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Development, Evaluation, and Applications of Menthosomal Gels in Current Medicine

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Abstract Menthosomal gels are a new efficient system for the drug delivery system which use the ability of the menthol to enlarge the skin permeability, and lipid vesicle structures. These formulations respond to problems typical of conventional drugs and dosage forms, including solubility, biopharmaceutical and pharmacokinetic problems, as well as side effects due to systemic delivery. As menthol dissolves the lipid layer of the SC, the menthosomal gels improve skin penetration and drug accumulation. Their ability to encapsulate both polar and non-polar drugs increases the possibilities for their use in dermatological, transdermal, systemic, and cosmetic spheres. This review aims to discuss the advancement, assessment, and uses of the menthosomal gels. It covers formulation approaches in terms of choice of lipids, cholesterol, menthol, gel bases and techniques of manufacture as thin film hydration and sonication. Detailed description of physicochemical characterization techniques, in vitro drug release profiles, and in vivo efficacy testing are described to demonstrate their efficiency and safety. It can be used for the topical treatment of diseases like psoriasis and acne as well as to deliver systemically administered drugs like hormones and NSAID's. Moreover, menthosomal gels could be used in activities such as wound healing, along with anti-aging properties and a method to deliver vaccines through the skin. While there are benefits of adopting concepts on SC in ASION, there are limitations or issues which can be attributed to scalability, stability, and the issue of getting appropriate approval from relevant authorities. The positive implications in present day practice in modern medicine are expected to be amplified by future evolution of such technologies such as integration of AI technology, personalized medicine, sustainable practices and many others. As current shortcomings show, menthosomal gels are all set to recast drug delivery as an innovative, patient-centered approach.

Keywords Drug delivery; Menthol; Menthosomal gels; Permeation enhancement; Transdermal systems; Vesicular systems

1. Introduction

As the contest of drug delivery systems undergoes changes, the concept of innovation is central to the advancement of therapeutic efficacy and patient concordance [1]. Various concrete conventional drug delivery systems though efficient poses huge problems including; low bioavailability, poor solubility, body related side effects, non-targeted release, and many more [2]. Solving these problems has catalyzed the development of

modern systems for drug delivery that emphasize targeted, highly effective and individualized approaches. Of these systems, vesicular carriers have emerged as favorites because they can accommodate and shield APIs from degradation and, at the same time, enable the controlled and site-specific release of drugs [3]. Among the prospective systems, the menthosomal gel appears to be most significant in that the biochemical characteristics of menthol are incorporated into vesicular drug delivery systems. Menthosomal gels are one of the recent advancements where permeability of menthol coupled with structural benefits of lipid based vesicle like liposomes and ethosomes are used [4]. Menthol is a naturally occurring compound synthesised from mint oils, and is famous for its therapeutic qualities of providing cool and soothing sensation with numbing effects. In addition, menthol increases the rate of skin permeation since it alters the lipid bilayer of the stratum corneum, the densest layer of epidermis through which most drugs diffuse poorly. This barrier is exploited by formulation, mentho-Somal gels exceed in overcoming this by including menthol into vesicular systems; thus, they are a multi-purpose, versatile platform: Topical and transdermal [5].

The need for the production of menthosomal gels is rooted in the fact that they produce higher drug penetration rates of various drugs ranging from hydrophilic to lipophilic drugs [6]. This versatility creates opportunities for small molecules in dermatology, systemic drug delivery, as well as in cosmetic sciences. Thus, in ailments including psoriasis, dermatitis or acne, the Menthosomal gels have demonstrated promising prospects for the improvement of the drug loading in the skin layers to deliver localized and prolonged therapeutic effects [7]. In the same manner, the menthosomal gels for transdermal delivery avoids the first pass metabolism which is predominant in oral administration and injectable formulations resulting to high systemic availability of the drug [8]. Production of menthosomal gels entails some skillful method that involves enhancement of physicochemical and pharmacological characteristics of the gels [9]. Techniques such as thin film hydration, reverse phase evaporation method, and sonicating are widely used to produce nanovesicles with ideal properties such as small particle size, high percentage of entrapment and zeta stability [10]. These parameters are Absolutely important to achieve a stable, effective and safe formulation in the formulation. Conversely the addition of menthol acts to increase finasteride diffusion across the skin and also has a cooling effect that is beneficial to the formulation regarding acceptability by patients [11].

The assessment, from a scientific point of view, of the menthosomal gels is a complex one. It starts from characterization of nanoparticles through particle size analysis, zeta potential analysis, as well as determination of stability of nanoparticles under different conditions of temperature, pH and the presence of salts. In vitro release and permeation data are crucial in defining the compulsory release profile of the formulation and identification of the improved permeability. Such findings are usually followed by in vivo tests, for the determination of pharmacokinetics, biodistribution, and therapeutic and toxicological effects. Such comprehensive evaluations are of top importance for fine-tuning the formulation and establishing it has no contraindicative characteristics for application in clinical practice. The distinct advantages of menthosomal gels are that they have multiple benefits over the traditional drug delivery systems. As drug solubility and permeability boosters, linked with the potential for controlled and sustained drug release, they can be a helpful tool from the therapeutic perspective. Further, topical and transdermal formulations' virtue of not requiring invasive methods enhances patient compliance in diseases that require extended usage. Moreover, the qualities of menthol such as cooling, soothing and so on are again valuable in some dermatological as well as cosmetic uses [12–14].

However, there are some challenges encountered in the development and application of menthosomal gels continued below. There are remaining questions regarding scalability, because the methods for preparing such systems at the laboratory level may not be directly applicable at a commercial scale [15,16]. Another issue is stability, which may be an issue for formulations containing delicate APIs or products that will be stored for a long time [17]. Practical concerns, such as the labor costs and costs of procuring high purity excipients and/or high-technology equipment/ machinery, may also have a constricting function in their application. However, regulatory constraints which require much time before preclinical and clinical research before marketing can take place need to be resolved More [18]. New developments in the last five years have seen an increased interest in studying menthosomal gels for new uses and different approaches of delivery systems [19]. For example, the enhancement of the menthosomal gels with microneedles, skin ions, and other transdermal enhancement systems have been found to enhance drug delivery and penetration systems. The use of either existing or hebert tools like artificial intelligence (AI) and machine learning (ML) in formulating and optimizing the formulation process is also under consideration to enhance formulation mentation and maximize formulation improvement. Such developments are indicative of the fact that, in the future of a personalised medical approach where, the menthosomal gels stand to assume greater prominence in the therapy based on patient requirements [20].

