

Effective Quality-by-Design Methodologies in the Fabrication and Evaluation of Innovative Niosomal Gel Formulations

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Abstract Background of the Research: Niosomes have gained significant attention in drug delivery due to their aptitude to reduce toxicity, enhance pharmacokinetics, and modify bioavailability. Their topical application can improve drug habitation time in the stratum corneum and epidermis while minimizing systemic absorption. Niosomal gels combine the advantages of niosomes with the convenience of gels, offering enhanced therapeutic efficacy and improved patient compliance. This review aims to deliver a comprehensive impression of niosomal gels, including their formulation, characterization, and broad applications in the pharmaceutical and cosmetic fields. Additionally, the research explores the preparation of niosomes utilizing the Quality by Design (QbD) approach, which integrates quality principles into the progress of drug delivery systems. **Methodologies:** The preparation approaches for niosomal gels—such as thin film hydration, reverse-phase evaporation, and nanoprecipitation—are reviewed, along with their respective advantages and limitations. Characterization techniques, focusing on physicochemical properties, stability studies, and drug release kinetics, are highlighted to evaluate the performance of niosomal gels. **Principal Results:** The review demonstrates that niosomal gels offer structural integrity, controlled drug release, and targeted delivery. Their diverse applications include transdermal

drug delivery, gene delivery systems, and cosmetic formulations. Utilizing QbD in niosome preparation further enhances the precision and efficiency of drug development. **Major Conclusions:** Niosomal gels represent a promising drug delivery platform with the potential for significant therapeutic benefits. The integration of QbD principles into the development process ensures high-quality formulations and addresses critical aspects of drug delivery. **Contributions to the Field:** This study contributes to the rising body of knowledge on niosomal gels by giving insights into their formulation, characterization, and applications. It also highlights the potential challenges and future opportunities in advancing niosomal gel technology, encouraging further research and development in pharmaceutical science.

Keywords Drug Delivery Systems, Characterization, Evaluation, Formulations, Niosomal Gels

1. Introduction

Targeted drug delivery involves plummeting the attentiveness of medication in nearby tissues while increasing its concentration in specific tissues, effectively

localizing the medicine and minimizing its impact on nearby tissues. This localization enhances drug efficacy by preventing unnecessary dispersion. Various carriers such as liposomes, microspheres, serum proteins, immunoglobulins, erythrocytes, and niosomes have been utilized for this purpose, with niosomes standing out as particularly effective [1].

Niosomes, also termed non-ionic surfactant vesicles, are tiny lamellar assemblies shaped by uniting Cholesterol (CHL) and non-ionic surfactants of the alkyl or dialkyl polyglycerol ether class. These amphiphilic surfactants utilize energy to form closed bilayer vesicles in aqueous environments, with hydrophilic heads facing the solvent while hydrophobic portions face away. The stability of the vesicular structure is ensured through a combination of fundamental physical forces that work together to maintain its integrity. These include van der Waals forces, which provide attractive interactions between molecules; entropic repulsive forces, which arise due to the thermodynamic tendency of molecules to adopt configurations that maximize entropy; electrostatic interactions, which depend on the charges present on the vesicle's surface and surrounding medium; and short-range repulsive forces, which prevent the collapse or aggregation of vesicles by counteracting overly close molecular interactions. Together, these forces create a dynamic equilibrium that preserves the vesicle's structural stability and functionality [2].

Factors influencing niosome stability include surfactant type, nature of encapsulated drug, storage conditions, use of lipids spanning the membrane, and inclusion of charged molecules. Because of their hydrophilic, amphiphilic, and lipophilic components, niosomes can hold drugs with diverse solubility levels, acting as a depot for gradual drug release. This prolonged release delays drug clearance, shields it from biological degradation, and confines its effects to targeted cells, enhancing therapeutic efficacy [3].

Similar to liposomes, niosomes exhibit liposomal behavior *in vivo*, extending drug circulation and modifying its organ distribution and stability during metabolism. The arrangement of the bilayer and the making process influence niosome characteristics, with reports suggesting that CHL intercalation in bilayers can reduce entrapment efficiency (EE) by decreasing the entrapment volume during formulation [4].

Gels are semi-rigid systems characterized by a three-dimensional network of macromolecules or particles dispersed within a liquid medium. The structural integrity and strength of the gel are influenced by the solubility of the macromolecules in the medium and the interactions between the particles within the network. These interactions form a cohesive matrix, enabling gels to maintain their shape while exhibiting properties of both solids and liquids. The terms "jelly" and "gel" share a linguistic root, both stemming from "gelatin." Derived from Latin, "gelu" translates to "drop," while "gel" signifies "freeze" or "solidify." Topical gels, and

homogeneous semi-solid solutions, find application in treating and preventing skin disorders. Their hydrophilic nature facilitates the rapid release of medication or active ingredients. Gels comprise a cross-linked material with sufficient liquid to form a sturdy network. Upon application, the gel's thin layer, formed by the gel-forming matrix, quickly covers the skin as the liquid evaporates. The flexibility of a gel arises from its intricate network formed by interlocked particles of the gelling agent. This network provides a balance between rigidity and adaptability, enabling the gel to conform to different shapes and surfaces. The gel's properties and structural characteristics are significantly influenced by the type of nanostructure present and the composition of the particles within the network, which together determine its mechanical strength, elasticity, and functional behavior [5].

Topical gel formulations offer effective drug delivery, reduced greasiness and easy removal from the skin. They excel in cutaneous and percutaneous drug delivery, circumventing issues related to gastrointestinal pH affecting drug absorption and interactions with food or beverages. Gels can be a viable alternative when oral administration is unsuitable, bypassing the first-pass effect during early drug passage through the body [6].

