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Review Article

A Comprehensive Review: Recent Advances in Melasma Treatment Using Niosomes

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ABSTRACT

Melasma is a common acquired hyperpigmentary disorder characterized by symmetrical brown-to-gray patches on sun-exposed areas of the skin, particularly the face. It is a multifactorial condition influenced by genetic predisposition, ultraviolet (UV) radiation, hormonal changes, inflammation, and oxidative stress. Although several conventional treatment options, including topical depigmenting agents, chemical peels, oral therapies, and laser-based procedures, are available, their long-term effectiveness is often limited by poor skin penetration, frequent recurrence, local irritation, systemic adverse effects, and reduced patient compliance. Consequently, there is a growing need for advanced topical drug delivery systems that improve therapeutic efficacy while minimizing unwanted effects. Nanotechnology-based drug delivery systems have emerged as promising alternatives for melasma management, among which niosomal gel has gained considerable attention. Niosomes are non-ionic surfactant-based vesicular carriers capable of encapsulating both hydrophilic and lipophilic drugs, thereby enhancing drug stability, bioavailability, skin permeation, and controlled drug release. Incorporation of niosomes into a topical gel further improves drug retention at the target site, prolongs therapeutic action, reduces systemic absorption, and enhances patient acceptability due to its non-greasy and convenient application. This review comprehensively discusses the epidemiology, risk factors, pathogenesis, diagnosis, and conventional treatment strategies for melasma, followed by an overview of recent nanotechnology-based approaches, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, transferosomes, Nano emulsions, metallic nanoparticles, nanocrystals, and niosomes. Special emphasis is placed on the formulation, mechanism of action, methods of preparation, characterization, evaluation parameters, therapeutic advantages, applications, challenges, recent patents, and future perspectives of niosomal gel systems. Future research should focus on the development of targeted, stimuli-responsive, and personalized niosomal formulations with improved stability and clinical efficacy.

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Overall, niosomal gel represents a promising and effective topical drug delivery platform for melasma, offering enhanced therapeutic outcomes, improved safety, sustained drug release, and better patient compliance compared with conventional treatment approaches.

INTRODUCTION

Melasma is a common acquired hyperpigmentary disorder characterised by light to dark brown macules and patches occurring on sun-exposed areas of the face and neck. The condition is multifactorial in origin, with major etiological factors including genetic predisposition, ultraviolet (UV) radiation, and hormonal influences. It predominantly affects women of reproductive age, especially those with Fitzpatrick skin types IV–VI, although men can also be affected. In addition to its physical presentation, melasma has a significant psychological impact and is often associated with conditions such as depression, anxiety, and adjustment disorders[1,2].

A recent global survey involving 324 women with melasma highlighted those multiple triggers—including pregnancy, hormonal contraceptive use, family history, and chronic sun exposure—play a crucial role in the onset and progression of the condition. Despite extensive research, the management of melasma remains challenging[3]Various therapeutic approaches, including topical agents, chemical peels, and laser-based treatments, have been explored. Among these, a triple fixed-combination cream containing hydroquinone, retinoic acid, and a corticosteroid is widely recommended and has shown better efficacy than hydroquinone monotherapy when used for a duration of up to 8 weeks[4].

Several topical depigmenting agents such as hydroquinone, arbutin, kojic acid, vitamin C, and azelaic acid, along with advanced energy-based techniques like lasers, microneedling, and iontophoresis, have been introduced for enhanced drug delivery[5] However, inconsistent therapeutic outcomes and adverse effects, including post-inflammatory hyperpigmentation, erythema, and skin barrier disruption, limit their long-term use.[4].

In recent years, there has been an increasing interest in the creation of new drug delivery systems that can deliver targeted, sustained, and safe Melasma treatment. Liposomes were the initial vesicular drug delivery systems, but they possess numerous drawbacks like toxicity and pH-dependent stability; for this reason, the research interest moved towards Niosomes[6]. Niosomes are ionic surfactant vesicles created by the self-assembly of non-ionic amphiphiles in aqueous systems, leading to closed bilayered structures.

Niosomal gel, a topical drug delivery system, has shown great promise in the treatment for melasma. Niosomal gels can withstand the physiological stress developed due to skin flexion and thus extend controlled release of the drug to the site of action[7].The gel drug delivery system offers an easy and patient-friendly delivery platform for transdermal administrations.

1.1 EPIDEMIOLOGY:

According to numerous epidemiologic studies, the prevalence of melasma is approximately 1% in the general population and ranges from 9% to 50% among individuals at higher risk [8,9]These wide-ranging estimates are likely due to differences in study populations and methodologies. There are significant differences in melasma prevalence by skin type, ethnic background, and UV exposure across regions. Consequently, the true global prevalence remains uncertain. The condition most commonly affects individuals aged 20 to 30, although the precise age of onset is unclear. Notably, one study found that individuals with mandibular melasma typically develop the condition in their 40s[9].

Melasma is more common in women, according to research. Despite the widely recognised 9:1 female-to-male ratio, a 39:1 ratio was discovered in a more recent large, multicenter investigation of 953 melasma patients in Brazil. A 4:1 female-to-male ratio was discovered in an Indian study involving 312 melasma patients[10] [21,22]. The incidence probably rises during pregnancy, as demonstrated by a cross-sectional study conducted in Tehran that found a 15.8% prevalence among pregnant women. Similarly, a 50.8% frequency was found in a randomly chosen sample of 2000 pregnant women in India [8,11 ,12]

1.3 Classification of melasma:[13, 14]

1. Epidermal Melasma

Epidermal melasma is characterized by increased melanin deposition in the superficial layers of the skin. It shows enhancement under Wood's lamp examination, indicating a more superficial pigment location. This is the most responsive type to topical therapies such as depigmenting agents and generally has a better prognosis.

2. Dermal Melasma

Dermal melasma involves melanin deposition in the deeper dermal layers. It does not show enhancement under Wood's lamp and often appears bluish due to the Tyndall effect. This type is more resistant to treatment and typically shows a slower or minimal response to conventional therapies.

3. Mixed Melasma

Mixed melasma is the most common type and involves both epidermal and dermal pigmentation. It shows partial enhancement under Wood's lamp examination. Due to the combined involvement of skin layers, treatment response is variable and may require combination therapies for effective management.

1.4 PATHOGENESIS OF MELASMA:

Melasma is now viewed as chronic photoaging-related, multifactorial hypermelanosis rather than a simple melanocyte overactivity. It arises from the interaction of environmental triggers (especially light), hormones, genetics, and complex changes across the epidermis, basement membrane, and dermis.

