Medical Sains : Jurnal Ilmiah Kefarmasian
Vol. 9 No. 4, October - December 2024
https:/ojs.ummada.ac.id/index.php/iojs

REVIEW: ANALYTICAL NARRATIVE IN-DEPTH UNDERSTANDING OF FORMULATION METHODS AND TRANSFERSOME CHARACTERIZATION FOR THERAPEUTIC APPLICATIONS

Sukamto Jodi Setiyawan[1,2], Ika Yuni Astuti[3*], Hariyanti Hariyanti[4]
[1] *Faculty of Pharmacy, Science and Technology, Al-Irsyad University Cilacap, Cilacap, Centra Java, Indonesia;*
[2] *Master of Pharmacy, Muhammadiyah University, Purwokerto, Central Java, Indonesia;*
[3] *Department of Pharmacy, Pharmaceutical of Technology, Faculty of Pharmacy, Muhammadiyah University Purwokerto, Purwokerto, Central Java, Indonesia;*
[4] *Faculty of Pharmacy, Muhammadiyah University Purwokerto, Purwokerto, Central Java, Indonesia.*
**Email Corresponding: ikacaturdarma@gmail.com*

Submitted: June 10, 2024 Revised: November 26, 2024 Accepted: November 28, 2024

ABSTRACT

Transdermal drug delivery systems offer a non-invasive method for drug penetration through the skin but face significant challenges, especially in the stratum corneum layer, which inhibits drug penetration. Transfersome, an elastic vesicle developed from one of *the nanocarriers*, liposomes, has proven effective in increasing transdermal drug penetration. To examine manufacturing methods, evaluate potential safety aspects, and apply transfersomes to increase transdermal penetration of active ingredients. The results of the article search showed that transfersomes have advantages in terms of adsorption efficiency, elasticity, and the ability to carry drugs with various vesicle sizes. Several transfersome manufacturing methods have been developed, such as thin-film hydration, reverse evaporation, high-level homogenization, sonication, and ethanol injection, each with advantages and disadvantages. The thin-film hydration method is often used in research because it results in high adsorption efficiency, superior penetration ability, and good compatibility. Transfersomes have proven to be effective elastic vesicle delivery systems with phospholipids and surfactants. In transdermal applications, transfersome successfully improve the penetration and therapeutic effectiveness of antioxidant, anticancer, corticosteroid, and anti-inflammatory drugs, in the context of increasing drug penetration and therapeutic effectiveness. Transfersomes are promising drug delivery systems for transdermal applications, offering increased penetration, bioavailability, and therapeutic effectiveness. Appropriate formulation methods and in-depth characterization are needed to optimize the therapeutic potential of transfersomes for various medical applications.

Keywords: Transfersomes, transdermal delivery, lipid vesicles, entrapment efficiency, vesicle deformability, transfersome manufacturing method.

INTRODUCTION

A transdermal delivery system is a non-invasive method of drug delivery through the outermost skin, allowing the drug to penetrate the bloodstream through the skin (Akhtar et al., 2020). The transdermal delivery of drugs through the skin often faces various challenges that hinder optimal drug transport. The main obstacle to transdermal delivery is the very thick nature of the skin, especially the stratum corneum layer, which is the main barrier layer that reduces the penetration of most drugs (Khalil et al., 2019).

Researchers are trying to increase drug penetration to reach the systemic level, in this case, the transdermal drug delivery system, by using various carriers in the form of nanocarriers, which are classified into three main groups: polymers, non-polymers, and lipids. Various types of lipid nanocarriers exist, including liposomes, phytosomes, cubosomes, and solid lipid nanoparticles (Navarro-Partida et al., 2021). Transfersomes are one of the newest types of lipid nanocarriers. Transfersomes are vesicles developed from liposomes that are very flexible and elastic. The elasticity of the transfersomes is influenced by the addition of a surfactant, in this case as an edge activator, into the lipid bilayer. This surfactant can change the structure of the vesicle lipid layer, so that it increases its elasticity and flexibility in the transfersome double layer, which makes it very easy to change shape (Amnuaikit et al., 2018). The transfersome concept was first introduced in the early 1990s and continues to develop, with recent research showing its effectiveness in transdermal delivery (Rai et al., 2017).

Transfersomes are formed from phospholipids and surfactants with additional components, such as alcohol and buffer solutions, that facilitate their deformability. Transfersomes can also overcome the limitations of drug penetration via the transdermal route with conventional methods and are designed to carry drugs directly into the systemic circulation or deeper into the dermis, significantly increasing bioavailability and therapeutic effectiveness (Opatha et al., 2020).

In pharmaceuticals, transfersomes play an important role in increasing the effectiveness of drug delivery systems. According to Das et al. (2022), transfersomes have significant advantages over conventional drug delivery methods in efficiently crossing skin barriers, reducing the required drug dose, and minimizing side effects.

One of the latest studies is related to transfersomes as a drug delivery system ransdermal, which shows significant progress, namely transfersome combined with *microneedles* as an increase in drug penetration through the skin, as was observed in the results of research on aspirin delivery. Transfersome delivery systems combined with *microneedles* have a permeability potential four times higher than that of conversional preparations, which can increase the activity of drugs applied transdermally (Rahbari et al., 2023).

The use of transfersomes opens opportunities for widespread therapeutic use. These carriers can provide new therapies locally and systemically for active ingredients that have difficulty penetrating the stratum corneum effectively via passive diffusion (Kodi & Reddy, 2023).

This review aimed to provide insights for researchers and practitioners in developing more effective and safe transdermal drug delivery through the skin. This article discusses in-depth methods of transfersome formulation and characterization for therapeutic applications.

