WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 15, 1158-1184. Review Article ISSN 2277–7105

TRANSFEROSOMES: A NOVEL APPROACH FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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Article Received on
21 June 2024,

Revised on 11 July 2024,
Accepted on 31 July 2024

DOI: 10.20959/wjpr202415-32810

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ABSTRACT

Transferosomes are also known as the ultra deformable vesicles. It acts as a penetration enhancer due to its remarkable ability to penetrate deep into the skin layers and efficiently deliver therapeutic agents. This review provides a comprehensive overview of transferosomes, highlighting their structure, mechanism of action, and application in various fields, including pharmaceuticals, cosmetics, and biotechnology. The unique structure of transferosomes, comprising phospholipids bilayers with added edge activators, imparts them with flexibility and deformability, enabling them to squeeze through narrow pores and bypass biological barriers with ease. various techniques, such as ethanol injection methods, reverse phase evaporation, rotatory evaporation, and centrifugation methods, are employed for the preparation of transferosomes. each offering distinct advantages in terms of vesicle size, stability, and drug encapsulation efficiency. Various characterization s Transferosomes have immense potential to enhance the transdermal delivery of drugs. Particularly hydrophilic and macromolecule compounds that face challenges in permeating the skin permeating the skin barrier.by exploiting the flexibility of transferosomes. minimizing systemic side effects and improving patient compliance. Moreover, transferosomes find applications beyond pharmaceuticals, including the formulation of skin care products, where they enhance the delivery of active ingredients for improved efficacy in treating various dermatological conditions. Despite their immense potential, challenges such as stability

during storage, and regulatory approval remain to be addressed for the widespread commercialization of transferosome-based formulations. Future research efforts should focus on optimizing fabrication techniques, exploring novel edge activators, and conducting extensive preclinical and clinical studies to validate the safety and efficacy of transferosome-based drug delivery systems. In conclusion, transferosomes represent a promising platform for overcoming barriers to drug delivery, offering enhanced therapeutics outcomes and expanded possibilities in pharmaceuticals, cosmetics, and biotechnology. continued advancements in this field hold the potential to revolutionize the way we administer therapeutics and address unmet medical needs.

KEYWORDS: Transdermal drug delivery system, novel characterization, stratum corneum, mechanism action of transferosome, vesicular delivery system; phospholipid; edge activator. Methods of preparation, factors affecting.

INTRODUCTION

Most of the time, an effective therapeutic therapy cannot be administered for a variety of reasons, including hepatic first-pass metabolism, unfavorable side effects, patient noncompliance, and rejection of invasive treatments.[1] To address these issues, many medication delivery strategies have been created and researched during the past few decades. Transdermal delivery systems are one promising strategy because they are non-invasive and have no first-pass effects. However, attention needs to be paid to the skin's barrier function, which inhibits or lessens the transdermal transport of medicinal substances.[2,3] To get around the aforementioned problem, liposomes or other lipid-based vesicular systems have been employed in nanoencapsulation.[4] Drug transport into the skin is facilitated by liposomes through three possible mechanisms: fusion with the stratum corneum's lipid matrix, which increases drug portioning through the skin; adsorption to the skin's surface followed by a transfer of the drug directly from vesicles to skin; and lipid exchange between the liposomal membrane and cell membrane, which promotes drug diffusion across the membrane.[5,6] Nevertheless, the issue with traditional liposomes is that they are unable to thoroughly penetrate blood circulation and living skin.[7,8,9] As a result, rather than being used for transdermal administration, liposomes have been frequently employed as drug carriers for cutaneous distribution. As a result, liposomes—rather than transdermal delivery—have been frequently employed as drug carriers for cutaneous delivery. Other drawbacks of conventional liposomes include their short half-life, unstable membrane that causes leaky

behavior, and low encapsulation efficiency of hydrophilic medicines.[10,11,12] Other unique vesicles including sphingosomes, bilosomes, transferosomes, ethosomes, and invasomes, niosomes have been discovered and developed as a result of these significant challenges. The first reports of niosomes date back to the early 1970s. They consist of cholesterol and occasionally ionic amphiphiles, as well as nonionic surfactants (such as those of the polyglycerol ether family, alkyl or di alkyl, alkyl amides or alkyl ethers or esters). While nonionic surfactants boost niosomes entrapment efficiency and size, cholesterol gives the vesicular bilayer stiffness.[13] Additionally, certain ionic amphiphiles are employed in niosomes to improve entrapment efficacy, stability, and efficiency, such as positively charged stearyl amine and negatively charged diacetyl phosphate.[14]

Furthermore, their strong chemical stability, high entrapment efficiency, high bioavailability and low cost make them a superior drug carrier system to liposomes. Niosomes have been shown in the literature to improve the duration of therapeutic drug residence in the epidermis and stratum corneum, while also increasing trapped drug penetration through the skin and decreasing systemic drug absorption.[15] Early in the 1990s, chitosomes—liposome-based vesicles covered in chitosan polymer—were first reported. Chitosan alters the liposomes' surface characteristics to increase vesicular stability.[16] Additionally, the liposomes' mucoadhesive qualities were supplied by chitosan.[17] Chitosan improves physicochemical stability of liposomes by decreasing membrane fluidity and increasing membrane structural integrity, as noted by Dimova and Mertins in 2011.[18] In the late 1990s, sphingosomes were initially described. They are recognized as phosphoglycosphingolipids and cholesterol-containing liposomes composed of sphingolipids (lysoglycosphingolipids, hexadecasphinganine, n-acylsphingosines, and phosphoglycosphingolipids). Because only ether and amides links, which are more resistant to hydrolysis than lecithin ester linkages, make up sphingolipids, phospholipid liposomes are less durable than sphingosomes. They are also less susceptible to rancidity than lecithin because they have fewer double bonds.[19] For bilosomes, they are vesicles composed of nonionic surfactants and bile salts (bile salts are incorporated into the noisomes membrane), which are considered non-lipoidal carriers. These novel vesicles were developed for vaccine oral delivery due to their resistance to the enzymes and bile salts in the gastrointestinal tract.[20] According to Yang et al. (2011), bile salts are considered endogenous surfactants that are comprehensively used as absorption enhancers to improve drug permeation across biological membranes.[21] A new type of carrier system namely, transfersomes—was introduced by Cevc et al. in the 1990s. transferosomes are

composed of phospholipids and edge activators, which is a membrane-softening agent (such as sodium cholate, span 80, tween 80) facilitates the ultra-deformable property of the transfersomes. When transfersomes reach the skin pores, they are capable of changing their membrane flexibility and passing through the skin pores spontaneously. In the 1990s, Cevc et al. presented transfersomes, a novel kind of carrier system. Phospholipids with an (EA) edge activators —a membrane-softening substance like Tween 80, Span 80, or sodium cholate— combine to generate transfersomes and enable their ultra-deformable characteristic. Transfersomes can spontaneously pass through skin pores by altering the flexibility of their membrane once they get there. This is the deformability that is referred to as self-optimizing.[22] Transferosomes may also bend a great deal, which makes it easy for them to pass through even incredibly small pores.[23] These highly deformable, self-optimizing lipid aggregates have proven effective in a variety of phase I and II clinical trials, extensive preclinical testing, transcutaneous delivery of proteins and peptides and sustained release of targeted therapeutic agents.[8,24] Currently, some formulations based on transfersomes are being evaluated at various phases of clinical studies. For instance, a phase III clinical trial was used to examin the safety and efficacy of ketoprofenintegrated in transferosomes (Diractin®) for the treatment of osteoarthritis in the knees. Over the course of six week treatment period, it has been established that the medication encapsulated in transfersomal carriers demonstrates higher therapeutic effectiveness in reducing knee osteoarthritis pain when compared to a placebo and comparably fewer side effects.[25] Phase I clinical trials is being conducted to examine the hypoglycemic effects of topical administration of insulin-loaded transfersomes (Transfersulin®). In rabbits with alloxan-induced diabetes, Transfersulin® was able to lower blood glucose levels in the preclinical trials.[26]

