



Invasomes as deformable vesicular nanocarriers for enhanced dermal and transdermal drug delivery: A review on composition, mechanism, formulation, characterization, applications and future perspectives

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Abstract

Invasomes are flexible phospholipid-based nano vesicular systems developed to enhance transdermal drug delivery. They are composed of phospholipids, ethanol, and terpenes, which act synergistically to improve skin penetration. Terpenes disrupt the stratum corneum lipid structure, while ethanol increases vesicle deformability and fluidity. This unique composition enables effective delivery of both hydrophilic and lipophilic drugs. Invasomes overcome the major barrier of the skin and provide improved drug deposition in deeper layers. They offer advantages such as non-invasive administration, sustained release, and improved patient compliance. Invasomes have demonstrated potential in the treatment of alopecia, cancer, acne, hypertension, and immunological disorders. Overall, invasomes represent a promising nanocarrier system for advanced topical and transdermal drug delivery.

Keywords: Invasomes, structure, preparation, applications

Introduction

Invasomes are flexible phospholipid-based nanoscale vesicular systems made of phosphatidylcholine, ethanol, terpenes, or a combination of terpenes that have significantly higher percutaneous permeability than normal liposomes [1, 2]. Terpenes are powerful permeation enhancers that significantly increase the stratum corneum drug partitioning, alter the packing of the stratum corneum, disturb its lipid structure, and interact with intracellular proteins [2, 3].

Invasomal vesicle penetration through the skin is facilitated by the synergistic effect of ethanol and terpenes found in the invasomes [4, 5]. Numerous benefits are provided by invasomes, including non-invasive drug delivery, enhanced drug penetration via the skin, distribution of both lipophilic and hydrophilic medicines, and higher patient compliance because the drug is available in semisolid form as a gel or cream [6].

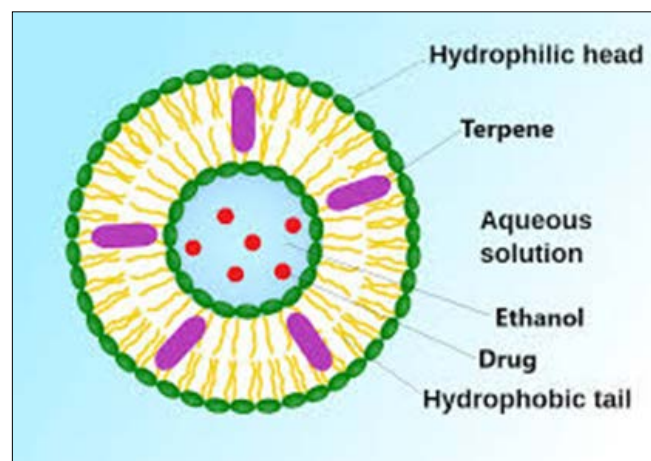


Fig 1: Invasome

Topical delivery provides various advantages over other forms of administration, particularly the oral route. It reduces pharmacological side effects by avoiding hepatic metabolism and delivering pharmaceuticals over an extended period of time [2]. However, a significant obstacle to topical medication distribution is the suppression of drug penetration through the stratum corneum (SC), the skin's outermost layer [7, 8].

Researchers have reported various nanotechnology gel-based formulations for transdermal delivery to improve the therapeutic activity of drugs, such as fusidic acid-loaded nanoemulgel [9], Fluconazole solid lipid nanoparticles gel [10], griseofulvin loaded solid lipid nanoparticles laden gel [11], amphotericin B-loaded Nanostructured Lipid Carriers gel [12], fluconazole loaded liposomes gel [13], tolnaftate pro-vesicular gel [14], clotrimazole loaded. Due to their unique advantages (high permeability) and exceptional adaptability, vesicular delivery systems (liposomes, niosomes, ethosomes, invasomes, etc.) are the potential drug carrier for topical delivery [15, 16].

