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Transferosome: A Transdermal Vesicular Drug Delivery for the Treatment of Skin Cancer

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ABSTRACT

Transferosomes are ultra-deformable vesicles for transdermal applications consisting of a lipid bilayer with phospholipids, edge activator.The ratios of individual surfactants and the total amount of surfactants control the vesicle flexibility.For a few days now, emerging drug delivery innovations have created new interest in the development of drug delivery.TDDS is the drug delivery to the skin.This offers many possible advantages over conventional pathways, such as limiting first-pass metabolism, predictable and sustained period of action, reducing unnecessary side effects, using short half-life products, improving physiological and pharmacological response.In this review, the detailed study of the transferosomes loaded topical preparations with anticancer drugs like 5-fluorouracil,cisplatin etc and to characterize the parameters like drug entrapment, skin permeation, drug content, vesicle morphology, penetration ability, *invitro* drug release,*invivo* study and physical stability are discussed.

Key words: Transferosomes, Edge Activator, Skin Cancer, Novel Drug Delivery System, Skin Cancer, Transdermal Drug Delivery System.

INTRODUCTION

In recent years, the study scenario has lead to the development of a new model of drug delivery system with the goal of high therapeutic efficacy and compliance with patients. With improved therapeutic activity, several drug delivery systems are developed, but some problems occur with some delivery systems that are not solved as such.[Chiara Sinico et al., 2009]Transferosomes consist of hydrophobic and hydrophilic moieties together and handle drug molecules with a wide range of solubility. It consists of phospholipid, surfactant and water for improved transdermal delivery[Jain, S et al.,2003].In order to increase the skin permeation of drug molecules, the deformability of liposomes can be accomplished by using surfactants in the required ratio. Transferosomes may solve the challenge of permeation by pressing themselves along the stratum cornea's inter-cellular sealing lipid.

The resulting versatility of the membranes of the transferosomes minimises the possibility of total rupture in the skin of the vesicle and makes transferosomes, after application to the skin, to follow the natural water gradient through the epidermis[Walve J.R et al.,2011].Due to the existence of amphiphilic surfactants and the membrane of lipophilic phospholipids, the ultra deformable transferosomes enable local and reversible modification of their membrane composition when entering the narrow pore.[Joshi, S.A et al., 2010]

The interdependence of the local composition and structure of the bilayer enables the vesicle

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to self-regulate as well as self-optimize. Lipid vesicles are one example of many successfully developed experimental models of bio-membranes as vehicles for controlled delivery[Cevc, G., 2003]

A transferosome carrier is an artificial vesicle built to be like a cell vesicle or cell involved in exocytosis, and is therefore ideal for regulated and potentially targeted drug delivery, as shown in Figure 1. For enhanced transdermal distribution, transferosomes are primarily composed of phospholipids, surfactants, and water [Khafagy, E.S et al.,2007]

The injection of an edge activator into the configuration of the lipid bilayer induces elasticity[Jain Set al., 1998]. Transferosomes are applied to the skin using an unoccluded technique and, as a consequence of hydration or osmotic force in the skin, have been shown to impregnate the stratum corneum lipid lamellar regions. A variety of small molecules, peptides, hormones, and vaccines have been used as drug carriers[Davis, S.N et al.,2005]

SALIENT FEATURES OF TRANSFEROSOMES

1. Biocompatibile and biodegradable
2. High entrapment efficiency for lipophilic drugs
3. Avoids metabolic degradation
4. Used for systemic and topical drug delivery
5. Used for both low and high molecular drugs
6. Highly flexible and higher rate of skin penetration**[**SkinKanitakis, J et al.,2002]

MECHANISM OF PENETRATION OF TRANSFEROSOMES

The mechanism of penetration of transferosomes can be described in 3 ways**[**James, W.D et al., 2006]

- Hydrophilic lipid residue and proximal water interaction creates polar lipids to attract water molecules that cause hydration and transfer lipid vesicles to the higher water conventration location. The difference in the concentration of water from the stratum corneum and epidermis creates a transdermal osmotic gradient that may contribute to transferosome penetration through the skin.[Pawar AY et al., 2016]
- Carrying out its course causes hydration that widens the pores of the hydrophilic skin from which drug release takes place. That binds to the targeted organ, therefore.[De Marco Almeida F et al., 2018]
- This also acts as penetration enhancers that disrupt the intercellular lipids from the beginning, which expand the pores of the skin and promote contact and device penetration through the skin. The components of transferosomes is shown in Fig.2 [Kim, M.-S et al., 2007]

