International Journal of Multidisciplinary Research and Growth Evaluation.

Transdermal patch: An effective transdermal drug delivery system

Jayasree Yerra [1], Praneetha Pallerla [2], Srinivas Nimmagadda [3*]
[1-3] Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Tarnaka, Secunderabad, Telangana, India

* Corresponding Author: **Srinivas Nimmagadda**

Article Info

ISSN (online): 2582-7138
Volume: 04
Issue: 05
September-October 2023
Received: 03-09-2023;
Accepted: 04-10-2023
Page No: 1070-1074

Abstract
Transdermal drug delivery systems (TDDS) are topically administered medicaments. Transdermal drug delivery is defined as a self-contained discrete dosage form, which when applied to the intact skin, will deliver the drug at a controlled rate to the systemic circulation. Transdermal patches are pharmaceutical preparation of varying sizes, containing, one or more active ingredient, intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers. Compared to oral or systemic dosage systems, TDDS can offer a controlled release of the drugs through the skin into the patients, which could reduce the first-pass metabolism effects, lessen systemic side effects, improve the dosage efficacy by enabling steadier blood drug profiles throughout the treatment, and enhance patient compliance. Through a diffusion process, the drug enters the bloodstream directly though the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow. Characterization of transdermal patch is used to check it's quality, size, time of onset & duration, adhesive property, thickness, weight of patch, moisture content, uniformity & cutaneous toxicological studies. The present poster discusses the methods of preparation, characterization and applications of transdermal patches.

DOI: https://doi.org/10.54660/.IJMRGE.2023.4.5.1070-1074

Keywords: Controlled release, charaterization, first-pass metabolism, transdermal patch

Introduction

In recent years, vesicular systems have gained prominence as a method for achieving sustained or controlled drug release. The term ‘’Transferosome’’ and its associated concept were first introduced in 1991 by Gregor Cevc. The name “Transferosome” originates from the latin word ‘Transfer’ meaning “to carry across” and the Greek word “soma” referring to a body [1].

In many instances, achieving an effective therapeutic treatment is challenging due to various factors, including hepatic first-pass metabolism, unwanted side effects, resistance to invasive treatments, and patient non-compliance. As a result, researchers have focused on developing drug delivery systems in recent decades to address these issues. Among these approaches, transdermal delivery systems stand out as a promising solution, offering minimally invasive administration without first-pass effects [2].

Vesicles are employed in transdermal drug delivery due to their dual role: they serve as carriers for delivering encapsulated drugs through the skin and also function as penetration enhancers due to their specific composition [3].

Numerous chemical and physical methods have been employed to enhance the effectiveness of material transfer through intact skin. These approaches include penetration enhancers, iontophoresis, sonophoresis, and the utilization of colloidal carriers like lipid vesicles such as liposomes and proliposomes as well as nonionic surfactant vesicles like niosomes and proniosomes [4].

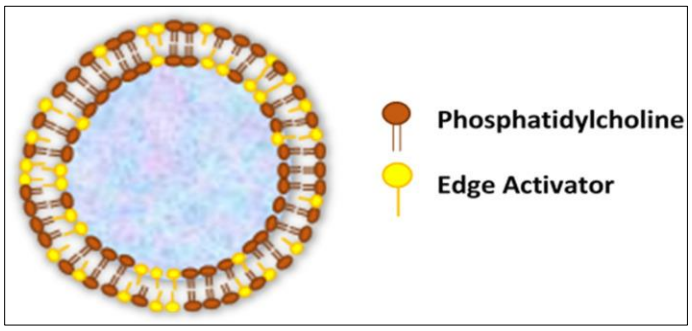

Fig 1: Proliposomes

Vesicles are colloidal particles filled with water. Their walls are made up of bilayers of amphiphilic molecules, including lipids and surfactants [5].

These vesicles act as reservoirs, providing a controlled release of active substances for topical formulations. Additionally, they function as barrier membranes that regulate systemic absorption in transdermal formulations [6].

