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A REVIEW ON INVASOMES: NOVEL VESICLES FOR TRANSDERMAL DRUG DELIVERY

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Abstract:

Transdermal drug delivery refers to the drug administration route through the skin that achieves the local or systemic treatment approved for the clinical use. It is the third-largest drug delivery system after oral administration and injection. The advantage of transdermal route is that the administration route of the drug is convenient and could reduce the fluctuations of blood drug concentration and toxic side effects. What is more the drug could bypass the first-pass side-effect of the liver to prevent the drug from being destroyed in gastrointestinal tract. Scientists are constantly looking for the introduction of unique drug delivery systems for the existing drug molecule. Since the skin is one of the primary and essential organs of the human body. It needs successful research development for the delivery of drug. While the skin is assumed a human body's multifunctional organ. It has minimal permeability across the stratum corneum. Since, this is an influential barrier for the active agent. Invasomes are novel vesicular systems that exhibit improved trans dermal penetration compared to conventional liposomes due to the presence of mixture of phospholipids, terpenes and ethanol in their structure. The rate of penetration of invasomes significantly greater than that of liposomes and Ethosomes.

The main advantages of these invasomes are lies in their ability to increase the permeability of the drug into the skin. And decreases the absorption into the systemic circulation. Thus limits the activity of various drugs within skin layer.

Key words: Invasomes, terpenes, phosphatidylcholine, transdermal drug delivery.

Introduction:

Transdermal drug delivery provides avoidance of first pass metabolism of drug. And it is an invasive method [1]. The main disadvantage of transdermal drug delivery is, which limits the diffusion rate of drug across the stratum corneum. This stratum corneum acts as a barrier and this barrier is structurally similar like brick wall [2,3]. Stratum corneum contains keratin rich Coenocytes as the bricks surrounded by the intracellular lipid lamellae [4]. Lipid lamella acts as barrier properties of stratum corneum [5]. Many methods (or) approaches are been introduced to disrupt stratum corneum. Such as chemical and mechanical methods like iontophoresis, micro needles and vesicular drug carriers like liposomes, noisome, transfersomes, ethosomes, flexosomes, vesosomes and polymerosomes [6].

Among all these methods, the novel vesicular carrier systems like invasomes are exhibit improved transdermal penetration when compared to conventional liposomes. These vesicles contains phospholipids, ethanol and terpenes in their structure [7, 8].

Conventional liposomes are not approved as appropriate system for transdermal delivery as they unable to permeate the inner layer of skin and their effects remains limits to the upper layer.

Novel elastic vesicles containing penetration enhancers are superior to conventional liposomes. Novel elastic vesicles are named as transfersomes. Which improves interaction with skin and better drug penetration [9,10] and these were developed by cevcetal in 1990s.

Niosomes are prepared mostly by non-ionic surfactant and cholesterol and ethosomes containing high amount of ethanol in their structure. Have displayed as potential drug carriers.

Invasomes are novel and flexible vesicles containing mixture of soy phosphatidylcholine (PC), terpenes Lysol phosphatidylcholine and ethanol which improves skin penetration comparison with liposomes, transfersomes niosomes and ethosomes. Terpenes in invasomes are hydrocarbon compounds of essential oils from many plans. These vesicles are deformable by addition of terpenes which increases fluidity of the lipid bilayers of the skin [11,12,13,14]. Thus, creates ability to permeate through skin layers. Enhances the ability of invasomes which exerts their effect by fluidizing bilayers structure of stratum corneum lipids and disrupting lipids and intracellular protein interaction [15]

Advantages:

