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Review Article

Invasomes as a Novel Delivery Carrier for Transdermal Delivery: Review Article

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Abstract

Transdermal drug delivery refers to the drug administration route through the skin that achieves the local or systemic treatment approved for clinical use. It is the third-largest drug delivery system after oral administration and injection. The advantages of the transdermal route are that the administration route of the drug is convenient and could reduce the fluctuation of blood drug concentration and toxic side effects. What is more, the drug could bypass the first-pass side-effect of the liver to prevent the drug from being destroyed in the gastrointestinal tract. Invasomes are new modified liposomes that differ from the liposomal vesicles in that they contain essential volatile oils, which are called terpenes. Also, ethanol in a low percentage is present in the vesicle either in the phospholipid layer or in the hydrous core. These modified newly discovered vesicles are intended to be used for topical and transdermal drug delivery due to their permeation effect and high deformability as compared to transferosomes.

Keywords: Invasomes; Transdermal drug delivery; phospholipids; terpenes; deformable vesicles

Introduction

Skin anatomy

As the largest and most essential organ in the body, the skin serves as the body's first line of defense against intruders. There are several layers of keratinocytes in the stratum corneum (SC), which is the most difficult layer for drug permeation, with an average thickness of 20-30 micrometers. This layer is responsible for retaining water from deeper skin layers and preventing the passage of harmful chemicals to the dermis layer, among other functions [1]. In the dermis, the papillary and reticular layers of the skin are comprised of collagen and elastin. Sebaceous glands and sweat glands are also found in the dermal layer. The connective tissue reticular structures of the hypodermis connect the dermis to the muscles or bones in the lowest layer of skin's fatty tissue. For transdermal drug delivery devices, understanding the skin's structure and function is essential (TDDS) [2].

Transdermal drug delivery

In clinical practice, transdermal drug delivery is a method of administering a medicine through the skin that has been approved for clinical usage. As a drug delivery method, it ranks right behind oral administration and injection. The benefits of transdermal drug delivery include a more comfortable route of administration and a reduced risk of drug concentration fluctuations in the bloodstream and hazardous side effects [3]. If the medicine is able to skip the liver's first-pass hepatic side-effect, it will be able to avoid being destroyed in the digestive system. However, the stratum corneum is a major impediment to the transfer of chemicals, medicines, and macromolecules, making this mechanism inefficient. It is imperative to develop a way to increase the efficiency of transdermal medicine delivery. If a molecule has the right physicochemical qualities, it can easily pass through the skin and reach the bloodstream without any intervention. Penetration enhancers and biological peptides can be added to chemical techniques. The skin's permeability may be temporarily increased by penetration enhancers that interact with SC components. Ultrasound and other physical approaches could also help enhance drug absorption through the skin [4].

Vesicular drug delivery systems

For both topical and transdermal medicine distribution, stratum corneum, the skin's most apical layer, is crucial (SC). Topical formulations face the problem of reduced pharmacological action due to ineffectiveness because of low medicine penetration into the skin. Only a few drugs with low molecular weight (MW), such as scopolamine, clonidine, nitroglycerin, nicotine, estradiol (alone or in combination with levonorgestrel or norethisterone), and others, are currently used in transdermal patches for transdermal drug delivery, i.e., absorption into the body's systemic circulation via patches. As a result, only molecules with specific physicochemical properties may readily permeate the SC, such as low molecular weight (MW) (600 Da), suitable oil and water solubility (log K octanol/water of 1-3), and a low melting point (log K MW/MW).If a drug doesn't match these requirements, penetration-enhancing measures can be used. The use of different penetration enhancers and manipulating the drug or medium in order to promote drug diffusion also includes iontophoresis, electroporation, ultrasound, and chemical penetration enhancement. Nanocarriers, such as liposomes, have been widely employed in several of these techniques. Liposomes have been widely studied as a medication carrier for transdermal and topical drug delivery [5].

Using vesicular drug delivery systems can lead to a significant increase in therapy effectiveness. Medicine distribution is controlled and maintained in vesicular delivery systems by managing and sustaining the release of the medication. Various vesicular drug delivery techniques, such as invasomes and liposomes, ethosomes, niosomes, transferosomes, pharmacosomes, colloidoids and herbal sphinosomes, are employed for transdermal drug administration. Invasomes, on the other hand, have received little attention despite the fact that vesicular drug delivery systems have been extensively explored. Several aspects of invasomes are described in this article, including their structure, substance, and skin penetration process. Ethanol, terpenes, and phospholipids make up the majority of invasomes' physicochemical composition. Invasomes have also been discussed as a treatment for hypertension, acne, cancer, pustular folliculitis, erectile dysfunction, and photodynamic therapy, among other conditions. Despite their apparent benefits, invasomes can only be used for transdermal pharmaceutical delivery due to their inherent stability [6].

