ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

Human Journals
Review Article
October 2023 Vol.:28, Issue:3
© All rights are reserved by Arjumand Begum Nooreen et al.

Transferosomes: A Novel Approach Transforming Transdermal Delivery of Drugs

Arjumand Begum Nooreen*, Prof. Dr. Syed Abdul Azeez Basha

Deccan School of Pharmacy, Dar-us-salam, Aghapura, Hyderabad 500001 India.

Submitted: 21 September 2023
Accepted: 28 September 2023
Published: 30 October 2023

ijppr.humanjournals.com

Keywords: Transferosomes, Vesicular systems, Edge activators.

ABSTRACT

Transdermal delivery of drugs is selectively permeable to many of the therapeutic molecules due to the barrier function of the skin. Vesicular systems are one of the most controversial methods for transdermal delivery of active substances. An advanced type of highly deformable lipid vesicle called as transferosome has been recently set forth, it was observed that these vesicular systems penetrate through tight junctions of intact skin. They are soft malleable vesicles tailored for enhanced delivery of active agents. Transfersomes are generally composed of, an amphipathic ingredient (which are the vesicle-forming components that create the lipid bilayer), surfactants/edge activators (improve the permeability), alcohol, and water. Deformability of transferosomes is achieved by using surface active agents in the proper ratio. The present paper aims to outline the theory of transferosomes, its mechanism of action, various methods of preparation and their recent applications in the transdermal delivery of drugs.

INTRODUCTION

The transdermal delivery system generally shows better regulation of blood levels, decreased occurrence of systemic toxicity, no first-pass hepatic metabolism, and higher compliance as compared with conventional formulations. Transdermal treatment systems are characterized as self containing and discrete dosage types, which supply the medication with a regulated rate of systemic circulation through the skin if applied to the intact skin. A major obstacle to dermal and transdermal drug delivery is the permeation characteristics of the stratum corneum, which limits drug transport, making this route of administration frequently insufficient for medical use. Stratum corneum is the top layer of the epidermis and consists of keratinized, flattened remnants of once actively dividing epidermal cells, impermeable to water and behaves as a tough flexible membrane. Many novel drug delivery systems have been investigated to evade this barrier. Novel drug delivery systems are engineered according to a rational design to enhance the delivery and the performance of existing drugs with respect to traditional systems. Novel drug delivery systems in comparison to traditional ones combine advanced techniques and new dosage forms in order to target, control and modulate the delivery of drugs. By the evolution of a drug from a conventional to a novel drug delivery system, the performance regarding efficacy, safety and patient compliance can be remarkably improved.[1]

Vesicular drug delivery systems (VDDSs) are favorable over conventional dosage forms due to the fact that both lipophilic and hydrophilic drugs can be entrapped in the bilayer, respectively in the aqueous core. Furthermore, the positives include improved bioavailability, especially of hardly dissolvable drugs, a retarded metabolization, prolonged systemic circulation and reduced toxicity.[2] [3]

Transferosomes are vesicular carrier systems that are specially designed to have at least one inner aqueous compartment that is enclosed by a lipid bilayer, together with an edge activator. [4] The concept of transfersomes was first invented in the 1990s and describes an utmost malleable vesicle with an elastic nature that enables penetration through pores minor than its own size.[5] Transfersomes are considered advantageous in topical and systemic drug delivery for the following distinctive features. On the one hand, transfersomes offer a great encapsulation efficacy up to 90% of drugs with a low or high molecular weight and a large variety in solubility. Moreover, the API is protected from biodegradation and a laggard, incrementally drug release is enabled due to depot function. Regarding production, an easy

expansion to large scale is possible. Despite these benefits, transfersomes still suffer from some shortcomings such as tendency of oxidative degradation, a range in purity of phospholipids from natural origin and an expensive production.[6][7] Transferosomes majorly involve the ingredients like amphipathic ingredients (a combination of hydrophilic and lipophilic molecules like soy phosphatidylcholine), surface activators (e.g., surfactants), alcohol, and water. Apart from phospholipids, edge activators such as tween 80 or span 60 are the main constituents in the formulation of transfersomes. This single chain surfactants effect the destabilization of the lipid bilayers leading to an increase in its malleability making them particularly suitable for skin penetration. [8] [9]

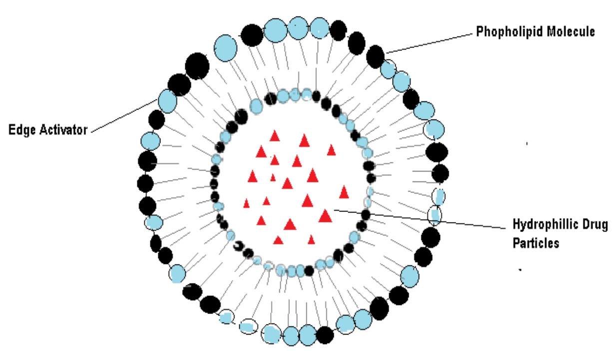

Figure 1: Structure of Transferosomes

ADVANTAGES OF TRANSFEROSOMES [10]-[13]

1. Transfersomes can squeeze themselves through constrictions of the skin barrier that are very narrow, such as 5 to 10 times less than the vesicle diameter, owing to their ultra-deformability and elastic properties.