Androgenetic alopecia (AGA), also known as female-pattern hair loss in women and male-pattern hair loss or common baldness in men, affects up to 70% of all males in later life and at least 50% of men by the age of 50 (Norwood, 1975). Although estimates of its frequency in women have fluctuated greatly, recent research indicates that it affects 6% of women under 50 and 30% to 40% of women over 70 (Norwood, 2001). The hair loss follows a specific pattern, is androgen-dependent, and is inherited. Androgen-stimulated hair follicle miniaturization is thought to target genetically predisposed hair follicles, gradually replacing large, pigmented hairs (terminal hairs) in affected areas with barely noticeable, depigmented hairs (vellus hairs) (Paus and Cotsarelis, 1999). As a result, the density of visible scalp hair gradually decreases [17].

Minoxidil is a piperidinopyrimidine derivative with the chemical formula: 2,6-diamino-4-piperidinopyrimidine-1-oxide (C₉H₁₅N₅O). For many years, minoxidil has been used to treat hair loss. By promoting hair development and decreasing hair loss, the drug has an impact on follicular cells. Within 12 to 24 weeks, therapy termination causes gradual hair loss. Two According to Mori and Uno, MS reduced the telogen phase in treated rats to 1 to 2 days as opposed to roughly 20 days in untreated rats. Anagen bulbs showed an increase in DNA synthesis, indicating that minoxidil stimulated telogen follicles' secondary hair germ cells and accelerated the transition to the anagen phase [18].

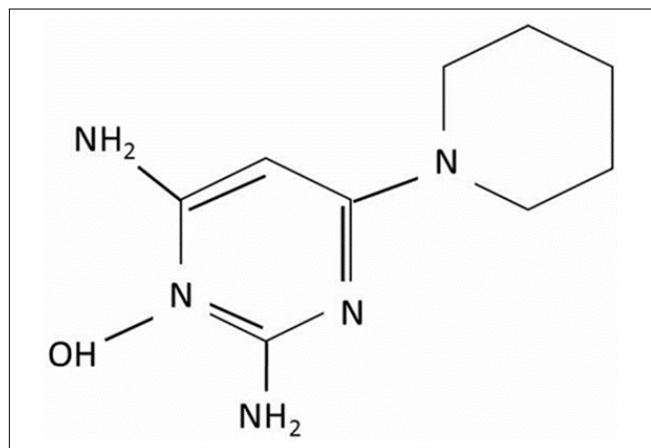


Fig 2: Chemical Structure of Minoxidil

Oral and topical minoxidil for hair loss Male hair growth peaked in the first year of five-year research using topical minoxidil at 2% and 3%, then regrowth gradually decreased in the following years. Nonetheless, over the course of the research, the minoxidil solution preserved non-vellus hair regrowth [19]. In a randomized clinical trial, the 5% minoxidil solution showed greater treatment benefit than 2% for female pattern hair loss [20]. Male AGA, FPHL, chronic telogen effluvium, and traction alopecia can all be safely and effectively treated with low-dose oral minoxidil, which ranges from 0.5 to 5 mg daily, according to several recent studies [21–25].

Invasomes:

Invasomes are soft liposomal vesicles containing trace amounts of ethanol and terpene or terpene assortments, which act as potential transporters with increased skin penetration [26]. Phospholipids (such as phosphatidylcholine, phosphatidylserine, Journal Pre-proof 5 soy phospholipid, egg lecithin, phosphatidylinositol, phosphatidic acid, and phosphatidylglycerol), terpenes (such as citral, cineole, limonene, and eugenol), and water make up these special lipid vesicles [27].

Terpenes, which have the general formula (C₅H₈)_n, improve the percutaneous absorption of both hydrophilic and hydrophobic medications. Terpenes are often utilized as penetration enhancers and are components of essential oils derived from natural sources. Terpenes do, however, have the added benefit of being less irritating to the skin at low doses. Terpenes are also categorized as generally safe by the FDA [28].

