A COMPREHENSIVE REVIEW ON INVASOMAL GEL TECHNOLOGY FOR ENHANCED TRANSDERMAL DRUG DELIVERY

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Abstract

Transdermal drug delivery faces challenges due to the limited penetration of certain therapeutic compounds, particularly those with poor solubility. This review explores the potential of invasomal gel formulations in improving skin permeability and therapeutic efficacy. Invasomes, vesicular carriers composed of ethanol and terpenes, have emerged as promising systems for enhancing drug penetration through the skin. Various studies have demonstrated that invasomal gels exhibit favorable characteristics, including optimal particle size, high entrapment efficiency, and suitable rheological properties. In-vitro release studies further highlight their ability to provide sustained drug release and improved bioavailability compared to conventional formulations. The development of invasomal gel technology presents a promising approach for optimizing transdermal drug delivery and enhancing patient outcomes in the treatment of dermatological conditions.

Keywords: Invasomal gel, Sustained release, Vesicular carriers, Drug penetration

1. Introduction

Transdermal drug delivery is one of the most widely used drug administration routes, which offer several advantages over other routes of drug delivery. The apical layer of the skin called the *stratum corneum* is the most dominant obstacle in the transdermal drug delivery, which restricts the passage of drugs across the skin. Considerable strategies have been applied to enhance the rate of permeation across the epithelial cells; however, the most widely used strategy is the use of sorption boosters, also known as permeation enhancers [1].

Invasomes are novel vesicular systems that exhibit improved transdermal penetration compared to conventional liposomes. These vesicles contain phospholipids, ethanol, and terpene in their structures; these components confer suitable transdermal penetration

properties to the soft vesicles. The main advantages 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. In this paper, several features of invasomes, including their structure, mechanism of penetration, applications, characterization, and potential advantages in dermal drug delivery, are highlighted. Overall, this review suggests that enhanced transdermal penetration of drugs using invasomes provides an appropriate opportunity for the development of lipid vesicular carriers [2].

1.2 Transdermal Drug Delivery

At present, the most common form for the delivery of drugs is oral route. While this has the notable advantage of easy administration, it also has significant drawbacks -namely poor bio availability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is a need for the development of new drug delivery system which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and number of doses [3]. New drug delivery system is also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e. peptides, proteins) to their site of action, without incurring significant immunodeficient or biological inactivation. Transdermal drug delivery is defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems. Drugs administered in the conventional dosage forms usually produce large range in fluctuations in plasma drug concentrations leading to undesirable toxicity or poor effectiveness. These factors as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of the controlled drug delivery system or therapeutic system [4]. A dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ is a controlled drug delivery system. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Transdermal therapeutic systems are defined as self-contained discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at controlled rate to the systemic circulation. The first Transdermal drug delivery (TDD) system, Transderm-Scop developed in 1980, contained the drug Scopolamine for treatment of motion sickness [5].

1.2.1 Advantages

Delivery via the transdermal route is an interesting option because transdermal route is convenient and safe. The positive features of delivering drug across skin to achieve systemic effect are [6]:

- The drugs by pass the hepatic and pre systemic metabolism i.e., Avoidance of first pass metabolism thereby increasing bio availability.
- Risks and inconveniences of IV therapy are avoided.
- Self –administration is possible.
- Minimizing undesirable side effect.
- Avoiding the fluctuation in drug level.
- Maintain plasma concentration of potent drug.
- Termination of therapy is easy at any point of time.
- Ability to deliver the drug more selectively to a specific site.
- Provide suitability for self-administration.
- Enhance therapeutic efficacy.

1.2.2 Disadvantages

The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dose required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult [7].

- Only relatively potent drugs are suitable candidates for TDDS because of the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application for one or more of the system components, necessitating discontinuation.
- Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

1.2.3 Physiology of Skin

Skin of an average adult body covers a surface of approximately 2m2 and receives about one-third of the blood circulating through the body [8]. Skin contains an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids [9]. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body [10].

