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Advancements in Transdermal Drug Delivery: A Comprehensive Review of Invasomal Gel Systems and Their Efficacy in Enhancing Drug Penetration

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Abstract:
For localized or systemic effects, the transdermal route is a crucial conduit. Several drugs need a skin penetrating barriers made of the stratum corneum, the outermost layer of skin. Many strategies have been devised to get over this obstacle, such as using nanocarriers and vehicles to enhance medication penetration. Several kinds of nanocarriers have been developed recently to enhance the percutaneous or dermal distribution of medications like "INVASOME." Our invasome gel, which is used to treat fungi, was filled with clotrimazole. The invasomal gel is prepared using the mechanical dispersion process. This preparation is assessed using a variety of factors, including appearance, solubility, spreadability, and in vitro drug diffusion.
Keywords: Invosomal, vesicle, terpene, antifungal.

Introduction to Invasomal Gel

To aid with the delivery of the built people, liquid or hydrophilic medicines can both be incorporated into liposomal vesicular systems. But because typical liposomes cannot penetrate the interior layers of skin, their effects are restricted by the outer layers, and they are not certified as suitable systems for transdermal drug delivery (Gupta & Krishnan, 2022). The enhanced skin contacts and greater drug penetration of novel elastic vesicles with enhancers of penetration are superior than standard liposomes. Cevc and others created initial flexible and flexible vesicles, known as Transferosomes, in the 1990s (Rai et al., 2017). Phospholipids and

edge activators, such sodium cholate and polysorbate, combine to form these vesicles, which result in elastic carriers for better transdermal medication administration. The creation of various innovative elastic vesicles through modifications in vesicular composition was prompted by the good outcomes observed with Transferosomes (Babaie et al., 2020). Previous studies indicate promise for elastic vesicles as medicinal transporters, drugs, including ethosome (all of which has a significant amount from alcohol in its structure) and niosome (which is mostly made of cholesterol and non-ionic surfactant) (Fadaei et al., 2024).

Liposomal vesicles called invasomes contain trace quantities of ethanol and terpenes, or terpene combinations, and they have the ability to penetrate the skin more deeply than other carriers (Sarangamath et al., 2024). When it comes with skin penetration, invasomes are more effective than liposomes and ethosomes. Among the many benefits that invasive species offer are increased medication effectiveness, better patient compliance, and more comfort (Verma & Pathak, 2010).

Historical Development of Invasomal Gel Technology

The advancement of drug delivery methods can be seen in the invention the invosomal gels technology. Here is a quick rundown of its evolution throughout history

Early Foundations (1960s-1980s)

1960: The idea of using liposomes to transport drugs first surfaced. It was found by scientists such as Alec Bangham that pharmaceuticals may be better delivered by encapsulating them in liposomes, which are spherical vesicles made of lipid bilayers.

1970s-1980s:

Optimization of stable as well as releasing traits are made feasible via advances in a liposome innovation & lipids chemistry. These early innovations prepared the way for more advanced delivery techniques.

Introduction of Invasomal Technology (1990s):

1990s : As liposomal formulations tailored for topical & epidermal drug administration emerged, the term "invasomal" started to take off. Enhancing the skin's ability to absorb medicinal substances was the goal of research.

1995: The notion of incorporating liposomes into topical gels, or invosomal gels, was presented. These formulations created systems that could more efficiently distribute medications via the skin by integrating gelatin matrices with liposome technology.

Refinement and Application (2000s)

2000s: The goal of research is to boost the compounds' release control, penetration, and stability. During this time, more research was conducted on a variety of medications, including those used as anti-inflammatory agents, painkillers, and cosmetics.

2004: The emergence of commercial invosomal products showcased the actual relevance for these methods. The aim for study has been to improve gel compositions and assess their efficacy in clinical contexts.

Modern Advances and Commercialization (2010s-Present)

2010s: Improvements in material science & nanoparticles have improved invosomal gels. There have been advancements made in skin absorption, drug packing efficacy, or a liposome strength.

2015-Present: The usage of invasive gels in cosmetics and medications has grown. They are used to provide a variety of medications, including anti-aging and painkillers. Industrial articles and approvals from regulators have increased, demonstrating the efficacy and promise of the technology.

Current Trends: Research is still being done to better optimize drug release patterns, improve skin permeability, and lower manufacturing costs in invosomal gels compositions. Further therapeutic uses and more individualized medical solutions have been investigated using this technology.

