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"Niosomal Delivery of Herbal Bioactives: A Review on Medicinal Plants Possessing Antibacterial Activity"

Pradeep Kumar Verma*, V.P Gupta, Suraj Singh, Gopesh Gunjan
Student- Globus College of Pharmacy, located in Bangrasia, Bhopal (M.P)
Professor & Principal- Globus College of Pharmacy, located in Bangrasia, Bhopal, (M.P)
Assistant Professor - Globus College of Pharmacy, located in Bangrasia, Bhopal, (M.P)
, *Assistant Professor - Globus College of Pharmacy, located in Bangrasia, Bhopal (M.P)*

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ABSTRACT
In recent years, lipid-based vesicular systems such as niosomes have emerged as promising nanocarriers for improving the therapeutic efficacy and bioavailability of herbal bioactives. Waltheria indica (Family: Malvaceae) is a medicinal plant traditionally used for its antimicrobial, anti-inflammatory, antioxidant, and wound-healing properties. However, poor solubility and stability of its phytoconstituents often limit its pharmacological potential. This review focuses on the formulation, development, and optimization of a niosomal drug delivery system encapsulating Waltheria indica extract to enhance its antibacterial efficacy. The review also explores the plant's phytochemical profile, mechanism of antibacterial action, and the role of niosomalnanocarriers in improving targeted delivery, controlled release, and therapeutic outcomes. Overall, niosome-based encapsulation of W. indica extract presents a novel and efficient approach for developing natural antimicrobial formulations with improved stability, bioavailability, and clinical potential.

Keywords: Waltheria indica, niosomes, lipid-based vesicular systems, nanocarrier, antibacterial activity, phytochemicals, formulation optimization.

I. INTRODUCTION

Nanotechnology is one of the most promising technologies of the 21st century and offers opportunities in all areas of scientific research, such as medicine, pharmaceutical and cosmetic sciences, medical chemistry, bioengineering, genetic engineering, and food technology **(Mazayenet al., 2022).**Engineering, life sciences, and technology of designing, fabricating, and applying systems at the nanoscale (range between 1 and 100 nm), known as nanotechnology, are emerging topics worldwide in this multidisciplinary research field **(Baydaet al., 2019).**

Currently, the aim is to integrate biotechnology and nanotechnology, thus offering a technology based on green chemistry, being ecological for the production, characterization, and application of nanomaterials**(Soniet al., 2022).**Typical examples include gold and silver nanoparticles, nano-vesicle systems, solid lipid nanoparticles, nanostructured lipid carriers, nano-micelles, dendrimers, polymeric nanoparticles, mesoporous silica nanoparticles, etc. In addition, using interdisciplinary approaches, the results of biotechnology, nanomaterials, pharmaceutical science, artificial intelligence, and genetic engineering can be applied in the field of healthcare systems, known as nanomedicine**(Mbungeet al., 2021).**

Researchers are focusing their attention on the development of new nano-systems that control the release of various molecules with biological activity, in addition to the development of nanomaterials. Nanocarriers and innovative pharmaceutical formulations play a significant role in improving the bioavailability of drugs or natural molecules, with a particular enrichment at the target site **(Alshawwaet al., 2022).**

II. NIOSOMES

Niosomes, the most recently developed vesicular system with an extraordinary range of applications, are bilayer structures formed by amphiphilic non-ionic surfactants and lipidic components (mostly cholesterol). They are more stable than liposomes and have the ability to encapsulate hydrophilic and lipophilic molecules with biological activity**(Paliwalet al., 2022).**

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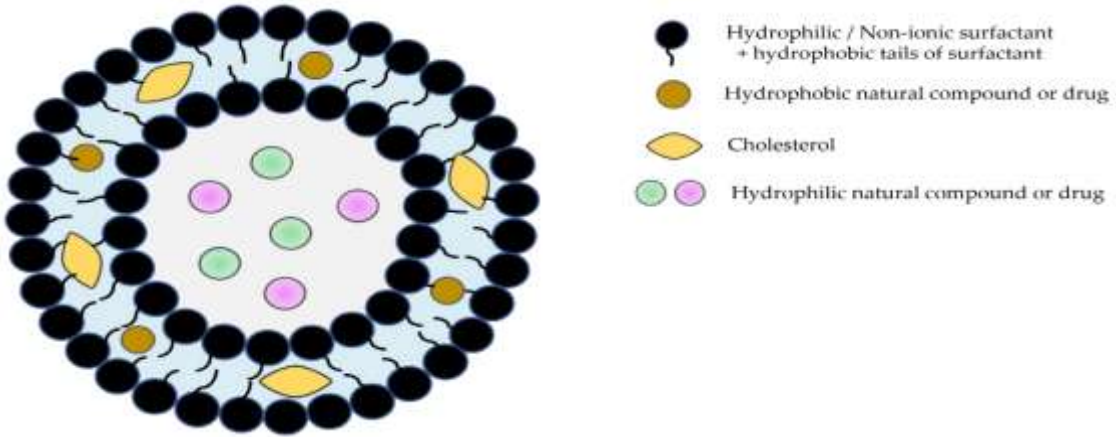

