Review Article

Invasomes-novel Vesicular Carriers for Enhanced Skin Permeation

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ABSTRACT

Invasomes are the liposomal vesicles embodying small amounts of ethanol and terpenes or terpene mixtures, which act as potential carriers with increased skin penetration. Invasomes have higher penetration rate through the skin as compared to liposomes and ethosomes. Invasomes provide a number of advantages including improving the drug's efficacy, enhancing patient compliance and comfort. This article reviews various aspects of invasomes including their preparation, characterization, potential advantages in drug delivery. Enhanced delivery of drugs through the skin and cellular membranes by means of an invasomal carrier opens numerous challenges and opportunities for research and future development of novel improved therapies.

Introduction

Transdermal delivery provides a leading edge over invasive methods and conventional oral routes increasing patient compliance and avoiding first pass metabolism respectively.[1] It brings forth many attractive advantages over other routes of administration, like sustained and controlled delivery over a prolonged period of time, reduction in side effects associated with systemic toxicity, direct access to target or diseased site, convenient and painless administration and so on.[2] The major limitation for topical drug delivery is the low diffusion rate of drugs across the stratum corneum (SC), which acts as the barrier.[3,4] SC is the outermost layer of skin and its structure is often compared to a brick wall, with the keratin-rich corneocytes as the bricks surrounded by the mortar of the intercellular lipid lamellae.[5] This layer consists of cells enriched with keratin embedded in lipid lamellae. The highly organized crystalline lipid lamellae play an essential role in the barrier properties of the SC.[6] Many approaches have been aimed to disrupt or weaken the highly organized intercellular lipids of SC such as chemical enhancers, iontophoresis, microneedles, vesicles, nanoparticles, etc.[7,8]

Since, past two decades colloidal lipid aggregates (liposomes) were developed as vesicular drug carrier systems. Vesicles are used in dermal and transdermal drug delivery as they might:[9]

a. Act as drug carriers to deliver entrapped drug molecules into or across the skin
b. Act as penetration enhancers for the penetration of the individual lipid components into the SC and subsequently altering the intercellular lipid lamellae within this skin layer
c. Serve as a depot for sustained release of dermally active compounds
d. Serve as a rate limiting membrane barrier for the modulation of systemic absorption, hence providing a controlled transdermal delivery system.

There are several new vesicle types, depending on the additives used for vesicle preparation. Such as niosomes, transferosomes, ethosomes, flexosomes, invasomes, vesosomes, ufasomes, and polymerosomes.[10] Description of these vesicles and drugs delivered by these vesicles as carriers is given in Table 1.

In previous studies liposomes (prepared from only phospholipids),[20,21] niosomes (prepared from surfactants and cholesterol)[22] has shown great potential as a drug delivery system. Parallel to this development, other classes of elastic vesicles without cholesterol were produced, which include transfersomes® (composed of phospholipids in combination with a surfactant),[23,24] ethosomes (ethanol being included into the vesicles to provide flexibility).[25,26] These elastic vesicles were more efficient in enhancing the transport of drugs than rigid vesicles.[27]

Invasomes are novel vesicles incorporating terpenes with enhanced penetration compared to the conventional liposomes.

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Table 1: Different vesicles as carriers in transdermal delivery

Vesicle	Composition	Permeant	Description	Reference
Liposome	Phospholipids and cholesterol	Triamcinolone acetonide	Four to five fold increase in drug concentration in epidermis and dermis when compared with conventional formulations	[11]
Niosome	Composed of non-ionic amphiphiles (surfactants)	Ammonium glycyrrhizinate	Improved percutaneous permeation by bola-surfactant	[12]
Transferosome	Phospholipids, cholesterol and an edge activator	Valsartan	When compared to rigid liposomes, amount of drug permeated was enhanced by 33.97 fold	[13]
Ethosomes	Phospholipid, ethanol and water	Econazole nitrate	Percent drug diffused was two fold higher than liposomal and hydroethanolic gels	[14]
Flexosome	Contained phospholipid, an edge activator and positively or negatively charged lipids	Low molecular weight heparin	2.6 fold higher permeability co-efficient than ethosomes	[15]
Invasome	Composed of phosphatidylcholine, ethanol and terpene	Temoporfin	Enhanced deposition of drug (3.87 fold) in stratum corneum when compared to liposomes	[16]
Vesosomes	Large lipid bilayer enclosing many smaller liposomes	Tetanus toxoid	Effective for topical delivery of vaccines	[17]
Ufasomes	Fatty acid vesicles	Methotrexate	Three to four fold increase in permeation when compared to plain drug solution	[18]
Polymer-somes	Self assembled vesicles of diblock/triblock copolymers	Insulin	Enhanced insulin activity	[19]