- **Ultraviolet and visible light:** Ultraviolet radiation (UVR) is the primary external trigger for melasma. It alters the expression of over 300 genes involved in melanogenesis, oxidative stress, barrier function, and lipid metabolism. UVR also causes basement membrane damage and leads to the "sinking" of melanocytes. In addition, visible light can further aggravate lesions[15].

- **Hormones and genetics:** Female sex hormones, such as those present during pregnancy or in women taking oral contraceptive pills (OCPs), stimulate melanogenesis. Increased estrogen and progesterone receptors in lesional skin further promote pigment production, particularly in individuals with a genetic predisposition [14].

- **Inflammation and oxidative stress**: They play a significant role in both the development and persistence of melasma, as inflammatory mediators, free radicals, and weakened antioxidant defences promote ongoing pigmentation[16].

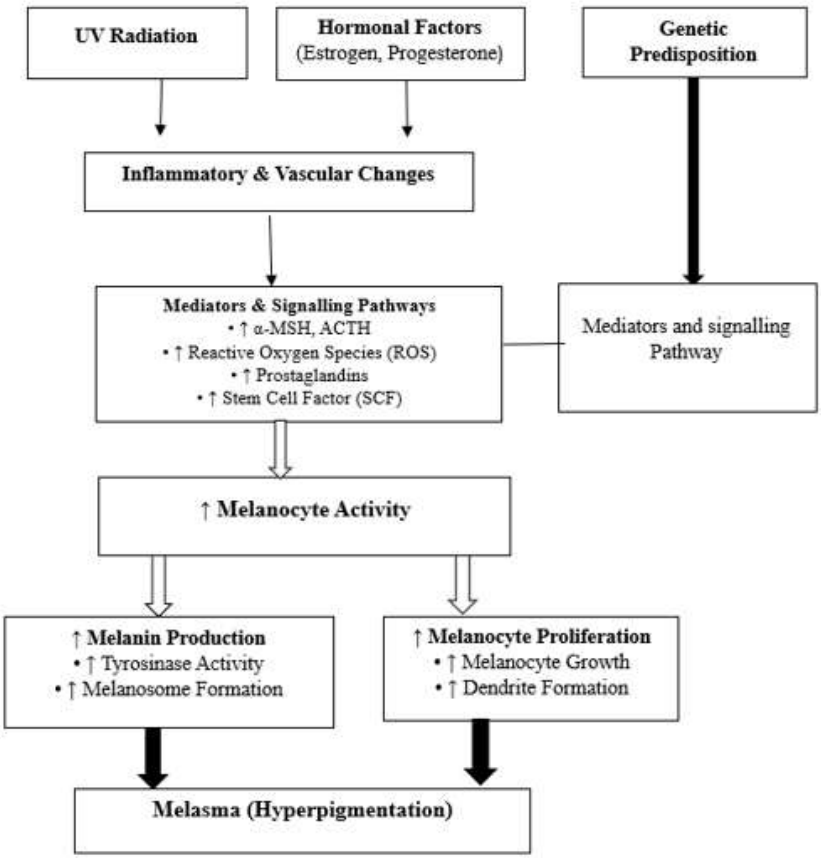

Fig. 5: Pathogenesis of Melasma

1.5 DIAGNOSIS OF MELASMA:

Morphologically, melasma appears as symmetric, reticulated patches of hyperpigmentation with irregular borders on the centrofacial region, malar cheeks, mandible, and, less commonly, the upper chest and extremities. Although melasma is more prevalent among individuals with darker skin types, it can occur in all skin types[17,18]

1.5.1 Wood's lamp examination:

Wood's lamp aids in assessing melasma depth, particularly in lighter skin. Epidermal pigmentation shows enhancement, while dermal pigmentation does not. Mixed patterns are common, and many cases show both components despite appearing superficia[19].

1.5.2 Dermoscopy

Dermoscopy reveals pigment distribution and depth through colour and network patterns. Superficial melanin appears dark brown and well-defined, whereas deeper or dermal pigment shows lighter brown to bluish-grey hues[2].

1.5.3 Histopathology

Histology shows increased epidermal melanin with normal but hyperactive melanocytes. Dermal features may include melanophages, mild inflammation, increased vascularity, and solar elastosis[20].

1.5.4 Reflectance Confocal Microscopy

RCM is a non-invasive imaging tool providing near-histological resolution. It detects hyperpigmented keratinocytes in the epidermis and melanophages with vascular changes in the dermis.[21].

1.6 Conventional Treatment Approaches for Melasma:

Conventional management of melasma primarily focuses on reducing melanogenesis, removing existing melanin, and preventing disease exacerbation. Treatment strategies mainly include photoprotection, topical depigmenting agents, chemical peels, and procedural therapies, either alone or in combination.

Table 3: Conventional Treatment Approaches for Melasma

Treatment Modality	Drugs Used	Examples / Methods	Mechanism of Action	Limitations	Reference (Author et al.)
Photoprotection	Zinc oxide, titanium dioxide, and iron oxides	Broad-spectrum sunscreens, protective clothing	Blocks UV and visible light; reduces ROS-mediated melanocyte activation	Inadequate protection against visible light alone, poor adherence in daily life, cannot reverse existing pigmentation	21,22
Topical depigmenting agents	Hydroquinone, azelaic acid, kojic acid, arbutin, liquorice extract	Creams, gels, lotions	Inhibition of tyrosinase and melanin synthesis	Skin irritation, sensitization, post-inflammatory hyperpigmentation, and limited long-term efficacy	23,24
Combination therapy	Hydroquinone + tretinoin + corticosteroid (fluocinolone acetonide)	Triple combination cream	Decreases melanogenesis, increases epidermal turnover, and reduces inflammation	Risk of skin atrophy, steroid-related side effects, rebound pigmentation, and poor patient compliance	23,24
Topical retinoids	Tretinoin, adapalene, tazarotene	Creams and gels	Enhances keratinocyte turnover and drug penetration	Irritation, erythema, peeling; slow onset of effect; not sufficient as monotherapy	25,
Chemical peels	Glycolic acid, salicylic acid, lactic acid, low-strength TCA	Superficial chemical peeling	Exfoliation of pigmented epidermis	Risk of post-inflammatory hyperpigmentation, recurrence is common; not suitable for all skin types	23,24
Oral therapy	Tranexamic acid	Oral tablets	Inhibits plasmin-mediated melanocyte stimulation	Systemic side effects, contraindicated in some patients; limited long-term data; variable efficacy	25

Laser and light therapies	—	Q-switched Nd: YAG laser, fractional laser, IPL	Selective photothermolysis of melanin	High cost, risk of rebound hyperpigmentation, and limited efficacy in darker skin phototypes	23,24