This review wishes to further explore the strategies on its conception, assessment, and use in the current medical practice of menthosomal gels. This will consider the formulation strategies as well as the assessment methods

applied in the enhancement of these systems, and their therapeutic applications in the various domains. This paper's intention is to highlight the menthosomal gel's future prospects, work around its present drawbacks and limitations, and demonstrate that it can transform drug delivery and boost medical science knowledge. It thereby hopes to present a valuable reference to researchers, clinicians, and industry personnel who wish to incorporate menthosomal gels toward enhancing their drug delivery systems.

2. Development of Menthosomal Gels

Mentholised gel formulation development is a complex process that involves the combination of advantages offered by the precise type of drug carrier called vesicles and the ability of the Menthol to enhance drug permeation. Using highly sophisticated formulation approaches and accurate optimization Profile menthosomal gels are aimed at addressing the shortcomings inherent with normal drug delivery systems especially as regards to the drug loading, stability and drug activity. This section describes the augmentation of the menthosomal gel formulation design, preparation approaches as well as optimization procedures critical in developing stable and efficient formulations [21].

2.1. Formulation Design

The packaging materials of menthosomal gels shall also be possibly chosen and compounded to make up the most efficacious drug delivery system. The main constituents of the formulation are the API, lipid vesicle forming agents, menthol and a gel base. The API is selected according to the intended therapeutic applications, whether dermatological or systemic, targeting heavily lipophilic and low solubility drugs mainly [22]. Phospholipids like phosphatidylcholine or lecithin make the structural scaffold of the vesicles and are a barrier to encased drug [23]. cholesterol was incorporated into the lipid composition to make the vesicles more rigid and stable, and to avoid rupture and desorption, as well as to modulate the rate of drug release [24].
Menthol is involved in the synthesis of menthosomal gels with the dual functions of a penetration enhancer and an agent that produces the cooling effect. It dissolves the intercellular lipid bilayers of the SC and enhances the permeability of the skin allowing deeper penetration of the drug molecules. Moreover, the menthol ingredient has a cooling effect which increases patient compliance and comfort during the use of the gel [25]. Menthol concentration has to be carefully adjusted to boost the permeation but at the same time there should not be side effects associated with menthol [26]. The gel base is responsible for forming the carrier matrix with vesicles while being sufficiently viscous, spreadable and stable. Carbopol, hydroxypropyl methylcellulose (HPMC) or xanthan gum are typical examples of polymers that can be used to obtain the gel like system [27]. It was also found that the gel base help maintain the controlled release of the drug through acting as a depot. Other ingredients are used as solubilisers (ethanol or propylene glycol) and surfactants (Tween 80 or Span 60) in order to enhance the solubility of menthol and the API and to avoid the aggregation of the vesicles. The last formulation is then optimized to have compatibility with all the ingredients, high drug loading efficiency within nanoparticles and efficient targeting of the site of interest[27].

2.2. Methods of Preparation

The formation of the menthosomal gels involve the preparation of nanovesicles of the API and menthol which is then incorporated in a gel system. This can be done by using several techniques, and all of them is quite effective but in different ways.

A. Thin-Film Hydration Method

It is one of the most used techniques for synthesizing menthosomal systems in many industries. Lipids and cholesterol as well as menthol are mixed with an organic solvent of chloroform or methanol to achieve a solution. Next the solvent is removed under reduced pressure employing a rotary evaporator and this results into formation of a thin lipid film at the walls of the flask. The film is then rehydrated with an aqueous phase to form vesicles with the API incorporated in their structures. This method enables the specification of the components and size of the vesicles with a high degree of accuracy. Vesicle size and homogeneity can be improved by resort to methods such as sonication or extrusion [28,29].

B. Reverse-Phase Evaporation Method

In this technique lipids and menthol are dispersed in a blend of organic and aqueous solvent phase. Reduced pressure evaporation of the organic solvent is conducted to produce a gel-phase substance. On further hydration, it becomes vesicles carrying the drug within it, thus making it an appropriate choice. Hydrophilic drugs are well

suited to this method since their solubility in water is well understood [30,31].

C. Sonication-Assisted Preparation

The size of the vesicles can be reduced and also uniform in distribution through sonicating the mixture. Once the vesriers have been prepared by thin-film hydration or reverse-phase evaporation, they undergo probe or bath sonication. This action of highly efficient coat proteins actually divides these large vesicles into smaller and more stable vesicles not to mention more permeable ones [32].

D. Microfluidization:

Microfluidization of the lipid-menthol mixture is accompanied by the use of the high-pressure channel with small calibers. This makes it possible to achieve the formation of vesicles of comparable size and maximum encapsulation effectiveness. While this method is less often applied in laboratory scale total syntheses, the scope of this approach is promising for large scale productions [33].

E. Incorporation into Gel Base:

After the preparation of the vesicles the gel base into which the vesicles are incorporated has already been prepared. In this step, pipetting should be gentle to facilitate homogenization and at the same time avoid disruption of vesicles composition and structure. Some of the vesicles are stabilized with gel base and this material gives it the right rheology for use [34].

2.3. Optimization Parameters

The enhancement of the menthosomal gels is a vital step to determine the stability of gels, its efficiency, and therapeutic effectiveness. This may include optimizing important factors in the formulation and carry out process factors to get the desired sizes, efficiencies of encapsulation, release rate and stability. Particle size is one of the important factors, because vesicle smaller than 200 nm are able to penetrate the skin well and their delivery efficiency is higher. Another one is the zeta potential, the measure of the surface charge of the vesicles, which in these experiments did not vary significantly depending on the lipid composition of the vesicles. The zeta potential greater than -30 mV is considered favorable for the stability of the colloids as it reduces the vesicle agglomeration [35,36].

The other relevant factor which directly determines the therapeutic effect is encapsulation efficiency that shows the extent of drug incorporation in the vesicles. Menthol concentration and lipid-to-drug ratio were determined to be critical factors within the process of attaining high encapsulation efficiency. Menthool is useful in two ways in the formulation; it is a permeation enhancer and it also has a cooling effect. Its concentration has to be optimised so as to enhance drug delivery into the skin yet at the same time it should not cause inflammation or other complications on skin. Logically, the rheological properties also play a great role when determining the spreadability and stability of the formulation within the gel matrix at the site of application. In the present study, thereby, an ideal viscosity allowed the gel to be easily applied on the skin; while it retained skin adhesion to ensure a continuous release of the drug. A stability study is designed to assess the physical, chemical and microbiological quality of the formulation in different conditions to include temperature, humidity and light exposure. Thus these studies, help in ensuring that the menthosomal gels retain it effective properties and the shelf life is not compromised [37].