RESEARCH METHODS

The methods applied in reviewing journals and articles include online data searches through platforms such as *the* National Center of Biotechnology Information (NCBI) in the subcategories of PubMed, ScienceDirect, Elsvier, and Google Scholar. In this search process, filtering was performed by limiting the publication date to the last 5 years. Article searches were carried out using several keywords such as: "Transfersomes" found 174 articles, "Transfersomes" *and Methods* found 56 articles, "Transfersomes" *and "Methods* " *and "* Transdermal *" or "Topical"* found 38 articles, "Transfersomes" *and " Methods* ” *and “* Transdermal” *or “Topical” and “Application”* found 7 articles, with several inclusion criteria such as transfesome, transdermal and topical with the help of the Mendeley reference manager.

The references used for this study consisted of journals and articles from both national and international sources that discussed related topics based on predetermined keywords and those published in the last decade.

RESULTS AND DISCUSSION

From the search results, the following are the active substance components and vesicle forming composition as well as several methods that can be used in making transfersomes along with their advantages and disadvantages:

1. Transfersome as a Vesicle Delivery System

Transfersomes can form elastic vesicles and change their shape when passing through the cell membrane. This ultra-deformability is also obtained because the liquid core is surrounded by a layer in the form of a complex lipid bilayer. The elasticity of transfersome vesicles is influenced by the lipid composition of the lipid double layer, namely phospholipids and surfactants, as edge activators. The ability of vesicles to penetrate the transdermal barrier and achieve controlled release is an advantage of the transfersome delivery system (Mahmood et al., 2021). **Table I** lists the various active substances and vesicle-forming compositions used in several formulations and transfersome manufacturing methods.

Table I. Various Types of Active Substances, Composition and Methods for Making Transfersomes

No	Active substance	Formulation Composition		Transfersome Manufacturing Method	Reference
		Phospolipids	Edge activator/Surfactant		
1	4-hydroxytamoxifen (4-OHT)	Soy phosphatidylcholine	Emu oil	Thin film hydration method	(Sundralingam et al., 2020)
2	Adapalene L-ascorbic acid	Soy lecithin phosphatidylcholine.	Sodium deoxycholate.	Reverse phase evaporation method.	(Vasanth et al., 2020)
3	Andrographolide (98%)	Phospholipon 90 G	Span 80	Thin film hydration method	(Surini et al., 2020)
4	Anthocyanins, flavan-3-ols, and flavonols	Phospholipon 90G (P90G)	Tween 80	Sonication Method	(Asensio-Regalado et al., 2022)
5	Ascorbic palmitate (AP)	Soybean phosphatidylcholine (SPC)	AP, SDC, Cumarin-6(Cou-6), and Sodium Dodecyl Sulfate (SDS)	Thin film hydration method	(Li et al., 2021)
6	Aspirin	L-α-phosphotidylcholine	Tween-80	Thin film sonication and hydration method	(Rahbari et al., 2023)
7	Berberine chloride (BBR)	Phospholipon 90G with unsaturated fatty acids such as oleic acid.	Tween 80	Thin film hydration method.	(Mayangsari et al., 2022)
8	Carvedilol	DSPC, SPC,	Tween-80,	Thin film	(Chen et

		HEPC.	sodium cholate.	hydration method.	al., 2020)
9	Catechins	Epicuron 200, Cholesterol	Tween 80	Thin film hydration method	(Hsieh et al., 2021)
10	Ebastine	Soya lecithin	Tween 80, Span 60	Thin film hydration method	(Raut et al., 2023)
11	Recombinant human epidermal (rhEGF)	Phospholipon 90G.	Sodium deoxycholate.	Thin film hydration method followed by extrusion.	(Surini et al., 2020)
12	Ibuprofen sodium salt	Soya Lesetin	Tween 80 and Span 80.	Thin film hydration method followed by sonication	(Vieira et al., 2023)
13	Glutathione	Phosphatidylcholine	Tween 80	Thin film hydration method	(Nurfitriyana et al., 2020)
14	Hydrocortisone (HC)	Egg Phosphatidylcholine (EPC)	Span 20 and Tween 80	Thin film hydration method	(Abdelwahd & Rasool, 2022)
15	Indomethacin	Soybean phospholipids (SPCs)	Sodium deoxycholate	Thin film hydration method	(Yuan et al., 2022)
16	Ivabradine HCl	Soya Lecithin	Tween 80	Ethanol Injection Method	(Balata et al., 2020)
17	Lidocaine	Soy phosphatidylcholine.	Span 80	Thin film hydration method	(Omar et al., 2019)
18	Lycorine (LR)	Phospholipids: Cationic lipids.	Modification of the R5H3 peptide.	Thin film hydration methods and by extrusion	(Li et al., 2023)
19	lynesterol	Soy phosphatidylcholine 90G	Tween 80	Thin film hydration method	(Nurfitriyana et al., 2020)
20	Meloxicam (MLX) and Dexamethasone (DEX)	Lecithin.	Span 80 and Tween 80	Evaporator method and thin film hydration	(Khan et al., 2022)
21	Methotrexate	Phospholipon 90 G	Span 80	Conventional rotary machine evaporation sonication method	(Modi & Bharadia, 2023)
22	N-acetylcysteine	Phosphatidylcholine	Tween 80	Thin film hydration method	(Harmita et al., 2020)

