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Review Article

Formulation and Evaluation of Niosome-Based Isotretinoin Gel: A Comprehensive Review

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Abstract

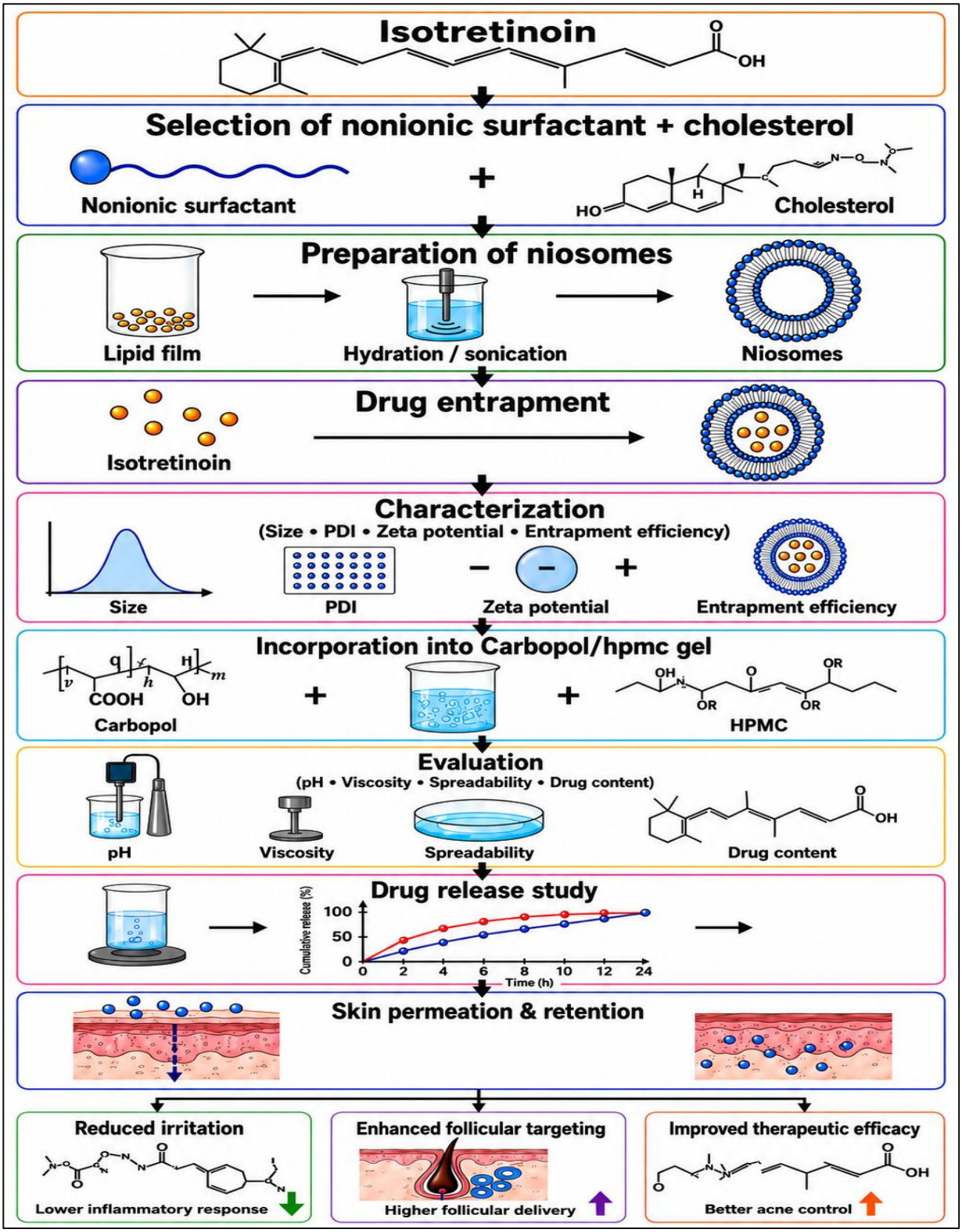
Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit affecting millions of adolescents and adults worldwide. Although isotretinoin remains one of the most effective retinoids for acne management, its conventional topical formulations are associated with poor aqueous solubility, limited skin penetration, photo-instability, irritation, erythema, and reduced patient compliance. Nano-vesicular drug delivery systems have emerged as promising alternatives to overcome these limitations. Among them, niosomes have attracted considerable attention owing to their excellent biocompatibility, chemical stability, ease of preparation, cost-effectiveness and ability to encapsulate both hydrophilic and lipophilic therapeutic agents. Incorporation of isotretinoin into niosomal vesicles followed by dispersion in a topical gel provides controlled drug release, enhanced skin retention, improved follicular targeting, reduced systemic absorption and minimized local adverse effects while maintaining therapeutic efficacy. This review comprehensively discusses the pharmaceutical aspects of isotretinoin-loaded niosomal gels, including formulation strategies, selection of surfactants and membrane stabilizers, methods of niosome preparation, vesicle characterization, gel formulation approaches, physicochemical evaluation, stability assessment and biological performance. Furthermore, recent advances in vesicular nanocarriers, quality-by-design approaches, optimization techniques and translational perspectives are highlighted. Current challenges related to large-scale manufacturing, regulatory considerations and clinical translation are also discussed. Overall, niosomal gel represents a promising topical delivery platform capable of improving the therapeutic performance of isotretinoin and may contribute to safer, more effective and patient-friendly acne treatment.

Keywords: Isotretinoin, niosomes, topical gel, vesicular drug delivery, acne vulgaris

Highlights

- ✓ Niosomes enhance topical delivery and follicular targeting of isotretinoin.
- ✓ Controlled drug release minimizes skin irritation and improves patient compliance.
- ✓ Niosomal gel improves drug stability, skin retention, and therapeutic efficacy.
- ✓ Surfactant composition and cholesterol concentration critically influence vesicle characteristics.
- ✓ Niosomal gels represent a promising nanocarrier platform for advanced acne therapy.

