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Innovations in Invasome Based Systems for Enhanced Transdermal Drug Delivery – A Novel Approach

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Abstract:

Transdermal drug delivery is a non-invasive way to administer medication without going via the liver. In addition to being the third-largest medication delivery mechanism, this is producing a localized effect. Drug distribution in a regulated way is made possible by this novel delivery. Reduced adverse effects and variations in the drug's blood levels are achieved by the transdermal method. Stop medications from being broken down by the digestive system. A new vesicular system called invasomes provides better transdermal penetration than liposomes. Methanol, ethanolic PBS, thymol, chloroform, and phosphatidylcholine make up this vesicular system. Ethanol, thymol, and phospholipids offer appropriate transdermal penetration characteristics. An invasome is made using the thin film lipid hydration technique. The Mechanical Dispersion Technique is another approach. Zeta potential, cryo TEM, SEM, entrapment efficiency, viscosity, drug content, and in vitro investigations were among the properties of the generated invasome that were evaluated. Fungal infections, skin cancer, acne, and breast cancer are all treated using invasomes. In general, invasomes improve medication delivery via the cellular membrane and epidermal layer. This vesicular carrier presents certain difficulties as well as research prospects for the creation of new, better treatments in the future.

Keywords: Invasome, Transdermal Drug Delivery, Cryo TEM, SEM.

INTRODUCTION:

Transdermal drug delivery systems (TDDS) are a novel, non-invasive method, this forms engineered for topical application on the skin. This system is used to increase the bioavailability of the drug. Unlike traditional methods, these systems facilitate a controlled, predetermined release of a pharmacologically active agent into the systemic circulation via the skin over a sustained period. maintained in the body, allowing drugs to remain within the therapeutic window (the range between minimum effective levels and the maximum tolerated dose). This allows for higher therapeutic effects, as well as reduced systemic toxicity and side effects. Additionally, the transdermal route avoids first pass metabolism in the liver. As a result, fragile molecules can avoid the low pH of the GI tract. Now recognised as the third-largest drug delivery platform globally, TDDS provides a steady–state drug profile, effectively eliminating the fluctuations often associated with oral or injectable bolus doses. Invasomes are a type of artificial vesicle nanocarrier that transports substances through the skin, the body's most superficial biological barrier. These small particles, surrounded by a lipid layer, can carry substances into and out of cells. Invasomes are bilayer vesicles composed of soy phosphatidylcholine (SPC), lysophosphatidylcholine (flexibility substances), terpenes, and ethanol (a permeation enhancer). The presence of penetrative boosters like terpene and ethanol gives invasomes a high penetration potential. Invasomes are a novel vesicular system that offers superior transdermal penetration compared to liposomes. [1,2,3]

Components of Invasome:

- Phospholipid
- Terpene

Biological membranes are primarily composed of phospholipid. Phosphatidylcholine (PC) is the most frequently used phospholipid in the invasome. [4,5]

The amphipathic compound PC molecule has-

A) A hydrophilic polar head containing phosphocholine.
B) A pair of hydrophobic acyl hydrocarbon chains.
C) A glycerol bridge.

Water does not dissolve the molecules of phosphatidylcholine. To reduce the undesirable contact within the elongated hydrocarbon fatty chain with the bulk aqueous phase, they are precisely orientated into planar bilayer sheets in aqueous condition. To create encapsulated closed vesicles, the sheets then wrap by themselves.

Some other examples of phospholipids are: Phosphatidylserine (PS), Dioleoyl phosphatidyl ethanolamine (DOPE). [5]

- **Terpene:**

Terpenes or terpene mixtures in extremely low doses are penetration enhancers (also known as sorption boosters or accelerants), which enter into the skin and reduce barrier resistance,

according to research on transdermal drug delivery systems. By upsetting the tightly packed lipid structure of the stratum corneum terpenes have also demonstrated the ability to improve the penetration

