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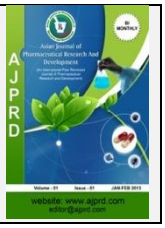

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Review Article

Niosomal Gel: A Promising Approach for Enhanced Topical Drug Delivery

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A B S T R A C T

This review highlights the formulation and evaluation of niosomal gels as an advanced strategy for topical drug delivery. Niosomes, vesicular systems composed of non-ionic surfactants, were developed and optimized based on critical parameters such as particle size, entrapment efficiency, and formulation stability. These optimized vesicles were then incorporated into a suitable gel base for effective dermal application. The resulting niosomal gel was systematically evaluated for physicochemical properties including pH, viscosity, spreadability, and drug content uniformity. Ex vivo skin permeation studies revealed significantly enhanced drug penetration compared to conventional gel formulations, while in vivo assessments demonstrated improved therapeutic outcomes and prolonged anti-inflammatory effects. Overall, niosomal gel systems offer a promising, controlled, and targeted approach to enhance the efficacy and patient compliance in topical drug delivery.

Keywords: Niosomal gel, topical drug delivery, vesicular system, formulation, controlled release, skin permeation.

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INTRODUCTION

Topical drug delivery refers to the application of pharmaceutical agents directly onto the skin to achieve localized therapeutic effects. The skin, being the largest and most accessible organ of the body, covers an average surface area of approximately 2 square meters in adults and receives about one-third of the total circulating blood. It plays a crucial role in thermoregulation, blood pressure control, and protection against environmental hazards, including ultraviolet (UV) radiation.(1)

Topical drug delivery offers several advantages, such as prolonged drug action, avoidance of first-pass metabolism, improved patient compliance, and reduced systemic side effects. However, it also presents limitations, including potential local irritation, erythema, itching, and low permeability of drugs through the stratum corneum—the outermost layer of the epidermis. This layer, composed of dead keratinized cells called corneocytes, acts as a tough, water-impermeable barrier. (2)

To overcome these challenges, various technologies have been explored to enhance drug permeation through the skin. Among them, vesicular carriers such as liposomes, transfersomes, ethosomes, and niosomes have emerged as promising tools. These systems, both lipid-based and non-lipid-based, offer improved drug stability, targeted delivery, and enhanced penetration, making them suitable alternatives to conventional topical formulations.(3)

Drug delivery systems using a novel vesicular carrier, such as liposome or niosome, have distinct advantages over microspheres, nanoparticles, and other carriers in terms of better entrapment of drugs (payload characteristics), target site specificity, and handling premature drug release (burst e etc). In 1985, niosomes were studied as an alternative to liposomes because they had some benefits over liposomes such as being more stable, nontoxic, and economical due to

the low cost of nonionicsurfactants as compared to phospholipids which are prone to oxidation. The incorporation of surfactants within niosomes may also enhance the efficacy of the drug, possibly by facilitating its uptake by the target cells. Niosomes are biodegradable, biocompatible, relatively nontoxic, and an alternative toliposomes. They can be utilized in the delivery of a wide variety of drugs as it can entrap hydrophilic, lipophilic, and amphiphilic drugs. For the transdermal route of administration, NSAIDs, hormones, antibacterial, and antifungal drugs are most preferably used [4]

SKIN

Skin is the body's largest organ, with a total area of about 20 square feet. It has several functions, the most important being a physical hedge between the body and the clime. Skin is a complex subcaste compound of several tissues forming a wall between our physical body and the outside climate. Still, this wall remains open to the environment. The skin has three layers: epidermis, dermis, and subcutaneous (hypodermis). [5]

The skin also

- Regulates body temperature
- Store water & fat
- Is a sensory organ
- Prevent water loss
- Prevent entry of bacteria
- Helps to make Vit. D when exposed to the sun.