Graphical Abstract



1. Introduction

Acne vulgaris is a common chronic inflammatory skin disorder affecting adolescents and adults worldwide. It originates in the pilosebaceous unit and involves excess sebum production, follicular hyperkeratinization, *Cutibacterium acnes* colonization and inflammation.[1] Topical therapy is preferred for mild-to-moderate acne because it provides localized treatment with minimal systemic exposure. Isotretinoin, a vitamin A–derived retinoid, effectively reduces sebum production, abnormal keratinization, bacterial proliferation and inflammation.[2] However, conventional formulations are limited by poor solubility, chemical instability, inadequate skin penetration and local irritation. Niosomes, composed of non-ionic surfactants and

cholesterol, offer improved drug stability, controlled release, skin penetration and follicular targeting.[3] Incorporating isotretinoin-loaded niosomes into a gel further enhances spread-ability, residence time, skin retention and patient acceptability**.** Therefore, optimized isotretinoin-loaded niosomal gels represent a promising nanocarrier-based approach for safer and more effective topical acne management. [4]

2. Skin anatomy and barrier function

The skin is the body's largest organ and acts as a protective barrier. It consists of three main layers: epidermis, dermis and hypodermis**.** The stratum corneum is the major barrier to drug penetration. Topical drugs penetrate mainly through intercellular, transcellular, and follicular pathways**.** Niosomes can improve skin penetration, hydration and follicular drug deposition, thereby enhance local drug delivery and reduce systemic exposure.[5]

3. Pathophysiology of acne vulgaris

Acne vulgaris is a multifactorial inflammatory disorder of the pilosebaceous unit involving hormonal, microbial, immune and genetic factors. Its main pathogenic mechanisms are **excess** sebum production, follicular hyperkeratinization, *Cutibacterium acnes* colonization and inflammation, resulting in comedones, papules, pustules, nodules and possible scarring.[6]

3.1 Sebaceous hyperactivity

Androgenic hormones stimulate sebaceous gland enlargement and excessive sebum secretion. Increased production of triglycerides, wax esters, squalene and free fatty acids creates a lipid-rich environment favorable for bacterial colonization. Oxidation of sebum lipids further contributes to inflammatory responses.[7]

3.2 Follicular hyperkeratinization

Abnormal differentiation and proliferation of keratinocytes result in excessive accumulation of corneocytes within the follicular canal. This leads to obstruction of the pilosebaceous duct and formation of micro-comedones, which subsequently develop into open (blackheads) or closed (whiteheads) comedones.[8]

3.3 Colonization by *cutibacterium acnes*

Cutibacterium acnes is a Gram-positive anaerobic bacterium that naturally resides within sebaceous follicles. Under conditions of follicular obstruction and excessive sebum production, bacterial proliferation increases significantly.[9] The organism produces lipases, proteases, hyaluronidases, porphyrins and various virulence factors that degrade sebum triglycerides into inflammatory free fatty acids, further aggravating follicular inflammation.[10]

3.4 Inflammatory cascade

TLR activation triggers NF-κB and MAPK pathways, leading to the release of inflammatory mediators such as IL-1β, IL-6, IL-8, IL-17, and TNF-α**.** Persistent inflammation promotes acne progression and scarring. Oxidative stress, inflammasome activation and microbiome changes also contribute to acne pathogenesis, supporting the development of targeted anti-inflammatory and nanocarrier-based therapies. [11]

Table 1. Major pathogenic factors in acne vulgaris

Pathogenic factor	Mechanism	Clinical outcome	Therapeutic target	Ref
Excess sebum production	Androgen-mediated sebaceous gland activation	Oily skin	Retinoids, Antiandrogens	12
Follicular hyperkeratinization	Keratinocyte proliferation	Comedone formation	Isotretinoin	13
C. acnes colonization	Lipase production and biofilm formation	Inflammation	Antimicrobial agents	14
Cytokine release	IL-1β, IL-6, IL-8, TNF-α	Papules and pustules	Anti-inflammatory drugs	15
Oxidative stress	ROS generation	Tissue damage	Antioxidants	16
Immune dysregulation	Innate immune activation	Chronic inflammation	Targeted immunomodulation	17

4. Isotretinoin: Pharmacology and therapeutic significance

Isotretinoin is a vitamin A–derived retinoid and a highly effective treatment for moderate-to-severe acne. It reduces sebum production, follicular hyperkeratinization, ***C. acnes*** colonization, and inflammation**.** However, conventional topical isotretinoin is limited by poor solubility, instability, low skin penetration and irritation**.** Niosomal gels can improve isotretinoin stability, skin penetration, follicular targeting, sustained release and reduce irritation. Acne develops mainly through excess sebum, follicular hyperkeratinization, *C. acnes* colonization and inflammation**.**[18]

5. Niosomes: An advanced vesicular drug delivery system

5.1 Introduction to niosomes

Niosomes **a**re vesicular drug carriers composed of non-ionic surfactants that can encapsulate both hydrophilic and lipophilic drugs. They offer good stability, biocompatibility, low toxicity, high drug-loading capacity and prolonged drug release**.** For topical delivery, niosomes enhance skin penetration, hydration, drug retention and follicular targeting**.** In isotretinoin therapy, they can improve drug stability and localized delivery while reducing irritation and systemic exposure**,** making them promising for acne management.[19]

5.2 Classification of Niosomes

Niosomes are classified based on vesicle size, lamellarity and method of preparation.

A. Based on lamellarity

Unilamellar vesicles (ULVs)

These vesicles possess a single phospholipid-like bilayer surrounding an aqueous core. They generally exhibit diameters ranging from 50 to 250 nm and provide efficient topical permeation due to their small size.[20]

Multilamellar vesicles (MLVs)

Multilamellar vesicles consist of several concentric bilayers resembling an onion-like structure. These vesicles demonstrate higher drug loading capacity and prolonged drug release but generally possess larger particle sizes.[21]

Large unilamellar vesicles (LUVs)

LUVs contain a single bilayer with a relatively larger internal aqueous compartment, making them suitable for encapsulating hydrophilic drugs.[22]

B. Based on size

Table 2. Based on size[23]

Type	Particle Size
Small unilamellar vesicles	20–100 nm
Large unilamellar vesicles	100–1000 nm
Multilamellar vesicles	0.5–10 µm

5.3 Composition of niosomes

The pharmaceutical performance of niosomes is largely determined by their composition. Each component contributes to vesicle formation, stability, drug encapsulation and release characteristics.