Transferosomes are composed of a lipid bilayer containing specialized properties, created by integrating edge activators like sodium cholate, sodium deoxycholate, span 80, and tween 80, around at least one inner one inner aqueous compartment [7].

Advantages

1. Transferosomes offer a clear advantage for achieving sustained drug release and extended activity duration [8].
2. They overcome the limitation of first- pass metabolism in oral drug administration, enhancing drug bioavailability [9].
3. These vesicles exhibit remarkable flexibility and elasticity, allowing them to navigate narrow skin barriers, even when dimensions are 5 to 10 times smaller than their size [10].
4. Their simple and efficient production process facilitates easy scalability [11].
5. Biocompatible and biodegradable [12]
6. Transferosomes consists of both hydrophilic and hydrophobic substances poses a higher solubility range [13].
7. High entrapment efficiency can be achieved [14].

Limitations

1. Transferosomes experience chemical instability due to oxidative degradation, which also contributes to their high cost [15].
2. The formulation of transferosomes can be challenging due to the impact of the purity of natural phospholipids on vesicles [16].

Mechanism of action

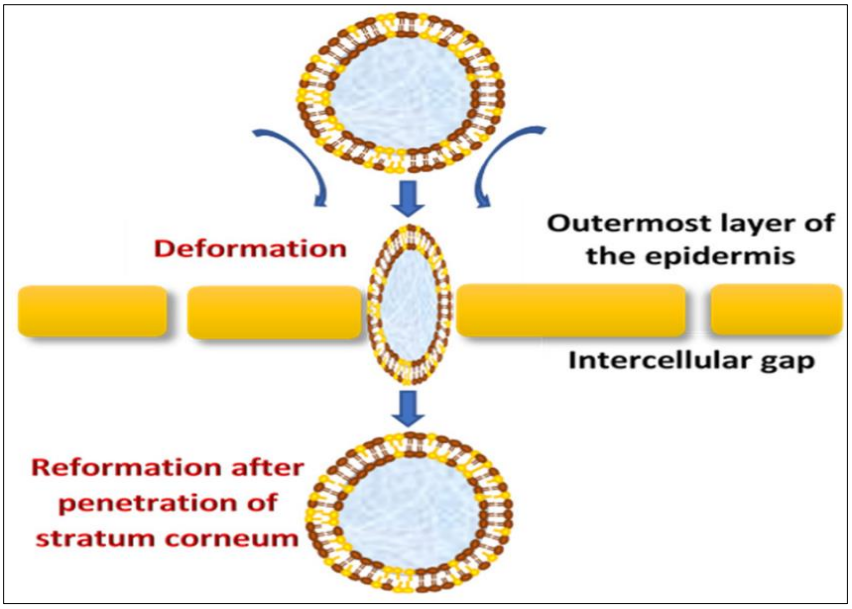

Fig 2: Mechanism of action

Transferosomes are specialized drug carriers that enter the skin intact. They function as both drug vectors nd penetration enhancers, disturbing intercellular lipids in the stratum corneum to aid dug penetration.

Cevc and co-workers proposed that deformable liposomes, known as transferosomes, use the skin's hydration gradient to cross the stratum corneum and enter circulation. Recent research suggests a combined mechanism for vesicle penetration, depending on active substance nature and transferosome composition.

Cevc and Blume's study identified hydrotaxis as the permeation mechanism, where transferosomes seek moisture

in deeper skin layers due to nonocclusive application [17].
Compared to conventional liposomes, transferosomes possess a similar structure but exhibit higher permeation efficiency through small skin channels [18].
Surfactant molecules act as "edge activators'' conferring ultra deformability to transferosomes, allowing them to pass through narrow stratum corneum channels [19].
Unlike liposomes, transferosomes up to 500 nm can penetrate the stratum corneum. Bilayer flexibility and permeability increase upon addition, enabling rapid adjustments in local bilayer concentration [19].