23	Natamycin	Phospholipon (PL) 90H.	Tween 80	Thin film hydration method	(Janga et al., 2019)
24	Nitazoxanide and Quercetin	Phospholipon 90G.	Tween 80	Thin film hydration method	(Bashir et al., 2023)
25	Peptides and Proteins	Phospholipon 90G comes from soybeans	Sodium deoxycholate	Thin film hydration method	(Leonyza & Surini, 2019)
26	Amniotic mesenchymal stem cell metabolite (AMSC-MP)	l-α-phosphatidylcholine.	Stearylamine, Sodium cholate and Tween 80	Thin film hydration method	(Miatmoko et al., 2022)
27	Proteins	Dipalmitoylphosphatidylcholine (DPPC)	Tween 80	Thin film hydration method	(Khayrani et al., 2024)
28	Quercetin (Qc)	Lecithin	Span 60 and Span 80	Thin film hydration method	(Abdallah et al., 2021)
29	Quercetin from Mulberries	Phospholipone 90g	Tween 80	Thin film hydration method	(Nangare et al., 2021)
30	Quercetin, the main flavonoid in lime peel extract.	Lecithin	Tween 20	Sonication method.	(Prasetyaningrum et al., 2023)
31	Quetiapine fumarate	Soybean-Phospholipids	Span 80	Ethanol Injection Method	(Shruti & Reddy, 2023)
32	Raloxifene hydrochloride (RXN)	soy lecithin	Span 80 and Span 80	Evaporator method and thin film hydration	(Mahmood et al., 2021)
33	Resveratrol (RSV)	phosphatidyl choline (PC)/ Lecithin	Tween 80 and Tween 20	High pressure homogenization method	(Wu et al., 2019)

2. Transfersome Creation Method

In this study, the conversion method for making transfersomes was the thin film hydration method, which is also known as the rotary evaporation-sonication method. Various manufacturing methods have been modified, including the reverse feeding, high-pressure homogenization, and ethanol injection methods (Opatha et al., 2020). Each of these methods is explained below.

2.1 Thin Film Hydration Method

This process involves mixing phospholipids with surfactants in an organic solvent. The mixture was evaporated until it formed a thin film, and then hydrated with a buffer solution from some of the water phase to form transfersome vesicles, which were used to make multi- lamellar vesicles.

A mixture of phospholipids and surfactants was dissolved in methanol and chloroform solvent in a ratio of 1:2 v/v (Khayrani et al., 2024). The solution was

then transferred into a round-bottom flask and evaporated with constant stirring at a temperature above the lipid glass transition temperature, and the pressure was gradually reduced. A layer of mixture between phospholipids and surfactant/edge activator is formed on the walls of the flask and hydrated using the water phase, which is then dissolved in the medium according to the solubility characteristics of the drug substance. The hydration process causes the swelling of lipids and formation of bilayer vesicles. This method produces that the polydispersity index (PDI) of the three transfesome formulations contained in rhEGF (Recombinant human epidermal growth factor) is less than 0.2, meaning it shows that the population of transfersome phospholipid vesicles is homogeneous, where the PDI threshold is less than 0.3 (Surini et al., 2020).

Results from other studies also state that using the thin film hydration method is very important in forming transfersome characteristics, including the polydispersity index (PDI), which can influence the formation and properties of lipid vesicles (Khayrani et al., 2024).

From research articles, it was determined that the widely used transfersome method is the thin film hydration method. The advantages of this method are its low cost, ease of use, scale-up to the laboratory scale, and increased adsorption efficiency. However, the drawback of this method is that it is not suitable for large-scale or industrial-scale production.

2.2 Reverse Evaporation Method

In the first reverse fermentation method, the lipid phase was dissolved in an organic solvent in a round-bottomed flask. Water containing a surfactant or edge activator was added under nitrogen protection. The drug dissolution process depends on the solubility of the drug, so it can be added to the water or lipid phase. After the system was formed, it was sonicated to make it a homogeneous dispersion and separated after sonicating for 30 minutes. Next, the solvent was removed under reduced pressure, and this system turned into a thick gel, followed by the formation of vesicles. The residual solvent and unencapsulated materials were then removed by dialysis or centrifugation (Vasanth et al., 2020). The reverse evaporation method has advantages, namely because it is easy to carry out and can be scaled up (Lu et al., 2014). The disadvantage of this method is that its adsorption efficiency is lower than that of the thin film hydration method (Morsi et al., 2016).

2.3 High Pressure Homogenization Method

This high pressure homogenization method combined with one of the methods in the form of the thin film hydration method is able to produce transfersomes with better quality (Avadhani et al., 2017). Phospholipids, surfactants, or edge activators and drugs are mixed evenly in a solution in the form of PBS solution or distilled water containing an organic solvent, namely alcohol, and a vibration process is then carried out with an ultrasonic device and stirred simultaneously. Once the mixture was ready, it was continuously subjected to ultrasonic vibrations. The resulting mixture was then homogenized using a high-pressure homogenizer and the final transfersome process was stored under appropriate and safe conditions (Wu et al., 2019).

2.4 Sonication Method

Phospholipids were dissolved in anhydrous ethanol to form an organic phase. Heat the aqueous phase containing the drug and surfactant and the organic phase to 50°C while stirring. After dissolution, the ethanolic phospholipid solution was slowly added to the water phase solution while stirring for 20 minutes. The lipids and surfactant are then allowed to form a bilayer wall that traps the hydrophilic drug in the core, thus forming a transfersome (Balata et al., 2020).

This method has the advantages of being simple, inexpensive, and can be performed in a short time (Kraft et al., 2014). However, a drawback is that the

resulting vesicles tend to be large and have a high degree of size variation (Kraft et al., 2014).

2.5 Ethanol Injection Method

In this method, the aqueous phase containing the drug is heated with continuous stirring at a constant temperature. An ethanol solution containing surfactants as edge activators and phospholipids was poured slowly into the water phase. Next, the lipid molecules precipitate and form a bilayer structure when in contact with the water phase (Pitta et al., 2018).

This method also has the advantage that it can be produced on an industrial scale because of its speed, safety, and non-hazardous nature; therefore, it can be produced in large quantities compared with the thin film hydration method. The ethanol injection method also has the disadvantage of requiring large amounts of solvent (Gouda et al., 2021).