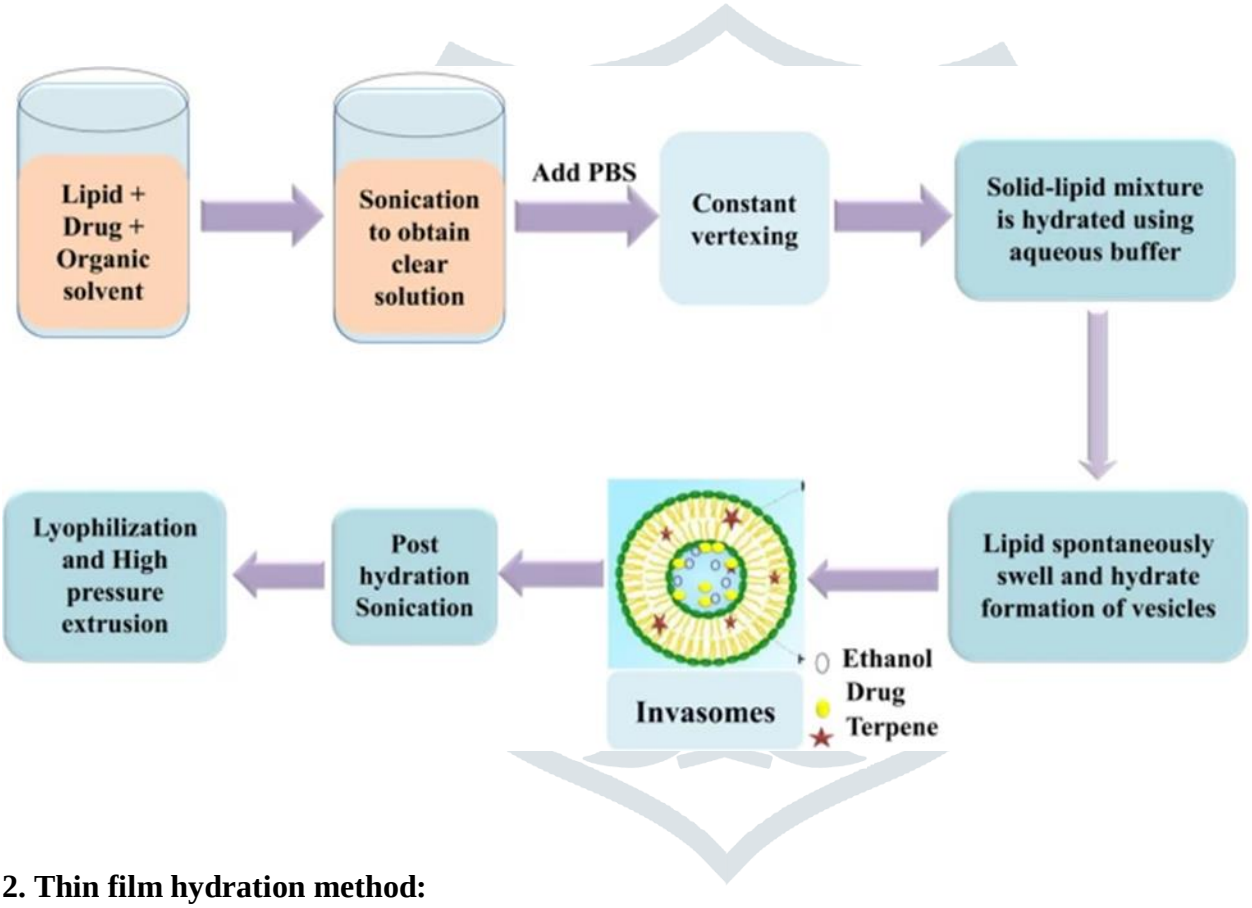
1. Non-invasive technique of drug delivery.[16]
2. Enhances permeation of drug through the skin for transdermal drug delivery. [17]
3. Contains non-toxic materials in formulation.[17]
4. Delivery of both hydrophilic [18]and lipophilic drugs.[19]
5. Patient compliance (as the drug can be administered as semi solid form like gel or cream).[17]

6. Simple method for drug delivery in comparison with iontophoresis, phonophoresis, and other complicated methods.[17]

Method of preparations:

1. Mechanical dispersion:

Drug and terpene or mixtures of terpenes are dissolved in ethanolic phospholipid solution. The mixture is vortex for 5 minutes and then sonicated for 5 minutes in order to obtain clear solution. Phosphate buffer saline (PBS) (Ph:7.4) is added to the solution by a syringe under constant vortexing is continued for additional 5 minutes to obtain final invasomal preparation. [20,21,22]



2. Thin film hydration method:

Invasomes can also be prepared by the conventional film method. Phospholipids in ethanol are dissolved in methanol: Chloroform (2%v/v). This mixture is dried to a thin film by slowly reducing the pressure from 500 to 1mbar at50°c using the rotary flash evaporator. The film is kept under vacuum (1mbar) for 2 hours at room temperature and subsequently flushed with nitrogen. Then the film is deposited in either hydrated for 30 mins at lipid transition with a mixture of phosphate buffer (Ph:7.4) containing ethanol and terpenes or it is hydrated using phosphate buffer (Ph:7.4) and after cooling to room temperature, ethanol and single terpene o or a terpene mixture are added in order to obtain invasomes.[18,23]

Penetration Mechanisms of Invasomes:

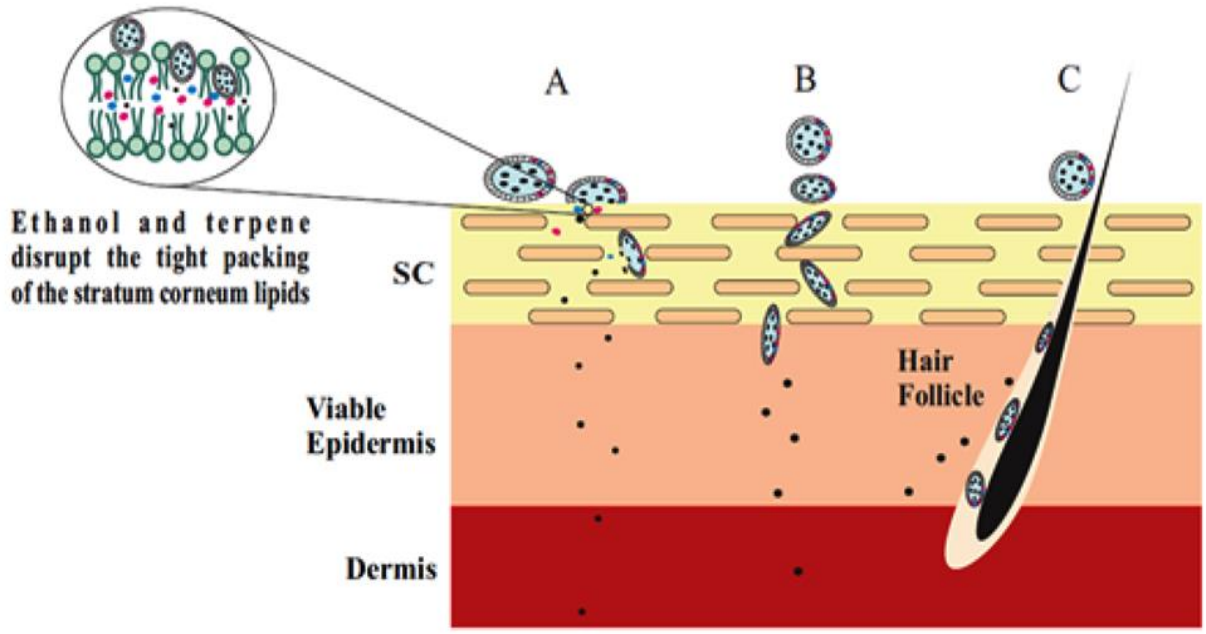
Terpenes are ethanol in the invasomes causes deformability of vesicles. And disrupts the stratum corneum bilayers structure.