Another factor which is relevant when assessing the function of the formation is drug release and permeation. Diffusion cells, in particular, are employed to investigate the rate and degree of drug release in experimental models. In vitro permeation studies utilising either human or animal skin find out the extent to which the penetrant has entered into the target tissue as well as the rate of penetration.

Moreover, the pH of the gel is also regulated to skin pH level with a range of 4.5 – 5.5 to avoid skin irritation interaction. Collectively, these optimisation parameters defined the respective menthosomal gels meeting the standard of efficacy, stability and patient compliance needed to make the menthosomal systems a preferred drug delivery system [38].

3. Assessment of Menthosomal Gels: Physicochemical, In Vitro, and In Vivo Studies

Table 1 describes the physicochemical characterisation, drug release profile, skin permeation, and therapeutic effectiveness of the menthosomal gels. Such evaluations guarantee the formulation has met the required stability and effectiveness, and the patient's safety. In this section, we describe the established approaches to assess the

menthosomal gels with regards to their physicochemical properties, in vitro and in vivo behavior [39].

3.1. Physicochemical Characterization

Menthosomal gel is the conclusion of the physical chemistry course, and its physicochemical characteristics are essential in its ability and stability. However, particle size remains one of the most critical parameters because smaller vesicles with an average diameter of less than 200nm demonstrate enhanced skin permeability and more homogeneous distribution of the drug. The most used methods of particle size analysis are dynamic light scattering (DLS) also known as laser diffraction techniques. Another important parameter is zeta potential which indicates the state of surface charge of vesicles. Any value higher than ±30mV shows good stability of colloids in order to prevent vesicle aggregation and to ensure the homogeneity of the formulation [40,41].
The entrapment efficacy of menthosomal vesicles is assessed to identify the extent to which the drug is loaded into the vesicles. High encapsulation efficiency also rules out the chances of the drug getting lost within the cartridge and leaking out slowly and steadily. This is determined through centrifugation or ultra filtration and then through the determination of free and entrapped of all drug through UV-Vis spectrometry, HPLC. This parameter is particularly important in drugs that have low Bioavailability or are slow release products that will be effective over a lengthy period. The spreadability/retention profile and the rheology of the gel are also analyzed during the formulation process. Viscometry or rheometry is used for rheological measurements that provide essential information on gel flow properties under various shear conditions to prevent gelation during storage and to facilitate even spreading on the substrate during application. Furthermore, the pH of the gel is determined for skin compatibility and pH range 4.5-5.5 that enhances irritation. Stability testing entail the exposing of the product to conditions such as temperature, humidity and light so as to examine the physical and chemical stability of the formulation. These studies are supported by visual inspection to check on any changes in colour, texture as well as smell in a bid to maintaining the product's acceptability to users until the shelf life reaches its climax [42,43].

3.2. In Vitro Evaluation

Studies have helped understand the menthosomal gels drug releasing and permeation behavior in- vitro. Such studies include the drug release studies which are usually done using Franz diffusion cells and the gel is placed in the donor chamber while the receptor chamber is filled with an appropriate medium to mimic biological conditions. These studies help to control the release rate and the type of release: it can be diffusion or erosion and it can occur in any proportion with the other. The collected data are then necrotized mathematically into some models (viz., zero order, first order, Higuchi or Korsmeyer-Peppas model) for the knowledge about the release profile and extrapolation of in vivo performance. The permeation studies are important for determining the efficacy in which the formulation can deliver the incorporated drugs through the skin. These studies employ the animal or human skin explants which are mounted on a diffusion cell. The extent to which a specific drug content is delivered and accumulated within the skin layers is measured, giving an idea of the efficiency of the formulation in topicals or transdermals. The improvement of permeation is one of the key benefits that can be obtained by using menthosomal gels, and these investigations provide evidence of the nature of menthol as a permeation enhancer. The accumulation of the drug in the epidermis and dermis layers is of great value for localized therapeutic actions, and measurement of drug concentrations in the receptor fluid points to its ability for the systemic administration [44,45]. Further testing, for instance the lipid compatibility test, may be performed to support the likelihood of the interaction between the Menthosomal vesicles and the skins lipid bilayer. These tests can
enlighten the researchers on the way in which the menthosomal gels improve permeation [46].

3.3. In Vivo Evaluation

The therapeutic effect of menthosomal gels has been confirmed in in vivo experiments carried out in higher organisms. The pharmacokinetic investigations are subjected to investigate the absorption, distribution, metabolism and eliminate or exploding the drug in case of using the menthosomal gels. These studies help to set a reference for the bioavailability of the drug with respect to the conventional formulations. Pharmacokinetics studies that involves the use of drugs with radioactive or other detectable labels, or other technique imaging could give information on the distribution and accumulation of the drug at the targeted site particularly for transdermal drug delivery system. The effectiveness of menthosomal gels is evaluated at the cellular level employing animal models related to the type of disease. For example, in the dermatological applications, inflammatory animal models of skin diseases, psoriasis, or wound healing are employed for assessing the anti-

inflammatory, antimicrobial or regenerative effects of the gel, respectively. These models assist in deciding some of the most important parameters, including the decrease of inflammation, the increase of the healing rate, or the prevention of worsening of the disease [47–49].

Additional necessary tests are toxicity studies in order to confirm that the formulation is safe. Irritant, redness, or rash reactions are determined in dermal toxicity tests conducted when applying the gel. Repeated application studies may also be done to assess long-term safety also. Further safety information is given by cytotoxicity studies, preferably employing cell lines as close as possible to the target tissue, especially for formulations developed for sensitive or Damaged Skin. It may be necessary to carry out haemocompatibility testing in case of transdermal formulations to check the lack of systemic effect. Recent and more refined in vivo imaging, for instance, fluorescence imaging or radioactivity labeling, are applied to map out the pathways of drug delivery and to demonstrate that the enthosomal gel does indeed transport the drug to the target area in the animal body. Real-time interpretation of biodistribution and the penetration of the designed formulation can be analyzed using these tools, which adds value to the formulation [50,51].

4. Applications of Menthosomal Gels in Modern Medicine

Menthosomal gels are used in the varied aspects of modern medicine due to their usefulness in imagery enhancement of drug solubility, stability, and permeation. The size and shape of their multivesicular structure together with the ability of menthol to improve permeability makes these sort of preparations useful for a wide range of medical and beauty applications. Outlined below are usages of statistical methods in different domains.

