Invasomes: A Novel Deformable Vasicular Nanocarrier For Enhanced Transdermal Drug Delivery

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ARTICLE INFO

ABSTRACT

Invasomes are liposomal vesicles that contain terpenes or terpene combinations and small amounts of ethanol. They function as potential carriers with improved skin penetration. Invasomes have a higher rate of skin perforation than liposomes and ethosomes. Invasomes are novel, elastic phospholipid vesicles that contain ethanol, phosphatidylcholine, and one or more terpenes. The capacity of terpenes to increase percutaneous penetration has been verified by numerous researchers. They interfere with intracellular proteins, alter stratum corneum lipids, and promote drug partitioning into the stratum corneum, all of which have the effect of increasing penetration. The capacity of vesicles to permeate the stratum corneum is enhanced by ethanol. Additionally, ethanol offers a net negative surface charge and inhibits the electrostatic repulsion that would otherwise cause vesicle aggregation. Terpenes and ethanol have a remarkable synergistic effect on the percutaneous absorption. Terpenes, naturally occurring volatile oils that are included among generally accepted as safe compounds and have reversible effects on the lipids of the stratum corneum at lower doses (1–5%), are regarded as clinically sustainable penetration enhancers. Invasomes offer a number of benefits in addition to promoting patient comfort and compliance and increasing drug efficacy. Through the use of an invasomes carrier, medication transport can now be improved through the skin and cellular membranes, which presents both obstacles and potential for future study and the creation of novel, improved medicines.
INTRODUCTION:
For regionalized or systemic effects, the transdermal route is a crucial route. For many medications, the stratum corneum, the top layer of skin, serves as a crucial skin penetration barrier. A number of strategies have been devised to get over this obstacle, including the use of techniques that alter the stratum corneum's (SC) continuity, such as ultrasound, electroporation, and iontophoresis, as well as the use of vehicles and nanocarriers to enhance drug penetration. To enhance the dermal and transdermal distribution of medications, various types of nanocarriers have recently been developed. Vesicular systems seem to be appropriate carriers because of their physicochemical characteristics, such as deformability, size, and charge, which may be tweaked by modifying lipid contents and manufacturing techniques.[1]

These vesicular systems available in a variety of kinds, including Niosomes, Phytosomes, Transferosomes, Electrosomes, Aquasomes, Enzymosomes, Ethosomes, Sphingosomes, and Invasomes, etc., depending on many factors, such as lipoidal and non-lipoidal barriers and therapeutic purposes. Although the nature of these nanosomes is relatively similar, they differ slightly in their composition and properties. [2-10]

First revealed by "Bangham" in 1965, the biological genesis of these vesicles. Drug carriers for controlled drug release are vesicles. Previous research has shown a significant interest in topical administration using liposomes. Deformable liposomes and transferosomes were first generation elastic vesicles introduced by Ceve and Blume in 1992 and were reported to permeate the skin under non-occluded conditions. There have also been reports of vesicles with penetration boosters frequently in recent years. Niosomes, on the other hand, are a class of vesicles made with non-ionic surfactants that were developed for the administration of medications through or into the skin. [11]

