**Recent trends in the emergence of invasomes for transdermal delivery of drugs**

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**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 actives 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 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

1. **INTRODUCTION**

The necessity of novel method for drug delivery has been increasing day by day to promote patient compliances. Despite occupying 70% of the market, tablet dosage form has some major drawbacks such as prone for enzymatic degradation, hepatic metabolism which in turn effects the performance of drug majorly reducing its bioavailability. The last 20 years have seen a surge in interest towards transdermal drug delivery systems (TDDS) due to their significant advantages over traditional and oral dosage forms. The strategy to maximize the drug's stability over the skin and its availability into the systemic circulation is by enhancing circulation, skin absorption and retention [1]. The main goal of the transdermal drug delivery system is to get around the challenges presented by the oral route. Improve bioavailability with controlled drug release, fewer adverse effects, and avoidance of first-pass metabolism are the major benefits of TDDS. The TDDS is a unique replacement for standard delivery method that overcome issues with most of the conventional systems. In TDDS, a patch or other system that permeate drug transversely through the skin barrier in a relatively small amount and delivers it to the targeted site. The drug reaches the bloodstream through the skin during the distribution process obtaining a larger concentration in blood [2]. Overwhelming the skin's natural transport barrier is the main challenge in designing TDDS. The first report on the potential value of liposomes for topical therapy was made in 1980 by Mezei and Gulasekharam. Since then, scientists have concentrated on creating lipid vesicles as drug delivery vehicles for the skin. These lipid vesicles' capacity to get over the stratum corneum’s (SC) threshold and retain in the thickest levels of stratum corneum while releasing their contents has practical benefits. However, lipid vesicles that have been produced are still a contentious class of cutaneous and transdermal carriers [3]. Both topical and cutaneous drug delivery have shown interest in the use of vesicular systems based on lipids. Vesicles were given special consideration for effective delivery of drugs by bridging the stratum corneum barrier in intact skin. This vesicular system can be divided into two groups according to the primary mechanisms and how they interact with the skin. The first category consists of those that maintain highly flexible bilayers, either by partnering with certain hydrophilic solutes or by including edge activators in the bilayers. These vesicles operate as drug carriers by penetrating intact skin through hydrophilic routes. The second group vesicles, on the other hand, feature permeability enhancers and, as a result have fluid bilayers. These vesicles serve as drug invaders into the skin as well. The stratum corneum is altered as a result of the permeability enhancers present in the vesicle structure working in concert [4]. The advantages rationalizing the use of lipid vesicles for topical and transdermal application include: (i) the lipophilic nature of the vesicle wall may serve as organic substances for poorly aqueous soluble substances as being lipophilic in nature they present superior penetration enhancing properties; and (ii) the lipid vesicles do not release the incorporated molecule instantaneously and can assist as indigenous garage system. Despite the listed advantage, the system suffers from poor permeability of drugs of molecular weight more than 500 Da [5]. The low permeability of drug was addressed by development of vesicular systems, which sparked a series of vesicle alterations, including the emergence of deformable vesicles. Liposomes, transfersomes, glycerosomes, niosomes, ethosomes, and invasomes are among the components of these deformable lipid vesicles. Some of them have already transitioned from the lab to the marketplace. These nanovesicles can be used to deliver medications that are both hydrophilic and lipophilic system. Delivery of drugs/diagnostics to various organs/tissues/cells via nanovesicles is considered to be a topic of long-standing interest with new challenges being posed to formulation scientists with new developments. Physiological and pathological conditions are the key challenge in this context, which make the delivery of drugs extremely difficult at the disease locus and makes their precise delivery ineffective [6]. Invasomes are a novel method of drug delivery that are phospholipid-based nanoscale vesicular systems composed of phosphatidylcholine, ethanol, terpenes or a blend of terpenes with considerably more percutaneous permeation than standard liposomes [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 invasomes extend a synergistic impact which promotes invasomal vesicle penetration through the skin [11][12]. These are novel vesicular systems, when compared to other traditional vesicles, significantly increase the transdermal penetration of active pharmacological compounds. Phospholipids, ethanol, and terpenes, or mixtures of terpenes, make up the architecture of these vesicles. These ingredients had good penetration qualities and served as an effective transdermal penetrator.