3. The quality of transfersomes after manufacturing can be evaluated using the following methods:

3.1 Determination of Transfersome Entrapment Efficiency

This determination uses an indirect method, namely, estimating the amount of drug trapped in the vesicles. Ultrasonics and centrifugation were used to separate the drug from the vesicle system; then, the supernatant was collected, and the concentration of drug that was not adsorbed in the vesicles was determined (Omar et al., 2019). This will, of course, be related to adjusting the ratio between the drug and phospholipids, namely by increasing the amount of phospholipids or reducing the amount of surfactant, which can significantly increase absorption efficiency (EE %). This indicates a direct relationship between the drug and phospholipid ratio and adsorption efficiency (Balata et al., 2020). The drug entrapment percentage (EE%) was calculated for 3 replications using the following formula:

$$EE\% = \frac{Total\ amaund\ of\ drug\ added\ -\ Amaund\ of\ untrapped\ drug}{Total\ amaund\ of\ drug\ added} x100$$

3.2 Measurement of Zeta Potential, Vesicle Size, and Size Distribution

The particle distribution and size as well as the zeta potential value of these vesicles were evaluated using a dynamic light scattering (DLS) tool and the Malvern Zetasizer tool. The samples were diluted with the appropriate media at room temperature before the measurement. All data were analyzed in triplicate to obtain good results (Omar et al., 2019).

The importance of measuring zeta potential is that it can affect particle stability, vesicle size below 300 nm allows transfersome particles to penetrate the skin epidermis effectively for transdermal delivery, and size distribution impacts drug delivery efficiency and targeting capabilities in transfersome formulations (Khayrani et al., 2024).

3.3 Transfersome morphology

a. Transmission Electron Microscopy (TEM).

In this tool, the morphology of the vesicles was observed using an acceleration voltage of approximately 80 kV, and 5 µL of the transfersome suspension was placed on a carbon-coated grid. The excess solution was carefully removed using filter paper, and the sample was then viewed at a magnification of 29,000 × up to 145,000 ×. Observation of vesicle morphology using transmission electron microscopy (TEM) is very important in this research because it helps to confirm that the resulting vesicles have a spherical structure and consist of one layer (unilamellar). TEM allows researchers to view vesicles with high resolution, providing visual evidence of the shape and internal structure of the vesicle, which is an important indicator of success in

transfersome formulations, with an average of less than 200 nm (Surini et al., 2020).

1. Scanning Electron Microscope (SEM)

   Vesicle morphology was evaluated using scanning electron microscopy (SEM). For the first observation, a vesicle sample was placed on the surface of the prepared glass. The copper precipitate layer was then dried and applied to the sample. After drying, all samples were visualized using SEM at an accelerated voltage of 30 kV, and images were taken at magnifications ranging from 5,000 × to 50,000 × (Khan et al., 2022). The importance of evaluating vesicle morphology. The use of SEM is an important step in transfersome research and development. This provides critical information that not only helps ensure vesicle quality and consistency but also enables optimization of the formulation process for more effective and safe therapeutic applications (Chaurasiya et al., 2019).

b. Degrees Deformability

Deformability measurement is an important parameter of the transfersome formulation. This degree of deformability can differentiate it from other vesicle-carrying transfersomes in the form of nanocarriers such as liposomes. This test can be performed using the extrusion method, where the particle size and vesicle distribution can be monitored via DLS measurements before and after filtration (Opatha et al., 2020). This evaluation aimed to assess membrane flexibility, differentiate transfersomes from conventional vesicles, and ensure the effectiveness of the formulation in achieving optimal drug penetration and delivery (Akhtar et al., 2020). The degree of deformability was calculated using the following formula:

$$D = J\left(\frac{rx}{rp}\right)^2$$

Information :
D: Veiskel Membrane Deformability
rx : Barrier Pore Size
rp: Vesicle size (after exit)
A: The amount of suspension extruded in 5 minutes

c. In vitro drug release studies

In this test, the release of drugs contained in the transfersome system can be measured using a modified drug release study to measure drug release from the dialysis bag installed in the dissolution chamber (Morsi et al., 2016). Drug release from transfersomes was evaluated to determine the amount of drug released from the vesicles under conditions resembling those in the body. This study used a dialysis bag installed inside a dissolution chamber to mimic biological conditions, and measured the rate and amount of drug released from the transfersomes. This is important to ensure that the drug reaches its target effectively and efficiently, as well as to optimize the formulation and predict the clinical performance (Khayrani et al., 2024).

d. Permeation studies

1. In Vitro Permeation Studies

   In vitro drug release studies can be performed by using Franz diffusion cells. The membrane was placed between the acceptor and donor compartments and centrifuged at 100 rpm at 37 ± 0.5°C. At predetermined time intervals, the samples were replaced with fresh media. Active ingredient samples were filtered through a 0.45 µm membrane, with the aim of measuring drug release from the delivery system studied in vitro and evaluating the effectiveness of the drug delivery system in releasing the active ingredient into the bloodstream. This review is important for research

related to understanding release kinetics to help predict and optimize drug release characteristics, which are important for designing safe and effective drug delivery systems (Bashir et al., 2023).

2. Ex-Vivo Permeation Study

Ex-vivo skin permeation studies were carried out using Franz diffusion cells on shaved ventral skin of mice. The skin was prepared by removing the subcutaneous fat and storing it in normal saline (pH 5.5). The skin was placed between the donor compartment and Franz diffusion cell receptor, and the recipient medium in phosphate buffer (pH 6.8) was agitated and maintained at 32 ± 0.5°C. The Transfersome formula contains active ingredients that are applied topically to the skin. Samples were collected at intervals of 0, 1, 2, 3, 4, 5 and 6 hours, then diluted and analyzed using a UV-visible spectrophotometer at λmax depending on the active ingredient used in the study. This review aims to evaluate the skin penetration efficacy of six transferable formulations (Khan et al., 2022). The purpose of this test is to evaluate the efficiency of drug delivery through the skin using transfersomes. This helps optimize the formulation to improve drug penetration and delivery efficiency as well as ensure safety and stability (Akhtar et al., 2020).

