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Review Article

INVASOMES: A NOVEL LIPID-BASED NANOCARRIER FOR IMPROVED SKIN PERMEATION AND DRUG DELIVERY

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ABSTRACT

Transdermal drug delivery systems have gained significant attention due to their ability to provide controlled drug release, improved patient compliance, and avoidance of first-pass metabolism. Among various advanced vesicular carriers, invasomes have emerged as a promising nanocarrier system for enhanced transdermal delivery. Invasomes are lipid-based vesicles composed of phospholipids, ethanol, and terpenes, which act synergistically to improve skin permeation. The presence of ethanol and terpenes enhances the fluidity and deformability of the vesicular membrane, allowing deeper penetration through the stratum corneum. Invasomes exhibit superior characteristics compared to conventional liposomes, including enhanced permeability, flexibility, and ability to deliver both hydrophilic and lipophilic drugs. Various preparation methods such as thin film hydration, reverse phase evaporation, ether injection, and freeze-drying are employed to formulate invasomes with desired properties. Characterization techniques including microscopy, particle size analysis, zeta potential measurement, and spectroscopy are essential for evaluating invasomal systems. Furthermore, invasomes have shown promising applications in the delivery of immunosuppressive, anticancer, antihypertensive, and antioxidant agents. Their ability to enhance drug penetration and improve bioavailability makes them a valuable tool in modern drug delivery. Despite certain limitations such as stability issues and high production cost, invasomes remain a highly effective and innovative approach for transdermal drug delivery systems.

Keywords: Invasomes, Transdermal Drug Delivery, Terpenes, Ethanol, Vesicular System, Lipid Nanocarriers, Skin Permeation, Controlled Release, Nanotechnology, Drug Delivery Systems.

INTRODUCTION

Invasomes

Transdermal drug delivery is a clinically approved method for administering medicine through the skin. It offers a more comfortable route of administration and reduces the risk of fluctuations in blood drug concentrations and hazardous side effects. Invasomes, similar to liposomes, contain lipids and cholesterol that enhance the encapsulation of pharmaceutical active components (Varenya *et al.*, 2024).

Invasomes are a type of artificial vesicle nanocarrier that transport 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.

The incorporation of ethanol and terpene in invasomes facilitates lipid fluidity in the vesicle structure, making them more flexible and less rigid than typical liposomes. Ethanol interacts with lipids in the stratum corneum (SC) polar group region, causing structural changes in the keratinized and lipophilic regions, decreasing lipid transition temperatures, and fluidizing and disrupting the tightly packed SC lipids.

The development of advanced carriers for efficient delivery of active pharmaceutical ingredients through various skin layers (dermis, epidermis, subcutaneous tissue, etc.) is essential. Recently, incorporating terpenes (alone or in combination) and ethanol into lipidic vesicular systems like invasomes has significantly enhanced the penetration of vesicles with active molecules through the skin. The combination of a bilayerforming agent, edge activator, and penetration enhancers provides a synergistic effect, offering superior penetration power to the drug/active ingredient and improving the flexibility and fluidity of invasomes. The ethanol's interaction with SC lipids induces structural changes in keratinized and lipophilic regions, decreases lipid transition temperatures, and fluidizes and disrupts tightly packed SC lipids. Balancing the potency and toxicity of terpene or terpene mixtures for humans is a crucial regulatory requirement during the development of invasome formulations (Patil *et al.*, 2023).

Structure of invasome

Invasomes are small particles surrounded by a lipid layer that can carry substances into and out of the cell. Invasomes are similar to liposomes and they comprised of soyaphosphatidylcholine, lysophosphatidylcholine, terpenes, and ethanol.

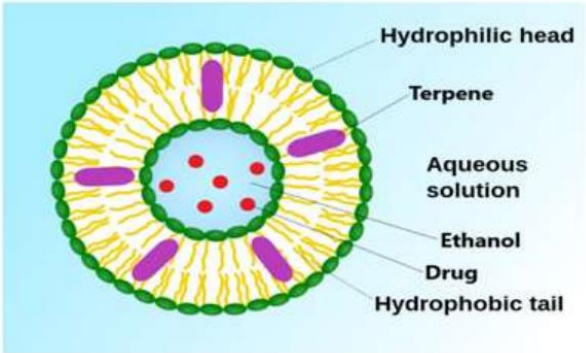

Figure 1: Structure of Invasome

Definition and Characteristics of Invasomes

Invasomes are specialized vesicular carriers designed to enhance the transport of medicinal drugs across biological membranes. They are similar to liposomes, however they are different in that they can independently successfully cross biological barriers. The inclusion of edge activators gives the vesicle membrane flexibility, allowing them to go through tight junctions and cellular barriers with this unique property (Babaie *et al.*, 2020).

