), demonstrating excellent long-term storage stability. This study provides an innovative strategy for the formulation of antifungal therapy that combines high delivery efficiency with long-term stability [135].

5.7. Tumor-Targeted Therapy

The role of chitosan-coated liposomal drug delivery systems in tumor therapy cannot be underestimated. Researchers have endowed the delivery systems with active targeting ability by conjugating antibodies. For example, Zhang et al. developed trastuzumab (TZ)-conjugated chitosan iodoacetamide (CsIA)-coated liposomal nanoparticles loaded with SN-38 for targeting HER2-positive lung cancer. The nanoparticles were spherical, approximately 77 nm in diameter, and had a positive zeta potential. SN-38 was released from the nanocarriers in a sustained manner over 24 h. TZ-conjugated nanoparticles exhibited remarkable cellular accumulation and significantly enhanced anticancer efficacy in HER2-positive Calu-3 lung adenocarcinoma cells, far superior to the drug solution and unconjugated nanoparticles [54]. In addition, the delivery system achieves optimal combination therapy through co-loading of two drugs. In breast cancer research, Sharma et al. co-loaded exemestane (EXM) and genistein (GNS) into CLPs. EXM is used for breast cancer treatment but causes bone loss, whereas GNS, a natural isoflavone, has bone-protective effects. They co-loaded both drugs into liposomes, coated them with chitosan, and evaluated the pharmacokinetic and pharmacodynamic behavior in a rat breast cancer model. The results showed that the chitosan-coated EXM-GNS liposome treatment group exhibited statistical significance ($p < 0.05$) in both bone health improvement and anticancer efficacy. Micro-CT analysis revealed significant restoration of trabecular bone structure, good bone matrix connectivity, and narrower inter-trabecular spaces in this treatment group, indicating that the chitosan coating not only improved drug stability and controlled-release properties but also provided additional advantages in biocompatibility and targeting potential [102]. Furthermore, de Souza et al. developed CLPs for the co-delivery of ciprofloxacin and 5-fluorouracil, simultaneously targeting pathogenic *Escherichia coli* that induce colorectal cancer [104]. The system was spherical, with a particle size of 114.6–194.8 nm and a zeta potential of +11.4 to +20.2 mV. It exhibited good stability

and adhesiveness under gastrointestinal conditions and showed strong antibacterial activity against *E. coli* (inhibition zone of 33–37 mm), providing a new strategy for the comprehensive treatment of colorectal cancer.

5.8. Immunoregulation and Vaccine Preparation

CLPs also show broad application prospects in immunoregulation and vaccine delivery. The positively charged surface of chitosan can effectively adhere to antigens and promote their uptake by antigen-presenting cells (e.g., dendritic cells and macrophages). Its inherent biodegradability and low immunogenicity make it an ideal vaccine adjuvant carrier, capable of co-delivering antigens and immunomodulators to the same antigen-presenting cell, thereby synergistically enhancing specific immune responses. Xing et al. encapsulated the immunomodulator resveratrol (Res) into quaternized chitosan (QCS)-coated liposomes to construct a novel delivery system (QCS-Res-LP), and adsorbed ovalbumin (OVA) as a model antigen onto the surface of QCS-Res-LP. The optimized QCS-Res-LP had a particle size of 96.3 ± 3.52 nm, a PDI of 0.280 ± 0.010 , a zeta potential of 9.59 ± 0.36 mV, an encapsulation efficiency for resveratrol as high as $76.22 \pm 1.02\%$, and an adsorption efficiency for OVA of $88.2 \pm 16.3\%$. QCS-Res-LP effectively promoted the co-uptake of antigen and resveratrol by dendritic cells (50-fold higher than Res-LP), promoted the expression of CD80, CD86, IL-2 and IL-12 in dendritic cells, and caused no hemolytic reaction. In OVA-immunized mice, QCS-Res-LP significantly increased the levels of OVA-specific IgG antibodies and cytokines in serum, inducing a mixed Th1/Th2 immune response [136]. Moreover, Chuang et al. used a novel single-step microfluidic synthesis strategy to prepare trimethylchitosan (TMC)-covalently-coated liposomes (named chitosomes) for anthrax vaccine delivery [52]. Flow cytometry showed that covalently TMC-coated chitosomes exhibited 16.5-fold higher cellular endocytosis efficiency than uncoated liposomes [52]. In a BALB/c mouse model, covalently TMC-modified chitosomes significantly improved the induction efficiency of anti-protective antigen IgG antibodies compared with hydrogen-bonded coated chitosomes and the group vaccinated with anthrax vaccine adjuvant alone, with humoral immunity being dominant [52]. This single-step microfluidic method offers the advantages of speed, low cost, easy automation and scale-up, providing a highly feasible and reproducible platform for the development of next-generation CLP-based drugs and vaccines. Therefore, as a multifunctional vaccine delivery platform, CLPs, through diversified strategies such as quaternization modification, antigen adsorption and co-delivery with immunomodulators, and single-step microfluidic preparation, can play a unique role in enhancing antigen uptake efficiency, activating antigen-presenting cell function, and inducing durable and balanced immune responses. They represent an ideal paradigm for advancing next-generation vaccines, especially recombinant protein subunit vaccines and mucosal vaccines.