There are three structural layers of the skin. The epidermis, the dermis & hypodermis/ subcutis. The epidermis is the outer layer, serving as the physical and chemical barrier between the interior body & exterior environment. The dermis is the deeper layer providing the structural support to the skin, while the subcutis or hypodermis a loose connective tissue layer is an important depot of fat.[5]

SKIN ANATOMY

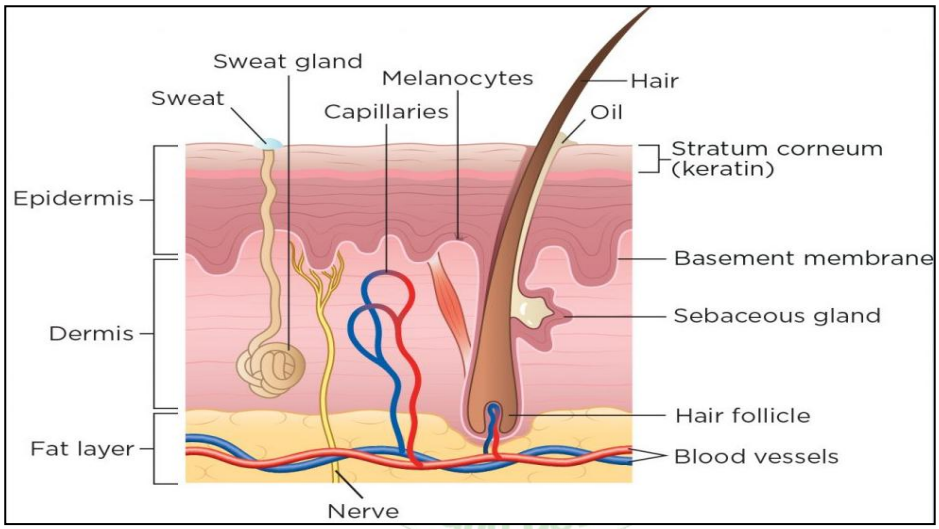

Figure 1: Skin

- **Epidermis** The epidermis is the outermost layer of the skin, serving as a waterproof, protective barrier and regulating body temperature. It contains no blood vessels and is nourished by oxygen from the surrounding air. The main cell types in the epidermis are keratinocytes, melanocytes, Langerhans cells, and Merkel's cells.[6]

  The epidermis contains 5 layers:

  1. Stratum basale
  2. Stratum spinosum
  3. Stratum Granulosum
  4. Stratum lucidum
  5. Stratum corneum

- **Dermis**: The dermis is the layer of skin beneath the epidermis that consists of epithelial tissue &cushions the body from stress & strain. It contains the hair follicles, sweat glands, sebaceous glands, apocrine gland, lymphatic vessels & blood vessels. The dermis is structurally divided into areas: A superficial area adjacent to the epidermis called the papillary region & a deeper thicker area known as the reticular region.
- **Hypodermis**: The Hypodermis tissue is a layer of fat & connective tissue containing larger blood vessels & nerves. This layer regulates the temperature of the skin & the body. The size of this layer varies throughout the body & also in individual specialized cells in the Hypodermis are:- Various cells like keratinocytes, Langerhans cells, melanocytes,Merkel cells, fibroblasts, sebaceous gland & sweat glands are present in this layer of skin.[6]

Niosomes

Niosomes are vesicles composed of non-ionic surface-active agent bilayers, which serve as new drug delivery systems.Niosomes are tiny and their size lies in the nanometric scale.Niosomes are formed on the combination of a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with posterior hydration in waterless media [5].Niosomes may be unilamellar or multilamellar depending on the system used to prepare those

[6].The niosome is made of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer.Hence, the vesicle holds hydrophilic medicines within the space enclosed in the vesicle, while the hydrophobic medicines are embedded within the bilayer itself.The operation of niosomal technology is extensively varied and can be used to treat several disorders. [7]