2. High vesicle deformability facilitates the transport of drugs across the skin without any measurable loss in intact vesicles and can be used for both topical, as well as systemic, treatments.

3. Transfersomes carriers are very versatile and efficient in accommodating a variety of agents nearly independent of their size, structure, molecular weight or polarity.

4. They are made up of natural phospholipids and EAs, therefore promisingly biocompatible and biodegradable.

5. They are capable of increasing the transdermal flux and improving the site specificity of bioactive agents.

6. Avoiding the first-pass metabolism, which is a major drawback in oral drug administration, and results in optimized bioavailability of the drug.

7. Minimize the undesirable side effects of the drug, as well as protect the drug from metabolic degradation; moreover, the utility of short half-life drugs.

8. Due to a short and simple production procedure, it is easy to scale up.

LIMITATIONS OF TRANSFEROSOMES [14]-[16]

1. Many drugs especially drugs with hydrophilic structures permeate the skin too slowly to be of therapeutic benefit.

2. The barrier function of the skin changes from one site to another on the same person, from person to person and also with age.

3. Drug molecules must be potent because patch size limits the amount that can be delivered.

4. Not suitable for high drug doses.

5. Adhesion may vary with patch type and environmental conditions.

6. Skin irritation and hypersensitivity reactions may occur.

7. Drugs that require high blood levels cannot be administered.

8. Along with these limitations the high cost of the product is also a major drawback for the wide acceptance of this product.

9. Transfersomes are chemically unstable because of oxidative degradation make its predisposition.

10. The purity of natural phospholipids is another criterion for achieve for adoption of transfersomes as drug delivery vehicles.

COMPOSITION OF TRANSFEROSOMES

Transferosomes are composed of amphipathic components, like phosphatidylcholine and edge activator which is a lipid bilayer constituent that leads to the formation of the vesicle.

Table:1 Composition of Transferosomes

S.No	Class	Examples	Uses
1	Phospholipids	Soya phosphatidylcholine, Egg Phosphatidyl Choline	Vesicles forming component
2	Surfactants	Tween-80, Span-80,	Provides flexibility
3	Alcohols	Ethanol, Methanol	Solvent
4	Buffering agent	Saline Phosphate buffer	Hydrating medium

MECHANISM OF ACTION OF TRANSFEROSOMES

Mechanism behind the penetration of transfersome is the development of osmotic gradient because while lipid suspension applies on skin surface water gets evaporated. Transfersomes have strong bilayer deformability and therefore they have increased affinity to bind and retain water. Upon application on skin surface (non-occluded), it penetrates skin barrier and reaches at the deeper strata (water-rich portion), where they get hydrated. Then, reach at deeper epidermal layer through the dehydration of lipid vesicles within the stratum corneum by natural transepidermal activity (Fig 2). Therefore, transfersome uptake is a function of hydration gradient that exists across the epidermis, stratum corneum, and ambient atmosphere [17,18].