<table>
<thead>
<tr>
<th>Vesicle</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomes</td>
<td>Phospholipids and cholesterol as constituents</td>
</tr>
<tr>
<td>Niosomes</td>
<td>Composed of non-ionic surfactants (amphiphiles)</td>
</tr>
<tr>
<td>Transferosomes</td>
<td>Phospholipids, cholesterol and an edge activator</td>
</tr>
<tr>
<td>Vesosomes</td>
<td>Large lipid bilayer enclosing many smallerliposomes</td>
</tr>
<tr>
<td>Flexosomes</td>
<td>Contained phospholipid, an edge activator and positively or negatively charged lipids</td>
</tr>
<tr>
<td>Invasomes</td>
<td>Composed of phosphatidylycholine, ethanol and terpene</td>
</tr>
<tr>
<td>Ethosomes</td>
<td>Phospholipid, ethanol and water</td>
</tr>
<tr>
<td>Ufasomes</td>
<td>Fatty acid vesicles</td>
</tr>
<tr>
<td>Polymer-somes</td>
<td>Self assembled vesicles made of diblock/triblock Copolymers</td>
</tr>
<tr>
<td>Aquasomes</td>
<td>Water, Ceramic core of calcium phosphate, Polyhydroxyoligomers as coating material</td>
</tr>
<tr>
<td>Sphingosomes</td>
<td>Ceramide, Cholesterol, Steryl Amine</td>
</tr>
<tr>
<td>Phytosomes</td>
<td>Phospholipid and Individual phytoconstituient</td>
</tr>
<tr>
<td>Enzymosomes</td>
<td>Vesicles made of Phospholipids, cholesterol, surfactant and entrapped enzymes such as β-glucosidase, β-lactanase, Alkaline phosphatise, etc</td>
</tr>
<tr>
<td>Electrosomes</td>
<td>Hybrid cathode: Dockerin containing reducing oxygen enzyme of copper oxidase. Hybrid anode: Dockerin containing enzymes of formaldehyde dehydrogenase, aldehyde dehydrogenase.</td>
</tr>
</tbody>
</table>

**Invasomes**: The research team led by Professor Alfred Fahr first introduced invasomes in 2002 [12]. Invasomes are liposomal vesicles that contain terpenes or terpene combinations and small amounts of ethanol. They function as potential carriers with improved skin penetration. Invasomes have a higher rate of skin penetration than ethosomes and liposomes. Invasomes offer a number of benefits, such as enhancing patient
comfort and compliance and promoting therapeutic efficacy [13,14]. They constituted a little amount of ethanol, a minor amount of a blend of terpenes (cineole, citral, and d-limonene), and unsaturated soybean lecithin with a high percentage of phosphatidylcholine. [12] Unsaturated phospholipids were chosen since they cause the production of liposomes to be in a liquid crystalline thermodynamic state because of their low melting temperature. Terpenes were introduced with the intention of giving the carrier some deformability. It was believed that because terpenes improve the fluidity of stratum corneum lipid bilayers, which are utilised as penetration enhancers, they would also increase the fluidity of vesicle bilayers. [15]

**Structural Features and Composition of Invasomes:**

Invasomes are the soft liposomal vesicles with minute amounts of ethanol and terpene or terpene mixtures that act as potential transporters with enhanced skin penetration.[16]These special lipid vesicles are composed of water, terpenes or a combination of terpenes (such as citral, cineole, limonene, and eugenol; 1–5% v/v), low concentrations of ethanol (3% to 3.3% v/v), and phospholipids (phosphatidylcholine, phosphatidylserine, soya phospholipid, egg lecithin, phosphatidylinositol, phosphatidic acid and phosphatidyglycerol). [17]The percutaneous absorption of hydrophilic and hydrophobic medicines is accelerated by terpenes, which have a general formula of (C5H8)n. Terpenes are natural-source components of essential oils that are widely employed as penetration enhancers. Terpenes, however, also have the benefit of minimal skin irritancy at low dosages. Terpenes are additionally categorised by FDA as usually safe. [18,19].

![Figure 1: Schematic Structure and Constituents of Invasomes](image)

**Advantages of Invasomes:**
- Non-invasive method of medication delivery
- Improved medication administration through the skin for transdermal drugs
- Drugs that are lipophilic and hydrophilic can be delivered.
- Contains non-toxic ingredients in the formulation
- Patient compliance since the medication can be given in semisolid form (gel or cream).
- Compared to phonophoresis, iontophoresis, and other complex procedures, this is a straightforward way of drug delivery. [21-24]