Difference between transferosome and other carriers

Transferosomes are actually related to the lipid bilayer cyst, the liposome. Transfersomes differ significantly from commonly used liposomes because they are more adaptable and flexible.[Elsayed MM, et al., 2007].The high flexibility of their membrane allows the transferosome to be forced even through pores that are much smaller than their own diameter due to the high flexibility of the transferosome membrane to integrate at least two lipophilic/amphilic components

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(phospholipids and bio surfactant)[Mulani, H.et al., 2017]

Transferosomes vary in two fundamental characteristics from the mixed autonomic particle; first, transferosomes are typically one or two orders of magnitude (in size) greater than the normal autonomic lipid particle.Second most significant, each vesicular consists of a water-filled centre where, as a micelle, there is a simple fatty droplet. As a result, transferosome can retain water as well as a fat soluble agent as compared to micelle.Autonomous particles can only incorporate a lipid substance. In order to distinguish the penetration potential of these carrier systems, the distribution of fluorescently labelled mixed lipid micelle transferosomes and liposomes as measured by confocal scanning laser microscopy (CLSM) in intact murine skin.[Pandit, J. et al.,2014]

TRANSFEROSOMES FOR SKIN DELIVERY

The current investigation shows that the transfersomes are drug moving mechanism which really penetrate, beyond undamaged within the skin. It was assumed that two factors were identified by unimpeded movement of such carriers: high elasticity (deformability) of the bilayer vesicles and the fact that the osmotic gradient beyond skin and carry drug over the whole skin.To resolve some of these issues in skin, a novel type transferosomes are supremely deformable lipid vesicle which has been announced latterly to go through unbroken skin.Skin function as a buffer,restricting the release of treatment modality transcutaneous. There have been a modern vesicular system which are far more elastic than vesicular system in serval aspects.[El Zaafarany et al.,2010]. Edge activator, phospholipids, sodiumcholate, constitute transferosomes and are applied in non-occulsive manner. Lipid residue and proximal water which makes the lipid to pull the water molecules insist the hydrating &lipid vesicles to move from site of higher water concentration to lower water concentration .Transdermal osmotic gradient superior to the penetration of the transferosome over the skin is expanded by variation in water content over the skin stratum corneum and epidermis[King, M.J et al.,2002] . Transferosomes gives that the variety of composition the crucial attribute of their application in order to maximize permeability and range of therapeutic molecules.Confocal microscopic studies have shown that intact liposomes cannot penetrate the granular layer of the epidermis, but rather remain on the upper layer of the stratum corneum. The rate of release and deposition of the drug can be adapted to the target site by adjusting the vesicular composition or surface properties.[Kumar, R et al.,2007]

FORMULATION OF TRANSFEROSOMES

The different additives used in the formulation of transferosomes is shown in table 1.

Thin film hydration technique:-

The sufficient quantity of soya lecithin and surfactant is added in round bottom flask and dissolved via shaking either chloroform, ethanol.AT 25℃ 600mm/hg pressure and 100rpm, the thin film was set up by rotatory evaporation for around 15 minutes. To dry the film a vacuum is applied for an hour. The drug is added and dissolved in 7.4 pH phosphate buffer about 10ml and heated up to around 55℃. Then the film was hydrated by the handshaking process occurs half an hour with warmed

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buffer, mixture was agitated by half an hour by orbital shaker and it was perceive under microscope and suspension which set aside in refrigerator at 4℃.[Cevc, G et al.,2003]

Rotary vaccum evaporation method:-

Mixture of vesicles, initiate an ingredient like surfactant, phospholipids which are dissolved in solvent like (methanol, ethanol) in round bottom flask. Organic solvent is seperated at room temperature (20℃) using rotory evaporator leaving thin layer of solid mixture that is settled on the wall of the flask. Dried surfactant film can be rehydrated with aqueous phase (phosphate buffer saline) at 0-60℃with moderate stirring in rotary evaporator for about 30mins. Then the mixture was sonicated in bath sonicator for 1hour.[Davis, S.N., et al.,2005]

EVALUATION

1**. Entrapment efficiency**: - It indicate the % entrapment of the drug is added and requires drug by using mini-column centrifugation following separation of unentrapped drug, these vesicles became distributed by utilize of 0.1% triton× -100 (or) 50% n propanol [B., Bhadra et al., 2003]

Entrapment efficiency= (amount entrapped/ total amount added)*100.