Ethanol is known for its disturbances of skin lipid bilayers organization, therefore when integrated into the vesicle membrane, it gives that vesicles ability to penetrate into the stratum corneum.[23]

Ethanol interacts with lipid molecules in the polar head group region, results in reducing the rigidity of the stratum corneum lipids and increases their fluidity.[24] In addition to the effect of ethanol on stratum corneum structure, the vesicle itself may interact with the stratum corneum barrier.[25]

The interdigitated, malleable vesicle can forge paths in the disordered stratum corneum. Terpenes in their structure explored as penetration enhancers, terpenes enhances diffusion of drugs by extracting lipids from stratum corneum.[26] Which results in reorganisation of lipid domain and barrier disruption. The barrier disruption may be due to the competitive hydrogen bonding of oxygen containing monoterpenes with ceramide head groups. Therefore, breaking of interlamellar hydrogen bonding network of lipid bilayers of stratum corneum. The mechanism of action of penetration enhancers are by

- Disruption of highly ordered structure of stratum corneum lipids.
- Interaction with intracellular proteins.[27]



Synergistic effect:

A synergistic effect between phospholipids and ethanol and terpenes on dermal absorption has been visibly observed.[28] Dragicevic-Curic et al. Suggest that, one pat of invasomes disintegrates during permeation in the upper layer of skin, and releases phospholipids and terpenes which acts as permeation enhancers that fluidizes the intracellular lipids and enhances the permeation of flexible or elastic vesicles. (By Dragicevic-Curic et al) the ethanol in the invasomal fluidizes the intracellular lipids and enhances the penetration of flexible vesicles through stratum corneum. [29,30]

Characterization of invasomes:

1. Entrapment efficiency
2. Surface morphology
3. Stability studies
4. Drug content
5. Vesicular size and shape
6. Ex vivo permeation studies

1. Entrapment efficiency:

Entrapment efficiency was studied by Ultracentrifugation method. 1ml of invasomal formulation was transferred to Eppendorf tubes, centrifuged at 15000rpm at 4°c for 15 minutes in two cycles to separate the unentrapped drug. The clear fraction was used to determination of free drug. Percentage entrapped is calculated indirectly from the amount of free drug from the formula.[31]

$$\boldsymbol{Entrapment\ efficiency}(\%) = \frac{\boldsymbol{total\ drug - free\ drug}}{\boldsymbol{total\ drug}} \times \mathbf{100}$$

2. Surface morphology:

Surface morphology was studied by placing a drop of preparation on clear glass slide. Air dried, coated with gold using sputter coater (polaronE5100, Watford, Uk) and visualized under scanning election microscopy. [31]

3.Stability studies:

Optimized invasomal formulation was sealed in 10 ml glass vial and stored at refrigerator temperature (4-8°c) and room temperature for one month. Entrapment efficiency, physical appearance was determined at regular intervals.[31]

4. Drug content:

Drug content of the invasomes can be determined by using ultraviolet spectrophotometer. This can be quantified by a modified high-performance liquid chromatography method [32].

5. Vesicular size and shape:

Invasomes can be visualised by using Transmission electron microscopy (TEM) and Scanning electron microscopy (SEM). Vesicle size and zeta potential particle size of the invasomes can be determined by Dynamic Light Scattering (DLS) and photon correlation spectroscopy [32]

6.Ex vivo permeation studies:

The permeation of invasomes formulation was determined by using the Franz diffusion cell. The effective surface area of cell was 2.0 cm^2 and has a receptor volume of 20 ml. Then skin was mounted on receptor compartment within stratum corneum side facing upward into the donor compartment. The top of the diffusion cell was covered with lid. The donor compartment was applied with invasomal preparation and 20 ml of p^H7. 4 phosphate buffer saline maintained at 37℃ was used as receptor medium. aliquot amount were withdrawn and replaced by fresh media to maintain a sink condition. samples were analysed using UV spectrophotometer.[33]