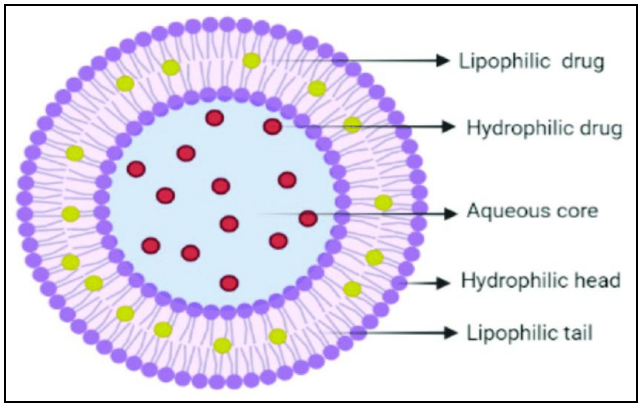

Figure 2: Noisome

Characteristics of Niosomes[8-9]

- Niosomes can entrap solutes like liposomes
- Niosomes are a bibulous supporter, active, and stable
- Niosomes retain an infrastructureconsisting of hydrophobic and hydrophilic substantially together and also accommodate the medicine molecules with a wide range of solubility.
- Niosomes have inflexibility in their structural characteristics (composition, fluidity, and size) and can be designed according to the demanded situation.
- Niosomes may also ameliorate the performance of the medicine molecules
- Better vacuum to the particular point of administration by guarding the medicine from the natural terrain. Niosomes surfactants are biocompatible and non-immunogenic.

ADVANTAGES OF NIOSOMES [10]

The niosomal drug delivery is an implicit drug delivery system for controlled and targeted drug delivery.The major advantages of these vesicular drug carriers are;

- Niosomal dissipation in a waterless phase can be emulsified in a non-aqueous phase to regulate the delivery rate of the medicine and administer normal vesicles in an external non-aqueous phase.
- The vesicle suspension is a water-grounded vehicle. This offers high case compliance in comparison with unctuous lozenge forms.
- They're osmotically active and stable, as well as they increase the stability of caught-up drugs.
- The administration and storehouse of surfactants require no special conditions.
- They ameliorate the oral bioavailability of inadequately absorbed medicines and enhance the skin penetration of medicines.
- They can be made to reach the point of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible, and non-immunogenic.
- They ameliorate the remedial performance of the medicine motes by delaying concurrence from rotation, guarding the medicine from the natural terrain, and confining goods on target cells.
- Niosomal dissipation in a waterless phase can be emulsified in a non-aqueous phase to regulate the delivery rate of the medicine and administer normal vesicles in the external non-aqueous phase.
- Niosomes retain a structure consisting of hydrophilic, amphiphilic, and lipophilic halves, and as a result, they can accommodate medicine molecules with a wide range of solubility.
- The characteristics of the vesicle expression are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, face charge, and attention can control the vesicle characteristics.
- The vesicles may act as a depot, releasing the medicine in a controlled manner.
- They enhance the remedial performance of the medicine most by delayed concurrence from the rotation, guarding the medicine from the natural terrain, and confining the medicine to the target cells.

Application of Niosomes

Niosomes have been successfully used in drug-targetingorgans such as skin, brain, liver, lung, ocular systems, tumour organs, etc. Niosomes show a higher bioavailability than conventional dosage forms [11]. Controlled and sustained release of drugs has been achieved by niosomes[12]. Permeation of drugs through the skin has been enhanced by niosomes. Niosome improves the stratum corneum properties both by reducing transepidermal water loss and by increasing smoothness via reloading lost skin lipids. Niosomes can be applied for drug protection from biological enzymes and acids, thereby increasing drug stability. [13]

NiosomesIn Comparison with Liposomes

Drug delivery systems using vesicular carriers such as liposomes and niosomes have distinct advantages over conventional dosage forms because the vesicles can act as drug-containing reservoirs. Modifying vesicle composition or surface can adjust the affinity for the target site, and not the drug release rate, and the slowed drug release rate may reduce the drug's toxicity. Hence, these carriers play an increasing vesicles wherein an aqueous phase is encapsulated in a highly ordered bilayer made up of non-ionic surfactant (niosomes) or lipid (liposomes) with or without other components like cholesterol and diacetyl phosphate.

