INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Invasomes: Potential Nanocarrier System for Transdermal Delivery of Drug Molecule

Mohite Chakradhar, Hucche Bhimashankar, Kazi Wasim, Kolsure Shripal

Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree) Latur, Maharasshtra- 413512

ARTICLE INFO

Published: 16 May 2025
Keywords:
Invasome, Terpenes, phospholipid, ethanol, transdermal.
DOI:
10.5281/zenodo.15440759

ABSTRACT

Transdermal drug delivery refers to the drug administration route through the skin that achieves the local or systemic treatment approved for clinical use. Invasomes are novel vesicular systems that exhibit improved transdermal penetration compared to conventional liposomes. These vesicles contain phospholipids, ethanol, and terpene in their structures; these components confer suitable transdermal penetration properties to the soft vesicles. Ethanol, terpenes and phospholipids are the key structural composition, systematize physicochemical properties of invasomes. Nanovesicles can enhance the skin's permeability, which means they allow larger or less penetrative drugs to reach deeper layers of the skin. nanovesicles reduce the drug's absorption into the bloodstream, helping to keep its effects localized. These vesicular systems, deliver the drugs at predetermined rate by controlling and sustaining release as per the requirement. Furthermore, invaomes used in the treatment of eczema, hypertension, acne, cancer, eosinophilic pustular folliculitis, erectile dysfunction, fungal infections, photodynamic therapy have also been discussed.

INTRODUCTION

Controlled Drug Delivery Systems are designed to optimize drug action by targeting the drug to specific sites in the body, reducing side effects, improving therapeutic efficacy, and minimizing undesired localization of the drug in healthy tissues. Additionally, these systems aim to prevent the rapid degradation or elimination of the drug from the body. Transdermal Drug Delivery Systems systems are an alternative method for delivering drugs into systemic circulation. They are particularly beneficial for poorly absorbable drugs and drugs that are degraded by enzymes in the digestive system. However, to increase the number of drugs that can be administered via the transdermal route, new drug delivery systems are being developed. To improve the transdermal

***Corresponding Author:** Hucche Bhimashankar
Address: *Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree) Latur, Maharasshtra- 413512*
Email ✉: bshucche18@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

delivery of drugs, both physical and chemical methods are being explored like physical methods include ontophoresis, sonophoresis, and microneedles, Chemical methods like penetration enhancers that improve drug absorption through the skin and biochemical methods means using liposomes, niosomes, invasomes, transferosomes, and ethosomes are being studied to enhance drug permeability through the skin. Invasomes are a novel class of elastic phospholipid vesicles that have been shown to enhance percutaneous (through the skin) drug penetration compared to conventional liposomes. These vesicles are composed of phosphatidylcholine, ethanol, and one or more terpenes (natural compounds). Terpenes have been shown to enhance drug penetration by disrupting the lipids of the stratum corneum (the outer layer of skin), interacting with intracellular proteins, and improving the partitioning of the drug into the stratum corneum (1)**.** Nanocarriers have been designed to enhance the delivery of medicines through the skin, whether by dermal (localized) or transdermal (systemic) routes. Vesicular systems, which include liposomes and novel elastic vesicles, have gained attention due to their ability to modify drug penetration into the skin. Vesicular Systems are appealing because they can be customized to optimize their physicochemical properties, such as size, deformability, and surface charge. This can be done by altering lipid components or preparation methods. Vesicular systems like liposomes can carry both lipophilic and hydrophilic drugs, which aids in drug penetration (2)**.**

INVASOMES IN COMPARISON WITH LIPOSOMES

Liposomes are spherical vesicles made up of phospholipids, cholesterol, and various lipids (neutral, cationic, and anionic). This composition allows them to encapsulate a variety of drugs with different solubility characteristics like Lipophilic, Hydrophilic, Amphipathic. Lipophilic (fat-soluble) drugs are incorporated into the lipid bilayer of the liposome. Hydrophilic (water-soluble) drugs are encapsulated in the aqueous core inside the vesicle. Amphipathic (both water- and fat-soluble) drugs are located in the intermediate layer of the bilayer. Invasomes differ from traditional liposomes in their composition. They are made from ethanol, phospholipids, and terpenes. It acts as a solvent that improves the fluidity of the lipid bilayer, making the vesicle softer and more flexible than traditional liposomes. These are organic compounds (found in many plants) that have been shown to enhance skin permeability by disrupting the tight lipid structure of the skin's outer layer (the stratum corneum). Invasomes have a more elastic, less rigid structure than liposomes due to the presence of ethanol. The combination of ethanol and terpenes makes invasomes potentially more efficient than conventional liposomes in delivering drugs across the skin, especially when using penetration enhancers like terpenes (3)**.**

INVASOMES

Invasomes are an emerging class of vesicles that significantly enhance the transdermal delivery of active pharmacological compounds. These vesicles are composed of key components including phospholipids, ethanol, and terpenes or mixtures of terpenes (4)**.**

STRUCTURE OF INVASOME

Invasomes are indeed small, lipid-based particles used to deliver substances across cell membranes. They have a structure that is similar to liposomes, but they are designed specifically to enhance the delivery of active ingredients into cells (5)**.**