1. **STRUCTURE OF INVASOMES**

Invasomes are soft liposomal vesicles that act as potential transporters with enhanced skin penetration. They contain small amounts of ethanol and terpene or terpene mixtures [8]. These special lipid vesicles are composed of water, terpenes or a combination of terpenes (such as citral, cineole, limonene, and eugenol; 1-5% v/v), low concentrations of ethanol (3% to 3.3% v/v), and phospholipids (phosphatidylcholine, phosphatidylserine, soya phospholipid, egg lecithin). Terpenes, with the general formula (C5H8)n, improve the percutaneous absorption of hydrophilic and hydrophobic compounds. Terpenes are natural ingredients of essential oils that are widely employed as penetration enhancers. Terpenes, on the other hand, have the added benefit of being non-irritating to the skin at low doses. Terpenes are also considered generally safe by the FDA [14].



**Figure 1: Structure of Invasomes**

**A. Ethanol:** To improve permeability, ethanol can be utilized. Vesicles in nano-vascular systems have a major effect due to their specific size, zeta potential, entrapment efficacy, and skin permeability. According to numerous studies, the size and entrapment efficacy of vesicles decrease as ethanol concentration increases. The vesicles disintegrate as the ethanol concentration rises. Increase in ethanol levels reduce membrane thickness and hence vesicular volume. It can also increase the fluidity of nanovesicles as well as disrupts the densely packed structure of SC lipids, causing them to split. Because ethanol influences the structure of keratinize or lipophilic domains, lipid transition temperatures can be lowered. In comparison to liposomal nanovesicles, ethanol-based nanovesicles have a softer and less rigid structure. Because of their negative surface charge and electrostatic repulsion, ethanol nanovesicles may be more stable in storage [10].

**B. Terpenes:** Terpenes or terpene mixtures at small doses have also been proven to be penetration enhancers (also known as sorption boosters or accelerants) in transdermal drug delivery systems, allowing them to enter the skin and reduce barrier resistance. Terpenes have minimum risk of skin irritation; hence they are classed as "Generally Recognized as Safe" (GRAS). Terpene's capacity to permeate the skin is influenced by their solubility, the dissolution of lipid and protein layers, and the loss of skin micro-ingredients. Terpene transdermal formulations look to be highly promising as a result, higher deposition into the skin with mTHPC (mTHPC) at 1% (w/v) in 2008 [15].

**C. Phospholipids:** In phospholipids, hydrophobic acyl chains are connected to the alcohol. Distinctions in head groups, aliphatic chains, and alcohols allowed a diverse range of phospholipids to survive. As a result, the modified phospholipid sources benefit the phospholipid classes. Natural and synthetic phospholipids, such as PEGylated Phospholipids, are used in a variety of formulations, including those for skin care products. Even hydrogenated phosphatidylcholine has been described as a way for forming nanovesicles [16].

1. **SKIN PERMEATION MECHANISM OF INVASOMES**

Invasomes are deformable new vesicles made by adding terpenes, which improve the penetration of active pharmacological molecules as compared to regular liposomes. These vesicles are delicate and have a high membrane fluidity. The presence of terpenes and ethanol distinguishes invasomes from liposomes [17]. There are two probable penetration enhancement mechanisms of invasomes: first, the invasomes themselves deed as the importer systems for drug wherein the integral vesicles go into the stratum corneum which transported the encapsulated drug into and across the skin [18]. The affinity of hydrophilic phospholipids to flee water-deprived settings is assessed as the primary dynamic force for deformable lipid vesicles exiting the skin via this mechanism [19]. Another putative mechanism for enhanced penetration of deformable vesicles is the presence of terpenes, which may improve drug permeability by disrupting stratum corneum lipid wrapping [20]. According to the results, the active drug molecules would first be released from the vesicles before entering deeper layers of skin or reaching the systemic circulation in the dermis. Following that, a non-occlusive claim is required to improve drug administration over the skin via deformable vesicles. The diminishing of transepidermal osmotic gradient in this application mode causes deformable vesicles to lose their diffusion driving power [21]. The deformable vesicles can then behave as penetration enhancers by interacting with the stratum corneum and modifying the intercellular lipid lamellae. The lipophilicity of the drug may affect drug penetration augmentation via this route. Depending on the physicochemical properties of the drug, the interaction of the two systems plays a crucial influence in drug penetration [22].