4.1. Dermatological Applications

Menthosomal gels have demonstrated potential towards dermatological disorders because of the capacity to administer the drug to the skin layers. They are especially suitable in situ conditions for which systemic drug delivery of the medication is not necessary, such as psoriasis, eczema, acne, and fungal infections. In psoriasis, menthosomal gels help the depot the anti-inflammatory or immunomodulatory agents to the skin and decrease the formation of inflammatory plaques. Similarly, in acne, penetration if antibacterial agents like clindamycin or benzoyl peroxide is better focusing on Propionibacterium acnes in the sebaceous follicles. Menthosomal gels are also an ideal method for the administration of Steroids which are normally used in the treatment of skin conditions. They afford valuable prodrug properties, such as the precise regulation of drug release duration to maintain therapeutic drug concentration whilst minimizing absorption of the drug into systemic circulation and consequently the adverse effects. In addition, properties of cooling and soothing associated with menthol as an ingredient assist in reduction of itch and irritation and increase compliance among patients [57,58].

4.2. Topical and Transdermal Applications

Thus, the improvement of the drug permeation through the skin by menthosomal gels makes them appropriate for topical/transdermal uses. Topically, menthosomal gels alleviate ailments and control drug concentrations in the superior cortex of the epidermis without reaching deep systemic circulation. This is beneficial for the treatment of focused soreness, inflammation and skin infection. Menthosomal gels as described in transdermal applications are used as depot systems and provide an extra advantage over the oral or parenteral routes for systemic drug delivery. It avoid first pass metabolism so enhances the bioavailability of drugs with poor oral absorption. NSAIDs, hormones and antihypertensive agents have also been successfully delivered using menthosomal gels. For instance, pain relievers like diclofenac are delivered through the skin and give extended pain relief to conditions like arthritis, while the estrogen or testosterone or other hormones with required concentration are also administered through skin.

Menthol increases the rate of transdermal release by breaking the lipid layers of stratum corneum to facilitate better tissue perfusion of drugs in to the systemic circulation. This makes menthosomal gels a preferable and patient compliant system for treating chronic diseases [59].

4.3. Systemic Drug Delivery

Even though menthosomal gels have been previously described as topical and transdermal delivery vehicles, there is evidence that they can be employed for systemic drug delivery as well. Since they can improve dissolution rates of BCS class II and IV drugs, they can certainly offer an effective delivery system for drugs to treat systemic diseases. For example, menthosomal gels are used for the dermal administration of antidiabetic drugs, cardiovascular agents and CNS medications, instead of oral or intravenous route of administration.

Menthosomal gels thus have a constant and slow drug release at the systemic level, thereby giving longer plasma

drug concentrations without the need for repeated administration. This application is especially useful for drugs that have low toxicity differences between the toxic and therapeutic doses, or for those that depend on constant concentrations in plasma. Thirdly, menthosomal gels do not cause GI side effects inherent with most oral formulations and this makes it ideal for sensitive patient populations [60–62].

4.4. Cosmetic Applications

As menthosal gelling agents have been more accepted by cosmetics industries for enhancing the skin hydrating efficacy and accelerating the penetration of active ingredients through the skin layers as compared to conventional systems. They are well incorporated in anti-aging products because they boost the ability of other ingredients like retinoids, hyaluronic acid and peptides which help minimize wrinkles, improve skin elasticity and hydration respectively. This creates an added value for these products because the sensation that comes with using products bearing the menthol trademark has additional cooling effect. Besides anti-aging features, the menthosomal gels are employed in skin- whitening preparations as carriers of substances including kojic acid and vitamin C. This allows for deeper skin layers penetration guaranteeing even pigmentation reduction and better skin tone. Menthosomal systems also apply for sunscreen formulations because of the improvement of stability and photoprotective action of UV filters [63,64].

4.5. Other Potential Uses

Going beyond the conventional uses, the gels in menthosomal structure make a versatile and broad- spectrum system. They have demonstrated promise as depots for antifungal and antiviral drugs especially for disorders such as onychomycosis and herpes simplex. Their increased penetration facilitates drug deposition in the affected sites, thus optimising the treatment results. Menthosomal gels are even in the process of being used in the wound dressing area also because it is helpful in the healing system because they can give growth factors, antibiotics, or anti-inflammatory agents that help the repairing of tissues without the possibility of infection. Menthol has a cooling side and that relieves the pain or discomfort of the area where the wound is located, and makes patient feel more comfortable.

Currently in oncology, they are investigating the use of menthosomal gels in chemotherapy where the drug is administered locally to skin cancer and hence reducing passing through the bloodstream bringing about toxicity to the body’s tissues. They also bear the possibility of using a patch to apply vaccines or biologics though the skin to deliver immunization [65].

5. Advantages of Menthosomal Gels

A. Enhanced Drug Permeation

Menthosomal gels enhance the drug follicle penetration through the skin layers by the use of menthol as a permeation promoter. Menthol destabilizes the lipid bilayer of the SC removing it as the chief barrier that prevents drug penetration to deeper tissues.

B. Improved Drug Solubility

A vesicular system in menthosomal gels improves the walt solubility of the compound that possess low water solubility. These drugs are insoluble in water and other solvents and the incorporation of these drug molecules into lipid vesicles enhances their uptake across biological membranes, for digestion.

C. Controlled and Sustained Drug Release

The feature of structural design of the liposomes that allows for the gradual release of the drug over an extended period is one of the important benefits. This timed liberation also prevents patient compliance by having to frequently apply the drug or cream in question.

D. Targeted and Localized Delivery

Menthosomal gels which enable selective targeting of the drug release at the site of action reduces side effects. These features are especially valuable in dermatological cases when treatment should be carried out only in a particular area of the skin.

E. Non-Invasive and Patient-Friendly

Through topical delivery system, the menthosomal gels reduce the health burdens that come with oral and

injectable methods of drug delivery. This gel formulation is also easily acceptable by the patients and its easier to apply enhances patient compliance.

F. Reduced Systemic Side Effects

Given that menthosomal gels can be designed for the release of drug within a localized region, the overall body exposure to the drug is minimal and therefore minimizing systemic toxicity, use of the agent for long term therapy is safer.

G. Versatility in Drug Compatibility

Menthosomal gels are multiple functional and associated with the ability to incorporose hydrophillic and lipophilic active agents. This versatility places them within a wide therapeutic utility category ranging from dermatological use to systemic.

H. Cooling and Soothing Effects

Menthol gives a cool. This feeling is calming on an inflamed/itchy area and is particularly beneficial in disorders such as psoriasis, eczema, or other inflammatory skin diseases.

