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COMPREHENSIVE REVIEW ON NIOSOMES USED IN ANTICANCER DRUG DELIVERY

Srajan Shetty[1]*, Arjun Nair[2], G. K. Bhrama[3], Kunal Dolas[4], Manish Madli[5], Shrikant Hikke[6]

[1,2,4,5,6]Student, Bachelor of Pharmacy, KBIPER, Talegaon Dabhade.

[3]Assistant Professor, Bachelor of Pharmacy, KBIPER, Talegaon Dabhade.

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***Corresponding Author**

Srajan Shetty

Student, Bachelor of Pharmacy, KBIPER, Talegaon Dabhade.

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ABSTRACT

Niosomes are non-ionic surfactant-based vesicular systems that have gained significant attention as smart nanocarriers for anticancer drug delivery. Their bilayer structure enables simultaneous encapsulation of both hydrophilic and lipophilic agents, improving solubility, stability, and therapeutic index of conventional chemotherapeutics. Recent advances in formulation design particularly the integration of pH-responsive and ligand-modified components allow niosomes to release drugs selectively within the acidic tumor microenvironment. Such responsiveness enhances intracellular uptake, prolongs systemic circulation, and minimizes off-target toxicity. Studies on co-delivery of drugs like doxorubicin, camptothecin, and curcumin demonstrate improved synergistic effects and reduced multidrug resistance. Moreover, niosomes exhibit favourable physicochemical properties, biocompatibility, and scalability, making them a cost-effective alternative to liposomes and polymeric nanoparticles. However, their clinical application still faces challenges related to long-term stability, reproducibility, and regulatory approval. Overall, niosomes represent a promising and adaptable platform for the next generation of targeted and controlled anticancer drug delivery systems.

KEYWORDS: Niosomes, Anticancer drug delivery, pH-responsive systems, Targeted therapy, Controlled release, Nanocarriers, Co-delivery, Tumor microenvironment, Biocompatible vesicles, Nanomedicine.

1. INTRODUCTION

Cancer continues to be one of the most challenging diseases worldwide, responsible for millions of deaths each year despite major progress in diagnosis and therapy. Conventional chemotherapeutic agents such as doxorubicin and cisplatin are effective against rapidly dividing tumor cells; however, their lack of selectivity toward normal tissues results in severe systemic toxicity, multidrug resistance, and sub-optimal therapeutic outcomes. These drawbacks have intensified the need for developing advanced drug delivery systems that can enhance the concentration of anticancer agents at the tumor site while minimizing adverse effects on healthy cells.[1, 5, 6, 12, 13, 15]

Among the various nanocarriers explored, niosomes that are vesicular systems composed of non-ionic surfactants and cholesterol have emerged as a versatile and promising platform for targeted drug delivery. Their bilayer structure resembles that of liposomes but offers higher chemical stability, lower cost of production, and better compatibility with a wide range of drugs. The ability of niosomes to encapsulate both hydrophilic and lipophilic molecules, protect labile drugs from degradation, and provide controlled release has made them an attractive alternative to conventional formulations.[5, 12, 20]

Recent studies have shown that niosomes can significantly improve the intracellular uptake of anticancer drugs through both passive and active targeting mechanisms. Passive targeting is primarily governed by the enhanced permeability and retention (EPR) effect, which allows nanosized vesicles to accumulate preferentially within tumor tissues. Active targeting can be achieved by conjugating ligands such as folic acid or PEG to the niosomal surface, facilitating receptor-mediated endocytosis and improving drug internalization by cancer cells.[1, 2, 4, 8, 10]

Moreover, the development of pH-responsive and stimuli-sensitive niosomal systems has further advanced the field of nanotherapeutics. These modified vesicles exploit the acidic tumor microenvironment to trigger site specific drug release, thereby improving therapeutic precision and reducing systemic exposure.

Such innovations have demonstrated remarkable potential in preclinical studies, especially for the co-delivery of synergistic drug combinations like doxorubicin–camptothecin and curcumin-based formulations.[2, 4, 17, 22, 25]

Despite these promising outcomes, challenges such as scalability, physical stability, and lack of regulatory approval still limit the clinical translation of niosome-based systems. Nevertheless, their adjustable design, ability to modify composition easily, and potential for targeted delivery make them an important focus for future anticancer drug delivery research.

2. Structure and Composition of Niosomes

Niosomes are self-assembled, bilayered vesicular systems composed mainly of non-ionic surfactants and cholesterol, enclosing an aqueous core. This organized structure allows the simultaneous encapsulation of both hydrophilic and lipophilic therapeutic agents, providing high versatility in pharmaceutical applications. Table 4 shows a brief comparison data between niosomes and other nano carriers.