Figure 1. Schematic representation of niosomes.

The first niosome formulations were patented in 1975 by researchers from L'Oréal (France) for cosmetic applications. Since that, numerous scientific articles have been published due to the extensive investigation of niosomes in various fields, including pharmaceutical, cosmetic, and food science industries**(Marianecciet al., 2014).** Given the immense potential in delivery systems, there is a growing interest in comparing the benefits of niosomes entrapment with those of liposomes. However, only a few studies have moved toward pre-clinical and clinical trials, most being focused on topical delivery in the cosmetic field because, compared to liposomes, niosome formulations have showed superior skin permeation potential and higher stability **(Sguizzatoet al., 2021).**

III. STRUCTURAL COMPONENTS OF NIOSOMES

3.1 Surfactants

A wide range of surfactants and their combinations in different molar ratios have been used to entrap many drugs in niosomes of varying features such as size.

3.2 Ether linked surfactants

These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic moieties are linked with ether. The general formula of this group is (CnEOm), where n can be 12-18 and m can be 3-7. Surfactants with polyhydroxyl head and ethylene oxide units are also reported to be used in niosomes formation. Single alkyl chain surfactant C16 mono alkyl glycerol ether with an average of three glycerol units is one of the examples of this class of surfactants used for the preparation of niosomes**(Das et al., 2024).**

3.3Ester linked surfactants

These surfactants have ester linkage between hydrophilic and hydrophobic groups and have been studied for its use in the preparation and delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis**(Miretet al., 2021).**

3.4 Sorbitan Esters

These are most widely used ester linked surfactants especially in food industry. The commercial sorbitan esters are mixtures of the partial esters of sorbital and its mono and di-anhydrides with oleic acid. These have been used to entrap wide range of drugs viz doxorubicin **(VM et al., 2018).**

3.5Alkyl Amides

These are alkyl galactosides and glucosides which have incorporated amino acid spacers. The alkyl groups are fully or partially saturated C12 to C22 hydrocarbons and some novel amide compounds have fluorocarbon chains **(Tsagogiorgas and Otto 2023).**

3.6 Fatty Acids and Amino Acid Compounds

These are amino acids which are made amphiphilic by addition of hydrophobic alkyl side chains and long chain fatty acids which form "Ufasomes" vesicles formed from fatty acid bilayers**(Arundhasreeet al., 2021).**

3.7Cholesterol

Steroids bring about changes in fluidity and permeability of the bilayer and are thus important components. Cholesterol a waxy steroid metabolite is usually added to the non-ionic

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surfactants to provide rigidity and orientational order. It does not form the bilayer itself and can be incorporated in large molar ratios. Cholesterol is an amphiphilic molecule; it orients its OH group towards aqueous phase and aliphatic chain towards surfactant's hydrocarbon chain. Rigidization is provided by alternative positioning of rigid steroidal skeleton with surfactant molecules in the bilayer by restricting the movement of carbons of hydrocarbon. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition **(Debnath and Kumar 2015).**

3.8Charge Inducers

Charge inducers increase the stability of the vesicles by induction of charge on the surface of the prepared vesicles. It act by preventing the fusion of vesicles due to repulsive forces of the same charge and provide higher values of zeta potential. The commonly used negative charge inducers are dicetyl phosphate, dihexadecyl phosphate and lipoamine acid and positive charge inducers are sterylamine and cetylpyridinium chloride **(Khan and Irchhaiya 2016).**

IV. ADVANTAGES OF NIOSOMES

- Improved stability of entrapped herbal actives
- Controlled and sustained release of bioactives
- Enhanced skin penetration for topical formulations
- Biodegradable, biocompatible, and non-immunogenic
- Cost-effective compared to liposomes
- Capability to encapsulate both hydrophilic and lipophilic compounds**(Mahomoodallyet al., 2021).**