Both niosomes and liposomes show desired interaction with human skin when applied through topical preparation by improving especially the horny layer characteristics, which in turn due to a reduction in transdermal water loss and an increase in smoothness via replenishing skin lipids. Although niosomes and liposomes possess more or less the same advantage, niosomes were preferred due to the high cost and

lower stability of lipids which non-ionic surfactants have replaced. Niosomes loaded with drugs for dermal applications show interactions with epidermal tissue without exerting immediate or strong systemic action.

Niosomes and liposomes have analogous operations in drug delivery but chemically differ in structural units. Niosomes consist of nonionic surfactant, whereas liposomes comprise phospholipids [14]. They're functionally the same, have the same physical parcels, and act as amphiphilic vesicles. Both can be used in targeted and sustained drug delivery systems. The property of both depends upon the composition of the bilayer and the styles of their medication. Studies have also shown that the function of niosomes in vivo is analogous to that of liposomes. Despite these similar characteristics, niosomes offer several advantages over liposomes natural skin penetration-enhancing parcels, advanced chemical stability, and lower costs. Both of the last features make the niosome more seductive for artificial manufacturing rings. Also, niosomes don't demand special conditions such as low temperature or inert atmosphere during preparation and storage [15]. Although the niosome shows better chemical stability, the physical insecurity during dissipation may be similar to that of the liposome. Both niosomes and liposomes are at risk of aggregation, emulsion, medicine leakage, or hydrolysis of trapped medicines during storage. Still, liposomes show better nontoxic biographies due to their analogous epidermal composition. [16]

Table 1: Niosomes In Comparison With Liposomes

	Niosomes	**Liposomes**
Components	Surfactant	Phospholipids
Components availability	High	Low
Components purity	Good	Variable
Preparation and storage	No special condition required	Inert atmosphere and low temperature
Stability	Very good	Low
Cost	Low	High

Gel

Gels are in a semisolid dosage form. Gels are formed by using synthetic polymers such as carbomer 934 and cellulose, such as hydroxypropyl cellulose and hydroxypropyl methylcellulose.[17]

Topical gels are topical drug delivery dosage forms commonly used in cosmetics and treatments for skin diseases because of their advantages over cream and ointment Gels refer to thick liquid or semi-solid preparations in which drugs and gel-forming excipients are made into solutions, suspensions, or emulsions. The gel is usually limited to topical application to the skin and body cavities (such as the nasal cavity, vagina, and rectum). [18]

FORMULATION OF NIOSOMES

The preparation methods should be chosen according to the use of the niosomes since the preparation methods influence the number of bilayers, size, size distribution, and entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

Ether injection method[19]

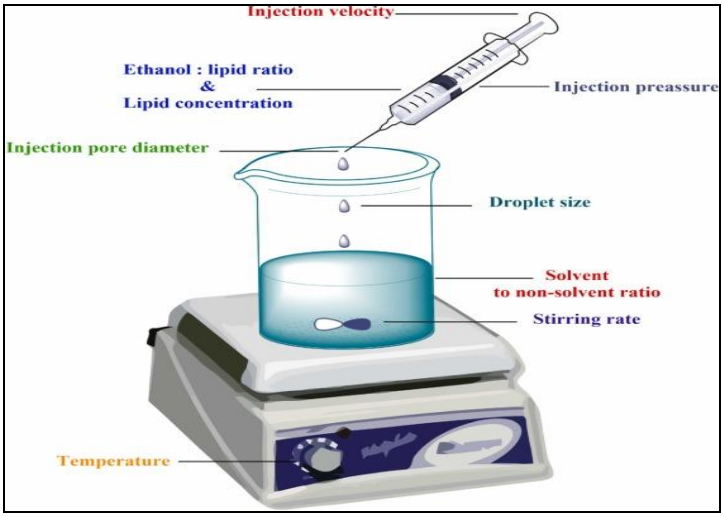

Figure 3: Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through a 14-gauge needle into an aqueous

solution of material. Vaporization of ether leads to the formation of single-layered vesicles. Depending upon the conditions used, the diameter of the vesicle ranges from 50 to 1000 nm (Mayer et al., 1985).