Non-ionic surfactants

Non-ionic surfactants are essential for niosome bilayer formation. Commonly used surfactants include Span 20, Span 40, Span 60, Span 80, Tween 20, Tween 40, Tween 60, Tween 80, Brij 35, Brij 52 and Brij 72**.** Among these, Span 60 is preferred due to its high membrane rigidity, excellent drug entrapment and sustained drug release.[24]

Cholesterol

Cholesterol acts as a membrane stabilizer by reducing bilayer permeability and preventing leakage of encapsulated drug. Appropriate cholesterol concentration increases vesicle rigidity, enhances physical stability, improves drug retention and prolongs storage life. Excessive cholesterol, however, may decrease drug entrapment by competing with drug molecules within the bilayer.[25]

Charge Inducers

Charge-inducing agents prevent vesicle aggregation by generating electrostatic repulsion. Common examples include dicetyl phosphate (negative charge) and stearylamine (positive charge)**.[26]**

Hydration Medium

Hydration media such as phosphate buffer (pH 7.4), phosphate-buffered saline (PBS) and distilled water are used for niosome preparation and influence vesicle size, drug entrapment, and release behavior.[27]

5.4 Mechanism of niosome formation

Niosomes are formed by the self-assembly of amphiphilic surfactants upon hydration, producing bilayer vesicles. Hydrophilic drugs are entrapped in the aqueous core, while lipophilic drugs (e.g., isotretinoin) are incorporated into the hydrophobic bilayer. Vesicle size can be reduced by sonication, extrusion, or high-pressure homogenization**.[28]** Figure 1 illustrates the structural organization of a niosomal vesicle, highlighting its amphiphilic bilayer architecture and the encapsulation of isotretinoin within the vesicular system.

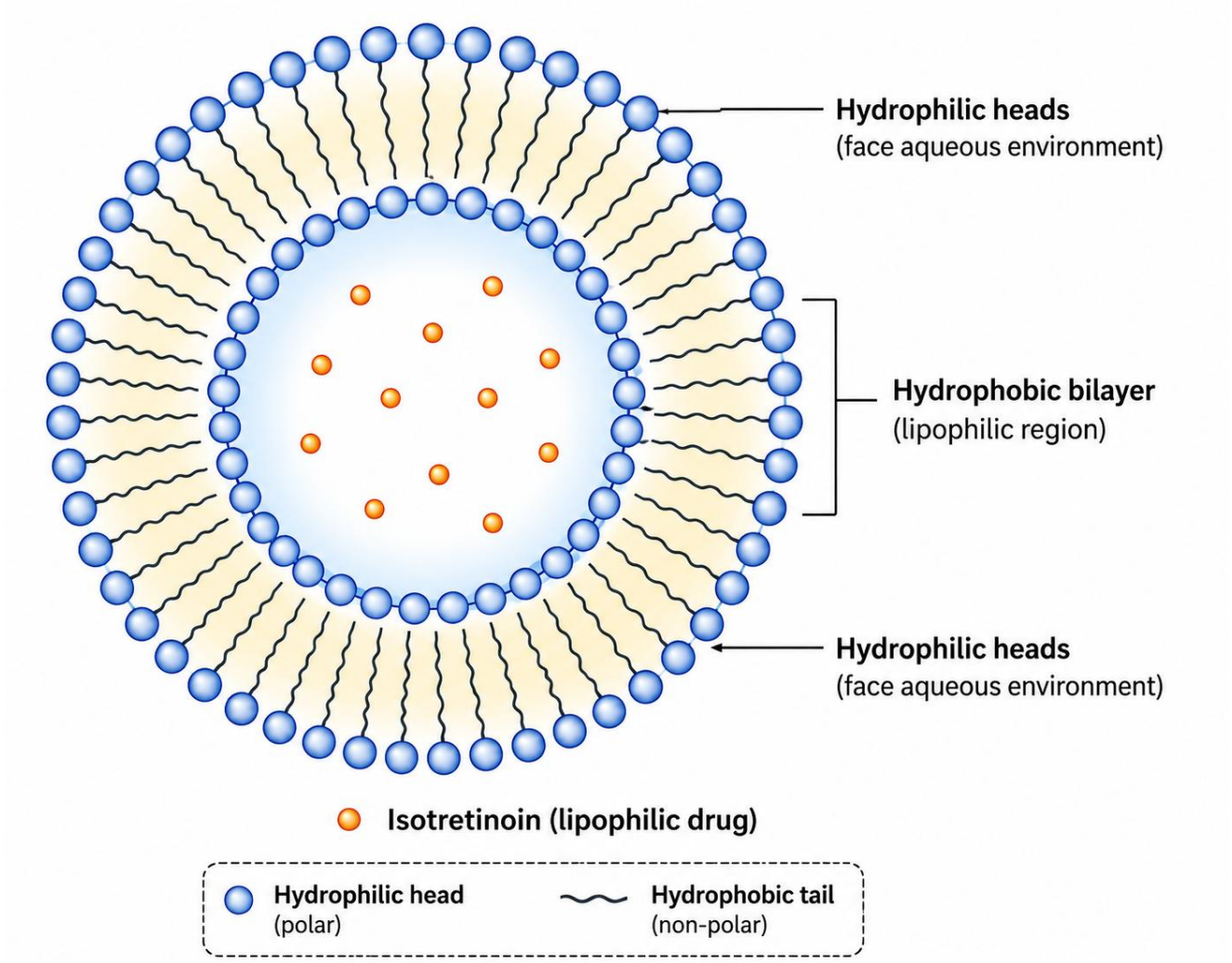


Figure 1: Structure of a niosome

(Schematic representation of a niosomal vesicle showing the non-ionic surfactant bilayer, hydrophilic head groups, hydrophobic tails, aqueous core and localization of isotretinoin within the lipid bilayer).