1. **INVASOMES BASED TRANSDERMAL DRUG DELIVERY**

A combination of ethanol and terpene mixture progressions focuses on increasing the invasomes penetration impact. Several researchers devised and documented numerous strategies and vesicular systems to improve skin penetration of active medicinal molecules via topical applications. As TDDS, invasomes of a novel-nanovesicle system gains notice. The great fluidity of phospholipids, as determined by Electron Spin Resonance (ESR), Differential Scanning Calorimetry (DSC), and cryoelectron microscopy, is expected to be a crucial dynamic strategy for invasomes' strong penetration-enhancing potential. Regardless of fluidity, additional phenomena are also engaged in the enhanced skin penetration mechanism of invasomes [23]. Invasomes and core-multishell (CMS) nanotransporters are well-established and widely used for drug delivery technologies in dermatology. Haag et al. (2011) evaluated invasomes and CMS nanotransporters for topical delivery of Protocatechuic acid (PCA) [24]. The results of Electron Paramagnetic Resonance Spectroscopy (EPRS) demonstrated that PCA was localized in the hydrophilic compartments of CMS nanotransporter solution and the invasomes dispersion. When compared to PCA solution alone, invasomes increased PCA penetration by 1.9 times and CMS by 2.5 folds. The step-by-step removal of the SC by tape stripping approach resulted in the deepest PCA penetration for invasomes. These findings indicated that the skin penetrating capabilities of both invasomes and CMS nanotransporters might be used for PCA or hydrophilic medication transdermal administration [25].

1. **INVASOMES VS LIPOSOMES**

Liposomes are phospholipid-based vesicular structures that facilitate the encapsulation of lipophilic, hydrophilic, and amphiphilic medicines by including anionic, cationic, and neutral lipids and cholesterol. Lipophilic compounds are inserted in the inner lipid bilayer, hydrophilic drugs in the aqueous core, and amphiphilic drugs in the vesicle interlayer [26][27]. Invasomes, on the other hand, are flexible liposomes made up of phospholipids, ethanol, and one terpene molecule or a combination of terpenes. Ethanol enhances the fluidity of lipids in the vesicle structure, resulting in a soft shape that is less stiff than typical liposomes and, as a result, improves skin permeability [28]. Terpenes, on the other hand, have been found to increase penetration by breaking the tight structure of SC lipids [29].

1. **FORMULATION OF INVASOMES**

**A. 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. Polycarbonate membranes with different pore sizes are utilized to extrude the multilamellar vesicles. Polycarbonate membranes are repeatedly perforated by invasomes dispersions [30][31].

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

**B. Film hydration technique** For the preparation of invasomes, traditional film hydration method can be employed. Firstly, the ethanol and chloroform at a ratio of 2:1 v/v is dissolved in phospholipid solution. Further, Rotary Flask Evaporator is used to dry this mixture at 50°C, also operated by reducing the pressure from 500 to 1 mbar that leaves a thin film layer around the wall of flask. The film is subjected to two hours of room temperature vacuum (1 mbar) before being flushed with nitrogen. To prepare invasomes from the film either PBS of pH 7.4 and terpenes/ ethanol combination or single terpene are added. After cooling at room temperature and 30 minutes of hydration, polycarbonate membranes with varied pore sizes are repeatedly extruded using a vortex and ultrasonicator for size the resultant vesicles [32][33].