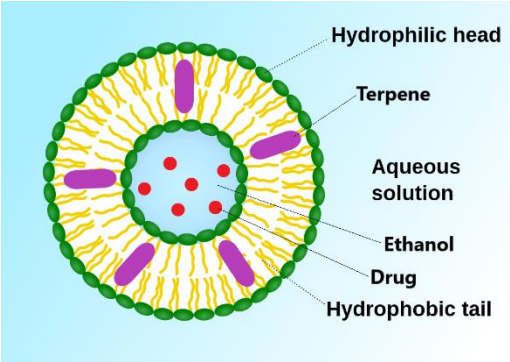

Figure 1: Structure of Invasome

of certain medications. Because terpenes are unlikely to cause skin irritation, they are categorized as "Generally Recognized As Safe" (GRAS). Terpenes can permeate the skin due to their solubility, the dissolving of lipid and protein layers, and the loss of skin micro-ingredients. Terpene transdermal preparations therefore seem highly promising. [5]

Purpose of Invasome

- The primary goal is to improve a drug's ability to pass through the skin's stratum corneum, the main barrier to transdermal delivery.
- By getting more of the drug into the skin and deeper tissues, invasomes can improve the drug's therapeutic effect.
- Transdermal delivery via invasomes can reduce the need for frequent injections or oral medications, making treatment more convenient and increasing how well patients stick to their regimen.
- Invasomes can protect the drug from degradation and improve its absorption into the body.
- Invasomes can be formulated to act as a depot, providing a sustained release of the drug over time, which is useful for long-term treatment.
- Invasomes are especially useful for delivering drugs that are not easily absorbed through the skin in conventional forms. [6]

Advantages:

- Non-invasive technique
- Patient compliance is high
- Delivery of hydrophilic and lipophilic drugs is possible.
- Enhanced drug delivery and penetration lead to improved drug effectiveness at the intended site.
- This formulation method provides a comfortable and painless drug delivery experience for the patient.
- It enhances the penetration rate of actives. [6]

Disadvantages:

- It requires a high cost for production.
- Chance of leakage and fusion of encapsulated active
- Invasome containing phospholipids may get oxidised/hydrolysed and affect the stability of vesicles. [6]

Structure of Skin

Skin is the largest organ of the body. It covers around 2 m^2 of the body. The thickness of skin varies from one region to another. The highest thickness of the skin is found on the heels (4 mm), and the lowest thickness is found on the eyelids (0.5 mm). Skin holds the body's contents together and protects the body's internal organs from the outside environment.[7,8]

The skin consists of three layers. This is the first layer, which is also the outermost layer of skin, whose thickness is ~ 100 µm. It limits the flow of organic compounds both inward and outward. Also, provide a waterproof barrier and create skin tone. Nerves, lymph vessels, blood vessels, and hair follicles are all part of the connective tissue matrix that makes up the 3–5 mm thick layer known as the dermis.[9]

An essential function of the cutaneous blood supply is to regulate the internal body temperature. Along with eliminating waste and impurities, it also gives the skin nutrition and oxygen. Most molecules that permeate the skin barrier find a sink condition in capillaries, which extend to within 0.2 mm of the skin's surface. Consequently, the blood supply maintains a drug's dermal concentration at an exceptionally modest level. Transdermal penetration depends critically on the concentration gradient that develops across the epidermis. Adipose tissue and loose connective tissue make up the hypodermis, sometimes referred to as the subcutaneous layer. The hypodermis provides support for the dermis and epidermis. It acts as a fat storage facility.

This layer offers mechanical protection, nutritional support, and temperature regulation assistance. A drug must cross all three of these layers to be administered via the transdermal pathway; however, only the stratum corneum needs to cross for the drug to be retained in the skin layers when applied topically. [10,11]