1.2.3.1 Skin Pathways for Transdermal Drug Delivery Systems

When drugs are applied on the skin surface, penetration into and through the skin can occur via various routes. Drugs penetrate either via the stratum corneum (transepidermal) or via the

appendages (transappendageal). During penetration through the stratum corneum, two possible routes can be distinguished, Penetration alternating through the corneocytes and the lipid lamellae (transcellular route) and Penetration along the tortuous pathway along the lipid lamellae (intercellular route) [11]. Generally, it is accepted that the predominant route of penetration through the stratum corneum is the intercellular route. This is mainly caused by the densely cross-linked cornified envelope coating the keratinocytes. However transcellular transport for small hydrophilic molecules such as water cannot completely be excluded. The appendage route or shunt route includes either the duct of the exocrine sweat glands or the follicular duct [12]. The content of the exocrine sweat glands is mainly hydrophilic, while the content of the follicular duct is lipophilic. This is mainly due to the sebum excreted into the opening of the follicular duct. It is generally accepted that due to its large surface area, passive skin permeation mainly occurs through intact stratum corneum [13].

1.2.4 Advance Development in TDDS

Drug in adhesive technology has become the preferred system for passive transdermal delivery, two areas of formulation research are focused on adhesives and excipients [14]. Adhesive research focuses on customizing the adhesive to improve skin adhesion over the wear period, improve drug stability and solubility, reduce lag time, and increase the rate of delivery. Because a one-size-fits-all adhesive does not exist that can accommodate all drug and formulation chemistries, customizing the adhesive chemistry allows the transdermal formulator to optimize the performance of the transdermal patch [15]. A rich area of research over the past 10 to 15 years has been focused on developing transdermal technologies that utilize mechanical energy to increase the drug flux across the skin by either altering the skin barrier (primarily the stratum corneum) or increasing the energy of the drug molecules. These so-called “active” transdermal technologies include Ionotophoresis which uses low voltage electrical current to drive charged drugs through the skin [16].

- Electroporation which uses short electrical pulses of high voltage to create transient aqueous pores in the skin.
- Sonophoresis (which uses low frequency ultrasonic energy to disrupt the stratum corneum) and thermal energy (which uses heat to make the skin more permeable and to increase the energy of drug molecules).
- Even magnetic energy, coined magnetophoresis has been investigated as a means to increase drug flux across the skin [17].

1.2.5 Applications of TDDS

- Nicotine transdermal patch marketed as Nico dermis to help in smoking cessation. It is the highest selling patch in United State.
- Two opioid medications Fentanyl (marketed as Duragesic) and Buprenorphine (marketed as BuTrans) used to provide round-the-clock relief for severe pain available in patch form

- Estradiol patches available as Estraderm for treat menopausal symptoms as well as postmenopausal osteoporosis. It is also available in combination with levonorgestrel as Climara Pro for menopausal symptoms.
- Nitroglycerin transdermal patches for the treatment of angina pectoris, prescribed in place of sublingual pills.
- Transdermal patch of clonidine available for treatment of hypertension.
- Transdermal patch of the selegiline (MAO inhibitor) became the first transdermal delivery agent for major depressive disorder.
- Transdermal delivery agent Methylphenidate for the Attention Deficit Hyperactivity Disorder (ADHD) [18].

1.3 Invasomes

Lipid-based nanocarriers called invasomes are made especially to improve medicine delivery through the skin by getting beyond the stratum corneum's natural barrier. Like liposomes, these are modified vesicular systems that are enhanced with ethanol and penetration enhancers like terpenes (such as limonene, cineole, and menthol) [19]. Because of their special makeup, invasomes have better permeability and deformability, which makes them useful for topical and transdermal medication administration [20].