A. Handshaking method (Thin film hydration technique)[20]

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform, or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using a rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

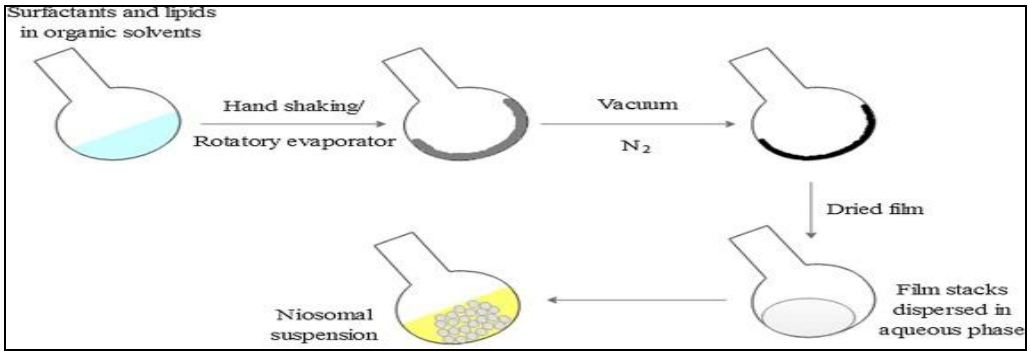

Figure 4: Thin film hydration technique

B. Sonication [22]

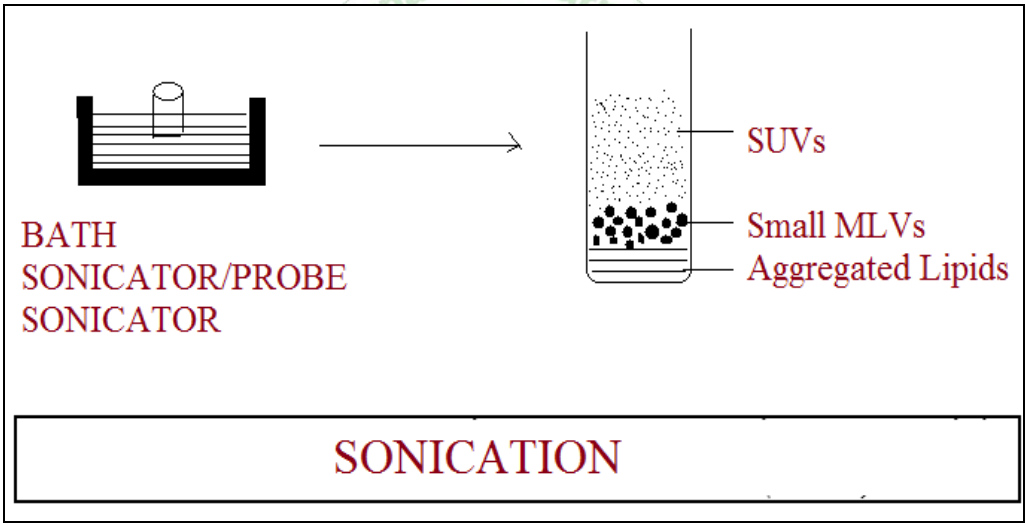

Figure 5: Sonication

A typical method of production of the vesicles is by sonication of solution as described by Cable. In this method, an aliquot of drug solution in the buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes (Baillie et al., 1986).

C. Micro fluidization [23]

It is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on the submerged jet principle in which two fluidized streams interact at ultra-high velocities, in precisely defined micro channels within the interaction chamber. The impingement of a thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size, and better reproducibility of niosomes formed (Mayer et al., 1985).