V. CLASSIFICATION AND FORMULATION TECHNIQUES OF NIOSOMES

5.1Micro-Fluidization Technique

This technique follows the principle of submerged jet to obtain small and uniform unilamellarniosomes. The two streams (aqueous phase and lipid dispersed phase) are forced to go to the membrane + pressurized vessel at very high pressure and high velocity through pneumatic pumps, where they collide**(Fenske and Cullis 2016).**The membrane + pressurized vessel is a continuous micro-channel that is responsible for turbulent mixing, creating a homogeneous pressure profile under very high pressure, which is necessary to achieve a narrow size and distribution of niosomes. The advantages of this technique include greater uniformity, smaller size, highest aqueous phase encapsulation, and high production rates. Degradation of the lipid phase is a potential negative effect of the high pressure in the interaction chamber **(Obeid et al., 2023).**

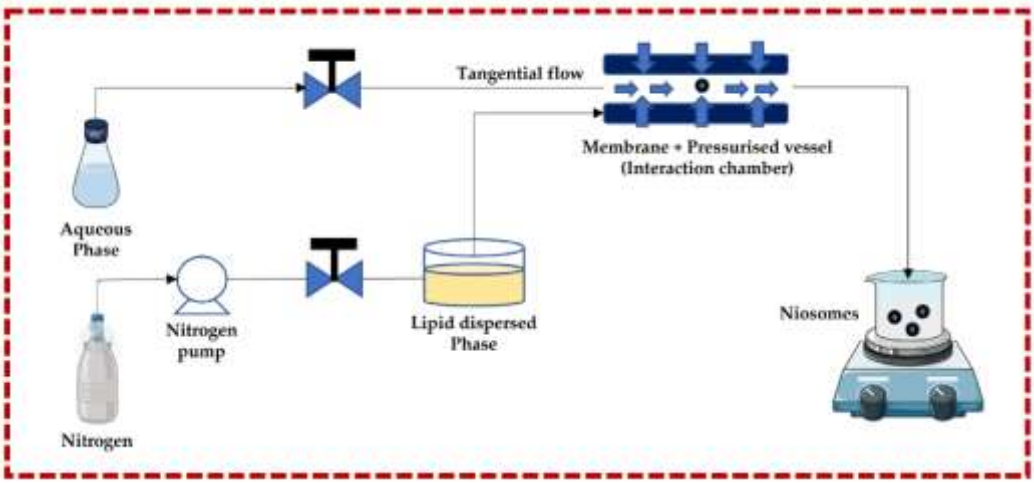

Figure 2:- Micro-Fluidization Technique

5.2 Sonication Technique

In this technique, cholesterol and a non-ionic surfactant are dispersed in a buffer solution containing the dissolved drug or natural compound. This mixture is further subjected to a bath sonicator to yield niosomes. Rapid size reduction and accurate temperature regulation are both advantages, but heat generation could be the main disadvantage **(Radmardet al., 2021).**

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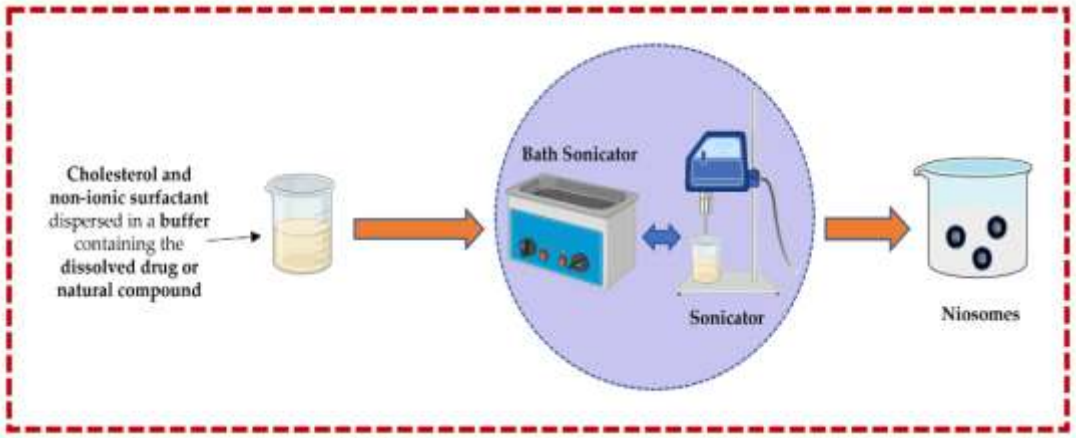