5.5 Mechanism of skin penetration

Niosomes improve topical drug delivery through multiple complementary mechanisms.

Hydration Effect

Niosomal vesicles increase hydration of the stratum corneum, causing swelling of keratinocytes and loosening of lipid packing. This transient modification facilitates drug diffusion.[29]

Lipid Interaction

Non-ionic surfactants interact with intercellular lipids, disrupting their highly ordered arrangement and reducing barrier resistance.[30]

Vesicle Adsorption

Niosomes adsorb onto the skin surface and gradually release isotretinoin over an extended period, maintaining prolonged therapeutic concentrations.[31]

Follicular Targeting

Hair follicles and sebaceous glands serve as reservoirs for nanosized vesicles. Because acne originates in the pilosebaceous unit, follicular accumulation of isotretinoin-loaded niosomes significantly enhances localized therapy while minimizing unnecessary exposure of healthy skin.[32]

Controlled Drug Release

Following penetration, isotretinoin diffuses gradually from the bilayer membrane, maintaining sustained therapeutic levels while reducing peak concentrations responsible for irritation.[33] Figures 2 and 3 illustrate the mechanism of topical delivery and therapeutic action of isotretinoin-loaded niosomal gel, highlighting skin penetration, interaction with the stratum corneum, follicular targeting, controlled drug release and localized therapeutic effects. Figure 3 further provides a comprehensive overview of the niosomal structure and the sequential events involved in efficient topical drug delivery.

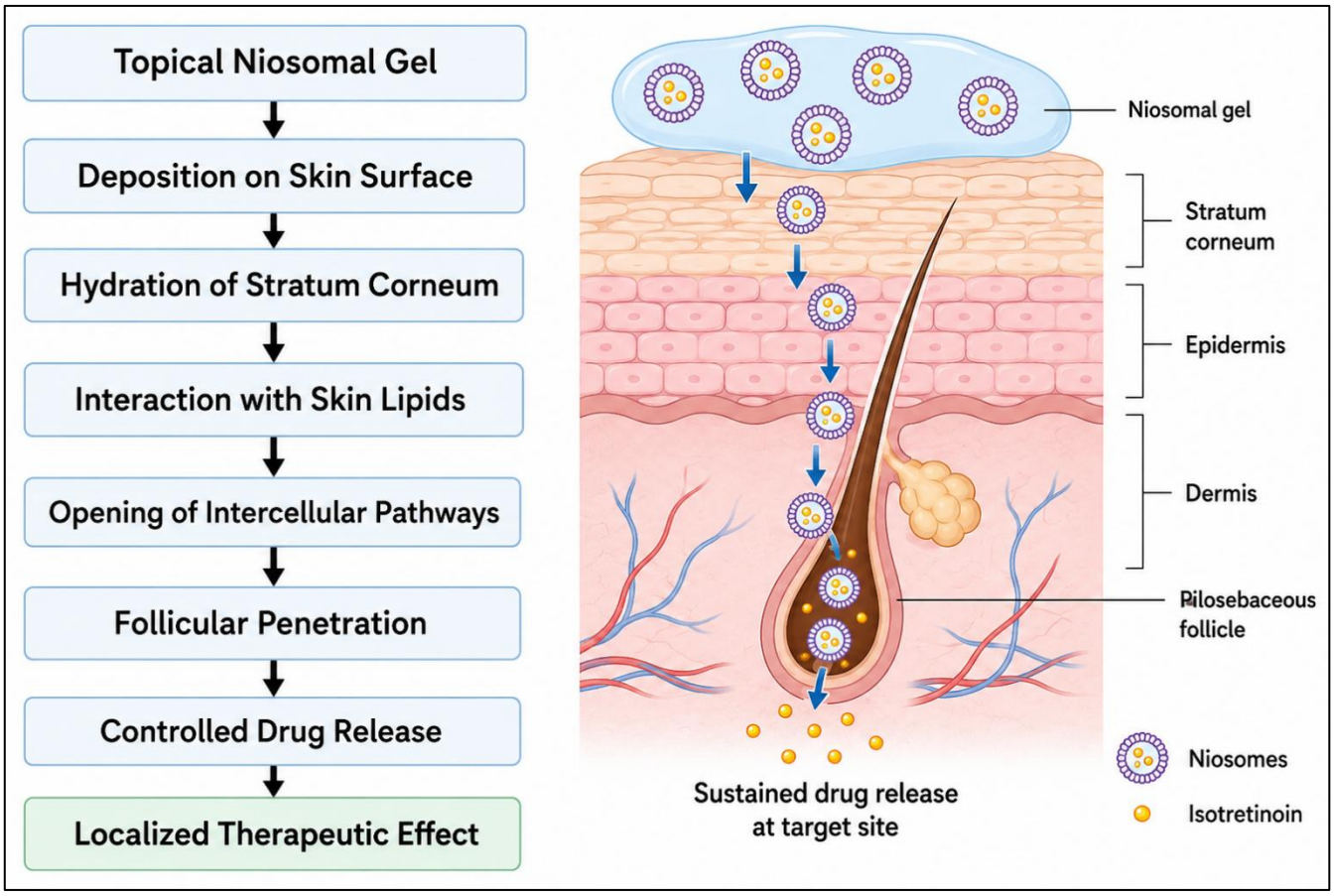


Figure 2: Mechanism of skin penetration and localized drug delivery of isotretinoin-loaded niosomal gel.

(Schematic illustration showing the deposition of isotretinoin-loaded niosomal gel on the skin surface, hydration of the stratum corneum, interaction with skin lipids, opening of intercellular pathways, follicular penetration, controlled drug release and localized therapeutic action.)