A randomized controlled trial was conducted to evaluate the risk-benefit ratio of topical triamcinolone acetonide in transferosomes versus commercially available traiamcinolone acetonide containing ointment and cream. The risk benefits ratio of topical triamcinole acetonide is considerly enhanced by transferosomes.[27] as a result, transferosomes are recognized as most exceptional and inventive transdermal drug carrier available today.[28] Experimenting with vesicle compostion, invasomes, and ethosomes were developed in response to the optimistic outcomes observed with those, transferosomes vesicles that contains water, phospholipids and high percentage of ethanol (20–50%). Ethosomes have high quantities of ethanol, which modifies the skin's lipid bilayer and increases the vesicles' capacity to penetrate the stratum corneum.[29,30] Terpenes, ethanol, and phospholipids

combines to form elastic phospholipids- based vesicles known as invasomes by rupturing the stratum corneum tight terpenes and lipid packing ethanol have the capacity to otentially enhanced medication penetration.[31,32] For researchers interested in or already conducting research in elastic vesicle- based on transfermal drug delivery, it will be helpful to understand the underlying concept, preparation, specific term and characterization methods, as well as factors affecting the properties of the first generation of elastic vesicles (transferosomes). In this review, we give a general overview of mechanism of action, various preparations, and characterization techniques—factors that influence the characteristics of transferosomes with a focus on their more recent uses in transdermal drug delivery.

➢ Structure of Transferosomes

Vesicular carrier systems known as transferosomes are specifically engineered to have an edge activator and at least one interior aqueous compartment surrounded by lipid bilayer. (figure1).[33]

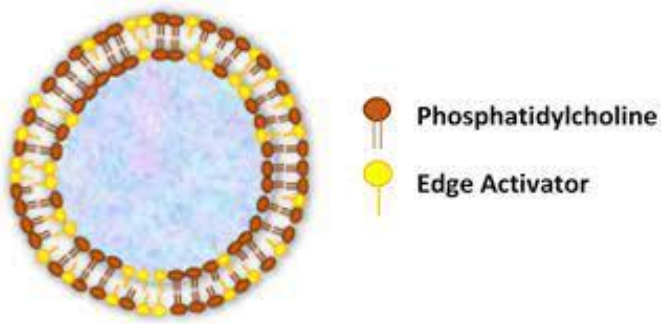

Figure 1: Structure of transferosomes.

➢ Composition of transferosomes

The components of a transferosome, a lipidic vesicular carrier, include edge activators and phospholipids, which can be manufactured or naturally occurring30–33. Following interaction with the aqueous environment, the lipids self-assemble to form a bilayer, enclosing a hydrophilic core at the center of the structure. By causing the lipid bilayer to break down, the edge activators—also known as softening agents—added throughout the formulation processes improve the lipidic vesicle's flexibility and deformability. Because of their flexibility, they can easily and unbrokenly pass through skin and membrane pores that are smaller than their own. Since lipids make up transferosomes, they can transport both lipophilic and hydrophilic medications. The components used in the formulation of transferosomes are listed in the (table1).[34][35]36]

Table 1: Composition of transfer some.

Components	Examples	Purpose
Phospholipids	Soya phosphatidylcholine, egg phosphatidylcholine, dipalmitoyl phosphatidylcholine.	Vesicles forming complexes[34]
Surfactant	Sodium Cholate, sodium deoxycholate, span 80, span 80.	It provides flexibility[34]
Alcohol	Ethanol, alcohol, chloroform	Used as a solvent[35]
Buffering agents	Saline phosphate buffer (PH6.8)	Used as a hydrating medium[36]
Dye	Example-Rhodamine 123, Nile red	For confocal scanning laser microscopy.[36]

- **Mechanism of transferosomes**

The Latin word "transferred," which means "to carry across," and Greek word "soma," which means "a body, "are the sources of the phrase "transfer some," which means "carrying body."[37] Phospholipid vesicles, a type of transferosome, can be employed as a transdermal medication carrier. Transferosomes are artificial vesicles that mimic the properties of cell vesicles, making them appropriate for regulated and possibly targeted medication delivery. Because of the way they are made, they serve as both penetration enhancers and drug carriers, helping to get entrapped drug molecules through the skin. Phospholipid, surfactant, and water make up their core composition, which aids in improved medication delivery.[38] Transferosome is claimed to be different due to its artificial membrane, which is softer, more flexible, and more customizable. confers self-regulation and self-optimization to the vesicle. They were first made available in early 1990s. Moreover, transferosomes are effectively able to pass across microporous barriers. They can still reach the target site even if the pore size is lower than the vesicle size.[39] mentioned in the figure 2.

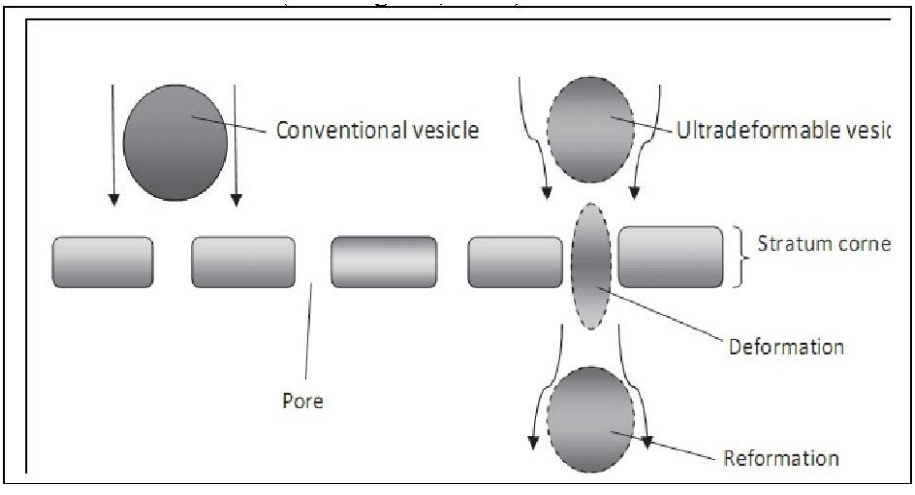

Figure 2: Mechanism action of transferosomes.

Therefore, transferosome-based medication administration can be regarded as a practical and secure technique. The ratio of specific surfactants to the total amount of surfactants regulates the vesicle's flexibility. Because they are more elastic than regular liposomes, vesicular transferosomes are ideal for skin penetration. By compressing themselves along the stratum corneum's intracellular sealing lipid, these vesicles can get past the barrier of skin penetration.[40],[41]

- **Comparison of transferosome with different vesicles**

Various vesicular systems have been extensively discussed, including liposomes, niosomes, transfersomes, and protransferosomes, proniosomes their advantages and disadvantages have been discussed briefly in (Table no.2).[42]

Table 2: Comparison of transfer some with different vesicles.

Method	Advantage	Disadvantage
Liposomes	Phospholipid Vesicle, Biocompatible, Biodegradable	Less skin penetration, less stable.[43,02,44]
Niosomes	Non-Ionic Surfactants Vesicles	less vesicles skin penetration, easy handling but will not reach up to deeper skin layer.[45]
Protransferosomes and Transferosomes	High Penetration, more stable due to High Deformability, Biodegradable and biocompactible, suitable for both high and low molecular weight. and also for Hydrophilic as well lipophilic Drugs And Reach Up to Deeper Skin Layers.	None, But for Some Limitations.[46]
Proniosomes	Greater Stability Will Convert Into Noisome In Situ, Stable	Easy handling, less skin penetration But Will Not Reach Up To Deeper Skin Layer.[47]

- Limitation of transferosomes,[48][49]

Additionally, transferases have a variety of drawbacks, some of which are mentioned below:

a) The propensity for oxidative breakdown makes transferosomes unstable chemically.

b) Another issue that formulators must deal with is the purity of the natural phospholipids employed in the transferosome formulation.

c) The cost of the formulated product is increased by the excipients, such as phospholipids, and equipment utilized in the transferosomes formulation.

