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Transferosomes: Unique vesicular carriers for effective transdermal delivery

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ABSTRACT

The utilization of vesicular carriers has recently emerged as a promising strategy to reduce the hindrance associated with the stratum corneum. Transferosomes are also recognized as ultradeformable lipids and elastic liposomes attract tremendous attention toward dermal delivery. They are predominantly used to treat various incidences of chronic skin disorders and also convenient for targeted as well as controlled delivery to manage patient compliance. These self-assembled nanocarriers are capable of molding themselves according to the pore size of the stratum corneum. Transferosomes may consist of edge activators (specialized surfactants), phospholipids, buffering agent, etc. The effect of edge activators and their concentration confers a desirable elasticity to assembled vesicles. Elastic liposomes are capable of optimizing the solubilization of the drug, effective drug loading capability, and permeability of therapeutic molecules. Transferosomes as nanocarriers exhibit advanced reflections and a versatile platform for successful transdermal applications. These unique nanocarriers also exhibit superior elasticity as well as penetration performance. These systems are considered secure with efficient delivery strategies for pharmaceutically as well as cosmeceutically active chemical moieties. Recent scientific observations indicating the importance of ultradeformable liposomes have shown reproducible and efficient permeation of active drugs. This manuscript covers the current research advancements along with informative reports addressing the important issues and usefulness of prospective transferosomes with a better bioavailability profile.

INTRODUCTION

Globally, nanotechnology is accepted as one of the leading vistas for improved therapeutic profiles of various drugs (Sadaf and Ajazuddin, 2010). Nanoformulations also reveal salient attributes, including enhancement in drug solubility, bioavailability, prevention from physicochemical degradation, as well as toxicity, and also overcoming drug leakage (Gangwar *et al*., 2012; Sadaf and Ajazuddin, 2010). Biocompatible vesicular systems have great potential for the administration of various active molecules to improve their clinical efficacy. It can also deliver several drugs for therapeutic, biochemical, and cosmetic benefits (Hussain *et al*., 2017; Rai *et al*., 2017). Various classes of "somes" have been introduced in nanotechnology and all "somes" are specifically utilized for their pivotal characteristics. Transferosomes are considered an improved form of liposomes and have numerous names – ultradeformable liposomes, deformable liposomes, flexible liposomes, ultraflexible liposomes, and elastic liposomes (Hussain *et al*., 2017). Transferosomes are distinct from liposomes because they have more elasticity and flexibility provided by the edge activator which modulates the vesicle according to the skin pores and reaches the systemic circulation (Jain *et al*., 2017b). Ultraflexible liposomes have also shown the ability to shrink the vesicle through channels and again reform its original diameter after crossing the biological membrane and ultimately reaching the systemic circulation (Jain *et al*., 2017b; Sawant *et al*., 2017; Srivastava *et al*., 2017). These vesicles respond to external stress by rapid shape modification with low energy (Podili and Firoz, 2014). Basically, it is specialized for their stretchable behavior which is attributed by the edge activators (Sala *et al*., 2016). These activators reduce the interfacial tension and consequently augment

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the shrinking ability of the carrier system. Vesicles can carry small, moderate, as well as highly, molecular hydrophobic, hydrophilic or amphiphilic chemical moiety in a better stable single vesicle system (Walve *et al*., 2011).

Transferosomes are accessible forms applied to non-occlusive skin and release the drug which depicts improved pharmacological effects, as well as minimum patient incompliance (Kumar *et al*., 2012; Walve *et al*., 2011). Furthermore, they can prevent hepatic first-pass metabolism and ultimately provide better pharmacokinetic efficacy (Eldhose *et al*., 2016; Pardhan *et al*., 2013; Sarangi *et al*., 2018). Also, ultradeformable vesicles can easily adopt herbal extracts and synthetic actives and deliver intact moiety without drug leakage in targeted sites (Kulkarni *et al*., 2011; Saraf *et al*., 2011). These vesicular carriers emerged as significant systems for the treatment of varied skin diseases by overcoming the penetration-limiting barriers and, consequently, enhancing the efficacy with substantial clinical benefits. These carriers also presented new dimensions for transdermal delivery of actives in a proficient and fascinating manner. Confocal scanning laser microscopy has been used for the investigation of the penetration mechanism of transferosomes (Gangwar *et al*., 2012). The transferosomal drug delivery form is widely used to treat various types of diseases successfully and achieve better biocompatibility, bioavailability, cost-effectiveness, and patient compliance (Eldhose *et al*., 2016; Kulkarni *et al*., 2011).