Niosomal gels represent a nano-vesicular carrier system capable of encapsulating both hydrophobic and hydrophilic medications. Comprising lipid bilayer-containing vesicles composed of non-ionic surfactants, niosomes offer enhanced stability, improved skin penetration, and controlled drug release. By enhancing patient adherence, reducing systemic exposure, and promoting drug penetration, these formulations address limitations associated with conventional topical therapies. The development of niosomal gels provides a promising alternative for patients seeking safe and effective treatments. Niosomes have shown considerable potential, particularly in accommodating various anti-inflammatory drugs like calcineurin inhibitors and corticosteroids. Encapsulation in liposomes enhances the stability of these medications while facilitating direct delivery to affected skin layers, thereby increasing drug penetration and minimizing systemic side effects [7].

1.1. Advantages of Niosomal Gels

The following are the merits of niosomal gels [8, 9].

- Enhanced patient compliance and suitability for self-medication are notable advantages of niosomes.
- Niosomal vesicle formulation offers controllable and customizable characteristics, making it convenient and easy to apply.
- Niosomes help avoid fluctuations in drug levels and associated risks, offering effectiveness at low doses and through continuous drug input.
- Niosomes help avoid gastrointestinal incompatibility and the risks associated with administration and

varied absorption conditions in oral or parenteral routes, such as pH changes, enzyme presence, and gastric emptying time.

- Niosomes offer the unique advantage of encapsulating both lipophilic and hydrophilic drugs, allowing for combination therapy across different drug classes.
- Simultaneous administration of multiple drugs with varied mechanisms of action can lead to improved treatment outcomes and yield synergistic effects.
- The water-based suspension system of niosomes, comprising hydrophilic, amphiphilic, and lipophilic moieties, enables the accommodation of drug molecules with diverse solubilities, enhancing patient compliance compared to oily dosage forms.
- They enable easy termination of medications when necessary and provide selective drug delivery to specific sites, optimizing drug utilization for drugs with short biological half-lives and narrow therapeutic windows.

1.2. Disadvantages of Niosomal Gel

The pitfalls of niosomal gels are as follows.

- Challenges such as fusion, combination, and escape of tricked drugs may arise, leading to physical instability.
- Contact dermatitis may occur due to certain drugs or excipients.
- Enzymes present in the epidermis can degrade drugs, affecting their effectiveness.
- Hydrolysis of summarised drugs can occur, warning the shelf life of the niosomal dispersion.
- Many drugs possess a high molecular weight and limited lipid solubility, resulting in poor absorption through the skin or mucous membranes.
- Niosomes are suitable only for drugs requiring low plasma concentrations for efficacy.
- The potential for local skin irritation at the application site is a concern.

2. Mechanisms of Drug Release from Niosomes

2.1. Diffusion through the Bilayer

Hydrophilic Drugs: These drugs are condensed in the aqueous core of the niosomes. They can slowly diffuse out through the bilayer, especially if the bilayer is not completely impervious.

Lipophilic Drugs: These drugs are located within the lipid bilayer of the niosome. They can diffuse out into the surrounding medium over time.

2.2. Bilayer Degradation

Environmental Factors: Factors like pH, temperature, and the presence of enzymes can lead to the degradation of the niosomal bilayer. For instance, in the acidic environment of a lysosome within a cell, the bilayer may break down more rapidly, releasing the drug.

Mechanical Stress: Shear forces in the bloodstream or at the site of action can cause the bilayer to break down, releasing the drug.

2.3. Fusion with Biological Membranes

Niosomes can fuse with cell membranes or endosomal membranes after endocytosis. This fusion can lead to the direct release of the drug into the cytoplasm or other intracellular compartments.

2.4. Endocytosis and Lysosomal Degradation

Cells can uptake niosomes via endocytosis. Once inside the cell, the niosomes can be trafficked to lysosomes where the acidic situation and digestive enzymes damage the niosomal bilayer, leading to the release of the encapsulated drug.

2.5. Targeted Release

Niosomes can be engineered to have surface ligands (like antibodies, peptides, or other molecules) that target specific receptors on cells. Upon binding to these receptors, the niosomes can be taken up by the cells, and the drug can be released once inside.

2.6. Osmotic Shock

Changes in osmotic pressure can cause the niosomes to swell and eventually burst, releasing the encapsulated drug. This can be particularly useful in targeted drug delivery where specific osmotic conditions are present at the target site.

3. Preparation of Niosomes

3.1. Thin Film Hydration Technique

Initially, an organic solvent (e.g., benzene, diethyl ether, and chloroform) is engaged to dissolve both the CHL and surfactant. Following solvent evaporation under low pressure in a vacuum evaporator, a mixture of solid surfactant and CHL coats the walls of the round-bottom flask. Subsequently, the surfactant layer undergoes swelling upon rehydration with an aqueous solution containing the medication, accompanied by continuous agitation (Figure 1). Eventually, the swollen amphiphiles reorganize into vesicles encapsulating the medications [10].

3.2. Ether Injection Method

This method involves the gradual infusion of a solution through a gauze needle into a preheated aqueous medium containing the therapeutic agent, maintained at 60°C. The infused solution comprises a defined proportion of CHL and surfactant, dissolved in ether. Upon vaporization of the ether, unilamellar vesicles are generated, encapsulating the

drug within surfactant layers. For heat-sensitive drugs, fluorinated hydrocarbons are employed as a substitute for ethers, as they evaporate at lower temperatures, reducing the risk of thermal degradation. The resulting niosomes typically measure between 50 and 1000 nm, with their size determined by the formulation components and experimental conditions (Figure 2) [11].

