

Functional Evaluation of Niosomes Utilizing Surfactants in Nanomedicine Applications

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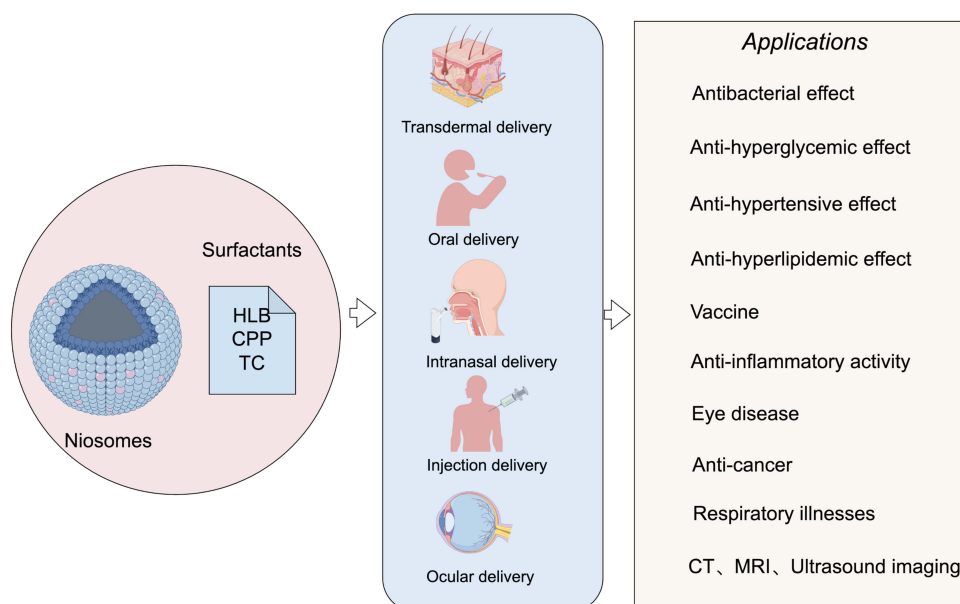
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Abstract: Niosomes are key nanocarriers composed of bilayer vesicles formed by non-ionic surfactants and cholesterol, offering advantages such as high physicochemical stability, biodegradability, cost-effectiveness, and low toxicity. This review discusses their significant role in drug delivery, including applications in anticancer therapy and vaccine delivery. It also highlights the impact of non-ionic surfactants on niosome formation, drug delivery pathways, and protein corona formation—a relatively underexplored topic. Furthermore, the application of artificial intelligence in optimizing niosome design and functionality is examined. Future research directions include enhancing formulation techniques, expanding application scopes, and integrating advanced technologies. This review provides comprehensive insights and practical guidance for advancing niosome-based drug delivery systems.

Keywords: niosomes, non-ionic surfactant, drug delivery systems, niosome functionalization

Graphical Abstract



Introductions

The development of novel drug delivery systems has drawn significant attention, owing to their potential to improve treatment efficacy, reduce drug toxicity and side effects, enhance patient compliance, and drive drug development.^{1,2} Ideal novel drug delivery systems must accomplish drug delivery at a predetermined rate and release the therapeutically effective amount of the drug at the target site.² Meeting these requirements with the traditional dosage forms is challenging, whereas vesicular systems excel at addressing them.³

Niosomes are a type of vesicular system and have emerged as a promising tool for drug delivery.^{4,5} Current research on niosomes mainly focuses on the following areas: (a) Drug delivery systems using niosomes as drug delivery carriers, thus enhancing the bioavailability and controlled release of therapeutic agents. Modifying niosomes allows for targeted delivery.^{6,7} (b) Vaccine delivery systems using niosomes as carriers for vaccines, thus improving stability, boosting efficacy, and providing long-term immune protection.^{8,9} (c) Cosmetics and skincare using niosomes for enhanced penetration of active ingredients (such as vitamins, antioxidants) into the skin barrier.^{10,11} (d) Diagnostics and imaging using niosomes as a versatile platform for enhancing the efficacy and specificity of diagnostic and imaging technologies.^{12–15} (e) Food and agricultural industries using niosomes as food additives, as well as for controlling pesticide release, reducing environmental impact.¹⁶

These vesicular structures, composed of non-ionic surfactants with or without cholesterol, mimic the lipid bilayers of liposomes, offering distinct advantages such as enhanced stability and versatility (Figure 1).¹⁷ Non-ionic surfactants are amphiphilic molecules with polar heads and non-polar tails that do not have specific, ionic-charged groups in their structure.¹⁸ They are pharmacologically non-toxic and inert. They exhibit low hemolysis, cause less irritation to the cell surface, and their pH tends to remain near that of physiological solutions.¹⁹ Therefore, non-ionic surfactants are well suited for incorporation into pharmaceutical formulations. The inclusion of a surfactant influences the particle size, polydispersity index (PDI), drug loading, zeta potential, and correlation with the apparent physical stability of nanoparticles (NPs).²⁰ The successful application of NPs in therapeutic targets requires an effective cellular uptake, with the effective interaction between NPs and cell membranes being a key step before cellular uptake.²¹ This biological interaction is highly dependent on the surface phenomena of NPs and therefore relies on surfactants.²¹ Consequently, further research on the role of non-ionic surfactants in niosomes and drug therapy is essential.

The unique composition of niosomes enables the encapsulation of a wide range of therapeutic agents, including hydrophilic and hydrophobic drugs.^{22–24} This highlights their significant potential for future therapeutic applications and their broad applicability in treating various diseases. Owing to their tunable properties and biocompatibility, niosomes can be administered via various routes, including the standard oral or parenteral methods, as well as by ocular, intranasal,

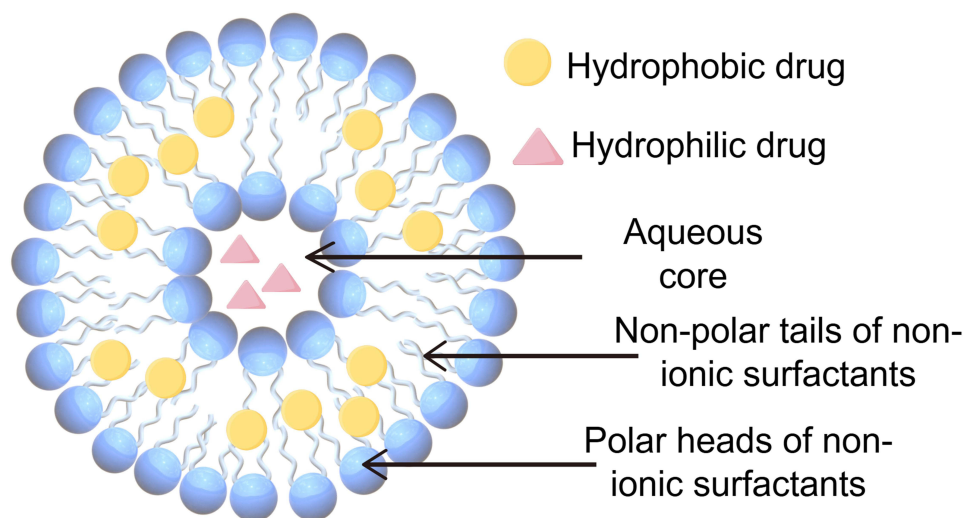


Figure 1 Schematic representation of niosomes. (By Figdraw).

transdermal, or vaginal methods, as well as inhalation.^{25–29} The applications of niosomes in various drug administration routes are systematically explored in this review, with a particular focus on the impact of non-ionic surfactants on niosome formation and functionality. The ways non-ionic surfactants influence the formation of niosomes and their roles in the different drug delivery pathways are also presented, highlighting their contributions to optimizing drug delivery efficiency and targeting. Additionally, the effects of non-ionic surfactants on protein corona formation are addressed, elucidating their potential in enhancing drug bioavailability and reducing immune responses. Through this review, we seek to provide a comprehensive understanding and forward-looking insights into the use of niosomes and their modification technologies in the field of drug delivery.

Preparation of Niosomes

Niosomes can be classified into three categories based on their number of bilayers and size: small unilamellar vesicles (SUVs, one bilayer, 10–100 nm), large unilamellar vesicles (LUVs, one bilayer, 100–3000 nm), and multilamellar vesicles (MLV, more than one bilayer, $\geq 5 \mu\text{m}$).^{30,31} Various preparation methods for niosomes are reported in the literature (Table 1), with the types of niosomes produced varying depending on the method used (Figure 2).