These are soft liposomal vesicles with very high membrane fluidity, containing terpenes, which are playing the role of penetration enhancement.[28,29] The presence of terpenes and ethanol makes invasomes unique. These vesicles have shown to possess the combined advantages of liposomes, which are potential carriers and penetration enhancement of the terpenes, which are having the ability to modify the order of SC packing thus promoting skin delivery.[30,31] Terpenes, the naturally occurring volatile oils are included in the list of generally recognized as safe substances with low irritancy[32] at lower concentrations (1-5%), with reversible effect on the lipids of SC are considered as clinically acceptable penetration enhancers.

Advantages

- Non-invasive technique of drug delivery.[33]
- Enhanced permeation of drug through the skin for transdermal drug delivery.[34]
- Delivery of hydrophilic[35] and lipophilic[36] drugs is possible.
- Contains non-toxic raw material in formulation.[34]
- Patient compliance as the drug can be administered as semisolid form (gel or cream).[34]
- Simple method for drug delivery in comparison to iontophoresis and phonophoresis and other complicated methods.[34]

Penetration enhancement mechanism

A combination of processes contributes to the enhancing effect of the invasomes. The SC lipid layers at physiological temperature are densely packed and highly conformationally ordered. Ethanol is known for its disturbance of skin lipid bilayers organization; therefore, when integrated into a vesicle membrane, it gives that vesicles the ability to penetrate the SC.[37] Furthermore because of the presence of ethanol, the lipid membrane is packed less tightly than conventional vesicles, but has equivalent stability, allowing a more malleable structure, giving it more freedom and ability to squeeze through small places such as the openings created in disturbing the SC lipid.[26] Ethanol interacts with lipid molecules in the polar head group region, resulting in reducing the rigidity of the SC lipids, and increasing their fluidity.[38] In addition to the effect of ethanol on SC structure, the vesicle itself may interact with the SC barrier.[39] The interdigitated, malleable vesicle can forge paths in the disordered SC.

In the experimental dermopharmacy and technology of transdermal drug delivery, terpenes are also intensively explored as penetration enhancers.[31] It is reported that terpenes enhance diffusion of drugs by extracting lipids from SC,[40] which results in reorganization of lipid domain and barrier disruption. The mechanism of barrier disruption may be due to the competitive hydrogen bonding of oxygen containing monoterpenes with ceramide head groups, thereby breaking the interlamellar hydrogen bonding network of lipid bilayer of SC and new polar pathways or channels are formed. The mechanism of action of permeation enhancers are by (i) disruption of the highly ordered structure of SC lipids, (ii) interactions with intracellular proteins or (iii) improvement in partitioning of the drug, into the SC [Figure 1].[41] A synergistic effect between terpenes and ethanol on the percutaneous absorption has being significantly observed.[42] The efficient drug delivery shown make this system a promising candidate for transdermal delivery of drug.

Methods of preparation

Mechanical dispersion technique

Drug and terpene or mixtures of terpenes are dissolved in ethanolic phospholipid solution. The mixture is vortexed for 5 min and then sonicated for 5 min in order to obtain a clear solution. Phosphate buffer saline (PBS) (pH: 7.4) is added to the solution by a syringe under constant vortexing. The vortexing is continued for an additional 5 min [Figure 2]. The last step is the extrusion of multilamellar vesicles through polycarbonate membranes of different pore sizes. The invasome dispersions are extruded through each polycarbonate membrane for several times.[16,43,44]

Film hydration technique

Invasomes can also be prepared by the conventional film method. Phospholipids in ethanol are dissolved in methanol: Chloroform

(2:1, v/v). This mixture is dried to a thin film by slowly reducing the pressure from 500 to 1 mbar at 50°C using the rotary flash evaporator. The film is kept under vacuum (1 mbar) for 2 h at room temperature and subsequently flushed with nitrogen. Then, the film deposited is either hydrated for 30 min at lipid phase transition with a mixture of phosphate buffer (pH: 7.4; PBS) containing ethanol and terpenes or it is hydrated using PBS (pH: 7.4) and after cooling to room temperature, ethanol and a single terpene or a terpene mixture are added in order to obtain invasomes. The obtained vesicles are vortexed, ultrasonicated and subsequently sized by extrusion for several times through polycarbonate membranes of different pore sizes [Figure 3].[35,37]

Characterization

Vesicle shape

Invasomes can be easily visualized by using transmission electron microscopy (TEM) and by scanning electron microscopy. Temoporfin vesicles were reported to be spherical and oval shape, unilamellar, bilamellar and also oligolamellar.[36] Finasteride invasomes were reported to be unilamellar and spherical shape.[45] By cryo-TEM carboxyfluorescein invasomes and temoporfin invasomes were reported to be almost unilamellar and bilamellar.[46] Hence, invasomes are observed as spherical or deformed vesicles with uni, bi, or oligo lamellarity.