Figure 3:-Sonication Technique

5.3 Multiple Membrane Extrusion Technique

This technique allows for the size of niosomes to be controlled. Surfactant, cholesterol, and diacetyl phosphate are dissolved in an organic solvent (e.g., chloroform), and then the solvent is removed by rotary evaporation to form a thin-film which is subsequently hydrated by using an aqueous solution containing the drug or natural molecule. The suspension is extruded through polycarbonate membranes to obtain the niosomes. Improved control of the niosomes size and the resulting reduction in the polydispersity are important advantages. However, there are also disadvantages, such as increased product loss and extended formulation time **(Moghtaderiet al., 2022).**

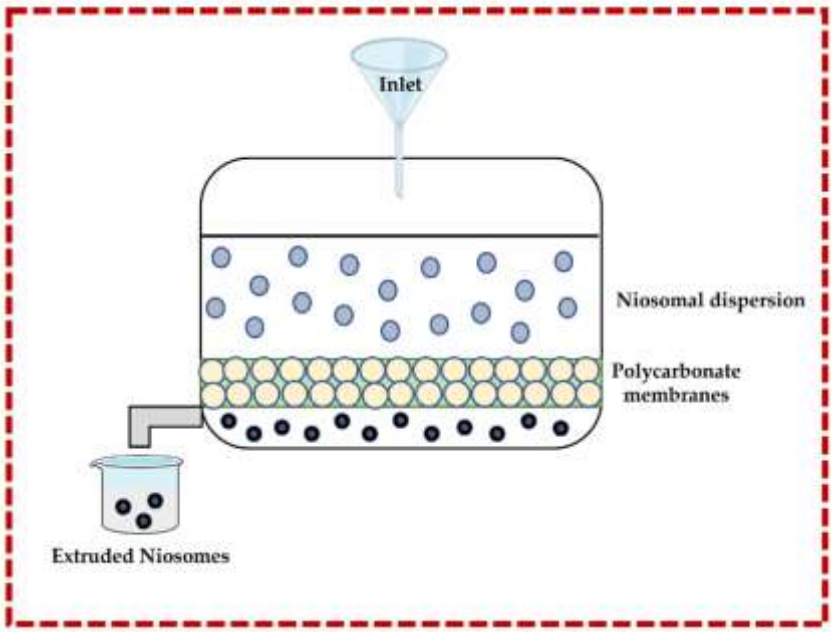

Figure 4:- Multiple Membrane Extrusion Technique

5.4 Ether Injection Technique

In this method, the lipidic component (cholesterol) and non-ionic surfactant are dissolved in ether and slowly injected through a needle into the aqueous phase containing a drug or natural molecule under stirring at a temperature above 60 °C in a heated water bath. The disadvantages include the extremely slow process and the presence of a limited amount of ether in the vesicle suspension **(Durga and Veera 2020).**

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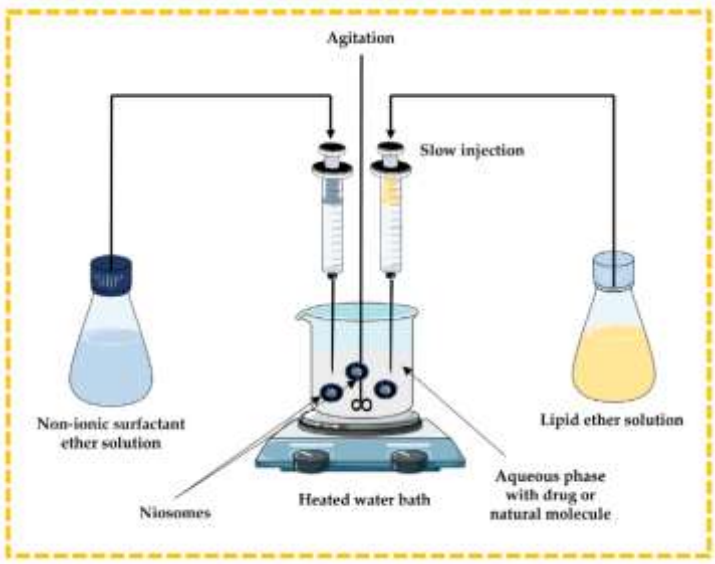

