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).

Transfersomes are accessible forms applied to non-occlusive skin and release the drug which depicts improved pharmacological effects, as well as minimum patient incompatibility (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 transfersomes (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 transfersomes, 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 transfersomes 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 transfersomes 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 transfersomes 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

Transfersomes 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 transfersomes is also associated with the purity of natural phospholipids.
- Higher cost associated with the expensive manufacturing procedure is essential for the fabrication of transfersomes 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

Transfersomes 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...
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 ultradeforible vesicles may be similar in both the methods (Duangjit et al., 2013; Kumar et al., 2012). Ultradeforible transfersomes 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 transfersomes 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 transfersomal 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 transfersomes have been studied to deliver proteins and peptides (Cevec 2003; Cevec et al., 1998; Paul, 1998; Yang, 2002).
- **NSAIDs:** Transfersomes are potentially employed to deliver anti-inflammatory and anti-pyretic drugs successfully, e.g., corticosteroids (Cevec et al., 1997), ketoprofen (Cevec 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 transfersomal 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 transfersomal 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 transfersomal 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-obesity agents:** Transfersomes of nanoemodin has been investigated for anti-obesity (Lu et al., 2014).
- **Anti-cancer drugs:** Transfersomes, nanovesicular systems have shown capability to deliver anticancerous 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 transfersosomes in the avenue of cosmetics and cosmeceuticals are enlisted as follows and are shown in Figure 2.
- **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]).

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**Table 1. Transdermal delivery of active moieties by ultra deformable liposomes.**

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

(Continued)
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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REFERENCES