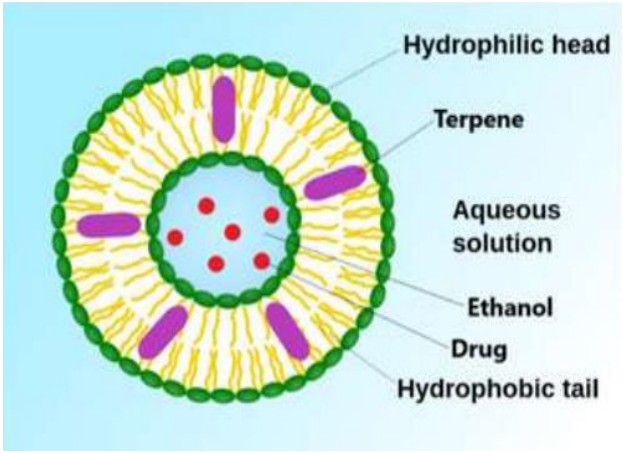

Figure 1. Invasome structure

COMPOSITION

Invasomes are a type of soft liposomal vesicle specifically designed to improve skin penetration and enhance the delivery of drugs through the skin. These vesicles contain a combination of several key components that work together to optimize drug absorption include ehanol, terpenes and phospholipids (4).

Ethanol

Ethanol plays a critical role in enhancing the skin permeability of nanovesicles by altering their size, structure, and fluidity. By disrupting the lipid layers of the skin and lowering the transition temperature of lipids, ethanol helps to facilitate drug absorption. Additionally, ethanol-based nanovesicles exhibit improved storage stability due to their negative charge and soft, flexible structure, making them a valuable component in transdermal drug delivery systems.

Terpene

Terpenes are valuable penetration enhancers in transdermal drug delivery systems. Their ability to dissolve lipid and protein layers and reduce the skin's barrier resistance makes them effective at enhancing the absorption of both lipophilic and hydrophilic drugs. With the "Generally Recognized As Safe" GRAS status ensuring their safety, terpenes hold great promise for use in topical formulations aimed at improving drug efficacy and minimizing side effects. The research by Dragicevic-Curic et al. (2008) also provides strong evidence of their effectiveness in improving drug deposition into the skin.

Phospholipids

Phospholipids are essential in the development of nanovesicle-based drug delivery systems, particularly for transdermal formulations. By altering the structure of phospholipids, such as adding PEGylation or using hydrogenated phosphatidylcholine, drug delivery can be optimized for better skin penetration, solubility, and stability. The example of curcumin incorporated into invasomes and combined with HPMC gel highlights how these vesicles can enhance drug delivery and bioavailability. Phospholipids, with their ability to adapt to various formulations, continue to be crucial for the success of topical and transdermal drug delivery systems.

ADVANTAGES OF INVASOMES

- Non-invasive drug delivery method.
- Drugs that are both lipophilic and hydrophilic can be delivered.
- Has non-toxic raw materials in its composition.
- Compliance among patients since the medication can be applied in a semisolid form (cream or gel).
- An easy approach to administering drugs in contrast to iontophoresis, phonophoresis, and other complex methods (6).

DISADVANTAGES OF INVASOMES

- It's high production cost.
- Leakage and fusion of encapsulated drug/ molecule.

- The phospholipid present may undergo hydrolysis/oxidation, thus affecting stability of Invasomes (7).

PENETRATION MECHANISM OF INVASOMES

The role of invasomes (lipid-based vesicles used for skin delivery) in enhancing the permeability of the skin's stratum corneum (SC), which is the outermost layer of the skin. Both terpenes and ethanol are involved in enhancing the skin penetration ability of invasomes. As the invasomes penetrate the skin, part of the vesicle disintegrates. This release includes compounds like terpenes, phospholipid fragments, and individual phospholipid molecules, which contribute to fluidizing the skin's lipids. Not all invasomes break apart during penetration. Smaller invasomes, in particular, may remain intact as they move through the skin. These vesicles can travel through either the hair follicle pathways or narrow hydrophilic channels in the SC's intercellular region. Some intact invasomes may reach deeper layers of the SC through the follicular transport pathway (hair follicles) or the narrow hydrophilic channels that exist in the intercellular spaces of the SC. These pathways are important for the penetration of substances that need to reach deeper skin layers. Research by Honeywell-Nguyen and others found that flexible, smaller vesicles were able to penetrate deeper into the SC, especially through channel-like areas that are typically (2).