The primary characteristics of invasomes are their nanoscale size, lipid-based makeup, and presence of edge activators. When combined, these qualities provide them a higher penetration rate, which makes them desirable choices for improving medication delivery across various biological interfaces.

Lipid Composition, Surfactants, and Other Components:

The lipid composition of invasomes has a major role in how they interact with cellular membranes and preserve their structural integrity. The primary lipid bilayer is often

composed of phospholipids, which contain cholesterol, phosphatidylcholine, and phosphatidylserine. The flexibility and stability of the invadesomes membrane are supported by these lipids. A characteristic that distinguishes invasomes apart from phospholipids is the incorporation of surfactants, namely edge activators. Edge activators such as the Span and Brij series cause disruptions in the lipid packing of the vesicle membrane, resulting in a decrease in the membrane's stiffness and an increase in its deformability.

This change allows invasomes to more easily navigate biological barriers and small places than liposomes did in the past (Kumar *et al.*, 2022). Stabilizers and hydration media are common extra components added to formulations to increase their stability and medication loading capacity. Stabilizers like trehalose or sucrose stop invasomes from clumping together and merging, ensuring a consistent and steady composition.

Advantages of invasomes

- Non-invasive technique of drug delivery(Saudagar and Bornare, 2016).
- Enhanced permeation of drug through the skin for transdermal drug delivery.
- Delivery of hydrophilic and lipophilic drug is possible (Lakshmi *et al.,* 2013)
- Contains non-toxic raw material in formulation.
- Simple method of drug delivery in comparision to iontophoresis and phonophoresis and other complicated methods

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 (Lakshmi *et al.,* 2013).

Method of Preparation:

Various Methods for Invasome Preparation:

Invasomes are produced using a range of methods, each of which offers a distinct advantage in terms of vesicle size, encapsulation efficiency, and scalability. Which method is best depends on the specific requirements of the drug and the desired characteristics of the invasomal formulation (Salih, 2022).

Thin Film Hydration

By dissolving lipid components in an organic solvent, this process produces a thin lipid coating on the container's surface. After that, the medication and surfactants are introduced to the film's aqueous phase, allowing invasomes to grow naturally. Thin film hydration is a popular, flexible technique that is well-known for being simple and scalable (Haag *et al.*, 2011).

Reverse Phase Evaporation

This method produces a water in oil (W/O) emulsion by dissolving lipids and the aqueous phase in an organic solvent. The emulsion is then allowed to evaporate, which leads to the development of invasomes. Reverse phase evaporation can be used to encase hydrophilic drugs, leading to high entrapment efficiencies.

Ether Injection Method

Lipids are dissolved in diethyl ether before the organic phase is added to an aqueous solution. The reason for the creation of spontaneous vesicles is the fast diffusion of the organic solvent into the aqueous phase. This method

has been used to create invasomes with small particle sizes and high drug encapsulation.

Freeze Drying Method

Invasomes are prepared using this procedure, and to improve their stability and extend their shelf life, they are then freeze-dried. This method works well for controlled drug release and long-term preservation since the freeze-dried invadesomes can be rehydrated prior to distribution.

Comparison of Different Techniques and Their Impact on Invasome Characteristics:

Every preparation method has advantages and disadvantages that impact the final invadesomes' characteristics. While thin film hydration is more practical and suitable for large-scale production, reverse phase evaporation is better at encapsulating hydrophilic medications. The ether injection approach produces small-sized invasomes, while freeze-drying increases stability (Jain *et al.*, 2021). The method of choice should be in keeping with the intended use and the specific requirements of the drug. Considerations like as stability, drug loading capacity, and vesicle size should be made while selecting the most effective preparation technique. Understanding how different approaches affect invasome characteristics is crucial for tailoring formulations to meet the various needs of drug delivery applications.

Characterization Techniques:

Analytical Methods for Characterizing Invasomes:

Precise characterization of these entities is required in order to fully understand their features and optimize their effectiveness for drug delivery. Numerous analytical techniques provide insight into the molecular, cellular, and physical properties of invasomes. Here, we go over a few important techniques used to characterize invadesomes:

Microscopy Techniques:

Optical Microscopy: Gives a general overview of the anatomy, size, and distribution of invadesomes.

