Herbal Niosomes in Drug Delivery: Recent Innovations, Challenges and Future Perspectives

[1]Khushi Mankar, [2]Zohra Firdous, [3]Manish Kamble, [4]Noopur Gaikwad
[1,2,3,4]Kamla Nehru College of Pharmacy, Butibori, Nagpur (M.S.) India-441108
[1] mankarkhushi123@gmail.com, [2.]zohrafirdous624@gmail.com,
[3.]manish.kamble2109@gmail.com, [4] 20noopur@gmail.com

Abstract-Herbal medicines have gained global attention due to their therapeutic efficacy and lower toxicity; however, their clinical application remains limited by poor solubility, instability, and low bioavailability. Niosomes are self-assembled vesicular systems composed of non-ionic surfactants and cholesterol which offer a promising approach to overcome these limitations. Herbal niosomes enhance solubility, stability, and permeability of phytoconstituents while enabling controlled and targeted drug release. These vesicles encapsulate both hydrophilic and lipophilic compounds, making them suitable for diverse herbal drugs. The incorporation of phytoconstituents into niosomes has shown improved therapeutic outcomes in anti-inflammatory, antimicrobial, anticancer, and antioxidant applications. Preparation methods such as thin-film hydration, reverse-phase evaporation, sonication, and microfluidization allow tailored vesicle size, entrapment efficiency, and release kinetics. Recent innovations include surface-modified, stimuli-responsive, PEGylated, and hybrid niosomes, which further enhance targeted delivery and prolong circulation time. Despite their advantages, challenges such as physical instability, leakage, sterilization difficulties, and scalability issues persist. Toxicity related to surfactant components also requires further investigation. Nonetheless, with advancements in nanoengineering and biocompatible surfactants, herbal niosomes represent a powerful platform for modern phytopharmaceutical development. This review summarizes the principles, preparation techniques, therapeutic applications, innovations, limitations, and future perspectives of herbal niosomal drug delivery systems, highlighting their expanding potential in evidence-based herbal therapy.

Index Terms—Niosomes, Herbal drug delivery, Non-ionic surfactants, Targeted delivery, Vesicular systems.

I. INTRODUCTION

Herbal medicines play an important part in both traditional and modern systems of therapy; physicochemical limitations hinder their clinical translation processes. Most of the phytoconstituents have poor aqueous solubility, low membrane permeability, instability to heat or oxidation, and fast systemic clearance. These pharmacokinetic flaws lead to reduced therapeutic efficacy and narrower margin for the development of dosage forms. Novel delivery systems like niosomes have effective solutions to these challenges as they improve the bioavailability of the active principle, protect the labile herbal compounds, and facilitate the targeted delivery. Niosomes are microscopic lamellar vesicles composed mainly of non-ionic surfactants and cholesterol. Hydration of these amphiphilic molecules self-assembles into a bilayer structure capable of encapsulating drug molecules. Niosomes have a similar structure to liposomes but possess superior chemical stability, cost-effectiveness, and lower toxicity attributed to the non-ionic surfactants used compared to the phospholipids used for liposome formulation [1–3]. Surfactants such as Span, Tween, and Brij form the vesicle membrane, while cholesterol increases rigidity and reduces permeability. Their peculiar architecture allows the simultaneous encapsulation of both hydrophilic and hydrophobic phytoconstituents within the vesicle core and the bilayer region, respectively [4]. (Fig 1)