Composition and Structure of Invasomal Gels

Penetration Mechanism of Invasomes

The invasomes' terpenes and ethanol distort the vesicles, interfere with the SC bilayer Smaller, non-divergent invasome vesicles pass through the SC unharmed (Kaltschmidt et al., 2020). The intact invasomes can enter the SC through the follicular transport pathway or the tiny hydrophilic channels seen in the SC's intercellular area after penetrating (Gaynanova et al., 2021). Smaller intact invasomes have the ability to enter the deeper SC through places that

resemble channels. The flexible vesicles of different sizes found in the channel-like locations in the SC's deeper layer and the skin surface vesicles were used to infer this (Loan Honeywell-Nguyen et al., 2006). Most invasomes break apart as they enter the SC, but adaptable tiny vesicles enter the deeper layers undamaged.

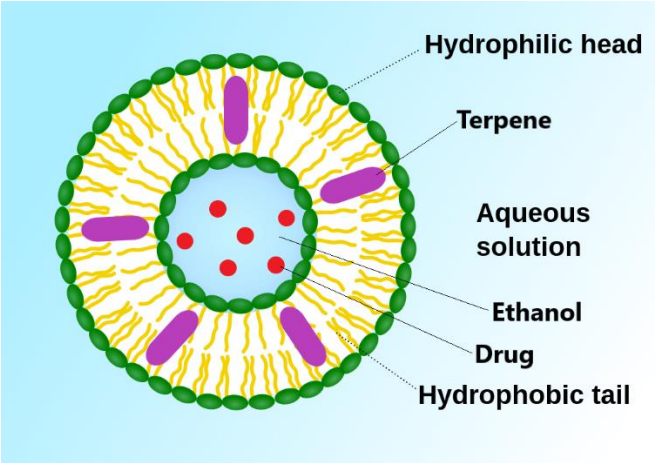

Figure no 1.1 Structure of invasome

skeleton, and promote penetration, increasing the invasomes' permeability (Sailaja & Meghana, 2020). Terpenes, phospholipid segments, and single phospholipid molecules are released from the vesicle during the invasome's penetration, improving the penetration and fluidizing the SC lipids (Dragicevic & Maibach, 2018).

Preparation Methods for Invasomal Gels

Method of Mechanical Dispersion - In an ethanolic phospholipid solutions, drugs & terpenes, or mixtures of terpenes, are dissolved. The combination is subjected to a 5-minute vortex and a 5-minute sonication to produce a transparent solution (Shree et al., 2022). A needle and syringe is utilized to always spin the mix when the PBS solution (pH: 7.4) is applied. Five more minutes of vortexing are required to get the ultimate invasomal preparation (Nangare & Dugam, 2020).

Figure no1.2 Invasomal gel

Lipid Film Hydration Method

A solution of phospholipids and methanol and chloroform (2:1 v/v) is used in the film hydration process to dissolve a combination of them. After that, the mixture is dried for two hours at 50°C at a lower pressure (500–1 mbar) has an evaporator that rotates (Šturm & Poklar Ulrih, 2021). The film is then exposed to a nitrogen purged during two hours under a pressure for 1 mbar. Either PBS (pH 7.4) or a combination of terpenes, ethanol, and PBS can be used to hydrate the deposited film for 30 minutes (Tawfik et al., 2020). Selected Terpenes or a terpene-ethanol combination is added to the liquid after it has cooled to create invasome vesicles via vortexing, sonication, and repeated extrusion onto polycarbonate membranes with varying pore size ranges, the prepared invasomes are collected (Kumar et al., 2022). This process guarantees the production of invasome vesicles with regulated characteristics appropriate for a range of biotechnology and medication administration uses (Nayak et al., 2022). Figure 1.2 illustrates how invasomes are formed using the membrane hydration approach.

Mechanical method:

After dissolving the active agent and terpene or terpene combination in an ethanolic phospholipid solution, the final invasome formulation may be prepared. For a solution that is clear, vortex the mix or 5 minutes then sonicate it for five minutes more. Phosphate buffered saline (PBS), with a pH of 7.4, should be added to the solution after sonication, being sure to continuously vortex the mixture with a syringe. This methodical procedure guarantees that the

active substance is properly encapsulated within the invasomes, allowing its distribution and possible effectiveness in a number of applications as seen in Fig.1.3

Image

Characterization Techniques for Invasomal Gels

Entrapment efficiency

As per entrapment of the invasomal composition is determined by means of the ultracentrifugation technique. The intracellular formulation was centrifuged at 15,000 rpm for 40 minutes using an ultracentrifuge (Dalal et al., 2022). After being collected, the silt was further diluted using ethanol. Utilizing UV spectrophotometry, the curcumin concentration at 426 nm was examined (Van Nong et al., 2016). After that, the following calculation was used to get the % entrapment efficiency:

$$\%\ Entrapment\ efficiency = \frac{amount\ of\ entrapped\ drug\ recovered}{total\ amount\ of\ drug} \times 100$$

Particle size

Zeta Sizer (Nano- ZS, Malvern, U.K.) was used to measure the vesicles' sizes. Every experiment was carried out three times.

