

# RECENT TRENDS IN THE EMERGENCE OF INVASOMES FOR TRANSDERMAL DELIVERY OF DRUGS

## Abstract

Transdermal delivery provides a leading edge over oral route or invasive method for drug delivery avoiding hepatic metabolism. Innovative delivery methodologies give a new aspect of delivering drug molecules effectively in a controlled manner. Invasomes are novel liposomal vesicular system that provides better transdermal penetration than liposomes improving drug efficacy thereby enhancing patient compliance and comfort. This vesicular system embodies small amount of ethanol and terpenes or terpene mixtures giving it very high membrane fluidity and the ability to modify the order of stratum corneum packing. Terpenes, the naturally occurring volatile oils are generally recognized as safe substances with minimum irritancy at low concentration. This book chapter presents an overview of invasomes, a unique and promising drug delivery method that combines the benefits of liposomes and in description of their substantial contributions to the field of drug delivery. The chapter opens by explaining the idea of invasomes and highlighting its unique properties such as their potential to improve skin permeabilities and target specific tissues and deliver a wide range of therapeutically active substances. It goes on to detail the various manufacturing procedures of invasomes such as thin film hydration, solvent injection and lipid film hydration emphasizing the significance of optimizing formulation parameters to obtain desired properties of the system. The chapter explores invasomes assessment techniques and finishes with a description of their substantial contributions to the

## Authors

### **Amit Kumar Das**

NETES Institute of Pharmaceutical Science (NIPS), Mirza Assam, India.

### **Shibanku Bhuyan**

NETES Institute of Pharmaceutical Science (NIPS), Mirza Assam, India.

### **Debasish Thakuria**

NETES Institute of Pharmaceutical Science (NIPS), Mirza Assam, India.

### **Chanam Melody Devi**

NETES Institute of Pharmaceutical Science (NIPS), Mirza Assam, India.

field of drug delivery. It emphasizes their ability to overcome biological barriers, improve drug bioavailability, and enhance therapeutic efficacy. With further research and development, invasomes hold great promise as an innovative drug delivery system, offering numerous opportunities for advancements in medical treatments and patient care.

**Keywords:** Invasomes; Liposomes; Drug delivery; Permeability; Bioavailability.

## I. INTRODUCTION

The demand for innovative drug delivery methods has been steadily increasing to enhance patient compliance. Despite oral dosage forms dominating 70% of the market, they suffer from significant limitations, including susceptibility to enzymatic degradation and hepatic metabolism, ultimately compromising drug performance and reducing bioavailability. Over the past two decades, there has been a notable surge in interest regarding transdermal drug delivery systems (TDDS) due to their considerable advantages over traditional oral administration. To optimize drug stability on the skin and facilitate its systemic circulation through transdermal preparations, strategies aim to enhance circulation while minimizing skin absorption and retention [1]. The primary objective of the transdermal drug delivery system (TDDS) is to circumvent the challenges inherent in the oral route of drug administration. TDDS offers significant advantages, including enhanced bioavailability through controlled drug release, a reduced incidence of adverse effects, and the avoidance of first-pass metabolism. Within the realm of Novel Drug Delivery Systems (NDDS), TDDS has emerged as a pivotal component. It stands as a distinctive alternative to conventional drug delivery methods, effectively addressing the shortcomings associated with many traditional approaches.

In TDDS, a patch or analogous system facilitates the transdermal transport of medication across the skin barrier to the targeted treatment area in a carefully controlled manner. This method ensures that a relatively small quantity of medication is administered. Importantly, since the drug is absorbed through the skin and directly enters the bloodstream during this process, it results in a higher concentration of the drug in the bloodstream, optimizing therapeutic outcomes [2].

The primary challenge in the development of Transdermal Drug Delivery Systems (TDDS) revolves around effectively bypassing the skin's natural transport barrier. The initial mention of the potential utility of liposomes in topical therapy dates back to 1980, when Mezei and Gulasekharam reported on it. Since then, researchers have been dedicated to designing lipid vesicles as carriers for delivering drugs through the skin. These lipid vesicles exhibit the unique capability to surmount the stratum corneum's formidable barrier and reside within the deeper layers of this outermost skin layer, all while gradually releasing their therapeutic agents or proteins. Nonetheless, it's worth noting that lipid vesicles remain a subject of debate within the realm of cutaneous and transdermal drug carriers [3].

In the realms of both topical and cutaneous medication delivery, there has been a keen interest in utilizing lipid-based vesicular systems. These vesicles have garnered special attention due to their potential to efficiently transport drugs while overcoming the formidable stratum corneum barrier in intact skin. These vesicular systems can be categorized into two distinct groups based on their primary mechanisms and their interactions with the skin. The first category encompasses vesicles characterized by highly flexible bilayers. This flexibility is achieved through various means, such as forming partnerships with specific hydrophilic solutes or incorporating edge activators into the bilayer structure. These vesicles serve as carriers for medications, gaining access to intact skin via hydrophilic pathways. In contrast, the vesicles in the second group are equipped with permeability enhancers, resulting in bilayers that are highly fluid in nature. These vesicles act as agents that facilitate drug penetration into the skin. Subsequently, the presence of permeability enhancers within the

vesicle structure collaboratively alters the integrity of the stratum corneum barrier. This classification underscores the diverse strategies employed by vesicular systems in tackling the challenge of effective drug delivery through the skin in both scholarly and practical contexts [4].

The rationale behind employing lipid vesicles for topical and transdermal applications is supported by several advantages:

1. The lipid vesicle's lipophilic nature, attributed to its vesicle wall composition, makes it a suitable carrier for poorly water-soluble substances. This lipophilicity imparts exceptional penetration-enhancing properties, facilitating the transport of substances that would otherwise have limited aqueous solubility.
2. Furthermore, lipid vesicles exhibit controlled release characteristics, ensuring that the encapsulated molecule is not rapidly released upon application. This controlled release feature makes them function effectively as an intrinsic reservoir system for the incorporated compounds.