e. Stability of the Transfersome

The stability of transportable vesicles can be assessed by monitoring their structure and size over time. Dynamic light scattering (DLS) and transmission electron microscopy (TEM) were used to determine the average particle size and observe structural changes. The optimized transferable formulation could be stored in tightly closed amber bottles at different temperatures (Opatha et al., 2020). According to the International Conference on Harmonization (ICH) guidelines, stability testing of new pharmaceutical ingredients and medicinal products is performed by storing them under certain conditions. For long-term testing, normal storage conditions were maintained at a temperature of 25 ± 2 °C with a relative humidity (RH) of 60 ± 5% or at a temperature of 30 ± 2 °C with a relative humidity (RH) of 60 ± 5% was 65% ± 5. % in 12 months. For accelerated testing, the storage conditions were 40 ± 2°C with a relative humidity of 75% ± 5% for six months. Drugs intended for refrigerated storage should be tested under long-term storage conditions at a temperature of 5 ± 3 °C for 12 months, and accelerated testing at a temperature of 25 ± 2 °C with a relative humidity of 60% ± 5% for 12 months. A significant change in a medicinal product is defined as one that does not meet its specifications. The purpose of transferable pouch stability testing is to ensure that the structure and size of the pouch remain stable during storage so that its effectiveness is maintained. and product safety. This test also aims to determine the optimal storage conditions using techniques such as dynamic light scattering (DLS) and transmission electron microscopy (TEM) to monitor changes in vesicle size and structure (Khayrani et al., 2024).

f. Advantages and Disadvantages of the Transfersome Method

Compared (Opatha et al., 2020) with other vesicles, this transfersome has several advantages, including:

1) These transfersomes have a high entrapment efficiency of approximately 90% for lipophilic drugs.
2) Transfersome penetration is much better than that of other liposomes owing to its elasticity.
3) This transfersome can also act as a carrier for high or low molecular weight drugs such as analgesics, corticosteroid anesthetics, sex hormones, anticancer drugs, insulin, albumin, and proteins.

4) Regarding transfersomes, they have a structure consisting of hydrophobic and hydrophilic molecules so they can accommodate drug molecules with a large solubility range.
5) Transfersomes can function as depots that slowly release drugs and gradually become more effective.
6) Transfersomes can be used to systemically deliver drugs.
7) Transfersomes are biocompatible, because they are composed of natural phospholipids.
8) Transfersomes can also be used to coat drugs and protect them from metabolic degradation.
9) Transfersomes are also easy to scale up because the process is quite easy and does not use additional ingredients that are not pharmaceutically compatible.

Some of the advantages of transfersomes have disadvantages, including those of Opatha et al. (2020):

1) Transfersome stability can be disturbed by the oxidation process, which will cause faster degradation.
2) The associated purity of natural phospholipids determines the quality of transfersomes and drug delivery systems.
3) However, transfersome formulations are expensive.

g. Transfersome Application as a Transdermal Delivery System

In recent years, transfersomes have been used in various applications as transdermal delivery systems. These vesicles can effectively carry drugs across the skin, increasing the penetration and bioavailability of active ingredients. Some of these applications are described below:

1. Antioxidant drug delivery

In an article search in 2022, Asensio-Regalado et al. studied the antioxidant-containing metabolites of the obtained Tempranillo grape pomace extract and characterized them qualitatively and quantitatively. This study used grape pomace extract in the transfersomes using the thin film hydration method to increase the antioxidant activity and bioavailability of the bioactive compounds. The aim of this study was to demonstrate the potential of this new nanoproduct for skin care applications. The results showed that the tempranillo grape pomace extract contained in the transfersomes increased the antioxidant effect on the cellular system. This shows great potential for use as an antioxidant in skin care products (Asensio-Regalado et al. 2022).

2. Delivery of Anticancer Drugs

A study by Chen et al.. in 2020, regarding the topical use of nanotransfersomes containing carvedilol for the prevention of skin cancer. In his research on metabolism using the thin layer hydration method. The transfersome includes the phospholipids used: DSPC, SPC, and HEPC, as well as surfactants or edge activators such as tween 80 and sodium deoxycholate, which have been shown to inhibit EGF-induced neoplastic transformation in JB6 P+ mouse epidermal cells and can inhibit UV-induced DNA. injury, inflammatory gene expression, and apoptosis (Chen et al., 2020).

3. Corticosteroid Drug Delivery

In 2022, research was conducted by Abdelwahd et al. on the transfersome formulation of hydrocortisone as an alternative route of administration to reach deeper skin layers or systemic circulation in order to reduce the side effects of hydrocortisone and increase bioavailability, which is made using the thin film hydration method. The research results showed that the simulated pharmacokinetics indicated that formula 15 had the highest AUC, MDT, and DE values. In addition, Formula 15 significantly

increased hydrocortisone permeation by up to 12-fold compared to controls in excised mouse skin. Skin irritation tests showed that Formula 15 is safe and compatible with the skin (Abdelwahd & Rasool, 2022).

4. Delivery of Anti-Inflammatory Drugs

In 2022, research was conducted by Khan et al. regarding meloxicam (MLX) in combination with dexamethasone (DEX) in a transfersome gel formulation, and the results showed that the MLX and DEX transfersome gel formulation could serve as an effective carrier for increased transdermal flux, potentially leading to increased anti-inflammatory effects. inflammation and better therapeutic outcomes (Khan et al., 2022).

CONCLUSION

Various methods for generating transfersomes have their own characteristics, advantages, and disadvantages. Therefore, choosing the appropriate method for making transfersomes must be adjusted to meet the needs and goals of research. This thin film hydration method is the most widely used method for the development of transfersomes on a laboratory scale. This is due to its ease of use and ability to produce high adsorption efficiency.