Table 1 Types of Niosomes Prepared by Different Methods and Their Advantages and Disadvantages

Preparation Technology	Type of Niosomes	Advantages	Disadvantages	References
Thin film hydration (TFH) method	Multilamellar vesicles (MLVs)	Simple technology	Organic solvents are difficult to remove	[32,33]
Trans-membrane pH gradient method	Multilamellar vesicles (MLVs)	High stability, high encapsulation efficiency	Organic solvents are difficult to remove, heterogeneity and great polydispersity index	[34,35]
Formation of niosomes from proniosomes	Multilamellar vesicles (MLVs)	Long term storage with high physical and chemical stability	Complex process, time-consuming	[36–39]
Microfluidization method	Small unilamellar vesicles (SUVs)	High degree of reproducibility and uniformity	Cannot be used for heat sensitive drugs, easily hydrolyzed and/or oxidized	[40–42]
Sonication method	Small unilamellar vesicles (SUVs)	Green method, no organic solvents needed	Expensive equipment and high energy consumption	[36,43,44]
Multiple membrane extrusion method	Small unilamellar vesicles (SUVs)	Reduced polydispersity	Increased drug losses	[31,45,46]
Ether injection method	Large unilamellar vesicles (LUVs)	Simple technology	Cannot be used for heat sensitive drugs, organic solvent residue	[47–49]
Bubble method	Large unilamellar vesicles (LUVs)	No organic solvents involved	Low long-term storage stability	[2,50]
Reverse phase evaporation method	Large unilamellar vesicles (LUVs)	High encapsulation efficiency	Possible residual organic solvents	[1,31,51,52]
Lipid injection method	Large unilamellar vesicles (LUVs)	Green method, no organic solvents needed	Cannot be used for heat sensitive drugs	[1,53]
Supercritical carbon dioxide fluid (scCO ₂) method	Large unilamellar vesicles (LUVs)	High encapsulation efficiency, no organic solvents needed	Requires specialized equipment, high cost	[7,54]
Heating method	Large multilamellar particles	Simple method, no organic solvents needed	Cannot be used for heat sensitive drugs	[50,55,56]

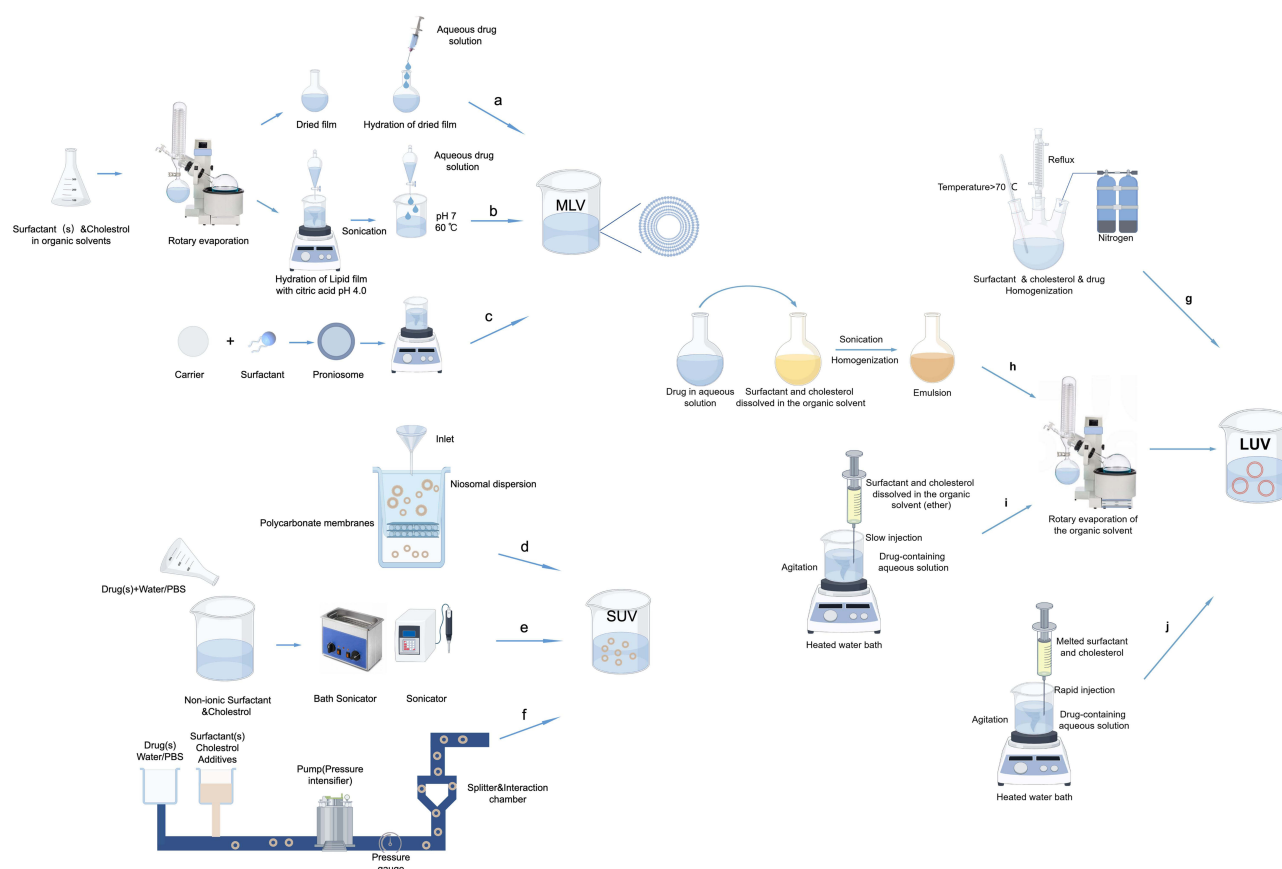


Figure 2 Schematic representation of various niosome preparation methods: (a) thin film hydration (TFH) method, (b) trans-membrane pH gradient method, (c) formation of niosomes from proniosomes, (d) multiple membrane extrusion method, (e) sonication method, (f) microfluidization method, (g) bubble method, (h) reverse phase evaporation method, (i) ether injection method, (j) lipid injection method. (By Figdraw).

The thin-film hydration (TFH) method involves dissolving lipids in an organic solvent, evaporating the solvent under reduced pressure, and then hydrating the lipid film with water at an elevated temperature to form vesicles. The TFH method generally forms MLVs, which can be produced using appropriate cut-off size membranes or ultrasonic treatment to produce small-sized niosomes.^{32,33} Preparation of niosomes loaded with nintedanib involves the TFH method. Dynamic light scattering analysis of niosome formulations revealed that an increase in cholesterol concentration results in a reduction in vesicle size. According to the polydispersity index (PDI) and evaluation of the particle size distribution, the PDI values of all formulations were within the range of 0.02–0.2, indicating that all developed formulations were uniform, narrowly dispersed, and free of agglomeration. The zeta potential or surface charge of the vesicles influences their biological characteristics, such as the ways they are taken up and internalized by cells. The amount of drug encapsulated in the formulation was measured by lysing the formulation, revealing that the vesicles had a relatively high encapsulation efficiency.²⁹ The trans-membrane pH gradient method involves dissolution of the surfactant and cholesterol in chloroform, evaporation of the solvent to form a lipid film, and hydration of this film with an acidic solution. After forming multilamellar vesicles (MLVs) through freeze-thaw cycles and sonication, an aqueous drug solution is added, and the pH is adjusted to allow the drug to be encapsulated within the vesicles by exploiting the pH gradient.^{34,35} To prepare niosomes from proniosomes, a proniosome powder—comprising a surfactant-coated water-soluble carrier—is rehydrated in hot water upon agitation. This rehydration forms MLVs, which can be further processed to produce SUVs through high-energy methods or coacervation phase separation. Proniosomes offer advantages in terms of stability, transportation, and scalability.^{36–39}

The microfluidization method affords niosomes via the use of precisely controlled microchannels to mix lipids and aqueous streams at high velocities, facilitating the formation of uniformly small vesicles (< 150 nm) with a low PDI by

the self-assembly of surfactant molecules.^{40–42} Sonication involves mixing cholesterol and a non-ionic surfactant with a drug-containing buffer, followed by ultrasonic treatment. This process initially forms multilamellar vesicles, which can be further sonicated to produce unilamellar vesicles, resulting in small and uniform niosomes.^{36,43,44} The multiple membrane extrusion technique affords niosomes by forming a thin film comprising the surfactant, cholesterol, and diacetyl phosphate in chloroform, followed by hydration with an aqueous drug solution and extrusion of the suspension through polycarbonate membranes to control the vesicle size.^{31,45,46}