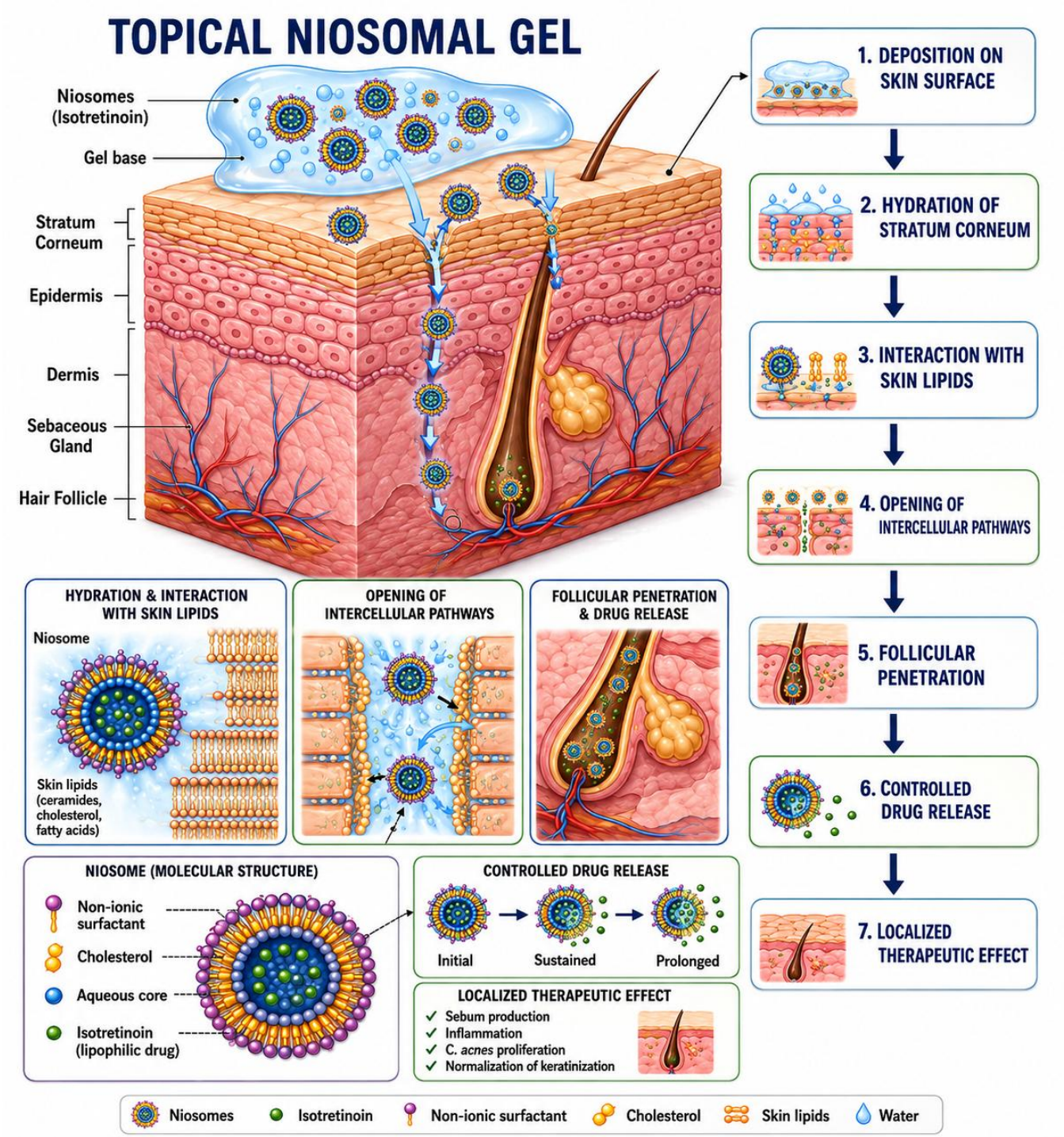


Figure 3: Biological mechanism of skin penetration and controlled release of isotretinoin-loaded niosomes.

(Comprehensive schematic illustrating the interaction of isotretinoin-loaded niosomes with the stratum corneum, enhancement of skin hydration, disruption of intercellular lipid domains, follicular targeting, sustained drug release, molecular organization of niosomes and localized therapeutic effects in acne vulgaris).

6. Advantages of niosomal drug delivery

Niosomal drug delivery systems provide numerous pharmaceutical and therapeutic advantages over conventional topical formulations. isotretinoin from photodegradation and oxidative degradation, improving formulation stability. Niosomes also reduce direct contact of free drug with the epidermis, thereby minimizing irritation, erythema, dryness and peeling commonly associated with topical retinoids. Additional benefits include high drug-loading efficiency, ease of preparation, cost-effective manufacturing, compatibility with various gel bases and the potential for scalable industrial production.[34–36]

7. Formulation of isotretinoin-loaded niosomal gel

7.1 Formulation strategy

The successful formulation of isotretinoin-loaded niosomal gel requires the systematic selection of formulation components and optimization of processing parameters to achieve high drug entrapment efficiency, nanosized vesicles, controlled drug release and excellent physicochemical stability. Owing to its highly lipophilic and photosensitive nature, isotretinoin is encapsulated within the hydrophobic bilayer of niosomes, which protects the drug from chemical and photodegradation while enhancing its penetration and retention within the pilosebaceous unit. The formulation process generally involves two sequential stages: (i) preparation of isotretinoin-loaded niosomes and (ii) incorporation of the optimized niosomal dispersion into a suitable gel base. The resulting niosomal gel should exhibit appropriate viscosity, excellent spread ability, skin-compatible pH, uniform drug content, prolonged residence time and sustained drug release to ensure enhanced therapeutic efficacy, improved patient compliance and reduced local irritation.[37–39]

7.2 Quality target product profile (QTPP)

The Quality Target Product Profile (QTPP) defines the desired characteristics of the finished topical product.