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

1. **EVALUATION OF INVASOMES**

**A. Determination of Particle size** For the particle size determination, zetasizer is used at the temperature of 25± 1◦C, it works on the principle of dynamic light scattering. The particle size should be under 194 ± 18 nm for transdermal drug delivery. The zetasizer takes the reading up to 3 times and gives a mean value in form of Zavg. The Zavg is considered as the average size of the particles [34][35].

**B. 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 polydisperse indicating presence of various size of particles [36][37].

**C. 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].

**D. 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 = $\frac{Amount of total drug – Amount of free drug}{Amount of total drug }$ X 100

**E. 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-Peppa’s equation to understand the release mechanism [43][44].

**F. 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].

**G. 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].

**H. 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].

**I. 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].

**J. 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].

1. **INVASOMES IN DESEASE TARGETING**

**A. HYPERTENSION**  Hypertension is a chronic medical condition, one of the most frequent risk factors for cardiovascular disease. There are numerous pharmacological categories of anti-hypertensive drugs available for the treatment of hypertension. However, these anti-hypertensive drugs have drawbacks such as low permeability, solubility, bioavailability, unfavourable side effects, and so on. These difficulties can be countered to some extent by selecting the appropriate drug delivery system and route of administration. Invasomes have also been studied for transdermal delivery of anti-hypertensive drugs [48]. A topical gel composed of invasomes of Olmesartan medoxomil was formulated by a group of researchers. According to the study, administering Olmesartan medoxomil via transdermal route in the form of invasomal gels enhanced bioavailability, which may lead to a reduction in dosing frequency. As a result, transdermal delivery may be preferable than oral administration [11].

**B. ACNE** Acne is a pilosebaceous unit infammatory chronic illness. Androgens are thought to have a key role in the development of acne. This infammatory disorder primarily affects the skin of the face, neck, chest, and back [49]. The progression of acne lesions can be split into four distinct stages. Acne formation begins with the production of inflammation mediators (CD4, and macrophages infiltrate the pilosebaceous area and enhance vasculature). This is followed by the creation of comedones as a result of change in production of the keratin layer. The third stage is distinguished by an increase in sebum production, which is regulated by androgens. The final stage is Propionibacterium acnes colonization of follicles [50]. Several therapeutic techniques, including oral antibiotics, topical formulations of retinoids, benzoyl peroxide, and antibiotics have been used to treat acne but with limited efficacy [51]. Isotretinoin taken orally proved effective for treating severe acne, although it has been linked to teratogenicity [52]. Researchers have also looked into invasomes for efficient drug delivery via a topical route for the treatment of acne.

El-Nabarawi et al. 2018 used the film hydration approach to create dapsone-loaded invasomes. According to different scientific literature investigations, dapsone possesses anti-inflammatory activity that has been shown to be beneficial in acne therapy. Four different terpenes, limonene, cineole, fenchone, and citral, were employed in different concentrations to create different sets of invasomes. They analysed the formulated invasomes and determined the effect of terpene concentration on its characteristics. The study discovered that invasomes can efficiently transfer dapsone into the deeper layers of skin, making them a more efficacious acne treatment technique [23]. Han HJ 2018 developed a topical antiacne product based on invasomes and crude extracts of *Ocimum basilicum*. According to their findings, invasomes-based topical formulations of crude extracts are highly efficient and stable. As a result, invasomes enabled development in the drug delivery method for acne treatment while also ensuring the antiacne effectiveness of *Ocimum basilicum* extracts [53].