Effect of composition of invasome to their physicochemical properties

Ethanol:

Ethanol works well as a permeation enhancer. By giving the vesicles unique appearances in terms of size, zeta potential, entrapment efficacy, skin permeability, and stability, it has a major impact on nano-vascular systems. The size and entrapment effectiveness of the vesicles diminish with increasing ethanol concentration, according to numerous studies. The vesicles became soluble as the ethanol concentration was raised further. Additionally, a high ethanol concentration decreases the thickness of the vesicular membrane and, eventually, the size of the vesicles. Ethanol penetrates the hydrocarbon chains, changing the vesicles' net charge and reducing their average size [29]. The addition of ethanol can also enhance the lipid nanovesicles' fluidity. The tightly packed SC lipids are disrupted by the ethanol's interaction with the lipid components of SC. Ethanol lowers the transition temperature of lipids and modifies the structure of keratinized or lipophilic domains. Compared to liposomes, ethanol-based nanovesicles are softer and less stiff because ethanol makes lipids more fluid. Additionally, ethanol-based nanovesicles have been shown to be more stable during storage, possibly as a result of electrostatic repulsion and the creation of a negative surface charge that prevent vesicle aggregation [30].

Terpenes:

The majority of investigational researchers working on transdermal drug delivery systems talked about how many terpenes or mixtures of terpenes in very small amounts are also intensively discovered as penetration enhancers (also called sorption supporters or accelerants), which penetrate the skin to reversibly lower the barrier resistance. Terpenes have limited potential to cause skin irritation and are part of the Generally Recognized as Safe (GRAS) ingredients. Increasing the solubility of medications in skin lipids, disrupting lipid/protein layers, and/or eliminating skin micro-ingredients that are in charge of preserving the skin's barrier qualities are some of the mechanisms by which terpenes improve percutaneous penetration. Terpenes appear to have enormous potential for usage in transdermal formulations as a result [31].

Phospholipids:

Hydrophilic head groups and hydrophobic acyl chains are linked to the alcohol in phospholipids. An inclusive selection of phospholipids survives due to differences in head groups, aliphatic chains, and alcohols. Therefore, the classes of phospholipids are also improved by the changed sources of phospholipids. Both synthetic (like PEG-ylated phospholipids) and natural (like soybean or egg phosphatidylcholine) phospholipids are frequently utilized in various formulations. There have also been reports of using hydrogenated phosphatidylcholine to manufacture nanovesicles [32].

Role of penetration enhancers in invasomes based drug delivery:

Penetration enhancers (PEs) boost medication diffusivity through the skin by lowering the SC's barrier resistance without harming living cells. PEs should have good solvent qualities, be affordable, odorless, colorless, tasteless, pharmacologically inert, non-irritating, non-toxic,

compatible with medications and excipients, and not show signs of losing bodily fluids, electrolytes, or other endogenous materials. It should be simple to remove from the skin and rapidly return to its natural barrier^[33]. Drugs have been penetrated through the skin using both physical and chemical penetration augmentation techniques^[34]. PEs reduce the potential of the skin's barrier properties and make it easier for medication molecules to quickly pass through the skin. PEs improve the diffusivity of pharmacological compounds across the stratum corneum (SC) via denaturing skin proteins or liquefying skin lipids. Permeation enhancers can function as enhancers, through intracellular protein interactions, or by rearranging the lipids in the skin. Co-enhancers or co-solvents can also be used to improve the drug's partition into the skin^[35]. Almost 360 PEs have been investigated and found to help molecules move through the SC thus far. Alcohol, glycol, terpenes, surfactants, urea, sulphoxides, laurocapram, pyrrolidones, fatty acids, fatty alcohols, and so forth are among them. Essential oils are aromatic compounds that are extracted from natural sources, primarily plants. As skin penetration enhancers, they partition into the stratum corneum and interact with tissue components to reduce the stratum corneum's barrier function without harming the skin cells beneath^[36].