Owing to the elastic attributes of transferosomes, these ultraflexible vesicular systems can effortlessly cross the physiological-limiting barriers and deliver the drug efficiently to its active site. In addition, the prime advantage of utilizing transferosomes as a nanocarrier includes triumphant delivery of macromolecules through the skin employing a non-invasive route, hence subsequently improving the patient's compliance. Also, they successfully deliver insulin, corticosteroids, high weighted protein and peptides, interferons, anti-cancerous drugs, anesthetics, non-steroidal anti-inflammatory drugs, and various herbal active moieties (Chaudhary *et al*., 2016; Chauhan *et al*., 2018a; Eldhose *et al*., 2016; Jain *et al*., 2017a; Kaurav *et al*., 2016; Kulkarni *et al*., 2011; Mota *et al*., 2017; Rady *et al*., 2018; Saraf *et al*., 2011). This review depicts the growth and benefits of transferosomes in a vesicular family for providing a better therapeutic profile and utility. In this manuscript, various important aspects, advantages, preparation methods, and salient applications of transferosomes have also been explored.

Major advantages

Various advantages are elaborated as follows (Hussain *et al*., 2017; Podili and Firoz, 2014; Rai *et al*., 2017; Walve *et al*., 2011):

- High entrapment efficacy.
- High efficiency to modify according to pore size, therefore better penetration ability.
- Deliver smaller, as well as larger, weighted molecules without any measurable loss.
- Depot drug, releases drug slowly and gradually in a controlled manner.
- Utilized for systemic as well as topical application.
- Avoid first-pass metabolism, physicochemical degradation, and provide protection to encapsulated drug.
- Site specificity and increased bioavailability.
- Simple procedure of formulation and evaluation.
- Biocompatible and biodegradable.
- Provide patient compliance and also suitable for unconscious patients.

Limitations

Transferosomes have crucial features in nanodrug delivery; however, some of the drawbacks are as follows (Hussain *et al*., 2017; Kumar *et al*., 2012):

- Sometimes, chemical formulations may become unstable due to their oxidative degradation.
- Reorganization of transferosomes is also associated with the purity of natural phospholipids.
- Higher cost associated with the expensive manufacturing procedure is essential for the fabrication of transferosomes as compared with other conventional gel preparations.
- It is very difficult to utilize the finest properties of a system for targeted therapy without cautious and rational formulation design.

Preparation methodology

Transferosomes are preferably prepared by two methods: the rotary evaporation sonication and vortexing-sonication methods, as shown in Figure 1.

The rotary evaporation sonication process comprises the dissolution of phosphatidylcholine along with the edge activator in a mixture of chloroform and methanol and is further followed by organic solvent removal utilizing the rotary evaporator under reduced pressure at a suitable temperature. While revolving the container at room temperature, the film deposited gets hydrated with therapeutic agent solution in an appropriate aqueous phase. The vesicles produced are allowed for swelling, followed by sonication

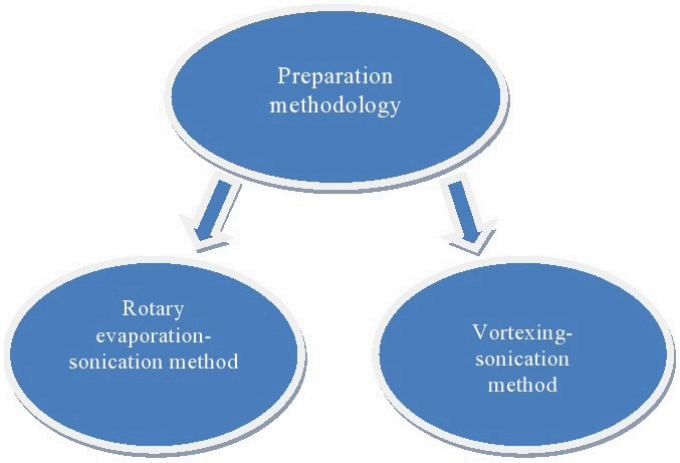

Figure 1. Preparation methods of transferosomes.

using a bath sonicator. Subsequently, the vesicle extrusion occurs through the polycarbonate membrane and the resulting vesicles are stored at an appropriate temperature for further use. In the vortexing sonication process, phosphatidylcholine and edge activators in addition to the therapeutic molecule are blended in a suitable phosphate buffer and then vortexed appropriately to achieve a milky suspension. The suspension is properly sonicated, followed by extrusion via a polycarbonate filter (Kumar *et al*., 2012). The chemical compositions for the formulation of ultradeformable vesicles may be similar in both the methods (Duangjit *et al*., 2013; Kumar *et al*., 2012). Ultradeformable transferosomes can be obtained successfully by utilizing these methods and stored in an appropriate environmental condition for long duration stability.