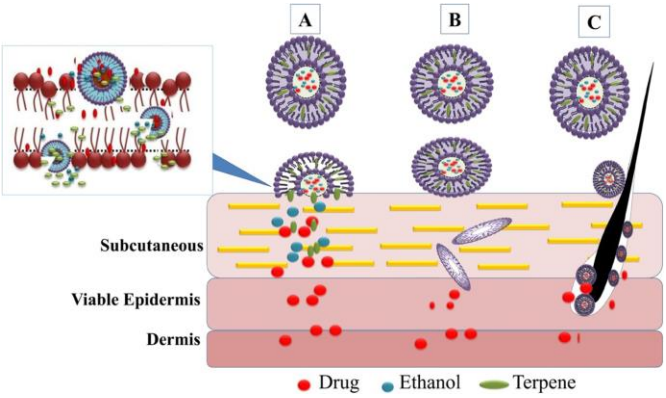

Figure 2. Penetration mechanism of invasomes through SC (a) Enhanced penetration (b) Intact penetration and (c) Trans-appendageal penetration

METHOD OF PREPARATION FOR INVASOME

Mechanical Dispersion Technique

Specifically using the mechanical dispersion technique the active drugs and terpenes (or a combination of terpenes) are dissolved in ethanol containing phospholipids. After initial mixing, the solution is vortexed (5 min) and sonicated (5 min) to ensure proper dispersion and uniformity of the components. The addition of a phosphate buffer (pH 7.4) or PBS helps to hydrate the lipid mixture, which allows for the formation of vesicles. Constant vortexing during hydration helps to prevent aggregation and ensures a uniform vesicle size distribution. The mixture is passed through polycarbonate membranes of varying pore sizes ranges (400 nm, 200 nm, 100 nm, 50 nm) to extrude multilamellar vesicles (MLVs) and the process is repeated multiple times to achieve a narrow size distribution, crucial for drug delivery applications (8).

Film Hydration Technique

The conventional film method is a widely used technique for preparing invasomes. Phospholipids

are dissolved in a mixture of methanol and chloroform (in a 2:1 ratio, v/v). The lipid solution is then dried to form a thin film. This is achieved by using a rotary flash evaporator, where the pressure is gradually reduced from 500 mbar to 1 mbar while keeping the temperature at 50°C. After forming the film, it is kept under vacuum (1 mbar) for 2 hours at room temperature to ensure that any remaining solvent traces are removed. To further remove any residual volatile solvents, nitrogen gas is passed over the film. The thin lipid film is hydrated for 30 minutes at the lipid phase transition temperature (where the lipid bilayer transitions from gel to liquid crystalline phase). During this hydration, a mixture of phosphate buffer (pH 7.4 or PBS) containing ethanol and terpenes is added. Alternatively, the film can be hydrated with phosphate-buffered saline (PBS) at pH 7.4. After cooling the hydrated film to room temperature, ethanol and the terpenes (either a single terpene or a mixture) are added in order to form invasomes (1)**.**

CHARACTERIZATION OF INVASOMES

- Drug Content
- Vesicular Size
- Vesicle Shape
- Stability Study
- Skin Permeation Study
- Surface Morphology
- Entrapment Efficiency
- Ex Vivo Permeation Studies

- **Drug Content**

Spectrophotometry and HPLC Both techniques are commonly employed for determining the drug content in formulations. Kamran et al. used the film hydration technique to formulate Nano-Invasomal Gel of Olmesartan Medoxomil gel. The drug content in the nano-invasomal formulation was determined using the UV-Vis spectrophotometric method and analyzed the formulation at 257 nm (9).

- **Vesicular Size**

Photon Correlation Spectroscopy (PCS) / Dynamic Light Scattering (DLS) techniques are commonly used for measuring the size of nanoparticles, including vesicles like invasomes and transferosomes. Amnuaikit et al. prepared the invasomes and transferosomes (a type of flexible liposome) containing phenylethyl resorcinol, and They compared the characteristics and performance of these novel vesicular systems against conventional liposomal formulations of phenylethyl resorcinol. The development of all the vesicular drug delivery systems for topical administration of phenylethyl resorcinol. The invasomes had a vesicle size range of 208.10 ± 12.00 to 819.30 ± 101.90 nm, with a PDI less than 0.3, indicating a relatively homogeneous size distribution. Haag et al. developed invasome vesicles of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl), a nitroxide free radical by mechanical dispersion method. The in vivo and ex vivo experiments mentioned are crucial for assessing the antioxidative capacity of the skin. They used photo correlation spectroscopy and found the mean size of the invasomes to be 86 nm and The polydispersity index (PDI) of 0.13 for the invasomes is a great result (9)**.**

- **Vesicle Shape**

The use of advanced microscopic techniques like scanning electron microscopy (SEM), transmission electron microscopy (TEM), and cryo-TEM is crucial for analyzing the morphology and shape of vesicles, such as invasomes. Ntimenou et al. Formulated Vesicles liposomes, transferosomes, and invasomes, all loaded with calcein and carboxyfluorescein. Cryo-TEM (Cryogenic Transmission Electron Microscopy)

was used to study the shape of the vesicles. invasomes were primarily composed of small unilamellar vesicles. Qadri et al. involving isradipine-loaded invasomes highlights the development of a transdermal drug delivery system designed for the treatment of hypertension. The invasomes were characterized using TEM (Transmission Electron Microscopy) to determine their shape and surface morphology. (9)