Composition of Transferosomes
Transferosomes are composed of several key components:
1. The primary ingredient, an amphipathic substance, often a mixture of lipids like soya phosphotidylcholine egg phosphotidylcholine. These lipids from the vesicles and create the lipid bilayer [20].
2. Surfactants or edge activators, which make up 10-25% of the composition. Commonly used edge activators include sodium sodium cholate, sodium deoxy cholate, tweens (such as tween 20, tween 60, and tween 80), Spans like (span 60, span 65, and span 80) these substances enhances bilayer flexibility and improve permeability [21].
3. About 3-10% alcohol (ethanol or methanol) serves as the solvent.
4. A hydrating medium, typically water or a saline phosphate buffer with a PH range of 6.5 to 7.

These components work together to form transferosomes, specialized vesicles designed for enhanced drug delivery [22].

Method of preparation
Phospholipids, surfactants, and the drug are initially dissolved in alcohol. Next, the organic solvent is eliminated through rotary evaporation at a reduced pressure of 40°C. [23] any remaining traces of solvent are further removed under vacuum conditions. The lipid film deposited as a result is then hydrated with an appropriate buffer by rotating it at 60 rpm for 1 hour at room temperature. Following this, the resulting vesicles are allowed to swell for 2 hours at room temperature. To obtain small vesicles, the multilamellar lipid vesicles are subsequently sonicated at room temperature [24].

Thin film hydration technique/ rotary evaporation sonication method
To create liposomes through thin film hydration technique/ rotary evaporation method start by dissolving phospholipids and edge activators which are the vesicle forming components in a round bottom flask using a volatile organic solvent mixture (Such as a suitable v/v ratio of chloroform and methanol). During this step, you can also incorporate a lipophilic drug if needed.
To form a thin lipid film, the organic solvent is evaporated above the lipid transition temperature while maintaining reduced pressure. This is achieved using a rotary vacuum evaporator. The process is continued under vacuum conditions to ensure the complete removal of any remaining traces of the solvent.
The deposited thin film is then hydrated using buffer solution with the appropriate pH (example pH 7.4) by rotation for a respective time t the corresponding temperature. During this stage you have the option to incorporate a hydrophilic drug into the vesicle forming process. After the initial steps, the resulting vesicles are allowed to swell at room temperature. To further refine their size and uniformity, the vesicles are then subjected to sonication using either a bath or probe sonicator, resulting in smaller vesicles. To ensure homogeneity, the sonicated vesicles are further processed through extrusion. This involves passing them through a sandwich consisting of polycarbonate membranes with pore size ranging from 200 nm to 100 nm. This step helps to achieve the desired vesicle size and consistency [25].

Ethanol Injection Method
An aqueous solution containing the drug is heated while continuously stirred at a constant temperature. Simultaneously, an ethanolic solution containing phospholipids and edge activators is introduced into the aqueous solution drop by drop. When the ethanolic solution makes contact with the aqueous medium, the lipid molecules precipitate and arrange themselves into bilayered structures. This approach offers several advantages compared to other methods, including its simplicity, reproducibility, and scalability for larger production volumes [26].

Vortexing –sonication method
Phospholipids, edge activators, and the drug combined in a phosphate buffer. This mixture is vigorously vortexed until it forms a milky transferosomal suspension. Subsequently, the suspension undergoes sonication, typically using a bath sonicator, for a specified duration at room temperature. To further refine the vesicles, the sonicated suspension is extruded through polycarbonate membranes, for instance, with pore size of 450 nm and 220 nm. This step is employed to achieve the desired vesicle size and consistency in the transferosomal formulation [27].