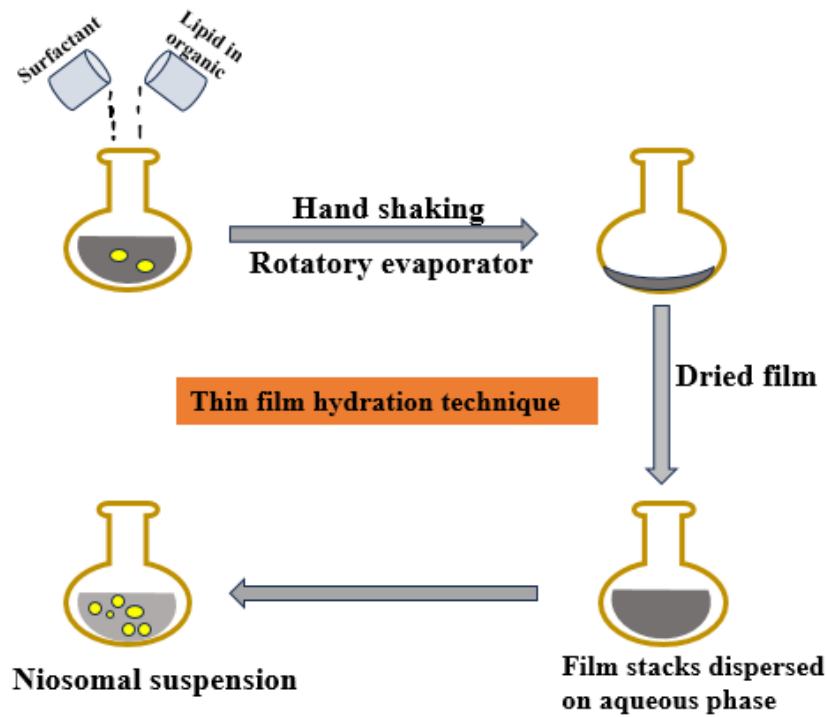


Figure 1. Thin film hydration technique for making niosomes

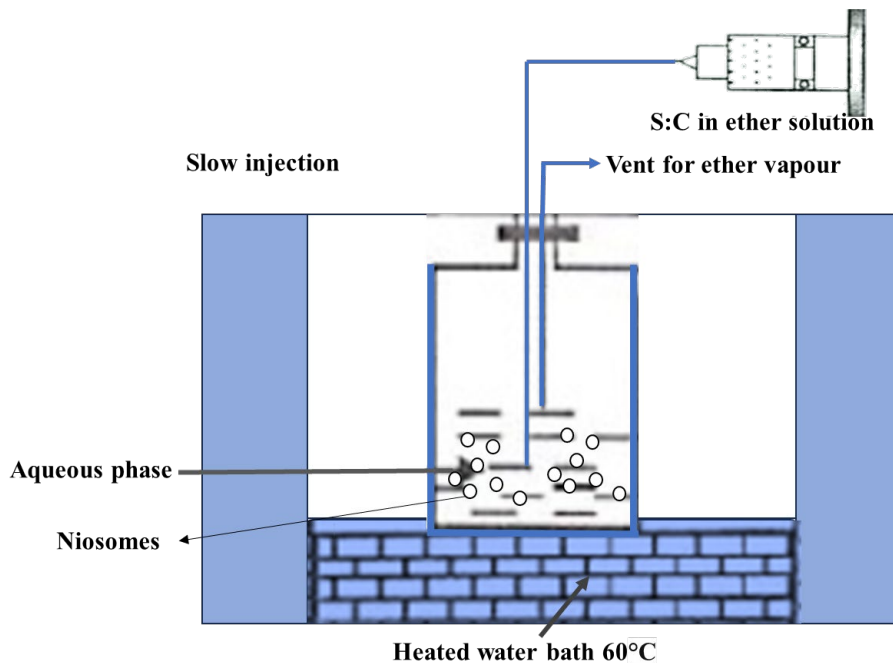


Figure 2. Sonication method of making Niosomes

3.3. Extrusion Method

This technique involves the gradual injection of a solution through a designated gauze needle into a warmed aqueous solution covering drugs, preserved at 60°C. The solution comprises a specific ratio of CHL to surfactant dissolved in ether. Vaporization of ether points to the formation of unilamellar vesicles containing the drug-loaded surfactants. As an alternative to ether for thermolabile drugs, fluorinated hydrocarbons are utilized, evaporating at a much lower temperature. The resulting niosomes range in size from 50 to 1000 nm, primarily influenced by formulation variables and experimental setup [12].

3.4. Reverse Phase Evaporation Technique

This method entails dissolving the surfactant in chloroform and subsequently adding it to a specific volume of phosphate saline buffer solution for emulsification, without the addition of water. Following the sollicitation of the mixture, chloroform is evaporated under low pressure. Initially, the lipid or surfactant gels, and then hydrates to form vesicles [13].

3.5. Sonication Technique

In this procedure, the surfactant-CHL mixture is initially isolated in the aqueous phase. Subsequently, a 10 min

probe sonication at 60°C is performed on this dispersion, leading to the formation of multilamellar vesicles (MLVs). These MLVs undergo further ultrasonication using either a bath or probe sonicator, resulting in the formation of unilamellar vesicles [14].

3.6. Transmembrane pH Gradient Drug Uptake Process

This principle asserts that the interior of the niosome maintains an acidic pH, which is lower than the exterior pH. This method enhances the EE of certain drugs by allowing added unionized basic drugs to cross the niosome membrane. Once inside the niosome, these drugs become ionized in an acidic environment, preventing them from exiting the niosome. Thus, the drugs are appropriated intracellularly by the acidic pH within the niosomes [15].

3.7. Microfluidization Method

This technique involves the application of energy to the system, focused specifically on the region of niosome formation. Two fluidized streams, one covering a drug and the other a surfactant, interact at extremely high velocities through exactly clear microchannels within the interaction compartment. This process, known as the submerged jet principle, results in enhanced reproducibility of niosome formulation, size reduction, and improved homogeneity (Figure 3) [16].

