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RESEARCH ARTICLE

TRANSFERSOMES AS NOVEL DRUG DELIVERY SYSTEM

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Abstract

Transdermal drug delivery appears to be most vital drug delivery system because of its merit over conventional systems. Transferosomes & the fundamental concept of transfersomes were launched by Gregor Cevc in the year 1991. The name means "carrying body" and is derived from the Latin word 'transferre', meaning 'to carry across' and the Greek word 'soma', meaning 'a body'. Novel drug delivery system aims to deliver the drug at a rate directed by need of body during the period of treatment and channel the active entity to the site of action. Transferosome is one of the novel vesicular drug delivery system which consists of phospholipids, surfactant and water for enhanced transdermal delivery. Transferosomes are able to reach intact deeper regions of the skin after topical drug administration while delivering higher concentrations of active substances making them a successful carrier for transdermal applications. These vesicular systems can deliver low as well as high molecular weight compounds. Targeted and controlled release formulations can also be prepared by transferosomes as it can accommodate drug molecules with wide range of solubility. Various strategies can be used to augment the transdermal delivery which includes iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, microneedles, & vesicular system (liposomes, niosomes, elastic liposomes such as ethosomes & transfersomes). It exists as an ultra-deformable complex having a hydrated core surrounded by a complex layer of lipid. It penetrates the stratum corneum by either intracellular route or the transcellular route by the generation of "osmotic gradient". Advantages of Transferosomes are wide range of solubilities, better penetration, biocompatible and biodegradable etc. Disadvantages of Transferosomes are oxidative degradation, expensive, etc. The transfersomes were formulated by the conventional rotary evaporation sonication method. Transferosomes can be applied in controlled release, transportation of large molecular weight compounds, target delivery to peripheral subcutaneous tissues, transdermal immunization etc.

Introduction:-

Transfersomes is a promising vesicular carrier for improved drug permeation through skin [1,2]. Transfersomes means "carrying body" that is derived from the Latin word "transferred" for carrying and "soma" for a body. These

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ultra-deformable vesicles are primarily composed of phospholipids (the membrane forming lipid) and surfactant (edge activator) which is responsible for the membrane ultra-flexible nature [3]. Interestingly, they are able to squeeze through pores in the stratum corneum less than one-tenth of their own diameter. Thus, even large vesicle sizes up to 200–300 nm can penetrate intact skin easily [4]. They offer controlled drug release especially for those with short half-life time, drug localization at the target site with less undesirable side effects, improved drug stability and improved bioavailability for drugs with first pass effect [5]. Novel drug delivery system aims to deliver the drug at a rate directed by need of body during the period of treatment and channel the active entity to the site of action. Transferosome is one of the novel vesicular drug delivery system which consists of phospholipids, surfactant and water for enhanced transdermal delivery. Transferosomes are able to reach intact deeper regions of the skin after topical drug administration while delivering higher concentrations of active substances making them a successful carrier for transdermal applications. These vesicular systems can deliver low as well as high molecular weight compounds. Targeted and controlled release formulations can also be prepared by transferosomes as it can accommodate drug molecules with wide range of solubility. Various strategies can be used to augment the transdermal delivery which includes iontophoresis, electrophoresis, sonophoresis, chemical permeation enhancers, microneedles, & vesicular system (liposomes, niosomes, elastic liposomes such as ethosomes&transfersomes). It exists as an ultra-deformable complex having a hydrated core surrounded by a complex layer of lipid. It penetrates the stratum corneum by either intracellular route or the transcellular route by the generation of "osmotic gradient". Advantages of Transferosomes are wide range of solubilities, better penetration, biocompatible and biodegradable etc. Disadvantages of Transferosomes are oxidative degradation, expensive, etc. The transfersomes were formulated by the conventional rotary evaporation sonication method. Transferosomes can be applied in controlled release, transportation of large molecules weight compounds, target delivery to peripheral subcutaneous tissues, transdermal immunization etc. Some evidence has shown efficacy for its use for drug delivery without causing skin irritation[7]

Advantages

1. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
2. They have high efficiency, in case of lipophilic drug near to 90%.
3. They protect the encapsulated drug from metabolic degradation eg: protein and peptides.

Disadvantages

1. Transfersomes formulations are too expensive.
2. It is time consuming process.
3. Transfersomes are chemically unstable because of their predisposition to oxidative degradation.

Methods of Preparation:-

1. Vertexing-Sonication Method

In this method, mixed lipids (i.e. phosphatidylcholine, EA and the therapeutic agent) are blended in a phosphate buffer and vortexed to attain a milky suspension. The suspension is sonicated, followed by extrusion through poly-carbonate membranes.

2. Suspension Homogenization Process

In this process, transferosomes are prepared by mixing an ethanolic soybean phosphatidylcholine solution with an appropriate amount of edge-activators, e.g. sodium cholate. This prepared suspension is subsequently mixed with Triethanolamine-HCl buffer to yield a total lipid concentration. The resulting suspension is sonicated, frozen, and thawed for 2 to 3 times.

3. Modified Handshaking Process

In this process, the transferosomes are prepared by modified hand shaking, 'lipid film hydration technique'. Drug, lecithin (PC) and edge activator were dissolved in ethanol: chloroform (1:1) mixture. Organic solvent was removed by evaporation while hand shaking above lipid transition temperature (43°C). A thin lipid film was formed inside the flask wall with rotation. The thin film was kept overnight for complete evaporation of solvent. The film was then hydrated with phosphate buffer (pH 7.4) with gentle shaking for 15 minute at corresponding temperature.