Modified handshaking, lipid film hydration technique
This method involves following steps
1. Initially, the preparation begins by dissolving the drug, lecithin (pc), and an edge activator in an ethanol: chloroform mixture at a 1:1 ratio. The organic solvent is then gradually removed through evaporation while hand shaking, and this process occurs above the lipid transition temperature, typically at around 43 °C. This results in the formation of a thin lipid film long the inner walls of the flask. The thin film is allowed to sit overnight to ensure complete evaporation of the solvent.
2. The next step involves hydrating the thin lipid film with a phosphate buffer (7.4) while gently shaking for approximately 15 minutes, maintaining the corresponding temperature. Subsequently the trnsferosomes suspension is further hydrated for upto 1 hour at a controlled temperature ranging from 2-8°C. This process contributes to the formation and stabilization of the tranferosomal vesicles [28].

Centrifugation Process
1. The phospholipids, edge activators, and lipophilic drug are initially dissolved in an oganic solvent.
2. The organic solvent is then removed by employing a rotary evaporator under reduced pressure, and this is done at the specific temperature required for the process.
3. Any remaining traces of solvent are thoroughly removed under vacuum conditions.
4. The lipid film deposited as a result of this process is

hydrated using an appropriate buffer solution, and this hydration step is achieved by centrifuging the mixture at room temperature. At this stage, hydrophilic drug incorporation can also be accomplished.
5. The vesicles obtained are allowed to swell further at room temperature.
6. These multilamellar lipid vesicles are subsequently subjected to sonication at room temperature [29].

Suspension homogenization method

To create transferosomes using the suspension homogenization method start by combining an ethanolic solution of phospholipids with the required quantity of an edge activator. Afterward, this prepared suspension is mixed with a buffer solution to achieve the desired total lipid concentration. The resulting formulation is then subjected to a cycle of sonication and freezing-thawing, typically repeated two times [30].

Characterization of Transferosomes

1. Visualization: Transferosomes can be visualized using transmission electron microscopy [TEM] and scanning electron microscopy [SEM].
2. Particle size and distribution: The size and size distribution of transferosomes can be determined using techniques such as dynamic light scattering [DLS] and photon correlation spectroscopy [PCS].
3. Drug entrapment efficiency: The efficiency of drug entrapment within transferosomes can be measured using the ultracentrifugation technique.
4. Vesicle stability: The stability of the vesicles can be assessed by monitoring changes in size and structure over time.
5. Drug content quantification: The amount of drug within transferosmes can be quantified using high performance liquid chromatography [HPLC] or spectrophotometric methods.
6. *In vitro* drug release: *In vitro* drug release from transferosomes can be measured using either a diffusion cell or a dialysis method [31, 32].

These techniques collectively provide valuable insights into the characteristics and performance of transferosomes in drug delivery applications.

Applications of transferosomes as the transdermal delivery system

Delivery of anticancer drugs: Transferosomes find valuable applications as a transdermal delivery system, including the delivery of anticancer drugs. In a study conducted by Jiang *et al*. in 2018, they explored the use of transferosomes-embedded oligopeptide hydrogels containing pacilaxel for topical chemotherapy of melanoma. These transferosomes in targeted and efficient drug delivey for cancer treatment. Transferosomes composed of phoshphotidylcholin, tween 80nd sodium deoxycholate were shown to effectively penetrate into tumor tissues [33].

Delivery of anti-inflammatory drugs: Several research groups have developed transferosomes loaded with drugs like diclofenac sodium, celecoxib, mefenamic acid, and curcumin for topical administration. These studies have indicated that transferosomes can enhance the stability aand effectiveness of these anti-inflammatory medications, offering potential benefits in the treatment of inflammatory conditions [34].

Delivery of corticosteroids: Transferosomes have also been investigated for the delivery of corticosteroids, specifically halogenated corticosteroid triamcinolone acetonide. Cevc and Blume conducted studies in 2003 and 2004, using the conventional thin-film hydration technique to prepare these transferosomes. Their findings revealed that transferosomes enhanced the biological potency and prolonged the effects of triamcinolone acetonide, ultimately leading to a reduction in the required therapeutic dosage. This highlights the potential of transferosomes in optimizing the delivery of corticosteroids for improved outcomes [35].

