Original Article

Transferosomes The Effective Targeted Drug Delivery System Overview

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DOI: 10.47750/pnr.2022.13.S08.548

Abstract

Now a day's Novel drug delivery systems is a creating a new interest in the development of drug deliveries or the transdermal route of drug delivery obtained a huge interest of pharmaceutical research .Transferosomes is a "carrying bodies" .The transferosomes word is comes from the Latin word "transferee" which means to carry across and the Greek word "soma" which is used for a body. The Transferosomes are a type of Liposomes. Even transferosomes are also called as Ultra deformable Vehicles for applying to skin holding a lipid bilayer with phospholipids and Edge activator along with watery or wet layer. Transferosomes are vesicular drug delivery systems which are used to upgrade the high penetration or high permeability of drugs in a non-invasive manner. Transferosomes also having the ability to collapse or contract themselves from 5 to 10 times less than their own diameter and redoing in order to pass through a narrow pore. Transferosomes are widely studied for their used in the treatment of various cancer Transferosomes hold an structure consisting of hydrophilic and hydrophobic components together and as a result can accommodate drug molecules with wide range of solubility .In the overview, we have discussed or focused on transferosomes on the novel drug delivery systems for targeted delivery of therapeutics and some important issues for future clinical applications.

Keywords: Transferosomes, Transdermal drug delivery, Targeted drug delivery or Novel drug delivery systems.

INTRODUCTION

In present day research scenery goes toward the development of new type of drug delivery system with the purpose of high therapeutic activity along with patient acceptance .A transferosomes is a device or a tool that can transfer drugs when applied on the targeted site through easy penetration of the skin1.Transfersomes is a ultra deformable vesicles which control an aqueous core surrounded by complex lipid bilayer it is preferred form. Transferosomes vesicles can also cross the micro porous barriers effective even if the porous are much smaller than the vesicles size[2].

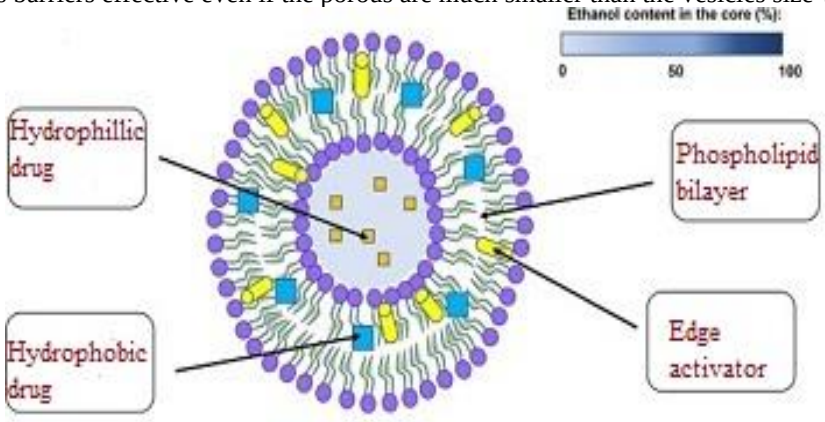

Fig 1: Diagram of Transferosomes

Transferosomes can effective pass through various transport barriers and then act as an efficient drug carrier for sustained release of therapeutic agents targeted drug delivery is due to these prosperities [3].In transferosomess the inner layer is also surrounded by a lipid bilayer having specially modified properties due to the addition of "Edge activators 'used widely are surfactants such as sodium cholate, sodium deoxycholate, span 80 and tween 80. Transferosomes have been developed which overcome the clarification problem and penetrate the skin barrier along the transcutaneous gradient or the transferosomes is recent novel drug delivery system and are special types of Liposomes which containing or having

phosphatidylcholine water an edge activator. Transferosomes are mainly use for skin because of their self-optimized and ultra flexible membrane properties [4].

Table: 1 various vesicular systems used for targeted drug delivery

Vesicular System	Advantages	Limitation
Liposomes	Biocompatible, Biodegradable	Stability issue, less penetration property
Niosomes	Improved stability due to use of non-ionic surfactants	Skin penetration is not much effective
Transfersomes	Ultra deformable with high stability, high penetration property, biodegradable, bio-compatible, incorporate low and high molecular weight drugs, penetrate deeper skin regions.	Difficulty in loading hydrophobic drugs
Phytosomes	Higher Bioavailability, enhanced capacity to cross the lipid rich biomembranes, better pharmacokinetic andtherapeutic profile	leaching of the phytoconstituents
Ethosomes	Increased stability, increased skin permeability and inexpensive to formulate	Loss of product during transfer form organic to water media

