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Review Article

Invasomes A Novel Drug Delivery for Transdermal Drug Delivery System

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ABSTRACT

Invasomes are a novel class of elastic phospholipid vesicles designed to enhance the percutaneous penetration of drugs, offering an improved alternative to conventional liposomes. These vesicles are composed of phosphatidylcholine, ethanol, and a variety of terpenes, which are known to significantly enhance skin penetration. Terpenes, such as citral, limonene, and cineole, disrupt the stratum corneum lipids, interact with intracellular proteins, and improve the partitioning of drugs into the skin, facilitating better drug absorption. Ethanol further enhances the vesicle's ability to penetrate the skin by providing a net negative surface charge and preventing vesicle aggregation through electrostatic repulsion. This synergistic effect between ethanol and terpenes significantly enhances the percutaneous absorption of both hydrophilic and lipophilic drugs. Moreover, the low irritancy of terpenes at concentrations between 1-5% makes them clinically acceptable penetration enhancers. This review discusses the composition, preparation methods, physicochemical characteristics, stability, and pharmaceutical applications of invasomes, highlighting their potential as an effective and non-invasive drug delivery system.

INTRODUCTION

Invasomes are novel vesicles with enhanced percutaneous penetration compared to the conventional liposomes. Invasomes are novel elastic phospholipid vesicles composed of phosphatidylcholine, ethanol and one or mixture of terpenes. Many researchers have already confirmed the capability of terpenes in enhancing percutaneous penetration. Their penetration enhancing activity is through the disruption of the stratum corneum lipids, interaction with intracellular proteins, and improvement of partitioning of the drug into the stratum corneum. Ethanol improves the vesicular ability to penetrate the stratum corneum. In addition, ethanol provides net negative surface charge and prevents vesicle

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aggregation due to electrostatic repulsion. A synergistic effect between terpenes and ethanol on the percutaneous absorption has been significantly observed (Mohamed and Rehab, 2018). Terpenes, the naturally occurring volatile oils are included in the list of generally recognised as safe substances with low irritancy at lower concentrations (1-5%), with reversible effect on the lipids of stratum corneum are considered as clinically acceptable penetration enhancers. Invasomes are characterised for size, surface morphology, zeta potential, stability. Non-invasive drug delivery techniques have gained significant attention due to their ability to deliver therapeutic agents without the need for injections or other invasive methods. One of the key advantages is the enhanced permeation of drugs through the skin, facilitating effective transdermal drug delivery. This method allows both hydrophilic and lipophilic drugs to be delivered, making it a versatile option for a wide range of pharmaceuticals (Bornare and Saudagar, 2016). Additionally, the formulation used in this method generally contains non-toxic raw materials, ensuring that the drug delivery system is safe for prolonged use. When compared to other advanced drug delivery methods such as iontophoresis and phonophoresis, non-invasive techniques provide a simpler and more user-friendly approach. These characteristics make non-invasive drug delivery a promising option for both patients and healthcare providers, offering an efficient and comfortable alternative to more complicated methods (Bornare and Saudagar, 2016).

Composition

The soft liposomal vesicles known as invasomes, which may operate as carriers with improved skin penetration, contain small quantities of ethanol and different terpenes or terpene combinations. They include phospholipids and a tiny amount of alcohol, as well as terpenoids (such as citral, limonene, and cineole), water, and a small quantity of ethanol (e.g., 3-3.3 percent by volume). Other components include terpenoids (such as citral, eugenol), water, and ethanol. To improve the absorption of hydrophilic and hydrophobic medications, terpenes (C5H8) have a general formula. The terpenes in essential oils are commonly used penetration enhancers. When used in low dosages, terpenes are less irritating to the skin. Terpenes are also considered safe by the FDA (D Singh, 2013).