Figure 5:- Ether Injection Technique

5.5 Lipid Injection Technique

There are no organic solvents involved in this technique. Molten surfactant and cholesterol are quickly injected into a heated aqueous phase containing the dissolved drug or natural molecules, resulting in the formation of noisome **(Izharet al., 2023).**

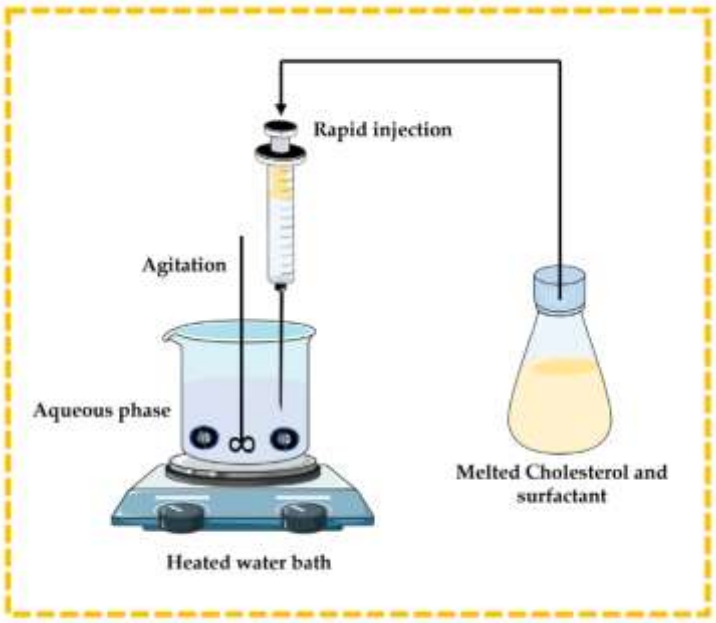

Figure 6:- Lipid Injection Techn

5.6 Bubble Technique

This is a unique single-step process used to prepare niosomes, especially to develop large unilamellar vesicles, without using any organic solvent. Cholesterol, buffer solution, and non-ionic surfactant are mixed and placed in a three-neck round bottom flask. The temperature is controlled using a thermometer and water-cooled reflux, while nitrogen is supplied from the third neck. The dispersion is introduced into a water bath at 70 °C to yield niosomes**(Yasaminehet al., 2022).**

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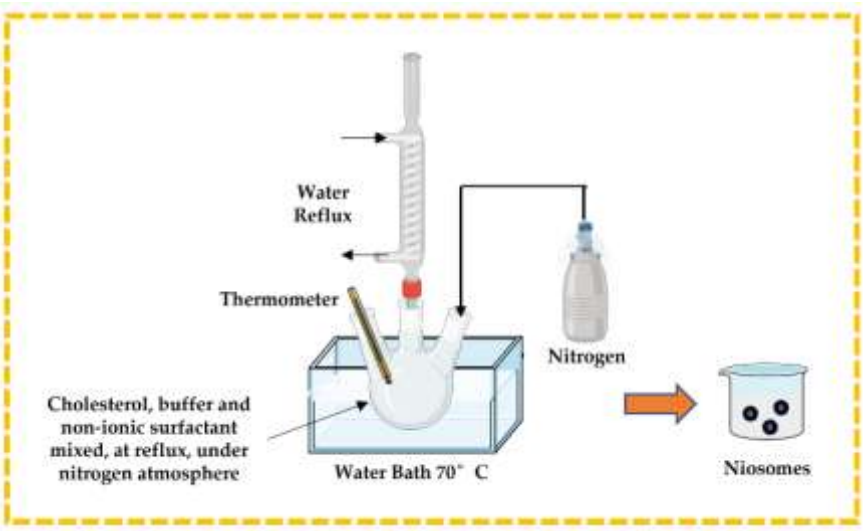

Figure 7:-Bubble Technique

5.7Reverse-Phase Evaporation Technique

Surfactant and cholesterol are dissolved in suitable organic solvent (e.g., chloroform, ethyl ether). An aqueous phase that contains the drug or natural molecule is added, and then the two immiscible phases are homogenized and sonicated. The organic solvent is removed from the formed emulsion by rotary evaporation to obtain niosomes **(Zhang et al., 2018).**