**Disadvantages of Invasomes:**
- It has a high cost of production.
- Leakage and fusion of a medication or molecule in its capsule.
- The stability of Invasomes may be impacted by either hydrolysis or oxidation of the phospholipid present. [21]
Difference Between Invasomes and Liposomes:
Invasomes after numerous studies prove that they are better absorbed and have specifically better clinical efficacy than liposomes but presence of terpenoids with ethanol makes invasomes unfit for oral, parenteral routes as these terpenoids content can do toxicity but safe for transdermal use and work as penetration enhancers. [26-30]

Table 2: Difference between Invasomes and Liposomes

<table>
<thead>
<tr>
<th>Characters</th>
<th>Invasomes</th>
<th>Liposomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vesicles</td>
<td>Bilayer lipid vesicles</td>
<td>Bilayer lipid vesicles</td>
</tr>
<tr>
<td>Lamellarity</td>
<td>Unilamellar to multilamellar</td>
<td>Unilamellar to multilamellar</td>
</tr>
<tr>
<td>Composition</td>
<td>Unsaturated Soybean lecithin, Ethanol and Mixture of Terpenes</td>
<td>Phospholipids and Cholesterol</td>
</tr>
<tr>
<td>Surfactant Role</td>
<td>Ethanol and Terpenes</td>
<td>Phospholipid (lecithin)</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Nanosized Spheres (vesicles)</td>
<td>Microscopic Spheres (vesicles)</td>
</tr>
<tr>
<td>Flexibility</td>
<td>High Deformability and Elasticity due to ethanol and terpenes</td>
<td>Less flexible than invasomes</td>
</tr>
<tr>
<td>Extent of Skin Permeation</td>
<td>Can easily penetrate to the skin due to ethanol and terpenes effect</td>
<td>Lower Permeation in the skin as stiff shape and large size</td>
</tr>
<tr>
<td>Permeation Mechanism</td>
<td>Fusion/Disruption of StratumCorneum/Trans appendageal Permeation</td>
<td>Diffusion/Fusion/Lipolysis</td>
</tr>
<tr>
<td>Route of Administration</td>
<td>Topical and Transdermal</td>
<td>Oral, Parenteral, Topical and Transdermal</td>
</tr>
<tr>
<td>Zeta Potential</td>
<td>Negative</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

