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Research Article

Ethosomes and Invasomes- A Vesicular Drug Delivery Carrier and their Applications in Transdermal Drug Delivery Systems

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Abstract

Vesicles have become the vehicle of choice in drug delivery. Vesicles are seen to be having major role in modeling biological membranes, and in the transport and targeting of active agents. Targeted drug delivery is a mode of delivering any therapeutic agent to the tissues of interest while reducing its relative concentration of therapeutic agent in the remaining tissues which improves the therapeutic efficacy and reduces the possible side effects. These systems also show improvement in the therapeutic index, solubility, stability and rapid degradation of drug molecules.

Key words: drug delivery; Ethosomes; Liposomes

Introduction

Vesicles have become the vehicle of choice in drug delivery. Vesicles are seen to be having major role in modeling biological membranes, and in the transport and targeting of active agents. Targeted drug delivery is a mode of delivering any therapeutic agent to the tissues of interest while reducing its relative concentration of therapeutic agent in the remaining tissues which improves the therapeutic efficacy and reduces the possible side effects. These systems also show improvement in the therapeutic index, solubility, stability and rapid degradation of drug molecules.

1.2 Introduction to ethosomes:

Skin is the largest organ of human body which consists of three functional layers i.e., epidermis, dermis, subcutaneous layers. Although skin has various functions one of its major functions include protection from chemical, microbial and physical influences and also protect skin from losing its moisture and loss of water. The barrier function of stratum coronium is the main problem experienced for delivery of drugs across the skin which is why transdermal route includes application of novel delivery systems. These systems work by including various physical means such as sonophoresis, microneedles, iontophoresis and various chemical means like penetration enhancers and biomedical means using Niosomes, transferosomes, liposomes, Ethosomes which have been reportedly enhancing the permeability of drug though S. Corneum[1,2].

Types of VDDS:

VDDS can be divided into various types into lipoidal biocarriers and non-lipoidal biocarriers.

1) Lipoidal biocarriers:
    1. Liposomes
    2. Transferosomes
    3. Enzymosomes
    4. Ethosomes
    5. Pharmacosomes
    6. Emulsosomes
    7. Sphingosomes
2) Non- Lipoidal biocarriers:
    1. Niosomes
    2. Biosomes
    3. Aquasomes

Ethosomes:

Ethosomes are soft vesicles that contain phospholipids, ethanol and water. These systems get easily penetrated through skin. This is due to the reason that ethanol cause fluidization of both ethosomal lipids and intercellular lipid of stratum corneum. Ethosomes are majorly used for delivery of drug through transdermal route where the drug gets entrapped in Ethosomes which have physicochemical characteristics like hydrophilic, lipophilic, or amphiphilic[3,4].

Composition of Ethosomes:

The drug delivery by application of Ethosomes can be modulated by either altering alcohol: water concentrations or Polymer: water concentration ratio

ADDITIVE CLASS	EXAMPLES	USE
Alcohol	Ethanol Isopropyl alcohol	Provide softness for vesicle membrane
Polyglycol	Propylene Glycol	Penetration enhancer
Phospholipid	Soya phosphatidylcholine Egg phosphatidylcholine	Vesicle forming components

Table 1.0: Various Additives included in the formulation of Ethosomes

1.2.1 Mechanism of Drug penetration:[6,7]

The main advantage of Ethosomes over liposomes is the increased permeations of the drug through the stratum corneum. The mechanism of drug absorption includes following two phases ethanol effect and ethosomal effect.

Ethanol effect:

Ethanol though provides softness also acts a penetration enhancer. Ethanol penetration through intercellular lipids and increase the fluidity of cell membrane lipids by decreasing the density of lipids.

Ethosomes effect:

Ethanol of Ethosomes will increase the cell membrane lipid fluidity resulting in increase in skin permeability.

1.2.2 Method of Preperation of Ethosomes:[8,9]

Hot method:

In this method the Phospholipid is dispersed in water, by heating in water bath at 40°C until a colloidal solution is obtained. In another separate vessel ethanol and propylene glycol was mixed and heated to 40°C. Once both the mixtures reach 40°c., The organic phase is added to aqueous phase. Drug is dissolved in water or ethanol depending on its hydrophobic / hydrophillic properties. The vesicle size of ethosomal formulation can be decreased by applying probe sonication extrusion method.

Cold method:

The drug and phospholipid are dissolved in ethanol and heated to 30°C±1 C in water bath. Double distilled water is added in a fine stream to lipid mixture, with constant stirring at 700 rpm, in a closed vessel. Kept for constant stirring at 700 rpm for 1 hr.

Mechanical dispersion method:

Soya phosphatidylcholine is dissolved in a mixture of chloroform: Methanol in a round bottom flas(RBF). The organic solvents are removed using rotary vacuum evaporator, to form a thin lipid film on wall of the RBF. Finally, traces of solvent mixtures are removed from the deposited lipid film by leaving the contents under vacuum overnight. Hydration is done using various concentration of hydroethanolic mixture containing drug by using Rotation of RBF.

1.3 Characterization of Ethosomes:

Visualization of vesicles

Vesicles are visualized by scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) and

Vesicle size

Vesicle size is measure using Dynamic light scattering (DLS) and photon correlation spectroscopy (PS).