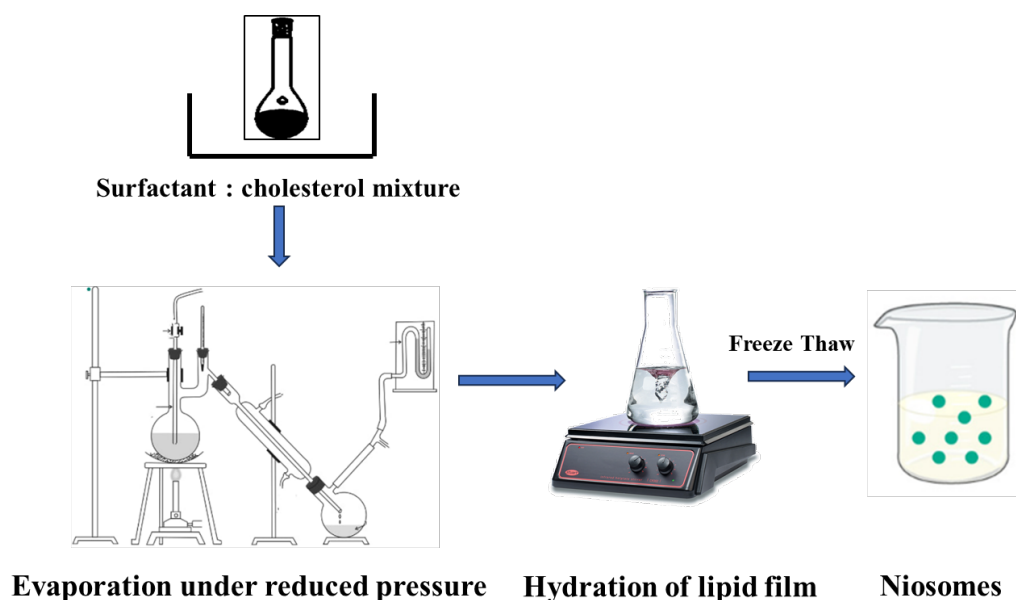


Figure 3. Microfluidization technique in making Niosomes

3.8. Formulation of Niosomal Gel

Purified water and Carbopol were thoroughly combined in a beaker and set aside to hydrate and swell for a period of 24 hours, allowing the Carbopol to fully absorb the water and achieve optimal consistency. After this hydration phase, a measured quantity of niosomes was carefully dispersed into the mixture, ensuring even distribution within the aqueous medium. To neutralize the Carbopol and stabilize the gel structure, triethanolamine was gradually added with constant stirring. This step adjusted the pH of the solution, facilitating the formation of a smooth, gel-like consistency. Following neutralization, glycerine was incrementally introduced into the mixture. Gentle stirring was maintained throughout this process to ensure homogeneity and prevent the formation of air bubbles or inconsistencies. The resulting gel not only served as an effective carrier for the niosomes but also acted as a moisturizing agent due to the hygroscopic properties of glycerine, enhancing the hydration and smooth application of the formulation. This method ensured the production of a stable, uniform gel suitable for topical delivery [17].

4. Evaluation

4.1. Drug Polymer Interaction Study

The study will involve the use of the drug in combination with various polymers, which could potentially lead to interactions between them. To assess and identify any such interactions, Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectroscopy will be employed. DSC will help evaluate thermal properties, providing insights into possible changes in the drug's melting point, crystallinity, or other thermal characteristics due to polymer interaction. Meanwhile, FTIR spectroscopy will analyze molecular vibrations to detect any chemical bonding or alterations in functional groups, offering a comprehensive understanding of the compatibility between the drug and polymers.

4.1.1. DSC Studies

The drug and natural polymers are accurately weighed and placed in a small aluminum pan, which is subsequently sealed securely by crimping to prevent any external interference. The sealed sample is then subjected to DSC analysis. The DSC is programmed with a controlled heating rate of 10°C per minute to ensure uniform thermal exposure. Pure nitrogen gas is used as a purge gas at a consistent flow rate of 20 mL/min to maintain an inert atmosphere, preventing oxidation or degradation during the analysis. This process facilitates the evaluation of thermal properties, such as melting points and possible interactions between the drug and polymers.

4.1.2. FTIR Studies

The infrared spectrum of pure drugs and mixtures of drugs with each polymer is recorded using an FTIR Spectrophotometer. The scanning range covers 400 cm⁻¹ to 4000 cm⁻¹, and the IR spectra of samples are obtained using the Potassium Bromide (KBr) disc method. Any alteration in the spectrum pattern of the drug resulting from the presence of polymers is examined to detect any potential chemical interaction.

4.2. Post Formulation Tests

4.2.1. Entrapment Efficiency

The EE of vesicular systems, which indicates the amount of active compounds loaded into the niosomal structure, can be determined spectrophotometrically using a UV-visible spectrophotometer. Additionally, UV densitometry is conducted after gel electrophoresis when dealing with materials. Moreover, fluorometric assessment of the EE can be achieved using a hydrophilic fluorescent probe [18].

4.2.2. Morphology

Vesicle formation was confirmed using optical microscopy at a resolution of 45x. A niosomal suspension was applied onto a glass slide and air-dried at room temperature. The resulting thin film exhibited vesicle formation. Microphotographs of the niosomes were captured using a digital camera attached to the microscope. Additionally, surface details of the selected niosomal formulation were further examined using a scanning electron microscope [19].

4.2.3. SEM Analysis

For the morphological assessment of the niosomal formulation, a scanning electron microscope (SEM) was employed. Before examination, the formulation was suspended in pH 7 phosphate buffer, deposited onto a clean slide cover, and air-dried at a temperature below 10°C in a desiccator overnight. Subsequently, the dried samples were coated with a thin layer of gold-palladium using a fine-coat ion sputter. Scanning was conducted, capturing photomicrographs across a range of 100 to 1000 nm, revealing the surface characteristics and structures of the formulation [20].