However, it is important to acknowledge that despite these advantageous attributes, the lipid vesicle system encounters challenges when dealing with drugs exceeding a molecular weight of 500 Da. These larger molecules face difficulties in permeating through the skin barrier, posing a limitation to the system's effectiveness in such cases, as observed and noted in scholarly discussions [5]. Drug's low permeability was addressed by the development of vesicular systems, which sparked a series of vesicle alterations, including the emergence of deformable vesicles. Liposomes, transfersomes, glycosomes, niosomes, ethosomes, and invasomes are among the components of these deformable lipid vesicles.

The stratum corneum, acting as a formidable barrier, inherently hinders the absorption of medications through the skin. However, innovative techniques, including iontophoresis, sonophoresis, microneedles, and lipid vesicle carriers, have emerged as effective strategies to address this challenge. Within the realm of Transdermal Drug Delivery Systems (TDDS), lipid vesicle carriers have garnered significant attention, encompassing various types such as ultradeformable liposomes (ULs), transfersomes, phytosomes, ethosomes, and invasomes. Among these lipid-based deformable nanovesicles, which include liposomes, niosomes, and ethosomes, have gained widespread acceptance as promising candidates for drug administration. Notably, some of these nanovesicle-based systems have successfully transitioned from laboratory research to commercial applications. They exhibit versatility by facilitating the delivery of drugs with both hydrophilic and lipophilic properties.

The delivery of drugs and diagnostics to specific organs, tissues, or cells using nanovesicles has long been an area of keen interest. However, it presents formulation scientists with new challenges, particularly in the context of physiological and pathological conditions. These factors can complicate drug delivery to the targeted disease site, rendering precise and effective delivery a complex endeavor.

In summary, the utilization of lipid vesicle carriers and nanovesicles in drug delivery represents a dynamic and evolving field, with ongoing developments and challenges arising from the intricate interplay between physiological and pathological conditions [6]. Invasomes, a cutting-edge approach to drug delivery, are nanoscale vesicular systems primarily

constituted of phosphatidylcholine, ethanol, and terpenes, either individually or in combination. These unique vesicles exhibit substantially enhanced percutaneous permeation capabilities when compared to conventional liposomes, marking a significant advancement in drug delivery technology, as documented in scholarly literature [7][8].

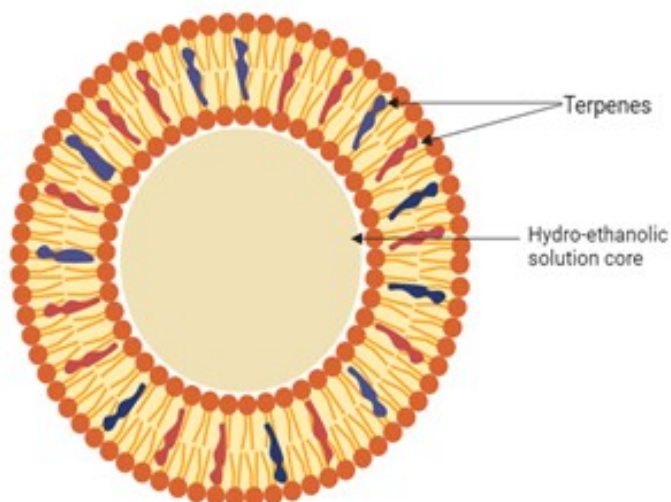
Terpenes are potent permeation boosters that readily affects the packing of stratum corneum, disrupt its lipid structure, react with intracellular proteins, and significantly augments the stratum corneum drug partitioning [9][10]. Ethanol and terpenes present in the invasomes extend a synergistic impact which promotes invasomal vesicle penetration through the skin [11][12].

These represent innovative vesicular systems that exhibit a marked enhancement in the transdermal penetration of active pharmacological compounds when contrasted with conventional vesicles. Comprising phospholipids, ethanol, and terpenes, either alone or in terpene blends, these vesicles have been strategically engineered to harness the excellent penetration properties of their constituent ingredients, thereby serving as highly effective transdermal permeation facilitators, as discussed in scholarly literature.

## II. STRUCTURE OF INVASOMES

Invasomes, classified as soft liposomal vesicles, serve as promising carriers designed to enhance skin penetration capabilities. They are formulated with minute quantities of ethanol and terpenes, either individually or as blends [13]. These specialized lipid vesicles consist of water, terpenes (such as citral, cineole, limonene, and eugenol, typically ranging from 1% to 5% v/v), low concentrations of ethanol (usually within the range of 3% to 3.3% v/v), and phospholipids (which may include phosphatidylcholine, phosphatidylserine, soya phospholipids, and egg lecithin).

Terpenes, characterized by the general chemical formula  $(C_5H_8)_n$ , play a pivotal role in enhancing the percutaneous absorption of both hydrophilic and hydrophobic drugs. These natural components, derived from essential oils, are widely recognized as effective penetration enhancers. Notably, terpenes offer the additional advantage of being non-irritating to the skin when used in low concentrations. Furthermore, they are generally considered safe for use, a designation upheld by the FDA, as corroborated in scholarly literature [14].



**Figure 1:** Invasome

- 1. Ethanol:** To enhance permeability, ethanol emerges as a valuable agent. Within nano-vascular systems, vesicles wield substantial influence due to their specific attributes, encompassing size, zeta potential, entrapment efficacy, and skin permeability. An abundance of research findings underscores the relationship between ethanol concentration and key vesicular characteristics. Notably, as the ethanol concentration rises, both the size and entrapment efficacy of vesicles tend to decrease, ultimately leading to vesicle disintegration. This phenomenon is attributed to the role of ethanol in reducing membrane thickness and, consequently, vesicular volume. Ethanol's impact extends to the modification of vesicle properties. It can infiltrate hydrocarbon chains and induce alterations in the net charge of vesicles, resulting in a reduction in the average vesicle size. Additionally, ethanol contributes to enhanced fluidity within nanovesicles. It achieves this by disrupting the densely packed structure of stratum corneum (SC) lipids, causing them to undergo structural changes. Furthermore, ethanol's influence on the keratinized or lipophilic domains serves to lower lipid transition temperatures.