- **Stability Study**

The stability studies carried out on finasteride-loaded invasomes, specifically the evaluation of vesicle size, shape, polydispersity index, and zeta potential over time. These parameters can be assessed through techniques such as DLS for particle size and polydispersity index, SEM or TEM for vesicle shape, and zeta potential for surface charge. Finasteride-loaded invasomes were subjected to stability tests at 4°C and 25°C for 120 days. At 4°C, the zeta potential and entrapment efficiency of the vesicles remained stable over the 120-day period. At 25°C, significant variations were noted. A reduction in the negative surface charge (zeta potential) led to vesicle aggregation, which in turn caused a decline in entrapped efficiency. This aligns with the findings of the tolterodine tartrate invasome stability study, which also recommended refrigeration at 4 ± 2°C as the optimal storage condition to prevent significant drug loss, compared to storage at 30°C. To maintain the stability of invasomal formulations, refrigeration at temperatures around 4°C is preferred, as it minimizes vesicle aggregation and helps preserve the entrapment efficiency and surface charge over time. Storing at higher temperatures, like 25°C, leads to physical instability and a reduction in efficacy (8).

- **Skin Permeation Study**

The use of various types of skin for permeation studies is critical to understanding how well invasomal formulations can penetrate the skin barrier. Studies typically use skin models such as Human (female) abdominal skin obtained after plastic surgery, Albino (male) Wistar rat skin, Porcine skin, Rabbit skin after removal of fatty tissue. For these studies, Franz diffusion cells are often employed to measure the diffusion of substances through the skin, with the receptor compartment usually containing phosphate-buffered saline (PBS) at pH 7.4. Confocal laser scanning microscopy (CLSM) is another key technique used to observe the ability of invasomal formulations to penetrate the skin. Through these studies, it has been confirmed that nano-invasomes can easily penetrate the skin. Invasomes can interact with the skin's lipids, particularly in the stratum corneum (SC), where they can alter lipid distribution and loosen tight lipid junctions, making it easier for the formulation to penetrate deeper layers of the skin. In one study, temoporfin-loaded invasomes with 1% w/v citral showed the highest penetration compared to those containing cineole or a mixture of both. Similarly, tolterodine tartrate invasomes containing 1% terpenes demonstrated enhanced skin penetration and accumulation, outperforming vesicles without terpenes (8).

- **Surface Morphology**

The surface morphology of the invasomal preparation was analyzed using a Scanning Electron Microscope (SEM). A small sample of the invasomal formulation is placed onto a clear glass slide. This allows a thin, even layer to form for optimal viewing under SEM. After applying the sample, it is left to air dry, which helps remove any solvents or moisture from the formulation, leaving behind the vesicles. The dried sample is then coated with a thin layer of gold using a sputter

coater (Polaron E5100, Watford, UK). This step is crucial because non-metallic samples (like biological preparations) can accumulate charge when exposed to the electron beam of SEM. The gold coating helps to conduct the electrons and provides clear, high-quality imaging by reducing charging artifacts. The sample, now gold-coated, is placed in the SEM, which uses electron beams to create high-resolution, 3D images of the surface structure of the vesicles. This allows for the detailed examination of the size, shape, and surface characteristics of the invasomes, providing valuable information on their stability and integrity (1)**.**

- **Entrapment Efficiency**

The entrapment efficiency of the invasomal formulation is an important measure to evaluate how much of the drug is successfully encapsulated within the vesicles, as compared to the free, unencapsulated drug. The ultracentrifugation method is commonly used for this purpose. 1 ml of the invasomal formulation is transferred into Eppendorf tubes. The tubes are then subjected to centrifugation at 15,000 rpm for 15 minutes at 4°C, twice. This process helps to separate the unentrapped drug (which remains in the supernatant) from the drug encapsulated within the vesicles, which forms a pellet at the bottom of the tube. The clear fraction (supernatant) is collected, which contains the free drug that was not encapsulated in the vesicles. The amount of free drug is measured from the clear supernatant, typically using an analytical method like UV spectrophotometry or HPLC. The entrapment efficiency is then calculated indirectly using the formula:

Entrapment Efficiency (%) = $total\ drug - free\ drug \div total\ drug \times 100$ (10)**.**

- **Ex Vivo Permeation Studies**

The permeation of invasomal formulations through the skin can be effectively studied using the Franz diffusion cell. The effective surface area of the diffusion cell is 2.0 cm^2, which represents the area through which the drug will permeate the skin. The receptor volume is 20 mL, and this chamber holds the receptor medium (in this case, phosphate-buffered saline at pH 7.4), which collects the drug as it diffuses through the skin. A piece of skin is mounted on the receptor compartment with the stratum corneum (outermost layer of the skin) side facing upward, into the donor compartment. The donor compartment is applied with the invasomal formulation, which contains the drug. The top of the diffusion cell is sealed with a lid to prevent evaporation and maintain a closed environment. 20 mL of pH 7.4 phosphate-buffered saline (PBS) is used in the receptor compartment, acting as the medium in which the drug diffuses after passing through the skin. The temperature of the receptor compartment is maintained at 37°C, which mimics the human body temperature to ensure physiological conditions during the experiment. At predetermined time intervals, aliquots of the receptor medium are withdrawn and replaced with fresh media to maintain sink conditions. The withdrawn aliquots are analyzed using a UV spectrophotometer to measure the amount of drug that has permeated through the skin (10)**.**