Invasomes

A new class of vesicles, called Invasomes, is playing a key role in improving the transdermal penetration of active pharmacological compounds. Phospholipids, ethanol, and various terpenes or mixtures of terpenes are found in the structure of these vesicles. The transdermal penetration characteristics of these components were excellent.

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 [7].

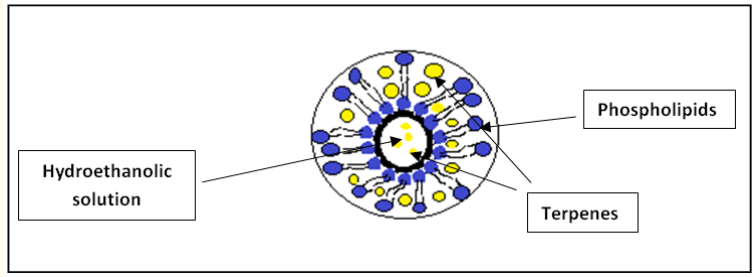

Figure 1: Schematic representation of invasomes.

Ethanol

Ethanol can be used to enhance permeability. Because of their particular size, zeta potential, entrapment efficacy, and skin permeability, vesicles in nano-vascular systems have a significant influence. According to various research, the vesicles' size and entrapment effectiveness decrease as the ethanol concentration rises. When the ethanol concentration increases, the vesicles dissolve. Increased levels of ethanol lead to decreased membrane thickness and, thus, vesicular volume. Ether penetrates hydrocarbon chains and alters the vesicles' net charge, resulting in smaller average vesicles. Fluidity of the nanovesicles can also be improved by ethanol. The densely packed structure of SC lipids is disrupted by ethanol, leading them to separate. Because ethanol has an influence on the structure of keratinize or lipophilic domains, the transition temperature of lipids can be reduced by this. In contrast to liposomal nanovesicles, nanovesicles based on ethanol have a softer and less rigid structure. Ethanol nanovesicles may also be more stable in storage because of their negative surface charge and electrostatic repulsion [8].

Terpenes

Research on transdermal drug delivery systems has also found that terpenes or terpene combinations in very low dose are penetration enhancers (also known as sorption boosters or accelerants), which penetrate into the skin and diminish barrier resistance. There is little danger of terpenes irritating the skin, hence they are classified as "Generally Recognized As Safe" (GRAS).Solubility, the dissolution of lipid and protein layers, and the loss of skin micro-ingredients all contribute to terpenes' ability to penetrate the skin. Therefore, terpene transdermal formulations appear to be quite promising. With mTHPC (mTHPC) with 1% (w/v) in it, Dragicevic-Curic and his colleagues in 2008 found that there was greater deposition into the skin [9].

Phospholipids

Water-loving hydrophobic acyl chains are linked to the alcohol in phospholipids. Dissimilarities in head groups, aliphatic chains, and alcohols allowed for an inclusive selection of phospholipids to survive. As a result, the phospholipid classes benefit from the modified phospholipid sources. For example, both natural and synthetic phospholipids, such as PEGylated Phospholipids, are commonly utilized in various formulations, such as those for skin care products. Even hydrogenated phosphatidylcholine has been reported as a nanovesicle formulation method. Curcumin transdermal gel had been described by Lakshmi et al. (2014). Solubility of curcumin was improved through the addition of CD and HPCD to the compound, which was subsequently incorporated into invasomes and finally HPMC gel [10-11].

Penetration mechanism through skin

To improve the penetration of active pharmacological molecules compared to standard liposomes, Invasome deformable new vesicles are created by integrating terpenes and frolicking in a liquid medium. There is a lot of flexibility in the membrane of these vesicles, which makes them easy to handle. Terpenes and ethanol are only found in invasomes, and this makes them special. Second, the inva-

somes themselves act as drug importer systems, allowing the encapsulated drug to enter and cross the stratum corneum; however, the invasomes themselves are not the only possible penetration enhancer mechanisms of invasomes. The presence of terpenes, which may improve drug permeability by disrupting SC lipid packaging, is another potential method by which the flexibility of deformable vesicles increases penetration [12]. Drug molecules were shown to be released from the vesicles and then infiltrate deeper layers of skin or the dermis' systemic circulation alone. The use of deformable vesicles in combination with a non-occlusive claim will be critical in the future. Diffusion of deformable vesicles becomes less effective when osmotic gradient across the skin is diminished. PEs may also be made from deformable vesicles because the lipid bilayers in these structures can be utilized to influence cell membranes by interfering with the intercellular lipid lamellae. Depending on a medication's lipophilicity, this method may or may not work. In some drugs, the interaction between these two channels is crucial for drug absorption; this depends on the physicochemical characteristics of the molecule [13].