Conclusion

Transferosomes are specialized vesicles designed for efficient drug delivery across biological barriers such as the skin. These vesicles exhibit remarkable deformability, responding to external stress with rapid and energy efficient shape transformations. In artificial systems, transferosomes can transverse even minuscule pores (as small as 100 nm) nearly as effectively as water, despite their much larger size. When loaded with drugs, transferosmoes can transport unprecedented amounts of drug per unit time across the skin. Transdermal drug delivery is favoured for its numerous advantages over other delivery routes. However, a major bottle neck in this method is the limited penetration of drugs through the stratum corneum, particularly for larger molecules. To address this limitation, vesicular systems like transferosomes have been developed. These elastic vesicles can deform themselves to penetrate the skin through pores, making them more efficient and safer in composition compared to other alternatives. Moreover, this approach allows for controlled drug release, tailoring it to specific requirements. Transferosomes offer a promising solution to the challenges faced by conventional drug delivery techniques.

References

1. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. Drug Discovery Today: Technologies. 2005;2(1):67-74.
2. Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: A novel technique for transdermal drug delivery. Journal of Drug Delivery and Therapeutics. 2019;9:279-285. DOI:10.22270/jddt.v9i1.2198.
3. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery. 1st ed. Delhi: CBS Publishers; c2002. p. 219-243.
4. Ting WW, Vest CD, Sontheimer RD. Review of traditional and novel modalities that enhance the permeability of local therapeutics across the stratum corneum. International Journal of Dermatology. 2004;43(7):538-547.
5. Hofl HEJ, Bouwstra JA, Spies F, Gooris G, Nagelkerke JF. Interaction of liposomes and niosomes with human skin. Journal of Pharmaceutical Sciences. 1994;83:1192-1196.
6. Fang YP, Tsai YH, Wu PC, Huang YB. Comparison of 5-aminolevulinic acid-encapsulated liposome versus ethosome for skin delivery for photodynamic therapy. International Journal of Pharmaceutics. 2008;356(1-2):44-52.
7. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to transdermal osmotic gradient and hydration force. Biochimica et Biophysica Acta (BBA) -