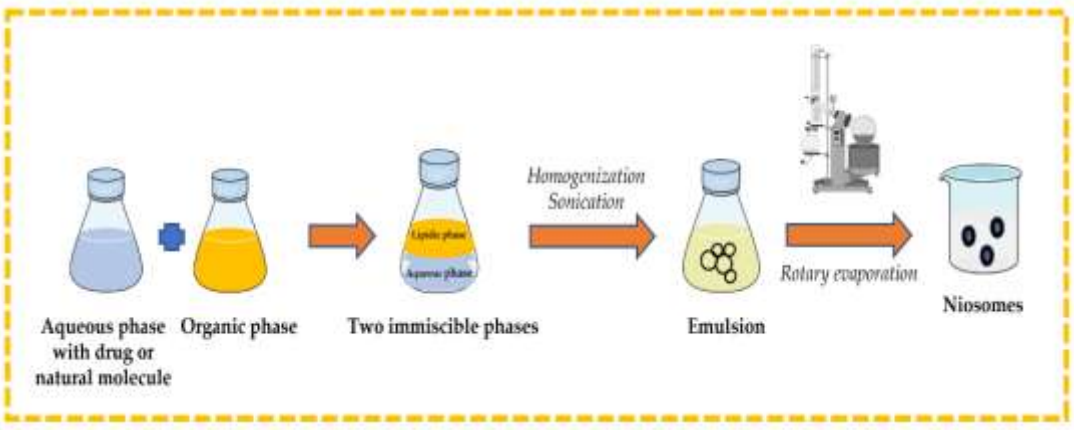

Figure 8:- Reverse-Phase Evaporation Technique

5.8 Thin-Film/Thin-Layer Hydration Technique

This technique is widespread in the formulation of niosomes. The surfactant and cholesterol are dissolved in a suitable organic solvent (e.g., ether, ethanol, chloroform). A dried thin-film layer forms inside the flask after the organic solvent is removed by vacuum/rotary evaporation. The drug is dissolved in an aqueous solution and then applied to the obtained film to hydrate it. To produce niosomes, the hydrated film must be incubated in a water bath above the transition temperature of the surfactants **(Thabetet al., 2022).**

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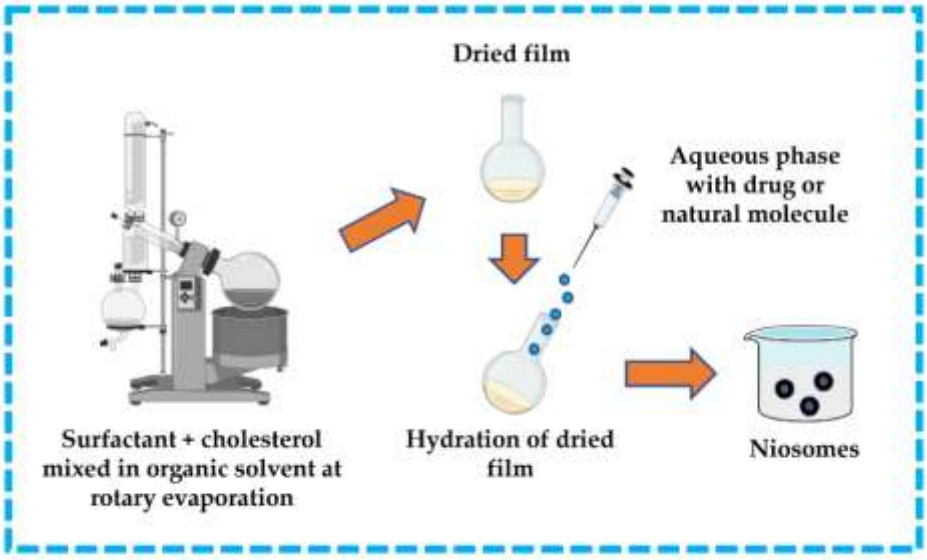

Figure 9:- Thin-Film/Thin-Layer Hydration Technique

VI. CHARACTERISATION OF NIOSOMES

- **Morphology:** Niosomal vesicles shape is assumed to be spherical. Mean diameter can be determined by laser light scattering method. The diameter of vesicles can also be determined by electron microscopy, freeze-fracture electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy. Fusion of vesicles during the cycle might be attributed to the increase in vesicle diameter due to freeze-thawing of niosomes**(Koifman and Talmon 2021).**
- **Bilayer formation:** X-cross formation under light polarisation microscopy characterizes the formation of bilayer vesicle owing to the assembly of non-ionic surfactants.
- **Number of lamellae:** Determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy **(Mertens and Svergun 2017).**
- **Membrane rigidity:** Measured by the mobility of a fluorescence probe as a function of temperature.
- **Entrapment efficiency:** Once niosomal dispersion is formulated, an unentrapped drug is separated. The entrapped drug remained in niosomes is determined by complete vesicle disruption using 50% n-propanol/0.1% Triton X100 **(Saraswathiet al., 2019).**