1.7 Novel Approaches for Melasma Treatment:

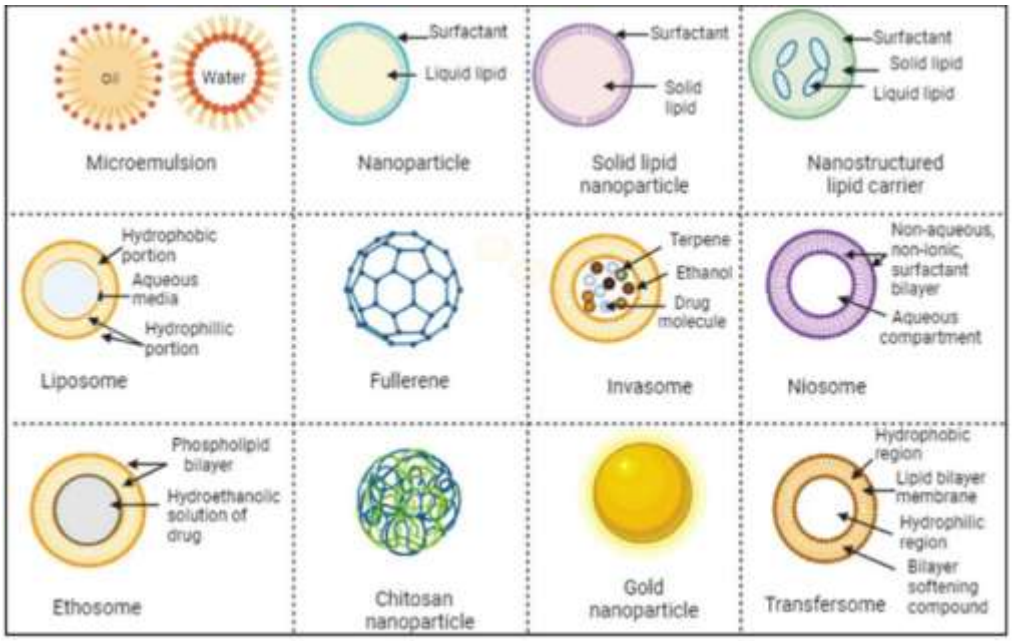

Fig no 6: Novel approaches for treatment of Melasma

To address these challenges, recent years have witnessed growing interest in advanced drug-delivery strategies, especially the application of nanotechnology for targeted topical delivery. Nanocarrier-based systems offer improved drug stability, enhanced skin permeation, controlled release, and reduced systemic exposure, thereby leading to better therapeutic outcomes [26].

Consequently, a wide range of nanoparticulate systems—such as lipid nanoparticles, nano emulsions and microemulsions, vesicular nanocarriers, polymeric nanoparticles, nanocrystals, and metal nanoparticles—have been extensively explored for topical delivery in melasma management.

1.7.1 SLNs

Solid lipid nanoparticles (SLNs) are lipid-based carriers with particle sizes typically ranging from 50 to 1000 nm, composed of lipids that remain solid at body temperature and stabilised by emulsifiers. Due to their solid core, SLNs help improve drug stability and promote better retention of drugs within the skin[27].

In melasma management, SLNs have shown significant potential for delivering depigmenting agents such as hydroquinone and kojic acid. Encapsulation of hydroquinone in SLNs improves its stability by preventing oxidative degradation, enhances epidermal deposition, and reduces systemic absorption. Studies have reported

significantly higher skin deposition (~46%) compared to conventional gels (~15%), along with increased drug retention and reduced transdermal flux, indicating lower systemic exposure[28].

Similarly, kojic acid-loaded SLNs exhibit enhanced dermal retention, controlled drug release, and improved tyrosinase inhibition activity. Overall, SLNs offer an effective and safer approach for topical delivery of anti-melanogenic agents in the management of melasma[5].

1.7.2 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs), the second generation of lipid nanoparticles, have also shown considerable advantages in topical depigmenting therapy. Studies have reported that encapsulation of hydroquinone within NLCs leads to improved drug stability, targeted delivery, and reduced skin irritation [(52)]. Hydroquinone-loaded NLCs have shown better skin retention and improved protection against UVA and UVB radiation compared to conventional formulations.

Azelaic acid-loaded NLCs have also been shown to possess enhanced occlusive properties, improved skin permeation, and targeted delivery to melanocytes, resulting in improved clinical efficacy[29]. Moreover, the sustained drug-release behaviour of azelaic acid-loaded NLCs offers an additional advantage by prolonging localised drug deposition within the skin layers, thereby enhancing therapeutic outcomes while minimising systemic exposure.

1.7.3 Liposomes

Liposomes are vesicular drug-delivery systems composed of phospholipid bilayers, often stabilised with cholesterol, capable of encapsulating both hydrophilic and lipophilic drugs. Their structural similarity to biological membranes enables them to interact with skin cells, enhancing drug penetration and promoting uniform distribution within the skin layers[30].

The application of liposomes in topical drug delivery is particularly attractive due to several advantages, including improved penetration through the stratum corneum, skin-moisturizing and barrier-restoring effects, controlled and sustained drug release, and excellent biocompatibility and biodegradability [31].

1.7.4 Niosomes:

Niosomes are vesicular nanocarriers composed of nonionic surfactants that possess inherent skin–permeation–enhancing properties. These vesicles are typically prepared through the self-assembly of nonionic surfactants in an aqueous medium, most commonly using techniques such as thin-film hydration or solvent injection methods [33].

Niosomes have been widely investigated for the topical delivery of depigmenting agents. In particular, the simultaneous encapsulation of kojic acid and hydroquinone within niosomal systems resulted in a topical formulation with sustained and prolonged drug-release behaviors, which is desirable for maintaining therapeutic drug levels in the skin while minimizing systemic exposure[34].

1.7.5 Transferosomes:

Transferosomes are highly flexible vesicular carriers composed of a phospholipid bilayer and an edge activator, which enhances their deformability. This unique structure allows them to squeeze through the narrow pores of the stratum corneum, resulting in improved skin penetration and prolonged drug retention.[35].

Loading niacinamide into transfersomal carriers significantly improved its skin permeation and depigmenting activity when compared with

conventional liposomal formulations. Similarly, the encapsulation of arbutin within transferosomes led to increased transdermal penetration and superior depigmenting efficacy of the drug[36].

1.7.6 Metal nanoparticles:

Gold nanoparticles, owing to their excellent aqueous stability, biocompatibility, and chemical inertness, have been widely recognised as suitable nanocarriers for topical drug delivery applications[37]

Arbutin incorporated into gold nanoparticle-based nanocomplexes demonstrated improved depigmenting efficacy by suppressing melanin synthesis, reducing inflammatory responses, and minimising toxicity, thereby offering advantages over the free drug for melasma management[38].

1.7.7 Nanocrystals:

Nanocrystals have gained attention in topical drug delivery due to their ability to enhance drug solubility, accelerate dissolution, and improve adhesion to the skin surface[39].