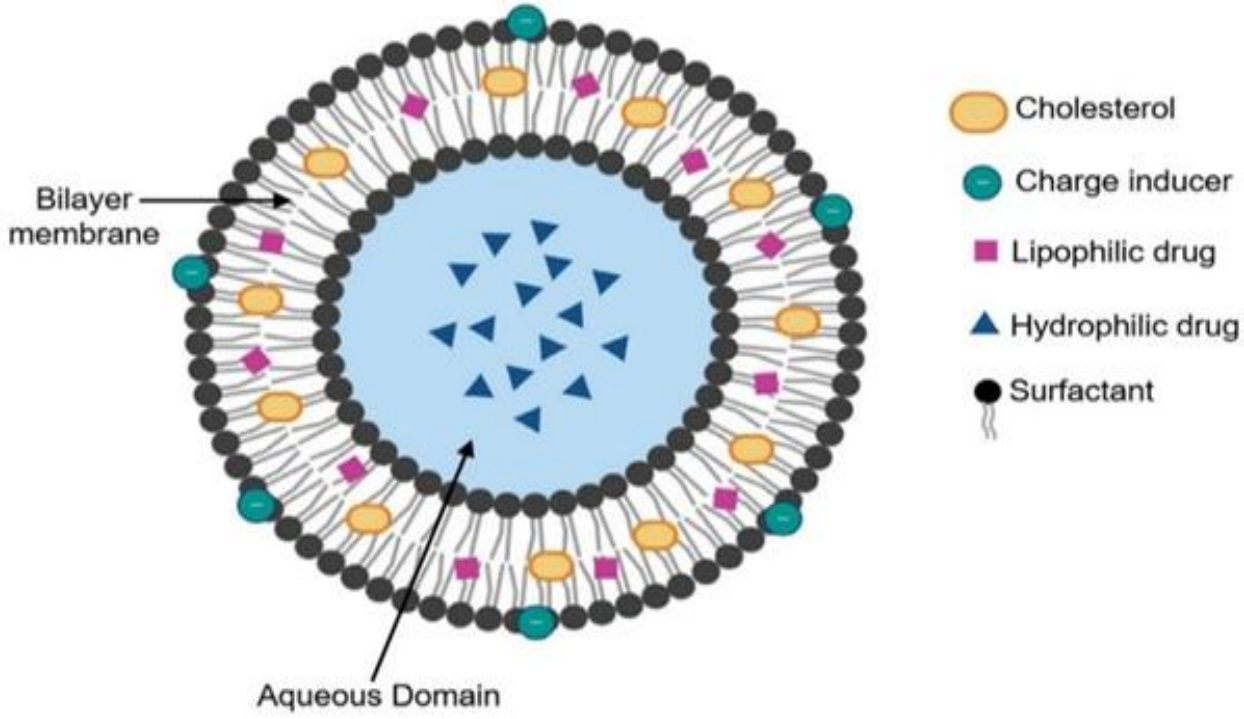

Figure 1: Structure of Niosomes

Herbal niosomes enhance the mode of drug delivery by various mechanisms. Encapsulation protects bioactive compounds from enzymatic degradation and oxidation, hence increasing stability [5]. Niosomes enhance the solubility and dissolution rate of poorly soluble

phytochemicals, thus enhancing absorption across the biological membrane. Optimizing the composition of lipids and the size of vesicles allows the controlled and sustained release of a drug, hence reducing fluctuations in the plasma concentration of drugs. Surface charge and functional groups enable chemical modification of niosomes for targeted delivery, thus offering site-specific accumulation in cancerous, inflamed, or infectious tissues [6,7].

Niosomes are classified into multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), and large unilamellar vesicles (LUVs), which differ in advantages concerning their drug loading capacity and release kinetics [8]. The preparation techniques, like thin-film hydration, reverse-phase evaporation, sonication, micro fluidization, and ether or ethanol injection, enable tailoring of vesicle size, polydispersity, and entrapment efficiency [9–12]. Herbal drugs incorporated in niosomes have been reported for enhanced therapeutic potential in several preclinical studies. For example, encapsulation enhances dermal penetration of herbal anti-inflammatory compounds, antimicrobial activity of various plant extracts, and selective cytotoxicity of herbal anticancer agents. (Fig 2)

Figure 2: Three main types of Niosomes

Recent advancements in niosomal technology have enhanced their applications in herbal medicine. Stimuli-responsive niosomes release their payload in response to pH, temperature, or enzymatic triggers, thus delivering the payload in a controlled manner at the diseased tissues. PEGylated and ligand-modified niosomes exhibit prolonged circulation and enhanced cellular uptake, which can be advantageously exploited in cancer therapy [13]. Co-delivery niosomal systems are being explored to combine various herbal components with each other, offering synergistic therapeutic effects. (Fig 3)