VII. WALTHERIA INDICA

Waltheria indica, commonly known as sleepy morning or velvet leaf, is a medicinal shrub widely distributed in tropical regions. Traditionally, it is used to treat infections, wounds, inflammation, and gastrointestinal disorders. Pharmacological studies have demonstrated that extracts of W. indica possess antibacterial, antifungal, antioxidant, and analgesic properties. The antimicrobial activity is attributed to the presence of various bioactive compounds such as alkaloids, flavonoids, tannins, terpenoids, phenolic compounds, and saponins, which interfere with bacterial cell wall integrity, inhibit protein synthesis, and induce oxidative stress within microbial cells **(Nirmala and Sridevi 2021).**

Despite these potent properties, the clinical applicability of W. indica extract is restricted due to its poor solubility and limited stability in biological systems. Therefore, encapsulating its extract into a niosomal delivery system can significantly enhance its therapeutic efficiency by improving solubility, protecting active constituents, and promoting sustained release at the infection site**(Ghoshet al.,2025).**

7.1 Antibacterial Activity of Waltheria indica Niosomes

The encapsulation of Waltheria indica extract into lipid-based vesicular systems such as niosomes has been found to significantly enhance its antibacterial efficacy. The phytochemical components of W. indica, which include flavonoids, alkaloids, phenolics, and tannins, are

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known for their ability to inhibit bacterial growth by multiple mechanisms**(Komaet al., 2017).**However, when delivered as a crude extract, these compounds often face limitations such as poor solubility, low permeability, and instability under physiological conditions. The use of niosomes as a delivery vehicle overcomes these drawbacks by protecting the bioactive compounds, enhancing their penetration into bacterial cells, and providing sustained release, thereby prolonging antibacterial activity**(Hemmatiet al., 2023).**

7.2 Mechanism of Action

The antibacterial activity of W. indica niosomes can be attributed to a combination of phytochemical actionandnanocarrier-mediated enhancement. The mechanisms include:

a) Disruption of Bacterial Cell Membranes

Phytoconstituents such as flavonoids, alkaloids, and phenolic acids present in W. indica have strong lipophilic characteristics that allow them to interact with bacterial cell membranes. They disrupt membrane integrity by increasing permeability, leading to leakage of essential cellular components such as ions, nucleotides, and proteins. This results in the loss of membrane potential and eventual cell death. Niosomal encapsulation enhances this effect by facilitating better adherence of the vesicles to bacterial surfaces, ensuring localized and concentrated delivery of active compounds**(Komaet al., 2017).**

b) Enhanced Penetration and Cellular Uptake

Niosomes possess a bilayer structure similar to biological membranes, which allows them to fuse with bacterial cell walls or cellular membranes of host tissues. This fusion promotes the direct delivery of the encapsulated W. indica phytochemicals into bacterial cells or infected tissues. The small particle size (typically below 200 nm) of optimized niosomes enhances their diffusion through bacterial biofilms and epithelial barriers, ensuring effective drug accumulation at the infection site**(Mehraryaet al., 2022).**

c) Controlled and Sustained Release

One of the key advantages of the niosomal system is its ability to provide controlled and sustained release of encapsulated phytoconstituents. Unlike free extracts, which may degrade or get metabolized rapidly, W. indica niosomes maintain a steady release of antibacterial compounds over an extended period. This ensures prolonged contact between the bioactive molecules and bacterial cells, reducing the likelihood of regrowth and resistance development**(Pandeyet al., 2021).**

d) Synergistic Effects of Phytochemicals

The combination of multiple bioactive components within W. indica—such as flavonoids, tannins, and alkaloids—exerts synergistic effects on bacteria. Flavonoids interfere with bacterial nucleic acid synthesis, tannins precipitate bacterial cell proteins, and alkaloids inhibit enzymatic pathways crucial for bacterial metabolism. Encapsulation within niosomes preserves these compounds in their active form, allowing simultaneous and sustained release, thereby amplifying the antibacterial potency**(Donadioet al., 2021).**

e) Antioxidant-Mediated Protection

Oxidative stress contributes to bacterial survival and virulence. The antioxidant phytochemicals in W. indica, such as phenolic acids and flavonoids, neutralize reactive oxygen species (ROS), disrupting bacterial defense mechanisms. Niosomal encapsulation further stabilizes these antioxidants, enabling them to maintain their redox activity during antibacterial interactions **(Liu et al., 2022).**