In comparison to liposomal nanovesicles, ethanol-based counterparts exhibit a softer and less rigid structural profile. Importantly, the negative surface charge they acquire through ethanol-induced alterations and subsequent electrostatic repulsion may confer greater stability to ethanol nanovesicles during storage, as indicated by scholarly research [10].

- 2. Terpenes:** Terpenes, or combinations of terpenes at exceedingly low concentrations, have indeed demonstrated their role as penetration enhancers, also referred to as sorption boosters or accelerants, within the domain of transdermal drug delivery systems. They effectively facilitate the entry of drugs into the skin while diminishing the resistance posed by the skin's natural barrier. Importantly, terpenes have a minimal risk of causing skin irritation, earning them the designation of "Generally Recognized As Safe" (GRAS).

The ability of terpenes to permeate the skin is influenced by several factors, including their solubility, their capacity to dissolve lipid and protein layers, and the alteration of skin microconstituents. Consequently, transdermal formulations containing

terpenes hold great promise, as demonstrated by their ability to achieve higher deposition of substances such as mTHPC (mTHPC) at a concentration of 1% (w/v) in 2008, as highlighted in scholarly research [15].

- 3. Phospholipids:** Phospholipids exhibit a distinctive molecular structure where hydrophobic acyl chains, which are water-repellent, are attached to an alcohol group. These structural variances, encompassing differences in head groups, aliphatic chains, and alcohol constituents, have given rise to a wide array of phospholipids with unique properties. Consequently, these modified sources of phospholipids offer significant advantages to various phospholipid classes. They find application in diverse formulations, including those used in skincare products, with examples ranging from natural phospholipids to synthetic variants like PEGylated Phospholipids.

Moreover, even hydrogenated phosphatidylcholine has been recognized as a viable means for the formation of nanovesicles, demonstrating the versatility and utility of phospholipids across different research and application domains, as elucidated in scholarly discussions [16].

### III. SKIN PENETRATION MECHNAISM OF INVASOMES

Invasomes represent a novel category of deformable vesicles, achieved through the incorporation of terpenes, which markedly enhance the penetration of active pharmacological compounds when compared to regular liposomes. These vesicles exhibit delicate characteristics and possess a notably high membrane fluidity, setting them apart from conventional liposomes [17].

In terms of penetration enhancement mechanisms, invasomes offer two plausible avenues: Firstly, invasomes themselves act as carriers for drug molecules, with the vesicles integrating into the stratum corneum to facilitate the transport of encapsulated drugs across the skin [18]. This phenomenon can be attributed to the hydrophilic phospholipids' propensity to seek out moisture-depleted environments, driving deformable lipid vesicles to exit the skin in this manner [19].

The second potential mechanism involves the presence of terpenes within invasomes, which may enhance drug permeability by disrupting the lipid structure of the stratum corneum [20]. As a result, active drug molecules are released from the vesicles, subsequently entering deeper layers of the skin or even entering the systemic circulation within the dermis.

In the context of this application, it is crucial to note that a non-occlusive approach is required to optimize drug administration via deformable vesicles over the skin. This approach relies on reducing the transepidermal osmotic gradient, leading deformable vesicles to lose their inherent diffusion driving force [21]. In turn, these vesicles can function as penetration enhancers, interacting with the stratum corneum and altering the structure of intercellular lipid layers. The lipophilicity of the drug can significantly influence the augmentation of drug penetration through this mechanism. The interaction between these two systems plays a pivotal role in determining the effectiveness of drug penetration, contingent upon the physicochemical characteristics of the drug [22]. These insights are corroborated by findings in scholarly research.

#### **IV. INVASOMES BASED TRANSDERMAL DRUG DELIVERY**

The collective effort of combining ethanol with terpene mixtures represents a concerted approach aimed at amplifying the penetration potential of invasomes. Numerous researchers have dedicated their efforts to devising and documenting a plethora of strategies and vesicular systems geared towards enhancing the skin penetration of active pharmaceutical molecules through topical applications. Within the context of Transdermal Drug Delivery Systems (TDDS), a notable surge of interest surrounds a novel nanovesicle system. Extensive characterization studies utilizing techniques such as Electron Spin Resonance (ESR), Differential Scanning Calorimetry (DSC), and cryoelectron microscopy have unveiled the remarkable fluidity of phospholipids, identified as a pivotal dynamic factor contributing to the potent penetration-enhancing properties of invasomes. Nonetheless, it's important to note that beyond fluidity, several additional phenomena play integral roles in the mechanism underlying the enhanced skin penetration facilitated by invasomes [23].

Both invasomes and core-multishell (CMS) nanotransporters have firmly established their status as widely employed drug delivery technologies within the field of dermatology. For instance, Haag et al. (2011) conducted an evaluation of invasomes and CMS nanotransporters in the context of the topical delivery of Protocatechuic acid (PCA), a compound with a log P value of 1.7 [24]. Findings from Electron Paramagnetic Resonance Spectroscopy (EPRS) indicated that PCA was localized within the hydrophilic compartments of both CMS nanotransporter solutions and invasome dispersions. Furthermore, in comparison to a PCA solution administered alone, invasomes led to a 1.9-fold increase in PCA penetration, while CMS nanotransporters demonstrated a 2.5-fold enhancement. Remarkably, step-by-step removal of the stratum corneum using a tape stripping approach revealed that invasomes achieved the deepest penetration of PCA. These results underscore the potential utility of both invasomes and CMS nanotransporters for transdermal administration of PCA or other hydrophilic medications [25]. These findings are substantiated by scholarly research in this field.