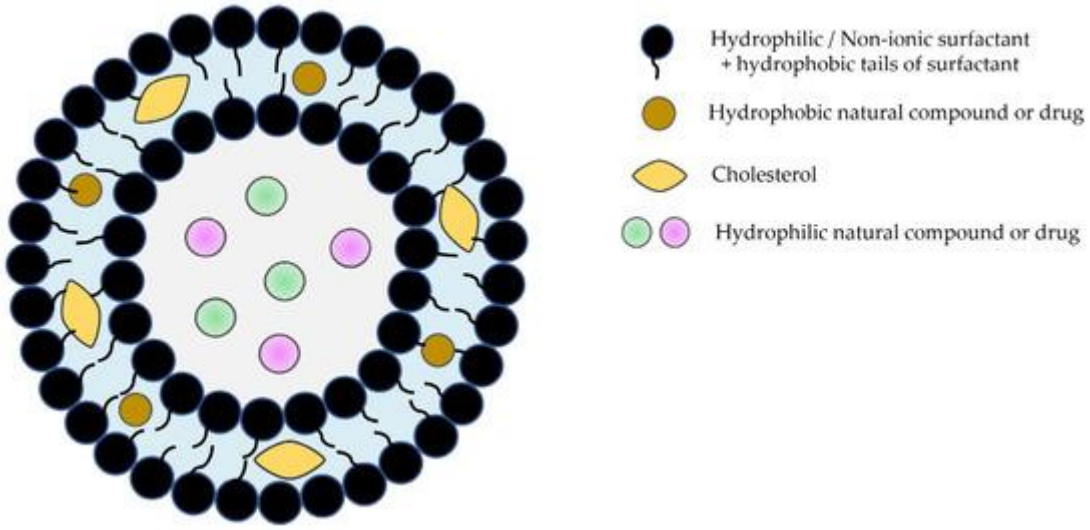

Figure 1: Structure and composition of niosomes (Adapted from 4).

2.1 Non-ionic Surfactants

Non-ionic surfactants form the basic framework of niosomes. Each molecule contains a hydrophilic head and a hydrophobic tail that spontaneously orient in aqueous environments to produce bilayer vesicles. Common surfactants include the Span and Tween series (Span 60, Span 80, Tween 20, Tween 80), Brij derivatives, and sorbitan esters. The physicochemical characteristics of the surfactant particularly its Hydrophilic-Lipophilic Balance (HLB) governs vesicle size, rigidity, and drug-release rate. Surfactants with low HLB values, such as

Span 60, generate more ordered and stable membranes with higher drug-retention capacity, whereas higher-HLB surfactants yield flexible vesicles that release drug more rapidly. Combining Span and Tween provides an optimal balance between fluidity and stability, enhancing both encapsulation and controlled-release behavior.[5, 12, 23, 25]

2.2 Cholesterol

Cholesterol serves as a membrane-stabilizing agent. By intercalating between surfactant molecules, it regulates bilayer rigidity and permeability, thus preventing aggregation or premature drug leakage. An appropriate surfactant-to-cholesterol ratio (typically 1:1 or 1:2) ensures mechanical stability and efficient drug entrapment. Excess cholesterol may induce phase separation and reduce encapsulation, while insufficient amounts can cause leaky vesicles.[12, 15, 20, 21]

2.3 Charge Inducers and Surface Modifiers

Charge-inducing agents such as dicetyl phosphate (negative) or stearylamine (positive) impart surface charge, promoting electrostatic repulsion and preventing vesicle aggregation. To extend systemic circulation and improve biocompatibility, polymers like polyethylene glycol (PEG) or chitosan are often grafted onto the vesicle surface (PEGylation). Ligands such as folic acid and transferrin can be conjugated for receptor-mediated uptake, enabling active targeting of cancer cells.[4, 14, 17]

2.4 Bilayer Architecture

The bilayer configuration of niosomes resembles natural biological membranes, providing structural compatibility and protection against enzymatic degradation. Based on lamellarity, niosomes are classified as unilamellar vesicles (ULVs) with a single bilayer or multilamellar vesicles (MLVs) containing several concentric bilayers. Vesicle size generally ranges from tens of nanometers to a few micrometers, depending on formulation variables and preparation technique.[4, 17, 20]

2.5 Hydration Medium

The aqueous phase used during hydration strongly influences vesicle characteristics. Buffers or distilled water are commonly employed, and the pH of the medium can be adjusted to improve drug solubility or impart pH sensitivity. Slightly neutral or mildly acidic conditions help maintain vesicle stability while preserving responsiveness to the acidic tumor microenvironment in targeted systems.[4, 5]

3. Methods of Preparation of Niosomes

The method adopted for niosome preparation has a decisive influence on the resulting vesicle size, lamellarity, entrapment efficiency, surface charge, and long-term stability. Parameters such as the ratio of surfactant to cholesterol, solvent polarity, hydration temperature, and agitation speed collectively determine the morphology and drug-loading capacity of the final formulation. Selecting an appropriate technique therefore becomes essential to achieve the desired physicochemical and therapeutic performance of the niosomal system.

3.1 Thin-Film Hydration Method

This is the most conventional and widely employed technique for niosome production. A mixture of non-ionic surfactant (typically Span or Tween derivatives) and cholesterol is dissolved in an organic solvent such as chloroform or a chloroform–methanol blend. The solvent is evaporated under reduced pressure using a rotary evaporator to form a uniform thin film on the inner wall of a round-bottom flask. The dry film is then hydrated with an aqueous phase containing the drug, usually at a temperature above the gel–liquid transition of the surfactant. Agitation causes the film to swell and detach, producing multilamellar vesicles (MLVs). Further size reduction by probe or bath sonication yields small unilamellar vesicles (SUVs).[5, 12,15]

Advantages: simple and reproducible, suitable for both hydrophilic and lipophilic drugs.