➢ **Methods of preparation of transferosomes**

The prepration methods of transferosomes is classified into the following types.

1. Suspension Homogenization Process

Using this technique, transferases are made by combining a solution of ethanol and soybean phosphatidylcholine with an appropriate quantity of an edge activator molecule, such as sodium cholate. Triethanolamine- HCL buffer was made in this way to produce total concentration of lipid. The finished suspension is finally frozen, sonicated and thawed two or three times.[50][51]

2. Thin flim hydration method

The surfactant PL and (vesicles formers) are added to a round-bottomed flask (RBF) that has the correct (v/v) ratio of methanol to chloroform. Lipophilic drugs can be added at this time. In rotatory vaccum evaporator, the organic solvent evaporates above lipid transition temperature under low pressure to produce a thin layer. After adding a hydrophilic medication, the resulting film is hydratedby using a buffer of the proper pH by spinning it at the proper temperature for the designated amount of time. At room temperature, this phase produces inflated vesicles, which are subsequently subjected to sonication by(using a bath or probe). Sonicated vesicles are homogenized by extrusion through a sandwich of 200 nm to 100 nm polycarbonate membrane.[52][53]

3. Centrifugation process

The organic solvent was used to dissolve all the components of the formulations i.e. PLs, surfactant, and lipophilic drug. The mixture was then subjected to rotary evaporators under reduced pressure to remove the solvent. Under vacuum, any residual solvent is cleaned up. By centrifuging the formed lipid film at the room temperature, proper buffer solution is soaked into it. Hydrophilic drugs can be incorporated at this stage. The vesicles that are obtained swell at ambient temperature. The resulting multilamellar vesicles are then sonicated at ambient temperature.[54]

4. Modified Hand Shaking Method

In ethanol: chloroform (1:1) combination, the drug Edge activator and lecithin (PC), are dissolved. Lipid transition temperature above (43°C), the organic solvent is evaporated with handshaking. Rotation causes the formation of a thin lipid layer inside the flask wall. The thin layer is left to dry overnight to ensure complete evaporation of solvent. The film is then

hydrated for 15 minutes at room temperature with phosphate buffer (pH 7.4) and moderate shaking. At 2-8°C, the Transferosomal suspension was hydrated for a further hour.[55][56]

5. Reverse phase evaporation method

Reverse phase evaporation method involves dissolving phospholipids in an organic solvent—chloroform, methanol, or ethanol, for example—and then putting the mixture in a flask37. The flask is filled with a hydrophilic medium that contains a surfactant, such as EA, and is purged using nitrogen gas. The medicine is either integrated into the lipophilic or hydrophilic media, depending on its solubility properties. To make sure that there is no separation, the resultant mixture is sonicated until it produces a homogeneous, transparent dispersion. This process is monitored for at least thirty minutes following sonication. Lastly organic solvent is eliminated from the preparation by treating the sonicated mixture at a lower pressure.[57][58]

6. Ethanol Injection Method

Constant stirring maintain the temperature of medication-containing aqueous solution at that level. A phospholipid solution with ethanol content and drops of edge activators are added to the aqueous solution. When the aqueous medium and the solution come into contact, the lipid molecules precipitate and create bilayered structures. The system has several advantages over other approaches, including being easy to use, highly reproducible, and scalable. shown in (Figure 3).[59][60]

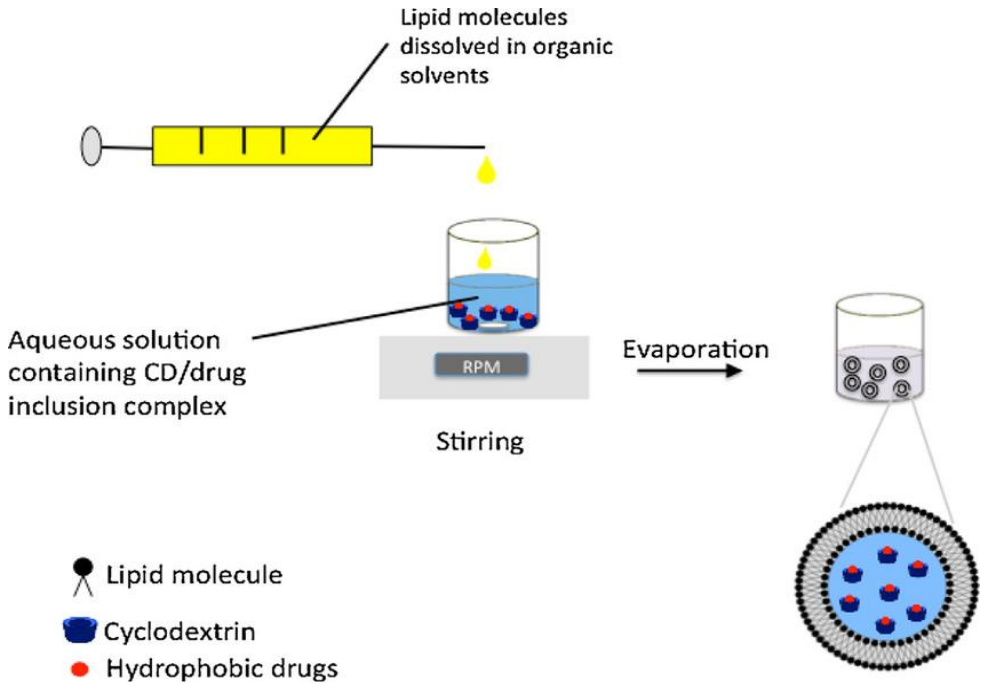

Figure 3: Ethanol Injection Method.

➢ **Characterization of Transferosomes**

The shape and size distribution, zeta potential, vesicle shape, number of vesicles per cubic millimeter, entrapment efficiency, polydispersity index, skin permeability, degree of deformability, measurements, and entrapment efficiency are among the published methods used to ascertain the characterization parameters of the transfersomes are shown in (Table no.3).

Table 3: Characterization of transferosomes.

Parameter	Method /equipment
Vesicle size, and vesicle size distribution	Dynamic light scattering (DLS)method by Malvern zeta sizer.[61]
Zeta potential	Electrophoretic mobility techniques by Malvern Zetasizer.[62][63]
Vesicles morphology	Transmission electron spectroscopy, Photon correlation spectroscopy, DLS Method,[63][02]
Number of vesicles for cubic mm	Entrapment efficiency. Hemocytometer, optical microscope. Directly or indirectly by using [HPLC] High-performance liquid chromatography.[64]
Entrapment efficiency	%Entrapment efficiency = Total amount of drug added amount of the drug entrapped x 100 % entrapment efficiency = total amount of drug added total amount of drug added – amount of free drug 100[65][66]
Drug content	Computerized analysis program and pump depending upon the analytical method of the active pharmaceutical agent.[67]
Degree of deformability	Transmission electron microscopy[TEM]DLS with Microporous filter,[67]
Charge Density and surface charge	DLS Method By Thin-Layer Chromatography, Malvern Zetasizer.[68]
In- vitro skin permeation studies	Franz diffusion cell.[63]
In-vivo skin permeation ability	Fluorescence microscopy,[CSLM] Confocal scanning laser microscopy and histological study are used to determine the bioadhesive potential and retention of transferases in the skin[68]
In-vitro drug release	Extrusion method, Franz diffusion cell with cellulose membrane[66][68]

➢ **Recent Advancements in Transferosome Preparation**

Transferosomes have proven to be an effective method for transdermal distribution of a range of therapies, including hydrophilic actives, peptides, bigger molecules, nucleic acid, proteins to get around the medication size and lipophilicity limits listed in the (Table no.4)

Table 4: Recent advancements in transferosome preparation.