***In vitro* drug release**

Franz's diffusion cell, having an inside cell volume and an effective permeation area of 10 ml & 0.196 cm2, each, were utilized for an in vitro release of drugs investigation. Clamping down on the receptor cells full of phosphate buffer saline (pH 7.4) was the donor cell carrying the invasomal formulation (Salamanca et al., 2018). The experiment was run for twenty-four hours at 37 ± 1 °C with continuous 600 rpm magnet stirring. Using a UV spectrophotometer set to 426 nm, samples were extracted from the receptor cell at prearranged intervals of time, specifically 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours, in order to assess the curcumin level. To determine the optimal invasomal formulation's releasing kinetics, information was evaluated utilizing multiple releasing kinetic models (Anitha & Satyanarayana, 2021).

***Ex-vivo* drug permeation studies**

Utilizing Franz's diffusion cells, an ex-vivo drug penetration research took out. The recipient cell volume and effective permeation area were 10 ml and 0.196 cm2, respectively (B. Sánchez

et al., 2019). Using animal hides taken from an existing animal, the level of the drug uptake was found. The receptor compartment holding phosphate buffer (pH 7.4) was encased by an invasomal composition which went into the donor compartment (Ammar et al., 2020).

Using a fitting, animal skins was put across both chambers. The experiment was run at 37 ± 1 °C over a full day while being continuously stirred by magnets. Using a UV spectrophotometer set to 426 nm, samples were extracted from the receptor cell at prearranged intervals of time, specifically 1, 2, 3, 4, 5, 6, 8, 10, and 24 hours. The samples' curcumin concentration was then calculated (Roche et al., 2019). Skin characteristics, such as flux (J, µg/cm2/h), cumulative permeation of curcumin over the skin per unit area (Q24, µg/cm2), permeability coefficient (Kp, cm/h), and enhancement ratio (ER), were assessed utilizing findings of the ex vivo research (A. Mishra, 2019).

Morphology and vesicular shape

The transmission electron microscope (TEM) (Technai) with an accelerating voltage of 100 kV was used to see the improved invasomal formulation. A 1% phosphotungstic acid aqueous solution was used to adversely stain the samples (Ackermann, 2013). The invasomal mixture was dried on a small carbon-coated grid before staining. Blotting was utilized to get rid of extra solution. Once the material had dried, it was inspected under a microscope (Snijder et al., 2017).

Advantages and Limitations of Invasomal Gel Technology

Advantage:

- Improved medication penetration via the skin for transdermal administration
- Both a lipophilic & hydrophobic medicine can be delivered.
- includes a non-toxic raw ingredient in the mixture.
- patient compliance since the medication is available in gel or cream form, which is semisolid.
- medication delivery technique that is less complex than phonophoresis, iontophoresis, and other similar techniques.

Disadvantage:

- The expense of manufacture is substantial.
- Drug/molecule encapsulation leakage and fusing.

- There is a chance that the phospholipid will be hydrolyzed or oxidized, which will impact the virus's stability (Yu et al., 2021).

Limitation:

- **High Manufacturing Costs: It** takes advanced technology and exact control over formulation procedures to produce invosomes. Compared to more straightforward drug delivery methods, this intricacy may result in higher cost of manufacture, that might restrict the product's price and accessibility, particularly for large-scale applications.
- **Scalability Issues**: The manufacturing of implicasomes may be hard to grow from the bench to a manufacturing level. Larger-scale item consistency and quality maintenance frequently necessitates more resources and quality control procedures, which might raise prices and complicate production procedures.
- **Limited Penetration**: Invosomes may not always be able to effectively penetrate all types of tissues or cells, despite the fact that they can improve medication delivery to particular targets. A number of variables, including the target tissue's properties and the liposomes' size, might affect how effective invosomes.
- **Regulatory and Safety Issues:** Invosomal formula difficulty could result in stricter regulatory oversight. Extensive testing and validation are needed to assure the safety and efficacy if such devices, which can raise costs and delay development.
- **Biodistribution and Clearance:** The liposome's composition and mode of administration are two elements that can affect their behavior and potentially affect the safety and efficacy of treatment.