Limitations: may yield heterogeneous size distribution and comparatively low entrapment for hydrophilic drugs.

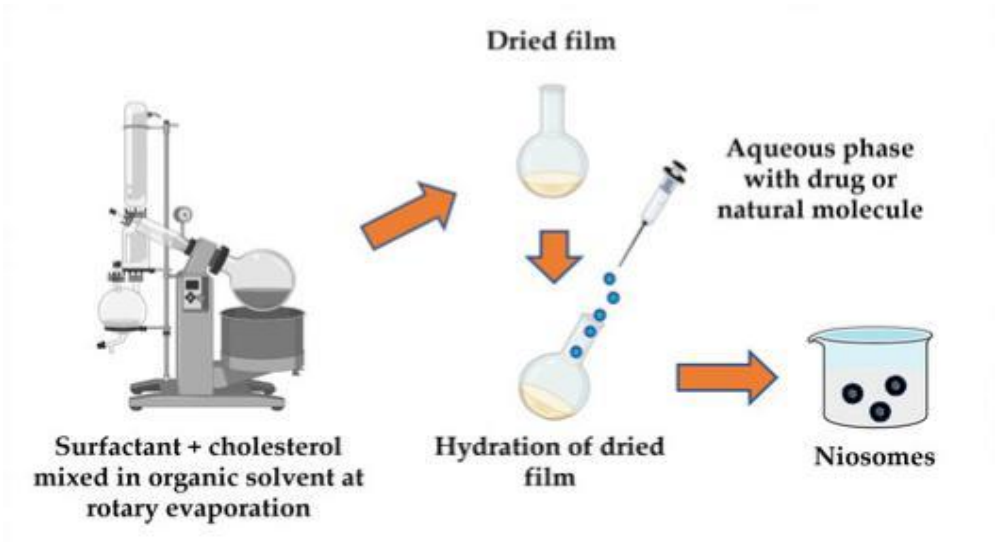

Figure 2: Thin-Film Hydration Method (Adapted from 15).

3.2 Reverse-Phase Evaporation (REV) Method-

In this technique, surfactant and cholesterol are first dissolved in an organic phase, followed by the addition of an aqueous phase containing the drug to form a stable water-in-oil emulsion under sonication. Subsequent removal of the solvent under reduced pressure leads to the formation of large unilamellar vesicles (LUVs) with high internal aqueous volume. REV provides greater entrapment efficiency for hydrophilic drugs and is preferred for thermolabile compounds since it allows lower processing temperatures.[12,15]

Drawback*:* residual traces of organic solvent may remain if evaporation is incomplete.

Figure 3: Reverse Phase Evaporation Method(Adapted from 12)

3.3 Ether-Injection Method

Here, the organic solution of surfactant and cholesterol is injected dropwise through a fine needle into a hot aqueous drug solution maintained at 60–65 °C. Rapid solvent vaporization results in spontaneous formation of uniform niosomes.[12,15,20]

Advantages: produces relatively small vesicles with narrow size distribution.

Limitation: unsuitable for heat-sensitive drugs because of elevated processing temperature.

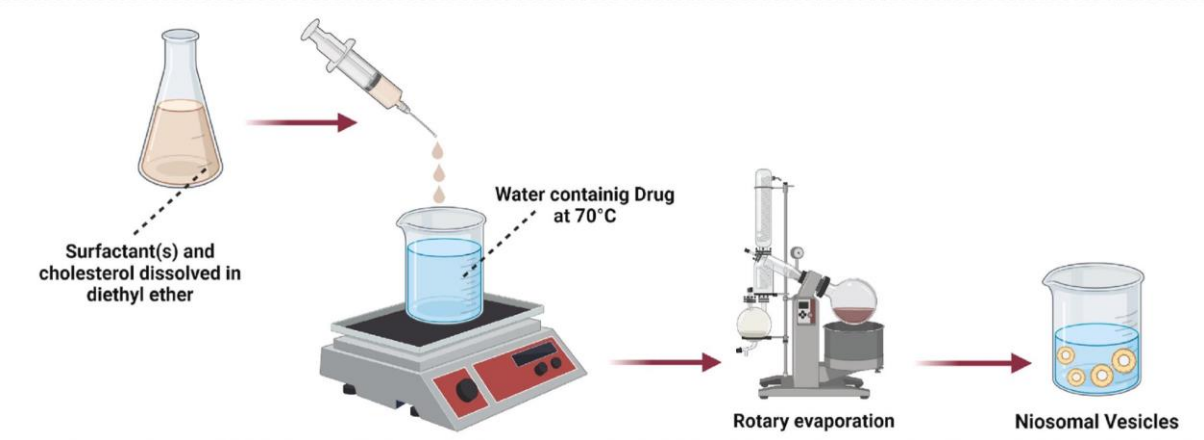

Figure 4: Ether Injection Method (Adapted from 12)

3.4 Sonication Method

Multilamellar vesicles obtained from thin-film hydration can be converted into smaller unilamellar vesicles by sonication using either a probe or bath sonicator. Sonication reduces particle size and improves uniformity but may cause localized heating and degradation of labile components. The process is often combined with extrusion through polycarbonate membranes for precise size control.[5, 12]