Although azelaic acid is water-soluble, the presence of two carboxylic acid groups limits its penetration through the skin. To overcome this drawback, azelaic acid nanocrystals formulated with Pluronic F127 and hyaluronic acid demonstrated improved solubility, faster dissolution, enhanced drug stability, and increased skin permeation[40].

1.7.8 Nano emulsions/microemulsions:

Nano emulsions are effective carriers for dermal drug delivery due to their ability to penetrate the skin's lipophilic barrier. Like microemulsions, they consist of oil and water phases stabilized by surfactants. They enhance drug solubility, improve skin penetration, and increase bioavailability, making them valuable in topical and cosmeceutical formulations[41].

In addition, incorporating hydroquinone into microemulsion systems significantly improved its permeability across the stratum corneum and enhanced its photostability[42].

1.7.9 Fullerenes

Fullerene and its analogues, particularly water-soluble fullerene analogues, have been dubbed cutting-edge, potent antioxidants that are supposed to minimize intracellular ROS and avoid oxidative cell injury while exhibiting reduced cytotoxicity [43].

Types of Nanocarrier Systems Used in Nanotechnology-Based Therapy for Melasma

Table 5: Novel treatment approaches for melasma

Nanocarrier Type	Advantages	Disadvantages	Reference(s)
Liposomes	Biocompatible, improves skin penetration, reduces drug irritation	Physical instability, possible drug leakage	[44]
Niosomes	High chemical stability, cost-effective, non-ionic surfactants	Lower penetration compared to ethosomes	[45]
Solid Lipid Nanoparticles (SLNs)	Controlled drug release, good physical stability, occlusive effect	Low drug loading, lipid crystallization	[27]
Nanostructured Lipid Carriers (NLCs)	Higher drug loading, improved stability, prolonged release	Complex formulation process	[46,47]
Transferosomes	Highly deformable vesicles, superior skin penetration	High production cost, stability concerns	[48]
Nano emulsions / Microemulsions	High drug solubilization, uniform skin distribution	Surfactant-induced irritation	[49]

Metallic Nanoparticles	Intrinsic antioxidant and anti-melanogenic activity	Risk of cytotoxicity and accumulation	[50]

2. Recent Patents on nanocarriers for Melasma Treatments:

Table 6: Recent Patents on nanocarriers for Melasma Treatments

Publication No.	Year	Title of Invention	Summary of the Invention	Reference
WO2024237777A1	2024	Compositions and Methods for Preventing and/or Treating Skin Pigmentation	Compositions to prevent/treat pigmentation disorders, including melasma, by modulating melanin synthesis or degradation pathways.	**51**
US20250090443A1	2025	Skin Care Compositions and Their Uses	Topical formulations for depigmentation and treatment of melasma/dark spots; include combinations of antioxidants and tyrosinase inhibitors.	**52**
US20250127700A1	2025	Methods of Treating Hyperpigmentation Disorders	Methods and compositions targeting tyrosinase or melanogenesis pathways to reduce hyperpigmentation like melasma.	**53**

3. Niosomes:

Niosomes are bilayered structures formed by non-ionic surface-active molecules. These thermodynamically stable, two-layered vesicles form only under specific conditions: the temperature exceeds the gel-liquid transition point, and surfactants and cholesterol are combined in the proper ratio[54]. The bilayered structure encloses an internal aqueous compartment, allowing niosomes to encapsulate both hydrophilic and hydrophobic drugs.

While hydrophobic medications partition into the bilayer matrix to enter it, hydrophilic drugs can be adsorbed onto the bilayer surface or trapped in the central watery core of niosomes [55].

3.1 Structure and Composition of Niosomes:

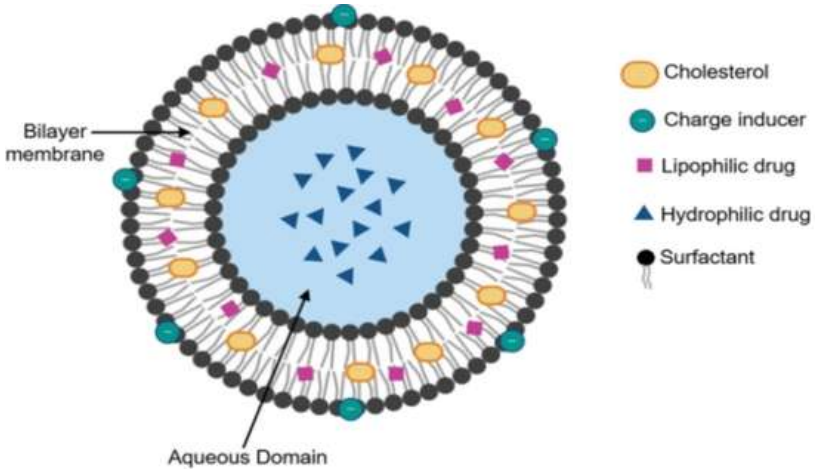

Fig No 7: Structure of Niosomes

The basic components of Niosomes include non-ionic surfactant, cholesterol hydration medium and charge inducer molecules**.**

3.1.1 Non-Ionic Surfactant:

Non-ionic surfactants are uncharged amphiphilic molecules. These are the most important parts of niosomes, which organise themselves into bilayer structures in a liquid medium. Typical non-ionic surfactants used in niosome formulation include Tween (polysorbates) and Span (sorbitan esters). Both hydrophilic and lipophilic medications can be trapped by the surfactants, which also stabilise the vesicles. By reducing the surface tension between the lipid phase and the aqueous phase, they facilitate the production of vesicles and enable the niosomal structure to form stable structures[56,57,58.]

3.1.2 Cholesterol

The Niosomal bilayer frequently contains cholesterol to improve the stability of the membrane. It is regarded as a "mortar" that strengthens the bilayer by sealing gaps between surfactant molecules. The inclusion of cholesterol can improve stability, decrease membrane fluidity, and change membrane permeability, all of which can improve the effectiveness of drug trapping in Niosomes.

The structural integrity of Niosomes depends on cholesterol, especially when the environment is changing[58,59,60.]

3.1.3 Charged Molecules:

Charged molecules are additives that impart either a positive or negative charge to the surface of Niosomes. This surface charge not only helps stabilise the vesicles but also influences their interactions with biological membranes. Among the most used charge-inducing agents are stearyl amine, which provides a positive charge, and diacetyl phosphate, which imparts a negative charge. Incorporating these molecules can prevent noisome aggregation, extend their circulation time in the bloodstream, and improve the cellular delivery of negatively charged drugs, such as polynucleotides [61,62,63].