Skin Penetration Mechanism of Invasomes:

Unlike traditional liposomes, invasomes are deformable new vesicles made by adding terpenes that improve the penetration of active pharmacological molecules. These vesicles have a high membrane fluidity and are squishy. Invasomes are distinguished by the presence of ethanol and terpenes^[37]. The primary dynamic force for the deformable lipid vesicles to enter the skin through this method is the hydrophilic phospholipids' desire to flee water-deficient situations^[38]. Additionally, terpenes may promote drug penetration by disrupting the lipid wrapping of SC, which is another potential method of penetration enhancement of elasticity of deformable vesicles^[39]. The results showed that the active drug molecules would first be liberated from the vesicles and then either enter the systemic circulation in the dermis or enter deeper layers of skin on their own. Therefore, using deformable vesicles to improve drug distribution across the skin requires a non-occlusive claim. In this application mode, the transepidermal osmotic gradient fades, which causes deformable vesicles to lose their diffusion driving force^[40]. The lipid bilayers then interact with the SC and alter the intercellular lipid lamellae in the deformable vesicles, which can also function as PEs. The lipophilicity of the medication may affect how this process enhances drug penetration. Depending on the drug's physicochemical characteristics, the interaction of the two processes is important for drug penetration^[41].

Advantages of Invasomes

1. Non-invasive drug delivery system.
2. Enhances penetration of active pharmaceutical ingredients through the skin.
3. Enables targeted delivery of both hydrophilic and lipophilic drugs.
4. Improves patient compliance due to gel or cream dosage forms.
5. Composed of non-toxic and biocompatible excipients.

Disadvantages of Invasomes

1. High production cost.
2. Possibility of drug leakage and vesicle fusion.
3. Phospholipid components may undergo oxidation or hydrolysis, affecting vesicle stability.

Preparation methods for Invasomes:

As per the literature, few methods are described for the proposed novel invasome drug carriers. The most famous approach is the technique of mechanical dispersion and film hydration.

Mechanical dispersion technique

In the mechanical dispersion process, the active drugs/biomolecules, terpenes, or a blend of terpenes are dissolved in an ethanol-containing phospholipid. To produce a straightforward solution, the mixture should be well mixed, vortexed for five minutes, then sonicated for five minutes. The phosphate buffer (pH 7.4), phosphate buffer saline (PBS), and appropriate solvent were then added to the solution for vesicle hydration using a syringe and continuous vortexing for five minutes. In order to extrude multilamellar vesicles using polycarbonate membranes with pore sizes of 400 nm, 200 nm, 100 nm, and 50 nm, the solution was finally sifted and repeated multiple times^[42, 43].

Film hydration technique

The film hydration approach involves dissolving a combination of ethanol and phospholipid in a 2:1 v/v mixture of methanol and chloroform. Using a rotary flash evaporator, this mixture was dried for two hours at 50 °C by reducing the pressure from 500 to 1 mbar. The film was then subjected to a nitrogen flush and maintained at 1 mbar pressure for two hours. For 30 minutes, the deposited film can be hydrated using either PBS (pH 7.4) or a mixture of terpenes, ethanol, and PBS. To create the invasome vesicles, the terpene or mixture of terpenes and ethanol should be introduced after the mixture has cooled. The produced invasome was vortexed, ultrasonicated, and then repeatedly extruded through polycarbonate membranes with different pore sizes^[26, 38].

Evaluation and characterization:

Vesicle shape

Several advanced microscopic techniques, including scanning electron microscopy (SEM) and transmission electron microscopy (TEM), can be used to determine the size of invasome vesicles.

Zeta potential

The zeta potential of drug-loaded invasomes can be calculated using Zetasizer. According to the research, vesicles' negative potential may increase the drug's penetration rate^[45]. Furthermore, the excellent zeta potential shows that the invasomal formulation is stable.

Drug entrapment:

The drug entrapment efficiency is an important evaluation criterion in the drug delivery system. Invasomal drug entrapment efficiency can be measured using a variety of methods, including ultracentrifugation techniques^[34].

Drug content:

An UV spectrophotometer^[46], modified high-performance liquid chromatography, etc., can be used to determine and

quantify the drug content of prepared drug-loaded invasomes [2, 47].