6. Challenges

Despite the considerable advances achieved in the development of CLPs, several critical hurdles remain before these systems can progress from laboratory research to clinical application. These challenges span safety, stability, and manufacturing, each requiring systematic investigation and resolution.

6.1. Safety

Although chitosan is generally regarded as biocompatible and biodegradable, the safety profile of CLPs is influenced by multiple factors beyond the polymer itself, and a thorough safety evaluation is essential for clinical translation. The cationic nature of chitosan, while beneficial for electrostatic coating and mucoadhesion, introduces potential safety concerns that must be carefully addressed.

6.1.1. Cytotoxicity and Hemolysis

The positive surface charge of CLPs can induce concentration-dependent cytotoxicity. For example, Chen et al. reported that positively quaternary CLPs exhibited cytotoxicity at coating concentrations above 6 mg/mL [137]. Hemolytic activity is also closely correlated with surface charge. Negatively charged liposomes generally do not cause hemolysis and are considered safe toward erythrocytes; however, CLPs exhibit increased hemolytic activity that correlates with the magnitude of positive zeta potential [138,139]. This charge-dependent hemolytic effect underscores the need to optimize coating density and surface charge to balance efficacy with hematological safety.

6.1.2. Immunogenicity and Complement Activation

The interaction of cationic CLPs with the immune system is more complex than often assumed. Chitosan-based nanoparticles can activate innate immune responses, and systemic toxicity is primarily driven by complement activation followed by neutrophil infiltration [140]. Furthermore, upon exposure to biological fluids, CLPs rapidly adsorb plasma proteins, forming a corona that profoundly influences their immunogenicity [141]. The protein corona can promote opsonization by adsorbing immunoglobulins and complement proteins, thereby accelerating macrophage uptake and then triggering inflammatory activation [142]. It can also shield surface-conjugated targeting ligands, compromising active targeting efficiency [143]. Corona formation can redirect biodistribution toward the reticuloendothelial system, increasing off-target toxicity [144]. These adverse effects underscore the critical need for effective anti-corona strategies under physiologically relevant conditions to facilitate the successful clinical translation of CLPs.

6.1.3. Long-Term Toxicity

A systematic review of in vivo toxicity studies on chitosan-based nanoparticles has reported generally favorable safety profiles. However, a comprehensive 2024 meta-analysis of more than 20 preclinical and clinical studies found that PEGylated chitosan nanoparticles induced anti-PEG antibodies in 8% of recipients [145]. This immunogenic response triggers the accelerated blood clearance, in which antigen–antibody reactions reduce bioavailability and exacerbate off-target accumulation in the liver and spleen, posing long-term safety concerns [146]. It should be noted, however, that these findings are derived primarily from studies on chitosan nanoparticles rather than specifically from CLPs. Consequently, the long-term toxicity, repeated-dose safety, and degradation behavior of CLPs—particularly those involving chemically modified chitosan derivatives—remain to be thoroughly investigated.

6.2. Stability

Stability remains a critical challenge limiting the clinical application of CLPs. Although chitosan coating significantly improves liposomal stability compared with uncoated formulations [30], several stability-related issues persist throughout the product lifecycle.