The ether injection method involves slowly injecting a mixture of cholesterol and surfactant dissolved in ether into a preheated aqueous drug solution, leading to the formation of vesicles as the solvent evaporates. This process creates heterogeneous vesicles with variable sizes, however, it exhibits slow rates and residual ether in the suspension.^{47–49} The “bubble” technique affords niosomes via dispersion of cholesterol and surfactants in a phosphate buffer at 70 °C, followed by homogenization of the mixture and bubbling nitrogen gas through it. The resulting LUVs can be further reduced in size if needed.^{2,50} The reverse phase evaporation method affords niosomes by dissolving cholesterol and surfactant in a mixture of ether and chloroform, followed by the addition of an aqueous drug phase and sonication. After forming an emulsion, the organic solvent is evaporated, and the resulting viscous suspension is diluted and heated to produce niosomes with a high aqueous space and encapsulation efficiency.^{1,31,51,52} The lipid injection method prepares niosomes by melting a mixture of lipids and surfactants and injecting it into a hot, agitated aqueous solution containing the drug, without using organic solvents.^{1,53} The supercritical CO₂ (scCO₂) method for preparing niosomes involves dissolving surfactants, cholesterol, PBS, and ethanol in a glass view cell, which is then pressurized with CO₂ at 200 bar and 60 °C. After 30 min of stirring, niosomes are formed, and the pressure is released, affording uniformly sized LUV niosomes without the need for toxic organic solvents.^{7,54} The heating method involves dissolution of cholesterol in a liquid heated to approximately 120 °C, followed by cooling to 60 °C and addition of other components while stirring. After preparation, the niosomes are left at room temperature for 30 min, followed by storage in a refrigerator at 4–5 °C under a nitrogen atmosphere. This approach avoids the use of harmful, volatile organic solvents and is a straightforward, one-step procedure.^{50,55,56}

Recent Studies on the Role of Non-Ionic Surfactants

Surfactants contain hydrophobic groups (tail) and hydrophilic groups (head), exhibiting amphiphilicity.⁵⁷ They can reduce surface tension and interfacial tension at the interfaces of solids, liquids, and gases, and can be used as emulsifiers, foaming agents, corrosion inhibitors, antistatic agents, dispersants, wetting agents, and detergents.^{20,57–59} Surfactants are typically classified based on the nature of their hydrophilic groups and primarily include anionic surfactants, cationic surfactants, non-ionic surfactants, and amphoteric surfactants. The robustness of non-ionic surfactants against pH and electrolytes gives them an advantage over ionic and other surfactants for pharmaceutical applications.⁶⁰ As summarized in Table 2, recent studies have highlighted the crucial role of non-ionic surfactants in pharmaceutical applications, especially in enhancing drug delivery systems, stabilizing proteins, and improving the performance of nanoparticles.

Table 2 Summary of Recent Studies on the Effects of Non-Ionic Surfactants

Application	Non-ionic Surfactant	Effect	References
Preparation of nanocarriers for drug delivery	Pluronic F127	Improve drug solubility and bioavailability	[61]
Affect the stability of biopharmaceuticals	Tween 20, Tween 80, Poloxamer 188, Brij 35	Improve the stability of therapeutic proteins and antibodies. Prevent aggregation during freezing or storage	[62,63]
Affect the stability of nanoparticles	Polysorbates, poly (vinyl alcohol), poloxamers	Stabilized the dispersion of nanoparticles. Enhanced the biocompatibility and size adjustability of nanoparticles	[20]
Affect biological barriers	Poloxamer 188, Brij 35, Tween 80, Tween 20	Affects the permeability of biological barriers and enhances the permeability of drugs through biological barriers	[64]

Non-ionic surfactants are widely used in the preparation of nanocarriers (such as niosomes, bilosomes, and micelles) to enhance drug bioavailability.^{8,65,66} For example, non-ionic surfactants self-assemble into micelles in aqueous phases and are able to encapsulate hydrophobic drug molecules. Mixed micelles composed of pluronic F127 and cremophor EL can effectively deliver norfloxacin, offering controlled release and good antimicrobial activity against various strains.⁶¹ Non-ionic surfactants can protect biologic therapeutic proteins and antibodies from the effects of various solid-liquid interfaces, such as cycloolefin-copolymer and model hydrophobic interfaces. Polysorbate 80 and 20, Poloxamer 188, and Brij 35 offer different levels of protection against these interfaces, highlighting the importance of the optimization of surfactant formulations to stabilize antibodies.⁶²

Non-ionic surfactants have been shown to protect proteins from freezing and surface-induced denaturation. Polysorbate 20 effectively prevents lysozyme aggregation during freeze and thaw, while poloxamer 188 can interact with lysozyme and prevent aggregation at high concentrations; however, some aggregation occurs during freezing but reverses upon thawing.⁶³

Non-ionic surfactants play a crucial role in the production of polymer NPs through emulsion-based methods. They significantly reduce the droplet size in emulsions and enhance the biocompatibility and size tunability of NPs. Additionally, these surfactants not only stabilize the dispersion of NPs but also have extensive effects on pharmacokinetics.²⁰

Non-ionic surfactants enhance the ability of NPs to cross biological barriers. A study reveals that the passage of NPs across the blood-brain barrier (BBB) is primarily influenced by the type of surfactant employed during their fabrication. Specifically, non-ionic surfactants (such as Poloxamer 188, Brij 35, Tween 80, Tween 20, and Lutensol AT80) and cationic surfactants (dextran) facilitate BBB penetration, whereas anionic surfactants, including sodium dodecyl sulfate (SDS), impede it. The particle size and zeta potential do not affect BBB permeability.⁶⁷ Polysorbate 80 reduced the expression of intestinal mucus barrier and mucosal barrier-related proteins (mucus protein mucin-2, tight junction proteins claudin-1 and occludin), altered the integrity of intestinal epithelial cells, and increased the intestinal epithelial mucosal permeability.⁶⁴

Impact of Non-Ionic Surfactants on Niosomes

Non-ionic surfactants are the fundamental elements of niosomes, and understanding their properties is crucial for the preparation of the desired niosomes. Common surfactants include alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, and poloxamers. The hydrophilic-lipophilic balance (HLB), critical packing parameter (CPP), and gel-liquid transition temperature (T_C) are essential for the selection of the non-ionic surfactant.

Hydrophilic-Lipophilic Balance (HLB)

The balance between the hydrophilic and lipophilic groups of non-ionic surfactants is represented by the hydrophilic-lipophilic balance (HLB) value, ranging from 0 to 20.⁶⁸ The HLB value affects the ability to form niosomes, as well as their particle size, distribution, and encapsulation efficiency (EE). Generally, surfactants with HLB values of 14–17 are not suitable for the formation of niosomal vesicles,^{7,50,69} because high HLB values demand increased cholesterol concentrations. Cholesterol forms hydrogen bonds with the hydrophilic heads of the surfactants to compensate for the impact of bulky head groups on the critical packing parameters.^{25,70,71} Pronosomes made from Brij 35 (high HLB) and different proportions of cholesterol were hydrated with hot water to produce niosomes. Analysis of their encapsulation efficiency revealed that niosomes with a 50% cholesterol ratio have higher encapsulation efficiency compared to those with a 20% cholesterol ratio.⁷²

As the HLB of the surfactants increases, the length of the alkyl chain and the vesicular size of the niosomes also increase. Niosomes generated using sorbitan laurate (Span 20 hLB: 8.6) were larger than those generated using sorbitan oleate (Span 80 hLB: 4.3).⁷³ Vesicle sizes prepared with Span 40 (HLB: 6.7) are generally smaller than those prepared with Brij 35 (HLB: 16.9).⁷² Furthermore, the size distribution of niosomes created with Span 40 was notably larger compared to the vesicles produced with Span 60 (HLB: 4.7).⁷⁴ Similar results have been reported in other studies.^{75,76} Such a finding can be attributed to the increase in surface energy as the number of hydrophilic groups increases, thus increasing the particle dimensions. The HLB of a surfactant affects the entrapment efficiency of niosomes. According to

a previous study, the entrapment efficiency of ibuprofen decreased when high-HLB surfactants were used, while the entrapment efficiency was higher with a lower HLB.⁷⁷ By mixing different amounts of Span 40 and Span 60 to achieve varying HLB values and using these surfactants to prepare niosomes, it was confirmed that an increase in the proportion of Span 60 (lower HLB) leads to improved encapsulation efficiency.⁷⁸ This may have occurred because hydrophilic surfactants, which are highly soluble in water, do not exhibit suitable vesicular structure formation in aqueous environments. Conversely, surfactants that are more lipophilic in nature and have lower HLB values can form vesicles and effectively encapsulate lipophilic and amphiphilic drugs.