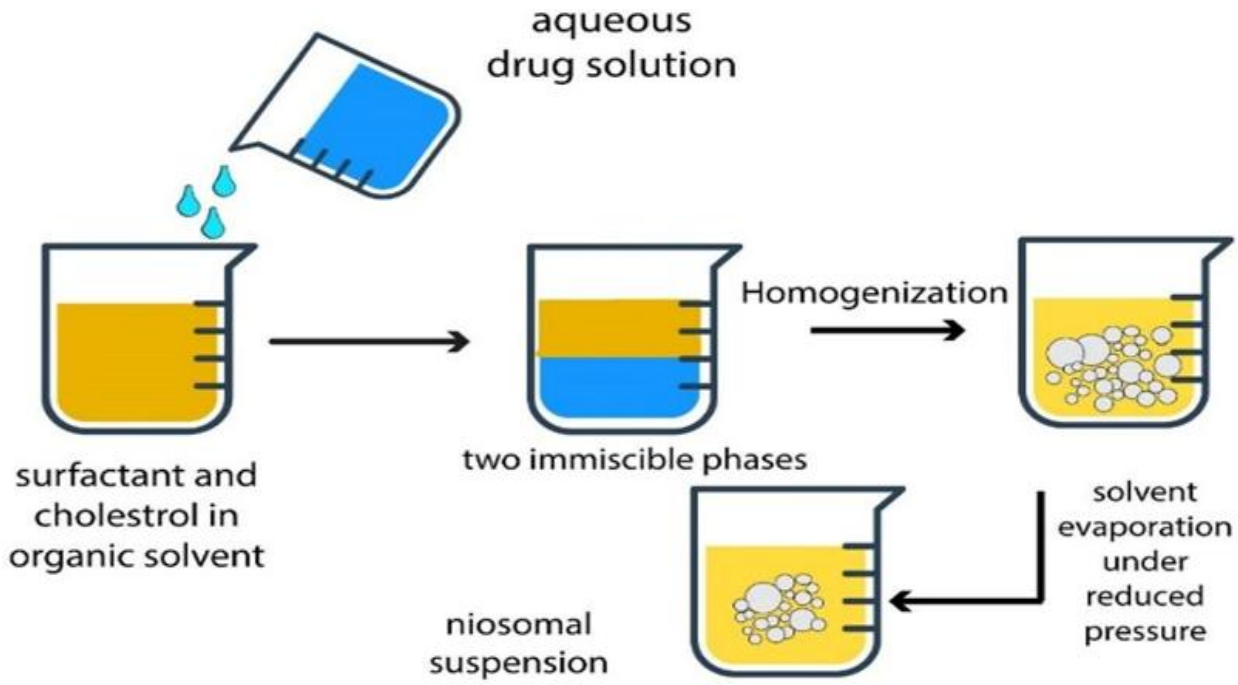

Figure 3: General method of preparation of niosomes

in the face of these promising features, limitations still exist. Physical instability, drug leakage, difficulty in achieving sterility, and toxicity due to surfactants are the major drawbacks that must be overcome prior to wide clinical applications. Besides, large-scale manufacturing techniques should be optimized to ensure reproducibility and cost-effectiveness [14]. Nevertheless, the potential benefits of niosomes in overcoming the inherent limitations of herbal drugs underscore their relevance in modern phytopharmaceutical science.

II. METHODOLOGY

Several methods have been developed to prepare niosomes, each influencing vesicle size, morphology, entrapment efficiency, and stability. These can be broadly categorized into passive and active drug loading methods.