Figure 5: Sonication Method (Adapted from 12)

3.5 Microfluidization (High-Pressure Homogenization)-

This modern technique forces two immiscible phases: organic and aqueous, through microchannels at high pressure to generate uniform vesicles via controlled shear. Microfluidization offers excellent reproducibility, scalability, and narrow particle-size distribution. It is particularly useful for industrial production of niosomal formulations intended for parenteral use.[5, 23,33]

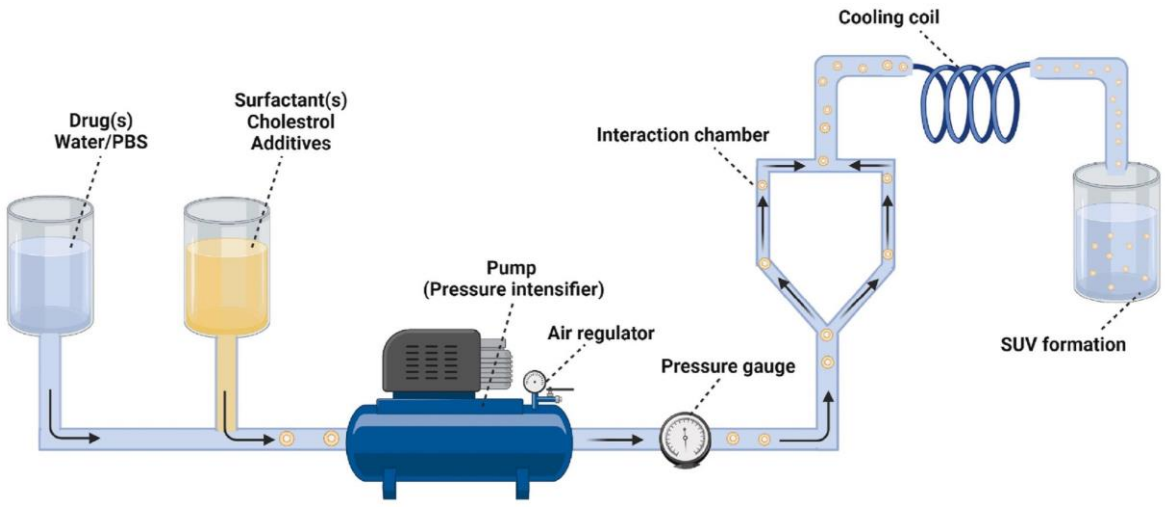

Figure 6: Microfluidization (Adapted from 15)

3.6 Bubble Method

A solvent-free and eco-friendly technique, the bubble method disperses surfactants in an aqueous phase under continuous nitrogen flow and mechanical agitation at 70 °C. The bubbling action forms stable niosomal vesicles without any organic solvent residue, enhancing biocompatibility. This approach is advantageous for large-scale preparation and for thermally stable drugs.[12, 20]

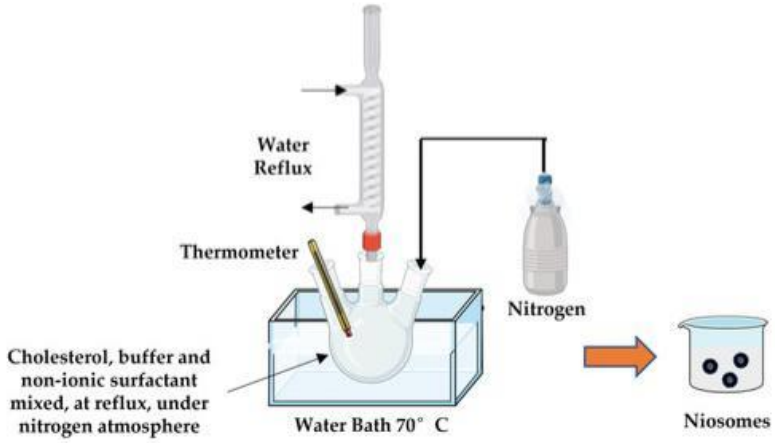

Figure 7: Bubble Method (Adapted from 12).

3.7 Emerging Techniques

Recent research has introduced advanced fabrication methods that provide greater control over vesicle size and minimize solvent exposure.

1. Microfluidic Chip Synthesis: This automated process combines surfactant and aqueous streams in micro-channels, allowing real-time control of mixing rate and particle size. It ensures reproducibility and is compatible with temperature-sensitive bio actives.
2. Supercritical CO_2-Assisted Assembly: A green technique that replaces organic solvents with supercritical carbon dioxide as a dispersion medium. The rapid depressurization of CO_2 induces self-assembly of surfactant molecules into niosomal vesicles. This process is clean, rapid, and scalable, aligning with modern environmental and safety standards.[5, 23,32]

A clear comprehensive overview of all the methods is clearly mentioned below (see Table 1)

Table 1: Overview of method of preparation of niosomes (Adapted from 5, 12, 15, 23, 25).