Methods of preparation

Mechanical dispersion technique

In an ethanolic phospholipid solution, drugs and terpenes, or terpene combinations, can be dissolved. So that the solution is clear, the mixture is vortexed and sonicated for 5 minutes. Addition of PBS (pH: 7.4) is made by continual vortexing of the solution with a needle attached to a syringe. For the next five minutes, the vortexing continues. Polycarbonate membranes of varying pore diameters are used to extrude the multilamellar vesicles. Polycarbonate membranes are repeatedly punctured by invasome dispersions [14].

Film hydration technique

The traditional film process can also be used to prepare invasomes. Chloroform (2:1 v/v) is used to dissolve phospholipids in ethanol. The rotary flash evaporator is used to steadily reduce the pressure from 500 to 1 mbar at 50°C to dry this mixture to a thin layer. Two hours of room temperature vacuum (1 mbar) is applied to the film before it is flushed with nitrogen. To make invasomes from the film, either PBS (pH:7.4) and an ethanol/terpene combination or a single terpene are added after cooling to room temperature and hydration for 30 minutes, respectively. In order to size the resulting vesicles, polycarbonate membranes with varying pore diameters are repeatedly extruded via a vortex and ultrasonicator [15].

Characterization

Vesicle shape

Transmission electron microscopy (TEM) and scanning electron microscopy are excellent tools for observing invasomes. Vesicles of the Temoporfin peptide have been shown to be spherical, oval, unilamellar, bilamellar, and even oligolamellar in shape. A spherical, unilamellar form was described for finasteride invasomes. Carboxyfluorescein and temoporfin invasomes were found to be nearly unilamellar and bilamellar, respectively, by cryo-TEM. This is why they can be identified as spherical or distorted vesicles with one, two, or more lamellae [16].

Vesicle size

Dynamic light scattering (DLS) and photon correlation spectroscopy can be used to measure the invasome particle size. Temoporfin invasomes have been shown to enhance the size of vesicles with an increase in terpene content. Zetasizer can be used to determine the formulation's zeta potential [17].

Drug entrapment

An invasome's entrapment efficiency can be assessed using ultra-centrifugation or other methods for estimating the amount of medication contained within vesicles. Hydroxy terpenes limonene and nerolidol have the highest and lowest entrapment efficiency, respectively, in finasteride invasomes. Entrapment was greatest of limonene, according to the results of this study. The hydrophilicity of the medication and the terpene added, as well as the concentration of the terpene added, were found to affect entrapment efficiency [18].

Methods of determination entrapment efficiency

Entrapment efficiency of drugs in invasomes can be determined by one of the following methods: [19].
Size Exclusion Chromatography (SEC).
Ultracentrifugation.
Dialysis.
Solvents with high dielectric constant like acetone.

Applications

Immunosuppressive drug delivery

Research found that CyA is lipophilic and has low penetration into the skin (partition coefficient: 4000). Psoriasis and other dermatological conditions may benefit from the use of CsA in the form of topical treatments. A nanocarrier for delivery of CsA and CyA was first created by Verma utilizing ethanol, citral:cineole:D-limonene combinations (0.5:1.0:1.5 percent w/v), and PBS up to 100 percent w/v mechanical dispersion, as well as unsaturated soybean phosphatidylcholine (10 percent w/v). When tested in vitro, it was found that invasome vesicles containing both ethanol and terpenes had a higher concentration of CdS in the deeper layers of skin (the viable epidermis as well as the dermis), as opposed to liposomes and aqueous/ ethanolic drug solutions [20].

Anticancer drug delivery

There is evidence to suggest that invasomes can enhance the feature of anastrozole skin deposition in the treatment of breast cancer in postmenopausal women in order to alleviate the problem of oral administration of the active ingredient. Thus, the use of anastrozole invasomal gel for breast cancer therapy in postmenopausal women can lead the way [21].

Treatment of erectile dysfunction

With an enhancement factor of 2.514 on excised abdominal Wistar rat skin, the optimized AVA invasomal film outperformed the raw AVA invasomal film in ex vivo permeation testing. Over four times greater bioavailability was detected in the invasome as compared to the raw avanafil-loaded film. Medication-loaded invasomal transdermal film could be used to address the issues of poor water solubility and substantial pre-systemic metabolism that are associated with oral drug absorption in the context of these findings. As a result, the skin penetration and bioavailability of avanafil can be improved via invasomal formulation. Because of this, it can be utilized to administer drugs for the treatment of erectile dysfunction in new ways [22].