Effect of Composition on the Physicochemical Characteristics of Invasomes

Effect of Ethanol

The addition of ethanol in the formulation of lipid nanovesicles is an effective strategy to increase the fluidity of the lipid bilayer of the skin. (Verma and Pathak, 2012). The interaction of ethanol with the lipid elements in the polar group area of the SC leads to alterations in the structure of the keratinized or lipophilic domains, decreased transition temperature of lipids, and consequently fluidization and disruption of the tightly packed SC lipids (Janisch and Valenta, 2003). Ethanol-based nanocarriers can fluidize and disturb the SC lipids. The presence of ethanol increases the flexibility of the intercellular lipid matrix due to the rotating freedom of the lipid acyl chains. Thus, ethanol increases the fluidity of lipids in the vesicle structure, resulting in a structure that has softer and less rigid properties than conventional liposomes. In addition to enhanced penetration ability, ethanol creates a net negative surface charge and limited vesicle aggregation due to electrostatic repulsion, leading to increased stability of invasomes under storage conditions. (Paolino *et al*., 2005).

Effect of Terpenes

Effect of Terpene on Penetration

X-ray diffraction and differential scanning calorimetry (DSC) results showed that terpenes lead to increased drug penetration by disrupting the tight bilayers and lipid packing in the SC Furthermore, breaking the hydrogen bonds and extracting SC lipids, enhancing the partition into the SC by improving lipid fluidity and increasing diffusion via the intercellular lipids are another mechanisms that have been reported to increase drug permeability by terpenes. (Dragicevic-Curic *et al*., 2008) revealed that various types of terpenes have a synergistic effect on the permeation of temoporfin. Invasomes containing a 1% mixture of three types of terpenes (citral, cineol, and limonene) demonstrated higher temoporfin permeability than invasomes containing 1% citral alone. In another study, (Dragicevic-Curic *et al*.,2008) demonstrated the relationship between the permeated amount of temoporfin and the amounts of terpenes in the invasomes. They indicated that vesicles containing 1% terpenes have a 1.7-fold higher temoporfin penetration effect than vesicles containing 0.5% terpenes. Therefore, incorporation of temoporfin in vesicles containing 1% terpenes could lead to deeper penetration.

Effect of Terpene on the Size of the Invasomes

Examination of particle size demonstrated that the size of the invasomes is directly correlated to the amount of terpenes; the size of the invasomes increases as the amount of terpene increases. The size of vesicles containing 1% terpenes was 124 nm, whereas the size of vesicles with 0.5% terpenes was 93.0 nm (Dragicevic-Curic *et al*., 2008). Prasanthi et al. showed that the size of finasteride-loaded invasomes was influenced by the molecular size of terpene and the concentration of the added terpene. The size of invasomes containing nerolidol (molecular size 222 g/mol) was around 11 to 13 µm. The vesicle sizes of nimesulide-loaded liposomes containing citral, limonene, and cineole were 194 nm, 216 nm, and 244 nm, respectively.

Effect of Terpene on the Shape of the Invasomes

The results of cryo-transmission electron microscopy (cryo-TEM) were in agreement with the DSC and ESR results, indicating the influence of terpenes on the shape of the invasomes, i.e., in addition to spherical vesicles, malformed vesicles of varied shapes also existed in invasomal dispersions (Dragicevic-Curic *et al*., 2008). Cryo-electron microscopy to observe the lamellarity and shape of invasomes with various percentages of terpenes. Their results revealed that invasomes with 0.5% terpenes were mostly unilamellar and bilamellar or oval and spherical in shape; however, in the invasomal formulation with 1% terpenes, the invasomes appeared to be unilamellar and bilamellar. Therefore, the combination of 1% terpenes with the invasomes increased the membrane elasticity of invasomes, the percentage of terpenes, and the amount of deformed vesicles. (Dragicevic-Curic *et al*., 2008)