Methods	Principle/Key steps	Advantages	Limitations	Vesicle type/Size
Thin-Film Hydration	Dissolve surfactant & cholesterol in organic solvent → Evaporate → Hydrate film	Simple, reproducible	Low hydrophilic drug entrapment	MLV / SUV
Reverse-Phase Evaporation	Create W/O emulsion → Evaporate solvent → Form LUVs	High entrapment, gentle process	Solvent residues	LUV
Ether Injection	Inject organic phase into hot aqueous phase	Uniform vesicle size	Not suitable for heat-sensitive drugs	Small vesicles
Microfluidization	High-pressure mixing	Highly reproducible, scalable	Requires equipment	Nano-scale
Bubble Method	Surfactant + aqueous phase bubbled with N_2	Solvent-free (green)	High temperature required	Stable vesicles
Sonication	Apply ultrasonic energy to MLVs	Uniform nano size	Possible drug degradation	SUV
Supercritical CO_2 / Microfluidic	Gas-assisted particle formation	Eco-friendly, precise control	Costly setup	Nano-vesicles

4. Evaluation and Characterization of Niosomes

Comprehensive evaluation of niosomal formulations is crucial to confirm their physicochemical quality, stability, and suitability for therapeutic use. Characterization mainly focuses on vesicle size, morphology, surface charge, entrapment efficiency, and in-vitro drug-release behavior. These parameters collectively determine the system's performance, stability, and targeting potential.

4.1 Particle Size and Size Distribution

Particle size plays a major role in biodistribution, drug-release rate, and the ability of niosomes to reach target tissues through the enhanced permeability and retention (EPR) effect. The vesicle size is usually determined using Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS). Smaller vesicles (<200 nm) are preferred for intravenous delivery because they remain in circulation longer and penetrate tumor vasculature more efficiently. The Polydispersity Index (PDI) expresses size uniformity; values below 0.3 indicate a narrow and uniform distribution suitable for reproducible outcomes.[5, 8,15,20]

4.2 Zeta Potential

Zeta potential measures surface charge and indicates colloidal stability. It is obtained using electrophoretic light-scattering instruments. Niosomes with zeta-potential values greater than ±30 mV show, strong electrostatic repulsion, which minimizes aggregation. The use of charge inducers such as stearylamine (positive) or dicetyl phosphate (negative) improves dispersion stability and prevents vesicle fusion during storage.[5, 12,23]

4.3 Morphological Analysis

The shape and surface characteristics of niosomes are examined by Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), or Atomic Force Microscopy (AFM). TEM reveals internal bilayer organization, whereas SEM visualizes the outer morphology. Uniform, spherical vesicles with smooth boundaries confirm successful formation and a stable surfactant–cholesterol bilayer.[15, 20]

4.4 Entrapment Efficiency (EE %)

Entrapment efficiency represents the fraction of drug successfully enclosed within vesicles relative to the total drug used. Unentrapped drug is separated by ultracentrifugation, dialysis, or gel filtration, and the entrapped portion is quantified using UV–Visible spectrophotometry or HPLC.

Entrapment Efficiency (EE%) = (Entrapped drug ÷ Total drug added) × 100

A higher EE % indicates stronger interaction between the drug and the bilayer matrix. Factors such as surfactant type, cholesterol ratio, and preparation method greatly influence encapsulation capacity.[5, 8,9,12]

4.5 In-Vitro Drug-Release Study

Controlled release is one of the key attributes of niosomal formulations. In-vitro release is generally assessed using dialysis membrane diffusion, Franz diffusion cells, or a USP dissolution apparatus. Samples are withdrawn at predetermined intervals and analyzed spectrophotometrically. Release kinetics often follow Higuchi or Korsmeyer–Peppas models, indicating diffusion-controlled or anomalous transport. Sustained or pH-dependent release patterns reflect efficient formulation design.[8, 9]

4.6 Stability Studies

The physical and chemical stability of niosomes is evaluated by storing them at different temperatures (4 °C, 25 °C, 40 °C) and periodically checking vesicle size, zeta potential, and EE %. Cholesterol enhances bilayer rigidity and reduces drug leakage. PEGylated or lyophilized niosomes show improved long-term stability and can be easily re-dispersed before use.[10, 18]

4.7 Additional Evaluation Parameter

1. Viscosity and pH: Measured using a Brookfield viscometer and pH meter to ensure formulation compatibility for topical or parenteral administration.
2. Optical Birefringence: Observed under a polarized-light microscope to verify vesicular nature.
3. Osmotic Shock Test: Determines the robustness of vesicles under osmotic stress to confirm structural integrity in physiological environments.

A complete brief overview about the evaluation parameters is mentioned below with their purpose and the analytical method /instruments used in the evaluation. **(see table 2)**

Table 2: Key evaluation and characterization parameters (Adapted from 5, 8, 12, 15, 23).