Transfersomes are promising transdermal drug delivery systems with high penetration ability and bioavailability. Its advantages include a high entrapment efficiency, superior penetration ability, and compatibility. However, formulation stability and cost are challenges that must be overcome.

ACKNOWLEDGMENTS

We, as authors, would like to thank all parties, especially the supervisors and lecturers in charge of the Seminar and Scientific Writing courses who gave the authors the opportunity to publish this journal.

REFERENCES

Abdallah, M., Nesseem, D. I., Elgazayerly, O. N., & Abdelbary, A. A. (2021). Topical delivery of quercetin loaded transfersomes for wound treatment: In vitro and in vivo evaluation. *International Journal of Applied Pharmaceutics*, *13*(5), 189–197. https://doi.org/10.22159/ijap.2021v13i5.41345

Abdelwahd, A., & Rasool, B. A. (2022). Optimizing and evaluating the transdermal permeation of hydrocortisone transfersomes formulation based on digital analysis of the in vitro drug release and ex vivo. *Recent Advances in Drug Delivery and Formulation*. https://www.benthamdirect.com/content/journals/raddf/10.2174/2666387816666220608115605

Akhtar, N., Singh, V., Yusuf, M., & Khan, R. A. (2020). Non-invasive drug delivery technology: Development and current status of transdermal drug delivery devices, techniques and biomedical applications. *Biomedizinische Technik*, *65*(3), 243–272. https://doi.org/10.1515/BMT-2019-0019

Amnuaikit, T., Limsuwan, T., Khongkow, P., & Boonme, P. (2018). Vesicular carriers containing phenylethyl resorcinol for topical delivery system; liposomes, transfersomes and invasomes. *Asian Journal of Pharmaceutical Sciences*, *13*(5), 472–484. https://doi.org/10.1016/J.AJPS.2018.02.004

Asensio-Regalado, C., Alonso-Salces, R. M., Gallo, B., Berrueta, L. A., Era, B., Pintus, F., & Caddeo, C. (2022). Tempranillo Grape Extract in Transfersomes: A Nanoproduct with Antioxidant Activity. *Nanomaterials*, *12*(5). https://doi.org/10.3390/NANO12050746

Avadhani, K. S., Manikkath, J., Tiwari, M., Chandrasekhar, M., Godavarthi, A., Vidya, S. M., Hariharapura, R. C., Kalthur, G., Udupa, N., & Mutalik, S. (2017). Skin delivery of epigallocatechin-3-gallate (EGCG) and hyaluronic acid loaded nano-transfersomes for

antioxidant and anti-aging effects in UV radiation induced skin damage. *Drug Delivery*, *24*(1), 61–74. https://doi.org/10.1080/10717544.2016.1228718/ASSET/BD7BBE91-4DE5475C9BED7A6AB3F6CA1E/ASSETS/IMAGES/IDRD_A_1228718_F0005_B.JPG

Balata, G. F., Faisal, M. M., Elghamry, H. A., & Sabry, S. A. (2020). Preparation and Characterization of Ivabradine HCl Transfersomes for Enhanced Transdermal Delivery. *Journal of Drug Delivery Science and Technology*, *60*. https://doi.org/10.1016/J.JDDST.2020.101921

Bashir, S., Shabbir, K., Din, F. ud, Khan, S. U., Ali, Z., Khan, B. A., Kim, D. W., & Khan, G. M. (2023). Nitazoxanide and quercetin co-loaded nanotransfersomal gel for topical treatment of cutaneous leishmaniasis with macrophage targeting and enhanced anti-leishmanial effect. *Heliyon*, *9*(11), e21939. https://doi.org/10.1016/J.HELIYON.2023.E21939

Chaurasiya, P., Ganju, E., Upmanyu, N., Ray, S. K., & Jain, P. (2019). *Transfersomes: a novel technique for transdermal drug delivery*. *Journal of Drug Delivery and Therapeutics*. *9*(1). https://doi.org/10.22270/jddt.v9i1.2198

Chen, M., Shamim, M. A., Shahid, A., Yeung, S., Andresen, B. T., Wang, J., Nekkanti, V., Meyskens, F. L., Kelly, K. M., & Huang, Y. (2020). Topical Delivery of Carvedilol Loaded Nano-Transfersomes for Skin Cancer Chemoprevention. *Pharmaceutics*, *12*(12), 1–17. https://doi.org/10.3390/PHARMACEUTICS12121151

Das, B., Nayak, A. K., & Mallick, S. (2022). Transferosomes: a novel nanovesicular approach for drug delivery. *Systems of Nanovesicular Drug Delivery*, 103–114. https://doi.org/10.1016/B978-0-323-91864-0.00022-X

Gouda, A., Sakr, O. S., Nasr, M., & Sammour, O. (2021). Ethanol injection technique for liposomes formulation: An insight into development, influencing factors, challenges and applications. *Journal of Drug Delivery Science and Technology*, *61*. https://doi.org/10.1016/J.JDDST.2020.102174

Harmita, H., Iskandarsyah, I., & Afifah, S. F. (2020). Effect of transfersome formulation on the stability and antioxidant activity of n-acetylcysteine in anti-aging cream. *International Journal of Applied Pharmaceutics*, *12*(Special Issue 1), 156–162. https://doi.org/10.22159/ijap.2020.v12s1.FF034

Hsieh, W. C., Fang, C. W., Suhail, M., Lam Vu, Q., Chuang, C. H., & Wu, P. C. (2021). Improved skin permeability and whitening effect of catechin-loaded transfersomes through topical delivery. *International Journal of Pharmaceutics*, *607*, 121030. https://doi.org/10.1016/J.IJPHARM.2021.121030

Janga, K. Y., Tatke, A., Dudhipala, N., Balguri, S. P., Ibrahim, M. M., Maria, D. N., Jablonski, M. M., & Majumdar, S. (2019). Gellan Gum Based Sol-to-Gel Transforming System of Natamycin Transfersomes Improves Topical Ocular Delivery. *Journal of Pharmacology and Experimental Therapeutics*, *370*(3), 814–822. https://doi.org/10.1124/JPET.119.256446