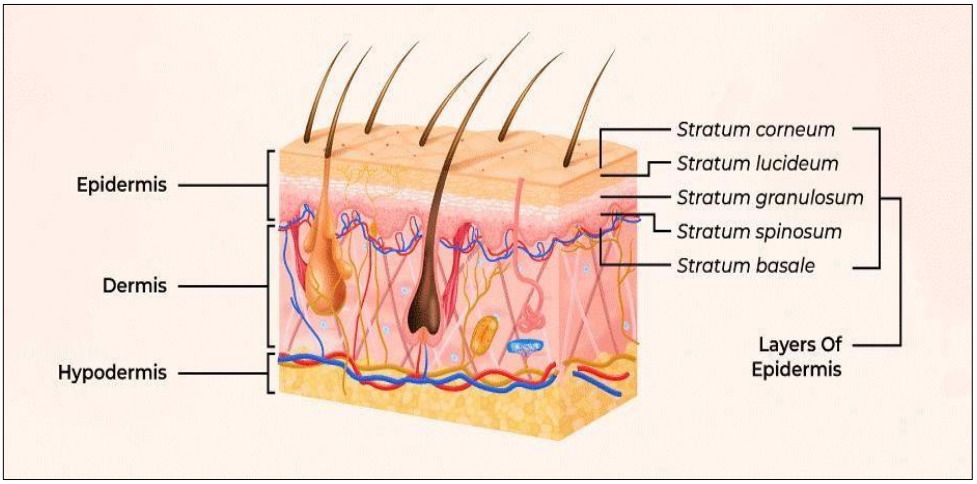

Figure 2: Structure of skin

Penetration Mechanism:

The Stratum Corneum (SC) is often described as a "bricks and mortar" structure, where the "bricks" are protein-rich corneocytes and the "mortar" is a highly organized lipid matrix. Invasomes don't just sit on top of this barrier; they actively re-engineer it. The drug's physicochemical characteristics determine the routes by which it can be absorbed through the skin. Drugs that are hydrophilic or lipophilic are absorbed in distinct ways. The skin's upper stratum corneum prevents drugs from being absorbed. Still, the existence of several absorption pathways makes it easier for drugs to enter the body and be transported to the systemic circulation. [11,12]

1. **Trans-follicular route:** The trans-follicular route, also called the trans-appendageal route, which offers a wide area for drug diffusion, is the fastest route a drug must take to enter the systemic circulation. The permeability of skin increases significantly when it comes into contact with water. Drug transport via these ducts provides a continuous conduit throughout the stratum corneum; however, the volume and composition of gland secretions, among other parameters, influence drug transport via this pathway. However, the trans-appendageal pathway barely makes up 0.1% of the skin's surface, making a minimal contribution. [12]
2. **Intercellular pathway:** The drug diffuses across the intercellular channel, which is a continuous lipid matrix that runs between the cells, as the name suggests. The drug can pass through the alternating lipid and aqueous domain because to the complex structure that corneocytes make. The drugs must diffuse to the inner side of the lipid **bilayer after** partitioning into it. Since water must travel 50 times further via this path, uncharged lipophilic medicines are the primary candidates for use. [12]
3. **Intracellular route:** This method of drug delivery involves passing via corneocytes, which have highly hydrated keratin that creates a hydrophilic channel. Lipids enclosing corneocytes serve as links between these cells. Therefore, a drug needs to go through several diffusion and partitioning stages. It is the pathway that is most frequently employed by different kinds of drugs. The drug enters the cell through the cytoplasm, or matrix, using the transcellular route. Hydrophilic drugs are appropriate for this approach. The drug enters the stratum corneum through the corneocytes. The hydrophilic drugs have an aqueous route thanks to the highly hydrated keratin. The drugs must go through several partitioning and diffusion stages in order to pass through the cell matrix. [13]

- **Chemical Synergism:** The Ethanol-Terpene Axis

The superior performance of invasomes over traditional liposomes is primarily due to the synergistic effect of ethanol and terpenes.

- **Ethanol's Role:** It serves as one of the principle "softening" factors. By softening the polar head groups of the SC lipids, it enhances the lipid bilayer's fluidity, thereby granting the vesicle the deformability required to squeeze through narrow intercellular spaces.