Skin Penetration Enhancing Mechanism of Invasomes:
The invasomes' boosting impact is caused by a number of different ways. When the stratum corneum is at physiological temperature, the lipid layers are tightly packed and have a high degree of conformational order. When ethanol is integrated into a vesicle's membrane, it gives that vesicle the ability to penetrate the stratum corneum because ethanol is known for disrupting the organisation of skin's lipid bilayers. [31] Due to the presence of ethanol, the lipid membrane is packed less tightly than usual vesicles while maintaining equivalent stability, allowing for a more malleable structure, giving it more freedom and the ability to squeeze through tight spaces, such as the gaps created by disturbing the lipid in the stratum corneum.[32] By interacting with lipid molecules in the polar head group region, ethanol causes the stiffness and fluidity of SC lipids to change. [33] Ethanol, eugenol (a terpene), and active are released in fractions as a result of the fusion of a few invasomes with skin. A local application over the membrane may be encouraged by such an initial release of active on the skin's surface [34–36]. With the release of trace amounts of ethanol through invasive dispersion, the SC lipids might fluidize (being outside vesicles). In addition, a significant portion of the invasomes are probably broken to enter the upper SC layers, releasing terpenes, ethanol, and unsaturated phospholipids. (Fig 2a). That would be consistent with the findings of many authors who claim that vesicle disintegrate on the skin's surface and that molecular penetration of vesicle components (such as phospholipids) into the intercellular lipid matrix changes the lipid layers and increases drug penetration by mixing with the SC's intercellular lipid. Free effects
on penetration will also result from the emissions of ethanol, terpenes, and unsaturated phospholipids [34–37]. As they all operate via this mechanism, it is suggested that these penetration improvements be made for the fluidization of intercellular SC lipids. As a result, there may be an increase in the free diffusion volume and the formation of microcavities, which may further improve the spreading coefficient of the medications released from the vesicle. The partitioning of the drug into the intercellular lipid bilayer of the SC is also enhanced by phospholipids, ethanol, and terpenes. The fact that invasomes have potent penetrating agents, however, means that they frequently penetrate by several pathways. Many theories are put out on the possibility of small, undamaged invasomes penetrating the SC. This is in reference to the penetration of invasome vesicles. It involves altered SC lipid organisation, elevated invasome vesicle fluidity brought on by the impact of ethanol, and permitted terpenes. Invasomes also had a higher penetration rate, which may have been a result of their great deformability, which was thought to be related to the high fluidity of vesicles. The invasome's reduced vesicle size aids in the drug's penetration as well. Additionally, since intact deformable, high hydrophilic vesicles appear to follow the skin hydration gradient, the transepidermal osmotic gradient's presence is essential (the driving force) for the diffusion of these vesicles. On the other hand, vesicles merging with the intercellular lipids of the SC may result in the medicine being released into the skin layers (Fig 2b). Moreover, the pilosebaceous units frequently served as a substantial pathway for invasome penetration into the skin (Fig 2c). The released terpenes are anticipated to reduce the perception of pain because of the analgesic characteristic of terpenes [34–37]. As a result of the vesicle's increased diffusivity, which helps to promote invasome penetration, we may say that it contains ethanol and eugenol. A lipidic layer of skin's matrix can be disturbed by the entire invasome vesicle to allow access to the deep dermal region, which is slowly reached by the pilosebaceous region. The many pores around the follicular unit also act as a conduit for unbroken invasomes to make it easier for them to localise in the target area using the hair follicle as a supporting wick. [34, 38].

**Figure 2: Mechanism of Action Possible for Invasomes through outer skin layer Stratum Corneum. (A) enhanced penetration, (B) intact penetration and (C) trans-appendageal penetration [19]. Copyright 2021 Elsevier**

**Synergistic Effects of Ethanol, Phospholipids and Terpenes:**

It has been proven that phospholipids, ethanol, and terpenes have a synergistic effect on cutaneous absorption.[25] According to Dragicevic-Curic et al., one component of the invasome splits apart during permeation in the upper layers of skin and releases phospholipids and terpenes, which act as permeation enhancers and fluidize the intercellular lipids. Additionally, the ethanol in the invasome fluidizes the intercellular lipids and facilitates the entry of flexible vesicles [39,40]. According to Verma et al., invasomes
boosted the transdermal penetration of cyclosporine A in comparison to an ethanolic solution. The increased effectiveness of invasomes in comparison to an ethanolic solution points to a possible synergistic interaction between phospholipid, terpenes, and ethanol. The improved temoporfin (mTHPC) permeability with 1% terpenes was shown by Dragicevic-Curic et al. to be caused by the concentration of terpenes and the synergistic actions of terpenes and ethanol [25]. The results of the studies mentioned above [18,25,41] thus indicate a synergistic interaction between phospholipid, terpenes, and ethanol in the reformation activity of invasomes in contrast to liposomes.

**Potential and Toxicity of Terpenes as a constituting part of Invasomes in Transdermal Drug Delivery System**

To advance the transdermal penetration of medicines, various strategies have been investigated. The most often used approach among them is the employment of powerful and secure kinds of penetration enhancers, such as natural terpenes. Even though penetration enhancers operate well in transdermal distribution, only a few number of drugs have received clinical approval due to their toxicity and skin irritability. The strength of penetration enhancers and their toxicity are often in balance. Even at low concentrations, terpenes exhibit significant lipophilic and hydrophilic chemical penetration efficacy. Interaction with SC intercellular lipids is the deliberate method by which terpene penetration takes place [42]. As permeation promoters for medicinal purposes, terpenes are used alone or in combination with various drug delivery systems [43-46]. Terpenes' toxicities should be taken into account in addition to their potency in comparison to various penetration enhancers. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay and assessment of trans epidermal water loss (TEWL) were used to test the toxicity of terpenes in two skin cell lines, and the results showed that natural terpenes are typically thought to be safer than synthetic ones [47].