I. Stability of Sensitive Drugs

Vesicular encapsulation of, for instance, in menthosomal gels offers an assurance of an extended shelf life through protection of the drug from light, heat, as well as oxidation processes.

J. Bypassing First-Pass Metabolism

Menthosomal gels utilized for DD of drugs across skin epidermis do not pass through the GI mucosa and liver; hence, no first-pass metabolism is experienced. This brings in drugs that would otherwise be cleared before getting to the systemic circulation making the bioavailability of the drugs high.

K. Applicability Across Multiple Domains

Interestingly, menthosomal gels can be versatilely applied in dermatological, transdermal or systemic treatments, as well as in cosmetic products. It makes them usable in many sectors of medicine and cosmetology since they can be adjusted with other products.

L. Improved Patient Compliance

Menthosomal gels are easy to apply and non-greasy making patients compliant with treatment regimens. They also improve the satisfaction of users mainly due to their calming nature .

M. Potential for Combination Therapies

Menthosomal gels also have the capability to encapsulate more than one drug and enhance efficient therapeutical outcomes with multi-tiered disorders [66,67].

6. Challenges and Limitations of Menthosomal Gels

A. Scalability Issues

There is one major problem in shifting from producing products in a laboratory to manufacturing on an industrial scale. Techniques like thin-film hydration, or reverse-phase evaporation work well for small scale operations, but are hefty for large scale production and call for changes and enhanced instruments.

B. Stability Concerns

Here again, menthosomal gels may have the disadvantage of stability problems especially during storage. Changes in menthol and lipid composition, ideal vesicle size and aggregation or leakage of the encapsulated drug can reduce the efficiency and the shelf life of the formulation.

C. Skin Irritation and Sensitivity

However, the concentration of menthol is known to improves permeation, but their concentration must be well regulated. However, due to its potential for skin sensitisation, overuse of menthol, especially on people with sensitive skin, results to rashing, redness, or dermatitis hence its restricted use.

D. Cost of Raw Materials and Production

Some of the excipients used in formulation of menthosomal gels such as high purity lipids and stabilizers can be costly. The high costs necessary for the procurement of such equipment as well as the elaborate procedures required results in high costs of production, which may prove a hindrance to their commercial exploitation.

E. Regulatory Hurdles

Approval for NDA of menthosomal gels is difficult because of many preclinical and clinical studies that have to be undertaken. All three components take time and efforts to prove safety, efficacy and stability of a product thus delaying market entry.

F. Limited Drug Load Capacity

This fact is important because the vesicular system has a limited capacity for encapsulating drugs – particularly, hydrophilic drugs. This limitation could limit the applicability of menthosomal gels where high drug concentration is needed, use of other strategies or supplementing menthosomal gels may be necessary.

G. Short-Term Cooling Effect

As much as menthol has the cooling effect, this effect only lasts for a few minutes at most. This is a considerable challenge in menthosomal gel formulations since getting the lovely prolongation of the sensory benefits implicated in this structure means also risking the stimulation of irritation.

H. Compatibility Issues with Certain Drugs

Some drugs however cannot be used with menthosomal gels because menthol or the lipids in the gels react chemically with the drug. They can theoretically cause such issues as, lower encapsulation efficiency, degradation of the drug, or a dose's decreased biological activity.

I. Environmental Sensitivity During Storage

Menthosomal gels have a tendency to change with conditions that prevail environmentally like temperatures, humidity and light. The integrity of the vesicular and the incorporated drug is also sensitive to the storage conditions required to preserve the properties of the vesicular system.

J. Limited Knowledge and Standardization

However, a lot of information about thus menthosomal gels is still scarce such as; the long term impact, industrial scale production of it and proper standard methods of assessment on it. This makes them limited in their usage across the pharmaceutical and cosmetic corporations.

K. Patient-Specific Variability

Unlike the individual ingredients in these gels, the overall efficacy of the menthosomal gels could also differ from one patient to another based on specific skin type or health condition, or even age. Ideally, consumers are very selective when making their choices and such variability can pose some hurdles when trying to devise stock conforming products.

L. Competition with Existing Systems

Table 2 shows overall efficacy of the menthosomal gels could also differ from one patient to another based on specific skin type or health condition, or even age. Ideally, consumers are very selective when making their choices and such variability can pose some hurdles when trying to devise stock conforming products [68–70].

7. Future Perspectives

Research into menthosomal gels continues to bring exciting breakthroughs that will help solve current issues and find new applications for the future. Research shows that adding artificial intelligence and machine learning systems will make it easier to design better formulations. AI tools enable developers to find the best amounts of menthol lipids and drugs for their products by predicting the best mix ahead of making gel samples. The growth of menthosomal gels depends on finding newer APIs to encapsulate. Through medicine development technology the menthosomal gel platform shows promise as a stable delivery system for proteins, peptides and nucleic acids. Menthosomal gel delivery systems show better penetration results when they partner with other drug delivery methods such as microneedles [71].

Personalized medical treatments will gain more value through the special features of menthosomal gels. Through personalized gel preparations menthosomal medicine can match patients' unique requirements for dermatology while optimizing drug matching to body profile and treatment aims. New green pharmaceutical processes will help make menthosomal gels more environment-friendly while answering rising customer demands for eco-friendly medicines. Menthosomal gel technology will receive more cosmetic use by extending to anti-aging treatments, skin lightening solutions, and sun protection products. Our research should create better methods to preserve cosmetic ingredients like vitamins and antioxidants while improving their effectiveness and appearance. Scientists see significant scientific potential in using menthosomal gels for worldwide medical solutions particularly in developing better vaccines for skin administration. Vaccines injected without needles would let more people get medical help in areas with weak healthcare systems. Through modern technology and improved designs menthosomal gels will gain widespread use in drug delivery systems and healthcare .

8. Conclusions

Recent advances in drug delivery technology show how menthol's permeation boosters benefit vesicular structures. Their capacity to deliver drugs that need water and oil-based environments through tissues demonstrates their many uses and future prospects. Menthosomal gels represent a gentle patient-friendly technique that allows medicines to enter body tissues while improving skin health. The applications of menthosomal gels extend from beauty products to new vaccine administration techniques because of their wide flexibility. The potential advantages of menthosomal gels need ongoing research to resolve production problems while meeting safety standards. Formulations that use modern techniques combined with artificial intelligence technology must follow sustainable standards to help us solve these barriers to innovation. Menthosomal gels can better treat patients because healthcare providers can personalize them with combination therapies according to each person's specific medical needs. Future research will increase the number of practical medical applications for this innovative medication system. Innovative drug delivery systems are changing how medicines work through technology while solving existing problems to help patients better [72].