#### **V. INVASOMES VS LIPOSOMES**

Liposomes, distinguished by their phospholipid-based vesicular structure, offer a versatile platform for encapsulating a wide range of pharmaceutical compounds, including lipophilic, hydrophilic, and amphiphilic drugs. This versatility is achieved through the incorporation of various lipid types, encompassing anionic, cationic, and neutral lipids, as well as cholesterol. In liposomes, lipophilic drugs find their place within the inner lipid bilayer, hydrophilic drugs are accommodated in the aqueous core, and amphiphilic drugs are situated within the vesicle's interlayer [26][27].

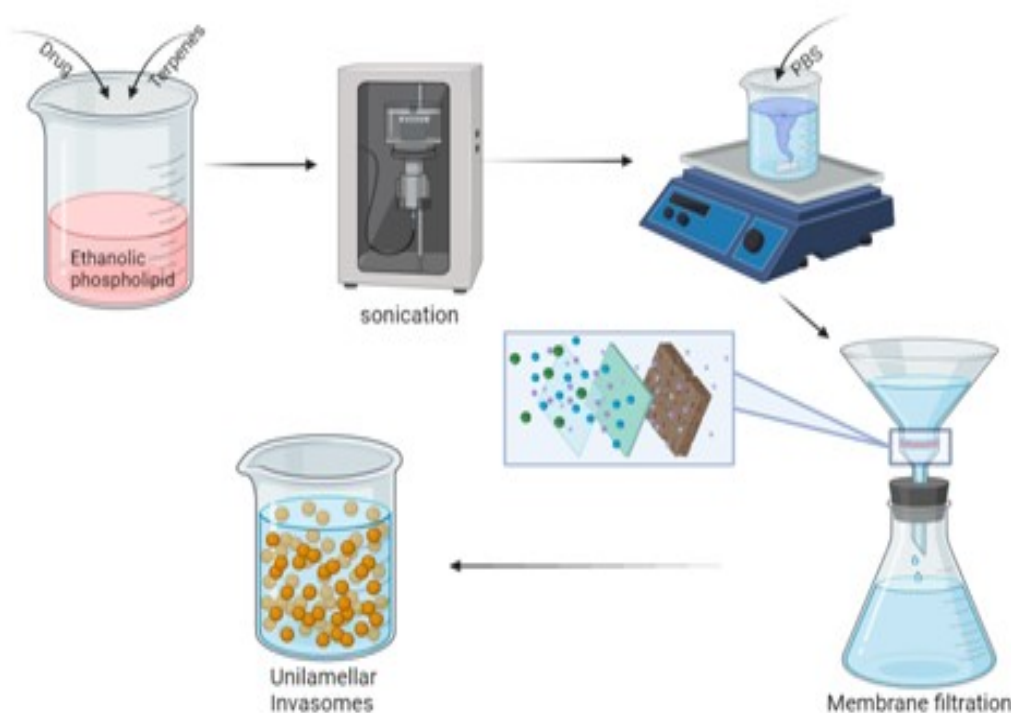
In contrast, invasomes represent a distinct category of flexible liposomes, comprising phospholipids, ethanol, and either a single terpene molecule or a combination of terpenes. Ethanol plays a pivotal role in enhancing the fluidity of lipids within the vesicle's structure, leading to a more pliable form that is less rigid compared to conventional liposomes. This property contributes to an improved capacity for skin permeation [28]. Terpenes, on the other hand, have been demonstrated to enhance penetration by disrupting the compact structure of stratum corneum lipids [29].



These insights highlight the nuanced differences between liposomes and invasomes, shedding light on their respective roles and mechanisms in drug delivery, as established in scholarly research.

## VI. FORMULATION OF INVASOMES

- 1. Mechanical dispersion technique:** In this process, the drug and terpenes are mixed with ethanolic phospholipid solution. Then the mixture is sonicated and vortexed for 5min so that the solution becomes clear. Phosphate Buffer Solution (PBS) of pH 7.3 is added by continuous vortexing. To extrude the multilamellar vesicles, polycarbonate membranes with varying pore diameters are used. Invasome dispersions repeatedly perforate polycarbonate membranes. [30][31].



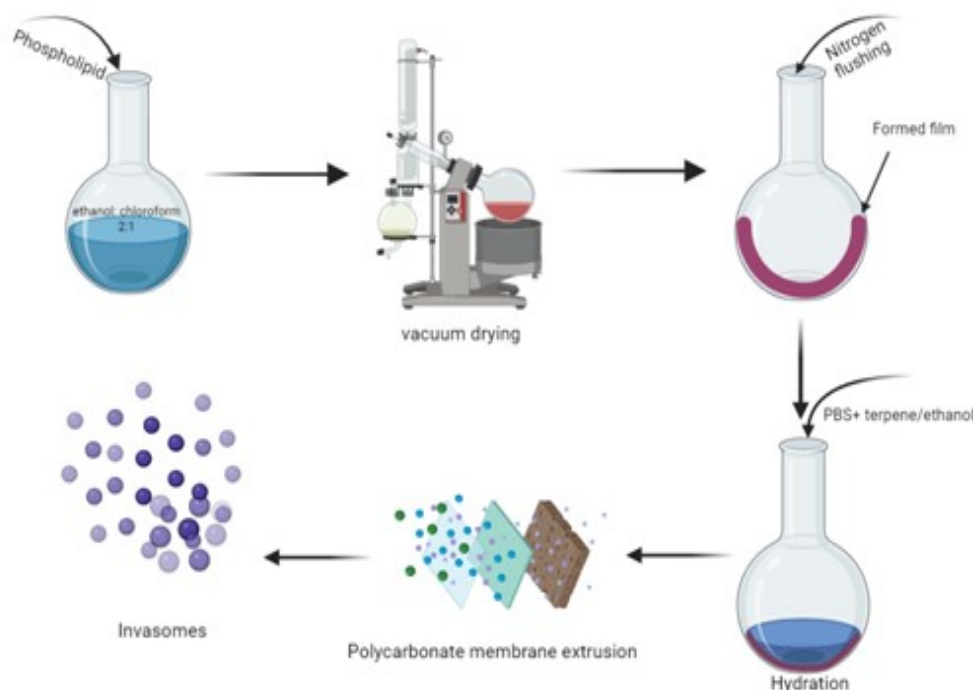
**Figure 2:** Mechanical dispersion technique for formation of invasomes