Invasome Stability

The physical stability of invasomes, or the size of the particles and the polydispersity index (PDI) value, is significantly impacted by the storage temperature. All invasomes exhibit a rise in particle size and value of PDI and kept in room temp, showing mechanical insecurity, and fusion or aggregate of their vesicles. In the Dragicevic-Curic et al. study, the invasomes' PDI was steady for a year if they stayed at 4 °C; yet, at six months, both invasomes' particle size and PDI value had dramatically risen. Lakshmi et al. found that in one month of cooling, 10% half the drugs content had been lost. Storing the medication as low temperatures resulted in half the amount of encapsulation.

Penetration Mechanism of Invasomes

Invasome terpenes and ethanol distort the vesicles, interfere with the integrity of the SC bilayer skeleton, and promote penetration, increasing the permeability of the invasomes. According to Dragicevic-Curic et al., terpenes, phospholipid segments, and single phospholipid molecules are released from the vesicle during the invasome's penetration, improving the penetration and fluidizing the SC lipids. Smaller, non-divergent invasome vesicles pass through the SC unharmed. Verma et al. state that intact invasomes can enter the SC through the follicular transport pathway or the tiny hydrophilic channels seen in the SC's intercellular area after penetrating. Smaller intact invasomes have the ability to enter deeper layers of SC through places that resemble channels, as demonstrated by Honeywell-Nguyen et al. Flexible vesicles of different sizes found at the channel-like locations in the SC's deeper layer and skin surface vesicles were used to infer this. Most invasomes break apart as they enter the SC, but flexible and tiny sacs enter the deeper layers undamaged

Effect of Composition on the Physicochemical Characteristics of Invasomes

Effect of Ethanol:

One efficient method for improving the skin's lipid bilayer's fluidity is to include ethanol into the lipid nanovesicle formulation. Ethanol reacts with the lipid components in the SC's polar group region, changing the keratinized or lipophilic domains' structural makeup, lowering the lipids' transition temperature, and ultimately causing the densely packed lipids of the SC to fluidize and break apart. Using nanocarriers based on ethanol, the SC lipids may become fluidized and disturbed. Because lipid acyl chains possess the capacity to spin if ethanol exists, its interstitial lipids barrier is more flexible (Hossain & Blanchard, 2021).

Therefore, ethanol makes the lipids in the vesicle structure more fluid, giving it a softer, less rigid shape than regular liposomes. Apart from its improved penetrating capacity, ethanol also generates a net negative surface charge and inhibits vesicle aggregation due to electrostatic attraction, making invasomes more stable when stored (Lombardo & Kiselev, 2022).

Effect Of Terpenes

Effect of Terpene on Penetration

Terpenes improve drug penetration by rupturing the tight bilayers and lipids packed of the SC, based on the results of difference scanning calorimetry (DSC) and X-ray diffraction. Other methods that have been found to promote drug permeability by terpenes are breaking bonds of hydrogen or removing SC lipids, improving lipids flexibility or partitioning within SC, or

enhancing diffusion across the intercellular lipids (Chen et al., 2016). Different terpene kinds work in concert to increase temoporfin's penetration. The temoporfin penetration of invasomes with a 1% combination of three different terpene types—limonene, cineol, and citral—was shown to be greater than that of invasomes containing 1% citral alone (Nastiti et al., 2017). Different investigations showed that there is a correlation between the quantity of temoporfin that permeates and the terpene content of the invasomes. They found that the temoporfin diffusion effect of vessels containing 1% terpenes is 1.7 times greater than those of particles containing 0.5% terpenes. Greater absorption may result from the addition of temoporfin into vesicles that contain 1% terpenes (Gaur et al., 2013).

Effect of Terpene on the Size of the Invasomes

Examination of particle size revealed a clear relationship between the quantity of terpenes and the dimension of the invasomes, with the size of the invasomes increasing as terpene concentration rises. Vesicles carrying 1% terpenes measured 124 nm in size, while ones carrying 0.5% terpenes measured 93.0 nm (P. K. Lakshmi et al., 2013). The molecular shape and concentration of the added terpene had an impact on the size of invasomes loaded with finasteride. The invasomes that contained nerolidol (molecular size: 222 g/mol) had a diameter of around 11 to 13 μm. Nimesulide-loaded liposomes containing cineole, limonene, & citral have vesicles diameters of 194 nm, 216 nm, and 244 nm, in that order (Prasanthi et al., 2014).