D. Multiple membrane extrusion method[24]

A mixture of surfactant, cholesterol, and diacetyl phosphate in chloroform is made into a thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution, and the resultant suspension is extruded through which isthen placed in series for up to 8 passages. It is a good method for controlling niosome size (Mayer et al., 1985). F. Reverse Phase Evaporation Technique (REV) Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing the drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate-buffered saline (PBS). The organic phase is removed at 40°C under low

pressure. The resulting viscous niosome suspension is diluted with PBS and heated in a water bath at 60°C for 10 min to yield niosomes (Raja et al., 1994). Raja Naresh et al. have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

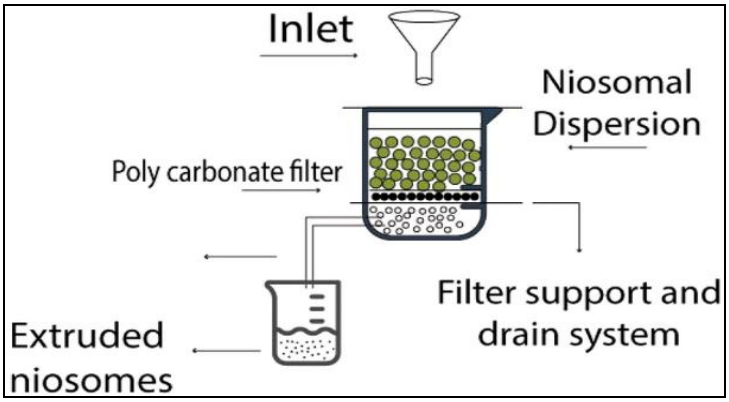

Figure 6: Multiple membrane extrusion method

E. TransmembranepH gradient (inside acidic) [25-27]

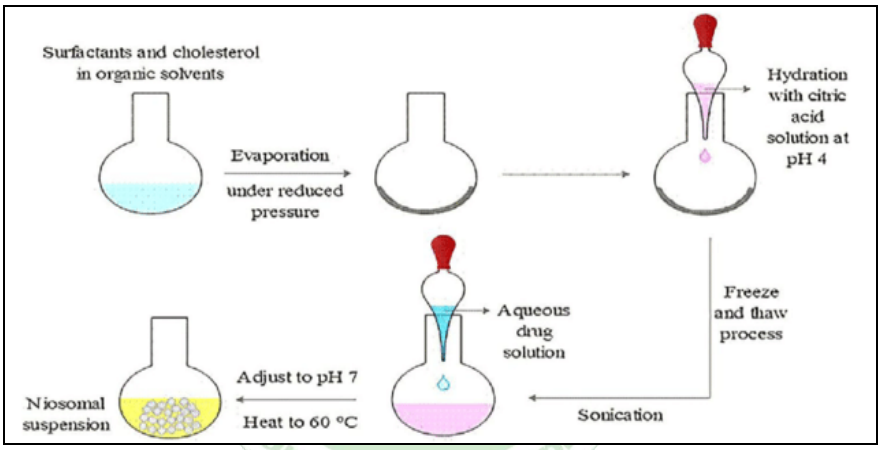

Figure 7: Tran's membrane pH gradient (inside acidic)

Drug Uptake Process (remote Loading) Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mm citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, an aqueous solution containing 10 mg/ml of the drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.

