IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Transferrosomes: A Unveiled Detailed Review of Transferrosomes

Sunandha[1],Anjali Kumari[*2] ,Dr Kapil Kumar Verma[3]

Minerva college Of Pharmacy [HP]

Corresponding Author

Anjali Kumari

Assistant Professor

Minerva College of Pharmacy

ABSTRACT

Chromosome territories (CTs) constitute a major feature of nuclear architecture. In a brief statement, the possible contribution of nuclear architecture studies to the field of epigenomics is considered, followed by a historical account of the CTs concept and the final compelling experimental evidence of a territorial organization of chromosomes in all eukaryotes studied to date. Present knowledge of non-random CTs arrangements, of the internal CTs architecture, and of structural interactions with other CTs is provided as well as the dynamics of CTs arrangements2 during cell cycle and postmitotic terminal differentiation. The article concludes with a discussion of open questions and new experimental strategies to answer them. The idea of evolution as a principle for the origin of biodiversity fits all phenomena of life, including the carriers of nuclear inheritance, the chromosomes. Insights into the evolutionary mechanisms that contribute to the shape, size, composition, number and redundancy of chromosomes elucidate the high plasticity of nuclear genomes at the chromosomal level, and the potential for genome modification in the course of breeding processes. Aspects of chromosome fusion, as exemplified by karyotype evolution of relatives of *Arabidopsis*, have recently received special attention. Transferosomes, also known as transfersomes, are ultradeformable vesicles for transdermal applications consisting of a lipid bilayer with phospholipids and an edge activator and an ethanol/aqueous core.Depending on the lipophilicity of the active substance, it can be encapsulated within the core or amongst the lipid bilayer. Compared to liposomes, transferosomes are able to reach intact deeper regions of the skin after topical administration delivering higher concentrations of active substances making them a successful drug delivery carrier for transdermal applications. Most transferosomes contain

phosphatidylcholine (C18) as it is the most abundant lipid component of the cell membrane, and hence, it is highly tolerated for the skin, decreasing the risk of undesirable effects, such as hypersensitive reactions. The most common edge activators are surfactants such as sodium deoxycholate, Tween® 80 and Span® 80. Their chain length is optimal for intercalation within the C18 phospholipid bilayer. A wide variety of drugs has been successfully encapsulated within transferosomes such as phytocompounds like sinomenine or apigenin for rheumatoid arthritis and leukaemia respectively, small hydrophobic drugs but also macromolecules like insulin. The main factors to develop optimal transferosomal formulations (with high drug loading and nanometric size) are the optimal ratio between the main components as well as the critical process parameters for their manufacture. Application of quality by design (QBD), specifically design of experiments (DoE), is crucial to understand the interplay among all these factors not only during the preparation at lab scale but also in the scale-up process.

1.Introduction:

Transferosomes is a carrying body for targeted transdermal drug delivery system. This are special types of liposomes, consisting of phosphatidylcholine and an edge activator. This system also takes advantage of phospholipids vesicles as transdermal drug carrier.[1] It penetrate the stratum corneum by either intracellular route or the transcellular route by the generation of "osmotic gradient". Advantages of Transferosomes are wide range of solubilities, better penetration, biocompatible and biodegradable etc. Advantages of Transferosomes are oxidative degradation, expensive, etc. The transfersomes were formulated by the conventional rotary evaporation sonication method.[2] It contains phospholipids, surfactant and the drug were formulated. Evaluation parameters of transferosome are as Vesicle size distribution and zeta potential, Vesicle morphology, No. of vesicles per cubic mm, Entrapment efficiency, Drug content, Turbidity measurement, Degree of deformability or permeability measurement, Penetration ability, Occlusion effect, Surface charge and charge density, In-vitro drug release, in-vitro Skin permeation Studies, Physical stability. Transferosomes can be applied in controlled release, transportation of large molecules weight compounds, target delivery to peripheral subcutaneous tissues, transdermal immunization etc.[3]

Transferosomes is a carrying body for targeted transdermal drug delivery system. This are special types of liposomes, consisting of phosphatidylcholine and an edge activator. This system also takes advantage of phospholipids vesicles as transdermal drug carrier. It penetrate the stratum corneum by either intracellular route or the transcellular route by the generation of "osmotic gradient".[4] Advantages of Transferosomes are wide range of solubilities, better penetration, biocompatible and biodegradable etc. Advantages of Transferosomes are oxidative degradation, expensive, etc. The transfersomes were formulated by the conventional rotary evaporation method.5 It contains phospholipids, surfactant and the drug were formulated. Evaluation Parameters of transferrosomes are as Vesicle size distribution and zeta potential, Vesicle morphology, No. of vesicles per cubic mm**,** Transferosomes are highly deformable vesicles with a complex lipid bilayer enclosing an aqueous core.[6] The vesicle is self-regulating and self-optimizing due to the interdependence of the bilayer's structure and local composition.[7] Transferosomes can administer both high and low molecular weight medications transdermally.[8] Transferosomes are highly flexible, specially engineered lipid supra molecular aggregates that may pass through intact mammalian skin to serve as a drug carrier for targeted, non-invasive drug delivery and long-term release of medicinal substances.[9]

Peripheral targeting results from transferosomes, which are colloidal carriers that readily collect in leaking synovial tissue. Additionally, transferosomes serve as a depot, creating a regulated drug delivery system. The osmotic gradient between the outer and inner layers of stratum corneum 4 provides the driving power for better

drug delivery by transferosomes, allowing them to spontaneously pass through intact skin while being influenced by the naturally occurring in vivo transcutaneous hydration gradient.[10] Transferosomes are excellent options for the non-invasive delivery of tiny, medium, and large medications because of their deformability.

The skin's barrier function typically limits the use of transdermal medication administration. One of the most contentious techniques for transdermal distribution of active ingredients is vesicular systems. The discovery of elastic vesicles such as transferosomes, ethosomes, cubosomes, phytosomes, etc. reignited interest in developing transdermal delivery systems.

The composition, penetration mechanisms, production processes, and characterization techniques of transferosomes as transdermal delivery vehicles for active ingredients are presented in this work.[11] A medicine must cross one or more biological membranes or barriers at different points in order to be absorbed, distributed into organs and tissues, and then removed from the body. Drug transport is the term used to describe this type of drug transportation across the membrane. The medications must pass through the membrane in order to enter the body.