**C. CANCER** Cancer is one of the most difficult diseases to treat in modern medicine. For the treatment of cancer, many therapeutic options involving the use of various chemotherapeutic drugs are available. However, many of these techniques still have a low success rate, and the use of these strategies and chemotherapeutic medicines has been linked to a number of significant side effects. As a result, it is required to develop or seek out newer therapeutic strategies and test them for their suitability in cancer treatment. Researchers also assessed the capacity of invasomes, which are innovative deformable vesicular structures, to transport anticancer medicines.Vidya et al. 2019 formulated anastrozole (aromatase inhibitor)-loaded invasomes using the film hydration approach to treat breast cancer in postmenopausal women. Phospholipon 80H, fenchone, and ethanol were used to prepare invasomes. The shape, size, zeta potential, and entrapment efficiency of the prepared invasomes were all assessed. Based on the results of these trials, the best invasomes formulation was chosen and put into the sodium carboxymethylcellulose gel to create an appropriate invasomes gel [54]. The study concluded that delivering anastrozole using invasomes as drug delivery system enhanced drug penetration and drug deposition within the skin. The prepared invasomal also displayed significant cytotoxicity against MCF-7 cell lines and can thus be used as a viable therapy alternative for postmenopausal women with breast cancer [55].

**D. ERECTILE DYSFUNCTION** Erectile dysfunction is a medical issue that primarily affects men over the age of 40 [56]. It is defined as the inability to achieve and maintain sufficient penile erection for satisfactory sexual intercourse [12]. Several factors have been identified and described as possible causes of erectile dysfunction in scientific literature investigations. Erectile dysfunction was classified into three kinds based on the components involved: psychogenic, organic, and mixed psychogenic and organic [57]. Psychogenic erectile dysfunction can be caused by a variety of psychosocial reasons. One of the most common psychological causes of erectile dysfunction is performance anxiety (fear of failing during sexual intercourse) [58]. To cure erectile dysfunction, researchers and biomedical scientists have researched and implemented a number of treatment options. Invasomes have also been studied for their potential use in the treatment of erectile dysfunction. Using the Box-Behnken experimental design, Ahmed OAA and Badr-Eldin SM 2019 created avanafil invasomes [37]. Several drug-related and body-related problems, such as poor water solubility, significant first pass metabolism, and decreased absorption in the presence of foods, hampered avanafil's successful drug delivery [59]. They assessed the prepared invasomes for entrapment efficiency, size, and form. They calculated the effect of phospholipid, ethanol, terpene, and terpene type concentrations in the formulation on the shape, size, and entrapment efficiency of invasomes.

**E. ANTI-OXIDANT THERAPY** The human body produces free radicals as a byproduct of several metabolic processes. These radicals function as both signalling molecules and mediators in a variety of physiological responses. However, reactive oxygen, nitrogen, and chlorine species are examples of free radicals that have the potential to seriously harm cells [60]. The body's antioxidant defence system was in charge of regulating the amount of these free radicals in the environment. Some of these antioxidant defence system's components, such as vitamins E and C and minerals copper, zinc, and magnesium, are produced by the cell through endogenous mechanisms. Numerous naturally occurring plant substances, such as ferulic acid from rice, wheat, and oats and citric acid from citrus fruits, are vital antioxidants needed by biological cells [61]. Idebenone, an active pharmaceutical ingredient with antioxidant and anticancer activity and azelaic acid, another API with antiacne activity, were combined to create liposomes, invasomes, and Leciplex by Shah et al. 2015. For both drugs, two distinct kinds of Leciplex were developed, the first using cetyltrimethylammonium bromide (CTAB) and the second using didodecyldimethylammonium bromide (DDAB). They evaluated the form, size, zeta potential, and entrapment efficiency of the liposomes, leciplex, and invasomes of both APIs. The examination of particle size using the dynamic light scattering method revealed that invasomes have the smallest particle size for idebenone, with a polydispersity index of less than 0.1. Invasomes also have the lowest particle size when it comes to azelaic acid [30].