- 2. Film hydration technique:** The preparation of invasomes through the traditional film hydration method involves a systematic procedure. Initially, a mixture of ethanol and chloroform in a 2:1 v/v ratio is dissolved in a solution containing phospholipids. Subsequently, this mixture is subjected to a controlled drying process using a Rotary Flask Evaporator maintained at 50°C, while gradually reducing the pressure from 500 to 1 mbar. This results in the formation of a thin film layer along the inner surface of the flask.

The formed film is then subjected to a two-hour vacuum treatment at room temperature (1 mbar), followed by a nitrogen flush to ensure optimal conditions. To create invasomes from this film, either a combination of PBS with a pH of 7.4 and

terpenes/ethanol mixture or a single terpene is introduced. After this, the system is allowed to cool to room temperature, and a hydration process of 30 minutes takes place.

To achieve the desired vesicle size, the hydrated mixture is subsequently subjected to multiple rounds of extrusion through polycarbonate membranes with various pore sizes. This is achieved by utilizing a combination of vortex mixing and ultrasonication techniques [32][33].



**Figure 3:** Film hydration technique for formation of invasomes

## VII. EVALUATION OF INVASOMES

- 1. Determination of Particle Size:** For the particle size determination zetasizer is used at the temperature of  $25 \pm 1^\circ\text{C}$ , it works on the principle of dynamic light scattering. The particle size should be under  $194 \pm 18$  nm for transdermal drug delivery. The zetasizer takes the reading upto 3 times and gives a mean value in form of  $Z_{avg}$ . The  $Z_{avg}$  is considered as the average size of the particles. [34][35]
- 2. Determination of Polydispersity Index (PDI):** The polydispersity index is measured by zetasizer. The polydispersity index should be less than 0.5, which indicates homogenous particle size distribution. Formulation that are having PDI greater the 0.5 will be considered as polydispersed indicating presence of various size of particles [36][37]
- 3. Zeta Potential:** The zeta potential provides information about the surface charge, stability and ability to interact with the skin. For determining the surface charge zetasizer is employed. The zeta potential is a measure of the intensity of attraction between adjacent particles that are similarly charged. A high zeta potential means stability and

ensures that the dispersion will not tolerate aggregation. The difference between stable and unstable. In most cases, unstable dispersion is set at a higher or lower value of 30mV. The presence of ethanol, which has a net negative effect surface charge and inhibits vesicle aggregation caused by electrostatic repulsion, is cause of a charge that is negative[38][39].

- 4. Drug Entrapment/ Entrapment Efficiency:** To calculate the drug entrapment High-Speed Centrifuge or Ultracentrifuge can be utilized. The supernatant obtained was appropriately diluted and analysed spectrophotometrically at the designated wavelength to measure the amount of drug present.[40,41,43]

$$\% EE = \frac{\text{Amount of total drug} - \text{Amount of free drug}}{\text{Amount of total drug}} \times 100$$

- 5. Drug Release and Release Kinetics:** The drug release from invasomes can be studied by performing *in-vitro* dissolution study. The kinetics of drug release can be determined using various kinetic equations: zero-order release kinetics, first-order release kinetics, and Higuchi model. The data obtained was calculated using different parameters. The parameters “*n*” and time component “*k*,” the release rate constant, and “*R*” the regression coefficient was determined by Korsmeyer-Peppas’s equation to understand the release mechanism [43][44].
- 6. Stability Analysis:** The stability of invasomes depend on the storage temperature. At room temperature the values of particle size and polydispersity index increases, which leads to aggregation or fusion of the vesicles during storages. The invasomes are stored at 4°C for 12 months. However, increase in storage time for 6 months shows significant increase in polydispersity and particle size value. [45][46][47][48]
- 7. Surface Morphology:** The surface morphology can be observed using Scanning Electron Microscopy (SEM) and transmission electron microscopy (TEM) can be utilized. Both TEM and SEM works on the principle of electron transmission, which provides a 2-Dimensional image of the particles. However field-emission scanning electron microscopy (FE-SEM) provides a more distinctive image by providing a 3-Dimensional image of the particles [49].
- 8. Skin Irritation and Sensation:** It is essential to evaluate for the safety purpose, side effects, skin irritation or any kind of adverse reaction of the invasomes. For these test animal and human model are taken for trails [50].
- 9. Drug Content:** The drug content of the formulation is estimated by UV V spectrophotometer and high-performance liquid chromatography (HPLC). In spectroscopic method of evaluation the formulation is centrifuged and the supernatant is collected which are then spectroscopically analysed to measure the amount of free drug which in turns gives the drug content [51].

**10. Skin Permeability Study:** A skin permeability study of a nano carrier involves investigating how effectively the nano carrier can penetrate the skin barrier and deliver its payload. It's crucial for assessing the carrier's potential in drug delivery or cosmetic applications. Different methods like Franz diffusion cells or *in vitro* skin models are commonly used for such studies [76].