1.3.1 Penetration Mechanism of Invasomes

The invasomes' ethanol and terpenes distort the vesicles, interfere with the SC bilayer skeleton, and improve penetration, which increases the invasomes' permeability [21]. One portion of the vesicle breaks apart during invasome penetration, releasing its constituents, including terpenes, phospholipid segments, and single phospholipid molecules, which improve penetration and fluidize the SC lipids, according to Dragicevic-Curic et al. Smaller invasome vesicles pass through the SC undamaged because they do not break down [22]. Verma and colleagues claim that intact invasomes can enter the SC through the follicular transport pathway or the SC's intercellular region's tiny hydrophilic channels after penetrating [23]. According to Honeywell-Nguyen et al., tiny intact invasomes can pass through the channel-like regions and into the deeper portion of the SC. This was inferred from the flexible vesicles of different sizes seen at the skin surface vesicles and channel-like regions in the deeper layer of the SC [10]. While smaller vesicles and flexible invasomes enter the deeper layers intact, many invasomes generally break apart when they enter the SC [24]. (Fig. 1)

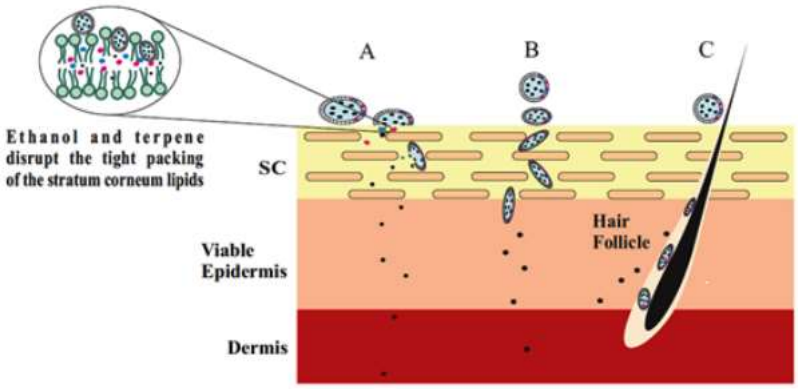

Figure 1. Penetration mechanism of invasomes through the stratum corneum (SC). Enhanced penetration (A), intact penetration (B), and trans-appendageal penetration (C).

1.3.2 Structure of Invasomes

Advanced lipid-based nanocarriers called invasomes are made to improve medicine penetration into the skin by getting beyond the stratum corneum's barrier [25]. Their main vesicle is a flexible phospholipid bilayer, usually composed of phosphatidylcholine, which encapsulates both lipophilic and hydrophilic medications. Ethanol is added to the bilayer to increase the vesicles' fluidity and deformability, which helps them pass through the skin's tiny intercellular gaps. The presence of terpenes, such as limonene, cineole, or menthol, which function as penetration enhancers by upsetting the stratum corneum's lipid matrix and stabilizing the vesicle, is another distinctive feature of invasomes. Invasomes are adaptable carriers because their lipid bilayer can hold lipophilic medications while their aqueous center offers a stable environment for hydrophilic pharmaceuticals. This structural design creates extremely flexible and stable vesicles that greatly increase medication penetration and delivery efficiency by fusing the advantages of ethanol and terpenes with the characteristics of traditional liposomes. Because of their hybridity and deformability, invasomes hold promise as a transdermal drug delivery vehicle [26].