1. PASSIVE LOADING TECHNIQUES

a. Thin-Film Hydration Method

Also known as the rotary evaporation method, this is the most widely used technique. A mixture of non-ionic surfactants, for example, Span 60 and Tween 80, and cholesterol is dissolved in an organic solvent, such as chloroform or methanol. The organic solvent is removed under reduced pressure in a rotary evaporator, yielding a thin film of lipid on the surface of the flask [15]. Hydration with an aqueous herbal extract solution at temperatures within a range of 40-60°C leads to swelling of the film, with the consequent formation of multilamellar vesicles. Sonication or extrusion may further reduce the size of the vesicles, giving SUVs.

b. Sonication Method

In this technique, hydrated multilamellar vesicles are subjected to probe or bath sonication which breaks down larger vesicles into smaller ones [16]. This generates SUVs suitable for transdermal or ocular applications. Sonication is advantageous for heat-stable herbal compounds but may cause degradation of thermolabile phytoconstituents.

c. Ether Injection Method

The solution of surfactant and cholesterol in diethyl ether is slowly injected into the warm aqueous phase containing the drug. By vaporization of ether, unilamellar vesicles are formed [17]. The size of the vesicles depends on the rate of injection, temperature of the chamber, and composition of surfactant.

d. Reverse-Phase Evaporation Technique (REV)

The organic solvents dissolve surfactants and cholesterol, followed by the addition of aqueous herbal extract to result in a water-in-oil emulsion. Organic solvent removal under reduced pressure results in a gel-like material that becomes large unilamellar niosomes upon hydration [18]. REV provides high entrapment efficiency for hydrophilic phytoconstituents.

e. Microfluidization

This advanced technique involves the use of high-pressure streams of lipid and aqueous phases that collide inside microchannels, hence generating uniform vesicles with narrow size distribution. Microfluidization is suitable for scale-up and gives rise to high reproducibility.

2. ACTIVE LOADING TECHNIQUES

a. pH-Gradient Method

Niosomes are prepared with an acidic interior environment; usually, citric acid is used. When herbal drugs with weakly basic properties are added, the drug diffuses into the vesicle and gets protonated, leading to efficient drug loading [20]. This enhances the entrapment efficiency and reduces drug leakage.

3. PREPARATION FROM PRONIOSOMES

Proniosomes are dry powder formulations with surfactant precoating of carriers like maltodextrin. These are hydrated at the time of need to give niosomal suspension. Proniosomes improve stability and minimize aggregation as compared to aqueous niosomes [21].

4. EVALUATION PARAMETERS

The formulated niosomes undergo various characterization tests:

- Morphology: The shape of the vesicles is determined by TEM and SEM.
- Particle Size and PDI: Determined via dynamic light scattering.
- Entrapment Efficiency: Measured by centrifugation and analysis of unentrapped drug.

• Thermal Analysis: DSC yields information on lipid phase transitions.
In Vitro Release Studies: Using the dialysis membranes.
• Stability Testing: This involves testing leakage, aggregation, and size change over time.

III. FUTURE PERSPECTIVE OF NEOSOME

One of the most motivating fields in scientific research is the medical application of nanocarriers. Due to the relatively high safety, easy production, and storage of the drug, niosome as a noble nanoparticle for drug delivery has attracted considerable attention in recent years. With great potential for encapsulating different kinds of toxics, sensitive, and degradable drugs, these allow the efficient targeting of particular organs without interfering with normal physiology of the cell and reducing the side effects; neosome will certainly play a major role in emerging treatments in medicine. A variety of niosomal formulations including a wide range of drugs that can be utilized in the therapy of cancer and treatment of tumour cells will definitely keep their importance in the upcoming decades. In the near future, niosome may find a wide range of applications because of the ability of this vesicle to encapsulate both hydrophobic and hydrophilic substances and pH sensitivity.