. These delivery methods were created with the goal of concentrating the medication in the targeted tissues while lowering the concentration of the medication in the other tissues. As a result, the medication has no effect on nearby tissues. Furthermore, drug loss is prevented by drug localization, resulting in optimal treatment efficacy. As a result, the carrier systems based on phospholipids are very interesting nowadays.[12]

Transfersomes are ultradeformable vesicles with a complex lipid bilayer enclosing an aqueous core. Transferosomes can hold medicinal molecules with a broad range of solubility because of their architecture, which is made up of both hydrophobic and hydrophilic moieties. 9. Without experiencing any discernible loss, transferosomes can distort and flow through narrow constriction that is five to ten times smaller than their own diameter.[13]

transferosomes vesicles are composed of phospholipids as the main ingredient (soya phosphatidylcholine, egg phosphatidylcholine, dipalmityl phosphatidylcholine, etc), 10- 25% surfactants for providing flexibility (sodium cholate, tween 80, span-80), 3-10% alcohol as a solvent (ethanol, methanol) and hydrating medium consisting of saline phosphate buffer (pH 6.5-7). There are two primary aggregates that make up the transfersome. The first is phosphatidylcholine, an amphipathic component in which the aqueous solvents self-assemble form a lipid bilayer that condenses into a straightforward lipid vesicle.[14] Second, a bilayer softening agent that improves the permeability and flexibility of lipid bilayers, like an amphiphile medication or biocompatible surfactant.[15] The existence of so-called edge-activators sets them apart from liposomes. Their primary constituents are phospholipids, with 3–10% ethanol and 10–25% surfactant (such as sodium cholate). The "edge activators," or surfactants, give the transferosomes their ultradeformability.[16] The amount and structure of the added surfactant are connected to the vesicle's flexibility. It has been asserted that transferosomes can carry their "payload" farther into the skin than liposomes can.

In recent decades, liposomes and niosomes have garnered a lot of attention as vesicular carrier systems for transdermal drug administration. Researchers have discovered ways to tag vesicles for cell selectivity in order to enhance drug delivery within the chambers of vesicles. Vesicles are employed in transdermal drug delivery because of their nature, which allows them to function as both drug carriers to transport encapsulated drug molecules over the skin and penetration enhancers. Additionally, these vesicles serve as a depot for the prolonged release of active substances in topical treatments and a rate-limiting membrane barrier to regulate systemic absorption.

KEYWORDS: Transferosomes, Transdermal drug delivery system, Modified Transferosomes.

2. Limitations of Transferrosomes:

• Composed of hydrophilic and hydrophobic components, transfersomes are a unique type of drug carrier that may disperse drugs with different solubility ranges.

• due to their exceptional elastic properties and deformability.

Very tiny skin barrier constrictions, five to ten times smaller than the vesicle diameter, can be penetrated by transfersomes.

• Because high vesicle deformability facilitates drug transport across the skin without observable loss of intact vesicles, it enables the administration of both topical and systemic treatments.

• Regardless of the polarity, size, structure, or molecular weight of the chemicals they contain, transfersomes are highly versatile and efficient.

• Hydrophilic and hydrophobic moieties combine to form transfersomes, a unique type of drug carrier that may disperse drugs with different solubility ranges.

- Transfersomes can penetrate skin barrier constrictions that are 5–10 times smaller than the vesicle diameter due to their exceptional deformability and elastic properties.
- Because high vesicle deformability facilitates drug transport across the skin without observable loss of intact vesicles, it enables the administration of both topical and systemic treatments.
- It makes sense to employ transfersomes in order to accomplish both a sustained drug release and an extended and reliable duration of activity.

  • They can improve the transdermal flow and site specificity of bioactive compounds.

  •Transfersomes can often achieve a relatively high entrapment efficiency (EE) of about 90% of the lipophilic medication. The highest entrapment efficiency attained for curcumin (CRM) and diclofenac diethylamine (DDEA) transfersome formulations was over 90%.

  • Using transfersomes is a sensible way to achieve both a prolonged and consistent duration of action and a sustained medication release.

• They can enhance the site specificity and transdermal flow of bioactive substances.
• preventing first-pass metabolism, a significant disadvantage of oral medication administration, and increasing the drug's bioavailability.

•A comparatively high entrapment efficiency (EE) of about 90% of the lipophilic drug can frequently be attained by transfersomes. Diclofenac diethylamine (DDEA) and curcumin (CRM) transfersome formulations have the maximum entrapment efficiency.

- Why reduce unwanted side effects and shield the medication from metabolic breakdown; brief half-lives are also beneficial.
- Transfersomes often achieve a relatively high entrapment efficiency (EE) of approximately 90% of the lipophilic medication.
  Why Minimize undesirable side effects and protect the drug from metabolic degradation; short drug half-lives are also helpful.
- Transfersomes frequently attain a comparatively high entrapment efficiency (EE) of roughly 90% of the drug that is lipophilic.
- Transfersomes can often achieve a relatively high entrapment efficiency (EE) of approximately 90% of the lipophilic medication.
- Transfersomes are a clear choice for attaining both a consistent and prolonged duration of activity and a sustained drug release.
  They have the ability to improve the site specificity of bioactive substances and raise the transdermal flow.
- Avoiding first-pass metabolism, a significant disadvantage of oral medication delivery, and maximizing the drug's bioavailability.
  reduce the drug's unwanted side effects and shield it from metabolic deterioration; additionally, short half-life medications are useful.
- Transfersomes may typically achieve a comparatively high entrapment efficiency (EE) of around 90% of the lipophilic medication. The highest entrapment efficiency attained for diclofenac diethylamine (DDEA) and curcumin (CRM) transfersome formulations was greater than 90% for both.
- They can improve the site specificity of bioactive substances and raise the transdermal flow.
- Optimizing the medicine's bioavailability by avoiding first-pass metabolism, a significant disadvantage in oral drug administration.
  Why Reduce the drug's unwanted side effects and shield it from metabolic deterioration; additionally, short half-life medications are useful.
- Transfersomes can often achieve a relatively high entrapment efficiency (EE) of almost 90% of the lipophilic medication. The greatest entrapment efficiency above 90% was attained for both diclofenac diethylamine (DDEA) and curcumin (CRM) transfersome formulations.
- They have the benefit of being composed of substances that are approved by pharmaceuticals.

- They have the benefit of being manufactured using conventional techniques and pharmaceutically acceptable substances, but each situation must be carefully considered and optimized.
- It is easy to scale up because the production process is brief and straightforward.

2. Limitations of Transfersomes:

- Because of their propensity for oxidative destruction, transfersomes are regarded as
- chemically unstable.
- Degassing and purging the aqueous medium with inert gases, including nitrogen and argon, can dramatically reduce the oxidation of transfersomes. Oxidation risk can also be decreased by storing at a low temperature and shielding from light.
- The storage stability of transfersomes can be increased by post-preparation processing techniques such freeze-drying and spray-drying.
- The challenge of finding substitutes is another barrier to using transfersomes as a drug delivery method.
- The raw materials used in lipid excipients and the costly equipment required to boost manufacturing are linked to the high cost of transfersomal formulations. Phosphatidylcholine is therefore the most commonly used lipid component as it.
- The challenge of finding substitutes is another barrier to using transfersomes as a drug delivery method.
- The cost of lipid excipients' raw materials and the costly machinery required to boost production are linked to the high cost of transfersomal formulations. Phosphatidylcholine is therefore the most commonly used lipid component due to its comparatively low cost.
- Because they are prone to oxidative destruction, transferosomes are chemically unstable. Another factor working against the use of transferosomes as drug delivery vehicles is the purity of natural phospholipids. Formulations for transferosomes are costly.
- The raw materials used in lipid excipients and the costly equipment required to boost manufacturing are linked to the high cost of transfersomal formulations. Phosphatidylcholine is therefore the most commonly used lipid component due to its comparatively low cost
- Because they are prone to oxidative destruction, transferosomes are chemically unstable. Another factor working against the use of transferosomes as drug delivery vehicles is the purity of natural phospholipids. Formulations for transferosomes are costly.