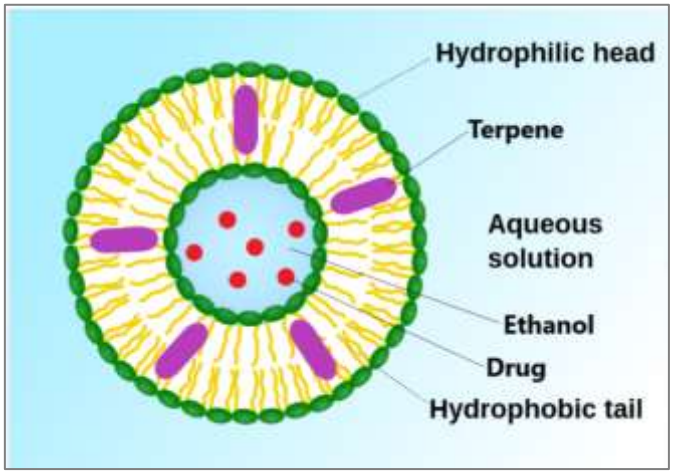

Figure 2: Structure of Invasomes

1.3.3. Effect of Composition on the Physicochemical Characteristics of Invasomes

1.3.3.1. Effect of Ethanol

One efficient method to improve the fluidity of the skin's lipid bilayer is to include ethanol into the formulation of lipid nanovesicles. Ethanol's interaction with the lipid components in the SC's polar group region causes changes to the keratinized or lipophilic domains' structure, lowers the lipids' transition temperature, and ultimately causes fluidization and disruption of the densely packed SC lipids. The SC lipids can be fluidized and disturbed by nanocarriers based on ethanol. Because ethanol allows the lipid acyl chains to rotate freely, it enhances the intercellular lipid matrix's flexibility. As a result, ethanol makes the lipids in the vesicle structure more fluid, which makes the structure softer and less stiff than traditional liposomes [27]. Ethanol increases the stability of invasomes in storage by producing a net negative surface charge and limiting vesicle aggregation through electrostatic repulsion, in addition to improving penetrating ability.

1.3.3.2. Effect of Terpenes

- **Effect of Terpene on Penetration**
  According to the results of differential scanning calorimetry (DSC) and X-ray diffraction, terpenes promote medication penetration by breaking down the SC's rigid bilayers and lipid packing. Additionally, it has been shown that terpenes promote drug permeability through the following mechanisms: boosting diffusion via the intercellular lipids, breaking hydrogen bonds and extracting SC lipids, and promoting the partition into the SC by improving lipid fluidity. Different terpene types have a synergistic effect on temoporfin penetration, according to Dragicevic-Curic et al. Compared to invasomes containing 1% citral alone, those having a 1% combination of three terpene types—citral, cineol, and limonene—showed greater temoporfin permeability. Dragicevic-Curic et al. showed in another investigation that the quantities of terpenes in the invasomes and the quantity of temoporfin that penetrated were related. They found that compared to vesicles with 0.5% terpenes, those with 1% terpenes had a 1.7-fold greater temoporfin penetration impact. Consequently, deeper penetration may result from adding temoporfin to vesicles that contain 1% terpenes. [28].

- **Effect of Terpene on the Size of the Invasomes**
  An analysis of particle size revealed a clear relationship between the size of the invasomes and the terpene content, with the invasomes getting bigger as the terpene content rises. Vesicles carrying 1% terpenes were 124 nm in size, whereas those containing 0.5% terpenes were 93.0 nm. Prasanthi et al. demonstrated that the molecular size of terpene and the concentration of the added terpene affected the size of finasteride-loaded invasomes. Nerolidol-containing invasomes had a molecular size of 222 g/mol and ranged in size from 11 to 13 μm. Nimesulide-loaded liposomes with citral, limonene, and cineole had vesicle diameters of 194 nm, 216 nm, and 244 nm, respectively [29].

- **Effect of Terpene on the Shape of the Invasomes**
  Invasome shape was influenced by terpenes, as evidenced by the results of cryo-transmission electron microscopy (cryo-TEM), which showed that invasomal dispersions contained deformed vesicles of various forms in addition to spherical vesicles. Dragicevic-Curic et al. examined the morphology and lamellarity of invasomes with different terpene fractions using cryo-electron microscopy. According to their findings, invasomes containing 0.5% terpenes were mostly oval and spherical or unilamellar and bilamellar in shape; in contrast, the invasomes in the invasomal formulation including 1% terpenes seemed to be both. 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 [30].