Critical Packing Parameter (CPP)

CPP is a dimensionless scale for surfactants and plays a significant role in their assortment.¹ The following equation is used to determine the CPP values, where V represents the volume of the nonpolar group, l_c is the length of the critical nonpolar group, and a_0 is the area of the polar head group.

$$CPP = V / l_c \times a_0$$

CPP values help predict the types of vesicles formed by surfactants. A CPP value below 1/3 indicates the formation of spherical micelles; a value ranging from 1/3 to 1/2 suggests the presence of cylindrical micelles; and a value between 1/2 and 1 indicates the transformation into bilayer vesicles. A CPP value exceeding 1 indicates the formation of inverted micelles.^{69,79,80}

Gel-Liquid Transition Temperature (T_C)

The gel-liquid transition temperature (T_C) is a crucial factor that directly affects the entrapment efficacy, which is affected by the alkyl-chain length of the surfactant and impacts the fluidity of the vesicles formed.¹ The temperature should remain consistently higher than the gel-to-liquid phase transition temperature of the system. At T_C , the niosome bilayer undergoes a transition from an ordered gel phase to a disordered liquid phase.⁸¹ When the temperature is below the T_C value, the surfactant molecules are tightly packed, forming a rigidly ordered gel phase. As the temperature approaches T_C , the tightly packed surfactants begin to relax, leading to a less ordered liquid phase.⁸² Generally, an increase in the carbon count in the alkyl chain leads to a higher T_C , consequently leading to a higher entrapment efficiency.^{7,83}

Mixed Non-Ionic Surfactants

Mixed surfactants exert a synergistic effect. Dejan Ćirin et al investigated the interactions between various surfactants at the interface using Rosen's model for mixed monolayers. Synergism was also observed in the Brij S20/poloxamer 407 mixture.⁸⁴ Compared to Brij-35 or Poloxamer 407 alone, oral niosomes loaded with tacrolimus (TLM) prepared using a mixture of Brij-35 and Poloxamer 407 as surfactants exhibited a synergistic effect on the dissolution of TLM. They also exhibited greater drug solubility and higher encapsulation efficiency.⁸⁵

Role of Non-Ionic Surfactants in Niosome Drug Delivery Pathways

The route of administration plays a crucial role in determining drug pharmacokinetics and the appropriate concentration at the target site.⁸⁶ Niosomes can be administered via almost all delivery routes, such as oral (eg, tacrolimus, atorvastatin),^{85,87} transdermal (eg, sulfadiazine sodium salt, curcumin),^{39,88} as well as pulmonary, parenteral, intranasal, and ocular (Table 3).

Oral Delivery

Among the different methods of drug administration, the oral route has gained significant attention owing to its distinctive benefits, including adaptability, safety, and patient adherence.¹²⁴ The oral route is non-invasive, convenient, and cost-effective.¹²⁵ However, this route of drug administration is also subject to poor or erratic bioavailability owing to a variety of reasons, such as poor water solubility, efflux by gut wall transporters, and first-pass metabolism,¹²⁶ especially for drugs that belong to the class II biopharmaceutical classification system (BCS II) category.^{85,94} To overcome these problems, various nanotechnology-based drug delivery systems have been investigated, including polymers,^{127,128} polysaccharides,^{129,130} solid

Table 3 The Mechanism and Application of Niosomes Utilizing Surfactants in Delivering Drugs

Drug	Delivery Route	Surfactant	Mechanism	References
Tacrolimus	Oral	Brij-35 and poloxamer 407	Improve solubility	[85]
Ciprofloxacin	Oral	Tween 85 and Span 80	Improve stability and inhibit bacterial biofilm formation	[89]
Streptomycin Sulfate	Oral	Span 60 and Tween 60	Improve stability and inhibit bacterial biofilm formation	[90]
Levofloxacin	Oral	Sugar surfactant	Extend release and improve gastrointestinal membrane permeability	[91]
Cefdinir	Oral	Span 60	Improve gastrointestinal membrane permeability	[92]
Griseofulvin	Oral	Span 20, 40, 60	Extend release	[93]
Repaglinide	Oral	Tween 80	Improve solubility	[94]
Nateglinide	Oral	Span 60	Improve absorption (translymphatic transport)	[95]
Insulin	Oral	Brij 52, Brij 92, Span 60	Improve solubility	[96]
Glimepiride	Oral	Span 20, 40, 60, 80, Tween 20, 40, 60	Extend release	[97]
Telmisartan	Oral	Span 60	Improve stability and extend release	[98]
Carvedilol	Oral	Span 60, Tween 60	Improve stability	[99,100]
Candesartan cilexetil	Oral	Span 60 and Pluronic P85	Improve solubility and stability	[101]
Atorvastatin	Oral	Span 60	Improve dissolution rate	[87]
Tetanus toxoid	Oral	Span 60	Improve stability	[102]
Loratadine	Transdermal	Span 40, 60, 80	Enhance penetration and solubility	[103]
Salidroside	Transdermal	Span 40	Improve permeability	[74]
Propofol	Transdermal	Span 80	Improve release and reduce adverse reactions	[104]
Clarithromycin	Transdermal	Span 40, 60, 80, Tween 60, 80	Improve permeability	[105]
Gallic acid	Transdermal	Tween 61	Improve stability and permeability	[106]
Salidroside	Transdermal	Span 40	Improve permeability	[74]
Felodipine	Transdermal	Span 60	Improve permeability and extend release	[107]
Diclofenac sodium	Transdermal	Tween 20 and Span 20	Control release	[108]
Diacerein	Transdermal	Span 40, 60	Improve permeability	[109]
Celecoxib	Transdermal	Span 40, 60, poloxamer 407	Extend release	[110]
Pilocarpine hydrochloride	Ocular	Tween 60	Extend eye retainment and prevent drug metabolism degradation	[44]
Latanoprost	Ocular	Pluronic F127	Improve release and	[52]

(Continued)

Table 3 (Continued).

Drug	Delivery Route	Surfactant	Mechanism	References
Tacrolimus	Ocular	Poloxamer 188	Improve ocular retention time, aqueous humor pharmacokinetics and transcorneal permeability	[111]
Flurbiprofen	Ocular	Span 60	Prolong contact time with ocular tissues	[112]
Betaxolol	Ocular	Span 40	Improve ocular retention time	[113]
Hydrochloride naltrexone	Ocular	Span 60	Enhance corneal permeability	[114]
Paclitaxel	Intravenous	Span 40	Extend elimination half-life	[115]
Tocotrienols	Intravenous	DSPE-PEG (2000)-carboxylic acid	Improve targeting	[116]
Paclitaxel	Intravenous	Span 40	Improve stability	[115]
Paeonol	Intravenous	Span 60	Improve stability	[117]
Nefopam hydrochloride	Nasal	Span 20, 40, 80, 85	Enhance drug penetration through nasal mucosa	[118]
Bromocriptine	Nasal	Span 60	Enhance permeation across nasal mucosa	[119]
Pentamidine	Nasal	Tween 20	Enhance mucosal adhesion and reduce drug clearance	[26]
Olanzapine	Nasal	Spans	Improve nasal mucosal permeability	[120]
Buspirone hydrochloride	Nasal	Span 60	Improve nasal mucosal permeability	[121]
Salbutamol sulfate	Pulmonary	Span 60	Improve lung deposition and retention	[122]
Cilomilast	Pulmonary	Span 60	Improve lung uptake	[123]
Nintedanib	Pulmonary	Span 60	Extend release and enhance cellular internalization	[29]
Gemcitabine and cisplatin	Pulmonary	Span 60, Tween 65	Control release	[56]

nanodispersion,¹³¹ solid lipid nanoparticles,¹³² self-nanoemulsifying drug delivery systems,^{133,134} nanocrystals,^{135,136} and vesicular drug delivery systems (VDDS).¹³⁷ Among these approaches, niosomes belonging to the VDDS have been widely investigated owing to their biocompatibility, non-immunogenicity, high chemical stability, and low cost.^{55,87}