3. Mechanism of Action

Vesicles are known as colloidal particles, which are an aqueous compartment enclosed by a concentric bilayer that are made-up of amphiphilic molecules. They are very useful as vesicular drug delivery systems, which transport hydrophilic drugs encapsulated in the inner aqueous compartment, whereas hydrophobic drugs are

entrapped within the lipid bilayer With regard to transfersomes, they are highly deformable (ultra-flexible) and self-optimizing novel drug carrier vesicles, in which their passage across the skin is mainly associated with the transfersomes' membrane flexibility, maintain the vesicle's integrity.

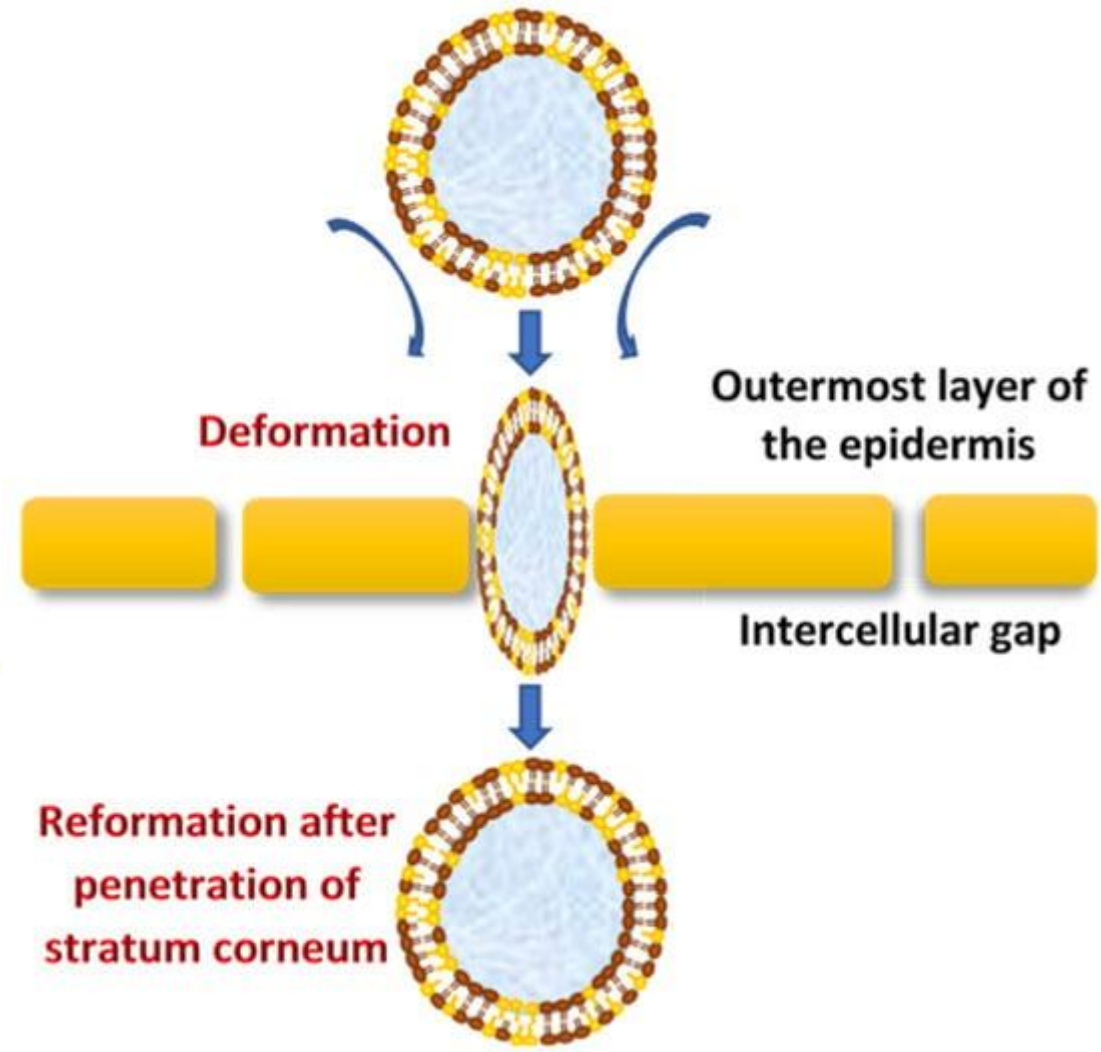


Figure 2. The mechanism of action of transfersomes.

If administered under nonocclusive conditions, they effectively penetrate intact skin; this particular nonocclusive state of the skin is necessary primarily to establish a transepidermal osmotic gradient across the skin.

Through transfersome vesicles, the transdermal water activity difference—which results from the natural transdermal gradient—creates a powerful force that acts on the skin, forcing the widening of intercellular junctions with the least resistance and producing transcutaneous channels that are 20–30 nm wide. With regard to the hydration gradient, these formed channels enable the passage of ultra-deformable, slimed transfersomes throughout the skin.

Additionally, body heat causes the skin's surface water to evaporate, creating the osmotic gradient, which acts as the driving.

If administered under nonocclusive conditions, they effectively penetrate intact skin; this particular nonocclusive state of the skin is necessary primarily to establish a transepidermal osmotic gradient across the skin.

They efficiently penetrate through the intact skin if applied under nonocclusive conditions; this specific nonocclusive state of the skin is required mainly to initiate a transepidermal osmotic gradient across the skin.

These created channels allow the transfer of ultra-deformable, slimed transfersomes across the skin with respect to the hydration gradient .

Transfersomes demonstrate a higher permeation efficiency (through small skin channels) compared to conventional liposomes but have a similar bilayered structure that facilitates the encapsulation of lipophilic and hydrophilic, as well as amphiphilic, drugs and Transfersomes vary from liposomes, primarily due to their softer, better adjustable and ultra-deformable artificial membranes.

Interdependency of the local composition, as well as the shape of the lipid bilayer, makes the vesicles both self-optimizing and self-regulating. This property enables the transfersomes vesicles to cross numerous transport barriers efficiently.

4. Composition of Transfersomes

The primary component of transfersomes is typically an amphipathic substance (such as soy phosphatidylcholine, egg phosphatidylcholine, etc.)

which may consist of a combination of lipids, the vesicle-forming elements that form the lipid bilayer. Second, apply 10–25% surfactants/edge activators. The most popular edge activators in transfersome preparations are biocompatible bilayer-softening compounds, such as sodium cholates, sodium deoxycholate, Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65, and Span 80), and dipotassium glycyrrhizinate.