1.3.3.3 Synergistic Effects

Phospholipids, ethanol, and terpenes have been shown to work in concert to improve cutaneous absorption. The phospholipids and terpenes, which function as permeation enhancers that fluidize the intercellular lipids, are released when one portion of the invasome breaks down during penetration in the epidermis' outermost layers, according to Dragicevic-Curic et al. Additionally, the ethanol in the invasome facilitates the entry of flexible vesicles and fluidizes the intercellular lipids. According to Verma et al., invasomes enhanced cyclosporine A's transdermal penetration when compared to an ethanolic solution. A synergistic action of phospholipid, terpenes, and ethanol is suggested by the increased efficiency of invasomes when compared to an ethanolic solution. Dragicevic-Curic et al. showed that the terpene concentration and the synergistic effects of ethanol and terpenes were responsible for the enhanced penetration of temoporfin (mTHPC) with 1% terpenes [31]. Therefore, as compared to liposomes, the results of the aforementioned research indicate that phospholipid, terpenes, and ethanol have a synergistic impact on the reformation activity of invasomes.

1.3.4 Invasome Stability

The size of the particles and the polydispersity index (PDI) value, which measure the physical stability of invasomes, are significantly impacted by the storage temperature. All invasomes exhibit physical instability, or vesicle fusion or aggregation, during room temperature storage, as evidenced by an increase in particle size and PDI value. For 12 months, the PDI of the invasomes kept at 4 ◦C in the Dragicevic-Curic et al. research remained constant; however, after 6 months, the invasomes had a markedly elevated particle size and PDI value [32]. Lakshmi et al. found that after a month of refrigeration, 10% of the encapsulated medication was lost in terms of drug content. The loss of encapsulated drug increased to 50% when stored at room temperature.

1.3.5 Pharmacokinetics perspective of invasomes

Since the beginning, the drug-loaded system has been investigated for in vivo research that necessitates superior pharmacokinetic properties, such as the transport of the active agent to the designated site, blood circulation time, appropriate absorption, target site access, half-life clearance, etc. And we saw that medications with the aforementioned exceptional qualities are taken into consideration for real-world uses. According to the literature, invasome's distinctiveness is what is making it a viable alternative for a range of medicinal applications. It's interesting to note that a crucial stage in the creation of any pharmaceutical product is the impending requirement for fundamental knowledge of pharmacological and toxicological elements. As a result, one of the main guiding principles for creating invasomes for targeted administration in a therapeutic application may be the relationship between the pharmacokinetics and in vivo biodistribution of invasomes [33]. In general, a variety of physicochemical characteristics, such as vesicle size, shape, aggregation, solubility, penetration enhancers, and chemical compositions, influence the biodistribution and pharmacokinetics of invasomes. It may be altered by employing a variety of techniques, including iontophoresis, the use of terpene mixtures, and the microneedle technique. Numerous studies showed that the invasome must have significant absorption from the application location in order to have acceptable bioavailability [34]. To put it briefly, invasomes have been employed to provide the active medicinal substance to both the skin and cellular membranes. The types and compositions of penetration enhancers, lipids, various sophisticated techniques (such as dermaroller and iontophoresis), etc., all have a significant impact on the absorption of invasome. It is verified by the use of distinct vesicle types and their traditional dose form. Furthermore, invasomal formulation can be used for systemic as well as local applications. According to some research, the medication is either absorbed by the systemic circulation or deposited in the local tissue. In all, a large number of investigations have been conducted to determine the pharmacokinetics of invasomes.

1.3.6 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.

1.3.6.1 Mechanical dispersion technique

When using the mechanical dispersion approach, phospholipid containing ethanol is used to dissolve the active medication or biomolecule, terpene, or a combination of terpenes. To create a straightforward solution, the mixture should be properly mixed, vortexed for five minutes, and then sonicated for five minutes. Next, using a syringe with continuous vortexing for five minutes, the phosphate buffer (pH 7.4), phosphate buffer saline (PBS), or appropriate solvent was added to the solution for vesicle hydration. Ultimately, the fluid was sieved and repeatedly extruded into multilamellar vesicles using polycarbonate membranes with pore sizes ranging from 400 nm to 200 nm to 100 nm to 50 nm [35]. The preparation of invasome by employing mechanical dispersion is depicted in Fig.2.