Mechanism of Non-Ionic Surfactants in Niosomes Oral Drug Delivery

Non-ionic surfactants, which are the primary constituents of niosomes, can solubilize poorly soluble drugs owing to their amphiphilic properties.⁷ Following ingestion, the small size of niosomes enables a substantial interfacial surface area that is conducive to intestinal absorption.⁹⁴ In addition, niosomes achieve sustained release of drugs and prolong their duration of action by encapsulating them within the lipophilic bilayers. Surfactant elements can also reduce P-glycoprotein (P-gp)-mediated effluxes (Figure 3a). The efflux membrane transporter P-gp is extensively distributed throughout the body and functions as a physical barrier by expelling foreign substances and poisons from cells.^{138,139} P-gp belongs to a family of ATP-dependent membrane transport proteins responsible for expelling substrates from cells via an ATP-driven process.¹⁴⁰ These ATP-dependent transporters interact with numerous substrates, most of which are hydrophobic, such as antitumor medications, therapeutic agents targeting central nervous system (CNS) and the cardiovascular system, as well as antibiotics.^{141–143} The efflux properties of P-gp are important factors that contribute to the low bioavailability of therapeutic substrates. Therefore, it is crucial to investigate P-gp inhibitors to overcome the low bioavailability of drugs. Notably, certain non-ionic surfactants demonstrate inhibitory properties against P-gp.^{19,144} Their inert, non-toxic, uncharged nature and rapid access to the cytosolic lipid membrane (site of interaction with the P-gp efflux protein) enable them to function more efficiently as P-gp inhibitors. The observed inhibitory effects have

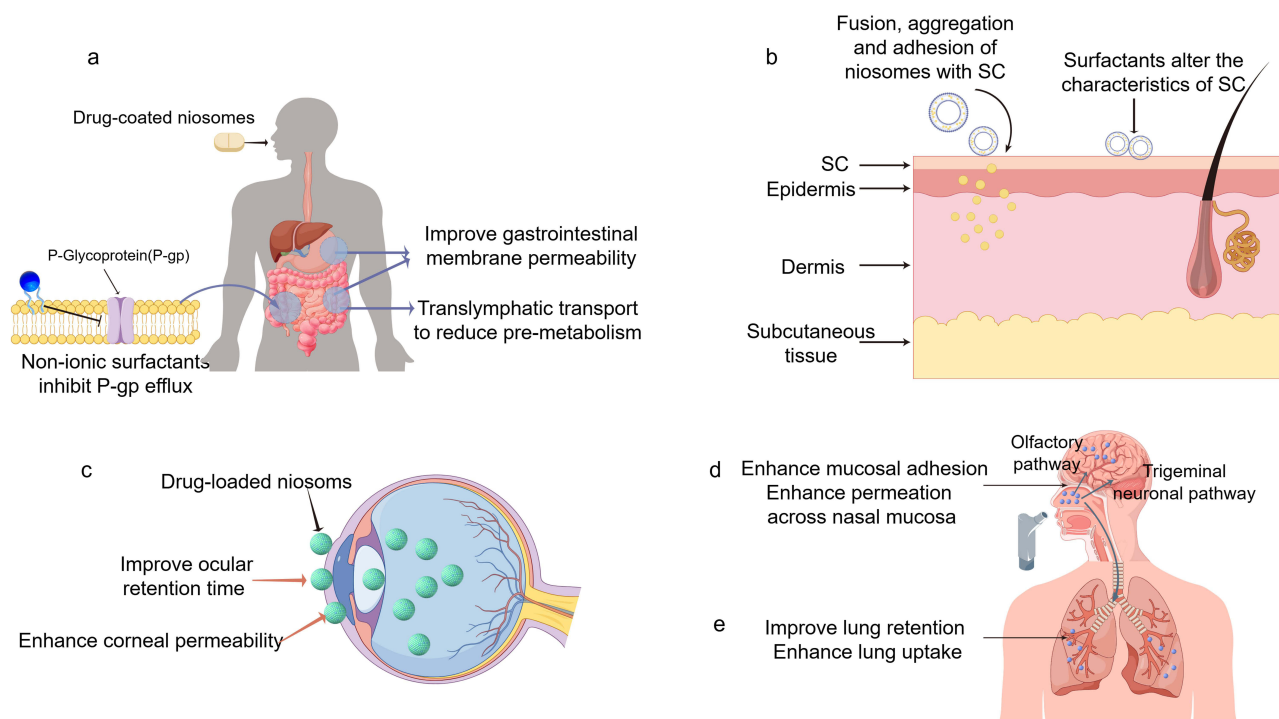


Figure 3 The potential mechanisms of niosomes for improving the oral (a), transdermal (b), ocular (c), intranasal (d), pulmonary (e) bioavailability. (By Figdraw).

been linked to the modulation of membrane fluidity, suppression of the ATP-binding cassette of the transporter P-glycoprotein, and attachment of surfactants to the drug-binding domain from the cytoplasmic leaflet.^{19,145,146} Zhao et al demonstrated that the underlying mechanisms behind the inhibition of P-gp include changes in fluidity of the intestinal membrane and suppression of the P-gp ATPase function by two polyoxyethylene alkyl ethers (polyoxyethylene 10-oleyl ether and polyoxyethylene 9-lauryl ether).¹⁴⁷

Application of Niosomes in Oral Drug Delivery

Antibacterial Activity

The application of niosomes enhances antibacterial activity. Improper use of antibiotics can lead to drug resistance; thus, widely used antibiotics require strategic and optimal methods to avoid drug resistance. Niosomal formulations loaded with ciprofloxacin induce the inhibition of biofilm formation in *Escherichia coli* and *Staphylococcus aureus*.⁸⁹ The effectiveness of streptomycin sulfate-loaded niosomes against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* surpassed that of the free drug, demonstrating significantly increased antimicrobial and anti-biofilm activities. Moreover, the minimum inhibitory concentration values decreased by a factor ranging from 4 to 8.⁹⁰ Imran et al synthesized a novel sugar-based twin-tailed surfactant (bergenin-based non-ionic surfactant) for the preparation of niosomal vesicles, leading to the improved oral bioavailability of levofloxacin.⁹¹ Compared with plain drug solutions and commercially available suspensions, cefdinir oral niosomes prepared via sonication using Span-60, cholesterol, and soy lecithin as raw materials improved the permeability of cefdinir across goat intestinal membranes. These findings suggest that niosomes exhibit better oral absorption. Studies on antimicrobial activity have shown that niosomal formulations augment the antibacterial activity of cefdinir compared to commercially available suspensions.⁹² Hanif et al employed niosomal encapsulation to enhance the solubility of tacrolimus and improve its oral bioavailability.⁸⁵ Griseofulvin, which is an antifungal agent, exhibits low water solubility and limited absorption via the oral route. Consequently, conventional oral administration often fails to yield effective plasma drug profiles. Niosomes prepared from Span 60 have exhibited rapid absorption in vivo, facilitating faster attainment of peak plasma concentrations and prolonged maintenance of high levels of griseofulvin.⁹³

Niosomes are also extensively used to treat chronic diseases. Owing to the frequent and long-term treatment requirements, oral administration is an important route for managing chronic conditions. This mode of administration facilitates patient compliance and enhances treatment compliance while providing a steady and sustained drug concentration.

Anti-Hyperglycemic Effect

Nateglinide exhibits poor water solubility and lipophilicity, and its degree of ionization depends on the pH of the absorption sites, which results in a narrow absorption window. Compared with simple solutions of nateglinide, niosomal dispersions offer a quicker onset of action and higher oral bioavailability. This is attributed to niosomes enhancing the dissolution of nateglinide and increasing its absorption via paracellular pathways, potentially bypassing systemic pre-metabolism.⁹⁵ Recombinant human insulin embedded in multilamellar niosomes comprising polyoxyethylene alkyl ether surfactants (Brij 52 and Brij 92), sorbitan monostearate (Span 60), and cholesterol exhibited good stability in bile salt solutions. Furthermore, compared to a free insulin solution, the vesicles demonstrated significant protection against proteolytic enzymes.⁹⁶ Using the thin-film hydration technique, niosomes encapsulating glimepiride demonstrated a seven-fold increase in oral bioavailability, along with a prolonged duration of action. This approach allows for reduced dosage and dosing frequency, potentially minimizing drug-related adverse effects.⁹⁷

Anti-Hypertensive Effect

Niosomes containing telmisartan were formulated to improve its antihypertensive activity, significantly attenuating the elevated mRNA and protein levels of the angiotensin II type-1 receptor (AT1R) gene.⁹⁸ Carvedilol has a limited systemic availability owing to its high metabolism, and nanoniosomes are promising as stable carriers for its oral delivery.⁹⁹ Compared with drug suspensions, niosomes enhance the oral bioavailability of carvedilol by twofold. In addition, bile salt-enriched (sodium cholate or sodium taurocholate) niosomes exhibit stronger intestinal absorption than conventional niosomes.¹⁰⁰ Candesartan cilexetil-loaded niosomes prepared using a combination of surfactants, Span 60/Pluronic p85, demonstrated enhanced drug release and stability.¹⁰¹