4. Aqueous Lipid Suspension Process

In this process, Drug-to-lipid ratio in the vehicles is fixed between 1/4 and 1/9. Depending upon the particular formulation type, the composition is preferred. This would ensure the high flexibility of the vesicle membrane in

comparison to the standard phosphatidylcholine vesicles inthe fluid phase. Specifically, vesicles with the size ranging from 100-200 nm are prepared by using soy phosphatidylcholine with the standard deviation of sizedistribution (around 30%). This formulation could be prepared by suspending the lipids in an aqueous phase wherein the drug is dissolved.

5. Centrifugation Process

In this process, phospholipids, surfactants and the drug are dissolved in alcohol. Then the solvent is removed by rotaryevaporation under reduced pressure at 40□C. Final traces of solvent are removed under vacuum. Then the deposited lipid film is hydrated with the appropriate buffer by centrifuging at 60 rpm for 1 hour at room temperature. At room temperature, the resulting vesicles are swollen for 2 hours. The multi-lamellar lipid vesicles obtained which are further sonicated at room temperature[6,7].

Evaluation

1. Vesicle Size Distribution And Zeta Potential

Dynamic light scattering method (DLS) using a computerized inspection system by Malvern Zetasizer used for determination of vesicle size, size distribution, and zeta potential.

2. VESICLE MORPHOLOGY

Photon correlation spectroscopy or DLS method generally used for vesicle diameter determination. Prepared sample in distilled water was filtered through 0.2 mm membrane filter and diluted with filtered saline and then size measurement done using photon correlation spectroscopy or DLS measurements. Transmission electron microscopy (TEM) and phase contrast microscopy can be commonly used for visualization of transferosomes vesicles. The stability of vesicle can be determined by assessing the size and structure of vesicles with respect to time. DLS and TEM used for mean size and structural changes, respectively.

3. NUMBER OF VESICLES PER CUBIC MM

This parameter is very important for optimization of composition and other process variables. Transferosome formulations which are unsolicited are diluted 5 times with 0.9% sodium chloride solution. Hemocytometer and optical microscope are used for further study. The transferosomes in 80 small squares are counted and calculated using the following formula: Total number of transferosomes per cubic mm = (Total number of transferosomes counted × dilution factor × 4000)/total number of squares counted

4. ENTRAPMENT EFFICIENCY

Generally, expressed in terms of % drug entrapment. In this method, unentrapped drug first separated using nanocolumncentrifugation method. After that, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol. The entrapment efficiency is expressed as:

Entrapment efficiency = (Amount entrapped/Total amount added) × 100

5. DRUG CONTENT

The drug content is determined using one of the instrumental analytical methods such asmodified high-performance liquid chromatography method using an ultraviolet detector, column oven, auto sample, pump, and computerized analysis program depending on the analytical method of the pharmacopoeia drug.

6. TURBIDITY MEASUREMENT

Nephelometer is one of the methods which generally used for turbidity measurement in aqueous solution.

7. SURFACE CHARGE AND CHARGE DENSITY

Surface charge and charge density of transferosomes can be determined using zetasizer.

8. IN-VITRO DRUG RELEASE

In vitro drug release study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and theinformation fromin vitrostudies are used to optimize the formulation before more expensive in-*vivo* studies are performed. For determining drug release, transferosomes suspension is incubated at 32°C and samples are taken at different times and the free drug is separated by nanocolumn centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

Dicussion:-

Formulation transfersomes

DRUG	INDICATION	REMARKS	REFERENCE
Meloxicam	NSAID	**Improved skin permeation**	**SureewanDuangjit et al.2010**

Methotrexate	**Anti cancer drug**	**In ceasing skin permeation**	**Trotta et al.2004**
Oestradiol	**Estrogen**	**Improved transdermal flux**	**Maghraby et al.1998**
Curcumin	**NSAID**	**Improved bioavailability and permeability**	**Patel 2009**
Corticosteroids	**Vitiligo**	**Improved site specificity and drug safety.**	**Ceve et al.1997**
Norgesterol	**Progestin**	**Improved transdermal flux**	**Jain et al.1998**
Tamoxifen	**Chemotherapy**	**Improved transdermal flux**	**Jain et al.1998**
Soluble proteins		**Non-invasive immunization through normal skin**	**Paul et al.1995**
Human serum albumin			**Paul and cevec1998**
Interferon-α	**Antiviral protective**	**Efficient delivery means**	**Hafter et al.1999**
Insulin	**Hypoglycemic**	**High encapsulation efficiency**	**Ceve et al.1998**
Tetracaine	**Topical analgesic**	**Suitable for the noninvasive treatment of local pain.**	**Planas et al.1992**

Conclusion:-

Transfersomes can pass through even tiny pores (100 nm) nearly as efficiently as water, which is 1500 times smaller. Drug loaded transfersomes can carry unprecedented amount of drug per unit time across the skin (up to 100mg cm^2h^{-1}). Transdermal drug delivery system is frequently used due to its several advantages over other routes of drug delivery but the penetration of drug via the stratum corneum is a rate limiting step, its major limitations like, it cannot be able to transport the larger size molecule.

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