4.3. Evaluation for Niosomal Gel Assets

4.3.1. Homogeneity

The optimized niosomal gel was evaluated for homogeneity by transferring a sample into a transparent glass container. The gel was visually inspected under sufficient lighting to identify the presence of any aggregates, lumps, or phase separation. This assessment ensured a uniform distribution of the niosomes within the

gel matrix, a critical parameter for consistent drug delivery and overall product quality [20].

4.3.2. Spreadability

The spreadability of the niosomal gel was evaluated using a wooden block apparatus. This apparatus consisted of a stationary glass slide at one end and a movable glass slide at the other, connected to a weight pan that moved along a horizontally positioned pulley. During the test, a measured amount of niosomal gel was placed between the two glass slides. A specified weight was initially applied to the movable slide for 5 minutes to compress the gel. After this, an additional weight was added to the pan. The time required for the two glass slides to separate was then recorded in seconds, providing an indication of the gel's spreadability [21].

4.3.3. Extrudability

In the evaluation of extrudability, the force required to expel the niosomal gel from a lacquered aluminum collapsible tube was measured. This test involved determining the percentage of gel extruded in relation to the total amount of gel present in the tube. The assessment was based on the weight, in grams, applied to extrude at least a 0.5 cm ribbon of gel within a 10-second period. The amount of gel extruded under this condition provided a quantitative measure of the gel's extrudability [22].

4.3.4. pH Determination

The pH of the gel compositions was measured using a digital pH meter. Prior to any measurements, the pH meter was calibrated to ensure accuracy. After calibration, the glass electrode was immersed in the gel samples, and the pH readings were recorded directly from the meter. This process provided an accurate assessment of the gel's acidity or alkalinity, which is essential for evaluating its suitability for skin application [23].

4.3.5. Viscosity

The viscosity of the prepared gel batches was measured using a Brookfield viscometer. The viscometer assembly was placed in a water bath, which was thermostatically controlled to maintain a constant temperature of 25°C. A wide-mouth jar was filled with a sufficient quantity of the gel formulation to ensure that the spindle could be fully submerged. The spindle was then allowed to rotate freely within the emulgel, and the viscosity was recorded. This procedure was repeated for each formulation, and the corresponding viscosity values were noted, allowing for a comprehensive comparison of the gel's rheological properties [24].

4.3.6. *In vitro* Drug Permeation Study of Niosomal Gel

The setup for studying drug diffusion involves a glass cylinder open at both ends. A dialysis membrane, pre-soaked in distilled water for 24 hours, is securely

attached to one end of the cylinder using adhesive. Gel samples, which correspond to the drugs being investigated, are placed in the inner portion of the cylinder, referred to as the donor compartment. This assembly is then immersed in a beaker containing a buffer solution mixed with 10% v/v methanol, forming the receptor compartment, which ensures sink conditions. The apparatus is positioned so that the lower end of the gel is just above the surface of the diffusion medium. The medium is maintained at a temperature of $37 \pm 0.5^\circ\text{C}$ and continuously stirred with a magnetic stirrer. Throughout the experiment, samples are periodically withdrawn from the receptor compartment and replaced with an equal volume of fresh buffer. These samples are then analyzed using a UV-visible spectrophotometer to measure the concentration of the diffused drug. This setup facilitates the study of drug diffusion through the dialysis membrane into the receptor compartment, providing valuable insights into the release profile of the drug [25].

4.3.7. *In vitro* Drug Release

This evaluates the release profile of the drug from the niosomes over time. Techniques like dialysis or diffusion cells are used to simulate the release in a controlled environment.

4.3.8. Stability Studies

These studies evaluate the physical and chemical stability of the niosomal gel under different environmental conditions, including temperature, humidity, and light exposure. Stability testing is essential to determine how the gel maintains its properties and effectiveness over time. By simulating real-world storage conditions, these tests help assess the product's shelf-life, ensuring that it remains safe, effective, and of high quality throughout its intended use.

5. Quality by Design

Quality by Design (QbD) is a structured methodology for pharmaceutical development that emphasizes the integration of quality principles throughout the design, development, and manufacturing stages of drug delivery systems. At the core of the QbD approach are Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs). CQAs are the key characteristics of a drug product or process that must be controlled to ensure the desired product quality, while CPPs are the variables in the manufacturing process that directly impact the CQAs. By identifying and controlling these attributes and parameters, QbD ensures that drug products are consistently produced with the desired quality, safety, and efficacy [26].

CQAs are essential characteristics of a drug delivery system that significantly influence its safety, efficacy, and performance. These attributes include factors such as particle size distribution, drug release kinetics, stability,

and bioavailability. Identifying and understanding CQAs is crucial to ensuring that the final product consistently meets the established quality standards. CQAs guide both the formulation and manufacturing processes, acting as key benchmarks for evaluating product quality throughout development and production. By monitoring and controlling these attributes, manufacturers can ensure that the drug product performs as intended and meets regulatory and therapeutic requirements [27].

CPPs, on the other hand, are the key variables within the manufacturing process that significantly influence the CQAs of the drug delivery system. These parameters include factors like mixing speed, temperature, pH, and drying time. Controlling CPPs is essential for maintaining product quality and consistency during production. By monitoring and adjusting CPPs within defined ranges, manufacturers can optimize the manufacturing process to achieve desired product attributes and minimize variability.

5.1. Ensuring Consistent Product Quality and Performance

In drug delivery systems like nanoparticles, liposomes, or transdermal patches, QbD aims to ensure consistent product quality and performance while minimizing variability and the risk of product failure. By integrating quality principles into the design, development, and manufacturing processes, QbD helps identify CQAs and CPPs essential for product success. This systematic method allows for the optimization of formulation and manufacturing processes to meet predetermined quality standards reliably. Ultimately, QbD enhances product robustness, efficiency, and safety, leading to improved patient outcomes and satisfaction [28].