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

All authors contributed equally

REFERENCES

[1] Emeihe EV, Nwankwo EI, Ajegbile MD, Olaboye JA, Maha CC. Revolutionizing drug delivery systems: Nanotechnology-based approaches for targeted therapy. International Journal of Life Science Research Archive 2024;7:040–58.

[2] Basavaraj S, Betageri GV. Can formulation and drug delivery reduce attrition during drug discovery and development—review of feasibility, benefits and challenges. Acta Pharmaceutica Sinica B 2014;4:3–17.

[3] Kakkar A, Traverso G, Farokhzad OC, Weissleder R, Langer R. Evolution of macromolecular complexity in drug delivery systems. Nature Reviews Chemistry 2017;1:0063.

[4] Enaru B, Fărcaş A, Stănilă A, Socaci S, Diaconeasa Z. Novel methods for liposome formulation: advancements and innovations. 2023.

[5] Gonçalves S, Fernandes L, Caramelo A, Martins M, Rodrigues T, Matos RS. Soothing the Itch: The Role of Medicinal Plants in Alleviating Pruritus in Palliative Care. Plants 2024;13:3515.

[6] Apolinário AC, Hauschke L, Nunes JR, Lopes LB. Lipid nanovesicles for biomedical applications:'What is in a name'? Progress in Lipid Research 2021;82:101096.

[7] Singh S, Dodiya TR, Dodiya R, Ushir YV, Widodo S. Lipid nanoparticulate drug delivery systems: approaches toward improvement in therapeutic efficacy of bioactive molecules. Drug carriers, IntechOpen; 2022.

[8] Manjushree H, Nayak D, Halagali P, Rathnanand M, Tawale R, Ananthmurthy K, et al. Menthol-based Novel Ultra- Deformable Vesicle: Formulation, Optimization and Evaluation of an Antifungal Drug. AAPS PharmSciTech 2025;26:23. https://doi.org/10.1208/s12249-024-03021-3.

[9] Lin D, Kelly AL, Miao S. Preparation, structure-property relationships and applications of different emulsion gels: Bulk emulsion gels, emulsion gel particles, and fluid emulsion gels. Trends in Food Science & Technology 2020;102:123–37. https://doi.org/10.1016/j.tifs.2020.05.024.

[10] Thabet Y, Elsabahy M, Eissa NG. Methods for preparation of niosomes: A focus on thin-film hydration method. Methods 2022;199:9–15. https://doi.org/10.1016/j.ymeth.2021.05.004.

[11] Muramatsu H, Lam K, Bajusz C, Laczkó D, Karikó K, Schreiner P, et al. Lyophilization provides long-term stability for a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine. Molecular Therapy 2022;30:1941–51.

[12] Engelhardt RL, da Silva TM, do Carmo FA, Antunes Rocha HV. In vitro transdermal drug permeation tests: a regulatory scenario evaluation. Revista Colombiana de Ciencias Químico-Farmacéuticas 2022;51:41–67.

[13] Ball K, Bruin G, Escandón E, Funk C, Pereira JNS, Yang T-Y, et al. Characterizing the Pharmacokinetics and Biodistribution of Therapeutic Proteins: An Industry White Paper. Drug Metab Dispos 2022;50:858–66. https://doi.org/10.1124/dmd.121.000463.

[14] Akram MW, Jamshaid H, Rehman FU, Zaeem M, Khan JZ, Zeb A. Transfersomes: a Revolutionary Nanosystem for Efficient Transdermal Drug Delivery. AAPS PharmSciTech 2021;23:7. https://doi.org/10.1208/s12249-021-02166- 9.

[15] Nayak D, Tippavajhala VK. A comprehensive review on preparation, evaluation and applications of deformable liposomes. Iranian Journal of Pharmaceutical Research: IJPR 2021;20:186.

[16] Parhi R, Mohanta BC, Jena GK, Sahoo SK. Recent advancements in lipid-based nanocarriers for transdermal drug delivery. Green Sustainable Process for Chemical and Environmental Engineering and Science, Elsevier; 2023, p. 347–401.

[17] Kaur P. Flexible Vesicular Systems: A Mini Review on the Explored Areas for Transdermal Delivery. Systematic Reviews in Pharmacy 2023;14.

[18] Wadher K, Trivedi S, Rarokar N, Umekar M. Development and assessment of rutin loaded transfersomes to improve ex vivo membrane permeability and in vitro efficacy. Hybrid Advances 2024;5:100144.

[19] Shankar R, Kumar M, Upadhyay PK. Comparative Study on Enhanced Skin Permeation Efficiency of Phenylephrine via Novel Lipid Vesicles: A Promising Approach in Preventing Chemotherapy-induced Alopecia Management. CPB 2025;26:465–75. https://doi.org/10.2174/0113892010336809240815050316.

[20] Jafari A, Daneshamouz S, Ghasemiyeh P, Mohammadi-Samani S. Ethosomes as dermal/transdermal drug delivery systems: applications, preparation and characterization. Journal of Liposome Research 2023;33:34–52. https://doi.org/10.1080/08982104.2022.2085742.

[21] Balcao VM, Santos MG, Martins PR, Chaud MV, Oliveira Junior JM de, Tubino M, et al. Development and characterization of a gel formulation integrating microencapsulated nitrofurazone. Curr Pharm Biotechnol 2014;14:1036–47. https://doi.org/10.2174/1389201015666140113112323.

[22] Ghosh M, Singh D, Singh A. Recent advancements in nanocarrier based therapy against acne: The role of biosurfactants and status of patents. Health Sciences Review 2023;7:100088.

[23] Fernandes F, Dias-Teixeira M, Delerue-Matos C, Grosso C. Critical review of lipid-based nanoparticles as carriers of neuroprotective drugs and extracts. Nanomaterials 2021;11:563.

[24] Panchal K, Reddy A, Paliwal R, Chaurasiya A. Dynamic intervention to enhance the stability of PEGylated Ibrutinib loaded lipidic nano-vesicular systems: transitioning from colloidal dispersion to lyophilized product. Drug Deliv and Transl Res 2024;14:3269–90. https://doi.org/10.1007/s13346-024-01555-4.

[25] Kaur P. Flexible Vesicular Systems: A Mini Review on the Explored Areas for Transdermal Delivery. Systematic Reviews in Pharmacy 2023;14.

