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Overall Review on Invasomes

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ABSTRACT

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

Keywords: *Terpenes, Soya lecithin, Invasome*

INTRODUCTION

Controlled drug delivery system has been designed to obtain an optimal drug action and targeting the drug to the particular sites in order to reduce the side effect and improve therapeutic efficacy by preventing undesired drug localization in healthy tissue site and decreasing rapid degradation or elimination of drugs. Transdermal drug delivery system is used as an alternative delivery of drug into the systemic circulation. Although advantageous in avoiding problems of poorly absorbable drugs and enzymatic degradation. In order to increase the number of drugs administered via transdermal route, novel drug delivery systems has to be designed. These systems include physical means, such as iontophoresis, sonophoresis, micro needles, etc. and chemical means like penetration enhancers and biochemical means using liposomes, niosomes, invasomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum [(1)].Invasomes are novel vesicles with enhanced percutaneous penetration compared to the conventional liposomes. Invasomes are novel elastic phospholipid vesicles composed of phosphatidylcholine, ethanol and one or mixture of terpenes. Many researchers have already confirmed the capability of terpenes in enhancing percutaneous penetration. Their penetration-enhancing activity is through the disruption of the stratum corneum lipids, interaction with intracellular proteins, and improvement of partitioning of the drug into the stratum corneum. Ethanol improves the vesicular ability to penetrate the stratum corneum. In addition, ethanol provides net negative surface charge and prevents vesicle aggregation due to electrostatic repulsion. A synergistic effect between terpenes and ethanol on the percutaneous absorption has been significantly observed [(2)]. Terpenes, the naturally occurring volatile oils are included in the list of generally recognised as safe substances with low irritancy at lower concentrations (1-5%), with reversible effect on the lipids of stratum corneum are considered as clinically acceptable penetration enhancers. Invasomes are characterised for size, surface morphology, zeta potential, stability.

ADVANTAGES OF INVASOMES [(3, 4)]

- Non-invasive technique of drug delivery.
- Enhanced permeation of drug through the skin for transdermal drug delivery.
- Delivery of hydrophilic and lipophilic drug is possible.
- Contains non-toxic raw material in formulation.
- Simple method of drug delivery in comparision to iontophoresis and phonophoresis and other complicated methods.

DISADVANTAGES OF INVASOMES [(3)]

- It's high production cost.

- Leakage and fusion of encapsulated drug/ molecule.
- The phospholipid present may undergo hydrolysis/oxidation, thus affecting stability of Invasomes.

METHODS OF PREPARATION

Mechanical Dispersion Method

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 to obtain final invasomal preparation (3).

Thin Film Hydration Method

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 vaccum (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 (4).

CHARACTERIZATION OF INVASOMES

- Entrapment Efficiency
- Surface Morphology
- Stability Studies
- Drug Content
- Vesicular size
- Ex Vivo Permeation Studies

Entrapment Efficiency

Entrapment efficiency was studied by ultracentrifugation method. 1ml of invasomal formulation was transferred to Ephendroff tubes, centrifuged at 15000 rpm, 4°C for 15 min in two cycles to separate the unentrapped drug. The clear fraction was used for determination of free drug. Percentage entrapped is calculated indirectly from the amount of free drug from the formula [3].

$$\text{Entrapment Efficiency (\%)} = \frac{total\ drug - free\ drug}{total\ drug} \times 100$$

Surface Morphology

Surface morphology was studied by placing a drop of preparation on clear glass slide, air dried, coated with gold using sputter coater (Polaron E5100, Watford, UK) and visualized under scanning electron microscopy(3).

Stability Studies

Optimised invasomal formulation was sealed in 10ml glass vial and stored at refrigeration temperature (4 - 8°C) and room temperature for one month. Entrapment efficiency, physical appearance was determined at regular intervals [3].

Drug Content

Drug content of the invasomes can be determined by using ultraviolet spectrophotometer. This can be quantified by a modified high-performance liquid chromatographic method [4].

Vesicular Size and Shape

Invasomes can be visualised by using Transmission Electron Microscopy (TEM) and by 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 [4].