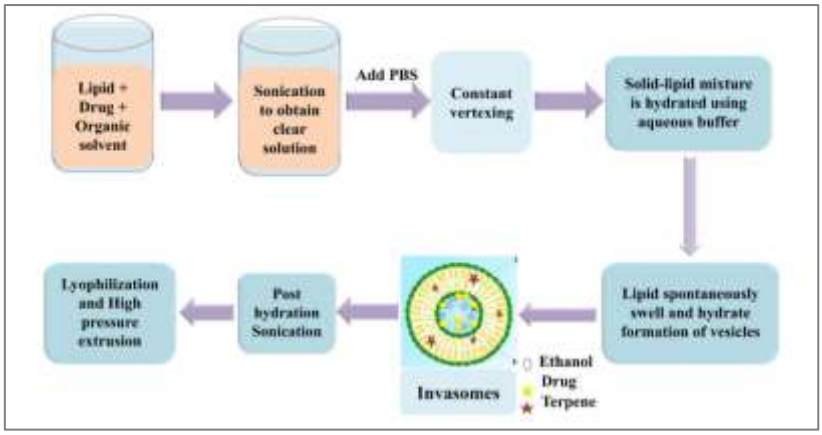

Figure 3: Preparation of invasomes using mechanical dispersion technique

1.3.6.2 Film hydration technique

The phospholipid and ethanol combination was dissolved in a 2:1 v/v mixture of methanol and chloroform in the film hydration process. Using a rotary flash evaporator, this mixture was dried for two hours at 50 °C by reducing the pressure from 500 to 1 mbar. The film was then stored for two hours at a pressure of one mbar while being flushed with nitrogen. The deposited film can be hydrated for 30 minutes using PBS (pH 7.4) or a solution of terpenes, ethanol, and PBS. To obtain the invasome vesicles, the fluid should be cooled before adding the terpene or combination of terpenes and ethanol. The prepared invasome was vortexed, ultrasonically sonicated, and then extruded through the different pore-sized polycarbonate membranes [36]. The formation of invasome by applying the film hydration method is represented in Fig.3

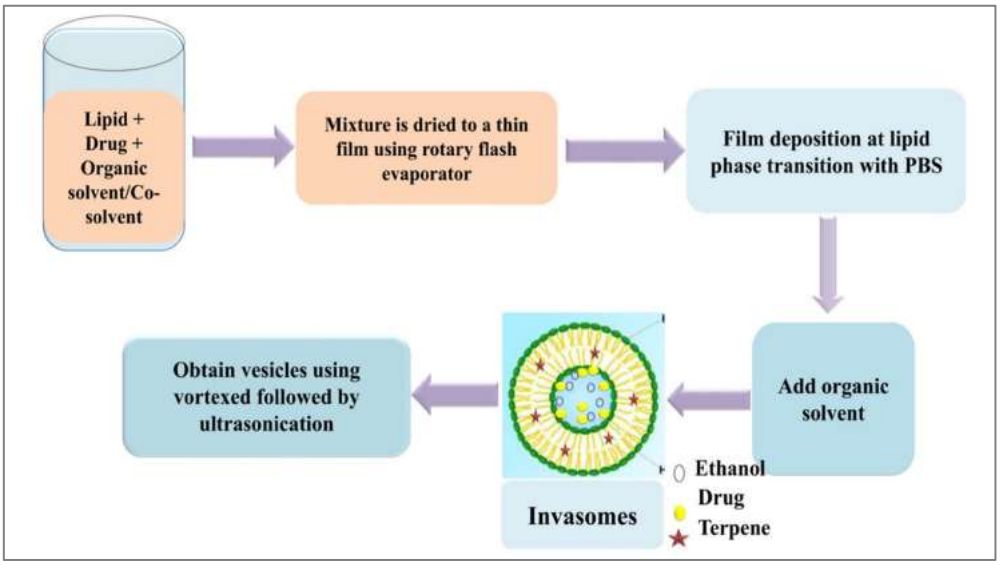

Figure 4: Preparation of invasomes using film hydration technique

1.4. Invasomal Gel

In recent years, invasomal gel formulations have emerged as promising vehicles for the delivery of antifungal agents. Improved drug absorption and sustained release features are offered by invasomes, which are innovative vesicular systems that can encapsulate hydrophilic and lipophilic medicines, by formulating isoconazole into invasomal gels, it is possible to enhance its bioavailability, prolong its retention at the site of infection, and improve therapeutic outcomes [37].