Sr.no	Drug	Drug category	Study conducted	Results obtained
1.	Pioglitazone	Antidiabetic	Skin permeation	Enhanced delivery of Pioglitazone via skin.[69]
2.	Ebastine	2 nd generation antihistamine	In vivo, in vitro characterizations and physiochemical considerations	Ebastine's bioavailability and antihistamine efficacy were significantly enhanced using highly [flexible transpersonal oral films.[70]
3.	Amphotericin	Antifungal	Nasal membrane permeation study	Enhanced permeation of Amphotericin through nasal membrane[71]
4.	Curcumin	Herbal drug (anti-inflammatory)	Skin penetration study	Improved penetration to arthritic skin tissue and exhibited potential effectiveness in the treatment of Freud's adjuvant-induced arthritis.[72]
5.	Mulberry leaf extract (Quercetin)	Bio-active compound (anti-oxidant)	Anti-oxidant activity	Transferosomes gel filled with mulberry leaf extract containing Quercetin is a promising and stable long-term delivery method for Qurcetin[73]
6.	Catechin	Herbal drug (anti-oxidant)	In vivo skin whitening study	The formulation was shown to be efficient in inhibiting Tyrosinase and to be compatible with the skin of guinea pigs in a study. It might be regarded as a therapeutic option for UV-induced oxidative damage to the skin.[73]
7.	Vancomycin	Anti-bacterial	Ex vivo studies	The drug's penetration and bioavailability might be improved with a vancomycin-HCl-loaded transferosome.[74]
8.	Retinyl palmitate	Vitamin A palmitate	Skin penetration study	The findings suggest that transferosomes might be an effective vehicle for delivering retinoids to the skin's inner layers, such as the epidermis.[75]
9.	Lornoxicam	NSAID	Skin Permeation Study	Lornoxicam transferosomal hydrogel is a potential topical product

				for treating local inflammatory disorders effectively.[76]
10	Tocopherol acetate	Tocopherols (Vitamin E)	In-vitro Biocompatibility, Anti-Oxidant activity-vitro wound closure study	Transferosomes containing tocopherols have the potential to be used as a topical delivery method with antioxidant and wound-healing effects.[77]
11.	Ivabradine HCL	Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers	Skin permeation	When compared to pure medication, films containing Ivabradine transferases had improved permeability and skin retention, as well as improved pharmacokinetic characteristics.[78],[79]

- **Application of transferosome**

Transferosomes as drug delivery system have potential to provide controlled release administered drug and increase the stability of labile drugs. Various applications of transferosomes are as follows.

1. Delivery of Insulin

Insulin-loaded transferosomes use a repeatable Idealistically, transfersomes have been employed as a promising carrier for protein and peptide transfer. These are large biogenic molecules that are difficult to transport to the correct location; when administered orally, they are broken down inside the GIT [Gastrointestinal tract]. The most effective way to solve these issues is to employ transferosomes. Once more, following several skin challenges, the adjunct immunogenic serum albumin was delivered via transferosomes with good efficiency and immunological activity comparable to that of analogous injected proteo-transferosome preparations. pharmacological effect to deliver the medication through the non-compromised epidermal barrier. Patients undergoing insulin treatment or solution infusions have shown comparable or even superior outcomes.[80]

2. Delivery of Corticosteroids

Patients can also get corticosteroids via transferosomes. The specificity of the site and medication safety of the corticosteroid delivery system into the skin is improved by transferosomes. Biochemically viable doses of corticosteroids arranged on transferases for disorders of the epidermis are many times lower than those used in the current formulation.[81]

3. Proteins and Peptides

Idealistically, transferosome has been employed as a promising carrier for protein and peptide transfer. These are large biogenic molecules that are difficult to transport to the correct location; when administered orally, they are broken down inside GIT [Gasterointestinal tract]. The most effective way to solve these issues is to employ transferosomes. Once more, following several skin challenges, the adjunct immunogenic serum albumin was delivered via transferosomes with good efficiency and immunological activity comparable to that of analogous injected proteo-transferosome preparations.[82][83]

4. Delivery of Interferon

It has been demonstrated that interferons such as leukocytic-produced interferon (INF-α) are carried by transferosomes. INF-α is a naturally occurring protein that has antiviral, antiproliferative, and immunomodulatory properties. Transferosomes can be used as drug delivery vehicles to increase the stability of labile drugs and offer regulated drug release. Researchers investigated the composition of transferosomes, including interleukin-2 and interferon-α, for potential transdermal use. It has been demonstrated that transferosome-trapped IL-2 and INF-α are sufficiently supplied for immunotherapy.[84]

5. Application in Cosmetics[85]

- Globally, there is a progressive increase in the need for cosmetics as people try to look better and prevent skin damage. Cosmetic products improve appearance and have therapeutic properties.
- Transferosomes in COSMETICS
- 1. Antiacne
- 2.Antiwrinkle
- 3.UV protectant

6. Delivery of Herbal drugs

Transferosomes can penetrate the stratum corneum and provide localized delivery of nutrients to the skin, hence facilitating its ongoing functionality. This field has created capsaicin transferosomes, which exhibit better topical absorption than pure capsaicin.[86]

➢ **Factors Affecting Transferosome Properties**

Numerous process variables may impact on transfersomes' qualities during the process of creating an optimal formulation. These factors mostly pertain to the production of transferosomal formulations denoted by the following:

1. Effect of phospholipids :Edge activators ratio : Phospholipid: Edge activator ratios should be tuned since they have a significant impact on vesicle size, permeation ability, and entrapment efficiency. Due to the configuration, for example, of surfactant molecules inside the lipid bilayer vesicular vesicle membrane permeability and increased fluidity and inducing the leaking of encapsulated medicines, EE decreased in higher surfactant concentration.[87]
2. The Effect of Different Solvents: The compatibility and solubility of the formulation ingredient (such as ethanol, and methanol) are taken into consideration when choosing a solvent. The formulation's solvents can also serve as penetration enhancers, increasing the drug's flow through the membrane.[88]
3. Effect of Different Edge activators: Vesicles' deformability and entrapment efficiency are impacted by a variety of edge activators, including Span 80, sodium deoxycholate and tween 80. By raising the surfactant concentration, the surfactant head group's hydrophilicity, the length of the carbon chain, and the hydrophilic-lipophilic balance (HLB), the vesicles' size decreases. A high surfactant concentration (over 15%) causes the vesicles size decrease.[89],[90]
4. Hydration Medium Effect: Saline phosphate buffer or wate (PH 6.5-7) can be used as the hydrating medium. A balance between biological application as well as formulation characteristics and as well as administration route, should be achieved by the formulation's pH level. Only unionized medicines stay in membrane bound to the enter cells and phospholipid bilayer through the intracellular route; the bilayer lipid of transferosomes resembles the cell membrane of phopholpid layer. Using the proper PH of hydrating medium is crucial since it maintains the drug's unionization, Increasing its entrapment and penetration.[91][92]

➢ **Novel Characterization of Transferosomes[93][94][95]**

Come to know more about the vesicle size, shape, entrapment efficiency, penetration ability, drug content, surface charge, occlusion effect, in vitro drug release, surface charge, in vitro skin penetration, etc. transferosomes can be characterized. It gives controlled release and makes labile medicines more stable. Mentioned in the following points.

- Because transfersomes have an infrastructure made up of both hydrophobic and hydrophilic molecules, they may hold a variety of medicinal compounds with varying solubility.

- Transfersomes exhibit negligible loss when they undergo deformation and squeeze through a constriction that is five to ten times smaller than their diameter. A higher degree of deformability allows intact vesicles to penetrate more easily.
- Both low and high-molecular-weight medications, including analgesics, sex hormones, anesthetic, anti-cancer, anesthetic, gap junction, insulin and protein transported via them. Since they are formed of naturally occurring phospholipids, which are similar to liposomes, they are both biocompatible and biodegradable. They also have a high entrapment efficiency—nearly about 90% in the case of lipophilic drugs—and shield the medication inside from being broken down metabolically.
- They serve as depots, progressively discharging their contents.
- They can be applied topically or systemically to deliver medications.
- The technique is straightforward, requires no lengthy steps or excessive usage of additives that are unsuitable for use in pharmaceuticals, and is therefore easy to scale up.