Evaluation

The overall investigation and characterization aspects include various crucial parameters such as vesicle size, zeta potential, polydispersity index (El-feky *et al*., 2019; Preeti *et al*., 2014), transmission electron microscopy (Chauhan *et al*., 2018a; Lei *et al*., 2013), scanning electron microscopy (Badr-eldin *et al*., 2016; Lei *et al*., 2013), differential scanning calorimetry (Elkomy *et al*., 2017; Tosato *et al*., 2018), confocal laser scanning microscopy (Podili and Firoz, 2014; Walve *et al*., 2011), etc. The vesicle diameter can be determined using photon correlation spectroscopy or dynamic light scattering method. Both polydispersity index and zeta potential can also be assessed by using this technique. The measurement of the zeta potential can present a prediction concerning the stability features. For morphological investigation of nano-sized vesicles, scanning electron microscopy and transmission electron microscopy are commonly employed. Differential scanning calorimetry is also comprehensively utilized in practice to inspect the crystallinity and polymorphic performance of the ingredients. The elasticity index of the vesicles can be estimated by extrusion measurement. Skin penetration study is generally accomplished using confocal laser scanning microscopy (Chauhan *et al*., 2018a; El-feky *et al*., 2019; Elkomy *et al*., 2017; Lei *et al*., 2013; Podili and Firoz, 2014).

These evaluation parameters contribute to a systematic practice to comprehend the effectiveness and achievement of drug loading capability, drug release profile, and ultimately therapeutic potential of ultraflexible liposomal formulation. The evaluation of transferosomes is essential to understand the relationship among various important components, as well as processing factors involved during the preparation of nanometric optimized formulations. Suitable characterization of ultraflexible nanocarriers is also necessary to control the product eminence and stability features, in addition to release kinetics. *In vitro* drug release, entrapment efficacy, penetration ability, flexibility measurement, turbidity measurement, drug content, occlusion effect, etc. can also be evaluated for transferosomal preparations (Kumar *et al*., 2012; Sachan *et al*., 2013).

Therapeutic applications

Ultradeformable vesicles can be widely utilized as effective carriers for the delivery of various drugs. They have shown better skin permeation for achieving promising pharmacokinetic profiles. Therapeutic applications utilizing these effective carriers are mentioned as follows:

- **Proteins and peptides' drug delivery:** Self-regulating transferosomes have been studied to deliver proteins and peptides (Cevc 2003; Cevc *et al*., 1998; Paul, 1998; Yang, 2002).
- **NSAIDs:** Transferosomes are potentially employed to deliver anti-inflammatory and anti-pyretic drugs successfully, e.g., corticosteroids (Cevc *et al*., 1997), ketoprofen (Cevc *et al*., 2008), diclofenac sodium (Ghanbarzadeh *et al*., 2013), etc.
- **Anti-hypertensive drugs:** Hypertension is a disease condition which can be treated by incorporating drug in transferosomal preparations, e.g., propranolol hydrochloride (Mishra *et al*., 2007), valsartan (Ahad *et al*., 2012), and nifedipine (Manvir *et al*., 2012), with better therapeutic effects.
- **Anti-fungal drugs:** Growth of microbes can be retarded by transferosomal applications, e.g., metronidazole (Vanić *et al*., 2013), itraconazole (Alomrani *et al*., 2014), miconazole nitrate (Pandit *et al*., 2014), amphotericin B (Singodia *et al*., 2010), and terbinafine (Ghannoum *et al*., 2011, 2012).
- **Local anesthetics:** Local anesthetic nanocarriers are explored to improve the action of drugs, e.g., butamben (Cereda *et al*., 2013), and butamben and benzocaine (Maestrelli *et al*., 2010).
- **Anti-androgenic alopecia:** Finasteride transferosomal vesicles have been investigated for the management of androgenetic alopecia (Ahmed and Rizq, 2018).
- **Anti-gout agents:** The elastic liposomal formulation of colchicine revealed great potential in the treatment of acute gout (Singh *et al*., 2009).
- **Anti-obestiy agents:** Transferosomes of nanoemodin has been investigated for anti-obesity (Lu *et al*., 2014).
- **Anti-cancer drugs:** Transferosomes, nanovesicular systems have shown capability to deliver anti-cancerous drugs effectively, e.g., celecoxib (Bragagni *et al*., 2012), cisplatin (Gupta, 2011), and vincristine (Lu *et al*., 2007).
- **Anti-migraine drugs:** Neurological disorder has been examined by the sustained delivery of anti-migraine drug rizatriptan (Garg *et al*., 2008).