Effect of Terpene on the Shape of the Invasomes

In accordance with the DSC & ESR outcomes, of cryo-transmission electron microscope (cryo-TEM) data showed that terpenes had an impact on the morphology of the invasomes. This means that invasomal dispersion contain distorted vesicle with various kinds in along with spherical vesicles (Emelyanov et al., 2020). The lamellarity and morphology of invasomes with different percentages of terpenes using cryo-electron microscopy. The findings showed that invasomes containing Nanomaterials 2020, 10, 341 5 of 13 0.5% terpenes were primarily oval and round in form and unilamellar or bilamellar; in contrast, the invasomes in the invasomal formulation containing 1% terpenes looked to be unilamellar and bilamellar. As a result, adding 1% terpenes to the invasomes enhanced their ability to stretch their membranes (Albash et al., 2021).

Synergistic Effects

It is evident that phospholipids, ethanol, and terpenes work in concert to enhance cutaneous absorption. During permeation in the top layers of the skin, a portion of the invasome collapses or release terpenes and phospholipids, which function as permeation enhancers and fluidize the intercellular lipids (Hmingthansanga et al., 2022). Additionally, the invasome's ethanol facilitates the entry of elastic vesicle via flowing its interstitial lipids. Invasomes enhanced cyclosporine's transdermal penetration. as opposed to a solution containing ethanol. The enhanced efficacy of invasomes in contrast to an ethanolic solution implies that phospholipid, terpenes, and ethanol work in concert (H. Liu et al., 2006). The enhanced temoporfin (mTHPC) penetration with 1% terpenes was a result of the terpene concentration and the combined actions of ethanol and terpenes. Therefore, as compared to liposomes, the reformed activity of invasomes exhibits a synergistic impact of phospholipid, terpenes, and ethanol, as indicated by the findings of the previously described experiments (R. Dwivedi et al., 2024).

Invasome Stability

The physical stability of invasomes, or the size of the particles and the polydispersity index (PDI) value, is significantly impacted by the storage temperature. All invadesomes exhibit a rise in particle size and value of PDI and held as room temp, showing physiological instabilities, and fusion of aggregate of the vesicles (Danaei et al., 2018). PDI of the invasomes from the Dragicevic-Curic et al. research was steady for a year as they were kept above 4 °C; yet, all invasomes revealed a considerably increased particle size & value for PDI during six weeks of storage. After a month for cold storage, 10% of the drugs content had been lost. When the medicine was kept as room temp, the volume in its capsule lost rose to 50% (B. Lakshmi et al., n.d.).

Potency Versus Toxicity of Terpenes as One of the Main Components of Invasome

Various methods have been investigated to advance medication transdermal penetration. Using safe and efficient kinds of penetration enhancers, including natural terpenes, is the most often used approach among them. Even though penetration enhancers work well in transdermal distribution, toxicology & dermatitis prohibit a lot of these from being approved to use in hospitals. Generally speaking, penetration enhancers' efficacy and toxicity are balanced. Even in low levels, terpenes show a significant entering capacity with both a lipophilic & hydrophilic atoms (Sztandera et al., 2018). Interaction with SC intercellular lipids is the key method by which terpenes penetrate. Terpenes are used either alone or in conjunction with other drug delivery methods to improve penetration for medicinal purposes. However, in addition to

terpene efficacy in relation to various penetration enhancers, terpene toxicity should also be taken into account. Using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and measuring trans epidermal water loss (TEWL), scientists examined a terpenes' toxic effects on two human skin cell lines and found that terpenes derived from natural sources are typically thought to be safer than those derived from synthetic sources (Lasoń, 2020).

Pharmaceutical Applications of Invasomes

Immunosuppressive drug delivery

Primary treatment for autoimmune disorders involves immunosuppression. Additionally, it is beneficial for the therapeutic usage of immunosuppressive medications currently in use that have been associated with a variety of adverse drug reactions (Hussain & Khan, 2022). By improving immunosuppressant delivery to target immune system cells, nanotechnology-cantered techniques can address the main constraints. Other important alternatives to immunosuppressive delivery methods involve reducing the amount needed to therapy & limiting delivery of drugs to non-target tissues (Lôbo et al., 2021).

Researchers are primarily focused on developing enhanced tiny size vesicle based on the sub-structure of lipidic vesicles in drug administration. According to a review of research, cyclosporine A (CsA, CyA) is a lipophilic drug with a low partition coefficient (4000) that makes it difficult to penetrate the skin's layers. The therapy of psoriasis and other dermatological conditions may benefit from the topical administration of CsA (P. Liu et al., 2022).

Firstly the invasome nanocarrier for the transport of CsA and CyA were created by dispersing PBS up to 100% w/v, ethanol (3.3% w/v), unsaturated soybean phosphatidylcholine (10% w/v), & citral:cineole:D-limonene combinations (0.5:1.0:1.5% w/v). The results of an in vitro penetration study indicated that, in comparison to liposomes in or an aqueous/ethanolic substance (that has no alcohol and terpenes), ready invasome vesicle showed a greater amount for CsA to the more layers for the skin (feasible the skin and dermis). Furthermore, the level of CsA in the superficial & deeper skin layers rose dramatically with increasing terpene concentrations (0.5 to 1.5%) (Nicolini, 2016).