➢ Different drugs are successfully loaded onto transfersomes which provide targeted as well as controlled drug delivery to the various body tissues listed in (Table No.5)

Table no. 5: Various drugs are loaded into transferosomes which provide targeted as well as controlled drug delivery to the various body tissues.

Sr.No.	Name Of Drug	Interference
1.	Curcumin[96]	Better permeation for the anti inflammatory activity.
2.	Ketoprofen[97]	Improved penetration for anti-inflammatory activity.
3.	Indinavir sulfate[98]	Improved influx for activity against [AIDS] aquired immune deficiency syndrome.
4.	Insulin[99]	Induced therapeutically significant hypoglycemia with good reproducibility and efficacy.
5.	Colchicine and capsacin[100]	Increases penetration of skin.
6.	Interferon-α[101]	Efficient delivery Because delivery of other route is difficult. controlled release overcome the stability problems.
7.	Human serum albumin[102]	Antibody is similar or slightly higher than subcutaneous injection.
8.	Tetanus toxoid[103]	For transdermal immunization.
9.	Tetracaine and Lignocain[104]	Suitable for the non-invasive treatment of local pain on direct topical drug application.
10.	Methotrexate Norgesterol and Oestradiol, Tamoxifen[103]	Improved transdermal flux.

➢ **Marketed Formulation of Transferosome**

1. Diractin

As far as we are aware, the only transpersonal formulation approved by SwissMedic in 2007 and brought to market was Diractin®, which contains ketoprofen. According to Rother et al. (2009), this formulation was recommended as a pain reliever for knee osteoarthritis. Compared to traditional anti-inflammatory gels, transferosomes allowed ketoprofen to reach deeper tissues, such as muscle (Kneer et al., 2009). But as far as we know, six months after the product was approved, Diractin®, which contains ketoprofen, was the only transpersonal formulation to be approved and put on the market by the Swiss Regulatory Agency (SwissMedic) in 2007. According to Rother et al. (2009), this formulation was recommended as a pain reliever for knee osteoarthritis. Compared to traditional anti-inflammatory gels, transferosomes allowed ketoprofen to reach deeper tissues, such as muscle (Kneer et al., 2009).[104]

2. Transfersulin

Ultra-Deformable Insulin Is Carried By The Vesicle Known As Transfersulin. A Single Non-Invasive Transfersulin Epicutaneous Injection Was Used To Establish Systemic Normoglycemia. Confirming The Treatment's Effectiveness In Lowering Blood Glucose Levels In A Patient With Type 1 Diabetes Was The Goal Of The Clinical Trial. When The Pharmacokinetic Properties Of Transfersulin Were Assessed in human volunteers, the glucose dynamic profile in blood after delivery showed a normal concentration ratio of insulin to C-peptide. This can sustain normal glucose levels for a maximum of sixteen hours. Ultralente insulin (Ultratard, Novo-Nordisk), which was injected subcutaneously, served as a comparator. The study's conclusions showed that transfersomes can both maintain blood glucose at an ideal level and lower it to a normal level.[105],[106]

3. Flexiseq

Created by Pro Bono Bio Manufacturing. This drug-free, transfersomal pain-relieving gel was created especially for osteoarthritis-related joint pain. By lubricating the cartilage in joints, the lubricant Flexiseq reduces stiffness and discomfort. Phospholipid bilayer-containing hydrophilic nanosized lipid vesicles are present in sequessome, an aqueous gel. The pro bono bio of the applicant states that the term "sequessome" is synonymous with "transfersome," which is composed of lipid bilayer vesicles. Flexiseq and Sequessome technology belong to Pro Bono Bio. Considered a medical device, Flexiseq is a drug-free

placebo gel. Ultradeformable vesicles called sequessomes can easily fit through the intercellular spaces in the skin without breaking down.[107]

4. TDT 067

Celtic Pharma Development Services is the manufacturer. An innovative topical medication called TDT-067 is used to treat antifungal therapies. Terbinafine transfersomes were developed to deliver the medication to the surrounding tissue and nails treat onychomycosis. This topical terbinafine formulation uses a vesicular carrier-based composition. Transfersome allows the treatment to get to a deeper layer of illness in the surrounding tissue, nail, and nail bed.h[108]

5. Triamcinolene Acetonide Transferosome

Topical glucocorticosteroid formulations are frequently used to treat eczema, dermatitis, rash, allergies, and other inflammatory skin problems. The therapeutic dosage of the drug can be absorbed by the triamcinolene acetonide (TAC) transferosome into the skin's deeper layers. To evaluate the effectiveness and anthropogenic potential of TAC transferosome, a double-blind placebo-controlled clinical trial was carried out and compared to commercially available was discovered to be 10-fold less potent at 2.5 g cm-2 as opposed to 25 g cm-2, making it bioequivalent to ordinary cream. In a clinical investigation, TAC transferosome was observed to improve the risk-benefit ratio after topical application six weeks into therapy.[109][110]

➢ **Future Perspectives**

With medicine that can't effectively permeate the stratum corneum by passive diffusion, the nanocarriers provide cutting-edge local and systemic novel therapeutics. Numerous therapeutic applications are possible due to the excellent efficiency and tolerance of these one vesicular system. when utilized in various application conditions, transferosomes can also be positioned almost solely and quantitatively directly into the viable skin region.

CONCLUSION

The vesicles known as transferosomes are made specifically to fit through skin pores that are far smaller than they are compared to alternative vesicular systems, transferosomes offer many benefits, such as increased stability, deformability, penetrating power through the skin and the capacity to transport medications systemically. Transdermal medication delivery systems are widely employed because of their many advantages over alternative drug

delivery methods. drug penetrate through the Stratum corenum(SC) is a rate-limiting phase; its primary drawback is that bigger molecules cannot be transported by it. so, the transferosome vesicular system can be used efficiently for the convenience of drug distribution. It is also possible to regulate drug release based on necessity. This strategy can thereby solve the issues that arise.

REFERENCES

1. Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: a novel technique for transdermal drug delivery. Journal of drug delivery and therapeutics, Jan. 15, 2019; 9(1): 279-85.
2. Modi CD, Bharadia PD. Transfersomes: new dominants for transdermal drug delivery. Am J Pharm Tech Res., 2012; 2(3): 71-91.
3. Jain AK, Kumar F. Transfersomes: Ultradeformable vesicles for transdermal drug delivery. Asian J. Biomater. Res., 2017; 3: 1-3.
4. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Lipid vesicles for skin delivery of drugs: reviewing three decades of research. International journal of pharmaceutics, Mar. 6, 2007; 332(1-2): 1-6.
5. Touitou E, Junginger HE, Weiner ND, Nagai T, Mezei M. Liposomes as carriers for topical and transdermal delivery. Journal of Pharmaceutical Sciences, Sep. 1, 1994; 83(9): 1189-203.
6. Hong K, Drummond DC, Kirpotin DB, inventors; Merrimack Pharmaceuticals Inc, assignee. Liposomes for drug delivery, 2017 May 31.
7. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. Critical reviews™ in therapeutic drug carrier systems, 1996; 13(3-4).
8. Rajan R, Jose S, Mukund VB, Vasudevan DT. Transferosomes-A vesicular transdermal delivery system for enhanced drug permeation. Journal of Advanced Pharmaceutical Technology & Research, Jul. 1, 2011; 2(3): 138-43.
9. Lymberopoulos A, Demopoulou C, Kyriazi M, Katsarou MS, Demertzis N, Hatziandoniou S, Maswadeh H, Papaioanou G, Demetzos C, Maibach H, Rallis M. Liposome percutaneous penetration in vivo. Toxicology Research and Application, Aug. 4, 2017; 1: 2397847317723196.