7.3 Critical material attributes (CMAs)

Critical Material Attributes (CMAs) are the physicochemical properties of raw materials that significantly influence the quality, stability and performance of isotretinoin-loaded niosomal gel formulations. Appropriate selection and optimization of these attributes are essential to achieve efficient vesicle formation, high drug entrapment efficiency, controlled drug release, and long-term formulation stability.[40]

7.4 Critical process parameters (CPPs)

Critical Process Parameters (CPPs) are the manufacturing variables that significantly influence the quality, reproducibility and performance of isotretinoin-loaded niosomal formulations. Proper control and optimization of these parameters are essential to ensure consistent vesicle formation, uniform particle size distribution, high encapsulation efficiency and long-term physicochemical stability.[41]

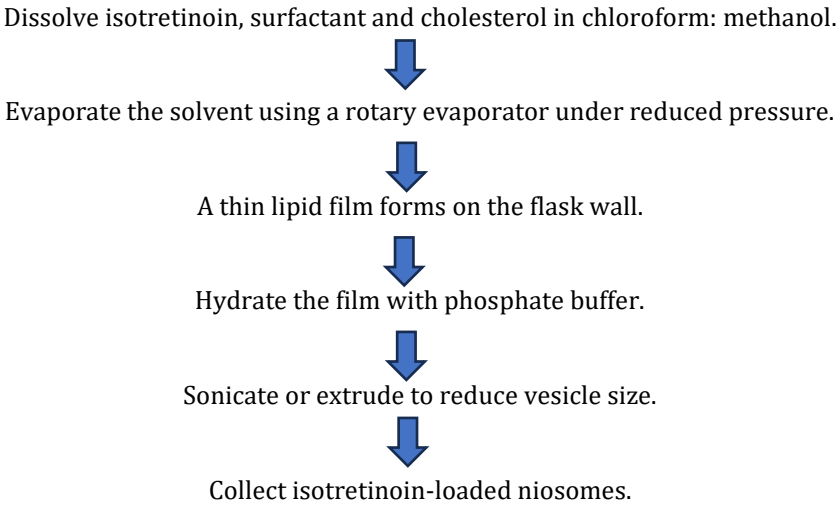
7.5 Methods of niosome preparation

Several techniques have been employed for preparing isotretinoin-loaded niosomes. The selection of the preparation method influences particle size, entrapment efficiency, scalability, and stability.

A. Thin film hydration method[42]

This is the most widely reported and preferred technique.

Procedure:



Advantages:

- High encapsulation efficiency.
- Uniform vesicle formation.
- Suitable for lipophilic drugs.
- Reproducible and scalable.

B. Ether Injection Method[43]

An organic solution containing surfactant and drug is injected slowly into a heated aqueous phase, producing unilamellar vesicles as the solvent evaporates.

Prepare organic phase (Dissolve isotretinoin and surfactant in an organic solvent).

↓

Prepare aqueous phase (Heat the aqueous phase under continuous stirring).

↓

Inject organic phase (Slowly inject the organic phase into the heated aqueous phase).

↓

Evaporate solvent (Allow the solvent to evaporate during stirring).

↓

Form vesicles **(**Unilamellar niosomes are formed).

↓

Cool and purify **(**Cool the dispersion and remove unentrapped drug/residual solvent).

C. Reverse phase evaporation method[44]

A water-in-oil emulsion is prepared, followed by solvent evaporation to form large vesicles with high encapsulation efficiency.

Prepare organic phase (Dissolve surfactant and isotretinoin in an organic solvent).

↓

Form emulsion (Add the aqueous phase gradually to form a water-in-oil emulsion).

↓

Evaporate solvent (Remove the organic solvent under reduced pressure).

↓

Form vesicles (Large niosomes are formed with high drug entrapment).

↓

Purify and characterize (Remove unentrapped drug and evaluate the vesicles).

D. Micro-fluidization[45]

High-pressure collision of fluid streams produces uniformly sized niosomes with narrow particle size distribution.

Prepare dispersion (Mix surfactant, cholesterol, drug and aqueous phase).

↓

High-pressure processing (Pass the dispersion through a microfluidizer).

↓

Reduce size (High-pressure fluid collision reduces vesicle size).

↓

Collect niosomes (Obtain uniformly sized niosomes with narrow size distribution).

E. Bubble method[46]

This solvent-free approach generates vesicles by bubbling inert gas through a surfactant solution at elevated temperature.

Prepare surfactant solution (Disperse surfactant and cholesterol in an aqueous medium).

↓

Heat (Maintain the dispersion at an elevated temperature).

↓

Bubble inert gas (Pass nitrogen or another inert gas through the solution).

↓

Form vesicles (Gas bubbling promotes vesicle formation).

↓

Cool and collect (Cool the dispersion to obtain niosomes).

7.6 Preparation of niosomal gel[47]

The optimized niosomal dispersion is incorporated into a gel matrix to improve topical application and increase residence time on the skin.

Typical Procedure

Disperse Carbopol 934 in purified water.

↓

Allow complete hydration for several hours.

↓

Add glycerol and propylene glycol under continuous stirring.

↓

Incorporate the optimized niosomal dispersion slowly.

↓

Adjust pH using triethanolamine.

↓

Mix until a homogeneous gel is obtained.

↓

Store in airtight, light-resistant containers.

↓

The resulting gel should be smooth, homogeneous, non-gritty and free from phase separation.

7.7 Optimization of formulation

Optimization is a crucial step in the development of isotretinoin-loaded niosomal gel, as it identifies the optimal combination of formulation variables required to achieve the desired product quality and therapeutic performance. A systematic optimization strategy, commonly employing Design of Experiments (DoE) or Response Surface Methodology (RSM), is used to evaluate the influence of formulation factors on the critical quality attributes of the final product.[48]

Table 3. Independent and dependent variables used for optimization of isotretinoin-loaded niosomal gel

Category	Variables
Independent Variables (Factors)	Surfactant concentration
	Cholesterol concentration
	Hydration time
	Sonication time
Dependent Variables (Responses)	Particle size
	Polydispersity index (PDI)
	Entrapment efficiency (%)
	Zeta potential
	In vitro drug release (%)
	Viscosity (cP)

7.8 Quality by design (QbD) approach

Application of Quality by Design (QbD) facilitates a systematic understanding of the relationship between formulation variables and critical quality attributes. Using Design of Experiments (DoE), such as factorial or Box–Behnken designs, researchers can optimize surfactant-to-cholesterol ratio, hydration conditions and sonication parameters to achieve targeted particle size, high entrapment efficiency and sustained drug release with fewer experimental trials.[49]