Vesicle size and zeta potential

Particle size of the invasomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy. With temoporfin invasomes, the sizes of vesicles were reported to increase with increasing the amount of terpenes in the vesicles. Wherein liposomes containing 3.3% w/v ethanol were of 82.7 ± 0.3 nm, invasomes with 0.5% terpenes were of 93.0 ± 0.3 nm and 1% terpenes were of 124.3 ± 0.6 nm.[36] With finasteride invasomes it was reported the terpene molecular size influenced the vesicle size. Wherein invasomes with carvone (molecular size 150.22 g/mol) resulted in vesicles of 4.54 ± 0.30 μm to 4.80 ± 0.01 μm and with nerolidol (molecular size 222.37 g/mol) vesicles of 11.23 ± 0.26 μm to 13.00 ± 0.20 μm.[45] Hence, vesicle size is influenced by the molecular size of the terpene incorporated[45] and the concentration of terpene mixture added.[36]

Zeta potential of the formulation can be measured by Zetasizer. Chen *et al*. have reported invasomes containing carboxyfluorescien or temoporfin exhibited zeta potential of −41.1 ± 1.5 mV and −39.4 ± 1.2 mV respectively when compared to conventional liposomes, which possessed zeta potential of −12.3 ± 0.7 mV and −6.2 ± 1.4 mV respectively.[46] With temoporfin invasomes it was reported an increase in concentration of terpenes in vesicles resulted in only slight increase in negative surface charge. Wherein invasomes containing 0.5% terpenes possessed a charge of −12.9 ± 0.3 mV and 1% terpenes possessed −13.9 ± 1.3 mV.[36] Ogiso *et al*. and Sinico *et al*. have reported negatively charged vesicles promoted permeation of drugs.[47,48]

Drug entrapment

The entrapment efficiency of invasomes can be measured by the ultra-centrifugation technique or the other techniques used for