APPLICATION OF INVASOME

- Immunosuppressive drug delivery
- Anticancer drug delivery
- Delivery of vitamin analog
- Used in alopecia treatment
- Delivery of anti-acne agent
- Delivery of anti-hypertensive agent
- Treatment of erectile dysfunction
- Antioxidant
- Tyrosine's inhibitors
- Anticholinergic agent

- Miscellaneous applications of invasomes

- **Immunosuppressive drug delivery**

Immunosuppressive drugs enhance the effectiveness of particularly in treating autoimmune diseases. The use of this nanosized drug delivery system (like lipidic vesicles) to improve the targeted delivery of these drugs, therby reducing theier side effects and enhancing their therapeutic effects. Cyclosporine A (CsA) is lipophilic, meaning it has difficulty penetrating the skin layers effectively. Cyclosporine A can limit its effectiveness when applied topically for conditions like psoriasis (or) other autoimmune skin diseases. Verma developed invasomes as a nanocarrier for cyclosporine A(CsA) delivery. This approach used a combination of unsaturated soyabean phosphatidylcholine (10% W/V), ethanol (3.3%W/V), and a mixture of citral:cineole:D-limonene (0.5:1.0:1.5%W/V) along with PBS upto 100% W/V to create invasome vesicle using mechanical dispersion method. The key innovation here is the incorporation of ethanol & terpenes, which enhanced the penetration of CsA into the deeper layers of the skin. The in vitro study conclude that the effectiveness of these invasome vesicles in delivering CsA more efficiently to the viable epidermis and dermis compared to other formulations, such as simple aqueous/ethanolic solutions or liposomes lacking ehanol and terpenes. This suggest that ehanol and terpenes play an important role in disrupting the skin barrier, allowing for deeper and more efficient drug delivery. This type of nanocarrier system could be particularly beneficial for dermatological treatments, where you need targeted drug delivery to the skin layers without systemic exposure. The invasomes used as a delivery system for hydrophilic drugs, such as immunosuppressive like CsA (cyclosporine A). The study seems to suggest that adding terpenes to the formulations improves the penetration of the drug into deeper skin layers, enhancing its potential for treating condition like autoimmune diseases. The correlation between terpene concentration and the amount of drug absorbed by the skin layers indicates that the invasome system could be a promising alternative to conventional methods for topical drug delivery (7)**.**

- **Anticancer drug delivery**

Despite all the advances in biomedical science, cancer treatment remains a complex and challenging field. The ineffctiveness of current therapeutic strategies contributes to the high mortality rates associated with ceancer. Thatswhy, there is an urgent need to develop better treatment options for cancer, especially considering the limitations of current therapies. Temoporfin, as a second-generation photosensitizer, is an exciting step forward in addressing some of these challenges like high tumor selectivity, short residual photosensitivity, photodynamic therapy. Temoporfin holds promise as an effective anticancer agent, particularly for early or recurrent carcinomas, when used in photodynamic therapy (PDT). The work by **Dragicevic-Curic** and colleagues on using **invasomes** for temoporfin delivery is quite groundbreaking, especially considering the challenge of delivering highly hydrophobic drugs like temoporfin effectively to their target. Temoporfin, a hydrophobic drug, is dissolved in an ethanolic solution containing phospholipids (phosphatidylcholine:ethanol: 75:25 W/W), which helps to form lipid-based nanocarriers. The addition of terpenes like limonene, citral, and cineole at a concentration of 1% w/v helps to improve the permeation of the drug through biological barriers, like skin or cellular membranes, due to their enhancing effects on membrane fluidity and the process of vertexing

followed by sonication for 5 minutes. The final step of adding PBS (phosphate-buffered saline) into the solution with constant vortexing for 5 minutes is a critical one in preparing the drug-loaded invasomes. The invasomes in this formulation have a particle size of approximately 105.4 nm and the polydispersity index (PDI) is about 0.066 (7)**.**

- **Delivery of vitamin analog**

The synthesis of isotretinoin-loaded invasomes described by Dwivedi and co-investigators is another great example of how drug delivery systems can be optimized to improve the therapeutic effectiveness of medications, specifically for eosinophilic pustular folliculitis in this case. Isotretinoin, a vitamin A analog was dissolved in eugenol. The dissolved isotretinoin-eugenol mixture is then added to an ethanolic egg lecithin solution, The mixture is subjected to vortexing for 60 minutes. The goal of vortexing is to achieve a homogeneous suspension where the drug is evenly distributed within the lipid carriers. After vortexing, the vesicles are hydrated by adding PBS (pH 6.8). Hydration is a crucial step for forming stable invasomes. The PBS buffer ensures that the pH is compatible with biological tissues and enhances the stability of the vesicles. The resulting mixture becomes a yellowish translucent suspension, indicating the formation of the isotretinoin-loaded invasomes (7)**.**