These substances improve the permeability and bilayer flexibility of the vesicles.roughly 3–10% alcohol as the solvent, and water or a saline phosphate buffer (pH 6.5–7) as the hydrating medium.

Transfersomes are generally composed offirstly, the main ingredient, an amphipathic ingredient (e.g., soy phosphatidylcholine, egg phosphatidylcholine, etc.) that can be a mixture of lipids, which are the vesicle-forming components that create the lipid bilayer.

sodium deoxycholate; Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65 and Span 80) and dipotassium glycyrrhizinate,

which are biocompatible bilayer-softening compounds that increase the vesicles' bilayer flexibility and improve the permeability. about 3–10% alcohol, as the solvent and, finally, hydrating medium consist with either water or a saline phosphate buffer (pH 6.5–7).

5. Factors Affecting Properties of Transfersomes

Numerous process variables may have an impact on the transfersomes' characteristics during the process of developing an optimal formulation.

These factors mostly pertain to the production of transfersomal formulations, which are distinguished by the following Because the phospholipid: Edge activator (lecithin:surfactant) ratio has a significant impact on the entrapment efficiency, vesicle size, and penetration ability, it should be tuned. It has generally been stated that a higher concentration of surfactant may result in a lower EE.

This could be the consequence of the arrangement of surfactant molecules inside the vesicular lipid bilayer structure, which could create pores within the vesicular membrane and result in an increased permeability of the vesicles' membrane.

The arrangement of surfactant molecules within the vesicular lipid bilayer structure may give rise to pores in the vesicular membrane, increasing fluidity and possibly causing the entrapped drug to leak.

This could be the cause of the increased membrane permeability of the vesicles. While the addition of modest concentrations of surfactants may cause the vesicle size to rise, a further increase in the edge activator content may cause pore formation in the bilayer and a decrease in the vesicles' ability to permeate.

Impact of Different Solvents A variety of solvents, including methanol and ethanol, are employed. The solubility of each formulation ingredient in the solvent and their compatibility with the solvent determine which solvent is best.

To improve the film-forming ability and stability following hydration, it is preferable for all of the excipients—including the drug—to fully dissolve in the solvent and yield a clear, transparent solution.

The formulation's solvents may also serve as penetration enhancers, increasing the flow of drugs over the membrane.

Ethanol was utilized in a number of investigations to increase the transit of levonorgestrel, 5-fluorouracil, hydrocortisone, and estradiol via rat skin (Williams and Barry, 2004). Ethanol, for instance, improves penetration by a variety of methods, including raising.

This could encourage the encapsulating effect of different edges (surfactants) to leak out as a result. The kind of edge activators included in the formulations of transfersome vesicles affects both their deformability and entrapment efficiency.

This might result from the EA's different chemical structure. Generally speaking, increasing the surfactant concentration, the hydrophilicity of the surfactant head group, the length of the carbon chain, and the hydrophilic lipophilic balance (HLB) results in a decrease in vesicle size.

When the transfersomes were prepared using the three surfactants—tween 80, span 80, and sodium deoxycholate—a decrease in vesicle size was seen at increasing surfactant concentrations. This could be because micelle production is induced by high surfactant concentrations (more than 15%).

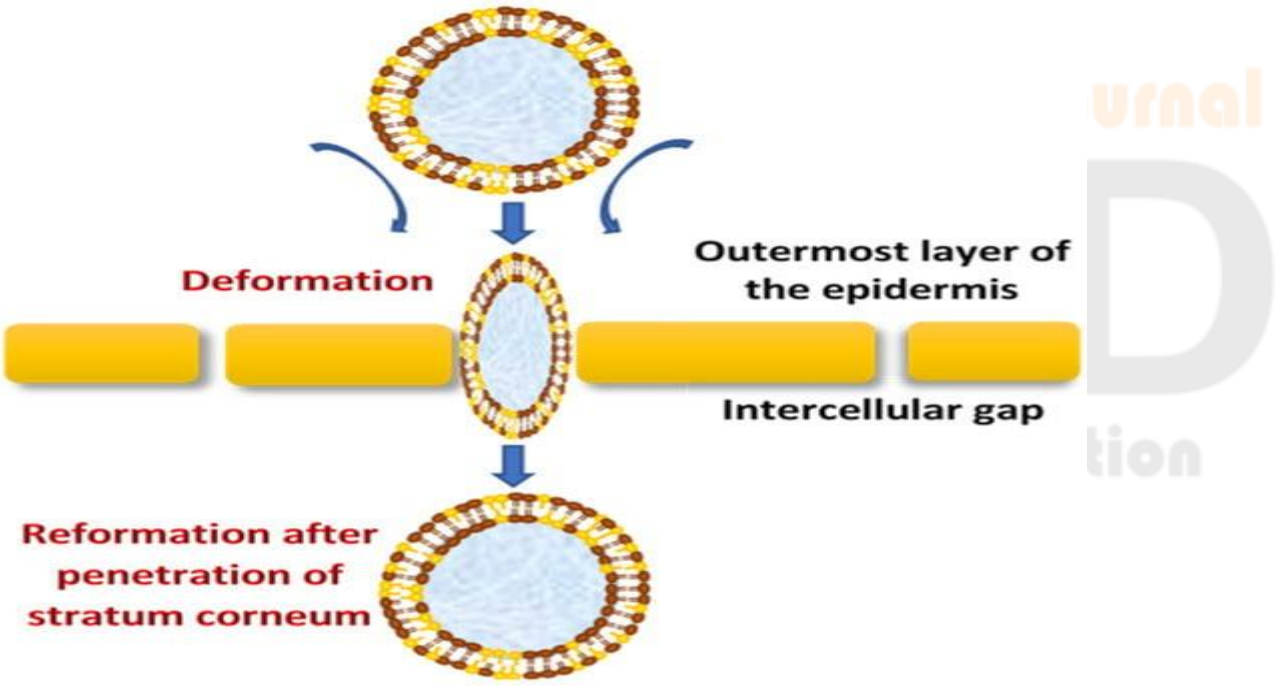
This may promote the consequent leakage of the encapsulated Effect of various edge (Surfactants).

It offers a homogenous formulation and is believed to be a significant factor in the decrease of interfacial tension. Furthermore, a higher concentration of surfactant may cause the vesicles to become more charged, which lowers vesicle aggregation and improves system stability. Furthermore, one of the characteristics of the surfactant is what gives the vesicles their entrapment efficiency; for instance, using a surfactant with a low HLB value would improve the entrapment of a lipophilic medication.

Using the right hydration medium pH is crucial because it maintains the drug together, increasing trapping and penetration.

Colloidal particles, or vesicles, are aqueous compartments surrounded by amphiphilic molecules arranged in concentric bilayers.