F. The "Bubble" Method [28-30]

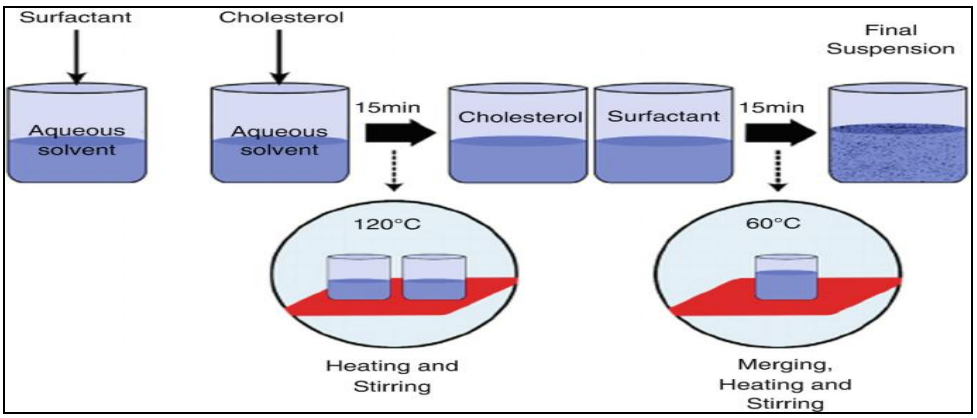

Figure 8: The "Bubble" Method

It is a novel technique for the one-step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of a round-bottomed flask with three necks positioned in a water bath to control the temperature. Water-cooled reflux and thermometer are positioned in the first and second necks, and nitrogen supply is through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion is mixed for 15 seconds with a high shear homogenizer, and immediately afterward "bubbled" at 70°C using nitrogen gas.

Niosomes-Based Gel

According to the results of the characterization of drug-loaded niosomes, niosomes coded as NS3 were chosen to be integrated into a gel dosage form. In the first step, the plain gel was prepared by incorporating 1 g Carbopol 934 in 100 mL distilled water at 50°C through continuous stirring at 450 rpm using a homogenizer (Eurostar, IKA-D-230,and Germany). Methyl paraben and propyl paraben were added in small quantities (0.02%) as preservatives to the gel. The NS3 formulation equivalent to 20 mg of fusidic acid was mixed thoroughly with the above-mentioned Carbopol gel. Then it was allowed to swell for 24 hours. Finally, a weighed quantity of triethanolamine was added as a neutralizer to increase the pH to 6.4 of the prepared Carbopol 940 mixture, and the formation of gel occurred.

EVALUATION OF NIOSOMES

Characterization of drug-loaded niosomes

Micromeretics

The mean particle size of the developed nanocarriers was determined using Zeta-Sizer. The mean value of three repeated measurements for each sample was reported as the final measurement [24].

Optical microscopy

The prepared niosomal vesicles were characterized for morphology, i.e., shape uniformity and lamellarity, employing a phase contrast microscope [24]. Transmission electron microscopy (TEM). The suspension was negatively stained with a 1% aqueous solution of phosphotungsticacid and dried on a microscopic carbon-coated grid, viewed and photographed under the TEM at suitable magnification(s) [31]

Percent entrapment efficiency (% EE)

% EE was determined in triplicate by centrifugation method. The niosomal suspension was centrifuged (M/s REMI CPR 24) at 10000 rpm at 4C for 10 min. Clear supernatant as well as the vesicular sediment after lysing with n-propanol was assayed for the drug content. The appropriate dilutions were made and analyzed by U.V spectrophotometer (M/s Systronics-Model-2202) at 288 nm % EE of the drug was calculated using the following equation:

$$\% EE = \frac{\text{Total Drug} - \text{free drug}}{\text{Total Drug}} * 100$$

Where T is the total amount of drug that is detected both in the supernatant and sediment, and C is the amount of drug detected only in the supernatant [32-36]

Sedimentation volume

The niosomal suspensions prepared from both TFH and EIM were kept in a 10 mL measuring cylinder. after 24 h, the volume of sedimentation was observed.[35]

In-vitro release

A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method (Parthasarthy et al., 1994). [42]

Characterization of drug-loaded niosomal gel

The prepared resveratrol-entrapped niosomal gel was characterised for its various attributes, includingcolour, odour, homogeneity, and pH. Approximately 2 g of gel was accurately weighed and dispersed in 20 mL of distilled water. The pH of the dispersion was measured by using a digital pH meter.

Evaluation Studies of Gel Physical Appearance: Clarity, colour, homogeneity, and the presence of foreign particles in the niosomal gel were determined.