- **Used in alopecia treatment**

Invasomes are innovative drug delivery systems designed to enhance the penetration of active ingredients through the skin. Their application in alopecia treatment is intriguing because they might improve the effectiveness of topical treatments, potentially leading to more sustainable, long-term results. Alongside advancements like invasomes, many patients turn to alternative and complementary therapies in search of a more natural or holistic approach to hair restoration. As for finasteride, it's indeed one of the main FDA-approved medications for treating androgenetic alopecia, especially in men. As a 5α-reductase inhibitor, it works by blocking the enzyme responsible for converting testosterone to dihydrotestosterone (DHT), a hormone linked to hair loss. Developing novel carriers that can enhance the penetration of finasteride through the dermis would likely increase its efficacy. Mechanical dispersion method used for preparing finasteride-loaded invasomes looks like a well-thought-out approach to enhance the drug's delivery across the dermis. By using a combination of terpenes like (limonene, nerolidol, and carvone: 0.5%, 1.5%, 1%) the researchers are utilizing the permeation-enhancing properties of these compounds. In brief, combining soya phosphatidylcholine (10% W/V) with ethanol (40% W/V)to create the ethanolic lipid mixture, followed by the addition of finasteride (0.35% W/V) and terpenes, and using sonication and vortexing(5 min). Multilamellar vesicles (MLVs) are particularly useful in drug delivery as they can encapsulate drugs and control their release, offering better stability and penetration. Using PBS (upto 100% W/V) for hydration and further sonicating (5 cycles 5 min, at 4°C) the vesicles ensures that the resulting formulations are stable and homogeneous (7)**.**

- **Delivery of anti-acne agent**

Acne is indeed one of the most common skin conditions worldwide. Dapsone, which is indeed a promising treatment for acne due to its anti-inflammatory properties. It's primarily known for its use in treating leprosy, but its application in dermatology has been gaining attention, especially for inflammatory acne. To enhance dapsone's effectiveness in acne therapy, an efficient delivery

system is key. The challenge lies in ensuring the drug reaches the targeted area of the skin in adequate concentrations without being lost or deactivated. Film hydration technique is used to prepare dapsone-loaded invasomes for acne treatment. A film hydration technique, which involves mixing dapsone (20 mg) and terpenes (limonene, cineole, citral, and fenchone) with phosphatidylcholine (200 mg) in methanol/chloroform, 2:1 v/ v, followed by rotary evaporation to remove the organic solvent at 120 rpm (60 °C) for 15 min, and finally hydrating using 3% v/v ethanolic: water mixture at 120 rpm (60 °C) for 1 h by the thin film to form invasomes. The terpenes mentioned are likely included to improve the penetration of the drug through the skin. The use of a mixture of ethanol and water to hydrate the thin film is a typical step in this method to achieve the final formulation of invasomes, which are then filtered (pore size 25 μm)) to remove any remaining drug crystals (8).**Delivery of anti-hypertensive agent**

Anti-hypertensive drugs are commonly used to treat hypertension (elevated blood pressure). Anti-hypertensive drugs, specifically isradipine, which is a calcium channel blocker used to treat hypertension. As mentioned, isradipine, like many other drugs, faces issues such as low aqueous solubility, low bioavailability, and a short biological half-life, low permeability. The first-pass metabolism further complicates the effectiveness of the drug. The issue of low oral bioavailability and first-pass metabolism is a significant challenge when administering drugs like isradipine orally. Kamran et al. accomplished developing invasomes for transdermal drug delivery, specifically for isradipine. The process uses Phospholipon® 90G (2% w/v), a phospholipid), β-citronellene (0.1% w/v, a terpene), and ethanol (10% W/V), which are incorporated into the lipid film using a conventional film hydration technique. Isradipine, the terpene (β-citronellene), and Phospholipon® 90G are dissolved in a chloroform:methanol mixture (2:1 v/v), which helps in creating a homogeneous solution. The organic solvents are then removed by rotary evaporation, followed by overnight drying in a vacuum cabinet to ensure complete removal of solvent traces. The dried lipid film is hydrated using phosphate-buffered saline (PBS) and ethanol, allowing for the formation of invasomes, which are essentially lipid vesicles that encapsulate isradipine. The mixture is rotated at 60 rpm for 1 hour to facilitate the hydration process. Finally, the resulting invasomal lipid formulation undergoes probe sonication at 40% output frequency at 4°C, which helps in reducing the size of the vesicles and ensuring uniform dispersion (8)**.**

- **Treatment of erectile dysfunction**

Erectile dysfunction (ED) is indeed a widespread condition affecting millions of men globally, and it's estimated that around 30 million new cases are reported annually, yet only a small fraction seek treatment. Avanafil is a selective phosphodiesterase type 5 (PDE5) inhibitor (FDA approved), widely used to treat erectile dysfunction (ED). Avanafil is used as an oral treatment for erectile dysfunction (ED). The poor aqueous solubility and extensive presystemic metabolism are major issues for oral bioavailability. Additionally, the alteration in absorption due to food intake is another significant factor. Ahmed et al. wera prepared the avanafil-loaded invasomes using the film hydration method. This is an interesting and effective approach to improving the delivery of avanafil for the treatment of erectile dysfunction. Avanafil (100 mg) and Phospholipon® 90G (a phospholipid) are dissolved in a methanol/chloroform mixture (1:2 v/v). The rotary

evaporation method is used to remove the organic solvents, leaving behind a lipid film. The deposited lipid film is kept in a vacuum cabinet overnight to ensure that all traces of the organic solvent are fully removed. The lipid film is then hydrated using a PBS/ethanol mixture (7:3), which helps to form the invasome vesicles. The hydration process is carried out in a rotary evaporator at 60 rpm and 25 ℃ for 1 hour. After hydration, the vesicle suspension is subjected to sonication in an ice bath to obtain nanosized invasome vesicles (8).