Anti-Hyperlipidemic Effect

Atorvastatin poses challenges in terms of its biopharmaceutical properties, including a low dissolution rate and extensive pre-systemic disposition, leading to decreased oral bioavailability, thus requiring higher doses and resulting in undesired side effects. Niosomes containing Span 60, cholesterol, and dicetyl-phosphate have been shown to enhance the anti-hyperlipidemic effects of atorvastatin. Further improvement in drug action was achieved by encapsulating niosomes with chitosan.⁸⁷

Vaccine

The niosomal system may be a potential candidate for oral vaccine delivery. Niosomes encapsulating inactivated vaccines offer a safe approach owing to their inability to replicate, mitigating the risk of disease generation, which are often associated with viral delivery systems. Moreover, compared to free, inactivated vaccines, niosomes that encapsulate these vaccines elicit a more potent immune response.¹⁴⁸ Tetanus toxoid (TT) antigens encapsulated in niosomes were evaluated for their immunostimulatory effects after oral administration by measuring serum IgG antibody levels, demonstrating better humoral reactions compared with their ordinary counterparts.¹⁰²

Transdermal Delivery

Mechanism of Non-Ionic Surfactants in Niosomes Transdermal Drug Delivery

Transdermal drug administration involves the regulated dispensation of medications via the skin to achieve consistent therapeutic concentrations in the body. This route is less invasive and prevents the drug from degrading in the extreme acidity of the stomach, enabling stable transportation of drugs.¹⁴⁹ However, there are biological barriers in the human body that are vital for the operation of numerous human organs and serve as shields from physical, chemical, and biological harm.¹⁵⁰ Medications must cross these barriers to reach the target site and exert their efficacy. The objective of a transdermal delivery system is to traverse the epidermis, primarily the stratum corneum (SC), and penetrate the dermal

capillaries before entering the systemic blood circulation. SC serves as the primary barrier and consists of densely packed and heavily keratinized deceased cells.¹⁵¹ A transdermal drug delivery route focuses on ensuring optimal drug penetration.¹⁴⁹ However, SC restricts drug penetration, making it difficult for most drugs to penetrate the skin.¹⁰⁵ The application of niosomes simplifies the encapsulation of various bioactive compounds, enhances their physicochemical stability, reduces severe side effects and skin irritation, and improves transdermal absorption, as well as the accumulation of payload at the delivery site.¹⁰⁶ Niosomes can engage with SC via fusion, aggregation, and adhesion processes, leading to a significant thermodynamic activity gradient of the drug at the vesicle-skin interface, thus inducing drug penetration.^{152,153} The skin permeation of niosomes is influenced by the particle size, type of surfactant, elasticity, surface charge, and the concentration of cholesterol.

Surfactants enhance drug permeability via SC by two primary means. First, their surface tension-reducing properties enhance fluidity and enable the solubilization and extraction of lipids from the epidermis, consequently leading to corneocyte disruption by binding and interacting with keratin filaments.¹⁵⁴ Second, the adhesion of niosomes to the skin surface induces changes in the SC properties by reducing epidermal water loss, consequently increasing skin hydration and loosening the tightly packed cellular structures (Figure 3b).¹⁵⁰

In addition, the stability and skin permeability of niosomes can be improved by incorporating additives into their structure. For example, the use of SDS to enhance the charge within the niosomal system or the introduction of essential oils as potential niosomal fluidizers alters the fluidity of the vesicle membrane.^{74,107}

Application of Niosomes in Transdermal Drug Delivery

Niosomes are lipid-based vesicles that enhance the penetration of drugs via the skin. They can act as reservoirs for the sustained release of active compounds in the skin. When non-ionic surfactants are incorporated into niosomes, the skin tends to tolerate them more effectively compared to when they are used in an emulsion, especially in the context of the local mucosal irritation caused by many anti-inflammatory drugs.²⁷ Diclofenac sodium is a potent nonsteroidal anti-inflammatory drug with significant analgesic effects requiring frequent administration owing to its short half-life; its long-term use can cause adverse gastrointestinal reactions, such as ulcers, bleeding, or intestinal wall perforation. Therefore, controlled transdermal administration is considered a more appropriate administration mode for diclofenac sodium. Niosomes prepared using span20, tween20, and cholesterol and loaded with diclofenac sodium gel demonstrated greater permeability of the skin layer and anti-inflammatory activity than a regular gel with diclofenac sodium.¹⁰⁸ Niosomes containing diacerein prepared using the thin film hydration method also demonstrated this superior effect.¹⁰⁹ Auda et al prepared niosomes containing celecoxib using a thin-film hydration method with various surfactants. The anti-inflammatory effects of different niosomal gel formulations were evaluated using the carrageenan-induced rat paw edema method. Their findings revealed that the poloxamer niosomal gel exhibited significant anti-inflammatory effects against rat paw edema.¹¹⁰ Besides anti-inflammatory drugs, many other drugs are also suitable for transdermal administration. Niosomes loaded with loratadine (LRD) were incorporated into transdermal patches for the treatment of allergies. Compared with control patches, niosomal patches demonstrated improved drug release and permeability, with the niosomal surfactants acting as penetration enhancers.¹⁰³ Another study prepared niosomes using Span 40, cholesterol, and SDS for transdermal delivery of salidroside. The inclusion of SDS significantly enhanced the zeta potential and stability of niosomes, with an optimal concentration of 0.1% SDS leading to the highest transdermal flux.⁷⁴ The niosomal gel for transdermal delivery of propofol addresses the issues of hypersensitivity and pain related to intravenous administration. Compared with the control gel, the niosomal gel demonstrated significantly improved propofol release and bioavailability in rats, indicating its potential as a non-invasive alternative for procedural sedation, particularly in pediatrics.¹⁰⁴

Ocular Delivery

Owing to the complex anatomical structure and physiological barriers of the eye, drug delivery to the intraocular tissues is highly challenging.¹⁵⁵ The ocular bioavailability of drugs administered in the conventional form is typically less than 5%.¹⁵⁶ Research indicates that niosomes are promising as carriers for drug delivery to ocular tissues. Primarily, their nano-scale size enables them to withstand the drainage caused by reflex tearing and blinking. Additionally, niosomes have demonstrated improved retention on

the ocular surface compared to alternative carriers (Figure 3c).¹⁸ Niosomes encapsulating pilocarpine hydrochloride offer greater permeability, longer ocular retention time, and drug metabolism protection compared to traditional formulations. Additionally, Tween 60 formulations provide more uniform dispersion, optimal ocular delivery particle size, and better entrapment efficiency compared to Span 60 formulations.⁴⁴ A study developed a niosome-in-gel system using latanoprost for sustained ocular delivery. Niosomes were optimized for drug encapsulation achieving a maximum efficiency of 98%. When incorporated into a Pluronic F127 gel, the formulation showed effective and prolonged intraocular pressure reduction in rabbits, without irritation, suggesting its potential for improving glaucoma treatment adherence compared to traditional eye drops.⁵² Zeng et al developed niosomes coated with mucoadhesive hyaluronic acid (HA) that improved the tacrolimus precorneal retention time, aqueous humor pharmacokinetics, and corneal permeability. Compared to suspensions or non-coated niosomes, the ocular bioavailability of tacrolimus increased by 2.3- or 1.2-fold, respectively.¹¹¹ Another study aimed to enhance the anti-inflammatory activity of flurbiprofen (FBP)-prepared niosome gel systems using the non-ionic surfactant Span 60. The gel prolonged the contact time of FBP in ocular tissues, exhibiting a rapid anti-inflammatory action and higher bioavailability in inflamed rabbit eyes.¹¹² Allam et al loaded niosomes by encapsulating betaxolol into pH-responsive in situ-forming gels to prolong the precorneal retention of the drug. This gel exhibited a more sustained in-vitro drug release compared to commercially available eye drops, leading to a prolonged reduction in the intraocular pressure in both normal and glaucomatous rabbits, along with a significant improvement in the relative bioavailability of betaxolol.¹¹³ In another study, niosomes were prepared and evaluated for the ocular delivery of hydrochloride naltrexone (NTX) using Span 60. In-vitro transcorneal permeation studies indicated that niosomes control NTX permeation and enhance corneal permeability.¹¹⁴