2. **Vesicle diameter:** - This method may insist by make use of spectroscopy photon correlation and process of dynamic light scattering (DLS) method. Sample is formulated in distilled water and filtered by way of membrane filter 0.2mm and diluted in filtered saline therefore, the measurement of size is concluded via spectroscopy of photon correlation, dynamic light scattering (DLS) measurements[Joshi, S.A et al., 2007]

3. **Penetration ability**: - It can be analyzed by using fluorescence microscopy for penetration ability.[Kim, M.-S et al., 2007]

4.**No.of.vesicles per cubic meter**: - It is the most dominant parameter for progressing framework of other proceeding variable. Unsonicated transferosome formulation are diluted 5times with 0.9% Naclsolution. Haemocytometer and optical microscope have been preowned for this study. [King, M.J et al., 2002]

5. ***Invitro*** **drug release**: - This study execute to demonstrate the permeation rate. Time is require to accomplish the steady state. Transferosome suspension is incubated at 32℃ and samples are taken at individual time intervals and amount of drug release is determined secondary to the amount of drug trapped at 0 times as the initial amount of drug release is isolated by centrifugation.[Kumar, R., et al., 2002]

6**. Measurement of turbidity**: - Drug turbidity in aqueous solution, probably measured by means of nephlometer.[Shukla A et al., 2016]

7**. Skin deposition studies on optimized formulation: -** surface of goat skin after the end of 24 hours permeation study, which is washed for 5 times with a solution that contains PBS (pH 7.4) in

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ratio 1:1 ratio besides, washing it with water the spare drug present on surface is removed. Ethanol and buffer solution having the range of pH 7.4 is used to cut the skin into small pieces after homogenization.[Tai A et al., 2014] It is then remain at room temperature for 6 hours. The drug content is determined by using appropriate phosphate buffer dilutions (pH 7.4) after shaking and centrifuging it at 500 RPM for 5 minutes. By Using T test results are compared with that of the control. [Tanure MAG et al., 2000]

SKIN CANCER: - It is the abnormal growth of skin cells and well established malignant disease found in Caucasians (white skinned).[Gallagher RP et al.,1995] These are foremost part evolve in areas that are exposed to sun, yet it can else formed in places that don't normally sun get exposure exceeding over 5.4million cases were reported worldwide in every year. Different types of skin cancers are named after the cell that are originated and their clinical behavior. [Thangabalan B et al., 2013]. Most common types are:

1. Basal cell carcinoma
2. Squamous cell carcinoma
3. Malignant melanoma
4. Non- malignant melanoma[Malakar J, et al.,2012]
5.

APPLICATIONS OF TRANSFEROSOMES

Different drugs can be used as a topical delivery of transferosome for various category of drugs.**[**Salem HF et al.,2015]

1. Delivery of Insulin
2. Delivery of Corticosteroids
3. Delivery of Proteins And Peptides
4. Delivery of Interferon
5. Delivery of Anticancer Drugs[Nagasamy Venkatesh D et al.,2014]
6. Delivery of Anesthetics
7. Delivery of NSAIDS
8. Delivery of Herbal Drugs
9.

SCOPE OF TRANSFEROSOMES:

Transfersome is best suited for non-invasive delivery of therapeutic molecules via open biological barriers. Furthermore, by integrating a variety of other techniques in the future, the vesicular system will play a central role in the delivery of novel drugs, especially in the field of diseased cell classification, diagnostics, genes and genetic materials, which are stable, targeted and effective in vivo.[Rajendra Pratap Singh, et al 2002]

CONCLUSION

Ultra-deformable vesicles, such as transferosomes, can provide a good solution for the delivery of

drugs and transport-related problems in the skin. They are mainly used to challenge the transmission of large molecules such as proteins and peptides[44].Ultra-deformable vesicles, such as transferosomes, can provide a good solution for the delivery of drugs and transport-related problems in the skin. They are mainly used to challenge the transmission of large molecules, such as proteins and peptides.