Synergistic Effects

A synergistic effect between phospholipids, ethanol, and terpenes on dermal absorption has been visibly observed. (Dragicevic-Curic *et al*., 2008) suggest that one part of the invasome disintegrates during permeation in the upper layers of skin and releases the phospholipids and terpenes, which act as permeation enhancers that fluidize the intercellular lipids. Furthermore, the ethanol in the invasome fluidizes the intercellular lipids and enhances the penetration of flexible vesicles. A compared to an ethanolic solution. The improved efficiency of invasomes compared to an ethanolic solution suggests a synergistic effect of

phospholipid, terpenes, and ethanol. Demonstrated that the improved permeation of temoporfin (mTHPC) with 1% terpenes was due to the concentration of terpenes and the synergistic effects of terpenes and ethanol. Thus, the results from the aforementioned studies point toward the synergistic effect of phospholipid, terpenes, and ethanol in the reformed activity of invasomes in comparison with liposomes.

Invasome Stability

The storage temperature has a significant effect on the physical stability of invasomes, i.e., the size of the particles and the polydispersity index (PDI) value. During storage at room temperature, all invasomes show an increase in the particles size and the PDI value, demonstrating physical instability, i.e., aggregation or fusion of the vesicles. In the case of the the PDI of the invasomes stored at 4 °C was stable during storage for 12 months; however, after six months of storage, the invasomes showed a significantly increased particles size and PDI value. With regard to drug content, determined that there was a loss of 10% of the encapsulated drug after one month of refrigeration. The loss of encapsulated drug increased to 50% when stored at room temperature. (Lakshmi *et al*., 2014).

Preparation methods for invasomes

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

Mechanical dispersion technique

In the case of the mechanical dispersion technique, the active drugs/biomolecule and terpene or a mixture of terpenes are dissolved in phospholipid containing ethanol. After proper mixing, the mixture should vortexed (5 min) and sonicated (5 min) to provide a simple solution. After that, the phosphate buffer (pH 7.4)/phosphate buffer saline (PBS)/suitable solvent added to the solution for hydration of vesicles by applying a syringe with constant vortexing (5 min). Finally, the solution was sifted for extrusion of multilamellar vesicles via polycarbonate membranes of pore size ranges (400 nm, 200 nm, 100 nm, 50 nm) and repeated several times (Badran et al., 2009; Dragicevic-Curic et al., 2010).

Film hydration technique

In the film hydration technique, the mixture of ethanol and phospholipid dissolved in a mixture of methanol and chloroform (2:1 v/v). This mixture dried by adopting a rotary flash evaporator by lowering the pressure (500 to 1 mbar) for 2 h (at 50 °C). After that, the film was kept for 2 h under 1-mbar pressure and accompanied by a nitrogen flush. The PBS (pH 7.4) or mixture with terpenes, ethanol, and PBS can be selected for the hydration of deposited film for 30 min. Finally, after cooling the mixture, the terpene/ mixture of terpenes and ethanol should be added to obtain the invasome vesicles. The prepared invasome was vortexed followed by ultrasonication and seized by using extrusion via polycarbonate membranes of the various pore size range several times.

Characterizations of Invasomes

Entrapment efficiency: It is determined by centrifugation and ultracentrifugation method. The drug concentration was determined at 260nm using uv spectrophotometer.

Measurement of Viscosity: Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm.

Vesicle Size: Microscopic analysis was performed to determine the average size of prepared invasomes.

pH Measurements: It is determined by using digital pH meter.Optimum pH is 9.2.

Drug Content: 100mg invasomal formulation+20ml methanol and filtered by whatmann filter paper.

Extrudability Study: It is performed based upon the quantity of formulation extruded from collapsible tube on application of load.

Spreadability: S = ML / T Where S is spreadability, M is weight tied to the upper glass plate, L is the length of the glass slide, and T is time in sec.

Homogeneity of invasome: It was measured by Visual inspection for their appearence and presence of any aggregates.