8. Characterization and evaluation of isotretinoin-loaded niosomes

Comprehensive characterization of isotretinoin-loaded niosomes is essential to ensure reproducibility, stability, drug-loading capacity and therapeutic performance. Physicochemical evaluation provides insight into vesicle morphology, particle size distribution, surface charge, encapsulation efficiency and drug release behavior all of which influence topical delivery and clinical efficacy.[50]

8.1 Preformulation studies

Preformulation studies provide essential information regarding the physicochemical properties of isotretinoin and its compatibility with excipients used in the development of niosomal gel formulations. These investigations form the basis for rational formulation design by facilitating the selection of suitable surfactants, membrane stabilizers, solvents and gel-forming polymers to ensure optimal drug loading, stability and therapeutic performance.[51,52]

Table 4. Major pre-formulation parameters evaluated for isotretinoin

Preformulation Parameter	Purpose	Ref
Organoleptic properties	Identification of drug characteristics (color, odor, appearance)	[53]
Solubility profile	Selection of suitable solvents and formulation components	[54]
Melting point	Assessment of purity and thermal characteristics	[55]
Partition coefficient (Log P)	Determination of lipophilicity and membrane permeability	[56]
pKa	Prediction of ionization behavior and formulation pH	[57]
UV absorption wavelength (λmax)	Quantitative drug estimation by UV spectrophotometry	[58]
Drug–excipient compatibility	Evaluation of potential physicochemical interactions	[59]
Stability under light and temperature	Assessment of chemical stability during formulation and storage	[60]

8.2 Particle size analysis

Particle size, measured by DLS, influences skin penetration, follicular targeting, drug release, and therapeutic efficacy. An optimized isotretinoin niosomal formulation generally shows a size of **100–300 nm** for effective follicular localization and skin retention.[61]

8.3 Polydispersity index (PDI)

PDI, measured by DLS, indicates niosomal size uniformity. A PDI < 0.30 suggests a narrow, homogeneous distribution and good formulation stability.[62]

8.4Zeta potential

Zeta potential measures the surface charge of niosomes and indicates colloidal stability by preventing vesicle aggregation, fusion and sedimentation. [63]

8.5 Entrapment efficiency

Entrapment efficiency (EE) measures the percentage of isotretinoin encapsulated in niosomes. Unentrapped drug is separated by ultracentrifugation, dialysis, or gel filtration and quantified by UV–Vis or HPLC.[64]

Formula:[65]

$$\text{Entrapment Efficiency (EE\%)} = \frac{\text{Total Drug} - \text{Free Drug}}{\text{2Total Drug}} \times 100$$

8.6 Drug content

Drug content analysis determines isotretinoin concentration and uniformity using UV–Vi's spectrophotometry or HPLC, with an acceptable range of 95–105% of labeled content.[66]

8.7 Morphological evaluation

Morphology influences vesicle stability, drug loading and release kinetics. Electron microscopy techniques are routinely employed for structural characterization.

Transmission electron microscopy (TEM)

TEM evaluates niosomal vesicle shape, bilayer structure, internal morphology and particle size for detailed morphological characterization.[67]

Scanning electron microscopy (SEM)

SEM evaluates niosome morphology, surface characteristics and aggregation. Optimized formulations show spherical, smooth, discrete and uniformly distributed vesicles with minimal aggregation.[68]

8.8 FTIR analysis

FTIR assesses drug–excipient compatibility by identifying functional groups and detecting potential chemical interactions or structural changes.[69]

8.9 Differential scanning calorimetry (DSC)

DSC evaluates isotretinoin's thermal behavior, crystallinity, phase transition and encapsulation by analyzing heat-flow changes after formulation.[70]

8.10 X-Ray diffraction (XRD)

XRD determines the crystalline or amorphous state of isotretinoin by comparing the diffraction patterns of pure drug and niosomal formulations.[71]

9. Evaluation of isotretinoin niosomal gel

Following incorporation into the gel base, additional quality control parameters are evaluated.

9.1 Appearance

Appearance is a key quality attribute; the niosomal gel should be smooth, homogeneous, non-gritty, lump-free and uniformly colored**,** indicating physical stability.[72]

9.2 pH

The formulation pH is measured using a calibrated digital pH meter. The optimized niosomal gel should have a skin-compatible pH of 5.5–6.8, minimizing irritation and maintaining drug stability.[73]

9.3 Viscosity

Viscosity is measured using a Brookfield viscometer and should be optimized to ensure **easy** application, adequate skin retention, controlled drug release and good patient acceptability.[74]

9.4 Spread-ability

Spread ability ensures easy, uniform application and drug distribution, improving patient compliance and therapeutic efficacy.[75]

9.5 Extrudability

Extrudability assesses the ease of gel expulsion from tubes, ensuring convenient dispensing and patient usability.[76]

9.6 Drug Content Uniformity

Drug content uniformity ensures homogeneous isotretinoin distribution, with an acceptable range of 95–105% for accurate dosing.[77]

9.7 Homogeneity

Homogeneity is assessed visually to ensure uniform dispersion and absence of air bubbles, phase separation, precipitation, or aggregation.[78]

10. *In Vitro* drug release studies

In vitro drug release studies evaluate the rate and extent of isotretinoin release, aiding formulation optimization and prediction of *in vivo* performance.[79]

Table 5. Parameters evaluated during *in vitro* drug release[80]

Parameter	Importance
Cumulative drug release (%)	Release profile
Release rate	Drug diffusion
Release duration	Sustained delivery
Diffusion coefficient	Permeation characteristics
Drug release kinetics	Mechanism of release

11. Drug release kinetic models

Mathematical modeling of release data provides insight into the mechanism of drug release from niosomal gel.