Table :2 List of transferosomes

S.No.	Example	Class	Uses
1.	Egg Phosphatidyl CholineSoya Phosphatidyl choline, , dipalamitoylphosphatidyl choline	Phospholipids	Vesicles forming component
2	Ethanol, methanol, isopropyl alcohol, chloroform	Solvents	As a solvent
3	Sod. Cholate, Sod. Deoxycholate, Tween-80,Span 80, Tween 20	Surfactants	Vesicles forming component (Edge Activators)
4	Saline phosphate buffer (pH 6.4), Phosphatebuffer pH 7.4	Buffering agent a hydrating	As medium
5	Rhodamine-123 Rhodamine –DHPE Fluorescein –DHPE Nile-red	Dye	For CSLM study

ADVANTANGES OF TRANSFEROSOMES[5,6,7,8,9]

1. Transferosomes hold an structure consisting of hydrophilic and hydrophobic portions together and as a result can accommodate drug molecules with wide range of solubilities transferosomes can deform or pass through narrow constriction their own diameter due than 5 to 10 times.
2. Self administration is also possible with this targeted drug delivery system.
3. Transferosomes also be used for drugs with a narrow therapeutic window.
4. They must improve the bioavability.
5. Trasferosomes having high entrapment efficiency in case of lipophillic drug near to 90%.
6. Transferosomes also protect the encapsulated drug from metabolic degradation like example protein and peptides.
7. Scaling up is simple due to the tiny and simple production method.
8. However of size, molecular weight, polarity or shape these carries are highly universal and efficient in accommodating of range of agents.
9. Transferosomes can act as a carrier for high molecules as well as low molecular weight drugs example analgesic, anesthetic, corticosteroids, sex hormone, insulin, anti cancer and albumin.

DISADVANTANGES OF TRANSFEROSOMES[10,11,12]

1. The formation of transferosomes is expensive.
2. They are chemically unstable because of their predisposition to oxidative degradation.
3. Purity of natural phospholipids is another criteria militating against adoption of transferosomes as drug delivery vehicles.

MATERIALS FOR TRANSFEROSOMES PREPARATION.

Transferosomes is a optimized mixed lipid aggregate and self adaptable or composed of phospholipids like phosphatidylcholine which self assembles into lipid bilayer in watery on aqueous atmosphere and close to form a vesicl[13]. A bilayer softening component such as amphiphilic drug or bicomptabile surfactant is a mix to increase flexibility and permeability of lipid bilayer and the second component is known as edge activator. The edge activator usually consists of single chain surface which cause destabilization of the lipid bi- layer thereby they increasing fluidity and elasticity[14]. Transferosomes vesicles can change this shape to surrounding stress easily and rapidly. This flexibility also minimizes

the risk of complete vesicle capture in the skin and allows transferosomes to follow the natural water gradient cross the epidermis under the occlusive condition. Materials commonly used for the formation or preparation of transferosomes[15].

Table: 3 Materials commonly used for the preparation of transfersomes are summarized in

Ingredient	Examples	Functions
Phospholipids	Soya Phosphatidylcholine Egg Phosphatidylcholine Disteryl Phosphatidylcholine	Vesicle formingComponent
Surfactant	Sodium Cholate Sodium deoxy Cholate Tween 80 Span 80	For Providing Flexibility
Alcohol	Ethanol Methanol	As a Solvent
Dye	Rhodamine-123 Rhodamine-DHPE Flurescein-DHPE Nil red 6 Corboxy fluorescence	For Confocal ScaningLaseer Microscopy (CSLM) Study
Buffering Agent	Saline phosphate buffer(PH 6.5) 7% v/v ethanol Tris buffer (PH 6.5)	As a hydratingmedium

METHOD OF PREPARATION[16,17,18,19,20]

The method of preparation of transferosomes is given below:

1. Suspension homogenization process.
2. Vortexing sonication method.
3. Thin film hydration method.
4. Modified handshaking method process.
5. Centrifugation process.