[26] Clemente CM, Onnainty R, Usseglio N, Granero GE, Ravetti S. Preformulation Studies of Novel Menthol Prodrugs with Antiparasitic Activity: Chemical Stability, In Silico, and In Vitro Permeability Assays. Drugs and Drug Candidates 2023;2:770–80.

[27] Jacob S, Nair AB, Shah J, Sreeharsha N, Gupta S, Shinu P. Emerging Role of Hydrogels in Drug Delivery Systems, Tissue Engineering and Wound Management. Pharmaceutics 2021;13:357. https://doi.org/10.3390/pharmaceutics13030357.

[28] Nayak D, Shetty MM, Halagali P, Rathnanand M, Gopinathan A, John J, et al. Formulation, optimization and evaluation of ibuprofen loaded menthosomes for transdermal delivery. International Journal of Pharmaceutics 2024;665:124671.

[29] Manjushree H, Nayak D, Halagali P, Rathnanand M, Tawale R, Ananthmurthy K, et al. Menthol-based Novel Ultra- Deformable Vesicle: Formulation, Optimization and Evaluation of an Antifungal Drug. AAPS PharmSciTech 2025;26:23. https://doi.org/10.1208/s12249-024-03021-3.

[30] Enaru B, Fărcaş A, Stănilă A, Socaci S, Diaconeasa Z. Novel methods for liposome formulation: advancements and innovations. 2023.

[31] Jafari A, Daneshamouz S, Ghasemiyeh P, Mohammadi-Samani S. Ethosomes as dermal/transdermal drug delivery systems: applications, preparation and characterization. Journal of Liposome Research 2023;33:34–52. https://doi.org/10.1080/08982104.2022.2085742.

[32] Mohapatra S, Mirza MA, Ahmad S, Farooq U, Ansari MJ, Kohli K, et al. Quality by design assisted optimization and risk assessment of black cohosh loaded ethosomal gel for menopause: Investigating different formulation and process variables. Pharmaceutics 2023;15:465.

[33] Garg U, Jain K. Dermal and transdermal drug delivery through vesicles and particles: Preparation and applications. Advanced Pharmaceutical Bulletin 2021;12:45.

[34] Abdallah MH, Lila ASA, Unissa R, Elsewedy HS, Elghamry HA, Soliman MS. Brucine-Loaded Ethosomal Gel: Design, Optimization, and Anti-inflammatory Activity. AAPS PharmSciTech 2021;22:269. https://doi.org/10.1208/s12249-021-02113-8.

[35] Parhi R, Mohanta BC, Jena GK, Sahoo SK. Recent advancements in lipid-based nanocarriers for transdermal drug delivery. Green Sustainable Process for Chemical and Environmental Engineering and Science, Elsevier; 2023, p. 347–401.

[36] Kiranjeet K, Gurpreet K, Hanum S, Ravika N, Kaura NJ. Current Status and Future Perspective of Transferosomes- an Effective Vesicular Carrier for Delivery of Drugs. Journal of Coastal Life Medicine 2022;10:325–38.

[37] Maritim S, Boulas P, Lin Y. Comprehensive analysis of liposome formulation parameters and their influence on encapsulation, stability and drug release in glibenclamide liposomes. International Journal of Pharmaceutics 2021;592:120051.

[38] Reginald-Opara JN, Svirskis D, Paek SY, Tang M, O'Carroll SJ, Dean JM, et al. The involvement of extracellular vesicles in the transcytosis of nanoliposomes through brain endothelial cells, and the impact of liposomal pH- sensitivity. Materials Today Bio 2022;13:100212.

[39] Szymczak J, Cielecka-Piontek J. Fisetin—In search of better bioavailability—From macro to nano modifications: A review. International Journal of Molecular Sciences 2023;24:14158.

[40] Nayak D, Shetty MM, Halagali P, Rathnanand M, Gopinathan A, John J, et al. Formulation, optimization and evaluation of ibuprofen loaded menthosomes for transdermal delivery. International Journal of Pharmaceutics 2024;665:124671.

[41] Duangjit S, Takayama K, Bumrungthai S, Mahadlek J, Ngawhirunpat T, Opanasopit P. Development of invaethosomes and invaflexosomes for dermal delivery of clotrimazole: optimization, characterization and antifungal activity. Pharmaceutical Development and Technology 2023;28:611–24. https://doi.org/10.1080/10837450.2023.2229104.

[42] Nayak D, Shetty MM, Halagali P, Rathnanand M, Gopinathan A, John J, et al. Formulation, optimization and evaluation of ibuprofen loaded menthosomes for transdermal delivery. International Journal of Pharmaceutics 2024;665:124671.

[43] Wadher K, Trivedi S, Rarokar N, Umekar M. Development and assessment of rutin loaded transfersomes to improve ex vivo membrane permeability and in vitro efficacy. Hybrid Advances 2024;5:100144.

[44] Nayak D, Shetty MM, Halagali P, Rathnanand M, Gopinathan A, John J, et al. Formulation, optimization and evaluation of ibuprofen loaded menthosomes for transdermal delivery. International Journal of Pharmaceutics 2024;665:124671.

[45] Parhi R, Mohanta BC, Jena GK, Sahoo SK. Recent advancements in lipid-based nanocarriers for transdermal drug delivery. Green Sustainable Process for Chemical and Environmental Engineering and Science, Elsevier; 2023, p. 347–401.

[46] Nayak D, Tippavajhala VK. A comprehensive review on preparation, evaluation and applications of deformable liposomes. Iranian Journal of Pharmaceutical Research: IJPR 2021;20:186.

[47] ElShagea HN, Makar RR, Salama AH, Elkasabgy NA, Basalious EB. Ultradeformable nanocarriers for efficient transdermal drug delivery. Bulletin of Faculty of Pharmacy Cairo University 2023;61:9.

[48] Shankar R, Kumar M, Upadhyay PK. Comparative Study on Enhanced Skin Permeation Efficiency of Phenylephrine via Novel Lipid Vesicles: A Promising Approach in Preventing Chemotherapy-induced Alopecia Management. CPB 2025;26:465–75. https://doi.org/10.2174/0113892010336809240815050316.

[49] Mohd H, Dopierała K, Zidar A, Virani A, Michniak-Kohn B. Effect of Edge Activator Combinations in Transethosomal Formulations for Skin Delivery of Thymoquinone via Langmuir Technique. Scientia Pharmaceutica 2024;92:29.