10. Xu X, Khan MA, Burgess DJ. Predicting hydrophilic drug encapsulation inside unilamellar liposomes. International journal of pharmaceutics, Feb. 28, 2012; 423(2): 410-8.
11. Szoka Jr F, Papahadjopoulos D. Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaporation. Proceedings of the national academy of sciences, Sep. 1978; 75(9): 4194-8.
12. Crommelin DJ, Fransen GJ, Salemink PJ. Stability of liposomes on storage. Targeting of drugs with synthetic systems, 1986; 277-87.
13. Ge X, Wei M, He S, Yuan WE. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. Pharmaceutics, Jan. 29, 2019; 11(2): 55.
14. Marianecci C, Di Marzio L, Rinaldi F, Celia C, Paolino D, Alhaique F, Esposito S, Carafa M. Niosomes from 80s to present: the state of the art. Advances in colloid and interface science, Mar. 1, 2014; 205: 187-206.
15. Mujoriya RZ, Dhamande K, Bodla RB. Liposomal drug delivery system—a review. Int j appl pharm, May 28, 2011; 3(3): 7-10.
16. Ezzat HM, Elnaggar YS, Abdallah OY. The improved oral bioavailability of the anticancer drug catechin using chitosomes: Design, in-vitro appraisal and in-vivo studies. International journal of pharmaceutics, Jun. 30, 2019; 565: 488-98.
17. Manca ML, Manconi M, Valenti D, Lai F, Loy G, Matricardi P, Fadda AM. Liposomes coated with chitosan–xanthan gum (chitosomes) as potential carriers for pulmonary delivery of rifampicin. Journal of pharmaceutical sciences, Feb. 1, 2012; 101(2): 566-75.
18. Mertins O, Dimova R. Binding of chitosan to phospholipid vesicles studied with isothermal titration calorimetry. Langmuir, May 3, 2011; 27(9): 5506-15.
19. Jain S, Jain V, Mahajan SC. Lipid-based vesicular drug delivery systems. Advances in Pharmaceutics, Sep. 2, 2014; 2014: 1-2.
20. Mann JF, Scales HE, Shakir E, Alexander J, Carter KC, Mullen AB, Ferro VA. Oral delivery of tetanus toxoid using vesicles containing bile salts (bilosomes) induces significant systemic and mucosal immunity. Methods, Feb. 1, 2006; 38(2): 90-5.
21. Yang L, Tucker IG, Østergaard J. Effects of bile salts on propranolol distribution into liposomes studied by capillary electrophoresis. Journal of pharmaceutical and biomedical analysis, Nov. 1, 2011; 56(3): 553-9.
22. Rai S, Pandey V, Rai G. Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: The state of the art. Nano reviews & experiments, Jan. 1, 2017; 8(1): 1325708.

23. Cevc G, Schätzlein A, Richardson H. Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double-label CLSM experiments and direct size measurements. Biochimica et Biophysica Acta (BBA)-Biomembranes, Aug. 19, 2002; 1564(1): 21-30.
24. Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. Advanced drug delivery reviews, Mar. 27, 2004; 56(5): 675-711.
25. Rother M, Lavins BJ, Kneer W, Lehnhardt K, Seidel EJ, Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: a multicentre randomized controlled trial. Annals of the rheumatic diseases, Sep. 1, 2007; 66(9): 1178-83.
26. Kumar A, Pathak K, Bali V. Ultra-adaptable nano vesicular systems: a carrier for systemic delivery of therapeutic agents. Drug discovery today, Nov. 1, 2012; 17(21-22): 1233-41.
27. Fesq H, Lehmann J, Kontny A, Erdmann I, Theiling K, Rother M, Ring J, Cevc G, Abeck D. Improved risk-benefit ratio for topical triamcinolone acetonide in Transfersome® in comparison with equipotent cream and ointment: a randomized controlled trial. British Journal of Dermatology, Sep. 1, 2003; 149(3): 611-9.
28. Cevc G. Modified-Release Drug Delivery Technology. New York: Informa healthcare, 2008; 2: 311.
29. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. Journal of controlled release, Apr. 3, 2000; 65(3): 403-18.
30. Shah SM, Ashtikar M, Jain AS, Makhija DT, Nikam Y, Gude RP, Steiniger F, Jagtap AA, Nagarsenker MS, Fahr A. LeciPlex, invasomes, and liposomes: A skin penetration study. International journal of pharmaceutics, Jul. 25, 2015; 490(1-2): 391-403.
31. Qadri GR, Ahad A, Aqil M, Imam SS, Ali A. Invasomes of isradipine for enhanced transdermal delivery against hypertension: formulation, characterization, and in vivo pharmacodynamic study. Artificial cells, nanomedicine, and biotechnology, Jan. 2, 2017; 45(1): 139-45.
32. Lei W, Yu C, Lin H, Zhou X. Development of tacrolimus-loaded transfersomes for deeper skin penetration enhancement and therapeutic effect improvement in vivo. Asian journal of pharmaceutical sciences, Dec. 1, 2013; 8(6): 336-45.

33. Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Characterization and in vitro skin permeation of meloxicam-loaded liposomes versus transfersomes. Journal of drug delivery, 2011; 2011.
34. Aggarwal N, Goindi S. Preparation and evaluation of antifungal efficacy of griseofulvin loaded deformable membrane vesicles in optimized guinea pig model of Microsporum canis—Dermatophytosis. International journal of pharmaceutics, Nov. 1, 2012; 437(1-2): 277-87.
35. Dudhipala N, Phasha Mohammed R, Adel Ali Youssef A, Banala N. Effect of lipid and edge activator concentration on the development of aceclofenac-loaded transfersomes gel for transdermal application: in vitro and ex vivo skin permeation. Drug development and industrial pharmacy, Aug. 2, 2020; 46(8): 1334-44.
36. Pawar AY. Transfersome: A novel technique that improves transdermal permeability. Asian Journal of Pharmaceutics (AJP)., Dec. 21, 2016; 10(04).
37. Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics, Sep. 2020; 12(9): 855.
38. Gupta R, Kumar A. Transfersomes: the ultra-deformable carrier system for non-invasive delivery of the drug. Current Drug Delivery, May. 1, 2021; 18(4): 408-20.
39. Luiz MT, Viegas JS, Abriata JP, Tofani LB, de Menezes Vaidergorn M, da Silva Emery F, Chorilli M, Marchetti JM. Docetaxel-loaded folate-modified TPGS-transfersomes for glioblastoma multiforme treatment. Materials Science and Engineering: C., May. 1, 2021; 124: 112033.
40. Reddy YD, Sravani AB, Ravisankar V, Prakash PR, Reddy YS, Bhaskar NV. Transferosomes are a novel vesicular carrier for transdermal drug delivery systems. J. Innov. Pharm. Biol. Sci., 2015; 2(2): 193-208.
41. Bnyan R, Khan I, Ehtezazi T, Saleem I, Gordon S, O'Neill F, Roberts M. Surfactant effects on lipid-based vesicles properties. Journal of pharmaceutical sciences, May. 1, 2018; 107(5): 1237-46.
42. Lakshmi PK, Kalpana B, Prasanthi D. Invasomes-novel vesicular carriers for enhanced skin permeation. Systematic Reviews in Pharmacy, Jan. 1, 2013; 4(1).
43. Arora N, Agarwal S, Murthy RS. The latest technology advances in cosmaceuticals. Int. J. Pharm. Sci. Drug Res., 2012; 4(3): 168-82.
44. Chaturvedi M, Kumar M, Sinhal A, Saifi A. Recent development in novel drug delivery systems of herbal drugs. International Journal of Green Pharmacy (IJGP), 2011; 5(2).