Conclusion

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

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References

1. Harding CR. "The stratum corneum: structure and function in health and disease". Dermatologic therapy 17 (2004): 6-15.
2. Hao Y, Li W, Zhou X., et al. "Microneedles-based transdermal drug delivery systems: a review". Journal of biomedical nanotechnology 13.12 (2017): 1581-1597.

3. Alkilani AZ, McCrudden MT and Donnelly RF. "Transdermal drug delivery: innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum". Pharmaceutics 7.4 (2015): 438-470.
4. Haque T and Talukder M. "Chemical Enhancer: A Simplistic Way to Modulate Barrier Function of the Stratum Corneum". Advanced pharmaceutical bulletin 8.2 (2018): 169-179.
5. Dragicevic N, Verma DD and Fahr A. "Invasomes: Vesicles for enhanced skin delivery of drugs. In Percutaneous penetration enhancers chemical methods in penetration enhancement". Springer, Berlin, Heidelberg (2016): 77-92.
6. Jain S, Tripathi S and Tripathi PK. "Invasomes: Potential vesicular systems for transdermal delivery of drug molecules". Journal of Drug Delivery Science and Technology (2021): 102166.
7. D Singh. "Ultra deformable system: a carrier for transdermal drug delivery". IJPSR 4 (2013): 4098-4104.
8. S Babaie., et al. "Invasome: A novel nanocarrier for transdermal drug delivery". Nanomaterials 10.2 (2020): 341.
9. ND Curic, D Scheglmann, V Albrecht and A Fahr. "Temoporfin-loaded invasomes: Development, characterization and in vitro skin penetration studies". J. Control. Release 127 (2008): 59-69.
10. L Jing., et al. "A review on phospholipids and their main applications in drug delivery systems". Asian J. Pharm. Sci 10 (2015): 81-98.
11. PK Lakshmi, V Mounica, M Kumar and D Prasanthi. "Preparation and evaluation of curcumin invasomes". Int. J. Drug Deliv 6 (2014): 113-120.
12. G Cevc and G Blume. "Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force". Biochim. Biophys. Acta 1104 (1992): 226-232.
13. MM Elsayed, OY Abdallah, VF Naggar and NM Khalafallah. "Deformable liposomes and ethosomes as carriers for skin delivery of ketotifen". Pharmazie 62 (2007): 133-137.
14. Lakshmi P, Kalpana B and Prasanthi D. "Invasomes-novel vesicular carriers for enhanced skin permeation". Systematic Reviews in Pharmacy 4.1 (2013): 26.
15. Haag SF., et al. "Skin penetration enhancement of core-multi shell nanotransporters and invasomes measured by electron paramagnetic resonance spectroscopy". Int J Pharm 416 (2011): 223-8.
16. Chen M, Liu X and Fahr A. "Skin penetration and deposition of carboxyfluorescein and temoporfin from different lipid vesicular systems: In vitro study with finite and infinite dosage application". Int J Pharm 408 (2011): 223-34.
17. Sinico C, Manconi M, Peppi M, Lai F, Valenti D and Fadda AM. "Liposomes as carriers for dermal delivery of tretinoin: In vitro evaluation of drug permeation and vesicle-skin interaction". J Control Release 103 (2005): 123-36.
18. Aqil M, Ahad A, Sultana Y and Ali A. "Status of terpenes as skin penetration enhancers". Drug Discov Today 12 (2007): 1061-7.
19. Beaumont P, Courtois A, Richard T, Krisa S and Faure C. "Encapsulation of ε-Viniferin into Multi-Lamellar Liposomes: Development of a Rapid, Easy and Cost-Efficient Separation Method to Determine the Encapsulation Efficiency". Pharmaceutics 13.4 (2021): 566.
20. Nangare S and Dugam S. "Smart invasome synthesis, characterizations, pharmaceutical applications, and pharmacokinetic perspective: a review". Future Journal of Pharmaceutical Sciences 6.1 (2020): 1-21.
21. Vidya K and Lakshmi P. "Cytotoxic effect of transdermal invasomal anastrozole gel on MCF-7 breast cancer cell line". J Appl Pharm Sci 9 (2019): 050-058.
22. Ahmed OA and Badr-Eldin SM. "Development of an optimized avanafilloaded invasomal transdermal film: Ex vivo skin permeation and in vivo evaluation". Int J Pharm 570 (2019): 118657.

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