[50] Kaur P, Verma S, Tomar B, Vyas M, Kakoty V, Saha P, et al. Exploring Applications of Flexible Vesicular Systems as TransdermalDrug Delivery. CDD 2024;21:1062–72. https://doi.org/10.2174/1567201821666230830125253.

[51] Yingngam B. Advances in Nanomaterials for Drug Delivery. Cutting-Edge Applications of Nanomaterials in Biomedical Sciences 2024:22–85.

[52] Ashizawa K. Nanosize Particle Analysis by Dynamic Light Scattering (DLS). Yakugaku Zasshi 2019;139:237–48. https://doi.org/10.1248/yakushi.18-00171-1.

[53] Smith MC, Crist RM, Clogston JD, McNeil SE. Zeta potential: a case study of cationic, anionic, and neutral liposomes. Anal Bioanal Chem 2017;409:5779–87. https://doi.org/10.1007/s00216-017-0527-z.

[54] Amini Y, Amel Jamehdar S, Sadri K, Zare S, Musavi D, Tafaghodi M. Different methods to determine the encapsulation efficiency of protein in PLGA nanoparticles. Bio-Medical Materials and Engineering 2017;28:613–20. https://doi.org/10.3233/BME-171705.

[55] Yunoki S, Sugimoto K, Ohyabu Y, Ida H, Hiraoka Y. Accurate and Precise Viscosity Measurements of Gelatin Solutions Using a Rotational Rheometer. FSTR 2019;25:217–26. https://doi.org/10.3136/fstr.25.217.

[56] Jayadev S, Yusuff I. Robust U-HPLC Method Development of Desonide and its Application to *In Vitro* Release Testing (IVRT) of Topical Cream Products. CPA 2024;20:327–44. https://doi.org/10.2174/0115734129298659240606103013.

[57] Kaur P, Verma S, Tomar B, Vyas M, Kakoty V, Saha P, et al. Exploring Applications of Flexible Vesicular Systems as TransdermalDrug Delivery. CDD 2024;21:1062–72. https://doi.org/10.2174/1567201821666230830125253.

[58] Nayak D, Tippavajhala VK. A comprehensive review on preparation, evaluation and applications of deformable liposomes. Iranian Journal of Pharmaceutical Research: IJPR 2021;20:186.

[59] Harwansh RK, Mishra S, Mazumder R, Deshmukh R, Rahman A. Recent Updates on Transdermal Drug Delivery Approaches for theManagement of Gout and its Clinical Perspective. CPB 2023;25:159–78. https://doi.org/10.2174/1389201024666230606143827.

[60] Munir M, Zaman M, Waqar MA, Hameed H, Riaz T. A comprehensive review on transethosomes as a novel vesicular approach for drug delivery through transdermal route. Journal of Liposome Research 2024;34:203–18. https://doi.org/10.1080/08982104.2023.2221354.

[61] Jafari A, Daneshamouz S, Ghasemiyeh P, Mohammadi-Samani S. Ethosomes as dermal/transdermal drug delivery systems: applications, preparation and characterization. Journal of Liposome Research 2023;33:34–52. https://doi.org/10.1080/08982104.2022.2085742.

[62] Parhi R, Mohanta BC, Jena GK, Sahoo SK. Chapter 14 - Recent advancements in lipid-based nanocarriers for transdermal drug delivery. In: Inamuddin, Neves Cruz J, Altalhi T, editors. Green Sustainable Process for Chemical and Environmental Engineering and Science, Elsevier; 2023, p. 347–401. https://doi.org/10.1016/B978-0-323- 95171-5.00001-7.

[63] Khan P, Akhtar N. Phytochemical investigations and development of ethosomal gel with *Brassica oleraceae* L. (Brassicaceae) extract: An innovative nano approach towards cosmetic and pharmaceutical industry. Industrial Crops and Products 2022;183:114905. https://doi.org/10.1016/j.indcrop.2022.114905.

[64] Sallustio V, Farruggia G, Di Cagno MP, Tzanova MM, Marto J, Ribeiro H, et al. Design and Characterization of an Ethosomal Gel Encapsulating Rosehip Extract. Gels 2023;9:362. https://doi.org/10.3390/gels9050362.

[65] Alqahtani A, Raut B, Khan S, Mohamed JMM, Fatease AA, Alqahtani T, et al. The Unique Carboxymethyl Fenugreek Gum Gel Loaded Itraconazole Self-Emulsifying Nanovesicles for Topical Onychomycosis Treatment. Polymers 2022;14:325. https://doi.org/10.3390/polym14020325.

[66] Manjushree H, Nayak D, Halagali P, Rathnanand M, Tawale R, Ananthmurthy K, et al. Menthol-based Novel Ultra- Deformable Vesicle: Formulation, Optimization and Evaluation of an Antifungal Drug. AAPS PharmSciTech 2025;26:23. https://doi.org/10.1208/s12249-024-03021-3.

[67] Sevinç-Özakar R, Seyret E, Özakar E, Adıgüzel MC. Nanoemulsion-Based Hydrogels and Organogels Containing Propolis and Dexpanthenol: Preparation, Characterization, and Comparative Evaluation of Stability, Antimicrobial, and Cytotoxic Properties. Gels 2022;8:578. https://doi.org/10.3390/gels8090578.

[68] Munir M, Zaman M, Waqar MA, Hameed H, Riaz T. A comprehensive review on transethosomes as a novel vesicular approach for drug delivery through transdermal route. Journal of Liposome Research 2024;34:203–18. https://doi.org/10.1080/08982104.2023.2221354.

[69] Kaur P, Verma S, Tomar B, Vyas M, Kakoty V, Saha P, et al. Exploring Applications of Flexible Vesicular Systems as TransdermalDrug Delivery. CDD 2024;21:1062–72. https://doi.org/10.2174/1567201821666230830125253.

[70] Jafari A, Daneshamouz S, Ghasemiyeh P, Mohammadi-Samani S. Ethosomes as dermal/transdermal drug delivery systems: applications, preparation and characterization. Journal of Liposome Research 2023;33:34–52. https://doi.org/10.1080/08982104.2022.2085742.

[71] Kiranjeet K, Gurpreet K, Hanum S, Ravika N, Kaura NJ. Current Status and Future Perspective of Transferosomes- an Effective Vesicular Carrier for Delivery of Drugs. Journal of Coastal Life Medicine 2022;10:325–38.

[72] Amirinejad M, Haghighizadeh A, Etemad L, Rajabi O. Vesicular Carriers for Follicular Drug Delivery. Pharm Sci 2024;31:22–42. https://doi.org/10.34172/PS.024.40827.