Table 6. Common drug release kinetic models for isotretinoin-loaded niosomal gel

Kinetic Model	Principle	Interpretation / Desired Outcome	Ref
Zero-order model	Drug is released at a constant rate independent of drug concentration.	Provides sustained drug release and maintains constant therapeutic levels.	81
First-order model	Drug release depends on the concentration of drug remaining in the formulation.	Release rate decreases as drug concentration declines.	82
Higuchi model	Drug release occurs by diffusion through the gel or matrix system.	Indicates diffusion-controlled drug release.	83
Korsmeyer–Peppas model	Empirical model used to analyze the mechanism of drug release.	Identifies whether release follows Fickian diffusion, non-Fickian (anomalous) transport, Case II transport, or erosion-controlled mechanisms.	84

12. *Ex Vivo* skin permeation and skin retention studies

Ex vivo skin permeation studies are essential for evaluating the penetration, retention and permeation behavior of isotretinoin-loaded niosomal gel across biological skin barriers. In this method, excised animal or human cadaver skin is mounted on Franz diffusion cells to simulate topical drug application under controlled laboratory conditions.[85] These studies quantify the amount of drug that permeates through the skin, is retained within the epidermis, dermis and pilosebaceous follicles and remains in the formulation over time.[86] Compared with conventional formulations, niosomal gels may exhibit enhanced drug deposition within the epidermis, dermis and pilosebaceous follicles while limiting systemic permeation.[87]

Table 7. Evaluation parameters for *Ex Vivo* skin permeation

Parameter	Method/Instrument	Desired result	Ref
Skin permeation	Franz diffusion cell	Controlled drug permeation	88
Skin drug retention	Tape stripping / Skin extraction	High epidermal and dermal retention	89
Follicular deposition	Skin extraction / Microscopy	Enhanced pilosebaceous localization	90
Permeation flux	Franz diffusion cell	Sustained permeation rate	91
Systemic permeation	Drug assay (UV–Vis/HPLC)	Minimal transdermal absorption	92

13. Skin irritation and safety assessment

Safety evaluation is an essential component of isotretinoin-loaded niosomal gel development, particularly for formulations intended for long-term topical application. Skin irritation studies are performed to assess the potential for erythema, edema, dryness, itching and other local adverse reactions following repeated application.[93]

14. Stability studies

Stability studies are essential to evaluate the ability of isotretinoin-loaded niosomal gel to maintain its physicochemical characteristics, drug content and therapeutic performance throughout its shelf life. These studies are performed under real-time and accelerated storage conditions in accordance with ICH stability guidelines to assess formulation integrity during storage.[94]

Table 8. Stability evaluation parameters of isotretinoin-loaded niosomal gel

Parameter	Method/Instrument	Expected outcome	Ref
Appearance	Visual inspection	No phase separation, discoloration, or precipitation	95
Particle size	Dynamic Light Scattering (DLS)	Minimal or no significant change	96
Polydispersity Index (PDI)	Dynamic Light Scattering (DLS)	< 0.30 with minimal variation	97
Zeta potential	Zetasizer	≥ ±30 mV; maintained stability	98
pH	Digital pH meter	5.5–6.8 with no significant change	99

Viscosity	Brookfield viscometer	Stable viscosity throughout storage	100
Drug content	UV–Visible Spectrophotometry / HPLC	≥95% of initial drug content retained	101
Entrapment efficiency	UV–Visible Spectrophotometry / HPLC	Stable with minimal reduction during storage	102
In vitro drug release	Franz diffusion cell / Dissolution study	Comparable to the initial release profile	103

15. Recent advances in isotretinoin niosomal gel

Recent advances in pharmaceutical nanotechnology have substantially improved the design, optimization and therapeutic performance of isotretinoin-loaded niosomal gels.[104] Modern formulation strategies increasingly incorporate Quality by Design (QbD) and Design of Experiments (DoE) to systematically optimize critical material attributes (CMAs) and critical process parameters (CPPs), resulting in formulations with improved reproducibility, stability, and quality.[105] The development of novel non-ionic surfactants, edge activators and membrane stabilizers has enhanced vesicle deformability, drug encapsulation efficiency and skin penetration, thereby improving follicular targeting and sustained drug release.[106] In addition, the integration of artificial intelligence (AI) and machine learning (ML) has emerged as a promising approach for predicting formulation behavior, optimizing excipient selection and accelerating pharmaceutical product development while reducing experimental workload.[107]

16. Future perspectives

Future research should focus on clinical validation, scale-up, long-term stability, regulatory approval and formulation standardization of isotretinoin-loaded niosomal gels. QbD, AI, personalized therapy, targeted niosomes and combination therapy may further improve efficacy and safety. These advances could support the clinical translation and commercialization of niosomal gels for acne management.

17. Conclusion

Isotretinoin-loaded niosomal gel is a promising topical system that improves isotretinoin stability, skin penetration, follicular targeting, retention and controlled release**,** while reducing irritation and systemic exposure. QbD, DoE and AI-assisted optimization can enhance formulation quality and reproducibility. Further research should focus on stability, clinical validation, scale-up and regulatory approval**.**

Abbreviations

AI : Artificial Intelligence

CMAs : Critical Material Attributes

cP : Centipoise

CPPs : Critical Process Parameters

DLS : Dynamic Light Scattering

DoE : Design of Experiments

DSC : Differential Scanning Calorimetry

EE : Entrapment Efficiency

ELS : Electrophoretic Light Scattering

FTIR : Fourier Transform Infrared Spectroscopy

H&E : Hematoxylin and Eosin

HLB : Hydrophilic–Lipophilic Balance

HPLC : High-Performance Liquid Chromatography

IL : Interleukin

Log P : Partition Coefficient

MAPK : Mitogen-Activated Protein Kinase

ML : Machine Learning

MLVs : Multilamellar Vesicles

MMPs : Matrix Metalloproteinases

NF-κB : Nuclear Factor-Kappa B

PBS : Phosphate-Buffered Saline

PDI : Polydispersity Index

pH : Potential of Hydrogen

pKa : Acid Dissociation Constant

QbD : Quality by Design

QTPP : Quality Target Product Profile

RAR : Retinoic Acid Receptor

ROS : Reactive Oxygen Species

RSM : Response Surface Methodology

RXR : Retinoid X Receptor

SEM : Scanning Electron Microscopy

TEM : Transmission Electron Microscopy

TLR : Toll-Like Receptor

TNF-α : Tumor Necrosis Factor-Alpha

ULV : Unilamellar Vesicle

UV : Ultraviolet

UV–Vis : Ultraviolet–Visible Spectrophotometry

XRD : X-Ray Diffraction

λmax : Maximum Absorption Wavelength

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