3.2 Mechanism of action of Niosomes on melasma

Niosomes are vesicles made of non-ionic surfactants and cholesterol that self-assemble into bilayers, encapsulating both hydrophilic (e.g., glutathione, magnesium ascorbyl phosphate, hydroquinone) and lipophilic agents[64,65] . They disrupt and “loosen” the stratum corneum lipids and can fuse/adhere to the skin surface, increasing permeability and drug flux into the viable epidermis where melanocytes reside [43,66]

When dispersed in a Carbopol or similar gel, the gel acts as a reservoir, providing prolonged release and higher skin retention than the solution or cream form. This controlled, localised delivery raises drug concentration in epidermis while limiting deeper/systemic exposure and irritation [67].

3.3 Advantages of Niosomal gel over other formulations:

Niosomal gel merges the advantages of niosomes with the convenience of gel formulations, providing superior benefits compared to oral medications, conventional topical creams, and other vesicular systems like liposomes and ethosomes

1. **Enhanced Drug Stability**
   Niosomes are prepared using non-ionic surfactants, which exhibit greater chemical stability than phospholipid-based vesicles such as liposomes that are susceptible to

oxidative degradation. Incorporation of niosomes into a gel matrix further improves vesicle stability by preventing aggregation and drug leakage, thereby maintaining the integrity and efficacy of the encapsulated drug [67].

2. **Improved Skin Penetration**
Niosomal gels enhance dermal penetration by interacting with the lipid components of the stratum corneum, resulting in improved drug permeation and deeper skin deposition. The gel base prolongs residence time at the application site, offering superior penetration compared to conventional creams and ointments[54].

3. **Controlled and Sustained Drug Release**
The vesicular architecture of niosomes enables the controlled release of the drug, while the gel matrix serves as an additional diffusion barrier. This dual mechanism provides sustained drug release, maintaining therapeutic concentrations over an extended period and reducing dosing frequency[68,69]

4. **Reduced Systemic Absorption and Side Effects**
Niosomal gels promote localised drug targeting within skin layers, thereby minimizing systemic absorption. This localized delivery significantly reduces adverse effects such as irritation, erythema, and toxicity, which are commonly observed with conventional topical formulations, especially in long-term dermatological therapy[70].

5. **Improved Patient Compliance and Cosmetic Acceptability**
Niosomal gels are non-greasy, easily spreadable, and cosmetically acceptable. Sustained drug action and reduced skin irritation further enhance patient compliance compared to conventional topical dosage forms[71,72].

3.4 Comparison table: Niosomal Gel vs Other Delivery Systems

Table 7: Comparison table: Niosomal Gel vs Other Delivery Systems

Feature	Niosomal Gel	Oral Formulations	Topical Non-Vesicular Systems	Vesicular Systems (Liposomes, Ethosomes)
Stability	High	High	Moderate	Low to Moderate
Skin Penetration	High (enhanced epidermal retention)	None	Limited to superficial layers	Moderate (Liposomes), High (Ethosomes)
Avoids First-Pass Metabolism	Yes	No	Yes	Yes
Controlled Release	Yes	No	No	Yes (limited by vesicle stability)
Cost	Moderate	Low	Low	High
Patient Compliance	High	Moderate	High	Moderate
Irritation Potential	Low	Moderate (systemic side effects)	Low to Moderate	Moderate to High (Ethosomes)

3.6 Methods of Niosomes Preparation:

1. Thin Film Hydration Technique:

Thin-film hydration, also known as the lipid thin-film hydration or hand-shaking method, is a commonly employed conventional technique for the preparation of Niosomes. In this method, surfactants and lipids are initially dissolved in various ratios in a suitable organic solvent. The solvent is then evaporated under reduced pressure using a rotary evaporator, leading to the formation of a thin lipid film on the inner surface of a round-bottom flask[73].

The resulting dry film is subsequently hydrated with an aqueous phase at a temperature slightly above the surfactants' phase-transition temperature. During the hydration period, gentle and occasional shaking is applied, allowing the lipid layers to swell and peel off from the flask wall, resulting in vesicle formation [74].

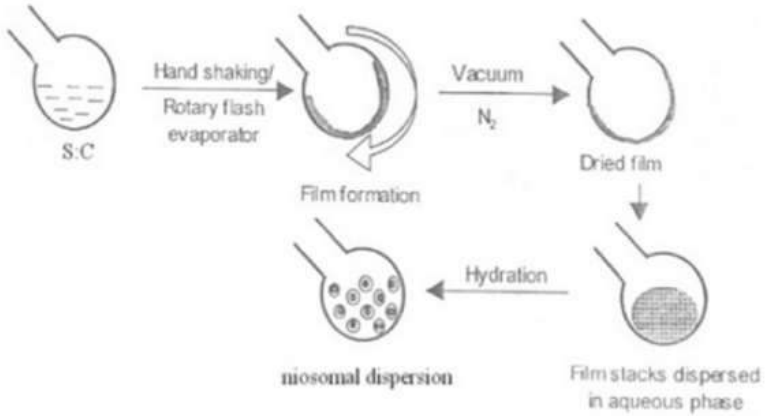

Fig. 7: Thin Film Hydration Technique

2. Ether Injection Method:

The ether injection method, first described by Deamer and Bangham in 1976 , involves dissolving non-ionic surfactants and other components in diethyl ether and then injecting this mixture into a preheated aqueous solution maintained at 60–65 °C. The temperature difference between the organic and aqueous phases facilitates the gradual evaporation of ether, leading to the formation of Niosome vesicles. This technique is particularly effective for economically producing large unilamellar Niosomes. One advantage of this method is its suitability for lipophilic drugs, which dissolve readily in ether and incorporate efficiently into the vesicle bilayer. However, a limitation is the potential presence of trace amounts of residual ether in the final suspension, which can be challenging to remove. This issue can be addressed by applying evaporation under reduced pressure, improving the safety profile for pharmaceutical use[75].

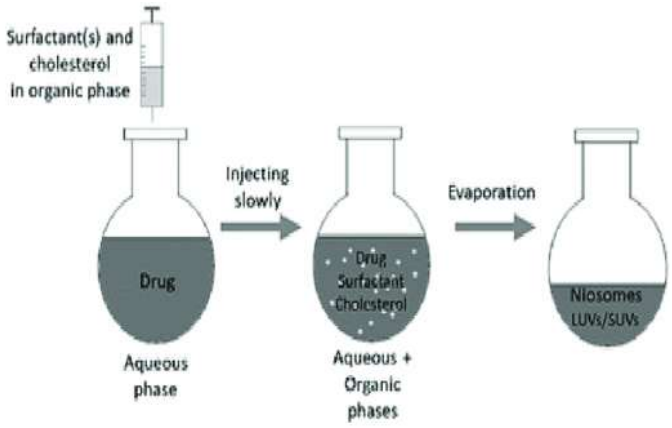

Fig. No 8: Ether Injection Method

3. Ethanol Injection Method:

The ethanol injection method is a quick and straightforward approach for preparing small unilamellar Niosomes. In this technique, an ethanolic solution of lipids is injected directly into an aqueous phase, where vesicles form spontaneously. To improve lipid solubility and enhance drug encapsulation, co-solvents such as isopropanol can be added to the ethanol. Additionally, parameters such as the injection rate and temperature can be adjusted to control vesicle size and reduce aggregation, making this method highly versatile[76].