## VIII. INVASOMES IN DESEASE TARGETING

**1. Hypertension:** Hypertension, a chronic medical condition, represents one of the most prevalent risk factors for cardiovascular disease. The treatment of hypertension involves a wide range of pharmacological categories of anti-hypertensive drugs. However, these medications have their own set of limitations, including poor permeability, solubility, bioavailability, and the potential for adverse side effects.

To mitigate these challenges, researchers have explored the use of suitable drug delivery systems and routes of administration. In the context of hypertension management, invasomes have emerged as a subject of study for the transdermal delivery of anti-hypertensive drugs [48]. A specific investigation focused on formulating a topical gel utilizing invasomes to deliver Olmesartan medoxomil.

The study indicated that administering Olmesartan medoxomil via the transdermal route in the form of invasomal gels resulted in improved bioavailability. This enhancement in bioavailability could potentially lead to a reduction in the frequency of dosing required for effective hypertension treatment. Consequently, transdermal delivery may offer advantages over traditional oral administration in the management of hypertension. [11].

**2. Acne:** Acne is a chronic inflammatory condition affecting the pilosebaceous units, with a significant role attributed to androgens in its development. This inflammatory disorder predominantly affects the facial, neck, chest, and back skin areas [49]. The progression of acne lesions can be categorized into four distinct stages. The onset of acne involves the release of inflammatory mediators, leading to the infiltration of CD4 cells and macrophages into the pilosebaceous region, consequently enhancing vascularization. This is followed by the formation of comedones due to alterations in the keratin layer. The third stage is characterized by an upsurge in sebum production, regulated by androgens. The final stage involves the colonization of follicles by *Propionibacterium acnes* [50].

Various therapeutic approaches, including oral antibiotics, topical retinoids, benzoyl peroxide, and antibiotics, have been employed to treat acne, albeit with limited efficacy [51]. Oral isotretinoin has proven effective in severe acne treatment, but it is associated with teratogenicity concerns [52]. Researchers have explored the potential of invasomes for efficient drug delivery via topical routes for acne treatment.

El-Nabarawi et al. in 2018 employed the film hydration method to formulate dapsone-loaded invasomes. Dapsone, known for its anti-inflammatory properties, has shown promise in acne therapy. Different terpenes, such as limonene, cineole, fenchone, and citral, were used in varying concentrations to create distinct sets of invasomes. The study examined the characteristics of the formulated invasomes and assessed the impact

of terpene concentration. The findings demonstrated that invasomes effectively facilitated the penetration of dapsons into deeper skin layers, making them a more efficient approach for acne treatment [23].

In 2018, Han HJ developed a topical anti-acne product based on invasomes and crude extracts of *Ocimum basilicum*. Their research indicated that invasome-based topical formulations of these crude extracts exhibited high efficiency and stability. Consequently, invasomes have played a pivotal role in advancing the drug delivery method for acne treatment, while also ensuring the anti-acne effectiveness of *Ocimum basilicum* extracts [53].

- 3. Cancer:** Cancer remains a formidable challenge in the field of modern medicine, demanding innovative approaches to treatment. Despite the availability of various chemotherapeutic drugs, their success rates are often limited, and they can entail significant side effects. As a result, there is a pressing need to explore novel therapeutic strategies for cancer treatment.

In a study conducted by Vidya et al. in 2019, researchers investigated the potential of invasomes, which are advanced deformable vesicular structures, for delivering anticancer medications. They focused on formulating invasomes loaded with anastrozole, an aromatase inhibitor used in the treatment of breast cancer in postmenopausal women. The formulation process involved the use of Phospholipon 80H, fenchone, and ethanol, utilizing the film hydration technique.

Several parameters, including shape, size, zeta potential, and entrapment efficiency, were rigorously evaluated to optimize the invasome formulation. Once the optimal formulation was identified, it was incorporated into a sodium carboxymethylcellulose gel to create a suitable invasomes gel [54].

The study's findings indicated that delivering anastrozole through invasomes as a drug delivery system significantly improved drug penetration and deposition within the skin. Moreover, the prepared invasomes exhibited substantial cytotoxicity against MCF-7 cell lines, suggesting their potential as a promising therapeutic option for postmenopausal women with breast cancer [55].

- 4. Erectile Dysfunction:** Erectile dysfunction is a medical condition primarily affecting men aged 40 and above, characterized by the inability to achieve and sustain a satisfactory penile erection for sexual intercourse [12]. Extensive scientific research has identified various factors contributing to erectile dysfunction. It has been categorized into three main types based on its underlying components: psychogenic, organic, and mixed psychogenic and organic [57]. Psychogenic erectile dysfunction can stem from a range of psychosocial factors, with performance anxiety (fear of sexual performance failure) being one of the most common psychological causes [58].

In the pursuit of effective treatments for erectile dysfunction, researchers and biomedical scientists have explored various therapeutic options. In this regard, invasomes have garnered attention as a potential approach. In a study conducted by Ahmed OAA and Badr-Eldin SM in 2019, avanafil-loaded invasomes were created using the Box-Behnken

experimental design [37]. Avanafil faces several challenges related to drug delivery, including poor water solubility, substantial first-pass metabolism, and reduced absorption in the presence of food [59]. The researchers evaluated the prepared invasomes for parameters such as entrapment efficiency, size, and morphology. They also investigated the impact of different concentrations of phospholipid, ethanol, terpene, and terpene type in the formulation on the characteristics of the invasomes.

- 5. Anti-Oxidant Therapy:** The human body naturally generates free radicals as byproducts of various metabolic processes. These radicals serve essential roles as signaling molecules and mediators in numerous physiological responses. However, certain free radicals, including reactive oxygen, nitrogen, and chlorine species, have the potential to inflict significant damage to cells [60]. To maintain a balanced environment, the body relies on its antioxidant defense system, which regulates the levels of these free radicals. Some components of this antioxidant defense system, such as vitamins E and C, as well as essential minerals like copper, zinc, and magnesium, are produced internally by cells. Additionally, various naturally occurring plant compounds, such as ferulic acid from grains like rice, wheat, and oats, as well as citric acid from citrus fruits, play crucial roles as antioxidants in cellular biology [61].