IV. LIMITATIONS AND CHALLENGES IN THE DEVELOPMENT OF NIOSOMES

Niosomes are promising nanosystems for delivering natural and anticancer therapeutics because they can encapsulate both hydrophilic and hydrophobic drugs and offer better stability, flexibility, and low production cost compared to many conventional carriers. Their structure can be easily tailored by modifying formulation parameters, making them suitable for various pharmaceutical and cosmetic applications. Despite these advantages, niosomes face several challenges, particularly in sterilization, as heat and steam may damage surfactants and cause drug leakage. Membrane filtration is limited by vesicle size, and the effects of gamma radiation remain insufficiently explored. Concerns also exist regarding the potential toxicity of nonionic surfactants, with limited in vivo safety data available. Physical instability, drug leakage during storage, oxidation of components, low entrapment efficiency, and scale up difficulties further restrict their broader application. Continued research is essential to improve safety, stability, and manufacturing feasibility.

V. DISCUSSION

Herbal niosomes offer a revolutionary approach toward the delivery of plant-based therapeutics, solving long-standing problems of solubility, stability, and bioavailability. The vesicular bilayer structure protects phytoconstituents from degradation, while simultaneously allowing controlled release. This makes niosomal formulations superior to all conventional herbal formulations. It has been reported that herbal drugs, after incorporation into niosomes, show enhanced

pharmacological activity because of improved permeability and sustained delivery. For example, niosome-encapsulated herbal extracts containing antioxidants have shown enhanced free-radical scavenging activity and improved dermal absorption. The selection of appropriate surfactants and cholesterol is an important factor to influence vesicle stability. Span 60, due to its higher phase transition temperature, forms stable vesicles with high entrapment efficiency for many herbal compounds. However, levels of cholesterol should be optimized, as higher concentration may reduce membrane fluidity and restrict the release of drugs.

PEGylated and ligand-modified vesicles represent advanced niosomal systems with enhanced targeting efficiencies, which are of prime importance in cancer therapy owing to the need for selective accumulation in tumor tissues. Stimuli-responsive and hybrid herbal niosomes further expand their therapeutic scope in inflammatory, infectious, and metabolic diseases. Despite these advantages, scalability and sterilization remain major obstacles. Heat sterilization might cause degradation in some non-ionic surfactants, while vesicular size limits filtration techniques. Moreover, the in vivo toxicity data regarding many surfactants is still scant and requires further study. In conclusion, the combination of herbal therapeutics with advanced niosomal technology is a landmark achievement in modern phytopharmaceutical science, showcasing pathways toward safer and effective herbal drug delivery.

VI. CONCLUSION

Herbal niosomes offer a promising platform for delivering phytoconstituents by encapsulating both hydrophilic and lipophilic molecules, protecting them from degradation, enhancing solubility, and enabling controlled release. Their biocompatibility and biodegradability make them well suited for herbal formulations. Advanced approaches such as surface modification, stimuli responsive systems, PEGylation, and microfluidic preparation have expanded their use in managing chronic diseases, cancer, infections, and inflammatory conditions. These systems improve bioavailability and targeting, increasing the clinical potential of herbal therapeutics. However, challenges remain, including physical instability, aggregation, drug leakage, surfactant related toxicity, difficulties in sterilization, and limitations in large scale production. More in vivo studies and clinical evaluations are needed to confirm safety and therapeutic benefits. With ongoing research and improved formulation techniques, herbal niosomes hold strong potential as next generation carriers that connect traditional herbal medicine with modern nanotechnology for safer and more effective treatments.

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REFERENCES

[1] K. M. Karim, "Niosomes: a future of targeted drug delivery systems," *J. Adv. Pharm. Technol. Res.*, vol. 1, no. 4, pp. 374–380, 2010.

[2] R. Muzzalupo, "Niosomal drug delivery for transdermal targeting: recent advances," *Res. Rep. Transdermal Drug Deliv.*, vol. 4, pp. 23–33, 2015.

[3] M. F. Ansari and A. Alam, "Niosomes as novel drug delivery system: review article," *Int. J. Pharm. Res. Appl.*, vol. 7, no. 1, pp. 171–178, 2022.

[4] R. M. Handjani-Vila *et al.*, "Dispersions of lamellar phases of nonionic lipids in cosmetic products," *Int. J. Cosmet. Sci.*, vol. 1, pp. 303–314, 1979.