5.2. Design Space and Optimization

Design Space and Optimization are fundamental concepts within the QbD framework, aiming to enhance the robustness and efficiency of pharmaceutical development processes.

Design Space refers to the multidimensional range of input variables and process parameters that can interact in various ways to achieve the desired quality attributes of a drug delivery system. It defines the operational conditions under which the system can be consistently developed to meet predetermined quality standards. By understanding and mapping the Design Space, manufacturers can identify the optimal set of conditions for formulation and process parameters that result in a robust, high-quality product. This approach allows for flexibility in manufacturing while ensuring that the final product consistently meets its required specifications, reducing the risk of defects or inconsistencies. It delineates the acceptable ranges for

these variables and parameters, ensuring that the product consistently meets predefined quality standards. Design Space provides flexibility and guidance to manufacturers, allowing them to make adjustments within specified boundaries without compromising product quality [29].

Optimization involves systematically refining the formulation and manufacturing processes within the established Design Space to achieve the desired product attributes efficiently. It entails employing scientific principles, experimental design techniques, and statistical analyses to identify the optimal conditions that maximize product performance while minimizing variability and manufacturing risks. Optimization efforts may involve fine-tuning parameters such as ingredient concentrations, processing conditions, and equipment settings to enhance product quality, yield, and cost-effectiveness.

By delineating the Design Space and optimizing the manufacturing processes, QbD enables pharmaceutical developers to [30, 31]:

- *Enhance Product Quality:* By identifying and controlling critical variables and parameters, QbD ensures consistent product quality and performance, reducing the likelihood of manufacturing deviations and failures.
- *Improve Efficiency:* Optimization within the Design Space streamlines the development and manufacturing processes, reducing time, resources, and costs associated with product development.
- *Facilitate Regulatory Compliance:* A well-defined Design Space demonstrates a thorough empathy for the creation and its making process, facilitating regulatory approval and compliance with quality standards.
- *Foster Innovation:* Optimization encourages exploration and innovation by providing a structured framework for systematically evaluating and refining product formulations and manufacturing techniques.

5.3. Scientific Principles and Risk-Based Imposts

Scientific Principles and Risk-based Assessments play a central role in the QbD approach, guiding product design and process development in pharmaceuticals.

Scientific principles underpin the QbD methodology, ensuring that decisions throughout the development lifecycle are based on sound scientific knowledge and understanding. This entails employing established scientific theories, principles, and methodologies to elucidate the relationships between formulation components, manufacturing processes, and product performance. By leveraging scientific principles, developers can make informed decisions, predict outcomes, and design robust drug delivery systems that meet desired quality attributes [31].

Risk-based assessments complement scientific principles by systematically identifying, evaluating, and mitigating potential risks throughout the product lifecycle. Quality risk management techniques are employed to assess both known and potential risks associated with formulation, manufacturing, and analytical processes. This includes recognizing CPPs and CQAs, assessing their impact on product quality and performance, and implementing appropriate controls to mitigate risks effectively. By proactively addressing risks, developers can prevent quality issues, ensure product safety and efficacy, and expedite regulatory approval.

Experimental design and statistical analysis are essential tools utilized within the QbD framework for systematically evaluating and optimizing formulation components, manufacturing processes, and analytical methods. Design of Experiments (DoE) enables developers to efficiently explore the effects of multiple variables and interactions, allowing for the identification of optimal conditions within the design space. Statistical analysis facilitates the interpretation of experimental data, enabling developers to make data-driven decisions, optimize processes, and enhance product quality and performance.

5.4. Continuous Improvement and Innovation

QbD encourages a proactive approach to improvement, promoting ongoing refinement of product development processes. By engaging stakeholders from diverse backgrounds, including formulation scientists, process engineers, regulatory experts, and quality assurance professionals, QbD facilitates the exchange of ideas and expertise. This collaborative environment allows teams to pool their knowledge and perspectives, enabling a comprehensive assessment of product development challenges and opportunities [32].

Through multidisciplinary collaboration, QbD enables companies to leverage collective expertise to identify areas for enhancement and innovation. By integrating insights from various domains, teams can identify novel approaches, technologies, and strategies to optimize product quality, performance, and efficiency.

Moreover, QbD promotes a culture of incessant education and improvement, encouraging teams to embrace feedback and incorporate lessons learned into future iterations of product development. By systematically evaluating outcomes and implementing improvements, companies can enhance their processes and capabilities over time, driving innovation and competitive advantage.

5.5. Structured Framework for Development

QbD provides a structured framework for the development of harmless, real, and high-quality drug delivery systems. This framework integrates quality considerations into every stage of product development and manufacturing, ensuring that patient needs are met while adhering to regulatory standards and minimizing risk [33].

At its core, QbD emphasizes a proactive approach to product development, focusing on understanding and CQAs and CPPs from the outset. By systematically identifying and addressing potential risks and challenges, QbD enables companies to anticipate and mitigate issues before they arise, thereby enhancing product safety and efficacy [34].

Moreover, QbD promotes the use of scientific principles, risk-based assessments, and advanced analytical techniques to inform decision-making throughout the development process. This evidence-based approach ensures that product design and manufacturing processes are optimized to achieve desired outcomes consistently.

By incorporating QbD principles into product development, companies can streamline regulatory approval processes. By providing a robust scientific rationale and evidence of quality control measures, companies can more effectively demonstrate product safety, efficacy, and reliability to regulatory agencies.

5.6. Experimental Design in QbD for Niosomes

5.6.1. Defining Objectives

- *Primary Goal:* Establish the main objective of the study, such as optimizing drug encapsulation efficiency, particle size, or release rate.
- *Secondary Goals:* Include secondary objectives like improving stability, scalability, or cost-effectiveness.