**Preparation Techniques for Invasomes: Mechanical dispersion technique**

In the mechanical dispersion process, the active drugs/biomolecules are dissolved in phospholipid containing ethanol together with a terpene or a combination of terpenes. After thoroughly blending, the mixture should be vortexed (5 minutes) and sonicated (5 minutes) to produce a simple solution. Then, using a syringe and constant vortexing, phosphate buffer (pH 7.4), phosphate buffer saline (PBS), or another suitable solvent was added to the solution for hydrating the vesicles (5 min). The solution was then repeatedly sifted for the extrusion of multilamellar vesicles using polycarbonate membranes with pore size varying range (400 nm, 200 nm, 100 nm, and 50 nm) [48, 49]. Figure 3 shows how invasome is prepared by mechanical dispersion.

![Figure 3](image-url)
Film Hydration Technique: The film hydration method involved dissolving an ethanol and phospholipid mixture in a 2:1 v/v solution of methanol and chloroform. By using a rotary flash evaporator and lowering the pressure (from 500 to 1 mbar) for 2 hours (at 50 °C), this mixture was dried. The film was then maintained for a further 2 hours under 1 mbar of pressure while being flushed with nitrogen. It is possible to choose PBS (pH 7.4) or a mixture of terpenes, ethanol, and PBS for the deposit film to be hydrated for 30 minutes. In order to create the invasome vesicles, the mixture must first be cooled before the terpene or terpene combination and ethanol are added. The prepared invasome was vortexed, subjected to ultrasonication, and repeatedly extruded through polycarbonate membranes with a range of pore sizes to capture it [39, 50]. Fig. 4 illustrates the development of an invasome using the film hydration approach.

![Figure 4: Invasomes preparation using film hydration technique](image)

Characterization of Invasomes:

Vesicle Size- The invasome particle size can be determined using photon correlation spectroscopy and dynamic light scattering (DLS). It has been demonstrated that temoporfin invasomes increase vesicle size when terpene content rises. [51]

Zeta Potential- The zeta potential measures the strength of attraction between nearby, similarly charged particles. A high zeta potential indicates stability and guarantees that the dispersion will withstand aggregation. The threshold between stable and unstable dispersion is typically set at a higher or lower value of ±30 mV. [44] The formulation's zeta potential can be calculated using Zetasizer. [51] The presence of ethanol, which generates net negative surface charge and hinders vesicle aggregation due to electrostatic repulsion, is responsible for the high negative charge. [44]

Vesicle Shape- For studying invasomes, the best instruments are transmission electron microscopy (TEM) and scanning electron microscopy. There is evidence that Temoporfin peptide vesicles can take on a variety of shapes, including spherical, oval, unilamellar, bilamellar, and even oligolamellar. Finasteride invasomes were reported as having a spherical, unilamellar shape. By using cryo-TEM, it
was discovered that carboxyfluorescein and temoporfin invasomes were, respectively, essentially unilamellar and bilamellar. They are therefore recognised as spherical or deformed vesicles with one, two, or more lamellae. [52]

**Drug Entrapment** Using techniques for calculating the amount of medication stored within vesicles, an invasome's entrapment efficiency can be evaluated. The entrapment efficiency of the hydroxy terpenes limonene and nerolidol in finasteride invasomes is highest and lowest, respectively. The findings of this study indicated that limonene had the highest degree of entrapment. Entrapment efficiency was found to be influenced by the terpene added, its concentration, and the medication's hydrophilicity [53]. Various methods for entrapment efficiency determination are Size Exclusion Chromatography (SEC), [54] Ultracentrifugation, [55] Dialysis.[56]