Injection Administration

The routes of injection administration include subcutaneous injection, intramuscular injection, intravenous injection, and intradermal injection, which can quickly deliver drugs into the body. Intravenous administration enables drugs to directly enter the systemic circulation, leading to a rapid onset of action and high bioavailability. Niosomes can be also delivered via intravascular pathways. Niosomes improve drug stability and extend their presence in the bloodstream. The administration of paclitaxel-loaded niosomes prepared using Span 40 significantly extended the elimination half-life of paclitaxel and delayed its excretion from plasma.¹¹⁵ In addition, targeted delivery to specific sites can be achieved with certain modifications. Tan et al developed a targeted transferrin receptor 6-O-palmitoyl ascorbic acid-based niosome for the intravenous injection of tocotrienols (T3) in breast cancer. They conjugated transferrin to the surface of niosomes using chemical linkers. Mice treated in vivo with tumor-targeted niosomes exhibited an average tumor volume 12 times lower than that of the untreated group.¹¹⁶ He et al formulated PEGylated niosomes containing paeonol to enhance its stability, bioavailability, and prolong cellular uptake. The formulated paeonol exhibited superior cytotoxicity compared to the free drug in HepG2 cells.¹¹⁷ Niosomes can also serve as vaccine carriers, overcoming the limitations associated with the instability of pristine antigens, RNA and DNA molecules, improving efficacy and providing long-term immune protection.^{8,9} Furthermore, some vaccines using lipid NPs for the prevention of COVID-19 have been approved by the Food and Drug Administration (FDA) or are in clinical trials.⁹

Intranasal Delivery

Intranasal delivery is suggested as a non-invasive approach for administering therapeutic agents to the brain. The transportation of drugs from the nasal cavity to the brain can be accomplished by two methods: direct transport via the olfactory and trigeminal neuronal pathways or indirect transport via systemic absorption.¹⁵⁷ The direct route from the nose to the brain through the olfactory pathway offers excellent brain targeting efficacy (Figure 3d).¹⁵⁸ Niosomes composed of non-ionic surfactants can interact with the nasal mucosa, owing to their lipophilicity, thereby enhancing permeability.¹¹⁹ Nefopam hydrochloride (NF) is an analgesic drug with low bioavailability (approximately 36%) due to first-pass metabolism. Nasal delivery of NF-loaded niosomes bypasses first-pass metabolism, enhances drug permeation through the nasal mucosa, and prolongs release time.¹¹⁸ Reports on niosomal systems for bromocriptine to enhance brain delivery via the nasal route, reveal significant improvements in brain targeting and pharmacodynamics. The optimized formulation demonstrated superior brain bioavailability and safety, with a nearly 6.47-fold increase in brain availability compared to the oral equivalent, indicating it as a promising alternative to oral delivery for Parkinson's Disease

management.¹¹⁹ Rinaldi et al prepared and characterized chitosan glutamate-coated niosomes loaded with pentamidine. These formulations showed promising mucosal adhesion and stability, with effective drug embedding and interaction with mucins.²⁶ Olanzapine (OL) is an atypical antipsychotic drug that exhibits enhanced bioavailability when formulated in niosomes. Compared to the intranasal drug solution, the optimized nasal niosomes coated with OL afforded a three-fold higher concentration of OL in the brain.¹²⁰ A niosomal in situ nasal gel loaded with buprenorphine hydrochloride was developed for treating anxiety, with in vitro permeation studies through sheep nasal mucosa revealing 83.49% drug permeation after 8 h.¹²¹

Pulmonary Delivery

Pulmonary administration is generally the preferred route of drug delivery for treating respiratory-related diseases such as pulmonary infections, asthma, and lung cancer. Delivering niosomal drugs via the pulmonary route presents several benefits, including enhanced mucus penetration, prolonged drug release, targeted delivery, and improved therapeutic outcomes (Figure 3e).⁷ Niosomes encapsulating salbutamol sulfate (SS) were prepared using a reverse-phase evaporation method and formulated into inhalable dosage forms. The SS-loaded niosomes effectively reduced the clearance rate of the drug, improving the deposition and retention of water-soluble SS in the lungs.¹²² In another study, cilomilast, a phosphodiesterase-4 inhibitor that is used to treat inflammatory lung diseases, was encapsulated within PEGylated phosphatidylcholine-rich niosomes to improve pulmonary delivery via the strong binding of niosomes to the pulmonary surfactant film. A twofold improvement in lung uptake was revealed as well as fewer adverse effects after encapsulation.¹²³ Niosomes loaded with nintedanib for inhalable delivery against non-small cell lung cancer (NSCLC) showed increased drug encapsulation, optimal vesicle size, and size distribution due to cationic modification, resulting in enhanced internalization and significant cytotoxic effects on NSCLC cells.²⁹ Gemcitabine (Gem) and cisplatin (Cis) are used for lung cancer treatment, however, they are highly toxic at high doses. Saimi et al developed a niosome formulation containing low-dosage Gem and Cis and optimized it using a simple heating method, revealing a high aerosol output (96.22%) and controlled drug release over 24 h. Cytotoxicity studies indicated that niosomes significantly reduced Gem and Cis toxicity compared to free drugs, suggesting their potential as a promising aerosolized treatment for lung cancer.⁵⁶

Other Applications

Niosomes also play a crucial role in diagnostics and imaging. Various imaging tests, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound imaging, utilize imaging agents or contrast agents to improve contrast and image visualization.^{159–162} Niosomes can be engineered to deliver imaging agents or contrast agents specifically to target tissues or cells, enhancing the precision of diagnostic imaging and minimizing side effects. Niosomes modified with transferrin (Tf) containing integrated magnetic iron oxide NPs (MIONs) and quantum dots (QDs) were formulated for effective imaging of gliomas, supported by magnetic and active targeting. The developed niosomes exhibited a high potential for cell specific dual targeting (active targeting and magnetic targeting) and dual imaging (magnetic resonance imaging and fluorescence imaging) in gliomas.¹² Niosomes labeled with the radioactive technetium-99m isotope and prepared via the thin-film hydration method demonstrated good in-vitro stability and high cancer-cell incorporation capacity.¹⁶³ Furthermore, niosomes can be designed to carry both diagnostic and therapeutic agents, enabling simultaneous imaging and therapy, which is particularly useful in tracking the progress of treatment. Theranostic pH-responsive niosome preparations for doxorubicin delivery and bio-imaging of breast cancer exhibited good anti-cancer activity at low concentrations.¹³ Theranostic niosomes used for direct intratumoral injection exhibited significantly enhanced tumor retention and anti-cancer effects.¹⁴ In addition, niosomes can be used to deliver probes or biomarkers that bind specifically to disease markers, facilitating early detection and monitoring of diseases. Niosomes comprising Tween 20 and Tween 21 used as colloidal nanocarriers for delivering molecular probes and therapeutic agents were detected with high sensitivity and accuracy using HPLC-FLD devices.¹⁵

Role of Non-Ionic Surfactants in Protein Coronas

Protein coronas influence the biodistribution, trafficking, and interactions of nanoparticles (NPs) with cell receptors. After NPs are administered by different means, they are promptly exposed to high protein levels in the bloodstream and

quickly bind to proteins on their surface, resulting in the formation of complex protein coronas.¹⁶⁴ Two types of distinct corona layers are found on the surface of NPs: hard and soft. The hard corona is the initial tightly bound layer of proteins, whereas the soft corona refers to the outer layer of proteins (not directly bound to the NPs).¹⁶⁵ The presence of protein coronas may trigger immune responses, leading to the rapid degradation of the macrophage phagocytic system and non-specific cellular uptake, further affecting drug efficacy and targeting.^{166,167}

Non-ionic surfactants can reduce the nonspecific adsorption of proteins onto nanoparticles, thereby decreasing the formation of protein coronas, which may be owing to the formation of hydrophilic shells on the surface of the nanoparticles, resulting in reduced protein-binding affinity. Additionally, when surfactants strongly bind with nanoparticles, it is difficult for proteins to displace them.¹⁶⁸ PEGylation is the conventional method used to reduce protein adsorption. PEGylated drugs and nanocarriers exhibit extended half-lives in the blood and reduced non-specific cellular uptake compared with unmodified drugs.^{169,170} However, PEG, which is a nonbiodegradable polyether, may accumulate in the body upon prolonged use of drug-PEG conjugates, leading to potential adverse effects.^{171,172} Therefore, finding alternatives to PEG is crucial, and non-ionic surfactants have gained attention owing to their non-toxicity and biocompatibility. Mueller et al employed the non-ionic surfactant polyphosphoester (PPE) to coat nanoparticles, offering a simplified approach for modulating protein coronas and their biological effects. After incubation with plasma, protein adsorption on the nanoparticles coated with PPE decreased, and the uptake by the macrophages was reduced.¹⁶⁸