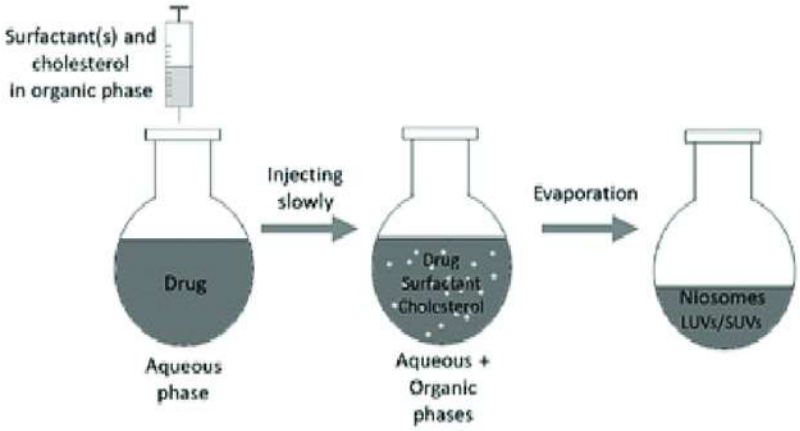

Fig. No 9: Ethanol Injection Method

4. Reverse Phase Evaporation Technique (REV)

The process of manufacturing Niosomes using the Reverse-Phase Evaporation Technique begins with dissolving the cholesterol and surfactant in a chloroform-ether mixture. A mixture. Next, a medication is introduced from the aqueous phase into the organic phase. After that, there are two stages, and to make it gel-like in phase, it is sonicated at low temperatures between 4 and 5°C. Lastly, sonication is carried out once more after adding a tiny amount of phosphate-buffered saline. At 40°C, the organic solvent is removed under low pressure, creating a viscous suspension of Niosomes. After diluting the solution in PBS, it was incubated at 60°C to finish the production of niosomes[77]

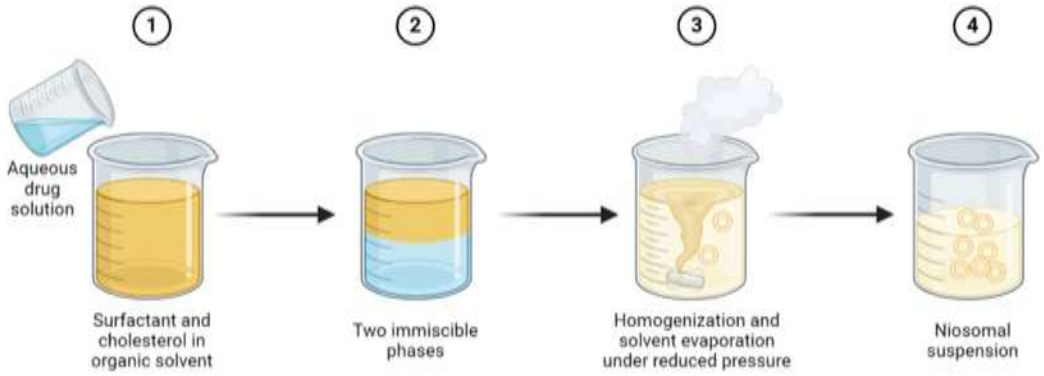

Fig no 10: Reverse Phase Evaporation Technique (REV)

5. Sonication Method:

Sonication is a simple and efficient method for the preparation of niosomes. In this technique, cholesterol and a non-ionic surfactant are first dissolved together, and the drug intended for encapsulation may be incorporated into the same solution. The resulting mixture is transferred into a glass vial, followed by the addition of a suitable buffer to obtain the desired concentration. The formulation is then subjected to probe sonication using a titanium sonicator, usually maintained at a controlled temperature of approximately 60 °C. The application of high-frequency ultrasonic waves generates intense shear forces, which break down surfactant aggregates and promote the formation of uniform niosomal vesicles[78]

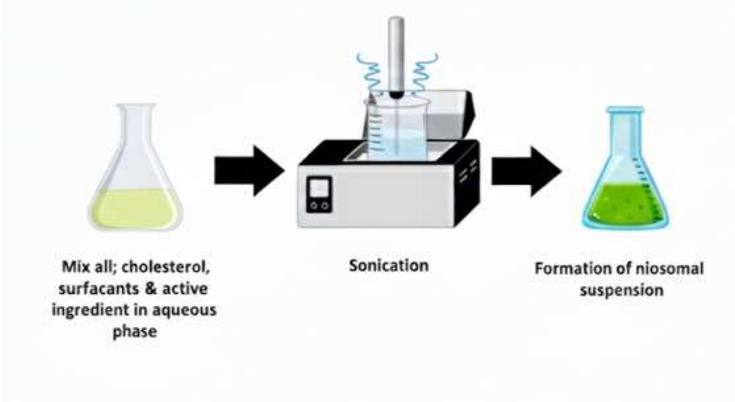

Fig no 11: Sonication Method

6. Micro fluidization method:

Niosomes can also be prepared using microfluidics-based techniques, which employ devices containing central channels flanked by side channels. In this approach, the aqueous and organic phases are separately pumped through different microchannels at controlled flow rates and pressures, allowing them to mix within a cooled interaction chamber, often maintained using ice. The formed niosomes are then collected from the mixing channels into a glass vial[79]. This method is known to produce niosomes with uniform morphology, small particle size, and well-defined cholesterol incorporation. niosomes prepared using microfluidics exhibit significantly smaller diameters compared to those obtained by the thin-film hydration technique[80] .

Additional advantages of the microfluidics method include precise control over formulation and

process variables, reduced consumption of chemicals, and the potential for scalable niosome production[60].