In a study conducted by Shah et al. in 2015, the researchers explored the combination of idebenone, an active pharmaceutical ingredient with antioxidant and anticancer properties, and azelaic acid, another API known for its antiacne activity. They employed different delivery systems, including liposomes, invasomes, and Leciplex, to formulate these drugs. Two distinct types of Leciplex were developed for both drugs, one incorporating cetyltrimethylammonium bromide (CTAB) and the other utilizing didodecyldimethylammonium bromide (DDAB). The researchers thoroughly evaluated various parameters such as shape, size, zeta potential, and entrapment efficiency for the liposomes, Leciplex, and invasomes containing both APIs. Dynamic light scattering analysis revealed that invasomes exhibited the smallest particle size for idebenone, with a polydispersity index of less than 0.1. In the case of azelaic acid as well, invasomes displayed the smallest particle size [30].

- 6. Psoriasis:** Psoriasis is a chronic inflammatory skin disorder characterized by the presence of erythematous and papulosquamous lesions, as well as the abnormal and excessive differentiation of keratinocytes [62]. Scientific literature has described four main types of psoriasis, which are plaques, pustular, guttate, flexural, and erythrodermic, with classification primarily based on the characteristics of the skin lesions [63]. The initiation of psoriasis is rooted in the activation of T lymphocytes in both the epidermal and dermal layers of the skin. Notably, in psoriasis, there is a predominant activation of T lymphocyte CD8<sup>+</sup> cells in the epidermis and CD4<sup>+</sup> cells in the dermis [19].

In a study conducted by Dragicevic-Curic et al., invasomal dispersions containing temoporfin, a hydrophobic photosensitizer beneficial for treating skin conditions such as basal cell carcinoma and psoriasis, were formulated. These invasome formulations consisted of 0.15% w/v temoporfin, 3.3% w/v ethanol, and 1% w/v concentrations of either a terpene mix (terpene mix 1, 2, 3, and 4) or a single terpene (cineole, citral, and d-limonene). The research demonstrated that invasomes can effectively deliver temoporfin

deep into the skin, making them a promising option for the treatment of skin diseases like basal cell carcinoma, psoriasis, and acne [64].

- 7. Alopecia:** Alopecia is a chronic inflammatory dermatological condition that affects hair follicles and is quite common. It results in hair loss in various patterns, which can include specific areas of the scalp, the entire scalp, or even the entire body. Consequently, alopecia is categorized into four main forms: androgenetic alopecia (male pattern alopecia), alopecia areata (characterized by hair loss in small circular patches on the scalp), alopecia totalis (involving total hair loss from the scalp), and alopecia universalis (resulting in hair loss across the entire body) [65]. While alopecia is not a life-threatening condition and is not physically painful, it can have a profound impact on the psychological well-being of affected individuals.

The exact cause of alopecia remains incompletely understood, but research in scientific literature has suggested a role for androgens, particularly dihydrotestosterone, in the development of androgenetic alopecia [66]. Alopecia areata has been associated with the invasion of T cells, including CD4+ and CD8+ cells, into hair follicles [67].

In a study conducted by Prasanthi D and K Lakshmi P in 2013, invasomes containing finasteride, a 5-reductase inhibitor, were formulated for transdermal administration via iontophoresis. The researchers prepared nine invasomal formulations using three different terpenes (limonene, carvone, and nerolidol) at concentrations of 0.5%, 1.5%, and 1%. These formulations were evaluated for various parameters, including lamellarity, size, shape, zeta potential, entrapment efficiency, and in vivo permeation. Most of the formulated invasomes exhibited a spherical shape and a unilamellar vesicle membrane structure [43]. The study's findings suggested that the iontophoresis approach could effectively facilitate the transdermal delivery of finasteride [35].

**Table 1: Therapeutic Application of Invasomes**

DRUG	APPLICATION	STUDY OUTCOME	REFERENCE
AVANAFIL	Treatment of erectile dysfunction	Optimized <u>invasomal</u> film improved the bioavailability and transdermal permeation of Avanafil	Osama A.A. Ahmed et al., 2019
IDEBENONE AZELAIC ACID	Antioxidant, anticancer, anti-acne	<u>LeciPlex</u> shows higher permeation of <u>idebenone</u> and <u>invasomes</u> exhibited higher permeation of azelaic acid	Sanket M. Shah et al., 2015
CURCUMIN	Anti-inflammatory, antioxidant, and anticancer activity	Physicochemical characteristics of the formulations influenced by terpene and Tween 20	<u>Duangjit S</u> et al., 2017
CURCUMIN	Anti-inflammatory, anti-carcinogenic	<u>Invasome</u> with 0.5% limonene improved intradermal penetration of curcumin	Lakshmi P et al., 2014
TEMOPORFIN	Photodynamic therapy	<u>Invasomes</u> containing a 1% <u>terpene</u> mixture decreased <u>tumor</u> size significantly by photodynamic therapy.	Dragicevic-Curic N et al., 2008
DAPSONE	Treatment of Acne	When compared to traditional liposomes, it demonstrated increased skin deposition and enhanced medication	<u>El-Nabarawi</u> MA et al., 2018