It demonstrates the exact relationship between the quantity of drug incorporated into the terpene mixture and the quantity of drug present in the epidermal layer. It can be employed to

treat immune-mediated conditions as of the major advances for immunosuppression agent-loaded invasomes. When considered as a whole, it shown that hydrophobic medication transport to the deeper levels of the skin may be effectively replaced by invasomes (Romero & Morilla, 2013).

Anticancer drug delivery

Cancer therapy has been challenging to beginning in the biomedical research period. Many deaths have been happening annually as a result of the inefficiency of the treatment techniques that are now being used. As a result, there is a need to create a cutting-edge replacement to address the problem of cancer treatments that don't work (Chehelgerdi et al., 2023). It's interesting to note that temoporfin is a strong photosensitizer (second generation). It has a short half-life of one week and high tumor sensitivity. In photodynamic treatment for early or recurrent tumors, it could be considered a useful antitumor agent. According to Dragicevic-Curic and colleagues, invasomes serve for putting a highly hydrophobic photosensitive agent (temoporfin) into the skin layer (SC) .

In short, the mechanical dispersion approach was used to create temoporfin-loaded invasomes. In that, a 1%w/v terpene solution (limonene, citral, and cineole) including temoporfin and phosphatidylcholine: ethanol (75:25 w/w) were added, and the mixture was then vertexing and sonicated for five minutes (Senge & Brandt, 2011).

The aforementioned clear solution were then continuously vortexed for five minutes after the addition of PBS. About 105.4 nm particle sizes and 0.066 PDI were observed in the drug-loaded invasome (1%, w/v cineol). The human female abdominal skin was collected after plastic surgery, and penetration was performed using the nominal surface of the Franz cells (3.14 cm2). Cineole (1% w/v) had the most penetration ability, and it was followed by a combination (1% w/v) of cineole, citral, and D-limonene (45:45: 10 v/v) (Zheng et al., 2022).

Based on the results from the research, one terpene can spread temoporfin, & an array in terpenes might have a synergistic effect that would enable active penetration to the deeper levels of skin & visceral areas. Also, the stability analysis showed that the invasomes with 1% w/v cineole were present in Nangare and Dugam's Future Journal of Pharmaceutical Sciences (2020) 6:123 Page 10 of 21demonstrated a slight rise in PDL values so size of particles, over a full year, it may be deemed to be in a physically stable condition. In the future, invasomes may prove as a useful vehicle for delivering hydrophobic active compounds to the systemic/local

place in a safe concentration. But there's no hard-and-fast rule when it comes to applying terpenoid & its mixture to penetration. After being lowered from 500 to 1 mbar at 45 °C, the pressure was left there for 24 hours. The final film was hydrated for 30 minutes with PBS, ethanol, medication, and fenchone. Using an extrusion process utilizing a polycarbonate membrane, the final invasomal vesicles were ultrasonically induced. Fascinatingly, studies have indicated that fenchone & anastrozole jointly had a high anastrozole as trapping rate (Salih, 2022). Additionally, the large amount of fencing offers a low temperature, significant amount, and lipophilicity. Lowering the boiling point of terpene gives molecules little cohesion, which makes it easier for them to attach to lipids from SC and changes the barrier property.

Particle size, PDI, and zeta potential of the drug-loaded invadesome were determined to be 226.4 nm, 0.540, and − 20.9 mV, respectively. The presence of ethanol in the sample caused the invasome vesicles to exhibit a low negative possibility, that inhibits vesicle aggregation by exhibiting electrostatic repulsion. It would be more advantageous to guarantee invasomal dispersion stability. Ex vivo invasome penetration and skin deposition on male Wistar rat skin demonstrated improved transdermal flow, better penetration, and 73% drug skin deposition.(Nasr et al., 2022) Because terpenoid was hydrophilic or lipophilic vesicles reject each other, the percentage entrapment, penetration, and accumulation rate of actives were increased as compared to a medication that did not have a vesicle carrier.