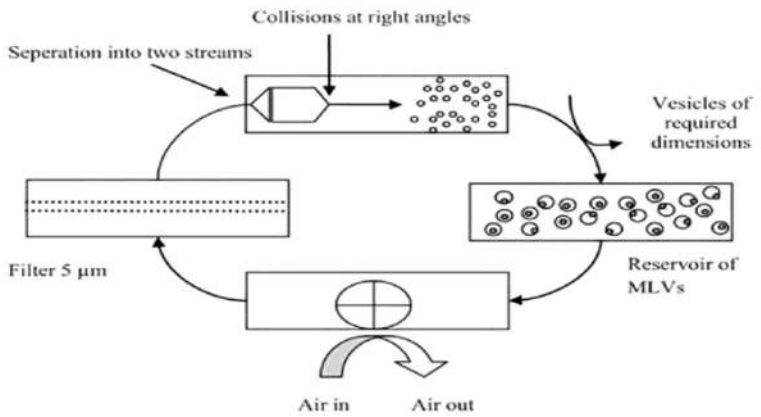

Fig no 12: Micro fluidization method

7. Formation of Niosomes from Proniosomes:

Preparation of niosomes from proniosomes involves a straightforward process of hydration. Proniosomes are powdered free-flowing systems which are a blend of surfactants, cholesterol, and a drug, often coated on a carrier, for example, maltodextrin or other hydrophilic substances. A suitable aqueous phase, typically phosphate buffer or distilled water, must be mixed with the proniosomes along with mild agitation or heat treatment for proniosome-to-niosome conversion. This process also hydrates the surfactant layer, resulting in the self-assembly of niosomes, which are vesicular structures that encapsulate the drug[81].

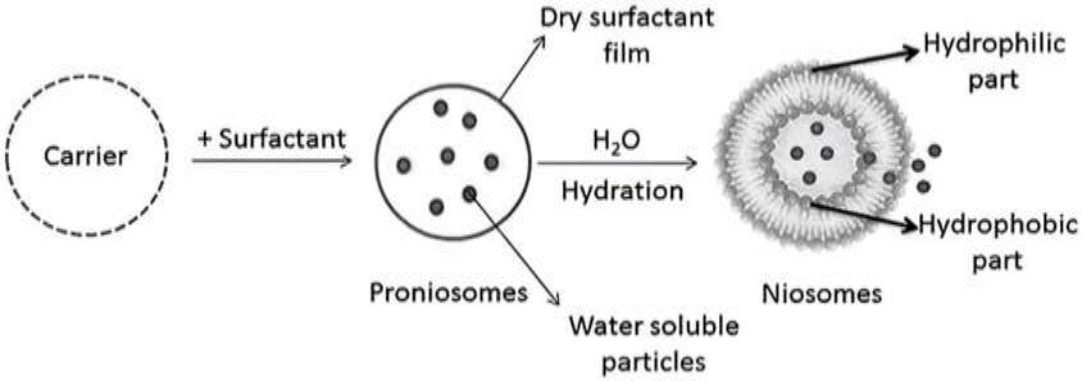

Fig no 13: niosomes from the proniosomes method

8. Bubble Method:

The Bubble Method for preparing niosomes involves introducing air bubbles into a mixture of surfactants and cholesterol in an aqueous solution. This technique takes advantage of the aeration provided by the bubbles to facilitate the formation of niosomes. The continuous agitation and collision of bubbles create shear forces that help in the dispersion of surfactants and promote the assembly of niosomal structures. The resulting niosomes can vary in size and encapsulation efficiency, depending on the parameters such as

surfactant concentration and the size of the air bubbles introduced[82].

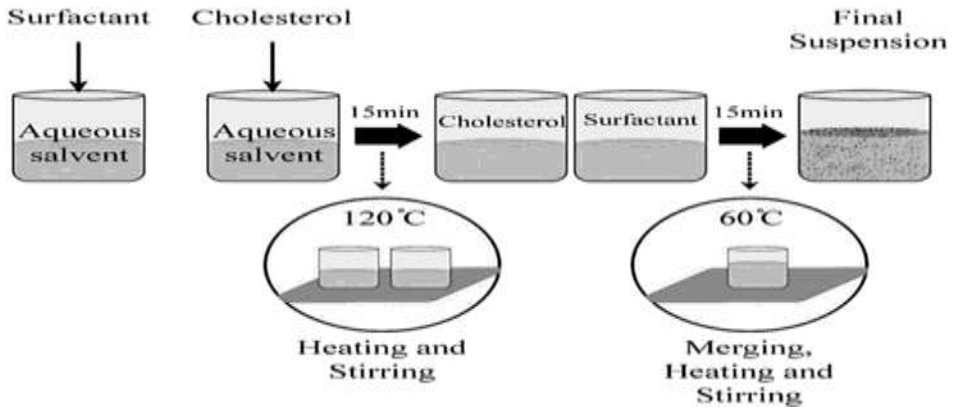

Fig no 14: Bubble Method

9. Freeze-Thawing Method:

The Freeze-Thawing Method for preparing niosomes involves alternating cycles of freezing and thawing the niosomal suspension. Initially, the niosomes are frozen at –20°C for a specified duration (typically 24 hours). Following this freezing period, the suspension can thaw back to ambient temperature. This process is usually repeated several times, which facilitates the fusion of niosomes and can increase vesicle diameter. The repeated freeze-thaw cycles help enhance the stability and uniformity of the niosomes. This method is appreciated for its simplicity and effectiveness in producing Niosomes with desired characteristics for drug delivery applications [83].

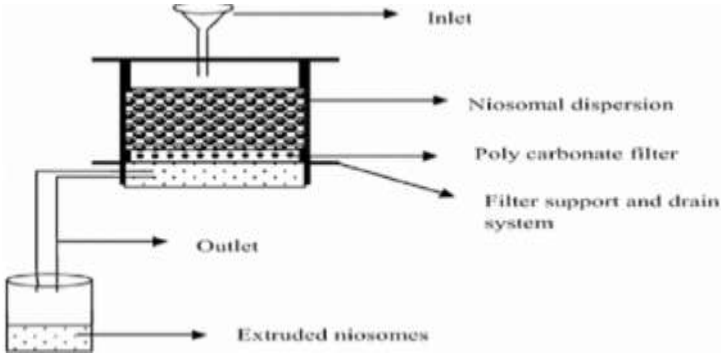

Fig. No 15: FREEZE THAWING METHOD

3.5 Evaluation of Niosomal Gel:

Table 8: Evaluation study for niosomal gel

Parameter	Purpose / Significance	Method / Technique	References
pH	Ensures skin compatibility	Digital pH meter	84
Viscosity	Determines consistency and ease of application	Brookfield viscometer	85
Spreadability	Assesses ease of spreading on skin	Glass plate/ slip & drag method	86,87
Homogeneity	Ensures uniform appearance and drug distribution	Visual inspection	88
Drug content uniformity	Confirms consistent drug distribution	UV–Vis spectrophotometry / HPLC	86

In vitro drug release	Evaluates release profile from gel	Franz diffusion cell	89
Ex vivo skin permeation	Assesses penetration and skin retention	Franz diffusion cell with excised skin	65
Stability studies	Assesses formulation stability over time	ICH stability conditions	90