Entrapment Efficiency % = (Eliminated Drug concentration/Total Drug concentration) × 100

**Confocal Laser Scanning Microscopy Study (CSLM)**- The use of CLSM to clarify how elastic invasomal formulations penetrated the skin. Rhodamine 6G fluorescent probe was added to the formulations (Rh6G, red). Different skin layers were examined for the fluorescence signal of Rh6G-loaded nanovesicles. Before beginning the CLSM investigation, a skin penetration study must be completed. The skin mounted on Franz cells was covered with a vesicle that was labelled with rhodamine 6G, and after 8 hours of treatment, the skin was gently rinsed and the treated area was excised. The sample was taken from a mechanical vertical piece of the skin that had been mechanically frozen at -60 °C and had a thickness of 10 m. The investigation was done with CLSM at 560 nm for the emission wavelength and 543 nm for the excitation wavelength for the Rhodamine 6G probe.[57]

**Histopathological study**- To ascertain how the skin changed histopathologically after being exposed to liposomes, a histological study can be conducted. The treated area of the rat skin removed, submerged in a solution of 10% formalin, and vertically sectioned at a distance of 10 μm after the post-application of formulations to the skin. Light microscopy was used to view the segment after it had been put on glass slides and stained with eosin and hematoxylin (E and H).[57]

**Fourier Transforms Infrared Spectroscopy and Differential Scanning Calorimetry**- It is possible to conduct a differential calorimetry scanning investigation to analyse the thermal behaviour of the distinct lipid vesicles. Any interactions between the medication and the vesicle membrane components are investigated using infrared spectroscopy.[58].

**Degree of deformability Study**- A distinctive and significant parameter of deformable vesicular formulation is the degree of deformation. Unlike other vesicular carriers like liposomes, which are unable to traverse the intact stratum corneum, it can spread over it. The extruder was used to calculate the relative deformities of the vesicles. The polycarbonate filters in the extruder, which have pore diameters ranging from 50 to 200 nm, were used to filter the vesicular suspension. Utilizing the Malvern Zeta Sizer and the Dynamic Light Scattering technique, size distribution and vesicle measurement were evaluated after extrusion [59]. Using the formula, the deformability value D is obtained.

\[ D = \frac{J \times (r_v)}{r_p}^2 \]

\[ J = \text{weight of the suspension extruded through polycarbonate filters.} \]

\[ r_v = \text{the size of the extruded vesicles.} \]

\[ r_p = \text{pore size of a barrier.} \]

**Number of vesicles per cubic mm**- For composition and other process factors, the most crucial optimization parameter is the number of vesicles/cubic millimetre. A hemocytometer using optical microscopy can be used to count deformable vesicles.[60].

Total no. of vesicles per cubic mm = \( \frac{[\text{Number of counted vesicles} \times \text{dilution factor} \times 4000]}{[\text{Total number of counted Squares}]} \)