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Competing interests

The authors declare that they do not have competing interests.

Authors' contributions

All authors have read and approved the final manuscript.

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Class	Example	Uses
Phospholipids	Phosphatidylcholine, Egg Phosphotidylcholine, Dipalmitoylphosphatidylcholine	Formation Of Vesicles
Surfactant	Sodium Cholate, Tween-80, Span-80, Tween-20, Sodium Deoxycholate	To Provide Flexibility
Alcohol	Ethanol, Methanol, Chloroform	Solvent
Buffering Agent	Salinephosphate Buffer (Ph 6.4), Phosphate Buffer (Ph 7.4)	Hydrating Medium

TABLE .1 DIFFERENT ADDITIVES USED IN THE FORMULATION OF TRANSFEROSOMES

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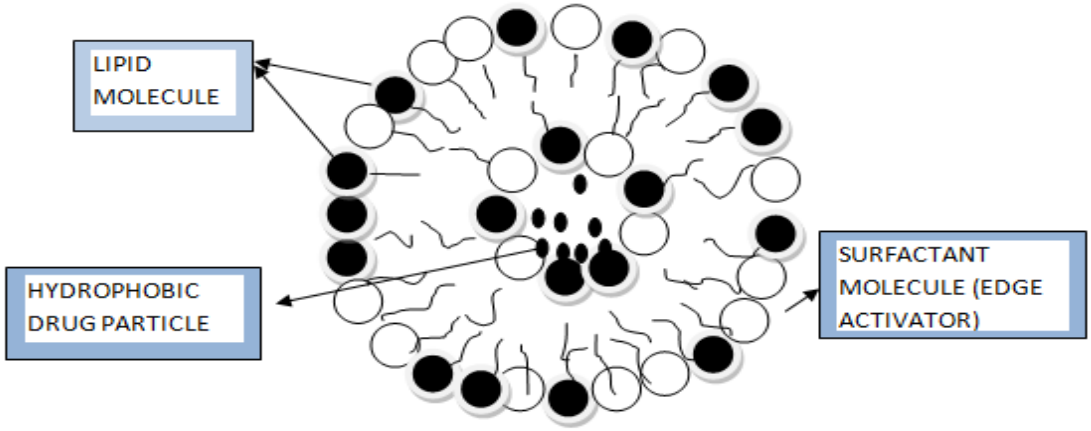

Fig.1: Structure of transferosomes

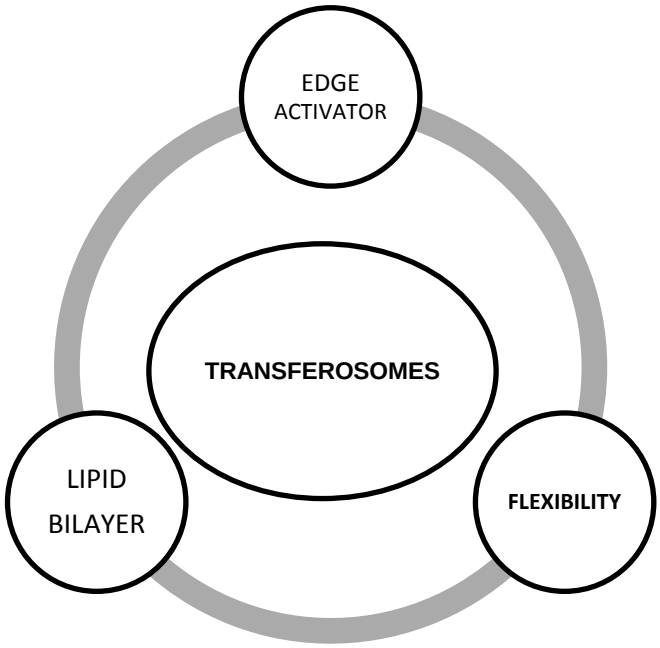

Fig.2: Features of transferosomes

TABLE 1: DIFFERENT ADDITIVES USED IN THE FORMULATION OF TRANSFEROSOMES

Fig.1: Structure of transferosomes
Fig.2: Features of transferosomes