Skin permeation studies:

According to the literature review, permeation experiments have been conducted using a variety of skin types, including human (female) abdominal skin obtained following plastic surgery [48], albino (male) Wistar rat skin [46], pig skin, and rabbit skin following the removal of adipose tissue. Additionally, the diffusion investigations were conducted using Franz diffusion cells, and pH7.4 PBS was present in the receptor compartment [46]. The capacity of an invasomal formulation to enter the skin can be assessed using confocal laser scanning microscopy [43]. Interestingly, these investigations verified that nano-invasomes can readily permeate the skin [46]. Additionally, the invasomes can mix with the skin's lipids and change the distribution of SC, which loosens the tight lipid junctions [35].

Stability studies:

The stability of invasomal dispersion, gel, or suspension can be assessed by monitoring the change in invasome vesicle size, PDI, using DLS. We can use SEM, TEM, or other suitable methods to confirm the invasomal formulation's shape based on stability studies. The zeta potential of invasomal vesicles can be used to calculate the particle-containing charge changes [49].

Penetration enhancement mechanism:

Numerous studies have confirmed that invasomes behave better than normal lipidic vesicles. Here, it has been demonstrated that some components, such as phospholipids, ethanols, and terpenes, are extremely potent penetration enhancers. Regarding phospholipids, phosphatidylcholine, a component of invasomes, is a potent penetrator because of its head group, which has a potent boosting impact. On the other hand, phosphatidylcholine with unsaturated acyl chains enhances the capacity of phospholipids to penetrate [35, 39, 40].

Applications:

1. Immunosuppressive therapy:

Immunosuppressive therapy is improved by nanotechnology-based drug delivery because it reduces side effects and increases targeted delivery. The topical administration of the lipophilic medication cyclosporine A is successfully enhanced by invasomes, a lipid-based nanocarrier. Greater drug deposition in deeper skin layers is made possible by the presence of ethanol and terpenes, which improve skin penetration. Invasomes are therefore a possible method of administering hydrophobic immunosuppressive medications for autoimmune skin conditions.

2. Cancer therapy:

It is still difficult because of the adverse effects and poor efficacy of traditional treatments. Through improved skin penetration, invasomes, a lipid-based nanocarrier technology, promote the administration of hydrophobic anticancer medications. Research revealed that by decreasing tumor size, temoporfin-loaded invasomes greatly enhanced drug deposition in deeper skin layers and enhanced photodynamic therapy results. Similarly, despite reducing systemic side effects, anastrozole-loaded

invasomes improved drug deposition, stability, cytotoxic efficacy, and skin penetration. All things considered, invasomes present a viable method for the focused and efficient topical administration of anticancer medications.

3. Vitamin delivery:

To enhance skin and follicular delivery, isotretinoin, a vitamin A analog used for eosinophilic pustular folliculitis, was successfully incorporated into invasomes. The improved isotretinoin-loaded invasomes demonstrated high drug entrapment, high stability, and nanosized particles. While eugenol improved solubility, deformability, and penetration, increased lipid concentration increased vesicle size and drug entrapment. Ex vivo research showed regulated drug release and high skin penetration. All things considered, isotretinoin invasomal gel is a promising method for targeted follicular distribution; however, prior to human application, clinical research is necessary.

4. Alopecia:

By improving the transdermal distribution of medications that promote hair development, invasomes have demonstrated encouraging prospects in the treatment of alopecia. Because finasteride-loaded invasomes contain ethanol and terpenes, which break down the stratum corneum lipid barrier, they have better skin penetration, stability, and bioavailability than oral administration. In a similar vein, invasomes loaded with minoxidil greatly enhanced drug deposition in the skin while restricting systemic absorption. All things considered, invasomes provide an efficient and focused topical delivery method for the treatment of alopecia, enhancing medication efficacy and lowering adverse effects.