In addition, non-ionic surfactants may influence the composition and structure of the protein corona, thereby altering the interactions of nanoparticles with cells or other biomolecules (Figure 4). The specific effects depend on factors such as the type and concentration of non-ionic surfactants, as well as the characteristics of the nanoparticles. The type and relative abundance of proteins influence the intracellular uptake and regulate the internalization of nanoparticles. Among the numerous proteins adsorbed onto nanoparticle surfaces, only a fraction can bind to cells. Less than 27% of the protein coronas can undergo antibody binding owing to steric hindrance.¹⁷³ Furthermore, only a limited number of cell receptors bind to the different serum proteins present on the surface of nanoparticles for

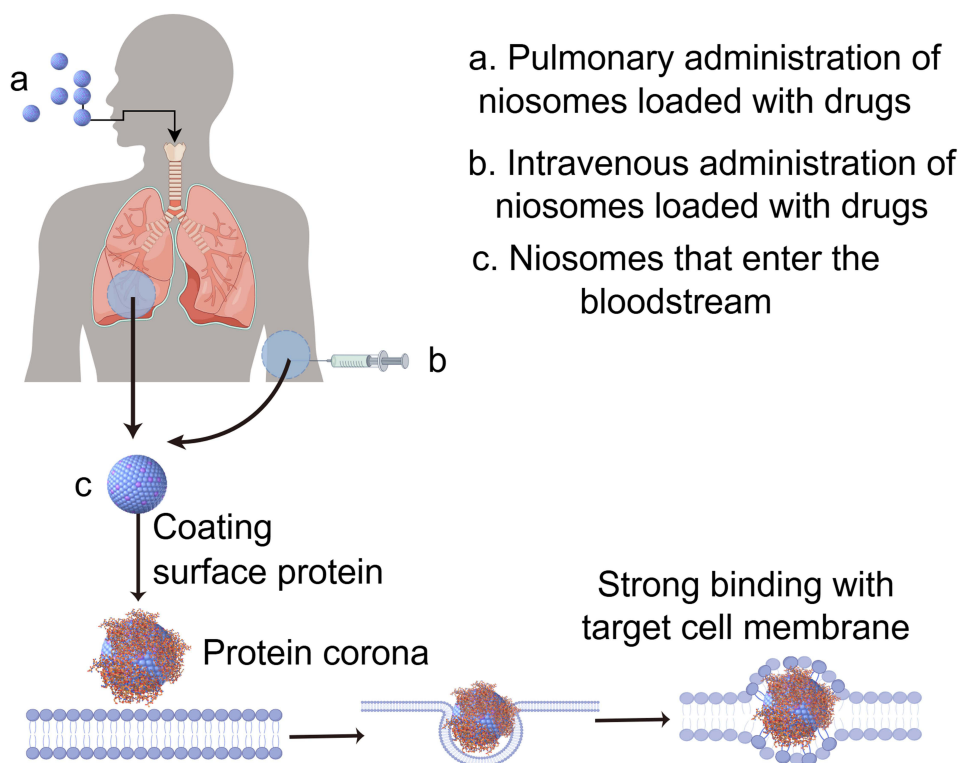


Figure 4 The impact of protein coronas on the characteristics and behavior of niosomes. (By Figdraw).

uptake.¹⁷⁴ If the protein corona can be personalized to promote preferential internalization of the protein corona nanoparticle by diseased cells rather than by healthy cells, the therapeutic efficacy of the drug may be enhanced. For example, the formulation of niosomes with different surfactants and their varying proportions may influence the characteristics of protein adsorption, thereby affecting the in-vivo targeting performance of nanoparticles. Upon comparing niosomes synthesized from different Tween derivatives (Tween20, Tween21, and Tween80), formulations containing both Tween20 and Tween21 were found to have a relatively higher content of absorbed C1QC protein in the protein coronas and exhibited a higher tendency for internalization by cancer cell lines (HeLa cells for cervical cancer).¹⁷⁵

Applications of Artificial Intelligence

Artificial intelligence (AI) and nanomedicine play crucial roles in advancing personalized medicine. AI has been used in several notable areas of nanomedicine, including for predicting the structure-activity relationships, composition, safety, and efficacy of niosomes, as well as for pharmacokinetics (Figure 5).¹⁷⁶ Complex functions or data can be interpreted, managed, and analyzed more precisely using AI algorithms.¹⁷⁷

Various artificial intelligence techniques, including machine learning are currently available to assist in the preparation of niosomes. For example, a machine learning approach was employed to optimize niosome drug formulations. By screening literature with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) system, 114 niosome formulations were analyzed. Eleven properties influencing the particle size and drug entrapment were identified and used to train a neural network model with a hyperbolic tangent sigmoid transfer function and the Levenberg-Marquardt backpropagation algorithm. The model achieved a high prediction accuracy for drug entrapment and particle size. Sensitivity analysis highlighted the drug/lipid ratio and cholesterol/surfactant ratio as key factors. The model's accuracy was validated through the preparation of donepezil hydrochloride niosome batches, demonstrating a prediction accuracy of over 97%. The study concluded that the global artificial neural network outperforms the local response surface methodology for niosome formulations.¹⁷⁸ Machine-learning algorithms can be used to optimize the composition, structure, and properties of niosomes, providing predictive information regarding their stability, drug loading ability, and release, leading to better drug release and absorption effects at a lower cost and time.^{178,179} These artificial intelligence methods offer more efficient and accurate approaches for preparing and improving the performance of niosomes than traditional methods. However, experimental validations are necessary when applying these technologies to ensure their feasibility and safety.

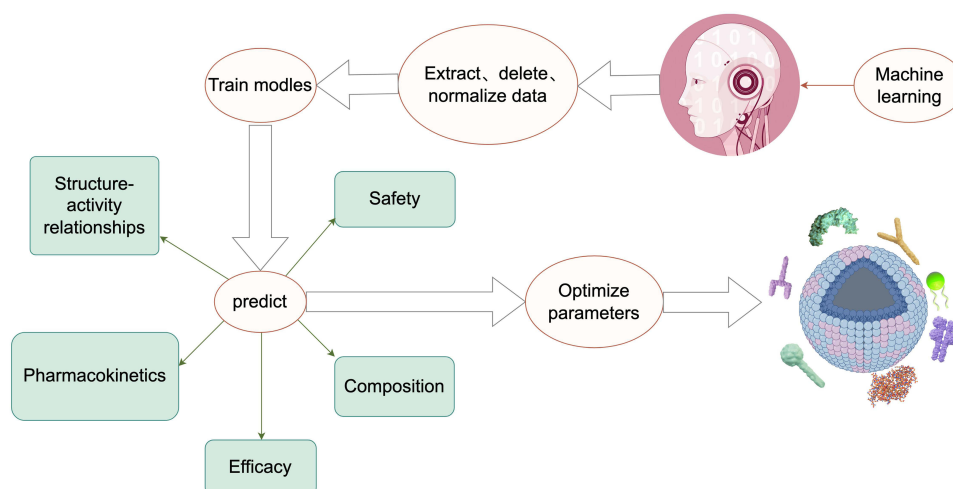


Figure 5 Machine learning optimization of niosomes. (By Figdraw).

Conclusion

Niosomes offer multiple advantages as drug delivery systems. Comprising non-ionic surfactants and cholesterol, they demonstrate excellent biocompatibility, minimal toxicity, and fewer adverse effects in vivo. The presence of non-ionic surfactants contributes to the formation of stable structures, playing a crucial role in various administration routes for niosome-mediated drug delivery and enhancing drug permeability and absorption in tissues. Based on current research, we believe that niosomes hold significant potential as multifunctional and efficient drug delivery carriers, and continued investigation is essential to unlocking their full therapeutic potential. Expanding the application of non-ionic surfactants in this area could lead to substantial advancements in drug efficacy and patient outcomes. Furthermore, future developments in niosome technology could benefit from the integration of artificial intelligence to further optimize their design and functionality. This would not only improve therapeutic outcomes but also pave the way for broader clinical applications across various medical fields, including cancer therapy, gene delivery, and vaccine management. Overall, niosomes exhibit high controllability and are promising as significant therapeutic tools in the future of medicine. To fully harness their potential, continued and rigorous research into their key components, especially non-ionic surfactants, is essential for advancing niosome technology and expanding its clinical applications.

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Disclosure

The authors report no conflicts of interest in this work.

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