Determination of pH: Weighed 1 g of gel formulation was transferred toa 100 ml beaker and measured using the digital pH meter. pH of the topical gel formulation should be between 3 – 9 to treat the skin infections. [45]

Spreadability: The spreadability of the gel formulation was determined by measuring the diameter of 1gof gel between horizontal plates (20×20 cm2) after 1 minute. The standardized weight tied to the upper plate was 125 g. Viscosity Brookfield viscometer was used to determine the viscosity of the niosomal gel. [45-46]

Drug content: Weighed 10 g of each gel formulation was transferred toa 250 ml volumetric flask containing 20 ml of alcohol and stirred for 30 min. The volume was made up to 100 ml and filtered. 1 ml of the above solution was further diluted to 10 ml with alcohol, and again, 1 ml of the above solution was further diluted to 10 ml with alcohol. The absorbance of the solution was measured spectrophotometrically at 226 nm. Drug content was calculated by the following formula. [52]

$$\text{Drug content} = \text{Dilution factor} \times \text{Absorbance/slope} * 1/1000$$

Table 2: Methods of preparation with various Non-ionic surfactants ad stabilizer with its application

Drug	Method	Surfactant	Application	Reference
Clarithromycin	Thin film-hydration technique	Span 60, Cholesterol, dicetylphosphare (DCP)	To treat Bacterial infections	69
Folic acid	Lipid layer hydration method	Span 60, Cholesterol	Anaemia	70
Ketoprofen	Thin film-hydration method an Ether injection method	Tween 40, Cholesterol	Nonsteroidal anti-inflammatory drugs (NSAID); Inhibiting synthesis of prostaglandin. Analgesic and antipyretic effects.	71
Candesartan	Sonication method	Span 60, Cholesterol, dicetylphosphare (DCP), stearylamine (SA)	Angiotensin II receptor antagonist; Hypertension	72
Diltizem	Thin film-hydration technique	Span 60, Cholesterol	Calcium channel blocker; hypertension, angina pectoris, and some types of arrhythmia	73
Ketorolac tromethamine	Thin film-hydration technique	Span 60, Cholesterol, solulan C	NSAID; To treat metabolic acidosis	74
Tenofovir	Thin film-hydration technique	Span 60, Cholesterol, dicetylphosphare (DCP)	To treat chronic (long term) HBV	75
Diacerein	Thin film-hydration technique	Span 60, Cholesterol	Inhibiting interleukin-1 beta; Osteoarthritis	76
Griseofulvin	Lipid layer hydration method, an Ether injection method	Span 60, Cholesterol, dicetylphosphare (DCP),	To treat skin infections	77
Zidovudine	Thin film-hydration technique	Tween 80, Cholesterol, dicetylphosphare (DCP),	NRTIs: Nucleoside reverse transcriptase inhibitors, to prevent passing the HIV to the unborn baby in pregnant women	78
Loratadine	Lipid film-hydration method	Span 60, Cholesterol	Antihistamine; Allergies	79
Acyclovir	Thin film-hydration technique	Span 60, Span 80, Cholesterol	Anti-viral infections	80

CONCLUSION

Delivery of drugs to the target region of the skin is a great challenge in terms of the therapeutic aspect. In this context, formulation of topical product Niosomal gel plays a key role in the penetration of the drugs across the skin. Besides, the physicochemical properties of drug molecules, such as lipophilicity, are also an effective parameter. Generally, topical drugs are highly lipophilic compounds, which can affect the penetration of drugs across the stratum corneum. Niosomal gel drug delivery is very useful in the treatment of superficial and systemic. Niosomal gel can be topical application applied topically by ocular and topical routes. Niosomalgel can be applied by the ocular, topical route. Niosomalgel has prolonged retention and enhanced penetration, and that will automatically improve therapeutic properties. Niosomal gel will be used for the treatment of eye diseases and fungal infections. Various formulation strategies have emerged over recent years to optimize new drug delivery carriers of antifungal drugs.

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