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		percutaneous absorption.	
<b>ISOTRETINOIN</b>	Delivery of Vitamin analog	Delivery of isotretinoin to the follicular unit and targeting pilosebaceous in this way results in effective treatment of eosinophilic pustular folliculitis	Dwivedi M et al., 2016
<b>ADAPALENE</b>	Acne treatment	Adapalene invasomal gel increases the drug's permeability across the membrane, enabling successful rapid drug release.	Targhotra M et al., 2020
<b>FINASTERIDE</b>	Enhancing skin permeation	Invasomes with an iontophoretic approach greatly improved finasteride penetration compared to aqueous solution.	Prasanthi D et al., 2013
<b>NITROXIDE TEMPO</b>	Measuring the antioxidative capacity	Invasomes improved measurement times of antioxidative capacity by two-fold	S.F. Haag et al., 2011
<b>FERULIC ACID</b>	Drug delivery through skin	Invasomes, Liposomes and Ethosomes were tested for ferulic acid and ethosomes showed high entrapment than invasomes and liposomes.	Chen M et al., 2010

<b>ISRADIPINE</b>	Delivery of Anti hypertensive agent	By administration of <u>isradipine</u> loaded <u>invasomal</u> trans gel, it was observed that blood pressure decreased in hypertensive rats caused by deoxycorticosterone acetate.	Qadri G et al., 2017
<b>VISMODEGIB</b>	Enhancing the Bioavailability and efficacy of anti cancer treatment of skin	In comparison to oral <u>vismodegib</u> , <u>vismodegib</u> loaded gel improved the drug's skin penetration, resulting in 3.59 times greater bioavailability and superior anticancer activity	Salem H et al., 2022
<b>2-METHOXYESTRADIOL AND APAMIN</b>	Suppression of A549 lung cancer cells	In relatively little dosages, it might easily penetrate the cell membrane and cause apoptosis.	Awan Z et al., 2022
<b>ECONAZOLE</b>	Antifungal Treatment	For the prolonged distribution of econazole to the area of the skin that is afflicted.	Patel DK et al., 2022
<b>PHENYLETHYL RESORCINOL</b>	Delivery of skin lightening agent with potent <u>antityrosinase</u> activity in deep skin tissues	<u>Invasomes</u> are more successful than traditional liposomes at delivering Phenylethyl Resorcinol into the deeper layers of the skin, making them ideal for skin lightening products.	<u>Amnuakit T et al.</u> ,2018

<b>CALCEINE CARBOXYFLUO RESCEIN</b>	Low-molecular weight hydrophilic model drugs	Calcein penetration improved two- and seven-folds by transfersomes and invasomes, respectively	Ntinenou et al., 2012
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## IX. PHARMACOKINETIC PERSPECTIVE OF INVASOMES

From the inception of drug-loaded systems, researchers have been dedicated to exploring their potential for *in vivo* studies, focusing on achieving optimal pharmacokinetic characteristics. These characteristics encompass crucial aspects such as targeted drug delivery, extended blood circulation time, efficient absorption, access to the target site, half-life, and clearance rate, among others [74]. Medications that exhibit these outstanding qualities are given serious consideration for use in therapeutic applications.

The uniqueness of invasomes has positioned them as a preferred choice for a wide range of pharmacological applications [43]. It's worth noting that an essential aspect in the development of any pharmaceutical product is the necessity for a comprehensive understanding of pharmacological and toxicological elements. Consequently, a fundamental design consideration for invasomes intended for targeted administration in therapeutic applications is the correlation between the *in vivo* biodistribution of invasomes and their pharmacokinetics [74].

In general, physicochemical factors like vesicle size, shape, aggregation, solubility, penetration enhancers, chemical composition, and more play a pivotal role in determining the biodistribution and pharmacokinetics of invasomes [14]. These characteristics can be modified using various techniques, including the use of terpene mixtures, microneedle application, iontophoresis, and more. Numerous studies have demonstrated that invasomes must achieve adequate absorption from the application site to ensure bioavailability [8].

Invasomes have been effectively employed for the delivery of active pharmaceutical agents through cellular membranes and the skin. The choice of penetration enhancers, lipids, and various advanced techniques such as dermarolling and iontophoresis significantly impacts the absorption of invasomes. These factors have been explored across different types of vesicles and their typical dosage forms. Invasomal formulations are versatile, serving both systemic and local applications. Several medications are administered topically, accumulating in local tissues and eventually entering the circulatory system [8][75].

Interestingly, invasomes enhance skin permeability while minimizing adverse effects associated with low-dose medication administration. They have demonstrated diverse applications as a topical carrier for both local and systemic drug delivery, including effective targeting of medications to the skin by facilitating penetration across the stratum corneum and deposition in the epidermal and dermal layers. Terpene compounds have been extensively employed in invasome formulations, encompassing a range of concentrations, all while considering safety and toxicity concerns.

Moving forward, the establishment of comprehensive standards for selecting appropriate concentration ranges and types of terpenes for invasome production will be essential. Despite the availability of various synthesis methods, achieving repeatability and scalability in nanoformulations of invasomes remains a significant challenge. This is primarily due to their unique ability to enhance drug penetration across the stratum corneum and target specific skin layers, making them a versatile and promising tool in the field of pharmaceutical delivery [8][75].

## X. CONCLUSION

Invasomes are a novel drug delivery system with enormous potential to transform healthcare and enhance patient outcomes. They are crucial allies in the fight against complicated diseases because of their capacity to enable targeted and individualized therapy, deliver several medications at once, and get past biological barriers. The integration of invasomes into nanotechnology and vaccine development further expands their scope and potential public health implications. The future looks bright for invasomes as research and technology advance, providing innovative solutions to longstanding drug delivery challenges. However, careful safety assessment, a thorough regulatory approval process, and addressing scalability issues are essential to realize the full potential of invasives and usher in a new era of advanced therapies. Invasomes have the potential to revolutionize healthcare and influence the course of medicine if academics, business, and regulatory organizations work together continuously.

## XI. FUTURE PROSPECTS OF INVASOMES

Invasomes, a promising class of lipid-based drug delivery systems, have garnered significant attention in recent years due to their potential to revolutionize the pharmaceutical industry. These vesicular carriers offer unique advantages, such as improved drug stability, enhanced permeation, and targeted delivery to specific tissues or cells.

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