- **Terpene Disruption:** Terpenes (such as limonene or cineole) act as potent "penetration enhancers." They insert themselves into the lipid lamellae of the SC, disrupting the tightly packed crystalline

structure. This transition from a "gel" state to a more fluid "liquid-crystalline" state significantly lowers the resistance of the skin barrier.[14]

- **The "Deformability" Advantage**
- As highlighted by **Honeywell-Nguyen**, the defining characteristic of an effective invasome is its elastic nature. Traditional vesicles are often too rigid and get "trapped" in the superficial layers.[15]
- **Stress-Dependent Shape Change:** Because invasomes are highly flexible, they can undergo significant shape deformation to squeeze through hydrophilic channels in the intercellular region that are much smaller than the vesicle's own diameter. [16]
- **The Hydration Gradient:** These vesicles are often driven by the osmotic gradient—the difference in water content between the dry surface and the hydrated deeper layers of the epidermis—effectively "pulling" the intact invasome inward. [17,18]

Dual Penetration Pathways

Table 1: Invasomes utilize a multi-pronged approach to bypass the SC:

Pathway	Mechanism	Significance
Intercellular Route	Vesicles navigate the winding, lipid-filled spaces between corneocytes.	The primary route for sustained drug release.
Follicular (Shunt) Route	Vesicles travel via hair follicles and sebaceous glands.	Bypasses the SC entirely, allowing for rapid, deep dermal delivery.
Vesicular Disintegration	Partial breakdown releases phospholipids that integrate into the skin's own lipids.	Creates "micro-reservoirs" of the drug within the SC.

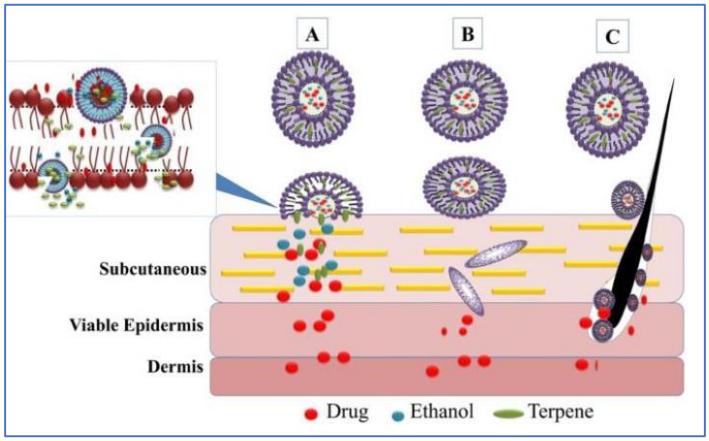

Figure 3: Penetration mechanism of invasomes through SC (a) Enhanced penetration, (b) Intact penetration and (c) Trans-appendageal penetration

Preparation Method of Invasome

Various Methods for Invasome Preparation:

- **Mechanical Dispersion Technique:**

This method involves dissolving a medication, terpene, or combination of terpenes in ethanol that contains phospholipids. After vortexing, this mixture is sonicated for five minutes. After that, hydrate with Phosphate Buffer Saline at pH 7.4 while continuously vortexing. Subsequently, invasomes are created and grow on their own. Finally, it is necessary to do sonication, lyophilization, and high-pressure extrusion.[19,20]

- **Thin Film Hydration Method:**

One traditional technique for making invasomes is thin-film hydration. Assemble the 2:1 v/v ethanol and chloroform mixture. After that, the medication, terpene, and phosphatidylcholine were dissolved in a mixture of ethanol and chloroform in an RBF. Using a rotary evaporator, the organic solvent was eliminated. The thin film should next be hydrated using phosphate buffer at a pH of 7.4. After that, the produced vesicles were sonicated to create smaller vesicles.[21,23,24]

Characterisation of Invasomes

- **Entrapment Efficiency:**

10 ml Invasomal formulation was filled in the centrifuge tube, then kept in the ultracentrifuge at 5000 rpm for 30 min. After centrifugation, the supernatant was separated, and the transparent part was collected in the test tube, then diluted with buffer. Then the drug concentration was measured by using a UV-Spectrophotometer at specified wavelengths. The EE was evaluated by using the formula: [25,30]

% Entrapment= (Total amount of drug- Free drug)x 100/ Total amount of drug.