6.2.1. Physical Stability

Liposomes are thermodynamically metastable and prone to aggregation and fusion during storage [147]. Chitosan coating reduces particle aggregation through steric hindrance and electrostatic repulsion, but long-term storage stability remains a concern [148,149]. Coated liposomes have demonstrated better resistance to aggregation than uncoated ones when stored at ambient temperature for up to 45 days; however, extending storage stability to commercial timeframes (typically 12–24 months) requires further optimization [31,58]. The inherent fragility of phospholipid membranes presents additional challenges for industrial-scale production [150].

6.2.2. Chemical Stability

Phospholipids, particularly those containing unsaturated fatty acid chains, are susceptible to oxidative degradation, which can compromise membrane integrity, alter drug release profiles, and reduce therapeutic efficacy [151]. Chitosan coating can mitigate but not completely eliminate this issue [152]. Encapsulation efficiency and drug retention must be carefully monitored, as drug leakage can occur during storage, especially under suboptimal conditions [153]. Sterilization adds further complexity: heat sterilization may disrupt liposomal integrity, while filtration may be hindered by the increased viscosity imparted by chitosan coating [154–156]. Although gamma irradiation has been explored as a potential sterilization method for liposomal dispersions, its effects on CLPs remain to be fully validated [157].

6.2.3. Microbiological Stability

Strict control of microbial contamination and endotoxin levels is essential [158,159]. Chitosan, being a natural polysaccharide, may introduce variability in microbial load and endotoxin content depending on its source and purification process [160,161]. Robust quality control parameters for sterility and endotoxin testing are therefore critical for regulatory compliance.

6.3. Manufacture Process

The transition of CLPs from laboratory-scale research to industrial-scale production presents substantial challenges related to characteristics of chitosan, scalability, reproducibility, and regulatory compliance.

6.3.1. Characteristics of Chitosan

The physicochemical properties of chitosan—including molecular weight, degree of deacetylation, viscosity, purity, and source—exert a profound influence on the coating efficiency, stability, mucoadhesion, and overall performance of CLPs [162]. Primarily, chitosan from different biological sources exhibits distinct physicochemical characteristics. Insect-derived chitosan, for example, generally has a degree of deacetylation (DDA) in the range of 75.75–89.21%, while chitosan obtained from crustacean sources (e.g., shrimp shells) can reach DDA values exceeding 97% [163–165]. DDA dictates charge density and mucoadhesive potential, with higher DDA enhancing electrostatic interactions with liposomal surfaces and mucin, thereby improving coating efficiency [64]. Furthermore, molecular weight plays a critical role: higher molecular weight chitosan provides superior stabilization against salt, heat, and storage, whereas lower molecular weight chitosan yields smaller vesicles and lower viscosity, presenting a trade-off between stability and particle size control [62,166–168]. Simultaneously, viscosity affects coating thickness and manufacturing steps such as filtration, and batch-to-batch viscosity variability has been shown to alter drug release profiles, complicating process standardization [169–171]. Equally critical is purity, since residual proteins, heavy metals (e.g., Fe, Cr, and Ni), and especially endotoxins (>0.01 EU/mg) pose significant safety risks through the induction of inflammatory responses, in addition to adversely affecting formulation performance [172–174]. Collectively, the inherent variability of these chitosan characteristics—particularly across different sources and batches—represents a critical barrier to industrial scale-up and subsequent clinical translation. Overcoming this challenge requires rigorous quality control and comprehensive batch characterization, including molecular weight, DDA, viscosity, and purity testing, as essential components of regulatory documentation to ensure reproducible manufacturing.

6.3.2. Scalability and Reproducibility

Scaling up the production of CLPs while maintaining consistent quality is extremely challenging. Most laboratory-scale preparation methods, such as thin-film hydration and electrostatic deposition, are not directly transferable to industrial settings due to differences in mixing efficiency, temperature control, and shear forces [175]. Batch-to-batch reproducibility requires precise control over numerous parameters, including chitosan molecular weight, degree of deacetylation, chitosan-to-lipid ratio, coating conditions (pH, temperature, mixing rate), and drying procedures [60]. Variations in any of these parameters can substantially affect particle size, polydispersity, zeta potential, encapsulation efficiency, and coating thickness [176]. The sourcing of chitosan itself introduces variability, as chitosan from different origins (shrimp, crab, fungal) differs in molecular weight distribution, purity, and batch consistency [177,178].