The Michigan Cancer Foundation MCF-7 cancer cell line was used in the cytotoxic assay to demonstrate the cytotoxic impact of an improved formulation at 5 µL/mL [34]. These results suggest that the focused pharmacological effect of anastrozole can be enhanced using invasomes to treat cancer of the breast for postmenopausal women, therefore resolving the issue of oral delivery of the active ingredient. Therefore, it may open the door for postmenopausal women to get anastrozole as invasomal gels in treatment for cancer of the breast.(Ali et al., 2021)

Delivery of vitamin analog

A vitamin A analog called isotretinoin is used to treat eosinophilic pustular folliculitis. Dwivedi and associates have successfully synthesized isotretinoin invasome by the mechanical dispersion approach in recent attempts. In it briefly, ethanol eggs choline was added to soluble the substance from isotretinoin and vortexed for 60 minutes to produce a homogenous solution. Subsequently, PBS (pH 6.8) was used to hydrate the vesicles, yielding the yellowish transparent

invasomes containing suspension. At last, the suspension was subjected to sonication for three cycles and fifteen minutes, yielding exceptional invasomes. (M. Dwivedi et al., 2017)

Using a dialysis bag, the free isotretinoin has been isolated from the invadesomes. This study's crucial determinant showed that different formulational parameters had an impact on the invasomes' rate of penetration. The improved batch's particle size, PDI, zeta potential, and entrapment efficiency were determined to be 148 nm, 0.16, -69.2 mV, and 85.78%, respectively.(Umalkar et al., 2014) Interestingly, the size of invasomes increased when the level on eggs lecithin increased. However, the size of the invasome vesicles is not impacted with the eugenics concentration. The polar head group of the alone hydrophilic eggs lecithin chain produced strong positive curve intra membranes at larger concentrations of the protein, increasing the length of the invasome vesicle.(Kazi et al., 2010)

Aside from this, a higher lipid content enhanced the isotretinoin's entrapment efficiency since there more lipid able to trap the drug. Furthermore, isotretinoin's solubility and entrapment were enhanced by the application of eugenol. The high concentrations of lecithin & eugenol exhibited great deformability in invasome vesicles. Utilizing a Franz diffusion cells, the ex vivo permeation on the skin of rats which was shaven is over. The results indicated a cumulative isotretinoin penetration rate of 85.94% and an oral flow of about 78.82 μg/h/cm2 (Jmax).(Ashfaq et al., 2023)

The synthesized invasome gel had a diffusion ratio of 1.135, a zero-order release, & a substance level of 97.12%. Additionally, it completed 85.21% of the total isotretinoin penetration in just 8 hours. Additionally, invasomes gel stopped cell proliferation up to 82% of the time with little effects. All things considered, isotretinoin might be delivered to the follicular unit using invasome gel, allowing for pilosebaceous targeting. Clinical studies (phases I, II, and III) will be required in the future before using human subjects.(Cunha et al., 2023)

Used in alopecia treatment

Encouraging solutions for effective alopecia therapy are desperately needed. According to the research, using invadesomes has self-satisfactory long-term consequences. In an effort to find a safe, effective, and natural hair restoration treatment, people now often turn to complementary and alternative therapies. In this case, the FDA authorized the 5α reductase inhibitor finasteride, which is currently widely recommended for the treatment of alopecia. Nevertheless, a unique carrier for the transdermal administration of finasteride remains to be developed. Through

mechanical dispersion, the authors have synthesized the finasteride invasome utilizing limonene, nerolidol, and carvone at concentrations of 0.5%, 1.5%, and 1%, respectively (Hosking et al., 2019).

In short, an ethanol lipids mix was made in vortexing 10% w/v soya phosphatidylcholine in 40% w/v ethanol for five minutes. Subsequently, finasteride (0.35% w/v) was added to terpene at varying concentrations (0.–1.5% w/v), which was then continuously vortexed and sonicated for 5 minutes to provide a clear solution. Using PBS (up to 100% w/v) and continuous stirring for five minutes, vesicles were successfully hydrated. The drug-loaded multilamellar invasome vesicles were then exposed to five cycles of 5 minutes of probe sonication at 4 °C. The optimised invasomes in 0.5% the chemical content demonstrated about 84.56% entrapment efficiency, − 69.1 mV zeta potential, 5.81 μm particle size, and 5.94 μg/cm2 cumulative quantity penetrated (Pilch & Musiał, 2018).

Because of the alcohol that was present, the finasteride-loaded invasomes in that case showed a charge of zero on the vesicle surface. Additionally, it produced electrostatic repulsion, which gives the invasomal dose form more stability. The high spinning energy that produces a high negative charge or potential is provided by the sonication of the invadesome (Raina et al., 2023).