Zeta potential determination: Malvern zetasizer with an electric field of 15.24v/cm 10. Stability Studies: It was carried out at two temperatures, Refrigerator temperature (4.0 ± 0.2º c) and room temperature (25-28 ± 2º c)

***In-vitro* Studies**

Particle size distribution: Particle size distribution was measured by photon correlation spectroscopy employing a 25 mW He–Ne laser (Wavelength 632.8 nm) incident on the sample at an angle of 90°. invasomeswere diluted with filtered PBS pH 7.4 to achieve optimal scattering intensity ((1–10) x10^5 counts/s). Samples were equilibrated at 24 °C before measuring particle size. (Raslamol *et al*., 2024)

Entrapment efficiency: Entrapment efficiency was determined by diluting the delivery system with saturated sodium chloride solution followed by ultracentrifugation at 80000 rpm for 45min at 4°C. The supernatant was analyzed by using the HPLC method and % of entrapment efficiency was calculated.

Skin permeation studies: The in vitro skin permeation of invasomes system was studied using Franz's diffusion cell having an effective permeation area and receiver cell volume of 2cm² and 15 ml, respectively. The receptor cell contained 15 ml of phosphate buffer saline pH 7.4 and ethanol (ratio 70:30), which was constantly stirred with a magnetic stirrer at 100 rpm. Experiments were carried out for 24 h at 32 °C ± 1 °C. Samples were withdrawn through the receiver cell sampling port at 0.5,1.0,2.0,4.0, 8.0,12.0, and 24.0 h and analyzed for drug content by UV spectrophotometer at 330 nm. The receptor cell after each withdrawal was replenished with an equal volume of fresh vehicle.

Drug release studies: The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared invasomal drug. Dry films of known thickness is to be cut into definite shape,weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500ml of the dissolution medium or phosphate buffer (pH 7.4) and the apparatus was equilibrated to 32± 0.5°C. The paddle was then set at a distance of 2.5cm from the glass plate and operated at a speed of 50 rpm. Samples (5ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

Stability studies: Stability studies are to be conducted according to the ICH guidelines by storing the invasomal samples at 40±0.5°c and 75±5% RH for 6 months. The samples were

withdrawn at 0, 30, 60 ,90 and 180 days and analyze suitably for the drug content.

Dose-response Relationships

In vivo studies help establish the relationship between the dose of invasomes administered and the biological response. This information is crucial for determining the optimal therapeutic dose that achieves the desired effect without causing undue toxicity.

Therapeutic Efficacy

Assessing the therapeutic efficacy of invasomes involves studying the biological response to the drug in vivo. This could include measuring changes in disease markers, monitoring physiological parameters, or assessing the overall therapeutic outcome.

Toxicity Studies

Evaluating the potential toxicity of invasomes is essential for assessing their safety. In vivo toxicity studies investigate the impact of invasomes on various organs and systems, aiming to identify any adverse effects associated with their administration.

Skin Irritation study

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to1.5 kg). The dorsal surface (50 cm) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The drug is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

Pharmaceutical Applications of Invasomes

Immunosuppressive drug delivery: The main method used to treat autoimmune disorders is immunosuppression. As a significant substitute for immunosuppressive drug delivery, lowering the dosage advised for therapeutic effect and decreasing drug distribution to non-target tissues can be helpful. Researchers are primarily considering developing advanced nanosized vesicles based on the sub-structure of lipidic vesicles in drug delivery.AP1: Cyclosporine A (CsA, CyA) is a lipophilic medication with a low partition coefficient (4000) that shows poor penetration efficiency into the skin layers.[1] The management of psoriasis and other dermatological conditions may benefit from the topical administration of CsA. utilizing unsaturated soybean phosphatidylcholine (10% w/v), ethanol (3.3% w/v), citral:cineole:D-limonene combinations (0.5:1.0:1.5% w/v), and PBS up to 100% w/v utilizing mechanical dispersion, invasomes transport CsA and CyA via nanocarrier. CsA levels in the deeper epidermal layer and subcutaneous layer considerably rose with increasing terpene content (0.5 to 1.5%). It demonstrates the exact relationship between the amount of medication present in the epidermal layer and the amount added to the terpene mixture. It is possible to treat autoimmune illnesses with immune-suppressive agentloaded invasomes according to promising research findings. When considered as a whole, it shown that invasomes can serve as a reliable stand-in for hydrophobic drug transport to the dermal layers of the skin (sailaja and Meghana, 2021).