- **Suspension homogenization process**- In this method transferosomes are prepared by mixing an ethanol soybean phosphatidylcholine solution with an suitable amount of edge activator molecule example: sodium cholate. This prepared triethanolamine –HCL buffer to yield a total lipid concentration[21]. After all this at last the resulted suspension is sonicated, frozen and thawed for 2 to 3 times
- **Vortexing sonicated method**- In this technique mixed lipids (phosphatidylcholine, EA and the therapeutic agent are put together in phosphate buffer and vortexed to attain a milky suspension.After this suspension is sonicated followed by extrusion through poly- carbonate membranes[22].
- **Thin film hydration method-** In this method of preparation surfactants and phospholipids are dissolved in acceptable organic medium, such as methonal-chloroform and make a thin film using rotary evaporator. The organic solvent were evaporatated at the above the lipid transition temperature at 50 ^{o} c is added to hydrate load of film and afterwards kept for rotation at 60 rpm for 1 hr .And kept at room temperature for 2 hrs till the enlargement of vesicle is completed. Subsequently to achieve crave size and then the dispersion is sonicated[23].
- **Modified handshaking process-** In this method of preparation transferosomes are prepared by modified hand shaking lipid film hydration technique and this method is also known as lipid film hydration technique. The drug lecithin(Pc) and edge activator were dissolved or mixed in ethanol-chloroform in the ratio of 1:1 .In this mixture drug ,lipid and edge activators are the evaporator at the temperature is (43^{0}c) hand shaking is achieved with a constant rotation [24].The thin lipid film is formed insite the flask.This film were kept for overnight for the complete evaporation of solvent .At the last the film was hydrated with the phosphate buffer (PH 7.4) with gentle shaking for 15 minute at appropriately temperature .
- **Centrifugation process**- In this method phospholipids, surfactants and the drug are mixed in alcohol, then the solvent is removed by rotatry evaporation under reduced pressure at 40^{0}c.Detected solvent are removed under vacuum .After that set down or place lipid film is hydrated with appropriate (suitable) buffer by centrifuging at 60rpm for 1 hr at room temperature[25] .The resulting vesicles are swollen for 2 hrs. Then the multi –lamellar lipid vesicles obtained which are further sonicated at room temperature.

CHARACTERIZATION OF TRANSFEROSOMES[26,27,28,29]

The characterization of transferosomes is generally similar to liposome's, noisome.

- **Vesicle size distribution and zeta potential-** The vesicle size, size distribution and zeta potential were determined by dynamic (DLS) light method by Malvern zeta seizer distilled water is used the preparation of sample when the sample is passed through a membrane filter of 0.2 mm the samples are thinned out or dilute with filter saline.
- **Entrapment efficiency-**Generally entrapment efficiency is expressed in terms of % drug entrapment or the amount of drug were entrapped in % of what is added is called entrapment efficiency. In this method the un-entrapped drug by use of mini –column centrifugation method. After that centrifugation, the vesicles were disrupted using 0.1% Triton X-100 or 50% n-propanol.The entrapment efficiency is calculated by using this formula.

ENTRAPMENT EFFICIENCY= (AMOUNT OF DRUG ENTRAPPED /TOTAL AMOUNT ADDED) 100

- **Vesicle morphology-** It can be determined by using photon correlation spectroscopy or dynamic light method (DLS) .These sample were prepared in distilled water, filtered through 0.2mm membrane filter and diluted with filtered saline and then size measurement done by using photon correlation spectroscopy or dynamic light scattering (DLS) measurements. Vesicles of transferosomes can be visualized by TEM (Transmission Electron Microscopy) stability of vesicle can be determined by assessing the size and structure of vesicles over time .The DLS and TEM used for mean size measured by DLS and structural changes are obtained or observed by TEM.

- **Drug content-** Drug content can be determined or expressed using one of the instrumental analytical methods such as a modified (HPLC) High performance liquid chromatography method using a UV detector (ultraviolet), column oven, pump, autosample and computerized analysis program and depending on the analytical method of the pharmacopoeial drug.

- **Turbidity measurement-** The method of Nephelometer is generally used for turbidity measurement in aqueous solution [30].

- **Penetration ability-** The Fluorescence microscopy is generally used for the penetration ability of transferosomes.

- **Number of vesicles per cubic mm-** The important parameter for optimization of composition and other process variables .Transferosomes which are unsonicated are diluted 5 times with 0.9% sodium chloride solution .At the further studies Hemocytometer and optimal microscope are used.

- **Surface charge and charge densisty-** It can be determined using zeta sizes for surface charge and charge density of transferosomes[31].

- **In vitro drug release-** This study is performed for determining the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from in vitro studies are used to optimize the formulation before more expensive in vivo studies are performed .For determining drug release, transferosomes suspension is incubated at 32^0 c and samples are taken the free drug is separated by mini column centrifugation[32] .The amount of drug released is the calculated in directly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

- **In vitro skin permeation studies-** Trans diffusion apparatus which is modified are used for this study. The effective diffusion area is 2.50cm^2 was for this study. In vitro study was performed using goat skin in phosphate buffer solution (pH 7.4) .Fresh abdominal skin goat were collected from slaughterhouse and used in the permeation experiments. Abdominal skin hairs were removed and the skin was hydrated is normal saline solution[33]. The adipose tissue layer of the sin was removed by rubbing with a cotton swab. Skin was kept in isopropyl alcohol solution and stored at 40^0c. By using instrumental analytical technique the samples were analyzed[34].