Khalil, R. M., Abdelbary, A., Kocova El-Arini, S., Basha, M., & El-Hashemy, H. A. (2019). Evaluation of bilosomes as nanocarriers for transdermal delivery of tizanidine hydrochloride: in vitro and ex vivo optimization. *Journal of Liposome Research*, *29*(2), 171–182. https://doi.org/10.1080/08982104.2018.1524482

Khan, M. I., Yaqoob, S., Madni, A., Akhtar, M. F., Sohail, M. F., Saleem, A., Tahir, N., Khan, K. ur R., & Qureshi, O. S. (2022). Development and In Vitro / Ex Vivo Evaluation of Lecithin-Based Deformable Transfersomes and Transfersome-Based Gels for Combined Dermal Delivery of Meloxicam and Dexamethasone. *BioMed Research International*, *2022*. https://doi.org/10.1155/2022/8170318

Khayrani, A. C., Fahmi, M., Nurhayati, R. W., Manas, N. H. A., & Suhaeri, M. (2024). Effect of Freeze-Thaw Cycles Method to Transfersome Characteristics for Growth Protein Encapsulation. *International Journal of Technology*, *15*(2), 267–278. https://doi.org/10.14716/IJTECH.V15I2.6670

Kodi, S. R., & Reddy, M. S. (2023). Transferosomes: A Novel Topical Approach: A NOVEL TOPICAL APPROACH. *Journal of Drug Delivery and Therapeutics*, *13*(2), 126–131. https://doi.org/10.22270/JDDT.V13I2.5952

Kraft, J. C., Freeling, J. P., Wang, Z., & Ho, R. J. Y. (2014). Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. *Journal of Pharmaceutical Sciences*, *103*(1), 29–52. https://doi.org/10.1002/JPS.23773

Leonyza, A., & Surini, S. (2019). Optimization of sodium deoxycholate-based transfersomes for percutaneous delivery of peptides and proteins. *International Journal of Applied Pharmaceutics*, *11*(5), 329–332. https://doi.org/10.22159/IJAP.2019V11I5.33615

Li, J., Duan, N., Song, S., Nie, D., Yu, M., Wang, J., Xi, Z., Li, J., Sheng, Y., Xu, C., Wei, Y., & Gan, Y. (2021). Transfersomes improved delivery of ascorbic palmitate into the viable epidermis for enhanced treatment of melasma. *International Journal of Pharmaceutics*, *608*. https://doi.org/10.1016/j.ijpharm.2021.121059

Li, Y., Tai, Z., Ma, J., Miao, F., Xin, R., Shen, C., Shen, M., Zhu, Q., & Chen, Z. (2023). Lycorine transfersomes modified with cell-penetrating peptides for topical treatment of cutaneous squamous cell carcinoma. *Journal of Nanobiotechnology*, *21*(1). https://doi.org/10.1186/S12951-023-01877-4

Lu, K., Xie, S., Han, S., Zhang, J., Chang, X., Chao, J., Huang, Q., Yuan, Q., Lin, H., Xu, L., Shen, C., Tan, M., Qu, S., Wang, C., & Song, X. (2014). Preparation of a nano emodin transfersome and study on its anti-obesity mechanism in adipose tissue of diet-induced obese rats. *Journal of Translational Medicine*, *12*(1), 1–14. https://doi.org/10.1186/1479-5876-12-72

Mahmood, S., Chatterjee, B., & Mandal, U. K. (2021). Pharmacokinetic evaluation of the synergistic effect of raloxifene loaded transfersomes for transdermal delivery. *Journal of Drug Delivery Science and Technology*, *63*. https://doi.org/10.1016/J.JDDST.2021.102545

Mayangsari, F., Surini, S., & Iswandana, R. (2022). Development of transfersomal emulgel to enhance the permeation of berberine chloride for transdermal delivery. *Journal of Applied Pharmaceutical Science*, *12*,(2), 048–055. https://doi.org/10.7324/JAPS.2021.120205

Miatmoko, A., Marufah, N. A., Nada, Q., Rosita, N., Erawati, T., Susanto, J., Purwantari, K. E., Nurkanto, A., Purwati, P., & Soeratri, W. (2022). The effect of surfactant type on characteristics, skin penetration and anti-aging effectiveness of transfersomes containing amniotic mesenchymal stem cells metabolite products in UV-aging induced mice. *Drug Delivery*, *29*(1), 3443–3453. https://doi.org/10.1080/10717544.2022.2149895

Modi, C. D., & Bharadia, P. (2023). In-Vitro and Ex-Vivo Evaluation of Transfersomal Gel of Methotrexate. *Brazilian Journal of Pharmaceutical Sciences*, *59*, e22643. https://doi.org/10.1590/S2175-97902023E22643

Morsi, N. M., Aboelwafa, A. A., & Dawoud, M. H. S. (2016). Improved bioavailability of timolol maleate via transdermal transfersomal gel: Statistical optimization, characterization, and pharmacokinetic assessment. *Journal of Advanced Research*, *7*(5), 691–701. https://doi.org/10.1016/J.JARE.2016.07.003

Nangare, S., Bhatane, D., Mali, R., & Shitole, M. (2021). Development of a novel freeze-dried mulberry leaf extract-based transfersome gel. *Turkish Journal of Pharmaceutical Sciences*, *18*(1), 44–55. https://doi.org/10.4274/TJPS.GALENOS.2019.98624

Navarro-Partida, J., Castro-Castaneda, C. R., Cruz-Pavlovich, F. J. S., Aceves-Franco, L. A., Guy, T. O., & Santos, A. (2021). Lipid-Based Nanocarriers as Topical Drug Delivery Systems for Intraocular Diseases. *Pharmaceutics 2021*, *Vol. 13*, *Page 678*, *13*(5), 678. https://doi.org/10.3390/PHARMACEUTICS13050678