With hydrophilic pharmaceuticals contained in the inner aqueous compartment and hydrophobic drugs confined within the lipid bilayer, they are highly effective vesicular drug delivery devices. The passage of transfersomes through the skin is primarily linked to the membrane's flexibility, hydrophilicity, and capacity to preserve the vesicle's integrity. Transfersomes are extremely deformable (ultra-flexible) and self-optimizing new drug carrier vesicles.



The mechanism of action of transfersomes.

They efficiently penetrate through the intact skin if applied under nonocclusive conditions; this specific nonocclusive state of the skin is required mainly to initiate a trans epidermal osmotic gradient across the skin.

The transdermal water activity difference, which originates due to the natural transdermal gradient, creates a significantly strong force that acts upon the skin through transfersomes vesicles, which enforce the widening of intercellular junctions with the lowest resistance and thereby generate transcutaneous channels 20–30 nm in width. These created channels allow the transfer of ultra-deformable, slimed transfersomes across the skin with respect to the hydration gradient. Moreover, the osmotic gradient develops as a result of evaporation of the skin surface water due to body heat, which exerts its action as the driving force to facilitate the flexible transport across the skin to deliver therapeutic agents from the site of application to the target area for local or systemic treatments in effective therapeutic concentrations and minimum systemic toxicity. Transfersomes demonstrate a higher permeation efficiency (through small skin channels) compared to conventional liposomes but have a similar bilayered structure that facilitates the encapsulation of lipophilic and hydrophilic, as well as amphiphilic, drug. Transfersomes vary from liposomes, primarily due to their softer, better adjustable and ultra-deformable artificial membranes. Interdependency of the local composition, as well as the shape of the lipid bilayer, makes the vesicles both self-optimizing and self-regulating. This property enables the transfersomes vesicles to cross numerous transport barriers efficient.

Transfersomes are ultra-deformable carriers that facilitate the delivery of a diverse array of drug molecules across the skin barrier with superior efficacy compared to the conventional vesicular systems. The osmotic gradient is the main driving force for the transport of transfersomes into the deeper skin layers. Importantly, transferosomes are specifically designed vesicular systems that need to be optimized in accordance with individual cases of drugs of interest to achieve the most effective formulations and ultimate pharmacological responses. Further scientific studies associated with transfersomes may lead to novel promising therapeutic approaches against many types of diseases.

The EAs used in transfersomal formulations can also facilitate the solubilization of hydrophobic drugs, thereby increasing the drug entrapment efficiency of the formulations. Moreover, the EAs have the potential to solubilize and fluidize the skin lipids, resulting in skin permeation enhancements. The effect of EAs associated in skin permeations depends on their types and concentrations. Surfactants are one of many different compounds that act as edge activators and penetration enhancers. They are known to be amphiphilic molecules that consist of a lipophilic alkyl chain that is connected to a hydrophilic head group.Generally, rather than cation anionic surfactants are furthermore effective in enhancing the skin penetration, and the critical micelle concentration is also lower, whereas nonionic surfactants with an uncharged polar head group are better-tolerated than cationic and anionic surfactantsThe mechanism of action of transfersomes. They efficiently penetrate through the intact skin if applied under nonocclusive conditions; this specific nonocclusive state of the skin is required mainly to initiate a transepidermal osmotic gradient across the skin.

Advantages of Transfersomes as Vesicle-based Transdermal Drug Delivery Systems

- Transfersomes carrier moieties are hydrophilic as well as hydrophobic, hence providing a novel drug carrier system that allows the delivery of therapeutic agents over wide ranges of solubility.

- The ability of transfersomes to squeeze through narrow constrictions at the skin barrier has been attributed to their ultra-deformability and elastic properties, indeed constrictions as narrow as 5 to 10 times smaller than the diameter of the vesicle.
- High vesicle deformability leads to unmediated drug transport across the skin without any detectable loss in intact vesicles and may be used for topical as well as systemic treatment.
- The Transfersomes carriers are highly versatile, efficient to accommodate agents of very diverse types almost irrespective of their size, structure, molecular weight, or polarity.
- They are composed of natural phospholipids and EAs, so promisingly biocompatible and biodegradable.
- Transfersomes may be used for the delivery of a wide range of active agents, such as proteins and peptides, insulin, corticosteroids, interferons, anesthetics, NSAIDs, anticancer drugs and herbal drugs.
- Transfersomes would thus obviously be candidates for sustained drug release and predictable and extended duration of activity.
- They can improve transdermal flux and site-specific delivery of bioactive agents.
- This helps avoid first-pass metabolism, a big drawback for oral drug administration and so leads to optimized bioavailability of the drug.
- Minimize the undesirable side effects of the drug, as well as protect the drug from metabolic degradation; furthermore, utility of short half-life drugs.

  Transfersomes can even lead to nearly 90% entrapment efficiency (EE) of the lipophilic drug in most cases. Maximum entrapment efficiency more than 90% was obtained for the transfersome formulations of both DDEA and CRM.
- The entrapment efficiency can variate due to various reasons, as, when the lipid concentration was more, a high entrapment efficiency could be observed. The EE decreases when the surfactant concentration increases above certain concentrations due to the formation of mixed micelles. According to the literature, in case of a low EE .
- Further enhancement of encapsulation of the lipophilic drug can be achieved if a surfactant with a low HLB value is added to it. This is observed to be a fact where transfersomes exhibit the very high encapsulation property of lipophilic drugs.
- They are advantageously prepared from pharmaceutically acceptable starting materials with conventional techniques, but have to be prepared and optimized on a case-to-case manner.
- This can be easily used due to a very short and simple procedure for its production.

4. Composition of Transfersomes:

Transfersomes are generally composed of:

- Transfersomes are chemically unstable as they are prone to oxidative degradation. Oxidation of transfersomes can be substantially reduced if the aqueous media is degassed and purged with inert gases like nitrogen and argon. Storage at low temperature and under protection from light also reduce the chance

of oxidation. Some post-preparation processing such as freeze-drying and spray-drying can enhance the storage stability of the transfersome.

- Another barrier to using transfersomes as a drug delivery system is that achieving the high purity of the natural phospholipids is very difficult. Therefore, phospholipids might be from synthetic origin.
- Transferosomal formulation can be associated with the expensiveness of raw materials, including lipid excipients, and also expensive equipment required in increasing their manufacture. The most commonly applied lipid component is phosphatidylcholine since it is relatively cheaper.
- It essentially comprises an amphipathic component, which may be a mixture of lipids of the type phosphatidylcholine, egg phosphatidylcholine, etc. These are vesicle forming components building up the lipid bilayer.
- Such a combination also contains the second most essential component 10–25% surfactants/edge activators; among the widely used edge activators in transferosome preparations, one can include: surfactants as sodium sodium deoxycholate; Tweens and Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65 and Span 80) and bilayer, and that are biocompatible bilayer-softening compounds that increase the bilayer flexibility of vesicles, thus enhancing permeability Transferosomes, also known as transfersomes, are ultradeformable vesicles designed for transdermal applications consisting of a lipid bilayer with phospholipids and an edge activator and an ethanol/aqueous core.