Ex Vivo Permeation Studies

The permeation of invasome formulations was determined by usingthe Franz diffusion cell. The effective surface area of cell was 2.0 cm^2 and has a receptor volume of 20ml. The skin was mounted on the receptor compartment with the stratum corneum side facing upwards 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 pH 7.4 phosphate buffer saline maintained at 37ºC was used as receptor medium. Aliquot amounts were withdrawn and replaced by fresh media to maintain a sink condition. Samples were analyzed using UV spectrophotometer [5].

APPLICATIONS OF INVASOMES

Improves Bioavailability

Lakshmi PK et al., (2014) has worked to prepare and evaluate curcumin loaded invasomes. Because curcumin has poor aqueous solubility and has bioavailability problems. Hence in this

study the solubility of curcumin was increased by complexing with Cyclodextrin (CD) and Hydroxy Propyl β Cyclodextrin (HPβCD). Improved solubility and stability was observed with HPβCD prepared by co-precipitation method than physical mixture method. Optimized complex i.e., 1:2 proportion complex is incorporated into invasomes with limonene, fenchone, nerolidol as terpenes which acted as phospholipid membrane flexibilizers, penetration enhancers. 1% soya phosphatidylcholine, 0.5% limonene was optimized which showed Q_{24}OF 70.32 µg/cm^2, SSTF of 3.34 µg/cm^2/hr^{-1}, permeability coefficient of 5.35 cm/hr, and decreased lag time of 1hr. formulation CHL1 was found to be better in all characteristics and was incorporated into 2% HPMC K4M gel formulation[6].

Effective Permeability of Drug into Cells

Gauhar R. Qadri et al., (2015) has worked to prepare Invasome of israpidine for enhanced transdermal delivery against hypertension formulation, characterization and in vivo pharmacodynamic study. It was observed that prepared isradipine-loaded invasomes delivers ameliorated flux, reasonable entrapment efficiency, and more effectiveness for transdermal delivery. The optimized formulation presented the particle size of 194±18nm, entrapment efficiency (88.46%), and attained mean transdermal flux of 22.80±2.10µg/cm^2/h through rat skin. Confocal laser scanning microscopy revealed an enhanced permeation of rhodamine-red-loaded isradipine invasome to the deeper layers of the rat skin. During hypertensive study, the treatment group showed a substantial and constant decrease in blood pressure, for upto 22hr. the isradipine invasomes formulation was found to be effective, with a 20% reduction in blood pressure by virtue of better permeation through wistar rat skin [7].

- Prolong the existence of the drug in systemic circulation (4,8).
- Overcome the problems of the drug insolubility, instability and rapid degradation (8).
- Both hydrophilic and lipophilic drugs can incorporated (3,8).

Table1. *Various Research Studies on Invasomes*

DRUG	SOLUBILITY	TESTED CONDITION	MODEL	REFERENCE
Temoporfin	Hydrophobic	Human epidermoid and colorectal cell lines	Cell lines	9
Temoporfin	Hydrophobic	Subcutaneously implanted tumours	Mouse	10
Temoporfin	Hydrophobic	Bilayer fluidity	--	11
Temoporfin	Hydrophobic	Skin permeation	Abdominal human skin	12
Temoporfin	Hydrophobic	Percutaneous penetration	Abdominal human skin	13
PCA	Hydrophilic	Percutaneous penetration	--	14
TEMPO	Hydrophobic	Percutaneous penetration	Ex-vivo penetration of porcine skin and in-vivo data on forearm of human volunteers	15
Carboxyfluorescein and temoporfin	Hydrophilic and hydrophobic	Skin penetration and deposition	Skin superficial layer	16
Finasteride	Hydrophobic	Permeation through skin	Ex-vivo in rat abdominal skin and in-vivo in rabbits	17
Ferulic acid		Skin delivery capability	Human skin	18
Carboxyfluorescein and radiolabelled mannitol	Hydrophilic	Skin permeation	Human full thickness skin	19
Carboxyfluorescein and calcein	Hydrophilic	Skin permeation ability	Human skin	20

CONCLUSION

In order to overcome the barrier properties of stratum corneum 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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