Biomembranes. 1992;1104(1):226-232.
8. Modi C, Bharadia P. Transfersomes: New dominants for transdermal drug delivery. American Journal of PharmTech Research. 2012;2:71-91.
9. Li J, Wang X, Zhang T, Wang C, Huang Z, Luo X, Deng Y. A review on phospholipids and their main applications in drug delivery systems. Asian Journal of Pharmaceutical Sciences. 2015;10(2):81-98.
10. Moawad FA, Ali AA, Salem HF. Nanotransfersomes-loaded thermosensitive in situ gel as a rectal delivery system of tizanidine HCl: Preparation, *in vitro* and *in vivo* performance. Drug Delivery. 2017;24(1):252-260.
11. Bnyan R, Khan I, Ehtezazi T, Saleem I, Gordon S, Neill FO. Surfactant effects on lipid-based vesicles properties. Journal of Pharmaceutical Sciences. 2018;107(5):1237-1246.
12. Walve JR, Bakliwal SR, Rane BR, Pawar SP. Transfersomes: A surrogated carrier for transdermal drug delivery system. International Journal of Applied Biology and Pharmaceutical Technology. 2011;2(1):201-214.
13. Modi CD, Bharadia PD. Transfersomes: New Dominants for Transdermal Drug Delivery. American Journal of PharmTech Research. 2012;2(3):71-91.
14. Solanki D. Transferosomes: A review. World Journal of Pharmacy and Pharmaceutical Sciences. 2016;5(10):435-449.
15. Trotta M, Peria E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. International Journal of Pharmaceutics. 2004;270(1-2):119-125.
16. Hafer C, Goble R, Deering P, Lehmer A, Breut J. Formulation of interleukin-2 and interferon-alpha containing ultra-deformable carriers for potential transdermal application. Anticancer Research. 1999;19(2c):1505-1507.
17. Mandal UK, Mahmood S, Taher M. Experimental design and optimization of raloxifene hydrochloride loaded nano transfersomes for transdermal application. International Journal of Nanomedicine. 2014;9:4331-4346.
18. Chauhan P, Tyagi BK. Herbal novel drug delivery systems and transfersomes. Journal of Drug Delivery and Therapeutics. 2018;8(3):162-168.
19. Chuanping N. Preparation and study on properties of ibuprofen transferosomes. Journal of Mathematical Medicine; c2010. p. 2.
20. Jiang T, Wang T, Li T, Ma Y, Shen S, He B, *et al*. Enhanced transdermal drug delivery by transfersome-embedded oligopeptide hydrogel for topical chemotherapy of melanoma. ACS Nano. 2018;12(10):9693-9701.
21. Jain AK, Kumar F. Transfersomes: Ultradeformable vesicles for transdermal drug delivery. Asian Journal of Biomaterials Research. 2017;3(4):1-13.
22. Pawar AY, Jadhav KR, Chaudhari LH. Transfersome: A novel technique which improves transdermal permeability. Asian Journal of Pharmaceutical Sciences. 2016;10(4):425-436.
23. Patel R, Singh S, Sheth NK, Gendle R. Development and characterization of curcumin loaded transferosomes for transdermal delivery. Journal of Pharmaceutical Science and Research. 2009;1(4):271-280.
24. Jain S, Jain P, Umamaheshwari RB, Jain NK. Transferosomes: A novel vesicular carrier for enhanced transdermal delivery: Development, characterization, and performance evaluation. Drug Development and Industrial Pharmacy. 2003;29(9):1013-1026.
25. Modi C, Bharadia P. Transfersomes: New dominants for transdermal drug delivery. American Journal of PharmTech Research. 2012;2(3):71-91.
26. Kumar A, Adde S, Kamble R. Development and characterization of liposomal drug delivery system for nimesulide. International Journal of Pharmaceutics and Pharmaceutical Sciences. 2010;2(4):87-89.
27. El Zaafarany GM, Awad GAS, Holayel SM, Mortada N. Role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery. International Journal of Pharmaceutics. 2010;397(1-2):164-72.
28. Gupta A, Aggarwal G, Singla S, Arora R. Transfersomes: a novel vesicular carrier for enhanced transdermal delivery of sertraline: development, characterization, and performance evaluation. Scientia Pharmaceutica. 2012;80(4):1061-1080.
29. Ganju PE, Upmanyu N, Ray SK, Jain P. Transfersomes: A novel technique for transdermal drug delivery. Journal of Drug Delivery and Therapeutics. 2019;9(1):279-285.
30. Ghai I, Chaudhary H, Ghai S, Kohli KKV. A review of transdermal drug delivery using nano-vesicular carriers: Transfersomes. Recent Patents on Nanomedicine. 2012;2(2):164-171.
31. Pandey S, Goyani M, Dev MV, Fakir J. Transferosomes: A novel approach of transdermal drug delivery. Delivery Science and Technology Research Library. 2009;1(2):143-150.
32. Boinpally RR, Zhou SL, Poondru S, Devraj G, Jasti BR. Lecithin vesicles for topical delivery of diclofenac. European Journal of Pharmaceutics and Biopharmaceutics. 2003;56(3):389-392.
33. Jain S, Umamaheshwari RB, Bhadra D, Tripathi P, Jain P, Jain NK. Ultra deformable liposomes: A recent tool for effective transdermal drug delivery. Indian Journal of Pharmaceutical Sciences. 2003;65(3):223-231.
34. El Zaafarany GM, Awad GAS, Holayel SM, Mortada N. Role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery. International Journal of Pharmaceutics. 2010;397(1-2):164-172.
35. Cevc G, Blume G. Biological activity and characteristics of triamcinolone-acetonide formulated with the self-regulating drug carriers, Transfersomes→. Biochimica et Biophysica Acta (BBA) - Biomembranes. 2003;1614(2):156-164.