**F. PSORIASIS** A chronic inflammatory skin disorder or cutaneous illness known as psoriasis causes erythematous and papulosquamous lesions as well as abnormally and excessively differentiating keratinocytes [62]. The four distinct kinds of psoriasis described in scientific literature studies include plaques, pustular, guttate, flexural, and erythrodermic [63]. This classification was based mostly on the characteristics of the lesion that had formed over the skin. T lymphocyte activation in the epidermal and dermal areas was the physiological cause of the beginning of psoriasis. In the case of psoriasis, predominant T lymphocyte CD8+ activation in the epidermis and CD4+ activation in the dermis were found [19]. Invasomal dispersions containing temoporfin (a hydrophobic photosensitizer helpful in treating skin conditions like basal cell carcinoma and psoriasis) were created by Dragicevic-Curic et al. 0.15% w/v, 3.3% w/v of 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). Invasome formulations can deliver temoporfin efficiently deep into the skin and therefore can be highly beneficial for treatment of skin diseases like basal cell carcinoma, psoriasis, acne, etc. [64].

**G. ALOPECIA** Alopecia is a chronic inflammatory dermatological condition that affects the hair follicles and is fairly frequent. Alopecia patients may experience hair loss from specific areas of the scalp, the entire scalp, or the entire body. Accordingly, there are four different forms of alopecia: androgenetic alopecia (male pattern alopecia), alopecia areata (hair loss from the scalp in small circular patches), alopecia totalis (hair loss from the entire scalp), and alopecia universalis (whole body hair loss) [65]. Although alopecia is not a life-threatening illness and is not painful, however, it has a profound effect on the patient's mentality. The cause of alopecia is not fully understood, but scientific literature research has provided evidence that androgens, particularly dihydrotestosterone, have a role in the onset of androgenetic alopecia [66]. Alopecia areata has been linked to T cell invasion of hair follicles (CD4+ and CD8+) [67]. Invasomes of finasteride (5-reductase inhibitor) were formulated by Prasanthi D and K Lakshmi P 2013 for iontophoresis-based transdermal administration. They prepared nine invasomal formulations using three terpenes (limonene, carvone, and nerolidol; 0.5%, 1.5%, and 1%) for the formulation. For lamellarity, size, shape, zeta potential, entrapment effectiveness, and *in vivo* permeation, they examined each formulation. The majority of the produced formulations had a spherical shape and a unilamellar vesicle membrane wall [43]. The study found that the iontophoresis approach may effectively delivered finasteride through the transdermal route [35].

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| Drug**Table 1: Therapeutic application of invasomes** | APPLICATION | STUDY OUTCOME | REFERENCE |
| Avanafil | Treatment of erectile dysfunction | Optimized invasomal film improved the bioavailability and transdermal permeation of Avanafil | Osama A.A. Ahmed *et al.,*2019 |
| Idebenone Azelaic acid | Antioxidant, anticancer, anti-acne | LeciPlex shows higher permeation of idebenone and invasomes 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 | Duangjit S *et al.,* 2017 |
| Curcumin | Anti-inflammatory, anti-carcinogenic | Invasome with 0.5% limonene improved intradermal penetration of curcumin | Lakshmi P *et al.,* 2014 |
| Temoporfin | Photodynamic therapy | Invasomes containing a 1% terpene mixture decreased tumor 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 percutaneous absorption. | El-Nabarawi MA *et al.,* 2018 |
| Isotretinoin | Delivery of Vitamin analogue | 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* |
| Adapalene | Acne treatment | Adapalene invasomal gel increases the drug's permeability across the membrane, enabling successful rapid drug release. | Targhotra M *et al.,* 2020 |
| Finasteride | Enhancing skin permeation | Invasomes with an iontophoretic approach greatly improved finasteride penetration compared to aqueous solution. | Prasanthi D *et al.,* 2013 |
| Nitroxide TEMPO | Measuring the antioxidative capacity | Invasomes improved measurement times of antioxidative capacity by two-fold | S.F. Haag *et al.,* 2011 |
| Ferulic Acid | 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 |
| Isradipine | Delivery of Anti- hypertensive agent | By administration of isradipine loaded invasomal trans gel, it was observed that blood pressure decreased in hypertensive rats caused by deoxycorticosterone acetate. | Qadri G *et al.,* 2017 |
| Vismodegib | Enhancing the Bioavailability and efficacy of anti-cancer treatment of skin | In comparison to oral vismodegib, vismodegib loaded gel improved the drug's skin penetration, resulting in 3.59 times greater bioavailability and superior anticancer activity | Salem H *et al.,* 2022 |
| 2-methoxyestradiol and Apamin | 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 |
| Econazole | Antifungal Treatment | For the prolonged distribution of econazole to the area of the skin that is afflicted. | Patel DK *et al.,* 2022 |
| Phenylethyl Resorcinol | Delivery of skin lightening agent with potent antityrosinase activity in deep skin tissues | Invasomes are more successful than traditional liposomes at delivering Phenylethyl Resorcinol into the deeper layers of the skin, making them ideal for skin lightening products. | Amnuaikit T *et al.,*2018 |
| Calceine Carboxyfluorescein | Low-molecular weight hydrophilic model drugs | Calcein penetration improved two- and seven-folds by transfersomes and invasomes, respectively | Ntimenou  *et al.,* 2012 |