Anticancer drug delivery: The need to create a cutting-edge replacement for cancer treatments that don't work is strong. It is noteworthy that temoporfin is a strong photosensitizer of the second generation. It exhibits barely two weeks of residual photosensitivity and good tumor selectivity. For early or recurrent carcinomas,

photodynamic therapy with this drug may prove to be an effective anticancer treatment. Accordingly, the skin layer stratum corneum is exposed to the extremely hydrophobic photosensitizer (temoporfin) by the use of invasomes. In short, the mechanical dispersion approach has been used to produce invasomes loaded with temoporfin. Invasome has the potential to be a highly effective transporter of hydrophobic active compounds to the systemic/local location at an effective concentration in the future.

Delivery of vitamin analog: Vitamin A analog called isotretinoin is used to treat eosinophilic pustular folliculitis. The mechanical dispersion method of isotretinoin invasome can be employed. The pace at which invasomes penetrated was influenced by several formulation parameters. Interestingly, the size of invasomes rose as the content of egg lecithin increased. However, the size of the invasome vesicle is unaffected by the eugenol concentration. In addition, because there were more lipids available to entrap the isotretinoin, the lipid concentration increased and so did the isotretinoin's entrapment efficiency (sailaja and Meghana, 2021).

Delivery of anti-acne agent: In the modern world, acne is a common skin condition. One of the most potent medicinal ingredients for treating leprosy is dapsone. Because of its anti-inflammatory properties, it holds great promise for the treatment of acne. An efficient carrier must be developed in order to deliver dapsone to the targeted location, much as it is necessary for the administration of topical medications. For the treatment of mild to moderate acne, terpene (limonene, cineole, citral, or fenchone) and phosphatidylcholine were used to manufacture dapsone-loaded invasomes by a film hydration approach.

Anticholinergic agent: Tolterodine tartrate used to control overactive bladder and it is taken orally can have adverse effects include tachycardia, dry mouth, dizziness, and gastrointestinal obstructive condition. Overcoming these significant obstacles is crucial in order to administer tolterodine tartrate in a way that minimizes side effects and boosts patient compliance. It should also keep the drug's plasma level constant for a predetermined amount of time and be able to be stopped under severe circumstances. Due to its substantial liver metabolism, tolterodine tartrate is a perfect candidate for transdermal drug administration. Using the film hydration process, soy lecithin, ethanol, limonene, fenchone, and anethole were used to create the tolterodine tartrate loaded invasomes. Terpenes and ethanol was present, which led to the formation of the incredibly flexible tolterodine tartrate invasomes (Nangare and Dugam, 2020).

CONCLUSION

Invasomes represent a promising advancement in transdermal drug delivery systems due to their ability to enhance drug permeation across the skin. The combination of phospholipids, ethanol, and terpenes in invasomes facilitates better skin penetration by disrupting the stratum corneum, improving drug partitioning, and reducing vesicle aggregation. The synergy between ethanol and terpenes has been shown to significantly boost the absorption of both hydrophilic and lipophilic drugs. Furthermore, terpenes are considered safe and non-irritating at lower concentrations, making invasomes a clinically viable option for drug delivery. The stability and physicochemical characteristics of invasomes, including their size, surface morphology, and zeta potential, are essential factors influencing their effectiveness. With continued research and development, invasomes have the potential to revolutionize non-invasive drug delivery, providing a safer and more efficient alternative to conventional methods.

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