Parameters	Purpose/Description	Analytical method
Particle size distribution	Determines uniformity and drug release behaviour	Dynamic light scattering (DLS)
Zeta potential	Indicates surface charge and stability	Electrophoretic mobility
Entrapment efficiency (EE%)	Measures % of drug encapsulated in vesicles	Ultracentrifugation + UV/Visible spectrophotometry
Morphology	Confirms shape	TEM / SEM / AFM
In-vitro drug release	Assess controlled/sustained release behaviour	Dialysis bag method / Franz diffusion cell
Stability studies	Monitors vesicle integrity overtime	Particle size, EE% and drug content after storage
pH responsiveness	Tests release under different pH conditions	Stimulated media at pH 5.5 and 7.4

5. Why pH-Responsive Agents Are Added to Niosomes

pH-responsive niosomes are a specialized class of vesicular systems designed to release their drug payload selectively in response to environmental pH variations. The purpose of incorporating pH-sensitive components is to achieve site-specific and controlled drug release,

particularly in cancer therapy and other pathological conditions characterized by altered pH levels.

5.1 Principle of pH-Responsiveness

The concept is based on the natural pH gradient that exists between normal physiological fluids (pH ≈ 7.4) and diseased tissues such as tumors (pH ≈ 6.5 or lower). Intracellular compartments like endosomes and lysosomes are even more acidic (pH ≈ 4.5-5.5).

By utilizing ionizable surfactants or polymers, niosomal vesicles are designed to remain stable at physiological pH but undergo structural changes in acidic environments. These changes destabilize the bilayer and facilitate triggered release of the encapsulated drug at the target site.[2, 3,4,8,17,32]

5.2 Role of pH-Responsive Agents

pH-sensitive agents such as cholesteryl hemisuccinate (CHEMS), polyacrylic acid (PAA), maleic anhydride copolymers, and imidazole-based surfactants are commonly incorporated into niosomal bilayers.

At neutral pH, these materials maintain bilayer integrity, whereas under acidic conditions, protonation increases hydrophilicity and disrupts membrane packing. As a result, drug molecules are released selectively in the tumor microenvironment or within acidic intracellular organelles, minimizing exposure to healthy tissues.[2, 4,14,17]

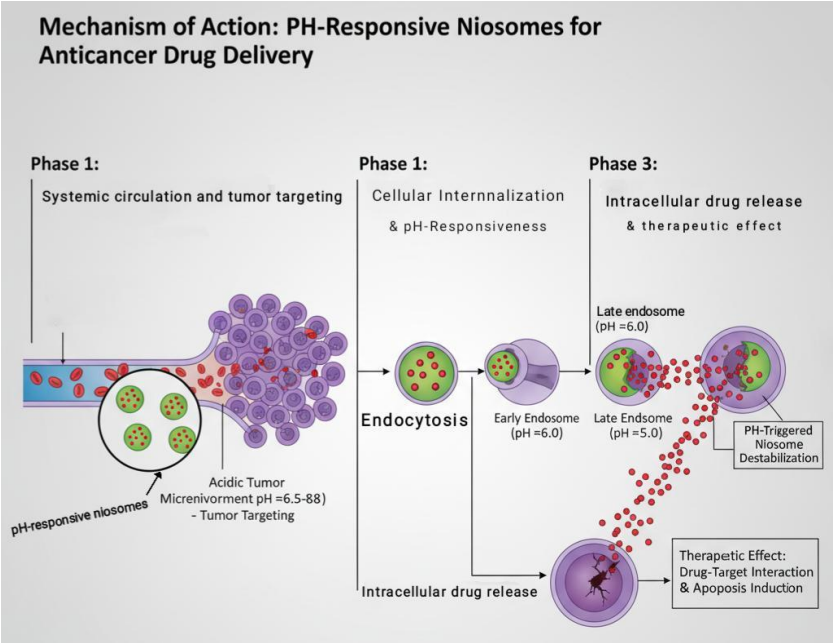

Figure 8: Mechanism of action of pH-responsive niosomes (Created based on data from 2,4).

5.3 Advantages of pH-Responsive Niosomes

- Targeted drug delivery: Enables release at acidic sites, reducing systemic side effects.
- Enhanced cellular uptake: Facilitates endosomal escape and improves intracellular delivery.
- Improved therapeutic efficiency: Enhances drug bioavailability and tumor-specific cytotoxicity.
- Reduced dosing frequency: Provides sustained release and better patient compliance.

5.4 Supporting Studies

Numerous investigations have demonstrated that pH-responsive niosomes play a major role mentioned in Table 4 which shows niosomes modified with polymers such as HD-PAA or folate-linked surfactants exhibit sustained and selective drug release in acidic environments, improving cytotoxicity against tumour cells and reducing systemic toxicity. Some formulations have progressed to pre-clinical evaluations in tumor-bearing models, where they showed enhanced accumulation at tumor sites and minimal drug loss during circulation, confirming their therapeutic promise.

Table 3: Recent key studies and the data collected (Adapted from 2, 4, 7, 14, 15, 33).

Author(year)	Drug/Agent	Polymer or modifier used	Target/cell line	Key findings
Gugleva V, et al (2024)	Curcumin	HD-PAA modified niosomes	MCF-7(Breast cancer)	Enhanced cytotoxicity and pH-triggered release
Rezaei T, et al (2022)	Doxorubicin + folate	Folate-PEG niosomes	MDA-MB-231	Improved cellular uptake and selectivity
Safari et al (2024)	Cisplatin + Doxorubicin	PEGylated + folic acid conjugation	Breast cancer cells	Higher drug loading and tumor-specific release
Saharkhiz S, et al (2023)	Quantum dots + drugs	Theranostic pH-sensitive hybrid	Imaging and therapy	Enabled simultaneous tracking and delivery
Zaer H, et al (2024)	Doxorubicin	3D-printed pH-sensitive composite	Solid tumor model	Sustained release, reduced systemic toxicity

6. Applications of Niosomes

Depending on the incorporated drug and therapeutic target, pH-responsive niosomes have been widely explored in various biomedical fields. Their structural versatility, stability under physiological pH, and selective drug release in acidic environments make them highly suitable for site-specific and controlled drug delivery, particularly in cancer therapy.