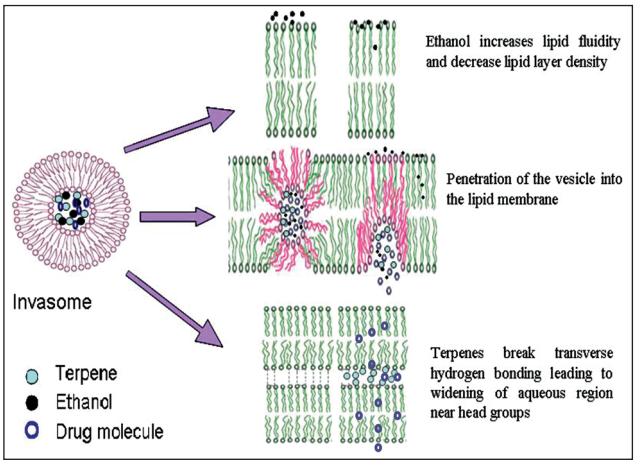

Figure 1: Proposed mechanism of action of invasomes

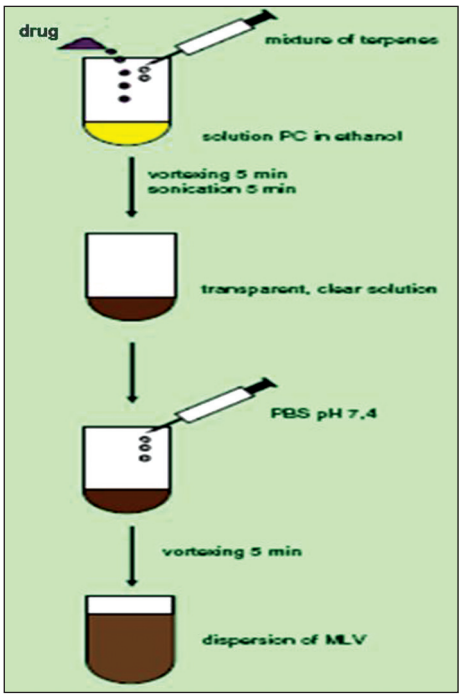

Figure 2: Invasomes preparation by mechanical dispersion technique

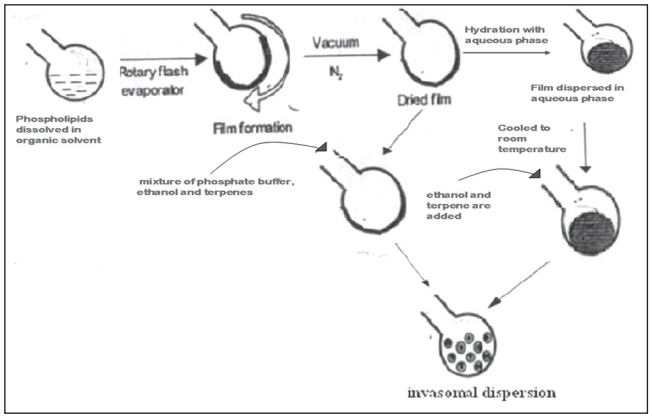

Figure 3: Invasomes preparation by film hydration technique

Table 2: Various research studies on invasomes

Drug	Solubility	Tested condition	Model	Reference
Temoporfin	Hydrophobic	Human epidermoid and colorectal cell lines	Cell lines	[43]
Temoporfin	Hydrophobic	Subcutaneously implanted tumours	Mouse	[49]
Temoporfin	Hydrophobic	Bilayer fluidity	—	[37]
Temoporfin	Hydrophobic	Skin permeation	Abdominal human skin	[50]
Temoporfin	Hydrophobic	Percutaneous penetration	Abdominal human skin	[36]
PCA	Hydrophilic	Percutaneous penetration	—	[35]
TEMPO	Hydrophobic	Percutaneous penetration	*Ex-vivo* penetration of porcine skin and *in-vivo* data on forearm of human volunteers	[51]
Carboxyfluorescein and temoporfin	Hydrophilic and hydrophobic	Skin penetration and deposition	Skin superficial layer	[46]
Finasteride	Hydrophobic	Permeation through skin	*Ex-vivo* in rat abdominal skin and *in-vivo* in rabbits	[45]
Ferulic acid		Skin delivery capability	Human skin	[52]
Carboxyfluorescein and radiolabelled mannitol	Hydrophilic	Skin permeation	Human full thickness skin	[44]
Carboxyfluorescein and calcein	Hydrophilic	Skin permeation ability	Human skin	[53]

PCA: 3-carboxy-2,2,5,5-tetramethyl-1-pyrrolidinyloxy, TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy

determining entrapped drug in vesicles. With finasteride invasomes maximum entrapment efficiency was reported with hydrophobic terpene limonene and minimum entrapment efficiency with nerolidol. With limonene, maximum entrapment was reported with 0.5% concentration (84.56 ± 0.25%) when compared with 1.5% concentration (71.56 ± 0.20%).[45] Entrapment efficiency was found to be influenced by hydrophilicity of drug and terpene added and concentration of terpene added.[28,45]

Drug content

Drug content of the invasomes can be determined using ultraviolet spectrophotometer. This can also be quantified by a modified high performance liquid chromatographic method.

Stability studies

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. Mean size is measured by DLS and structure changes are observed by TEM. Both temoporfin and finasteride invasomal suspensions were reported to be stable at 4°C.[36,45]

In vitro skin permeation studies

For the penetration studies human abdominal skin after the removal of the subcutaneous fatty tissue, obtained after plastic surgery, can be used. The diffusion studies can be carried out by using Franz diffusion cells, with PBS (pH: 7.4) in the receptor compartment. The ability of the invasomal preparation to penetrate into the skin layers can be determined by using confocal laser scanning microscopy.

Curic *et al*.[49] reported invasomes with 1% terpenes delivered temoporfin 2.7-fold higher than liposomes containing 3.3% ethanol. Moreover 1% terpenes, invasomes showed 2-fold higher deposition of temoporfin in the SC when compared to the ethanolic solution and 3.5-fold higher deposition when compared to conventional liposomes.[45] Chen *et al*. reported the influence of dose applied with carboxyfluorescien and temoporfin invasomes. With finite dose, carboxyfluorescien delivered into the deep skin layer was 52.9% and with infinite dose, it decreased to 37.8%. With temoporfin, with finite dose 8.8% was delivered into deep skin layer and with infinite dose 6.1% [Table 2].[46]

Conclusion

In order to overcome the barrier properties of SC several techniques were developed, including iontophoresis, electroporation, ultrasound, chemical penetration enhancement using different penetration enhancers and the use of vesicular systems, i.e., liposomes, ethosomes. One such technique is the formulation of invasomes, which could be a promising tool for delivering drugs through the skin and can provide better skin permeation than liposomes. Invasomes have been tested to encapsulate hydrophilic drugs and hydrophobic drugs. Hence, they can open up new challenges and opportunities for the development of novel improved therapies.

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