International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1093-1098 www.ijprajournal.com ISSN: 2456-4494

Invasome: A New Sight in Transdermal drugdelivery System

Raslamol K*[1], AiswaryaI S[2] , Dilshana A S[3], Mohamed Shahil[4], Mumthas NA[5], Sandra MS[6]

[1]*Department of Pharmaceutics, Nirmala College of Health Science, Meloor, Chalakkudi*
[2]*Nirmala College of Health Science, Meloor ,Chalakkudi*

Date of Submission: 15-05-2024 Date of Acceptance: 25-05-2024

ABSTRACT
Invasomes are novel vesicular system that exhibit improved transdermal penetration compared to conventional liposomes. These vesicles contain phospholipids, ethanol and terpene in their structure; these components confer suitable transdermal penetration properties to the soft vesicles. 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 and terpenes lead to increased drug penetration by disrupting the tight bilayers and lipid packing in the SC. The present work describe numerous aspects of invasomes including structural features, composition and skin penetration mechanism. Furthermore, invasomes applications in the treatment of hypertension, acne, cancer, eosinophilic pustular folliculitis and erectile dysfunction have also been discussed. The main advantage of these nanovesicles lie in their ability to increase the permeability of the drug into the skin and decrease absorption into the systemic circulation,thus limiting the activity of various drugs within the skin layer and also invasomes improve the drugs efficacy ,enhance patient compliance and comfort. Overall the enhanced delivery of drugs through the skin and cellular membranes by means of an invasomal carrier opens numerous challenges and opportunities for research and future development of novel improved therapies.

Keywords : Transdermal, liposome, invasome, terpene, ethanol, nanocarrier.

I. INTRODUCTION

Invasome

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.

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 bilayer-forming 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.

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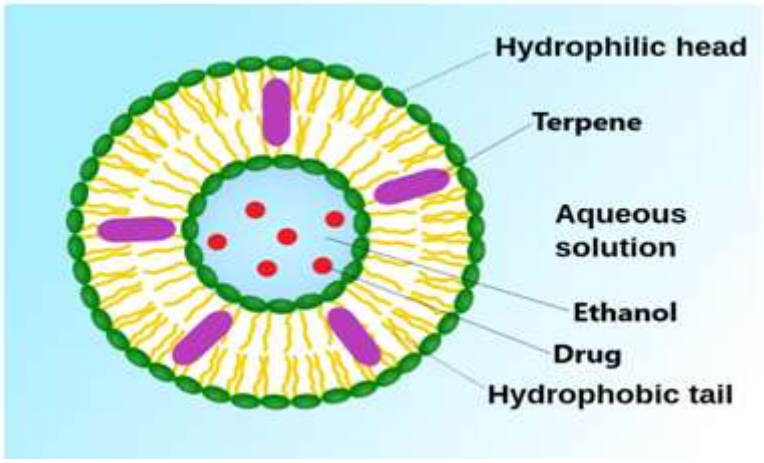
STRUCTURE OF INVASOME

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.



IDEAL PROPERTIES

- Penetration Enhancement
- Flexibility
- High Encapsulation Efficiency
- Stability
- Controlled and Targeted Drug Release

ADVANTAGES

- Non-invasive technique
- Patientcompliance is high
- Deliveryofhydrophilicandlipophilic drugsispossible.

DISADVANTAGES

- It requires high cost for production
- Chance of leakage and fusion of encapsulated active
- Short half life

APPLICATIONS

- Anastrazoleinvasomal gel is used for breast cancer therapy in post- menopausal women.
- Dapsone loaded invasome is used in acne therapy.
- The immunosuppressive drug,cyclosporin A is used in the treatment of psoriasis and other dermatological conditions.
- Finasteride and Minoxidil loaded invasome is used for the treatment of Alopecia.
- Skin penetration and bioavailability of Avanafil for the treatment of Erectile Dysfunction is improved via invasomal formulation.
- Isotretinoin invasomal preparation is a vitamin A analogue used to treat Eosinophilic Pustular Folliculitis.

II. MATERIALS AND METHODS

Mechanical DispersionTechnique:

For mechanical Dispersion Technique, the active drug and terpene or mixture of terpene are dissolved in Phospholipid containing Ethanol.Then vortexed and sonicated for about 5 min.Add Phosphate Buffer Saline(PBS) at pH 7.4 to hydrate the vesicle with constant vortexing.Then the lipid spontaneously swell and invasome is obtained.Finally post hydration sonication, lyophilization and high pressure extrusion should be done.