- The amphipathic component is the first major constituent of the transferosome, which is a vesicle-forming element composing the lipid bilayer. The commonly known amphipathic component is phospholipids like soy phosphatidylcholine, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, and egg lecithin. The two most frequently used natural and synthetic lipid components are lecithin and soy phosphatidylcholine. The phospholipids are integral in the building of transferosomes as they play a key role in the zeta potential, trapping efficiency, vesicle size and vesicle permeability properties of the vesicles (Abdulbaqi et al, 2017). The stability of the transferosomes is highly related to the stability of phospholipids used. Generally, phospholipids are unstable when exposed to air, sunlight, and high temperatures. Due to the presence of the hydroxyl functional group attached to the fatty acid group in the phospholipid structure, the compound is liable to oxidative degradation (Parkash, 2018). However, regarding the physicochemical properties of transferosomes: particle size, stability and entrapment efficiency without studying the effect of other excipients such as edge activators, which are also known as surfactants (Opatha et al 2020.,).

- For instance, it was demonstrated, that the encapsulation of felodipine in soya lecithin transfersomes resulted in obtaining nanosize particles, and it led to a better entrapment efficiency in contrast to the encapsulation with egg lecithin (Yusuf et al., 2014). Soya lecithin should be used instead of egg lecithin if the drug has bigger hydrophobicity (Yusuf et al., 2014). This study concluded that the drug with the chemical feature of the lipid led to disparity in the drug loading capacity. An additional study by Shuwaili et al., Pentoxifylline a vasodilator and anti-inflammatory agent was encapsulated in deformable

transferosomes using three different lipid carriers: egg yolk, soybean, and phospholipid 90G (Al Shuwaili et al., 2016). The formulation with egg yolk produced the smallest transferosome size. Though there was a difference in particle size, there were no differences that were observed in encapsulation efficiency between the three carriers (Al Shuwaili et al., 2016).

- The edge activators are the other major component of transferosomes with a content range of 10%–25%. They comprise compounds, which soften the biocompatible bilayer of the vesicles thereby improving their permeation and flexibility. Stearylamine, dodecyltrimethylammonium bromide, cetylpyridinium chloride monohydrate, sodium cholate, sodium deoxycholate, sodium lauryl sulfate, Tweens, Spans, and Brij 30 surfactants can be used in those carriers[13]. Besides these kinds of edge activators, oleic acid, eucalyptus oil, limonene, and castor oil are the examples of oils which could also be used as edge activators instead of using traditional surfactants. The nature of edge activator conditions deformability, trapping efficiency, and zeta potential of transferosome vesicles. This can be accounted for by their unique chemical compositions. More or less generally, increased concentration of surfactant results in smaller vesicles (Firoznezhad et al., 2022). It has been reported that positive charged particles are more penetrative than neutral or negative charged particles . This can be because of repulsive interaction with the negatively charged skin (Hasanovic et al., 2010; Kitagawa & Kasamaki, 2006).

- The second major constituent of transferosomes has a content range of 10%–25% of the edge activators. These are those compounds that soften the biocompatible bilayer of the vesicles thereby increasing their permeation and flexibility. Stearylamine, dodecyltrimethylammonium bromide, cetylpyridinium chloride monohydrate, sodium cholate, sodium deoxycholate, sodium lauryl sulfate, Tweens, Spans, and Brij 30 are all example of surfactants that can be used in these carriers. Beside these types of edge activators, oleic acid, eucalyptus oil, limonene, and castor oil are examples of oils that can also be used as edge activators instead of classic surfactants. The nature of the edge activator used in the formulation of transferosome vesicles affects its deformability, trapping efficiency, and zeta potential.This may be due to their different chemical structures. Generally, a high concentration of surfactant increases the surfactant content within the vesicles. This in turn results in smaller sizes of vesicles (Firoznezhad et al., 2022). NPs charged positively show better penetration than negatively charged or neutral nanoparticles. This arises from the repulsive interaction between the particles and the negatively charged skin (Hasanovic et al., 2010; Kitagawa & Kasamaki, 2006).

5. Factors Affecting Properties of Transfersomes

In the process of obtaining an optimized formulation of transfersomes, there are number of process variables that could affect the properties of the transfersomes. These variables basically involve the manufacturing of transfersomal formulations, which are identified as follows:

Phospholipids Edge Activator Ratio. The ratio of phospholipid Edge activator, that is, lecithin:surfactant must be an optimized ratio due to the fact that this greatly affects entrapment efficiency, vesicle size, and permeation ability. Generally, it has been reportedly that a higher concentration of surfactant may lead to a decrease in the EE. This might be attributed to the outcome of increased membrane permeability because of the arrangement of surfactant molecules within the lipid bilayer structure of the vesicle, which would possibly form pores within the vesicular membrane and increase its fluidity, prompting the leakage of the entrapped drug. Further increase in edge activator concentration will lead to pore formation in the bilayer, and the ability of the vesicles to permeate becomes reduced, while low concentrations of surfactants lead to the growth in the size of the vesicle. In addition to that, some other researchers also have documented the decrease in the size of vesicles due to high phospholipid concentrations.

Effect of Various Solvents Various solvents such as ethanol or methanol are used.Selection of appropriate solvent depends upon solubility of all the formulation ingredients in the solvent and compatibility with the solvent. Preferably, all the excipients, including drug, should completely dissolve in solvent and obtain a clear transparent solution to produce a better film-forming ability and good stability after hydration. The solvents in the formulation may also play their role as penetration enhancers that enhance the flux of the drug across the membrane.Williams and Barry (2004) state that ethanol was employed in various studies to enhance the flux of hydrocortisone, 5-fluorouracil, estradiol and levonorgestrel through rat skin . For an example, ethanol enhances permeation through various mechanisms, such as increase the solubility of the drug in vesicles by acting as solvent, further on permeating into the stratum corneum and alters the solubility characteristics of the Increasing the ethanol concentration in the formulation may lead to a decline in the %EE, which would be primarily due to increased permeability of the vesicular.