5. Delivery of anti-acne agents:

Invasomes enhance skin penetration and medication deposition, making them beneficial for topical anti-acne treatment. When compared to standard solutions, dapsoneloaded invasomes demonstrated superior stability, entrapment efficiency, and epidermal penetration and deposition, all of which led to increased bioavailability. Similarly, compared to liposomes and commercial formulations, capsaicin-loaded invasomes showed nanosized particles, high stability, and superior skin permeability. All things considered, invasomes show promise as carriers for the effective and targeted topical administration of anti-acne and associated therapeutic drugs.

6. Delivery of antihypertensive agents:

For antihypertensive medications with poor oral bioavailability and first-pass metabolism, invasomes provide an efficient transdermal delivery method. Because ethanol and terpenes provided vesicle deformability, isradipine-loaded invasomes demonstrated improved transdermal flux, increased skin penetration, and high drug entrapment. Olmesartan medoxomil invasomes also produced nanosized particles, enhanced drug penetration, prolonged release, and elevated bioavailability without irritating the skin. All things considered, invasomes show promise as transdermal delivery systems for antihypertensive medications, increasing therapeutic efficacy while reducing oral route constraints.

7. Delivery of anticholinergic agents:

Oral administration of tolterodine tartrate results in adverse consequences, although it is appropriate for transdermal delivery. Invasomes filled with tolterodine were created to enhance skin penetration, lessen adverse effects, and preserve regulated plasma levels. Vesicle flexibility, stability, and drug penetration were all improved by the presence of ethanol and terpenes, with limonene exhibiting the best penetration efficiency. In comparison to the free medication, invasomes greatly enhanced transdermal flow, particularly when paired with iontophoresis. All things considered, invasomes show promise as a transdermal administration method for anticholinergic drugs, increasing patient compliance and efficacy.

8. Delivery of antioxidant agents:

Invasomes are useful transdermal delivery systems for antioxidants like ferulic acid that have short half-lives. Due mostly to vesicle deformability and terpene–skin interactions, ferulic acid–loaded invasomes demonstrated better skin penetration, nanosized homogeneous vesicles, and good stability when compared to standard liposomes. Research using different antioxidants, such as idebenone and azelaic acid, showed that LeciPlex worked better for idebenone delivery, whereas invasomes are especially well suited for azelaic acid administration. Invasomes are a viable method for improving antioxidant skin delivery, and the choice of carrier ultimately depends on drug qualities^[44].

Drug Category	Drug Example	Purpose / Disease	Key Advantage of Invasomes	Route
Immunosuppressive	Cyclosporine A	Psoriasis, autoimmune skin disorders	Deep skin penetration, reduced systemic exposure	Topical
Anticancer	Temoporfin	Skin tumors, photodynamic therapy	Enhanced tumor penetration, improved PDT efficacy	Topical
Anticancer	Anastrozole	Breast cancer (postmenopausal)	Avoids first-pass metabolism, better skin deposition	Transdermal
Vitamin analog	Isotretinoin	Folliculitis, acne-related disorders	Follicular targeting, controlled release	Topical
Anti-alopecia	Finasteride	Androgenic alopecia	Increased bioavailability, reduced oral side effects	Transdermal
Anti-alopecia	Minoxidil	Hair growth stimulation	Higher skin retention, limited systemic absorption	Topical
Anti-acne	Dapsone	Mild–moderate acne	Higher skin deposition, improved penetration	Topical
Anti-acne / Analgesic	Capsaicin	Pain, acne-related inflammation	Better permeability than liposomes	Transdermal
Antihypertensive	Isradipine	Hypertension	Enhanced flux, bypasses first-pass metabolism	Transdermal
Antihypertensive	Olmesartan medoxomil	Hypertension	Improved bioavailability, sustained release	Transdermal
Anticholinergic	Tolterodine tartrate	Overactive bladder	Reduced side effects, controlled plasma levels	Transdermal
Antioxidant	Ferulic acid	Skin aging, inflammation	Improved stability, prolonged action	Topical
Antioxidant / Anti-acne	Azelaic acid	Acne, hyperpigmentation	Superior skin penetration	Topical

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