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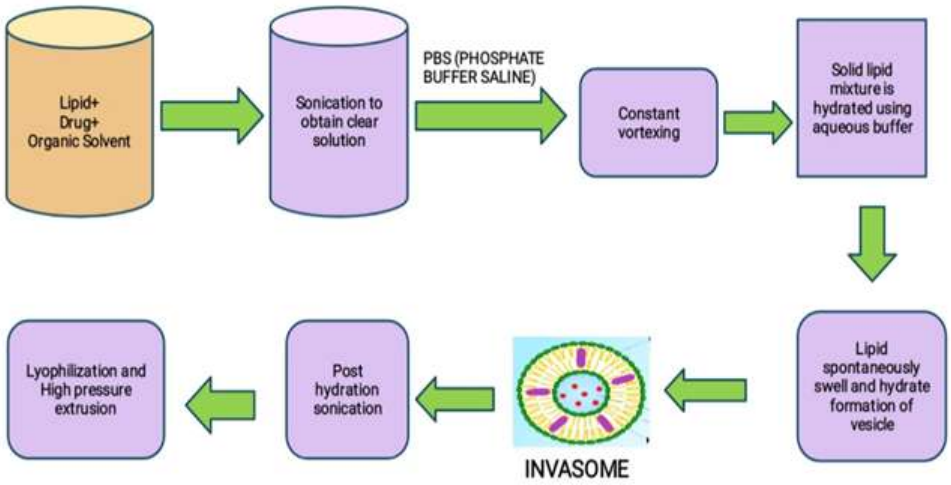
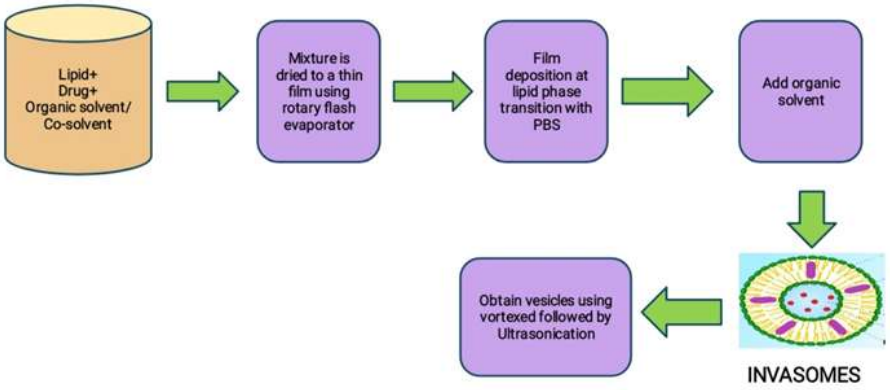


Film Hydration Technique:

For Film Hydration Technique ethanol and phospholipid dissolved in mixture of methanol and chloroform in 2:1 ratio. Dry the mixture by using Rotary Flash Evaporator for 2 hours at 50°C by lowering the pressure.Add Phosphate Buffer Saline(PBS) at pH 7.4 to hydrate the deposited film for 30 min.Then add organic solvent (Terpene or mixture of Terpene and Ethanol). Finallyinvasome is formed and undergo vortexing and ultrasonication to obtain vesicle.



STORAGE CONDITIONS

Invasomes should be stored in a cool and dry environment to prevent degradation. They are often refrigerated at temperatures between 2 to 8 °C. It's important to protect them from light and moisture, as these factors can affect their stability. Invasomes should be stored in airtight containers which helps to minimize exposure to oxygen.

EVALUATION PARAMETERS

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

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

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

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

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

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

7. 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.

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

9. 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 ± 0.2^0 c) and room temperature (25-28 ± 2^0 c)

INVITRO STUDIES

1.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.

2.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.

3.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.

4.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.

5.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.

INVIVO STUDIES

1.Pharmacokinetic study

Below is a general guide on how to conduct pharmacokinetic studies of invasomes:

Study Design and Protocol Development:

Define Study Objectives: Clearly outline the objectives of the pharmacokinetic study, such as assessing bioavailability, tissue distribution, and elimination kinetics.

Selection of Animal Model: Choose an appropriate animal model that is relevant to the intended application and provides insights into systemic drug behavior.

Ethical Approval: Obtain necessary ethical approvals for conducting animal studies inaccordance with regulatory guidelines.

Formulation preparation:

Optimization Studies: If not done previously, optimize the invasome formulation to achieve desirable characteristics such as size, stability, and drug encapsulation efficiency.

Radiolabeling (Optional): Consider radiolabeling the drug or invasomes for sensitive detection in biological samples.

Dosing and administration:

Dose selection : Determine the appropriate dose of the invasomal formulation based on the previous and expected pharmacokinetic parameter.

Route of administration : Choose the relevant route of administration (eg:intravenous, oral, topical) based on the intended clinical application.

In vivo pharmacokinetic studies focus on understanding the absorption, distribution, metabolism and excretion (ADME) of drugs delivered using invasomes. Blood concentration-time profiles are often measured to determine key pharmacokinetic parameters.

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2.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.

3.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.

4.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.

5. 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.

III. CONCLUSION

Invasomes represent a promising advancement in the field of transdermal drug delivery. Their unique composition, which includes soy phosphatidylcholine, lysophosphatidylcholine, terpenes, and ethanol, allows for enhanced penetration through the skin, making them highly effective for delivering both hydrophilic and lipophilic drugs. The flexible and fluidic structure of invasomes, facilitated by the incorporation of ethanol and terpenes, distinguishes them from traditional liposomes, providing superior penetration and encapsulation efficiency.

The development of invasomes addresses the necessity for advanced carriers capable of delivering active pharmaceutical ingredients through various skin layers. Their high penetration potential, stability, and controlled drug release offer significant advantages, such as non-invasiveness, improved patient compliance, and the ability to deliver a wide range of drugs. However, challenges such as high production costs, potential leakage, and short half-life must be considered.Invasomes have demonstrated considerable efficacy in various applications, including cancer therapy, acne treatment, and the management of psoriasis and alopecia. The mechanical dispersion and film hydration techniques are effective methods for preparing invasomes, ensuring optimal encapsulation and stability.

Storage conditions are critical to maintaining invasome stability, with refrigeration being the preferred method. Evaluation parameters such as entrapment efficiency, viscosity, vesicle size, pH, drug content, extrudability, spreadability, homogeneity, zeta potential, and stability are essential for assessing invasome quality.In vitro and in vivo studies further validate the effectiveness of invasomes, highlighting their potential in improving drug bioavailability and therapeutic outcomes. Pharmacokinetic, dose-response, therapeutic efficacy, toxicity, and skin irritation studies provide comprehensive insights into the safety and efficacy of invasomes.Overall, invasomes offer a cutting-edge solution for transdermal drug delivery, combining advanced nanocarrier technology with enhanced penetration capabilities to improve drug delivery and therapeutic outcomes. Continued research and development are essential to optimize their formulation, address challenges, and expand their clinical applications.

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