1.4.1 Composition of Invasomal Gel

1.4.1.1 Invasomes

- **Lipid vesicles composed of:**

- **Phospholipids**: Create bilayer vesicles for drug encapsulation.
- **Ethanol**: Enhances vesicle deformability and skin penetration.
- **Penetration Enhancers (Terpenes)**: Examples include cineole, limonene, or menthol, which disrupt the lipid matrix of the skin to enhance drug delivery.

1.4.1.2 Gel Base:

- A polymeric matrix (e.g., carbopol, HPMC) that provides viscosity, ensuring stability and ease of application.

1.4.1.3 Active Pharmaceutical Ingredient (API):

- Drugs incorporated into invasomal gels typically include anti-inflammatory agents, antifungals, analgesics, and other bioactive compounds [38].

1.4.2 Mechanism of Action [39]

The effectiveness of invasomal gels lies in their ability to synergistically combine penetration enhancers, ethanol, and deformable vesicles (invasomes).

- **Skin Barrier Disruption**: Terpenes and ethanol modify the structure of the skin's lipid layers, enhancing permeability.
- **Drug Encapsulation**: Invasomes encapsulate the drug, protecting it from degradation and delivering it in a controlled manner.
- **Deformable Vesicle Penetration**: The flexibility of invasomes allows them to squeeze through the tight intercellular spaces of the stratum corneum.

1.4.3 Advantages of Invasomal Gel [40]

- **Enhanced Permeation**:

- Improves drug delivery through the skin by bypassing its natural barriers.

- **Localized Action**:
- Enables targeted delivery, minimizing systemic exposure and side effects.
- **Sustained Release**
- Provides controlled drug release, reducing the frequency of application.
- **Improved Stability**
- Protects unstable drugs from degradation due to environmental factors.
- **Non-Invasive Administration**
- Provides a painless alternative to injections, enhancing patient compliance [41].

2. Conclusion

In conclusion, the study underscores the significant potential of invasomal gels as an advanced platform for transdermal drug delivery. These vesicular systems, composed primarily of phospholipids, ethanol, and terpenes, have shown enhanced skin penetration and improved drug bioavailability compared to conventional formulations. Their ability to bypass the gastrointestinal tract and first-pass metabolism makes them particularly suitable for delivering drugs in a controlled and sustained manner. The incorporation of therapeutic agents into invasomal gels results in prolonged drug release, better patient compliance, and targeted action, positioning them as a valuable alternative in the field of non-invasive drug delivery.

However, despite these advantages, several challenges need to be addressed for their widespread adoption. Stability issues, scale-up limitations, potential skin irritation due to ethanol and terpenes, and variability in skin permeability remain significant hurdles. These limitations also create opportunities for innovation—such as the use of biocompatible and less irritating terpenes, ethanol-free formulations, and integration of nanotechnology or smart polymers to enhance formulation stability and performance. Such advancements could further broaden the scope and efficiency of invasomal gels.

For future research and development, it is recommended that efforts focus on long-term stability studies, in vivo and clinical evaluations, and in-depth mechanistic studies to understand the precise mode of skin permeation. Additionally, formulation optimization with novel excipients, exploration of various therapeutic applications (like hormonal therapy or chronic pain management), and addressing regulatory and scalability issues are critical for translating laboratory success into market-ready products. Overall, continued exploration in this field holds great promise for the development of safe, effective, and patient-friendly transdermal therapies.

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