- **Antioxidant**

Ferulic acid is a bioactive compound that has garnered significant attention in recent years due to its antioxidant properties and its therapeutic effects, which include anticancer, anti-inflammatory, antidiabetic, anti-skin disorder, and cardiovascular protective effects. It found naturally in the cell walls of many plants. It faces challenges such as a short half-life in the body and the need for frequent dosing to maintain therapeutic effects. To overcome these limitations and improve the efficiency of ferulic acid delivery, transdermal vesicular systems (such as liposomes, nanosomes, or invasomes) could indeed be an effective solution. Chen and co-investigators prepared the, their approach leverages the film hydration method to create a nanosized invasomal system for improved delivery and enhanced therapeutic effect. Soybean phosphatidylcholine (133 mg/mL) is used as the lipid material, Ferulic acid (12 mg/mL) is dissolved in the lipid mixture, and terpenes (10 mg/ml such as limonene, citral, cineole) are included in a 1:4.5:4.5 v/v ratio. The prepared terpene-based invasomes were then compared with conventional liposomes, ethosomes, and Tween 80-based deformable liposomes. The solution is dissolved in a methanol and chloroform mixture (1:2 v/v), which helps solubilize the components. The organic solvents are removed using rotary evaporation under a vacuum at 43 °C. The lipid film is hydrated with PBS (pH 7.4) and ethanol (10% v/v), the hydrated lipid suspension is subjected to sonication in an ice-water bath for 15 minutes (5 minutes per cycle). After sonication, the suspension is passed through a polycarbonate membrane with a 100 nm pore size to further reduce the size and ensure the uniformity of the ferulic acid-loaded invasomes (8).

- **Tyrosine's inhibitors**

Phenyl Ethyl Resorcinol (PER) has strong potential as a skin-lightening agent due to its anti-tyrosinase activity. However, the challenges associated with its topical administration, such as solubility, skin irritation, flexibility, and permeation. A method for preparing phenyl ethyl resorcinol-loaded invasomes, developed by Amnuaikit and co-authors in 2018. Phenyl ethyl resorcinol is the compound to be encapsulated, Different terpenes are used, including fenchone, citral, and D-limonene (1% w/v concentration). 10% v/v absolute ethanol is included as a skin penetration enhancer. 15% w/w sodium deoxycholate is used to modify the vesicle membrane and improve drug delivery. A solution of water and 10% v/v absolute ethanol is used to create the aqueous phase. The active ingredient (phenyl ethyl resorcinol) and the terpenes are dissolved in an oil phase. The oil phase and aqueous phase are sonicated separately at 60°C for 30 minutes to achieve a homogeneous solution. The organic solvent (absolute ethanol) is removed from the oil phase using rotary evaporation. The remaining oil phase is then hydrated with the aqueous phase through shaking for 5 minutes. The vesicles are then sonicated for 30 minutes at 60°C to form complete invasomes. the phenyl ethyl resorcinol-loaded invasomes had a vesicle size of less than 500 nm, PDI was below 0.3, had a high

zeta potential, greater than 50% entrapment efficiency and good stability at 30°C and 75% relative humidity (RH) for 4 months. In full-thickness newborn pig skin (a model for human skin), the elastic carrier formulations (invasomes) demonstrated significantly higher accumulation of phenyl ethyl resorcinol compared to traditional liposomes. The in vitro permeation study resulted in an 85.38% recovery, which is close to the acceptable range of 90-110%. The slightly lower recovery could be attributed to the properties of the stratum corneum (SC), The phenyl ethyl resorcinol-loaded invasomes exhibited up to 80% anti-tyrosinase activity, The acute irritation test in rabbits confirmed that the 0.5% w/v phenyl ethyl resorcinol invasomal formulation is safe for skin application. The prepared invasomes and transfersomes demonstrated superior tyrosinase inhibition activity. The formulations showed a significant reduction of melanin in B16 melanoma cells. The study emphasizes the suitability of invasomes for delivering phenyl ethyl resorcinol, a compound known for its skin-lightening properties (8)**.**