[5] A. Semalty, M. Semalty, M. S. Rawat, and F. Franceschi, "Supramolecular phospholipid–polyphenolic interactions: the phytosome strategy," *Fitoterapia*, vol. 81, pp. 306–314, 2010.

[6] Z. Sarhadynejad, A. Pardakhty, A. Mandegary, S. Afsharypuor, and F. Sharififar, "Physicochemical characterization and antioxidant activity of Zereshk-e-Saghir," *J. Young Pharm.*, vol. 9, pp. 224–228, 2017.

[7] V. A. Duong, T. T. L. Nguyen, H. J. Maeng, and S. C. Chi, "Nanostructured lipid carriers containing ondansetron hydrochloride," *J. Drug Deliv. Sci. Technol.*, vol. 53, p. 101185, 2019.

[8] P. A. Makoni, K. W. Kasongo, and R. B. Walker, "Short-term stability testing of efavirenz-loaded lipid nanoparticles," *Pharmaceutics*, vol. 11, no. 8, p. 397, 2019.

[9] C. A. Hunter, T. F. Dolan, G. H. Coombs, and A. J. Baillie, "Vesicular systems for delivery of sodium stibogluconate in visceral leishmaniasis," *J. Pharm. Pharmacol.*, vol. 40, no. 3, pp. 161–165, 1988.

[10] V. P. Chandu, A. Arunachalam, S. Jeganath, K. Yamini, K. Tharangini, and G. Chaitanya, "Niosomes: a novel drug delivery system," *Int. J. Novel Trends Pharm. Sci.*, vol. 2, no. 1, pp. 25–29, 2012.

[11] A. Debnath and A. Kumar, "Structural and functional significance of niosome and proniosome," *Int. J. Pharm. Eng.*, vol. 3, no. 3, pp. 621–637, 2015.

[12] A. Sankhyan and P. Pawar, "Recent trends in niosome as vesicular drug delivery system," *J. Appl. Pharm. Sci.*, vol. 2, no. 6, pp. 20–32, 2012.

[13] A. Rogerson, "Distribution of doxorubicin in mice following administration in niosomes," *J. Pharm. Pharmacol.*, vol. 40, no. 5, pp. 337–342, 1988.

[14] L. D. Mayer, M. B. Bally, M. J. Hope, and P. R. Cullis, "Uptake of antineoplastic agents into large unilamellar vesicles in response to membrane potential," *Biochim. Biophys. Acta.*, vol. 816, no. 2, pp. 294–302, 1985.

[15] G. Singh, H. Dwivedi, S. K. Saraf, and S. A. Saraf, "Niosomal delivery of isoniazid," *Trop. J. Pharm. Res.*, vol. 10, no. 2, pp. 203–210, 2011.

[16] A. Lohumi, S. Rawat, S. Sarkar, A. B. Sipai, and M. V. Yadav, "A novel drug delivery system: niosomes review," *J. Drug Deliv. Ther.*, vol. 2, no. 5, pp. 129–135, 2012.

[17] N. V. S. Madhav and A. Saini, "Niosomes: a novel drug delivery system," *Int. J. Res. Pharm. Chem.*, vol. 1, no. 3, pp. 223–229, 2011.

[18] K. Jindal, "Niosomes as a potential carrier system," *Int. J. Pharm. Chem. Biol. Sci.*, vol. 5, no. 4, pp. 947–959, 2015.

[19] A. Sarker, I. J. Shimu, and S. A. A. Alam, "Niosome as dermal drug delivery tool," *IOSR J. Pharm. Biol. Sci.*, vol. 10, no. 2, pp. 73–79, 2015.

[20] A. Nasir, S. L. Harikumar, and A. Kaur, "Niosomes: an excellent tool for drug delivery," *Int. J. Res. Pharm. Chem.*, vol. 2, no. 2, pp. 2231–2781, 2012.

[21] P. Tangri and S. Khurana, "Niosomes: formulation and evaluation," *Int. J. Biopharm.*, vol. 2, no. 1, pp. 47–53, 2011.