Zeta potential

Zeta potential is an important parameter that affects the aggregation if vesicles, depicts the physical stability of vesicular system and it can be measured using zeta meter.

Entrapment efficiency

Entrapment efficiency is determined by Ultracentrifugation technique.

Stability of Ethosomes:

The stability of ethosomal formulation was checked by keeping the preparations at different temperatures., 25± 2c, 37±2c and 45±2c for different time periods.

1.3 INVASOMES:

Among novel vesicles invasomes hold greater important as they show increased percutaneous penetration compared to conventional liposomes. These contain phosphatidylcholine, ethanol and single or a mixture of terpene[10,11].

1.3.1 ADVANTAGES OF INVASOMES:

- Non-invasive method/ technique of drug delivery
- Enhance permeation through the skin for transdermal drug delivery
- Delivery of various hydrophilic and lipophilic drugs is clearly possible.
- Patient compliance as the drug can easily be administered as semisolid form.
- Simple method of drug delivery in comparision to iontophoresis and phonophoresis and other complicated methods.

1.4 INVASOMES AND LIPOSOMES COMPARISION:

Liposomes are vesicular structures composed of anionic, cationic, neutral lipids. Contrary, invasomes are flexible liposomes consisting of phospholipids, ethanol and one terpen molecule or mixture of terpenes.

1.3.4 Method of Preparation

Mechanical dispersion method:

Drug and terpene are both dissolved in ethanolic phospholipid solution. The mixture is vortexed for 5 mins and then sonicated for 5 mins again in order to obtain a clear solution. Phosphate buffer saline (PBS) is added to the solution by a syringe under constant vertexing. The vertexing is continued for an additional 5 mins Then the multilamellar vesicles were extruded through polycarbonate membranes of different pore sizes[12,13].

Film hydration technique:

Invasomes are prepared by conventional film method. Phospholipids are dissolved in methanol: chloroform (2:1 % v/v). The mixture was dried to a thin film by reducing the pressure from 500 to 1 mbar at 50°c using rotary evaporator. The film is kept under vaccum for 2 hrs under room temperature

and then flushed using nitrogen. The film deposited is hydrated for 30 mins at lipid phase transition with a mixture of pH 7.4 buffer containing ethanol and terpene[14,15].

1.1 Synergistic Effects:

A synergistic effect between phospholipids, ethanol, and terpenes on dermal absorption has been visibly observed. Dragicevic-Curicetal. Suggest that one part of the invasome disintegrates during permeation in the upper layers of skin and releases the phospholipids and terpenes, which act as permeation enhancers that fluidize the intercellular lipids. Verma et al. indicated that invasomes increased the transdermal permeation of cyclosporine A compared to an ethanolic solution. The improved efficiency of invasomes compared to an ethanolic solution suggests a synergistic effect of phospholipid, terpenes, andethanol. Dragicevic-Curic etal.demonstrated that the improved permeation of temoporfin (m THPC) with 1% terpenes was due to the concentration of terpenes and the synergistic effects of terpenes and ethanol. Thus, the results from the forementioned studies point toward the synergistic effect of phospholipid,terpenes, andethanol in the reformed activity of invasomes in comparison with liposomes.[16,]

1.5 CHARACTERIZATION OF INVASOMES:

Optical microscopy

The Invasomes were mounted onto glass slide and viewed under microscope with magnification of 1200x for morphological observation after suitable dilution.

Vesicle shape:

Invasomes can be easily visualized by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

Vesicle size

Particle size of the prepared invasomes can be determined by dynamic light scattering (DLS) and photo correlation spectroscopy. The vesicle formulation was diluted about 100 times in the same medium used for this preparation. Vesicle size was measured using particle size analyser.

Zeta potential

Zeta potential analysis is done to determining the colloidal properties of the prepared formulation.

Drug entrapment:

Entrapment efficiency of invasomes can be measured by the ultra-centrifugation technique used for determining entrapped drug in vesicles. 1ml of invasomal formulation was transferred to Eppendorf tubes, centrifuged at 15000 rpm, 4°c for 15 min in two cycles to separate the unentrapped drug.

$$EE\ (\%) = \frac{total\ drug - free\ drug}{total\ drug} \text{x } 100$$

Drug content

Drug content was determined using ultraviolet spectrophotometer. This can be quantified by modified high-performance liquid chromatographic method (HPLC).

Stability studies

Stability of the vesicles can be done by measuring by DLC and structure changes observed by TEM.

Invitro skin permeation studies

For the skin permeation studies human abdominal skin after removal of the subcutaneous fatty tissue. The diffusion studies can be carried out by using Franz diffusion cells, with PBS in the receptor compartment.

1.3.6 applications of invasomes:

- Improves bioavailability
- Effective in increasing permeation and permeability of drug into cell.
- Prolongs existence of drug in the systemic circulation
- Overcomes the problem of drug insolubility, instability and rapid degradation.
- Both hydrophilic and lipophilic drugs can be incorporated.

Conclusions

Ethosomes and invasomes are the vesicular drug delivery carriers having topical and transdermal applications. They are majorly used as carriers for the delivery of anti-fungal and anti-bacterial agents. The advantage of these carriers includes local as well as systemic action. Research has to be carried out to establish clinical efficacy of these carrier system in comparison to that of remaining transdermal drug delivery systems.

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