- **Particle size determination:**

The particle size of Invasome was measured by Photon Correlation Spectroscopy (PCS) at 25°C under a fixed angle of 90° in disposable polystyrene cuvettes. [26]

- **PDI:**

Polydispersity index is a measure used to describe the distribution of molecular massing a polymer sample. It indicates the degree of non-uniformity in the molecular weight of the polymer chains. [27,31,32]

- **Zeta potential determination:**

The zeta potential demonstrates the surface charges for various formulations of Invasome. It assesses the electrophoretic motion at 25±0.25 ^{0}C with 174° angle for elimination of numerous scattering impacts. The average zeta potential of the Invasome was analysed during the 60-second analysis period. Give the information about the stability of the formulation. [28,29]

- **SEM(Scanning Electron Microscopy):**

Scanning electron microscopy was used for visualising an invasome. A monolayer of the invasome dispersion was applied to one side of a double adhesive stub. These stubs were then platinum-coated with an auto fine coater. [30,33]

- **TEM (Transmission Electron Microscopy):**

Biological or soft-matter samples are quickly frozen to near-natural, near-liquid nitrogen temperatures (around 150 °C) using the transmission electron microscopy (TEM) technique. By maintaining the sample's natural state and preventing the damage that would otherwise result from the electron beam, this procedure enables the visualization of structures at nearly atomic resolution. A thorough 3D model of the specimen can be created by merging numerous 2D projections and applying computational analysis.[31,32, 34,35]

- ***In vitro* study:**

A semi-permeable Franz diffusion cell was used to perform an in vitro drug diffusion experiment. In order to maintain 37 °C, a phosphate buffer with a pH of 7.4 was retained in the receptor media and constantly swirled using a magnetic stirrer. On the membrane's donor side, the sample was applied. Gather the required amount of the sample, then dilute it with the buffer. Next, assess the sample at a particular wavelength using a UV spectrophotometer.[36,37,38]

Application of Invasome:

- **Dermatological Applications:**

By enabling the deep transdermal transport of medicinal drugs, the unique architecture of invasomes has demonstrated remarkable efficacy in the management of dermatological disorders. In contrast to traditional topicals, scientists have achieved significantly higher delivery into the layers of skin by loading anti-inflammatory agents into these flexible spheres. Due to this increased delivery, doctors can now target chronic conditions such as psoriasis and eczema accurately and locally. This means the medication can reach the inflammation below while limiting the amount absorbed into the body, which often causes undesirable side effects.[39,40]

- **Cancer Therapy:**

Invamedicine' s unique formulation has proven particularly effective in dermatological therapies as it allows pharmaceuticals to be delivered via transdermal absorption. When incorporated into these flexible vesicles, anti-inflammatory drugs have been shown to penetrate the multiple layers of skin far more efficiently than topical creams. Psoriasis and eczema are long-term skin diseases that can now be treated directly and precisely. This is due to the fact that invasomes allow the drug to reach the affected tissue below the skin surface. In addition, systemic absorption is reduced, avoiding many of the side effects associated with oral administration of medication. Cancer treatment may also benefit from invasomes' ability to penetrate deeper into the skin. By packaging cancer drugs in these nano-sized capsules, you can achieve higher concentrations at the site of the tumor while maybe avoiding the systemic toxicity seen with intravenous chemotherapy.[41]

- **Ophthalmic Drug Delivery:**

By addressing the specific anatomical challenges of the eye, invasome technology in eye treatments has significantly improved the management of eye disorders. These flexible lipid vesicles have a longer presence on the eye's surface and better penetration through the cornea.

This innovation tackles the common issues that standard eye drops face, such as limited effectiveness and rapid tear drainage. Invasome technology has the potential to transform the treatment of complex problems in the back part of the eye and to deliver glaucoma medications more reliably by ensuring that drugs spread consistently and deeply.This specialized delivery system allows active ingredients to bypass the corneal epithelium and reach target tissues in the aqueous humor and beyond. Compared to traditional rigid liposomal systems, the greater flexibility of invasomes helps them navigate the tight junctions of the eye's surface better. This leads to higher drug concentrations while reducing how often patients need to take doses.[42]

- **Infectious Disease:**

A powerful tactic in the contemporary treatment of infectious diseases, particularly those resistant to conventional antibiotic regimens, is the use of invasomes loaded with antimicrobial agents. Microbial biofilms, which are intricate, self-produced polymeric matrices that protect bacteria from both host immune responses and conventional medications, are a major obstacle in the treatment of chronic infections. Due to their exceptional flexibility and chemically adjusted lipid bilayers, invasomes possess the capacity to pierce these impenetrable biofilm structures, ensuring the direct delivery. This vesicular mechanism greatly improves the biocidal efficacy against multidrug-resistant bacteria by enabling deeper infiltration into infected tissues and colonies.