Effect of Different Edge Activators (Surfactants)Vesicle size of transfersomes and hence their deformability as well as entrapment efficiency depend upon the types of edge activators that are used for preparing formulations. It may be attributed to the difference in chemical structure among EA Typically, with an increase in concentration of the surfactant, the size of vesicle decreases. Further, HLB as well as hydrophilicity of the head group of the surfactant and length of carbon chain also play a significant role in determining the vesicle size. The three surfactants, tween 80, span 80, and sodium deoxycholate, were used to prepare the transfersomes, and a reduction in the vesicle size was observed when the higher surfactant concentration was used. It may be because the very high surfactant concentrations of more than 15% induce micelle formation rather than the vesicle formation. A relatively low PDI was achieved with the increased concentration of the surfactant. A very small PDI is taken as being responsible for a uniform size distribution, which is believed to be a critical requirement for reducing the interfacial tension and for providing a uniform formulation. Furthermore, an increase in the concentration of the surfactant can even enhance the charge on the vesicles, thereby reducing the aggregation of vesicles and enhancing the stability of the system. In addition, surfactant properties are among

the properties responsible for the entrapment efficiency of the vesicles, since for an example, the entrapment of a lipophilic drug would be enhanced with the use of a surfactant with a low HLB value. More importantly, it has been reported that at higher concentrations of surfactant, the number of formed vesicles increases, which leads to a greater volume of the hydrophobic bilayer domain available for the entrapment of hydrophobic drugs. However, if the amount of lipophilic drug exceeds the vesicular loading capacity it may cause disruption of vesicular membrane, leakage of the drug, reduction in entrapment efficiency and skin permeation ability. Furthermore, the membrane permeability of vesicles depends on carbon chain length along with transition temperature of the surfactant. The amount of surfactant employed in the preparation is dependent on the packing density of the phospholipid, involved and also on the interaction of the surfactant and phospholipid.Transferosomes may be affected in terms of their permeation property by surfactants. Concentration-dependent and type-specific properties were found for surfactants used, the amount of drug (ciprofloxacin) released was significantly higher with Tween 80 according to a 2014 study by Cipolla et al.

The hydration medium can be either water or saline phosphate buffer (pH 6.5–7). The pH value of the formulation should be suitable to balance, on the one hand, both the properties of the formulation and its biological applications and, on the other hand, the route of administration. The lipid bilayer of transfersomes simulates the phospholipid layer of the cell membrane, whereas only unionized drugs are bound to the membrane by the phospholipid bilayer and penetrate.It is very essential to use the suitable pH of the hydration medium, keeping the drug unionized, hence increasing the entrapment and permeation of the drug.

6. Conclusions

Transfersomes are ultra-deformable carriers that can drive across the skin barrier the diverse array of drug molecules with much better efficacy than the conventional vesicular systems. 33 Transfersomes are a kind of carrier that can induce transport into the deeper layers of the skin by the force of an osmotic gradient. Transfersomes are vesicular delivery systems that have specifically been designed and need to be optimized in relation to specific cases of drugs of interest to acquire the most effective formulations and, consequently, utmost pharmacological responses. Further scientific efforts connected with transfersomes may lead to new promising therapeutic strategies for diseases of various etiologies.
The term transferosomes is used for the transfersomes, and they are ultradeformable vesicles for transdermal applications comprising a lipid bilayer with an edge activator and an ethanol/aqueouscore. Transfersomes are ultradeformable vesicle having an aqueous core surrounded by the complex lipid bilayer. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility. Transferosomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss. The transfersome consists of two major aggregates namely. The first one is an amphipathic ingredient (phosphatidylcholine), in which the aqueous solvents self-assemble into lipid bilayer that closes into a simple lipid vesicle . The second one is a bilayer softening ingredient that includes surfactant, or an amphiphile drug

which in turn raises the flexibility of the lipid bilayer and permeability. Transferosomes vesicles consist of phospholipids as a major ingredient (soya phosphatidylcholine, egg phosphatidylcholine, dipalmityl phosphatidylcholine, etc.), 10-25% surfactants to provide flexibility (sodium cholate, tween 80, span-80), 3-10% alcohol as a solvent (ethanol, methanol) and hydrating med.
They are different from liposomes due to the presence of so-called edge-activators, and they contain phospholipids as the main ingredient with 10-25% surfactant (e.g. sodium cholate) and 3-10% ethanol.[44] The surfactants represent the "edge activators", which confer on the transferosomes an ultradeformability allowing them to penetrate the stratum corneum . The elasticity of the vesicle is correlated to the quantity and to the structure of the incorporated surfactant.[19] In comparison to liposomes, it has been claimed that transferosomes are capable to deliver their "payload" deeper into the skin.

Reference

1. Cevc G, Blume G. Lipid vesicles and lipid emulsions in drug delivery. *In: Drug Delivery Systems: Advanced Technologies. New York: Springer; 2008. p. 153-75.*

2. Cevc G, Caffrey M. Lipid vesicles and their applications in drug delivery. *Adv Drug Deliv Rev. 2002;54(3):323-37.* doi:10.1016/S0169-409X(02)00003-6.

3. Cevc G, Vierl U. Transferosomes: a novel type of drug carrier. *Drug Deliv. 2006;13(2):131-40.* doi:10.1080/10717540500450314.

4. Jain S, Ali J, Ahuja A, et al. Transferosomes: a novel vesicular carrier for drug delivery. *Indian J Pharm Sci. 2007;69(2):170-4.* doi:10.4103/0250-474X.32962.

5. Azeem A, Khawaja S, Bafakeeh O, et al. Transferosomes as a versatile drug delivery system: A review. *Saudi Pharm J. 2018;26(5):721-31.* doi:10.1016/j.jsps.2018.01.007.

6. Chaurasiya PG anju., E., Upmanyu N., Ray S.K., Jain P. Transfersomes: A novel technique for transdermal drug delivery. *J. Drug Deliv. Then.* 2019;9:279–285. doi: 10.22270/jddt.v9i1.2198.

7. Crommelin D.J.A., Fransen G.J., Salemink P.J.M. Stability of liposomes on storage. *Target. Drugs Synth. Syst.* 1986:277–287. Doi : 10.1007/978-1-4684-5185-6_20.

8. Ge X., Wei M., He S., Yuan W. Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. *Pharmaceutics.* 2019;11:55. doi: 10.3390/pharmaceutics11020055.

9. 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. *Adv. Colloid Interface Sci.* 2014;205:187–206. doi: 10.1016/j.cis.2013.11.018.

10. Mujoriya R.Z., Dhamande K., Bodla R.B. Niosomal drug delivery system—A review. *Int. J. App. Pharm.* 2011;3:7–10.

11. Ezzat H.M., Elnaggar Y.S.R., Abdallah O.Y. Improved oral bioavailability of the anticancer drug catechin using chitosomes: Design, in-vitro appraisal and in-vivo studies. *Int. J. Pharm.* 2019;565:488–498. doi: 10.1016/j.ijpharm.2019.05.034.

12. Manca M.L., Manconi M., Valenti D., Lai F., Loy G., Matricardi P., and Fadda A.M. Liposomes coated with chitosan–xanthan gum (chitosomes) as potential carriers for pulmonary delivery of rifampicin. *J. Pharm. Sci.* 2012;101:566–575. doi: 10.1002/jps.22775.

13. Mertins O., Dimova R. Binding of Chitosan to Phospholipid Vesicles Studied with Isothermal Titration Calorimeters. *Langmuir.* 2011;27:5506–5515. doi: 10.1021/la200553t.