Collectively, these mechanisms establish W. indica niosomes as a potent antibacterial delivery system that not only enhances efficacy but also minimizes degradation of phytochemicals and reduces the required dosage **(Jacob et al., 2025).**

7.3 Evaluation Methods

The antibacterial efficacy of Waltheria indica niosomes is evaluated using a series of in vitro microbiological assaysdesigned to determine both the qualitative and quantitative effects of the formulation on bacterial growth and survival**(Al-Enaziet al., 2023).** The following methods are commonly employed:

a) Agar Well Diffusion Method

This method is used to assess the zone of inhibition produced by W. indica niosomes against different bacterial strains.

- Nutrient agar plates are inoculated with standardized bacterial suspensions (e.g., Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa).
- Wells are made in the agar and filled with varying concentrations of W. indicaniosomal suspension, free extract, and standard

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antibiotics for comparison**(Rehmanet al., 2025).**

- After incubation (typically 24 hours at 37°C), the diameter of the inhibition zones is measured.. Larger inhibition zones in niosome-treated samples indicate enhanced antibacterial activity due to improved solubility and sustained release of phytochemicals **(Heidariet al., 2020).**

b) Minimum Inhibitory Concentration (MIC) Assay

The MIC is the lowest concentration of W. indica niosomes required to inhibit visible bacterial growth.

- Serial dilutions of niosomal formulations are prepared in nutrient broth.
- Each dilution is inoculated with a bacterial strain and incubated under controlled conditions.
- The MIC value is determined by observing the lowest concentration at which no visible growth (turbidity) is observed. Lower MIC values for niosomal formulations compared to free extracts indicate superior antibacterial potency and bioavailability **(Mehdipouret al., 2025).**

c) Minimum Bactericidal Concentration (MBC) Assay

The MBC test determines the lowest concentration of niosomal extract required to kill bacteria.

- Samples from tubes showing no growth in the MIC test are plated on agar and incubated.
- The concentration at which no bacterial colonies appear is recorded as the MBC. NiosomalW. indica often shows lower MBC values than free extracts, confirming its enhanced bactericidal effect**(Piri-Gharaghieet al., 2023).**

d) Time–Kill Kinetics Study

This dynamic study evaluates the rate and duration of bacterial killing by W. indica niosomes.

- Bacterial cultures are treated with the niosomal formulation and sampled at different time intervals (0, 2, 4, 8, 12, 24 hours).
- Viable bacterial counts are determined by plating and counting colony-forming units (CFUs).
- The results are plotted to assess the pattern of bacterial reduction over time.
- Sustained reduction in bacterial count over 24 hours suggests controlled drug release and prolonged antibacterial action of niosomes**(Abdelazizet al., 2015).**

e) Biofilm Inhibition and Disruption Studies (Optional Advanced Test)

Since bacterial biofilms protect pathogens from conventional drugs, the anti-biofilm potential of W. indica niosomes can also be assessed.

- Microtiter plate assays using crystal violet staining quantify the inhibition or disruption of biofilms by niosomal formulations.
- Niosomes often exhibit superior penetration through biofilm layers, reducing bacterial adherence and colony formation**(Kashefet al., 2020).**

7.4 Comparative Antibacterial Efficacy

Experimental findings from preliminary studies and similar herbal-niosomal formulations indicate that Waltheria indica niosomes demonstrate significantly higher antibacterial activity compared to unencapsulated plant extract. The enhanced efficacy has been observed particularly against both Gram-positive (Staphylococcus aureus) and Gram-negative(Escherichia coli, Pseudomonas aeruginosa) bacteria**(Shree et al., 2022).**

The improved performance of niosomes can be attributed to:

- Enhanced solubility and diffusion of phytochemicals,
- Stronger interaction with bacterial cell membranes, and
- Sustained, localized release ensuring prolonged antibacterial effect**(Uskokovic, 2015).**

VIII. CONCLUSION AND FUTURE PROSPECTS

The development of lipid-based vesicular systems such as niosomes provides a cutting-edge platform for delivering herbal bioactives with enhanced stability, bioavailability, and controlled release. Encapsulation of Waltheria indica extract in niosomes significantly enhances its antibacterial potential, demonstrating the synergistic advantages of phytomedicine and nanotechnology.

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