Furthermore, it demonstrated a homogenous and monodisperse solution with a good PDI <0.3, confirming the stability of the invasome formulation. Additionally, it exhibited negative zeta potential (from -52 to -58 mV), guaranteeing that vesicle aggregation would not occur. Additionally, a statistically significant improvement in minoxidil deposition in the upper skin was seen during an in vitro diffusing inquiry using baby pigskin as compared to drug liposomes and drug ethanolic solutions. Furthermore, it eschews minoxidil's transdermal administration, which raises the drug's cutaneous bioavailability. As a result, deformable vesicles performed better than normal ones if strengthening agents was utilized (Kumari et al., 2023)

Delivery of anti-acne agent

These days, acne is a common skin condition all over the world. One of the most potent medicinal ingredients for treating leprosy is dapsone. Because of its anti-inflammatory properties, it shows great potential in the treatment of acne. An efficient carrier needs to be developed in order to transport dapsone to the targeted location, much like it is for topical medication administration. El-nabarawi et al. therefore created the dapsone-loaded invasome

in treatment for severe mild to moderate pimples using an oral hydration approach with terpene (limonene, cineole, citral, or fenchone) and phosphatidylcholine. To sum up, 200 mg of phosphatidylcholine in an obvious 2:1 v/v methanol/chloroform mixture was paired in 20 mg for the drug & terpenes at several concentrations(Kurien et al., 2017).

Following that, this combination was exposed to rotary evaporation over 15 minutes at 120 rpm (60 °C) so as to remove the natural solvent. Isolated thin-film was then filtered (pore size 25 μm) to remove drug crystal and invasomes after hydrating over an hour around 120 rpm (60 °C) with a 3% v/v ethanolic:water combination. Dapsone's more effective trapping was demonstrated by the increased terpene content. Moreover, cineole, fenchone, citral, and limonene-containing invasomes had the greatest trapping efficiency. It could be as a result of the terpenes' lipophilicity. (D. Mishra et al., 2007) The optimal invasome loaded with drugs had a zeta potential of − 37.5 mV, showing the solidity of invasome vesicles, and a homogeneous, spherical, discrete morphology. The drug containing invasomes was transformed into an amorphous zone with a uniform distribution, as seen by the differential scanning thermogram. Curiously, the in vivo permeation investigation conducted on Wistar rats showed that the invasome's rates of penetration is twice as high than it was in solution form. Furthermore, they discovered that the level of dapsone coated on invasomes' skins in vivo rats was 4.11 μg/cm2, higher than the amount in the drug-alcoholic solution (1.71 μg/cm2). In particular, it has been demonstrated that invasome enhances the 2-fold AUC0–10 compared to the dapsone as liquid of Wister albino rats. All things considered, invasomes greatly accelerated dapsone's skin deposition. Therefore, an anti-acne chemical may be delivered using invasomes. Capsaicin is a significant pungent photo component that has been extensively researched in the pharmaceutical field, according to a literature review. In particular, it is used topically and orally to treat pain. Phosphatidylcholine & D-limonene were used for the invasomal mix for synthesized capsaicin (0.15%). Narrow size distribution (0.01–0.30) was seen in the optimized capsaicin-loaded invasomes.(D. Mishra et al., 2007)

not larger than 100 nm. Moreover, the stability of drug-loaded invasomes was confirmed via a low (− 20 mV) negative potential. Moreover, it provides superior skin permeability compared to retail goods & standard liposome formulations (0.15% capsaicin in ethanolic solution). The improved capsaicin invasomes can therefore be utilized in place of transdermal medication administration.(Castañeda-Reyes et al., 2020)

Conclusion

TDDS technology is most commonly used for drug injection in transdermal administration across a range of types of skin, as it represents an important advancement for mass distribution approach. It successfully gets beyond first pass metabolism and other sensitivities associated with using different ways to administer the medication. Drugs may easily pass through the skin's barrier and enter the bloodstream to have a therapeutic impact thanks to a range of devices and TDDSs. Numerous substances & active elements included in pharmaceuticals have great potencies but little therapeutic action. These substances offer a chance to target using invasomes, a unique carrier with remarkable and adjustable qualities. With their capacity for specific transport & enhanced bioavailability, invasomes provide a viable way to improve the therapeutic efficiency of such drugs. Invasomes are a great substitute for dermal, transdermal, and subcutaneous applications when considering the qualities and limits of the skin's barrier. Because they encapsulate the medication, their usage significantly improves pharmacokinetic characteristics. A number of variables, including penetration rate, the ability to distribute actives to specific areas, and low toxicity levels, affect how effective particular dose types of invasions.

Future prospective

These characteristics set invasomes apart as a creative and viable platform for cancer treatment in the future. This review offers a fresh company structure for invasomes and integrates the most recent research on cancer. It covers invasome composition, historical development, and preparation techniques, as well as the penetration mechanism that involves the impact of different formulation variables, anticancer mechanism analysis, and invasome application.

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