5.6.2. Identifying CQAs

CQAs are the physical, chemical, biological, or microbiological characteristics of a drug delivery system that must fall within specified limits to ensure the desired quality and performance of the final product. For niosomes, CQAs could include parameters such as particle size, polydispersity index (PDI), drug encapsulation efficiency, release profile, and stability. These attributes are essential in determining the safety, efficacy, and overall performance of the niosomal formulation. Monitoring and controlling CQAs throughout the development process ensures that the product consistently meets its intended quality standards and delivers the desired therapeutic outcomes.

5.6.3. Identifying CPPs

CPPs are process parameters that have a direct impact on CQAs. Examples include surfactant and cholesterol concentrations, hydration time, temperature, and mixing speed.

5.6.4. Design of Experiments

- *Factorial Designs*: Evaluate multiple factors simultaneously. For example, a 2³ factorial design tests three factors at two levels each.
- *Response Surface Methodology (RSM)*: Used for optimizing the process by exploring the relationships between several explanatory variables and one or more response variables.
- *Central Composite Design (CCD)*: A popular RSM design that includes factorial points, axial points, and center points to provide a spherical or rotational pattern.

5.6.5. Conducting Experiments

Perform the experiments as per the DoE plan. Ensure all conditions are controlled and recorded precisely.

5.6.6. Data Collection and Analysis

Collect data on CQAs and analyze the results using statistical software. Look for interactions between variables, significant factors, and the optimum conditions.

5.6.7. Optimization

Use the analysis results to determine the optimal levels of CPPs that achieve the desired CQAs. This step may involve creating models to predict outcomes under various conditions.

5.6.8. Validation

Conduct additional experiments to validate the optimized process and ensure reproducibility. This step confirms that the model accurately predicts the outcomes and that the process is robust.

5.7. Reputation of QbD in the Development of Niosomal Preparations

- Identify key variables and their interactions.
- Optimize the formulation by testing different combinations of surfactants, cholesterol, and other components.
- Ensure robustness by understanding how changes in process parameters impact the final product.

5.7.1. Risk Assessment

- *Material risks*: Quality and consistency of raw materials like surfactants and cholesterol.
- *Process risks*: Factors such as temperature, mixing speed, and pH levels that could impact niosome formation.
- *Product risks*: Attributes like particle size distribution, encapsulation efficiency, and stability.

5.7.2. Control Strategy

Developing a robust control strategy is essential in QbD. This includes:

- *In-process controls*: Monitoring and controlling key parameters during the production process to ensure consistency.
- *End-product testing*: Ensuring the final niosomal product meets all quality specifications.
- *Continuous monitoring*: Implementing real-time monitoring and control systems to maintain product quality.

5.7.3. Knowledge Management

- Collecting and analyzing data from all stages of development.
- Using advanced statistical tools to interpret the data and make informed decisions.
- Documenting findings and experiences to build a comprehensive knowledge base for future projects.

5.7.4. Real-World Example

For instance, if you are developing a niosomal drug delivery system for a specific therapeutic agent, you might start by using DoE to identify the optimal combination of surfactants and cholesterol to achieve the desired particle size and encapsulation efficiency. Risk assessments would help you pinpoint potential issues, such as variations in raw material quality or environmental conditions during production. A control strategy would be established to monitor and adjust critical parameters in real-time, ensuring a consistent and high-quality product.

These principles of QbD can significantly enhance the efficiency and effectiveness of developing niosomal preparations, ensuring that the final product is of high quality, safe, and effective for its intended use.

Table 1 highlights previous successful attempts with niosomes, while Table 2 provides a list of patents related to QbD-based niosomes.