14. Jain S., Jain V., Mahajan S.C. Lipid Based Vesicular Drug Delivery Systems. *Adv. Pharm.* 2014;2014:1–12. doi: 10.1155/2014/574673.

15. Mann J.F., Scales H.E., Shakir E., Alexander J., Carter K.C., Mullen A.B., Ferro V.A. Oral delivery of tetanus toxoid using vesicles containing bile salts (bilosomes) induces significant systemic and mucosal immunity. *Methods.* 2006;38:90–95. Doi: 10.1016/j.ymeth.2005.11.002.

16. Yang L., Tucker I.G., J. Effects of bile salts on propranolol distribution into liposomes studied by capillary electrophoresis. *J. Pharm. Biomed. Anal.* 2011;56:553–559. doi: 10.1016/j.jpba.2011.06.020.

17. Rai S., Pandey V., Rai G. Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: The state of the art. *Nano Rev. Exp.* 2017;8:1325708. doi: 10.1080/20022727.2017.1325708

18. Chaurasiya P., Ganju E., Upmanyu N., Ray S.K., Jain P. Transfersomes: A novel technique for transdermal drug delivery. *J. Drug Deliv. Ther.* 2019;9:279–285. doi: 10.22270/jddt.v9i1.2198.

19. Modi C., Bharadia P. Transfersomes: New dominants for transdermal drug delivery. *Am. J. PharmTech. Res.* 2012;2:71–91.

16. Jain A.K., Kumar F. Transfersomes: Ultradeformable vesicles for transdermal drug delivery. *Asian J. Biomater. Res.* 2017;3:1–13.

17. Elsayed M.A., Abdallah O.Y., Naggar V.F., Khalafallah N.M. Lipid vesicles for skin delivery of drugs: Reviewing three decades of research. *Int. J. Pharm.* 2007;332:1–16. doi: 10.1016/j.ijpharm.2006.12.005.

18. Touitou E., Junginger H.E., Weiner N.D., Nagai T., Mezei M. Liposomes as carriers for topical and transdermal delivery. *J. Pharm. Sci.* 1994;83:1189–1203. doi: 10.1002/jps.2600830902.

19. Elsayed M.A., Abdallah O.Y., and Naggar V.F., Khalafallah N.M. Lipid vesicles for skin delivery of drugs: Reviewing three decades of research. *Int. J. Pharm.* 2007;332:1–16. doi: 10.1016/j.ijpharm.2006.12.005.

20. Touitou E., Junginger H.E., Weiner N.D., Nagai T., Mezei M. Liposomes as carriers for topical and transdermal delivery. *J. Pharm. Sci.* 199483:1189;–1203. doi: 10.1002/jps.2600830902.

21. Yadav D., Sandeep K., Pandey D., Dutta R.K. Liposomes for drug delivery. *J. Biotechnol. Biomaterial.* 2017;7:1–8. doi: 10.4172/2155-952X.1000276.

22. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: Permeation enhancement, vesicle penetration, and transdermal drug delivery. *Crit. Rev. Ther. Drug Carr. Syst.* 1996;13:257–388. doi: 10.1615/CritRevTherDrugCarrierSyst.v13.i3-4.

23. Rajan R., Jose S., Mukund V.P.B., Vasudevan D.T. Transferosomes—A vesicular transdermal delivery system for enhanced drug permeation. *J. Adv. Pharm. Technol.* 24. Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. *Adv. Drug Deliv. Rev.* 2004;56:675–711. doi: 10.1016/j.addr.2003.10.028.

24. Rother M., Lavins B.J., Kneer W., Lehnhardt K., Seidel E.J., Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: Multicentre randomised controlled trial. *Ann. Rheum. Dis.* 2007;66:1178–1183. doi: 10.1136/ard.2006.065128.

25. Langer R. Transdermal drug delivery: Past progress, current status, and future prospects. Adv Drug Deliv Rev 2004; 56:557-8.

26.Barry BW. Breaching the skin's barrier to drugs. Nat Biotechnol 2004; 22:165-7.[11]

27. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. Drug Discov Today Technol 2005; 2:67-74.

28. Mura S, Manconi M, Sinico C, Valenti D, Fadda AM. Penetration enhancer-containing vesicles (PEVs) as carriers for cutaneous delivery of minoxidil. Int J Pharm 2009; 380:72-9.

29. Bhowmik D, Chiranjib V, Chandira M, Jayakar B, Sampath KP. Recent advances in transdermal drug delivery system. Int J Pharm Tech 2010; 2:68-77.

30. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 2001; 14:101-14.

31. Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Adv Drug Deliv Rev 2008; 60:1638-49.

32. Karande P, Mitragotri S. Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochim Biophys Acta 2009; 1788:2362-73.

33. Crommelin DJ, Eling WM, Steerenberg PA, Nässander UK, Storm G, De Jong WH, et al. Liposomes and immunoliposomes for controlled release or site specific delivery of anti-parasitic drugs and cytostatics. J Control Release 1991; 16:147-54.

34. Yavlovich A, Singh A, Blumenthal R, Puri A. A novel class of photo-triggerable liposomes containing DPPC: DC8, 9PC as vehicles for delivery of doxorubcin to cells. Biochim Biophys Acta 2011; 1808:117-26.

35. Modi CD, Bharadia PD. Transfersomes: A newdominants for transdermal drug delivery. Am J PharmTech Res 2012; 2:71-91.

36. Prajapati ST, Patel CG, Patel CN. Transfersomes: A vesicular carrier system for transdermal drug delivery. Asian J Biochem Pharm Res 2011; 2:507-24.

37. Transfersomes. From Wikipedia, the free encyclopedia. Available from: Transfersome. [Last accessed on 2016 May 28].

38. Cevc G, Blume G, Schatzlein A. Transferosomes mediated transepidermal delivery improves the regiospecificity and biological activity of corticosteroids in-vivo. J Control Release 1997; 45:211-26.

39. Cevc G, Schatzlein A, Blume G. Transdermal drug carriers: Basic properties, optimization and transfer efficiency in case of epicutaneously applied peptides. J Control Release 1995; 36:3-16.

40. Jain S, Umamaheshwari RB, Bhadra D, Tripathi P, Jain P, Jain NK. Ultra deformable liposome: A recent tool for effective transdermal drug delivery. Indian J Pharm Sci 2003; 65:223-31.

41. Kombath RV, Minumula SK, Sockalingam A, Subadhra S, Parre S, Reddy TR, et al. Criticalissues related to transfersomes - Novel vesicular system. Acta Sci Pol Technol Aliment 2012; 11:67-82.

42. Sharma N, Agarwal G, Rana AC, Bhat Z and Kumar D: A Review: Transdermal drug delivery system: A tool for novel drug delivery system. International Journal of Drug Development and Research 2011; 3:70-84.

43. Patel RP and Baria AH: Formulation and evaluation considerations of transdermal drug delivery system. International Journal of Pharmaceutical Research, 2011; 3:1-9.1.