Transmission Electron Microscopy (TEM): Provides high-resolution pictures that enable precise nanoscale invasome structural imaging (Salem *et al.*, 2020).

Scanning Electron Microscopy (SEM): Beneficial for evaluating the surface shape of invadesomes and for surface imaging (Kaltschmidt *et al.*, 2020).

Spectroscopy Techniques

Fourier Transform Infrared Spectroscopy (FTIR)

Finds functional groups inside invasomes, which helps to characterize the components that make up lipids and surfactants.

Nuclear Magnetic Resonance (NMR): Sheds light on the structural organization of lipid molecules and the composition of invasomes.

Particle Sizing Techniques

Dynamic Light Scattering (DLS): Ascertains the invasomes' size distribution in a suspension, assisting in the evaluation of their homogeneity and stability.

Zeta Potential Measurement: Determines the invasomes' surface charge, providing details about their stability and interactions with biological membranes (Ogiso *et al.*, 2001; Sinico *et al.*, 2005).

Differential Scanning Calorimetry (DSC): Understands the stability and phase transitions of invadesomes by analyzing their thermal behavior.

High-performance Liquid Chromatography (HPLC): Measures how

well drugs are encapsulated and how quickly they are released from invasomes (Lakshmi *et al.,* 2013).

Pharmaceutical applications of Invasomes

Immunosuppressive Drug Delivery

Immuno suppression is the primary approach to treat autoimmune diseases. Also, it is useful for clinical application of existing immunosuppressive agents that have been suffered from various drug side effects. The nanotechnology centred approaches can correct the major limitation by enhancing immunosuppressant delivery to target cells of immune system. Also, reducing the recommended dose for therapeutic function and reducing drug distribution to non-target tissue can be a key alternative to immunosuppressive drug delivery (Al-Lawati *et al.,* 2018). From the sub structure of lipid vesicles in drug delivery, it receives the primary consideration of investigation to develop advanced nano-sized vesicles. A literature survey mentioned that cyclosporine A (CsA, cyA) is a lipophilic drug and it exhibits poor penetration efficiency into the skin layers (partition coefficient: 4000).

The topical applications of Cs A can be suitable alternative for management of psoriasis and other dermatological diseases. Initially Verma were synthesised the invasomes nanocarrier for delivery of CsA CyA using unsaturated soybean phosphatidylcholine (10%w/v), ethanol (3%w/v), citrsal:cineole :D-limonene mixtures (0.5:1.0:1.5%w/v)and PBS up to 100%w/v using mechanical dispersion. In-vitro penetration study concluded that due to the presence of ethanol and terpenes showed a higher amount of CsA in the deeper layer of skin (viable epidermis and dermis) as compared with the aqueous/ ethanolic drug solution and liposomes (without ethanol and terpenes). Besides the increasing concentration of terpene (0.5to1.0%) significantly increased the amount of CsA in the deeper skin layer and subcutaneous layer. It shows the direct correlation between the amount of drug found in skin layer (Dragicevic *et al.,* 2016). Owing to excellent finding of immunosuppressive agent –loaded invasomes, it can used for treating auto immune diseases. Taken as whole confirmed that invasomes can be an effective substituent for hydrophobic drug delivery to the deeper skin layers.

Anticancer Drug Delivery:

From its inception, cancer treatment it is still a challenging field in the era of biomedical science. Due to the ineffectiveness of currently engaged therapeutic strategies, a large number of deaths have been occurring each year (Nangare *et al.,* 2020).

Therefore, there is an urge to develop an advanced substitute to resolve advanced substitute to resolve cancer ineffective treatment issues. Interestingly, the temoprofin is a potent (second-generation) photosensitizer. It shows high tumour selectivity and residual photosensitivity of only 2 weeks. Thus, this could be effective anti-cancer agent in photodynamic therapy of early or reoccurring carcinomas. DragicevicCuric and Co- authors were reported that the deposition of the highly hydrophobic photosensitizer (temoprofin) using invasomes into the skin layer of stratum corneum.