Table 1. Niosomes' past successful endeavors

Drug	Design	Independent variable	Dependent variable	References
Chlorpheniramine	2 ³ factorial design (FFD)	CHL (X ₁), span-60 (X ₂), and span-80 (X ₃)	% yield (Y ₁), drug content (Y ₂), drug loading (Y ₃), and EE (Y ₄)	[35]
Famesol	Box-Behnken Design (BBD)	CHL: Span 20 ratio (X ₁), and drug (X ₂)	Particle size (PS) (Y ₁), and % EE (Y ₂)	[36]
Cetirizine	BBD	Drug (X ₁), CHL: Surfactant ratio (X ₂), and total weight of niosomal components (X ₃)	Vesicle size (VS) (Y ₁), and % EE (Y ₂)	[37]
Valacyclovir	BBD	CHL (X ₁), Brij 72 (X ₂), and Diacetyl Phosphate (X ₃)	PS (Y ₁), EE (Y ₂), Drug release after 24 h (Y ₃)	[38]
Hexatriacontane	BBD	Lipoid (X ₁), ethanol (X ₂), and sodium cholate (X ₃)	PDI (Y ₁) and EE (Y ₂)	[39]
Tadalafil	BBD	Mixing time (X ₁), non-ionic surfactant to lipid ratio (X ₂), and the total weight of the preparation components (X ₃)	PS (Y ₁), PDI (Y ₂), and zeta potential (Y ₃)	[40]
Erythromycin	2 ³ FFD	Span-20 (X ₁), Span 60 (X ₂), and Span 80 (X ₃)	%EE (Y ₁), and <i>In vitro</i> Drug release performance (Y ₂)	[41]
Lovastatin	3 ³ BBD	CHL (X ₁), Soya lecithin (X ₂), and Tween 80 (X ₃)	PS (Y ₁), % EE (Y ₂), and % of drug release (Y ₃)	[42]
Loratadine	BBD	RHLB (X ₁), Rate of injection (X ₂), and Org/Aq phase (X ₃)	%EE (Y ₁), and PS (Y ₂)	[43]
Benzoyl peroxide	BBD	Span 60: Chol (X ₁), Hydration vol (X ₂), and DC (X ₃)	PS (Y ₁), and %EE (Y ₂)	[44]
Moxifloxacin	Simplex lattice design	Gellan gum (X ₁), sodium alginate (X ₂), and HPMC (X ₃)	Gel strength (Y ₁), adhesive force (Y ₂), viscosity (Y ₃), and drug release after 10 h (Y ₄)	[45]
Meloxicam	Complete crossover design	Span-80 (X ₁), Span-60 (X ₂), Tween-80 and Tween-60 (X ₃) CHL and drug (X ₄)	%EE (Y ₁), <i>in vitro</i> drug release (Y ₂), and <i>in vivo</i> performance (Y ₃)	[46]
Luliconazole	3 ² FFD	CHL (X ₁) and span 60 (X ₂)	% drug release (Y ₁) and % EE (Y ₂)	[47]
Bimatoprost	Central composite design (CCD)	Drug (X ₁) and CHL: Span 60 ratio (X ₂)	VS (Y ₁) and % EE (Y ₂)	[48]
Asparagus racemosus Extract	2 ³ FFD	Span 60 (X ₁) and CHL (X ₂)	VS (Y ₁), PDI (Y ₂) and % EE (Y ₃)	[49]
Lacidipine	BBD	Span 60 (X ₁), CHL (X ₂), sonication time (X ₃), and hydration time (X ₄)	VS (Y ₁), and %EE (Y ₂)	[50]
Propofol	BBD	CHL (X ₁), Span 80 (X ₂), and sonication time (X ₃)	PS (Y ₁) and EE (Y ₂)	[51]
Ketoprofen	CCD	Surfactant CHL ratio (X ₁), HLB (X ₂), and Lipid concentration (X ₃)	EE (Y ₁), <i>In vitro</i> release after 1hr (Y ₂), and <i>In vitro</i> release after 12hr (Y ₃)	[52]
Gamma oryzanol	FFD	Drug to span 60 (X ₁), Volume of hydration (X ₂), and stirring speed (X ₃)	VS (Y ₁), and EE (Y ₂)	[53]
Nitrendipine	BBD	Non-ionic surfactant (X ₁), CHL (X ₂), and Temperature (X ₃)	VS (Y ₁), PDI (Y ₂), and EE (Y ₃)	[54]
Desoximetasone	2 ⁵ FFD	Surfactant (X ₁), CHL (X ₂), mixing speed (X ₃), mixing time (X ₄), and addition rate (X ₅)	EE (Y ₁), PS (Y ₂), and PDI (Y ₃), Drug (X ₁), Surfactant (X ₂), and CHL (X ₃)	[55]
Levosulpiride	BBD	CHL(X ₁), Span 40 (X ₂), and sonication time (X ₃)	PS (Y ₁) and EE (Y ₂)	[27]
Carvacrol Oil	BBD	Drug (X ₁), Surfactant (X ₂), and CHL (X ₃)	VS (Y ₁), PDI (Y ₂), and EE (Y ₃)	[34]
Cefoperazone sodium	Custom design	Surfactant: CHL molar ratio (X ₁), rate of injection (X ₂), and hydration volume (X ₃)	PS (Y ₁), and EE (Y ₂)	[56]

Table 2. List of patents based on QbD-based niosomes

Patent number	Title	Description
US20100068264A1	Niosome-Hydrogel Drug Delivery System	A drug delivery system composed of non-ionic surfactant vesicles (niosomes) embedded in a biodegradable hydrogel network offers an innovative approach for controlled drug release. Niosomes, which are vesicles formed from non-ionic surfactants, serve as carriers for drugs, ensuring efficient encapsulation and protection of the active ingredient. When these niosomes are integrated into a biodegradable hydrogel matrix, they provide a controlled and sustained release of the drug over time. The hydrogel network can offer structural support and degrade at a controlled rate, ensuring that the drug is released gradually. This system is beneficial for enhancing drug bioavailability, reducing side effects, and ensuring prolonged therapeutic effects, making it particularly useful for the treatment of chronic conditions that require long-term, consistent drug delivery.
EP2521527A1	Niosomes, Freeze-Dried Powder Thereof and Their Use in Treatment	Focuses on niosomes in the form of freeze-dried powder for treating respiratory pathologies
US9522114B1	Improved Targeted Drug Delivery Using Chitosan Hydrogel Conjugated with Chlorotoxin	Integrates niosomes loaded with an anticancer therapeutic agent and chlorotoxin into a thermosensitive chitosan hydrogel network for targeted delivery to tumor cells.
RU2600164C2	Doxorubicin and organosilicon nanoparticle-niosomes-based pharmaceutical gel for the treatment of skin cancer	A pharmaceutical anticancer gel containing doxorubicin encapsulated in niosomes for higher efficiency and reduced cardiotoxicity.

6. Conclusions

The niosomal gels represent a promising avenue in drug delivery systems, offering a synergistic blend of niosome and gel technologies to improve therapeutic outcomes and patient adherence. This review has thoroughly examined the formulation, characterization techniques, and versatile applications of niosomal gels across pharmaceutical and cosmetic domains. By exploring diverse approaches in making viz., film hydration, reverse-phase evaporation, and nanoprecipitation, along with their respective advantages and limitations, we have gained insights into optimizing niosomal gel fabrication. Additionally, the characterization of niosomal gels has elucidated their physicochemical properties, stability profiles, and drug release kinetics, crucial for ensuring structural integrity and performance. The wide-ranging applications discussed, including targeted drug delivery, transdermal delivery, gene delivery, and cosmetic formulations, underscore the adaptability and potential of niosomal gels in meeting various therapeutic requests. Despite the promising advancements, challenges such as scale-up issues and regulatory considerations persist, necessitating further research and development efforts. Continuing innovation and collaboration in niosomal gel technology hold immense promise for advancing pharmaceutical science and ultimately improving patient care.

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