1. **PHARMACOKINETIC PERSPECTIVE OF INVASOMES**

Since the beginning, the drug-loaded system has been investigated for in vivo studies that call for the best pharmacokinetic characteristics, such as active agent delivery to a particular location, blood circulation time, correct absorption, access to the target site, half-life clearance, etc. And we saw that the medications that exhibited the aforementioned outstanding qualities were given consideration for use [74]. The research indicated that invasome's distinctiveness is what is making it a popular choice for several pharmacological applications [43]. It's interesting to note that a crucial stage in the creation of any pharmaceutical product is the forthcoming requirement for fundamental knowledge of pharmacological and toxicological elements. Therefore, a crucial design element for invasomes intended for targeted administration in therapeutic applications might be the correlation between in vivo biodistribution of invasomes and its pharmacokinetics [74]. Generally speaking, physicochemical factors such as vesicle size, shape, aggregation, solubility, penetration enhancers, chemical compositions, etc., affect the biodistribution and pharmacokinetics of invasomes. [14] It may be altered using a variety of techniques, including the use of terpene mixtures, the microneedle technique, iontophoresis, etc. Numerous studies showed that the invasome needed adequate absorption from the application site in order for it to be bioavailable [8]. Invasomes have been employed to distribute the active medicinal substance both via cellular membranes and the skin, to put it briefly. The content and kinds of penetration enhancers, lipids, and various sophisticated techniques (such as derma rolling and iontophoresis) are key determinants of how well invasome is absorbed. It has been verified utilizing several special kinds of vesicles and their typical dose form. Invasomal formulation can also be used for systemic and local applications. Several medications are delivered topically. According to certain research, the drug accumulates in the local tissue and is absorbed by the circulatory system [8][75]. Curiously, invasomes increase skin permeability and decrease the adverse effect connected to using the medication at low dose medication dosage is necessary. Invasomes are showing a variety of uses as a topical carrier for local and systematic drug delivery, including effective skin targeting because it improves the penetration of medications across the SC and deposits them in both epidermal and dermal layers. A variety of terpene compounds have reportedly been employed in invasomes with varying concentration ranges while also taking into account safety and toxicity concerns to develop the pioneered invasomes. In the future, it will be necessary to create broad standards for choosing a typical concentration range and terpene kinds for invasome manufacture. Although there are several synthesis methods available, the repeatability and scalability of invasomes in nanoformulations are a big challenge. Because it enhances the penetration of drugs across the SC and deposits them in both epidermal and dermal layers, invasomes are demonstrating a range of functions as a topical carrier for local and systematic drug delivery, including effective skin targeting. The developed invasomes were purportedly created using a variety of terpene chemicals in a range of concentrations while also taking into account toxicity and safety issues. Broad guidelines will need to be developed in the future for selecting a typical concentration range and terpene types for invasome production. The repeatability and scalability of invasomes in nanoformulations remain a significant issue, despite the availability of numerous synthesis techniques.

1. **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.

1. **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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