45. Pople PV, Singh KK. Development and evaluation of a topical formulation containing solid lipid nanoparticles of vitamin A. Aaps Pharmscitech, Dec. 2006; 7: E63-9.
46. Kumar A. Transferosome: A recent approach for transdermal drug delivery. Journal of Drug Delivery and Therapeutics, Oct. 15, 2018; 8(5-s): 100-4.
47. Veldurthi R, Sailaja AK. A Review on Transferosomes as Ultra Deformable Vesicular Carriers for Transdermal Drug Delivery. InnovatInt J Med Pharm Sci., 2017; 2(5): 48-56.
48. Ghai I, Chaudhary H, Ghai S, Kohli K, Kr V. A review of transdermal drug delivery using nano-vesicular carriers: Transfersomes. Recent Patents on Nanomedicine, Oct. 1, 2012; 2(2): 164-71.
49. Patel R, Singh SK, Singh S, Sheth NR, Gendle R. Development and characterization of curcumin loaded transfersome for transdermal delivery. Journal of pharmaceutical sciences and research, Dec. 1, 2009; 1(4): 71.
50. Shuwaili AH, Rasool BK, Abdulrasool AA. Optimization of elastic transfersomes formulations for transdermal delivery of pentoxifylline. European Journal of Pharmaceutics and Biopharmaceutics, May 1, 2016.
51. Qushawy M, Nasr A, Abd-Alhaseeb M, Swidan S. Design, optimization and characterization of a transfersomal gel using miconazole nitrate for the treatment of candida skin infections. Pharmaceutics. 2018 Feb 23;10(1):26. Qushawy M, Nasr A, Abd-Alhaseeb M, Swidan S. Design, optimization and characterization of a transfersomal gel using miconazole nitrate for the treatment of candida skin infections. Pharmaceutics, Feb. 23, 2018; 10(1): 26. 102: 101-14.
52. Agrawal R, Sandhu SK, Sharma I, Kaur IP. Development and evaluation of curcumin-loaded elastic vesicles as an effective topical anti-inflammatory formulation. AAPS PharmSciTech., Apr. 2015; 16: 364-74.
53. Singh HP, Utreja P, Tiwary AK, Jain S. Elastic liposomal formulation for sustained delivery of colchicine: in vitro characterization and in vivo evaluation of anti-gout activity. The AAPS journal, Mar. 2009; 11: 54-64.
54. Abdallah MH. Transfersomes as a transdermal drug delivery system for enhancement of the antifungal activity of nystatin. LIPOSOME & NANOTECHNOLOGY, 2013; 390.
55. Chen G, Li D, Jin Y, Zhang W, Teng L, Bunt C, Wen J. Deformable liposomes by reverse-phase evaporation method for an enhanced skin delivery of (+)-catechin. Drug development and industrial pharmacy, Feb. 1, 2014; 40(2): 260-5.
56. Sachan R, Parashar T, Singh V, Singh G, Tyagi S, Patel C, Gupta A. Drug carrier transfersomes A novel tool for transdermal drug delivery system.

57. Shreya Dhopavkar, PramodKadu. Transfersomes - a boon for transdermal delivery. Indo american Journal of Pharmaceutical Sciences, 2017; 4(09): 2908-2919.
58. Balata GF, Faisal MM, Elghamry HA, Sabry SA. Preparation and characterization of ivabradine HCl transfersomes for enhanced transdermal delivery. Journal of drug delivery science and technology, Dec. 1, 2020; 60: 101921.
59. Vinod KR, Kumar MS, Anbazhagan S, Sandhya S, Saikumar P, Rohit RT, Banji D. Critical issues related to transfersomes-novel vesicular system. ACTA Scientiarum Polonorum Technologia Alimentaria, Mar. 30, 2012; 11(1): 67-82.
60. Chauhan P, Tyagi BK. Herbal novel drug delivery systems and transfersomes. Journal of Drug Delivery and Therapeutics, May. 14, 2018; 8(3): 162-8.
61. Jain S, Umamaheswari RB, Bhadra D, Tripathi P, Jain P, NK Jain. Ultradeformable Liposomes: A recent tool for Effective Transdermal Drug Delivery. Indian Journal of Pharmaceutical Sciences, 2003; 65(3).
62. MohdKalim, Prem Shankar Tyagi, and Swarnakshi Upadhyay. A Review on Transfersomal Drug Delivery System. International Journal of Pharmacy & Life Sciences, 2021; 12(3).
63. Kulkarni PR, Yadav JD, Vaidya KA, Gandhi PP. Transferosomes: an emerging tool for transdermal drug delivery. International journal of pharmaceutical sciences and research, Apr. 1, 2011; 2(4): 735.
64. Das B, Nayak AK, Mallick S. Transferosomes: a novel nano vesicular approach for drug delivery. InSystems of nano vesicular drug delivery, Jan. 1, 2022: 103-114. Academic Press.
65. Jeevajothi M, Sinha P, Rathnam G, Ubaidulla U. Review on Background of Future Prospects of Transfersome in Drug Delivery System.
66. Nagasamy V., K. Kalyani, K. Tulasi, V. Swetha P., S. K. Abid A., H. C. Kiran. Transfersomes: A Novel Technique for Transdermal Drug Delivery, International Journal of Research in Pharmaceutical and Nano Sciences, 2014; 3(4): 266-276.
67. Hosny KM, Alhakamy NA. Nasal gel loaded with amphotericin nanotransferosomes as an antifungal treatment for fungal sinusitis. Pharmaceutics, Dec. 28, 2020; 13(1): 35.
68. Sana E, Zeeshan M, Ain QU, Khan AU, Hussain I, Khan S, Lepeltier E, Ali H. Topical delivery of curcumin-loaded transfersomes gel ameliorated rheumatoid arthritis by inhibiting NF-κβ pathway. Nanomedicine, Mar. 2021; 16(10): 819-37.

69. Islam N, Irfan M, Zahoor AF, Iqbal MS, Syed HK, Khan IU, Rasul A, Khan SU, Alqahtani AM, Ikram M, Abdul Qayyum M. Improved bioavailability of ebastine through the development of transfersomal oral films. Pharmaceutics, Aug. 23, 2021; 13(8): 1315.
70. Nangare S, Bhatane D, Rushikesh MA, Shitole M. Development of a novel freeze-dried mulberry leaf extract-based transfersome gel. Turkish Journal of Pharmaceutical Sciences, Feb. 2021; 18(1): 44.
71. Hsieh WC, Fang CW, Suhail M, Vu QL, Chuang CH, Wu PC. Improved skin permeability and whitening effect of catechin-loaded transfersomes through topical delivery. International Journal of Pharmaceutics, Sep. 25, 2021; 607: 121030.
72. Maji R, Omolo CA, Jaglal Y, Singh S, Devnarain N, Mocktar C, Govender T. A transfer some-loaded bigel for enhanced transdermal delivery and antibacterial activity of vancomycin hydrochloride. International Journal of Pharmaceutics, Sep. 25, 2021; 607: 120990.
73. Ibrahim SS, Elseoud OG, Mohamedy MH, Amer MM, Mohamed YY, Elmansy SA, Kadry MM, Attia AA, Fanous RA, Kamel MS, Solyman YA. Nose-to-brain delivery of chrysin transfersomal and composite vesicles in doxorubicin-induced cognitive impairment in rats: Insights on formulation, oxidative stress, and TLR4/NF-kB/NLRP3 pathways. Neuropharmacology, Oct. 1, 2021; 197: 108738.
74. Tawfeek HM, Abdellatif AA, Abdel-Aleem JA, Hassan YA, Fathalla D. Transfersomal gel nanocarriers for enhancement the permeation of lornoxicam. Journal of Drug Delivery Science and Technology, Apr. 1, 2020; 56: 101540.
75. Rabia S, Khaleeq N, Batool S, Dar MJ, Kim DW, Din FU, Khan GM. Rifampicin-loaded nanotransferosomal gel for the treatment of cutaneous leishmaniasis: passive targeting via topical route. Nanomedicine, Jan. 2020; 152): 183-203.
76. Piumitali B, Neeraj U, Jyotivardhan J. Transfersomes—nanoscience in transdermal drug delivery and its clinical advancements. International Journal of Nanoscience, Aug. 5, 2020; 19(04): 1950033.
77. Caddeo C, Manca ML, Peris JE, Usach I, Diez-Sales O, Matos M, Fernàndez-Busquets X, Fadda AM, Manconi M. Tocopherol-loaded transfersomes: In vitro antioxidant activity and efficacy in skin regeneration—international journal of pharmaceutics, Nov. 15, 2018; 551(1-2): 34-41.
78. Shende M, Bodele S, Ghode S, Baravkar A, Nalawade N. Transferosomes: A promising vesicular-based skin-oriented drug delivery system: https://doi. org/10.54037/WJPS. 2021.91009. World Journal of Pharmaceutical Sciences, Oct. 1, 2021: 46-55.