Briefly, temoprofin- loaded invasomes have been synthesized using the mechanical dispersion method. In that, the temoprofin and

1% w/v terpene (limonene/citral/cineole) were dissolved in ethanolic phospholipid solution. (Phosphatidylcholine: ethanol: 75:25w/w) and subjected to vortexing followed by sonication for 5 minutes. Finally, phosphatase buffer saline was added into the above-mentioned clear solution with constant vortexing for 5 minutes. The drug loaded invasomes (1%w/v cineole) showed about 105.4nm, particle sizes and about 0.066 Polydispersity index. After plastic surgery, the human female abdominal skin was obtained and penetration was carried out using the nominal surface of the Franz cells (3.14cm^2).

The use of cineole (1%w/v) shows the highest penetration ability fallowed by a mixture (1%w/v) of cineole: citral: D- limonene (45:45:10v/v). Experimental outcomes revealed that the single terpene could make an effective delivery of temoprofin and combination of terpenes could lead to the synergistic effect of active penetration to the subcutaneous and deeper skin layers.

Besides the stability study indicated that the invasomes containing 1%w/vc cineole showed a small increase in particle size and Polydispersity index value and can be considered a physically, stable form for 12 months. In the future invasomes can be an effective carrier for the delivery of hydrophobic active molecules with effective concentration to the systemic or local site. However, there is no thumb rule for the use of terpene and its mixture towards penetration (Dragicevic-Curic *et al.*, 2009).

Delivery of anti–hypertensive agent:

Anti-hypertensive are used to treat elevated hypertension. It has numerous problem such as low aqueous solubility, low bioavailability, and short biological half-life low permeability and I list of undesirable side effects (Chen *et al.*, 2010). This can be waved off using a suitable route for delivery and ethanol formulation. A calcium channel blocker, isradipine is generally used for the treatment of hypertension. Unfortunately, it has low oral bioavailability and it suffers the firs-pass metabolism. Kamran et al. accomplished the development of invasomes using phospholin 90G (2%w/v), b-citonellene (0.1%w/v terpene) and ethanol 10% w/v through conventional film hydration technique and used as a efficient carrier for the delivery of isradipine via transdermal route.

In brief, isradipine, terpene and phosphoric 90G were dissolved in chloroform: methanol (2:1v/v), then the organic solvents were removed through rotary evaporator and organic solvent traces were collected separately using a vacuum cabinet overnight. The hydration of isradipine invasomal lipid film has been performed using phosphate buffer saline: ethanol at 60 rpm using rotary evaporation for 1hr and then subjected to probe sonication (4°c) at 40% output frequency. The particle size, Polydispersity index, entrapment efficiency, and transdermal flux through rat skin of isradipine invasomes were found to be 194nm, 0.272, 88.46% and 22.80mg/cm^2 /h respectively, because of presences of ethanol and terpene, it provides particle deformability and enhances the penetration rate of isradipine. Interestingly, enhancement in the deformability of invasomes and lipid by layers of stratum corneum disruption facilitates the penetration of the isradipine invasomal vesicles.

Antioxidant:

Nowadays, ferulic acid (antioxidant) is gaining much attention from research scholars

due to its therapeutic effects such as anti-cancer, anti-skin disorders, anti-diabetes, anti-inflammatory, etc. Ferulic acid is normally located in many of the plant cell walls. Unfortunately, it takes a short half-life of removal and needed many dosages with regular administration. In addition this, the *in-vitro* permeation of ferulic acid from ethosomes through the human skin was found to be high as compared with the other formulations. It may be because of high concentration of ethanol in ethosomes. On the other hand, conventional liposomes have been expected to be effective for the delivery of drugs into the upper layers of skin. Besides, ferulic acid invasomes showed better permeation because of deformable vesicles and penetration enhancers interaction with lipid lamellae and skin layer (Chen *et al.*, 2010).

CONCLUSION

Invasomes are an advanced vesicular drug delivery system designed to enhance transdermal drug delivery. Their unique composition of phospholipids, ethanol, and terpenes improves membrane flexibility and skin permeation. The presence of penetration enhancers allows effective transport of drugs across the stratum corneum. Invasomes can deliver both hydrophilic and lipophilic drugs efficiently. They show improved bioavailability and controlled drug release compared to conventional systems. Various preparation and characterization techniques help in optimizing their performance. Invasomes have demonstrated potential in delivering drugs such as anticancer, antihypertensive, and immunosuppressive agents. Although challenges like stability issues and high cost exist, they can be overcome with advanced formulation strategies. Invasomes represent a promising and non-invasive approach for modern drug delivery applications.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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