**X-ray Diffractometry**– Based on their crystalline structure, certain crystalline substances can be identified via TX-ray diffractometry (XRD). According to the findings of comparable studies, active ingredients' powder X-ray diffraction patterns typically feature partial sharp crystalline peaks, which is a sign of an organic molecule with some degree of crystallinity. In contrast, because the medicine is enclosed inside in an amorphous state, phospholipids typically lack crystalline peaks. When compared to pure drugs and physical mixtures, the crystalline peaks typically vanish in invasions.[61]
Applications of Invasomes in various formulations and research studies:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Application</th>
<th>Study Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,2,6,6-tetramethyl-1-piperidinyloxyl</td>
<td>Antioxidative skin capacity measurements</td>
<td>Improved antioxidative capacity measurement times on porcine skin by two fold.</td>
<td>24</td>
</tr>
<tr>
<td>Temoporfin</td>
<td>Photodynamic Therapy</td>
<td>When compared to liposomes, an invasive formulation including a 1 percent combination of terpenes showed a considerably increased deposition of temoporfin in the SC.</td>
<td>25</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Delivery of Herbal formulation</td>
<td>Due to the interaction between terpenes and ethanol, the formulation containing terpenes demonstrated enhanced penetration in the skin.</td>
<td>29</td>
</tr>
<tr>
<td>Temoporfin</td>
<td>Photodynamic Therapy</td>
<td>Temoporfin-loaded invasomes were more cytotoxic in the A431 cells.</td>
<td>31</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Treatment of Acne</td>
<td>When compared to traditional liposomes, it demonstrated increased skin deposition and enhanced medication percutaneous absorption.</td>
<td>44</td>
</tr>
<tr>
<td>Carboxyfluorescein and Temoporfin</td>
<td>Enhancement of Skin penetration for hydrophilic drugs</td>
<td>Invasomes and ethosomes increased the delivery of hydrophilic drug in the deep layers of skin.</td>
<td>52</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Delivery of Anti hypertensive agent</td>
<td>By administration of isradipine loaded invasomal trans gel, it was observed that blood pressure decreased in hypertensive rats caused by deoxycorticosterone acetate.</td>
<td>62</td>
</tr>
<tr>
<td>Avanafil</td>
<td>Treatment of Erectile Dysfunction</td>
<td>It demonstrated the greatest skin penetration and was an excellent candidate for the transdermal delivery of medicines through the skin.</td>
<td>63</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Antifungal Treatment</td>
<td>Itraconazole loaded Invasomal gel showed increased permeation in the skin.</td>
<td>64</td>
</tr>
<tr>
<td>Econazole</td>
<td>Antifungal Treatment</td>
<td>For the prolonged distribution of econazole to the area of the skin that is afflicted.</td>
<td>65</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Delivery of Herbal Formulation</td>
<td>From the invasomal gel, there was a 2.60-fold increase in curcumin penetration through the skin of pig ears.</td>
<td>66</td>
</tr>
<tr>
<td><strong>Temoporfin</strong></td>
<td><strong>Photodynamic Therapy</strong></td>
<td>When compared to control groups, temoporfin invasomes with a 1% terpene mixture dramatically reduced tumour size after photodynamic therapy.</td>
<td>67</td>
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<tr>
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<tr>
<td><strong>Isotretinoin</strong></td>
<td><strong>Delivery of Vitamin analog</strong></td>
<td>Delivering isotretinoin to the follicular unit and targeting pilosebaceous in this way results in effective treatment of eosinophilic pustular folliculitis.</td>
<td>68</td>
</tr>
<tr>
<td><strong>Adapalene</strong></td>
<td><strong>Acne Treatment</strong></td>
<td>Adapalene invasomal gel increases the drug's permeability across the membrane, enabling successful rapid drug release.</td>
<td>69</td>
</tr>
<tr>
<td><strong>Anastrozole</strong></td>
<td><strong>Cytotoxic effect of transdermal invasomal anastrozole gel on MCF-7 breast cancer cell line</strong></td>
<td>For possible treatment of breast cancer in post-menopausal women, anastrozole loaded invasomes increased transdermal flow and achieved an enhanced effect of drug.</td>
<td>70</td>
</tr>
<tr>
<td><strong>Phenylethyl Resorcinol</strong></td>
<td><strong>Delivery of skin lightening agent with potent anti-tyrosinase activity in deep skin tissues</strong></td>
<td>Invasomes are more successful than traditional liposomes at delivering Phenylethyl Resorcinol into the deeper layers of the skin, making them ideal for skin lightening products.</td>
<td>71</td>
</tr>
<tr>
<td><strong>Calcein and carboxyfluorescein</strong></td>
<td><strong>Enhancement of Skin penetration for hydrophilic drugs</strong></td>
<td>Calcein penetration was increased by transfersomes and invasomes by two and seven times, respectively.</td>
<td>72</td>
</tr>
<tr>
<td><strong>2-methoxyestradiol and Apamin</strong></td>
<td><strong>Suppression of A549 lung cancer cells</strong></td>
<td>In relatively little dosages, it might easily penetrate the cell membrane and cause apoptosis.</td>
<td>73</td>
</tr>
<tr>
<td><strong>Vismodegib</strong></td>
<td><strong>Enhancing the Bioavailability and efficacy of anti cancer treatment of skin</strong></td>
<td>In comparison to oral vismodegib, vismodegib loaded gel improved the drug's skin penetration, resulting in 3.59 times greater bioavailability and superior anticancer activity.</td>
<td>74</td>
</tr>
<tr>
<td><strong>Finasteride</strong></td>
<td><strong>Enhancing skin permeation</strong></td>
<td>Invasomes with an iontophoretic approach greatly improved finasteride penetration through the rat epidermis as compared to aqueous solution.</td>
<td>75</td>
</tr>
<tr>
<td><strong>Ferulic Acid</strong></td>
<td><strong>Drug delivery through skin</strong></td>
<td>Invasomes, Liposomes and Ethosomes were tested for ferulic acid and ethosomes showed high entrapment than invasomes and liposomes.</td>
<td>76</td>
</tr>
</tbody>
</table>
FUTURE PERSPECTIVES:
In terms of vesicular delivery systems, the discipline of nanotechnology in medicine will offer a number of topics and solutions for dealing with healthcare issues in the coming decades. The structure and design of a topical or transdermal formulation combine artistic talent with scientific understanding of excipients, formulation physical qualities, skin physiology, and formulation dynamics. These invasome vesicular systems have a wide range of potential therapeutic uses due to their superior tolerability and performance. Advanced lipid based vesicles, such as elastic, flexible, and deformable ones, are used to deliver numerous therapeutic compounds and treat a variety of ailments. Future innovative delivery systems will be made possible by the variability of kinetic releases from vesicular carriers. Drugs ranging from hydrophilic to hydrophobic are transported by this drug transporter vesicular system. Researchers are still working to reinforce the vesicular carrier system by making it more durable in nature, in order to prevent content leaching, lipid oxidation, and absorption by biological defence systems. The development of efficient therapeutics for transdermal drug delivery is made possible by advancements in the transport of bioactive molecules through the skin via ultra-flexible, deformable invasomes.