Pharmaceutical applications of Invasomes:

Immunosuppressive Drug Delivery:

Immuno suppression is the primary approach to treat autoimmune diseases. Also, it is useful for clinical application of existing immunosuppressive agents that have been suffered from various drug side effects. The nanotechnology centred approaches can correct the major limitation by enhancing immunosuppressant delivery to target cells of immune system. Also, reducing the recommended dose for therapeutic function and reducing drug distribution to non-target tissue can be a key alternative to immunosuppressive drug delivery.[34] From the sub structure of lipid vesicles in drug delivery, it receives the primary consideration of investigation to develop advanced nano-sized vesicles. A literature survey mentioned that cyclosporine A (CsA, cyA) is a lipophilic drug and it exhibits poor penetration efficiency into the skin layers (partition coefficient:4000). The topical applications of Cs A can be suitable alternative for management of psoriasis and other dermatological diseases. Initially Verma were synthesised the invasomes nanocarrier for delivery of CsA CyA using unsaturated soybean phosphatidylcholine (10%w/v), ethanol (3%w/v), citrsal:cineole :D-limonene mixtures (0.5:1.0:1.5%w/v)and PBS up to 100%w/v using mechanical dispersion. In-vitro penetration study concluded that due to the presence of ethanol and terpenes showed a higher amount of CsA in the deeper layer of skin (viable epidermis and dermis) as compared with the aqueous/ ethanolic drug solution and liposomes (without ethanol and terpenes). Besides the increasing concentration of terpene (0.5to1.0%) significantly increased the amount of CsA in the deeper skin layer and subcutaneous layer. It shows the direct correlation between the amount of drug found in

skin layer.[35] Owing to excellent finding of immunosuppressive agent –loaded invasomes, it can used for treating auto immune diseases. Taken as whole confirmed that invasomes can be an effective substituent for hydrophobic drug delivery to the deeper skin layers.

Anticancer Drug Delivery:

From its inception, cancer treatment it is still a challenging field in the era of biomedical science. Due to the ineffectiveness of currently engaged therapeutic strategies, a large number of deaths have been occurring each year.[36]

Therefore, there is an urge to develop an advanced substitute to resolve advanced substitute to resolve cancer ineffective treatment issues. Interestingly, the temoprofin is a potent(second-generation) photosensitizer. It shows high tumour selectivity and residual photosensitivity of only 2 weeks. Thus, this could be effective anti-cancer agent in photodynamic therapy of early or reoccurring carcinomas. On this account, Dragicevic-Curic and Co- authors were reported that the deposition of the highly hydrophobic photosensitizer (temoprofin) using invasomes into the skin layer of stratum corneum.

Briefly, temoprofin- loaded invasomes have been synthesized using the mechanical dispersion method. In that, the temoprofin and 1% w/v terpene (limonene/citral/cineole) were dissolved in ethanolic phospholipid solution. (Phosphatidylcholine: ethanol: 75:25w/w) and subjected to vortexing followed by sonication for 5 minutes. Finally, phosphatase buffer saline was added into the above-mentioned clear solution with constant vortexing for 5 minutes. The drug loaded invasomes (1%w/v cineole) showed about 105.4nm, particle sizes and about 0.066 Polydispersity index. After plastic surgery, the human female abdominal skin was obtained and penetration was carried out using the nominal surface of the Franz cells (3.14cm^2) .

The use of cineole(1%w/v) shows the highest penetration ability fallowed by a mixture (1%w/v) of cineole: citral: D- limonene (45:45:10v/v). Experimental outcomes revealed that the single terpene could make an effective delivery of temoprofin and combination of terpenes could lead to the synergistic effect of active penetration to the subcutaneous and deeper skin layers.

Besides the stability study indicated that the invasomes containing 1%w/vc cineole showed a small increase in particle size and Polydispersity index value and can be considered a physically, stable form for 12 months.