6.3.3. Process Control and Quality Attributes

Industrial production of liposomes demands robust, validated manufacturing methods that consistently achieve uniform quality. For CLPs, critical quality attributes include particle size distribution, polydispersity index, zeta potential, encapsulation efficiency, coating thickness, degree of coating, and free chitosan content [179]. Establishing reliable analytical methods for real-time monitoring of these attributes during manufacturing is essential. The integration of quality-by-design principles and process analytical technology can facilitate process control and ensure product consistency [60]. Emerging in situ coating approaches, particularly microfluidic-based systems, offer advantages for continuous manufacturing and scalability [80]; nevertheless, challenges such as nonspecific adsorption of hydrophobic drugs onto chip materials (e.g., PDMS), residual solvent removal, and maintaining consistent flow characteristics across multiple chips remain unresolved [82].

6.3.4. Regulatory Considerations

CLPs are classified as non-biological complex drugs, for which regulatory frameworks are still evolving [180]. Although more than twenty clinical investigations have explored chitosan-based nanoparticles for chemotherapeutic delivery, no chitosan-based co-delivery therapy has yet received FDA or EMA approval, primarily due to production variability, stability limitations, and the absence of standardized clinical comparators [181]. Regulatory classification further complicates translation, as multifunctional chitosan systems frequently straddle drug–device and biologic categories [182]. The regulatory pathway demands comprehensive characterization of physicochemical properties—including particle size distribution, zeta potential, encapsulation efficiency, drug release kinetics, sterility, and stability—as well as rigorous toxicological assessments [183]. The variability inherent in chitosan molecular weight and the limited availability of nanotoxicology standards add additional regulatory hurdles [184]. Establishing standardized protocols for characterization, manufacturing, and quality control is essential to facilitate regulatory approval and clinical translation [185].

7. Conclusions

CLPs have emerged as a robust and versatile platform that addresses several major shortcomings of conventional liposomal carriers, including insufficient colloidal stability, rapid clearance, poor mucoadhesion, and limited target specificity. The intrinsic cationic property of chitosan enables stable electrostatic deposition onto negatively charged liposomal surfaces, forming a core–shell structure that improves stability, prolongs circulation, and facilitates functionalization with targeting ligands and stimuli-responsive groups. Various coating strategies—electrostatic deposition, layer-by-layer assembly, ionic crosslinking,

and microfluidic in-situ coating—each offer distinct benefits in terms of coating efficiency, particle size control, and scalability. These systems have demonstrated considerable pre-clinical therapeutic potential across oral, ocular, transdermal, pulmonary, anti-infective, tumor-targeted, and vaccine applications, with improved drug retention, controlled release, and enhanced bioavailability.

Despite these advances, clinical translation remains constrained by several interconnected challenges. Protein corona formation, insufficient long-term toxicity and immunogenicity data, and batch-to-batch variability in chitosan properties—such as molecular weight, deacetylation degree, viscosity, purity, and source—compromise reproducibility and performance. Manufacturability is hampered by the limited scalability of most laboratory methods, particularly layer-by-layer assembly, whereas microfluidic systems face throughput and material compatibility issues. Regulatory approval is further complicated by the classification of these systems as non-biological complex drugs, and to date, no chitosan-based co-delivery therapy has received FDA or EMA approval, despite more than twenty clinical investigations.

Future efforts should focus on: (i) comprehensive long-term safety and immunogenicity assessments; (ii) systematic characterization of protein corona effects; (iii) development of scalable, GMP-compliant manufacturing processes with clearly defined critical quality attributes; (iv) standardization of characterization protocols; and (v) early and ongoing regulatory dialogue to establish clear approval pathways. Addressing these challenges through multidisciplinary collaboration will be essential to translate the considerable preclinical promise of CLPs into meaningful clinical outcomes.

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