Applications in cosmetics

The demand of cosmetics rises worldwide progressively in order to intensify the appearance and avoidance of skin damage. Cosmeceutical products enhance beauty aspects and also confer various therapeutic benefits. Applications of transferosomes in the avenue of cosmetics and cosmeceuticals are enlisted as follows and are shown in Figure 2.

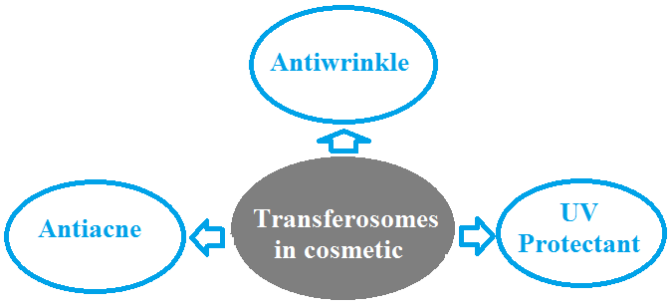

Figure 2. Schematic representation of transferosomes' applications in cosmetic technology.

- **Anti-wrinkle agents:** Anti-wrinkle effects have been investigated by incorporating *Curcuma longa* (Saraf *et al*., 2011) and rosemary extracts (Ezzat *et al*., 2016) into transferosomal vesicles.
- **UV protectant:** Formulation of transferosomal gel has been investigated for UV radiation skin damage, e.g., *C. longa* (Kaur *et al*., 2013) and quercetin (Liu *et al*., 2013).
- **Anti-acne agents:** Topical delivery of transferosomes has potential to reduce acne, e.g., clindamycin (Gupta *et al*., 2017) and Vitamin C (Vasanth *et al*., 2020).

Table 1. Transdermal delivery of active moieties by ultradeformable liposomes.

S. No.	Drug	Major findings	Reference(s)
1.	Lornoxicam	Superior entrapment efficacy and penetration	(Tawfeek *et al*., 2020)
2.	Ammonium glycyrrhizate	Potential anti-inflammatory therapy	(Barone *et al*., 2020)
3.	Tamsulosin	Enhanced permeation and bioavailability	(Almehmady *et al*., 2020)
4.	Retinyl Palmitate	Penetration increased	(Rodriguez *et al*., 2020)
5.	Adapalene	Improved *in vitro* skin delivery	(Vasanth *et al*., 2020)
6.	Methotrexate	Increased penetrating ability in inflammatory condition	(Bahramizadeh *et al*., 2019)
7.	Colchicine	Higher efficacy, rapid onset, and longer duration of action	(El-Feky *et al*.,2019)
8.	Felodipine	Increased permeation	(Kamani *et al*., 2019)
9.	Cilnidipine	Improved bioavailability	(Khatoon *et al*., 2019)
10	Iloperidone	Better permeation and sustained drug delivery	(Londhe *et al*., 2019)
11.	Natamycin	Improved topical ocular pharmacotherapy	(Janga *et al*., 2019)
12..	Lidocaine	Improved permeation and stability of drug	(Omar *et al*., 2019)
13.	Genistein	Reduced oxidative damage	(Langasco *et al*., 2019)
14.	Chlorine aluminum phthalocyanine	Increased skin permeability	(Escobar *et al*., 2018)
15.	Glycyrrhizic acid	Prolonged release of drug	(Chauhan *et al*., 2018b)
16.	Raloxifene hydrochloride	Increased flexibility and stability	(Joshi *et al*., 2018)
17.	3-O-cetyl ascorbic acid and tocopherol acetate	Improved bioavailability	(Fushimi *et al*., 2018)
18.	Felodipine	Enhanced drug bioavailability	(Kassem *et al*., 2018)
19.	Resveratrol	Higher efficacy	(Tosato *et al*., 2018)
20.	Trolamine salicylate	Higher permeability	(Makhmalzadeh *et al*., 2018)
21.	Curcumin	Increased penetration for treatment of breast cancer	(Abdel-Hafez *et al*., 2018)
22.	Epigallocatechin-3-gallate (EGCG) and hyaluronic acid	Higher skin permeation and deposition of EGCG	(Avadhani *et al*., 2017)
23.	Sertaconazole nitrate	Superior antifungal activity	(Abdellatif *et al*., 2017)
24.	Loratadine	Increased bioavailability	(Elkomy *et al*., 2017)
25.	Risperidone	Improved transdermal permeation	(Das *et al*., 2017)
26.	Sildenafil citrate	Extended absorption and higher bioavailability	(Badr-eldin *et al*., 2016)
27.	Pentoxifylline	Increased bioavailability	(Al shuwaili *et al*., 2016)
28.	Fluconazole	Increased drug efficacy	(Tejaswini *et al*., 2016)
29.	Timolol maleate	Increased bioavailability	(Morsi *et al*., 2016)
30.	Tramadol HCl	Better penetration of the drug	(Singh *et al*., 2016)
31.	5-fluorouracil	Biocompatible and better penetration	(Zhang *et al*., 2015)
32.	Repaglinide	Increased entrapment efficacy, maximum drug release, and better permeation	(Laxmi *et al*., 2015)
33.	Diclofenac sodium	Good entrapment efficiency and stability	(Sultana *et al*., 2015)
34.	Papaverine hydrochloride	Enhanced drug delivery	(Ali *et al*., 2015)
35.	Raloxifene hydrochloride	Higher drug permeation capability	(Mahmood *et al*., 2014)
36.	Celecoxib	Better entrapment	(Preeti *et al*., 2014)