6.1 Cancer Therapy

The most prominent and extensively studied application of niosomes is in targeted anticancer therapy. Tumor tissues typically exhibit a slightly acidic extracellular pH (6.5–6.8), unlike normal tissues pH (≈7.4). Incorporation of pH-sensitive components such as polyacrylic acid (PAA), cholesteryl hemisuccinate (CHEMS), or folate-linked surfactants enables the vesicles to remain stable during systemic circulation and undergo controlled destabilization within the tumor microenvironment.

Such stimuli-responsive systems improve drug accumulation in tumors through the enhanced permeability and retention (EPR) effect while limiting exposure to healthy tissues. For example, folate-PEGylated niosomes co-encapsulating cisplatin and doxorubicin achieved synergistic cytotoxicity against breast-cancer cells with reduced systemic toxicity. Likewise, HD-PAA-modified curcumin niosomes demonstrated three-fold higher cytotoxicity toward colon-cancer cells due to sustained pH-triggered release. These studies highlight the potential of niosomes in precision oncology and multidrug combination therapy.[1, 2,4,8,10,17,27]

6.2 Co-delivery and Multidrug-Resistance (MDR) Management

Niosomes are highly effective in the co-delivery of multiple chemotherapeutic agents, enhancing therapeutic synergy and overcoming drug resistance. The pH-sensitive co-delivery of doxorubicin and camptothecin enabled sequential release, maximizing cancer-cell apoptosis. Furthermore, PEGylation or folate modification enhances circulation time and receptor-mediated uptake, providing a means to bypass efflux transporters responsible for MDR. Such platforms are being investigated for refractory tumors including breast, lung, and hepatic cancers.[21, 22,33]

6.3 Gene and Protein Delivery

pH-responsive niosomes also serve as efficient carriers for genetic and protein therapeutics. During intracellular trafficking, endosomal acidification (pH ≈ 5.5) induces vesicle destabilization, releasing the encapsulated biomolecules into the cytoplasm and preventing lysosomal degradation. This mechanism improves transfection efficiency and facilitates the delivery of peptides, siRNA, or plasmid DNA valuable for emerging gene-based anticancer strategies.[5, 23,24]

6.4 Dermatological and Transdermal Applications

In dermatological formulations, niosomes enhance skin permeation and prolong drug residence within the epidermal layer. Incorporation of pH-sensitive lipids permits site-specific drug release under inflamed or infected skin conditions, where local acidity is elevated. Such systems have been developed for topical management of melanoma, psoriasis, acne, and wound healing, providing controlled delivery with minimal irritation compared to cationic carriers.[16, 22,33]

6.5 Theranostic and Imaging Applications

An emerging field involves theranostic niosomes, combining therapeutic and diagnostic capabilities within a single platform. Quantum-dot- or dye-labeled pH-responsive niosomes enable simultaneous imaging and drug release, allowing real-time visualization of biodistribution and treatment progress. This dual-function approach enhances precision and supports the advancement of personalized cancer nanomedicine.[7, 23,24,32]

6.6 Other Biomedical Applications

Beyond oncology, pH-responsive niosomes show promise in antimicrobial, antifungal, anti-inflammatory, and ocular drug delivery, where infection- or inflammation-induced acidity facilitates localized drug release. These systems improve bioavailability and reduce systemic side effects, demonstrating the versatility of niosomal technology across therapeutic areas.[23, 24]

7. Advantages of Niosomes

Niosomes present numerous advantages that make them valuable carriers for anticancer drug delivery and other therapeutic applications:[1, 2,5,10,14,17,23,27,31,32]

1. **Dual drug encapsulation**

   They can encapsulate both hydrophilic and lipophilic drugs due to their bilayered structure, enhancing solubility and stability of diverse compounds.

2. **Enhanced chemical stability**

   Unlike liposomes, niosomes are composed of non-ionic surfactants which are less prone to oxidation or hydrolysis, ensuring longer shelf-life and improved formulation stability.

3. **Cost effectiveness**

   The raw materials used (non-ionic surfactants and cholesterol) are inexpensive and readily available, making niosomal formulations more economical for large-scale production.

4. **Controlled and targeted drug release**

   Functionalization with targeting moieties like folic acid, PEG, or antibodies enables site-specific delivery, minimizing systemic toxicity and increasing therapeutic efficiency.

5. **pH-responsive behaviour**

   Incorporation of pH-sensitive agents allows selective drug release in acidic environments such as tumor tissues or endosomes, reducing premature drug leakage in systemic circulation.

6. **Improved bioavailability**

   Niosomes protect drugs from enzymatic degradation and enhance absorption through biological membranes, leading to better bioavailability.