APPLICATIONS OF TRANSFEROSOMES

a) Insulin Delivery- orally applied polypeptidic or proteinaceous drugs are digested in the gastro intestinal tract, by and large, and thus are therapeutically nearly inactive. Orally applied polypeptidic or proteinaceous drugs are digested in the gastro-intestinal tract, by and large, and thus are therapeutically nearly inactive. Transfersomes can transport their associated drugs, including the epicutaneously applied insulin, into the body spontaneously. This happens in spite of the fact thatinsulin is normally prevented from crossing the skin by its high molecular weight of 5808 Da. The self-regulating membrane deformability of transfersomes is closely related to the corresponding vesicles self- reparation capability, the latter being essential for the transfersome stability and practical usefulness. Insulin isinferred to be transported into the body between the intact skin cells with a bio-efficiency of at least 50% of the subcutaneous dose action[35].

b) Delivery of Interferon-Transfersomes loaded with immunomodulators, Interferon-α and interleukines-2 (IL-2) are successfully synthesized and observed that both the molecules retained their biological activity and could be efficiently

encapsulated in carrier[36].

c) Delivery of Anti-cancer drugs. Transfersomes are used as carrier for delivery of anti- cancer drugs; they are suitable specially for treating skincancers[37]. Transfersomes loaded with methotraxate was tried for treatment of skin cancer. Tamoxifen (TAM) anti breast cancer agent is carried through skin most efficiently by means of transfersomes and accelerate the growth of murine uteri, where it act as an anti-estrogen,even at low dose as 0.1-0.2 mg/kg/day.

d) Delivery of Proteins It is very difficult to transport big and large biogenic molecules such as body proteins and peptides into body. When administered through oral route, such molecule shows degradation in gastrointestinal tract. Transfersomes are the best suitable approach for thedelivery of all kinds of proteins into body[38]. It is observed that bioavailability of the molecules delivered bytransfersomes are similar to the drug administered by subcutaneous injections The protein preparation e.g. bovine serum albumin (immunogenic adjuvant) applied repeatedly in the preparation of transfersomes through epi-cutaneousroute, showed strong immunogenic response[39].

e) Delivery of various therapeutic agents-[40]

Table :3 Various Drugs used with Transfersomal drug delivery system

Drug	**Category**	**Therapeutic activity**
Dexamethasone	Corticosteroid Drug	Anti-edema activity
Diclofenac	NSAID agent	Formulation optimization
Tacrolimus	Immunosuppressive	Atopic dermatitis
Pentoxifyllin	Xanthenes Derivative	Chronic occlusive arterial disease.
Eprosartan Mesylate	Angiotensin receptor blockers (ARBs)	Management of Hypertension
Ciprofloxacin	Quinolone Antibiotic	Treatment of otitis media
Timolol maleate	Nonselective β-adrenergic blocker	Management of Hypertension
Ketoconazole	Azoles antifungal	Antimicrobial activity
Diclofenac diethylamine, Curcumin	NSAID and natural Phenol curcuminoid	Analgesic and Anti-inflammatory
Itraconazole	Antifungal triazoles	Formulation Optimization
Paromomycin sulfate	Antibiotic	cutaneous leishmaniasis
risperidone	antipsychotics	Formulation Optimization
Minoxidil and caffeine	Antihypertensive vasodilator	Treatment of alopecia
Raloxifene Hydrochloride	Selective eoestrogen receptor modulator (SERM)	Treatment of osteoporosis
sinomenine hydrochloride	Alkaloid	Formulation optimization Treatment of Rheumatism
Embelin	Benzoquinone derivative	Treatment of Cancer
Indinavir sulfate	Protease inhibitor used as a component of highly active antiretroviral therapy to treat HIV/AIDS	Treatment against AIDS with other protease inhibitors, nucleoside analogues or reverse transcriptase inhibitors
Stavudine	Reverse transcriptase inhibitors	Prevention and treatment of HIV/AIDS

CONCLUSION

In this review we have discussed that transferosomes has several advantages of transdermal drug delivery system including greater deformability greater penetration power across skin .They are made up of hydrophilic.They entrap both large and small molecules successfully through skin. The optimized formulation the most critical factor is correct ratio of edge activators and phospholipids which governs the flexibility ,vesicles layers integrity and entrapment efficiency and stability of the formulation .The micro and macro molecules are explored of transferosomes.

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