CONCLUSIONS:
One extensively researched non-invasive form of administration is topical medication application. For various reasons, including avoiding hepatic first-pass metabolism, not requiring having a pleasing taste, and avoiding gastrointestinal side effects, topical drug delivery systems offer an adequate and optimal alternate route of administration to the conventional oral route of administration. Additionally, this medication delivery method enables stable drug plasma concentrations, increased therapy adherence, decreased administration frequency, and gastrointestinal tract degradation. The chance of overdosing or underdosing is eliminated. For problems of the skin, there are numerous potent pharmacological compounds. However, their therapeutic efficacy has been constrained by unfavourable toxicity profiles and physicochemical characteristics. Due to their special qualities like high biocompatibility, ease of surface modification, and suitability as controlled delivery vehicles, vesicular delivery systems offer the potential to address these drawbacks. Transdermal delivery can be done using invasomes, which are non-toxic vesicular transporters. While incorporating both lipophilic and hydrophilic medicines, they can also aid in the penetration of the integrated substance. The major components of the invasome structure are phospholipids, ethanol, and terpenes. Furthermore, changes to these vesicles' composition can easily alter how deeply they penetrate. We highlight the tremendous potential of invasomal formulations in topical therapeutic applications based on the studies that are currently available. Future dermatology research potential are increased by these systems. However, more research is required to show that invasomes are clinically effective. Regarding the aforementioned capability of invasomes as drug carriers, we also recommend concentrating on the development of appropriate technology for the commercial production of invasomes as this will be required for the use of invasomes in the treatment and prevention of diseases in future dermatology research.

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