Nurfitriyana, N., Harmita, H., & Iskandarsyah, I. (2020). In vitro study of a transfersomal gel preparation containing lynestrenol as a transdermal drug delivery system. *International Journal of Applied Pharmaceutics*, *12*(Special Issue 1), 242–244. https://doi.org/10.22159/IJAP.2020.V12S1.FF052

Omar, M. M., Hasan, O. A., & El Sisi, A. M. (2019). Preparation and optimization of lidocaine transferosomal gel containing permeation enhancers: a promising approach for enhancement of skin permeation . *International Journal of Nanomedicine*, *14*, 1551–1562. https://doi.org/10.2147/IJN.S201356

Opatha, S. A. T., Titapiwatanakun, V., & Chutoprapat, R. (2020). Transfersomes: A Promising Nanoencapsulation Technique for Transdermal Drug Delivery. *Pharmaceutics 2020, Vol. 12, Page 855*, *12*(9), 855. https://doi.org/10.3390/PHARMACEUTICS12090855

Pitta, S. K., Dudhipala, N., Narala, A., & Veerabrahma, K. (2018). Development of zolmitriptan transfersomes by Box–Behnken design for nasal delivery: in vitro and in vivo evaluation. *Drug Development and Industrial Pharmacy*, *44*(3), 484–492. https://doi.org/10.1080/03639045.2017.1402918

Prasetyaningrum, N., Fuadiyah, D., Listari, K. M., Tsaqila, Q. H., Zaluchu, S. P., & Marwati, S. I. (2023). Wound Healing Effects of Nanotransfersome Gel of Lime Peel Extract (Citrus aurantifolia Swigle) on Mucosa Labial Ulcer of Wistar Rats. *Malaysian Journal of Medicine and Health Sciences*, *19*(April), 19–27.

Rahbari, R., Francis, L., Guy, O. J., Sharma, S., Von Ruhland, C., & Xia, Z. (2023). Microneedle-Assisted Transfersomes as a Transdermal Delivery System for Aspirin. *Pharmaceutics 2024, Vol. 16, Page 57*, *16*(1), 57. https://doi.org/10.3390/PHARMACEUTICS16010057

Rai, S., Pandey, V., & Rai, G. (2017). Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: the state of the art. *Nano Reviews & Experiments*, *8*(1), 1325708. https://doi.org/10.1080/20022727.2017.1325708

Raut, S. S., Rane, B. R., & Jain, A. S. (2023). Development and Evaluation of Ebastine-Loaded Transfersomal Nanogel for the Treatment of Urticaria (Autoimmune Disease). *Engineering Proceedings 2023, Vol. 56, Page 101*, *56*(1), 101. https://doi.org/10.3390/ASEC2023-15286

Shruti, K., & Reddy, M. S. (2023). Preparation and characterization of quetiapine fumarate loaded transfersome as a novel drug delivery system. *GSC Biological and Pharmaceutical Sciences*, *25*(2), 372–386. https://doi.org/10.30574/GSCBPS.2023.25.2.0463

Sundralingam, U., Chakravarthi, S., Radhakrishnan, A. K., Muniyandy, S., & Palanisamy, U. D. (2020). Efficacy of Emu Oil Transfersomes for Local Transdermal Delivery of 4-OH Tamoxifen in the Treatment of Breast Cancer. *Pharmaceutics*, *12*(9), 807. https://doi.org/10.3390/PHARMACEUTICS12090807

Surini, S., Leonyza, A., & Suh, C. W. (2020). Formulation and In Vitro Penetration Study of Recombinant Human Epidermal Growth Factor-Loaded Transfersomal Emulgel. *Advanced Pharmaceutical Bulletin*, *10*(4), 586. https://doi.org/10.34172/APB.2020.070

Surini, S., Nastiti, P. D., Putri, A. R., & Putri, K. S. S. (2020). Formulation of andrographolide transfersomes gel for transdermal delivery: A preliminary study. *International Journal of Applied Pharmaceutics*, *12*(Special Issue 1), 187–191. https://doi.org/10.22159/IJAP.2020.V12S1.FF043

Vasanth, S., Dubey, A., G.S, R., Lewis, S. A., Ghate, V. M., El-Zahaby, S. A., & Hebbar, S. (2020). Development and Investigation of Vitamin C-Enriched Adapalene-Loaded Transfersome Gel: a Collegial Approach for the Treatment of Acne Vulgaris. *AAPS PharmSciTech*, *21*(2). https://doi.org/10.1208/S12249-019-1518-5

Vieira, J., Castelo, J., Martins, M., Saraiva, N., Rosado, C., & Pereira-Leite, C. (2023). Mixed Edge Activators in Ibuprofen-Loaded Transfersomes: An Innovative Optimization Strategy Using Box–Behnken Factorial Design. *Pharmaceutics 2023, Vol. 15, Page 1209*, *15*(4), 1209. https://doi.org/10.3390/PHARMACEUTICS15041209

Wu, P. S., Li, Y. S., Kuo, Y. C., Tsai, S. J. J., & Lin, C. C. (2019). Preparation and Evaluation of Novel Transfersomes Combined with the Natural Antioxidant Resveratrol. *Molecules (Basel, Switzerland)*, *24*(3).

https://doi.org/10.3390/MOLECULES24030600

Yuan, M., Niu, J., Xiao, Q., Ya, H., Zhang, Y., Fan, Y., Li, L., & Li, X. (2022). Hyaluronan-modified transfersomes based hydrogel for enhanced transdermal delivery of indomethacin. *Drug Delivery*, *29*(1), 1232–1242. https://doi.org/10.1080/10717544.2022.2053761