7. **Biocompatibility and non-immunogenicity**

   Niosomes are biocompatible and cause minimal immune reactions, making them safer for long-term or repeated administration.

8. **Versatile formulation flexibility**

   Their composition can be modified to tune vesicle size, surface charge, and release kinetics according to therapeutic needs.

9. **Ease of preparation and storage**

   They can be prepared using simple laboratory techniques without the need for complex instruments, and can be stored for longer periods under normal conditions.

10. **Potential for combined delivery**

    Niosomes can be utilized for co-delivery of multiple drugs (e.g., chemotherapeutics and natural compounds) to achieve synergistic effects in cancer therapy.

11. **Improved patient compliance:**

    Reduced dosing frequency, minimized side effects, and enhanced therapeutic outcomes contribute to greater patient comfort and adherence.

Table 4: Brief comparison of niosomes with other nano carriers(Adapted from 1, 2, 4, 7)

Carrier type	Composition	Key features	Advantages	Limitations
Niosomes	Non-ionic surfactant + cholesterol	Amphiphilic bilayer vesicles	Stable, low cost, non-toxic, easy scaleup	Not yet FDA approved
Liposomes	Phospholipids + cholesterol	Natural lipid bilayer	Biocompatible, biodegradable	Prone to oxidation, costly
Micelles	Amphiphilic surfactant monomers	Single layered	Solubilize hydrophobic drugs	Poor hydrophilic drug loading
Solid lipid nanoparticles	Solid lipids stabilized by surfactants	Crystalline core	Controlled release	Limited drug loading
Polymeric nanoparticles	Synthetic / natural polymers	Dense matrix	High stability	Possible toxicity, complex synthesis

8. Limitations and Future Prospects

Despite their promising potential, niosomes still face certain limitations that restrict their widespread clinical translation. Understanding these challenges is essential for improving formulation design and ensuring future success.

Limitations[6, 10,12,20,23,33]

- **Physical and chemical instability**

Although more stable than liposomes, niosomes can still undergo aggregation, fusion, or leakage during long-term storage, especially at high temperatures or under mechanical stress.

- **Limited drug loading capacity**

Hydrophilic drugs often exhibit low entrapment efficiency due to limited aqueous core volume, affecting overall therapeutic potential.

- **Scalability issues**

Techniques like thin-film hydration or sonication are difficult to scale up industrially, leading to batch variability and inconsistent vesicle size distribution.

- **Toxicity of surfactants**

Some synthetic surfactants used in niosomes formulation may cause irritation or cytotoxicity depending on concentration and exposure duration, limiting their biomedical use.

- **Lack of regulatory approval**

Despite extensive research, no niosomal formulations are yet approved by the FDA for therapeutic use, primarily due to insufficient long-term safety and clinical data.

- **Short circulation time**

Unmodified niosomes are rapidly cleared by the mononuclear phagocyte system (MPS), reducing bioavailability and limiting in vivo performance.

- **Encapsulation of sensitive molecules**

Formulation processes involving solvents, temperature, or sonication can degrade proteins, peptides, or other biomolecules.

Future Prospects[5, 7,10,22,23,32,33]

1. **Surface modifications and stealth coatings**

PEGylation and ligand functionalization can enhance circulation time and provide active targeting to tumor tissues, overcoming rapid clearance issues.

2. Stimuli – Responsive systems

Development of multi-stimuli-responsive niosomes (pH, temperature, enzyme, or redox) may improve controlled and site-specific release for precision therapy.

3. Green and scalable preparation methods

Adopting solvent-free and microfluidic techniques can enable eco-friendly, reproducible, and industry-compatible production of niosomal formulations.

4. Combination and theranostic applications

Co-delivery of multiple drugs or imaging agents can facilitate synergistic therapy and real-time monitoring, paving the way for personalized treatment approaches.

5. Clinical and toxicological evaluation

More extensive preclinical and human studies are needed to establish pharmacokinetic profiles, safety, and efficacy for regulatory approval.

6. Integration with advanced nanoplatforms

Hybrid systems combining niosomes with hydrogels, nanoparticles, or biopolymers may enhance mechanical stability, targeted delivery, and sustained release performance.

9. CONCLUSION

Niosomes represent an innovative and highly adaptable nanocarrier platform with immense promise in anticancer drug delivery. Their bilayered structure, composed of non-ionic surfactants and cholesterol, enables the encapsulation of both hydrophilic and lipophilic drugs, thereby improving stability, solubility, and bioavailability of therapeutic agents.

Among the different variants, pH-responsive niosomes have shown particular significance in cancer therapy. These vesicles remain stable under physiological conditions but are designed to trigger the release of their contents rapidly in the acidic tumor environment. Such controlled and site-specific release enhances therapeutic efficacy while minimizing systemic side effects.

Despite remarkable research progress, challenges such as low large-scale reproducibility, limited long-term stability, and the absence of FDA-approved formulations continue to restrict their clinical applications. Future research should focus on green and scalable production methods, hybrid and multifunctional vesicle systems, and extensive in-vivo and clinical validation.

With ongoing innovations and interdisciplinary efforts, niosomal drug delivery systems hold immense potential to redefine cancer therapy by offering safer, more effective, and patient-friendly treatment strategies.

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