79. Patel Chirag J, Tyagi S, Pinkesh P, Kumar U, Jaimin P, Bharat C. Transferosomes: A Novel Technique For Transdermal Drug Delivery.
80. Qushawy M, Nasr A, Abd-Alhaseeb M, Swidan S. Design, optimization and characterization of a transfersomal gel using miconazole nitrate to treat candida skin infections. Pharmaceutics, Feb. 23, 2018; 10(1): 26.
81. Cevc G. Transdermal drug delivery of insulin with ultra deformable carriers. Clinical pharmacokinetics, Apr. 2003; 42: 461-74.
82. H. Yang, X. Wu, Z. Zhou, X. Chen, and M. Kong, "Enhanced transdermal lymphatic delivery of doxorubicin via hyaluronic acid based transfersomes/microneedle complex for tumor metastasis therapy," *Int. J. Biol. Macromol.*, Mar. 2019; 125: 9–16, doi: 10.1016/j.ijbiomac.2018.11.230.
83. Pallathadka LK, Pallathadka H. NOVEL CARRIER FOR TRANSDERMAL PATCHES USED IN TRANSFEROSOMES: A REVIEW.
84. Akram MW, Jamshaid H, Rehman FU, Zaeem M, Khan JZ, Zeb A. Transfersomes: a revolutionary nanosystem for efficient transdermal drug delivery. AAPS PharmSciTech., Jan. 2022; 23: 1-8.
85. Kadu SD. Transfersomes—A boon for transdermal delivery. Indo Am. J. Pharm. Sci., 2017; 4: 2908-19.
86. Williams AC, Barry BW. Penetration enhancers. Advanced drug delivery reviews, Dec. 1, 2012; 64: 128-37.
87. Shamma RN, Elsayed I. Transfersomal lyophilized gel of buspirone HCl: formulation, evaluation and statistical optimization. Journal of liposome research, Sep. 1, 2013; 23(3): 244-54.
88. N'Da DD. Prodrug strategies for enhancing the percutaneous absorption of drugs. Molecules, Dec. 12, 2014; 19(12): 20780-807.
89. Garg M, Mishra D, Agashe H, Jain NK. Ethinylestradiol-loaded ultra flexible liposomes: pharmacokinetics and pharmacodynamics. Journal of pharmacy and pharmacology, Apr. 2006; 58(4): 459-68.
90. Jalon GE. Ygartua P, Santoyo S. Topical application of acyclovir-loaded microparticles: quantification of the drug in porcine skin layers. J Control Release, 2001; 75: 191-197.
91. Jain NK. Advances in controlled and novel drug delivery. CBS publishers& distributors. New Delhi, 2001; 317.

92. Swarnlata Saraf SS, Gunjan Jeswani GJ, Kaur CD, Shailendra Saraf SS. Development of novel herbal cosmetic cream with Curcuma longa extract loaded transfersomes for anti-wrinkle effect.
93. Schatzlein AG, Cevc G. Skin penetration by phospholipid vesicles, transfersomes, as visualized using the confocal laser scanning microscopy. Amer Oil Chemists Society.
94. Rother M, Seidel EJ, Clarkson PM, Mazgareanu S, Vierl U, Rother I. Efficacy of epicutaneous Diractin®(ketoprofen in Transfersome® gel) for the treatment of pain related to eccentric muscle contractions. Drug design, development, and therapy, Sep. 21, 2009: 143-9.
95. Cevc G, Gebauer D, Stieber J, Schätzlein A, Blume G. Ultraflexible vesicles, Transfersomes, have extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin. Biochimica et Biophysica Acta (BBA)-Biomembranes, Jan. 19, 1998; 1368(2): 201-15.
96. Xiao-Ying L, Luo JB, Yan ZH, Rong HS, Huang WM. Preparation and in vitro and in vivo evaluations of topically applied capsaicin transfersomes. Yao xue xue bao= Acta pharmaceutica Sinica, May. 1, 2006; 41(5): 461-6.
97. Hofer C, Göbel R, Deering P, Lehmer A, Breul J. Formulation of interleukin-2 and interferon-alpha containing ultra deformable carriers for potential transdermal application. Anticancer research, Mar. 1, 1999; 19(2C): 1505-7.
98. Gupta PN, Mishra V, Singh P, Rawat A, Dubey P, Mahor S, Vyas SP. Tetanus toxoid-loaded transfersomes for topical immunization. Journal of pharmacy and pharmacology, Mar. 2005; 57(3): 295-301.
99. El Maghraby GM, Williams AC, Barry BW. Skin delivery of oestradiol from lipid vesicles: the importance of liposome structure. International journal of pharmaceutics, Jun. 20, 2000; 204(1-2): 159-69.
100. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. International journal of pharmaceutics, Feb. 11, 2004; 270(1-2): 119-25.
101. Vinod KR, Kumar MS, Anbazhagan S, Sandhya S, Saikumar P, Rohit RT, Banji D. Critical issues related to transfersomes-novel vesicular system. ACTA Scientiarum Polonorum Technologia Alimentaria, Mar. 30, 2012; 11(1): 67-82.
102. Molinaro R, Gagliardi A, Mancuso A, Cosco D, Soliman ME, Casettari L, Paolino D. Development and in vivo evaluation of multidrug ultra deformable vesicles for the treatment of skin inflammation. Pharmaceutics, Dec. 3, 2019; 11(12): 644.

103. Yusuf M, Sharma V, Pathak K. Nanovesicles for transdermal delivery of felodipine: Development, characterization, and pharmacokinetics. International journal of pharmaceutical investigation, Jul. 2014; 4(3): 119.
104. M. A. Hady, A. B. Darwish, M. S. Abdel-Aziz, and O. M. Sayed, "Design of transfersomal nanocarriers of nystatin for combating vulvovaginal candidiasis; A different perspective," *Colloids Surfaces B Biointerfaces*, 2022; 211: 112304.
105. Dixena B, Madhariya R, Panday A, Ram A, Jain AK. Overcoming Skin Barrier with Transfersomes: Opportunities, Challenges, and Applications. Current Drug Delivery, 2024.
106. Simrah, Hafeez A, Usmani SA, Izhar MP. Transfersome, an ultra-deformable lipid-based drug nanocarrier: an updated review with therapeutic applications. Naunyn-Schmiedeberg's Archives of Pharmacology, Feb. 2024; 397(2): 639-73.
107. Oyarzún P, Gallardo-Toledo E, Morales J, Arriagada F. Transfersomes as alternative topical nano-dosage forms for the treatment of skin disorders. Nanomedicine, Nov. 2021; 16(27): 2465-89.
108. Albalawi W, Alharbi S, Alanazi F, Alahmadi H, Alghamdi M, Soliman GM, Safwat MA. Elegant, Flexible Vesicular Nanocarriers for the Efficient Skin Delivery of Topically Applied Drugs. Current Nanoscience, Jul. 1, 2023; 19(4): 493-508.
109. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. International journal of pharmaceutics, Feb. 11, 2004; 270.