By maintaining deadly medication concentrations exactly where the infections reside, this intensive and targeted delivery method not only enhances therapeutic outcomes but also helps to reduce the possibility of additional resistance development.[43]

- **Neurological Disorder:**

Invasomes show great potential in neurotherapeutics. Their ability to navigate the complex environment of the central nervous system (CNS) is being carefully studied. One of the main obstacles in treating serious neurological diseases like Parkinson's and Alzheimer's is the blood-brain barrier (BBB). This barrier usually keeps most systemic drugs out. Invasomes, with their unique lipid-ethanol-terpene structure and high deformability, offer a promising way to deliver neuroactive drugs through the skin or nose. These vesicles can help transport therapeutic molecules across the blood-brain barrier by using their flexible properties, ensuring that essential medications reach the brain tissue. This approach not only improves the effectiveness of neuroprotective and symptomatic drugs but also provides a non-invasive alternative to direct delivery methods, marking an important step forward in treating ongoing neurodegeneration.[43]

- **Cardiovascular Inventions:**

The use of invasome-based delivery systems has greatly improved how cardiac drugs work in cardiovascular therapy. The complex lipid structure of these vesicles effectively tackles the common issue of limited bioavailability, which often arises from poor drug solubility or rapid first-pass metabolism. Invasomes offer sensitive cardiovascular substances a strong protective environment by forming a bilayer that combines certain phospholipids with fluidizing agents.

This unique composition allows for a controlled, sustained-release mechanism. It ensures better structural stability and delays premature breakdown. Invasomes reduce the need for frequent dosing and limit the fluctuations in blood pressure or heart rate that can lead to negative clinical outcomes. They help maintain steady plasma levels of medications like beta-blockers or calcium channel blockers over extended periods.

Moreover, the flexibility of the invasome surface allows for possible functionalization. This could lead to more precise targeting of myocardial cells or vascular endothelial tissues, enhancing the effectiveness of essential cardiac treatments.[43,39]

Conclusion

In summary, invasomes represent a notable improvement in transdermal medication delivery. They are particularly effective for delivering both hydrophilic and lipophilic medications due to their unique formulation, which includes soy phosphatidylcholine, lysophosphatidylcholine, terpenes, and ethanol. This formulation improves skin penetration. Invasomes differ from traditional liposomes because of their fluid and flexible shape, made possible by ethanol and terpenes. This feature allows for better penetration and encapsulation efficiency. The growing need for carriers that can transport active drugs through different layers of the skin is being addressed by the development of invasomes. Their controlled release, stability, and strong penetration potential make them a preferred option for pharmaceutical applications. Invasomes utilize new nanocarrier technology to improve penetration and therapeutic

results, offering a fresh approach to transdermal medication delivery. Their unique benefits, such as non-invasiveness, improved patient compliance, and flexibility in medication delivery, make them a viable choice for various medical uses. While ongoing research and development are crucial for enhancing their formulation and expanding clinical use, challenges such as production costs, leakage, and half-life need to be addressed. By using invasomes, we can significantly improve drug delivery and treatment results, ultimately benefiting patient care and public health.

List of Abbreviations:

TDDS: Transdermal drug delivery systems

PC: Phosphatidylcholine

PS: Phosphatidylserine

DOPE: Dioleoyl phosphatidyl ethanolamine

GRAS: Generally Recognized As Safe"

SC: Stratum Corneum

EE: Entrapment Efficiency

PCS: Photon Correlation Spectroscopy

PDI: Polydispersity index

ZP: Zeta potential

SEM: Scanning Electron Microscopy

TEM: Transmission Electron Microscopy

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Authors' contributions

We affirm that the writers listed in this article completed this research work. **Banhishikha Kar** conceptualization, methodology, formal analysis and **Dipannita Naskar**: contributed to the supervision, writing review, and editing the project. **Ujjal Manna** has contributed to writing of original draft preparation also formatted and removed typological errors from the manuscript.

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