- **Anticholinergic agent**

Tolterodine tartrate is known to undergo extensive liver metabolism and has high aqueous solubility (>1 mg/ml), making it suitable for transdermal drug delivery. Additionally, its molecular weight is less than 500 Da, and its half-life is less than 10 hours, which fits the ideal profile for a drug that can be delivered through the skin. Oral administration of tolterodine tartrate is linked to several side effects, including dizziness, tachycardia (rapid heart rate), dry mouth, and gastrointestinal issues. These side effects highlight the need for an alternative drug delivery system, like transdermal delivery, to improve patient compliance and reduce unwanted effects. Transdermal delivery can offer more consistent plasma levels of the drug, potentially reducing side effects. Formulation of Tolterodine Tartrate-Loaded Invasomes (2013) materials used Soylecithin a phospholipid, Ethanol, limonene, fenchone, and anethole by Film Hydration Method. Phospholipids (e.g., lecithin) are dissolved in chloroform, and the solvent is slowly evaporated using a rotary flash evaporator to create a thin lipid film.The pressure is decreased between 500 and 1 mbar at a temperature where the lipid undergoes a phase transition (lipid transition temperature). The dried lipid film is then hydrated using a mixture containing tolterodine tartrate, phosphate-buffered saline (PBS, pH 7.4), 10% ethanol, and 1% terpenes (limonene, fenchone, anethole) at the lipid transition temperature for 30 minutes. The resulting tolterodine tartrate-loaded vesicles are subjected to ultrasonication, which breaks them down into nanosized invasomes. The vesicle size of the tolterodine tartrate-loaded invasomes was found to be 1.3 μm, The PDI was 0.188, indicating that the invasomes have a uniform distribution, Entrapment Efficiency found that the lecithin concentration (up to 3%) had a direct proportional relationship with the tolterodine tartrate entrapment in the invasome vesicles (8)**.**

- **Miscellaneous applications of invasomes**

Curcuma longa Lin, the plant from which curcumin is derived, has various therapeutic benefits such as being effective against hepatic diseases, hypocholesterolemia, Alzheimer's, rheumatism, and more. It also has anti-inflammatory, anti-carcinogenic, and antimicrobial properties. The curcumin complex is mechanically dispersed into invasomes using an ethanolic solution of soya phosphatidylcholine (1-3% w/v). The solution is vortexed continuously for five minutes to help disperse the curcumin complex into the lipid structure, ensuring even

mixing of components. The resulting solution is then sonicated for another five minutes to break down larger lipid aggregates and form smaller, more stable invasome particles. To hydrate the lipid thin film, PBS (phosphate-buffered saline) at a concentration of 10% w/v is added to the mixture and vortexed again for five minutes. This results in the transformation of the solution into an invasome gel. The use of cyclodextrin or hydroxypropyl β-cyclodextrin is suggested to improve curcumin's solubility. Limonene, a terpene, is mentioned as a component at a concentration of 0.5%. It's known for its skin penetration enhancement properties, so it might help curcumin penetrate the skin when used in the invasome formulation (3)

CONCLUSION

Chemical penetration enhancement using different penetration enhancer and liposome, ethosomes, electroporation have all been created in order to overcome SC's barrier qualities. Iontophoresis and electroporation have also been developed in order to overcome the barrier properties of SC. Invasomes, for example, could be a potential method for delivering medications through the skin, given they have higher skin penetration than liposomes. Hydrophilic and hydrophobic medicines can both be encapsulated in invasomes. Because of this, new problems and opportunities for the development of new and improved medicines may arise.

REFERENCES

1. Afreen U, Shailaja AK. Overall Review on Invasomes. 2019;3(4):5–9.
2. Babaie S, Rahmani A, Bakhshayesh D, Ha JW, Hamishehkar H, Kim KH. Invasome: A Novel Nanocarrier for Transdermal Drug Delivery. 2020;1–12.
3. Article R, Mounika N, Ramya MG, Meghana S, Rajesh A. INVASOMES: A COMPREHENSIVE OVERVIEW OF THEIR DESIGN. 2024;13(22):561–76.
4. Sciences MP, Article R, Salih OS, Al-akkam EJ. Invasomes as a Novel Delivery Carrier for Transdermal Delivery: Review Article. 2022;2(3):11–6.
5. Raslamol K, Aiswaryai S, Dilshana AS, Shahil M, Na M, Ms S. Invasome: A New Sight in Transdermal drugdelivery System. 2024;9(3):1093–8.
6. Mathpati A, Suryawanshi A, Birajdar S, Mantri A. Formulation, Development and Evaluation of Posaconazole Loaded Invasomal Gel for Topical Applications. 2024;6(14).
7. Sailaja AK. Applications of Invasomal Drug Delivery System. Arch Pharm Pharmacol Res. 2021;3(1).
8. Nangare S. Smart invasome synthesis, characterizations, pharmaceutical applications, and pharmacokinetic perspective: a review. 2020;8.
9. Kumar B, Pandey M, Aggarwal R, Sahoo PK. A comprehensive review on invasomal carriers incorporating natural terpenes for augmented transdermal delivery. Futur J Pharm Sci [Internet]. 2022; Available from: https://doi.org/10.1186/s43094-022-00440-6
10. Sarangamath VS, Ganesh NS, Gopinath E, Nesalin JAJ, Chandy V. Invasomes: A vesicular carrier for transdermal delivery. 2024;17(January):427–37.

HOW TO CITE: Mohite Chakradhar, Hucche Bhimashankar, Kazi Wasim, Kolsure Shripal, Invasomes: Potential Nanocarrier System for Transdermal Delivery of Drug Molecule, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 5, 2652-2664. https://doi.org/10.5281/zenodo.15440759