3.6 Characterisation of Niosomal Gel:

Table 9: Characterisation studies of niosomal gel

Parameter	Purpose / Significance	Method / Instrument
Vesicle size & PDI	Determines uniformity, stability, and penetration ability	Dynamic light scattering (DLS)
Zeta potential	Indicates surface charge and predicts vesicle stability	Zeta potential analyser
Morphology	Confirms vesicular structure and shape	TEM / SEM / Optical microscopy
Entrapment efficiency	Measures drug encapsulation capacity	Centrifugation or dialysis + UV/HPLC
Drug–excipient compatibility	Detects interactions affecting stability	FTIR, DSC
Physical state of the drug	Determines crystalline or amorphous nature	XRD, DSC

3.7 Application of Niosomes in Cosmetics[91,75] :

1. Niosome as a Delivery System

Niosomes are widely used in topical and cosmeceutical formulations for the delivery of natural antioxidants such as resveratrol, curcumin, α-tocopherol, and mangostin. They enhance skin penetration and retention, improve the stability of sensitive compounds, and provide sustained drug release. These properties increase the effectiveness of antioxidants while reducing systemic exposure, making niosomes valuable in anti-ageing, photoprotective, and anti-inflammatory skincare applications

2. Niosomes as an Antioxidant and Whitening Delivery:

Niosomes enhance the topical delivery of antioxidants and whitening agents, such as ellagic acid, curcumin, resveratrol, and plant-derived oils, by improving skin penetration, retention, and stability. They offer controlled and biphasic release, prolonging therapeutic effects while protecting sensitive compounds from degradation. Niosomes also promote cellular uptake, increasing efficacy, making them highly suitable for cosmeceutical and dermatological applications.

3. Niosomes as an Anti-Scarring Delivery:

Elastic niosomes enhance the topical delivery of anti-scarring agents such as papain and gallic acid by improving dermal penetration, chemical stability, and therapeutic efficacy compared to conventional nanocarriers. Black tea extract, containing gallic acid and caffeine, was effectively delivered into the dermis via niosomes, demonstrating enhanced antioxidant and skin-protective effects. These findings highlight the potential of elastic niosomes as efficient carriers for anti-scarring and skin-repair formulations.

4. Niosomes as an Anti-Ageing Delivery:

Niosomes are effective carriers for anti-ageing compounds such as rice bran extract, morin, gallic

acid, and purple glutinous rice extract, enhancing skin penetration, stability, and bioavailability. By encapsulating these antioxidants and flavonoids, niosomes improve skin hydration, elasticity, pigmentation, and protection against oxidative stress, while providing controlled and sustained release. The synergistic effects of entrapped and unentrapped bioactives further enhance anti-ageing benefits, making niosomal formulations ideal for cosmetic and dermatological applications.

3.8 Challenges and Limitations of Niosomal Formulations[92,93] :

1. Stability Issues

Physical Instability: Niosomes are prone to aggregation and fusion over time, which can alter their vesicle size and reduce drug entrapment efficiency. For instance, transferosomes loaded with papaverine hydrochloride were observed to increase in size and show decreased entrapment when stored at higher temperatures. Interestingly, incorporating them into a gel system improved their stability over 30 days at 25 °C

Chemical Degradation: The non-ionic surfactants used to form niosomes can undergo oxidation or hydrolysis, compromising vesicle integrity. Nevertheless, niosomes are generally more resistant to chemical degradation compared to liposomes, which allows for relatively longer storage periods.

2. Drug Leakage

Premature Release: Encapsulated drugs may slowly leak from niosomes into the surrounding gel matrix over time. For example, doxycycline-loaded niosomal gels were reported to show drug leakage, exposing the free drug to light and causing degradation. This highlights the importance of designing more stable niosomal formulations to prevent premature drug release.

3. Formulation Challenges

Complex Preparation: Preparing niosomes involves multiple steps such as hydration, sonication, and size reduction. These procedures can be time-consuming and may introduce variability between batches.

Scalability Issues: Scaling up the production of niosomal gels remains difficult, which limits their commercial applicability.

4. Storage and Shelf Life

Temperature Sensitivity: Niosomes are sensitive to temperature fluctuations, which can negatively affect their stability. Maintaining proper storage conditions is essential to preserving their integrity over time.

FUTURE DIRECTIONS[94, 95, 96]

1. Smart and Stimuli-Responsive Niosomes

Future melasma management is likely to benefit from stimuli-responsive niosomes capable of releasing drugs in response to pH changes, temperature, enzymatic activity, or UV exposure specific to diseased skin. These smart systems can enable controlled and on-demand drug release, reducing prolonged exposure to depigmenting agents and minimising adverse effects, thereby improving long-term treatment safety and patient compliance.

2. Targeted Niosomal Systems

Targeted niosomal systems are being explored to achieve epidermal-selective drug delivery by modifying vesicle surfaces with ligands such as hyaluronic acid or peptides. Such ligands interact

with skin receptors like CD44, enhancing drug retention at melasma-affected sites while limiting deeper dermal penetration. This targeted approach may allow effective depigmentation at lower drug doses, reducing irritation and recurrence.

3.Combinatorial Nanocarrier Approaches

Combinatorial nanocarrier strategies, including niosomal gels, polymer-coated niosomes, and hybrid delivery systems, are emerging as advanced platforms for melasma therapy. Moreover, co-encapsulation of depigmenting agents with antioxidants or anti-inflammatory drugs within niosomes may address multiple pathogenic pathways simultaneously, potentially replacing aggressive multi-drug regimens.

4.Personalised Melasma Nanotherapy

Personalised nano therapy represents a future shift toward patient-specific melasma treatment, where niosomal formulations are tailored based on skin type, pigmentation depth, and disease severity. Optimization of vesicle size, surface charge, and drug loading may improve therapeutic outcomes and reduce relapse rates. Integration of dermal imaging and data-driven approaches could further support personalised niosomal treatment strategies.

CONCLUSION

Melasma is a chronic facial pigmentary disorder that carries a significant psychosocial burden, particularly due to its impact on appearance and quality of life. Although a variety of chemical and procedural treatment options are currently available, achieving consistent and long-lasting therapeutic outcomes remains challenging. In recent years, nanotechnology-based drug delivery systems have emerged as a promising strategy to enhance the physicochemical stability, skin penetration, and therapeutic efficacy of hypo pigmenting agents, enabling effective targeting of both epidermal and dermal melasma. While systemic therapies may occasionally serve as adjunctive treatment options due to their enhanced permeation, topical nanocarrier-based formulations are expected to remain the primary and most preferred approach for melasma management owing to their targeted action and improved safety pro

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