(*Continued*)

S. No.	Drug	Major findings	Reference(s)
37.	Ciprofloxacin	Increased drug permeation across ear skin	(Al-mahallawi *et al*., 2014)
38.	Piroxicam	Excellent release and permeation of drug	(Shaji and Lal, 2014)
39.	Buspirone HCl	Increased drug permeation	(Shamma *et al*., 2013)
40.	Tacrolimus	Enhanced skin permeation	(Lei *et al*., 2013)
41.	Resveratrol	Increased penetration	(Scognamiglio *et al*., 2013)
42.	Nystatin	Prolonged release and improved site specificity	(Abdallah *et al*., 2013)
43.	Insulin	Higher stability over enzymatic degradation	(Malakar *et al*., 2012)
44.	Ketoconazole	Higher *in vitro* drug release	(Rajan *et al*., 2012)
45.	Ketorolac tromethamine	Excellent loading efficiency	(Nava *et al*., 2011)
46.	Colchicine	Increased skin permeation and deposition	(Singh *et al*., 2010)
47.	Curcumin	Better permeation	(Patel *et al*., 2009)
48.	Methotrexate	Frequency of dosing reduced, improved efficacy, and patient compliance	(Vanaja *et al*., 2008)
49.	α-tocopherol	Improved *in vitro* skin delivery	(Gallarate *et al*., 2006)
50.	Methotrexate	Improved *in vitro* skin delivery	(Trotta *et al*., 2004)
51.	Estradiol	Improved *in vitro* skin delivery	(El Maghraby *et al*., 2000)
52.	Insulin	Better penetration and reduced chances of drug degradation	(Cevc *et al*., 1998)

Intensive research has been carried out on numerous moieties by utilizing ultradeformable liposomes. Table 1 shows the various transferosomal research reports of scientific community across the globe with impressive and encouraging observations.

CONCLUSION

The transdermal route has been the most preferable route of drug administration because of its unique and versatile characteristics. However, the major concern for transdermal delivery is impermeable the stratum corneum which creates an obstacle for the entry of drugs completely. Therefore, the transferosomal system emphasizes the effective delivery of hydrophilic and hydrophobic drugs along with amphiphilic compounds in a successful manner. Transferosomes are suitable and an excellent approach owing to their reduction in dose frequency, improved efficacy, enhanced loading capacity, and increased topical applications along with better stability aspects. Transferosomes have favorable and encouraging potential for the transportation of active drugs with site-specificity and also utilized in various cosmetic strategies. Several impediments are still remaining to be resolved concerning oxidative degradation, purity, and retention property. Hence, potential improvement in the process requires special considerations and technological advancements. Additionally, to facilitate future prospects of these talented nanocarriers, progress in synergistic potential of ingredients and active molecules also needs to be investigated across the globe. It is also highlighted that sophisticated research based on persuasive preclinical and clinical studies are required to gather the information essential to ascertain the safety aspect of challenging drugs ahead of industrial scale-up. Improvements are still needed on scientific vistas for the development of innovative transferosomes which will probably focus on the superior therapeutic regimens utilizing more advanced, promising, and well-organized new strategies. It is also important to explore new pharmaceutical excipients with additional features for minimizing the existing drawbacks associated with transferosomes. In future, industrial pharmaceutical companies may explore new opportunities for significant developmental characteristics of transferosomes with appropriately tailored features.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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