In the future invasomes can be an effective carrier for the delivery of hydrophobic active molecules with effective concentration to the systemic or local site. However, there is no thumb rule for the use of terpene and its mixture towards penetration. [37]

Delivery of anti–hypertensive agent:

Anti-hypertensive are used to treat elevated hypertension. It has numerous problem such as low aqueous solubility, low bioavailability, and short biological half-life low permeability and I list of undesirable side effects.[38] This can be waved off using a suitable route for delivery and ethanol formulation. A calcium channel blocker, isradipine is generally used for the treatment of hypertension. Unfortunately, it has low oral bioavailability and it suffers the firs-pass metabolism. Kamran et al. accomplished the development of invasomes using phospholin 90G (2%w/v), b-citonellene (0.1%w/v terpene) and ethanol 10% w/v through conventional film hydration technique and used as a efficient carrier for the delivery of isradipine via transdermal route.

In brief, isradipine, terpene and phosphoric 90G were dissolved in chloroform: methanol (2:1v/v), then the organic solvents were removed through rotary evaporator and organic solvent traces were collected separately using a vacuum cabinet overnight. The hydration of isradipine invasomal lipid film has been performed using phosphate buffer saline: ethanol at 60 rpm using rotary evaporation for 1hr and then subjected to probe sonication (4°c) at 40% output frequency. The particle size, Polydispersity index, entrapment efficiency, and transdermal flux through rat skin of isradipine invasomes were found to be 194nm, 0.272, 88.46% and 22.80mg/cm^2/h respectively, because of presences of ethanol and terpene, it provides particle deformability and enhances the penetration rate of isradipine. Interestingly, enhancement in the deformability of invasomes and lipid by layers of stratum corneum disruption facilitates the penetration of the isradipine invasomal vesicles.

Antioxidant:

Nowadays, ferulic acid (antioxidant) is gaining much attention from research scholars due to its therapeutic effects such as anti-cancer, anti-skin disorders, anti-diabetes, anti-inflammatory, etc. Ferulic acid is normally located in many of the plant cell walls. Unfortunately, it takes a short half-life of removal and needed many dosages with regular administration.

In this regard, appropriate transdermal vesicles may also be a safer choice for ferulic acid delivery. Chen- and Co- investigators prepared the terpene (limonene, citral, cineole-1:4.5:4.5v/v) based invasomes for the delivery of ferulic acid using the film hydration method and compared with conventional liposomes, ethosomes, tween-80 based deformable liposomes

In brief, soybean Phosphatidylcholine (133 mg/ml) ferulic acid (12mg/ml) and terpenes (10mg/ml) were dissolved in methanol and Chloroform mixture (1:2v/v) and then subjected to removal of organic solvent using rotary evaporation under specified vacuum. Condition for the appropriate time at 43°c. Then thin lipid film hydration was accomplished using phosphate buffer saline (p^{H}7.4)and ethanol (10% v/v). Further, ferulic acid

invasomes were subjected to sonication for 15 minutes (5 minutes/cycle) in an ice water bath. This gives the nanosized invasomes.

Finally, obtained invasomal suspension had been shifted to sized using polycarbonate membrane (pore diameter: 100 nm) which gives uniform ferulic acid invasomes. The ferulic acid invasomes exhibited about- 39-mv, zeta potential, 129.1-nm vesicle size and Polydispersity index<< 0.2.It confirmed that development suspension of ferulic acid invasomes had a stable, uniform, non-ionised and homogeneous form. In addition this, the in- vitro permeation of ferulic acid from ethosomes through the human skin was found to be high as compared with the other formulations. It may be because of high concentration of ethanol in ethosomes. On the other hand, conventional liposomes have been expected to be effective for the delivery of drugs into the upper layers of skin. Besides, ferulic acid invasomes showed better permeation because of deformable vesicles and penetration enhancers interaction with lipid lamellae and skin layer.[38]

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