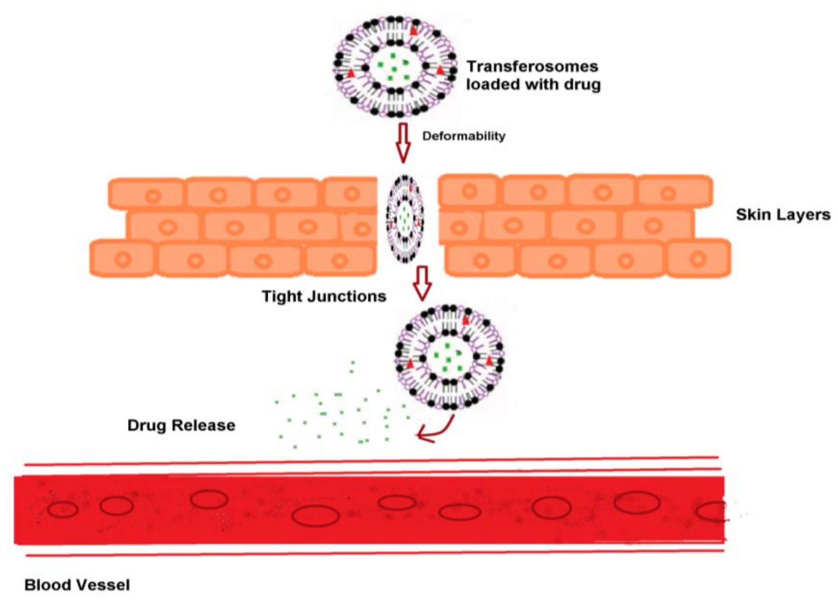

FIGURE 2: MECHANISM OF ACTION OF TRANSFEROSOMES

PREPARATION OF TRANSFEROSOMES

1. Rotary film evaporation method

This method is also known as the hand-shaking process, which was initially invented by Bangham.[19] In this process, the quantity needed of phospholipids and surfactants (as EAs) is essential to organize a thin film.[20][21] It is largely worn for the research of multilamellar vesicles. A solution of phospholipids and EAs is organized in a crude solvent such as a combination of chloroform and methanol. The prepared solution is transferred to a round-bottomed flask which is rotated at constant temperature and reduced pressure. A film of lipids and EA is formed on the walls of the flask. The twisted film is then hydrated using aqueous media containing drug. This causes lipids to swell and form bilayer vesicles. Vesicles of the desired size can be obtained by extrusion or by sonication of the superior vesicles.[22]

2. Reverse phase evaporation method

At this point, the scheme will alter to a viscous gel followed by the arrangement of vesicles. The nonencapsulated material and residual solvents can be indifferentiable using dialysis or centrifugation [22] In this method, lipids dissolved in organic solvents are collected in a round-bottomed flask. Aqueous media containing EAs is added under nitrogen purging. The drug can be added to the lipid or aqueous medium based on its solubility character. The system formed is then sonicated, awaiting its conversion into a standardized dispersion, and should

not separate for at least 30 min after sonication. The organic solvent is then removed under low-pressure.

3. Vortexing sonication method

In the vortexing sonication method, mixed lipids (i.e. phosphatidylcholine, EA and the therapeutic agent) are blended in a phosphate buffer and vortexed to attain a milky suspension. The suspension is sonicated, followed by extrusion through polycarbonate membranes[23]. Cationic transfersomes have also been set by this method, which involves mixing cationic lipids, such as DOTMA, with PBS to attain a concentration of 10 mg/ml followed by a count of sodium deoxycholate (SDC). The blend is vortexed and sonicated, followed by extrusion through a polycarbonate (100 nm) filter.

4. Ethanol injection method

In this process, the aqueous solution containing the drug is heated with unremitting stirring at constant temperature. Ethanolic solution of phospholipids and EAs is injected into aqueous solution dropwise. As the solution comes into contact with aqueous media the lipid molecules are precipitated and form bilayered structures. This process offers assorted advantages over other methods, which include simplicity, reproducibility, and scale-up. [24,25].

5.Freeze–thaw method

This method includes the exposure of multilamellar vesicles to alternate cycles of very low temperature for freezing followed by exposure to very high temperature. The geared-up suspension is transferred to a tube and dipped in a nitrogen bath (−30°C) for 30 s. After freezing, it is exposed to a high temperature in a water bath. This course is repeated eight–nine times[26].

6. Thin film hydration technique /Rotary evaporation-sonication method

The phospholipids and edge activator are dissolved in a round-bottom flask using organic solvent mixture of chloroform and methanol in a suitable (v/v) ratio to form a thin film. The solvent is evaporated beyond lipid transition temperature using a rotary evaporator and the obtained film is hydrated with a phosphate buffer o pH-6.5 by rotation of 60 rpm for 1 hour. The obtained vesicles are swollen at room temperature or 50°C for 30 min. By manually extruding a sandwich of 200 and 100nm polycarbonate membrane, the sonicated vesicles are homogenized [27,28,29].

CHARACTERIZATION OF TRANSFEROSOMES

1. Entrapment Efficiency

The entrapment efficiency (%EE) is the amount of drug entrapped in the formulation. The EE is determined by separating the unentrapped drug from the vesicles using various techniques, such as mini-column centrifugation. In this process, direct or indirect methods can be used to determine the %EE. After ultracentrifugation, the direct approach would be removing the supernatant followed by disrupting the sedimented vesicles using a suitable solvent that is capable of lysing the sediment. Subsequently, the resulting solution can be diluted and filtered using a syringe filter (0.22–0.45 µm) to remove the impurities. The drug content is determined by employing analytical methods, such as modified high-performance liquid chromatography (HPLC) or spectrophotometrically, which depends on the analytical method of the active pharmaceutical ingredient (API)[30]. The percentage of drug entrapment (the entrapment efficiency) is expressed as:

% Entrapment Efficiency = Amount of entrapped drug/ Total amount of drug X 100

2. Vesicle size, morphology and zeta potential

Generally, the dynamic light scattering (DLS) method or photon correlation spectroscopy (PCS) can be used to determine the vesicle diameter. The vehicle's suspension can be mixed with an appropriate medium, and the vesicular size measurements can be obtained in triplicate. Moreover, as another approach, the sample can be prepared in distilled water and filtered through a 0.2 mm membrane filter. The filtered sample is then diluted with filtered saline to measure the size of the vesicles by DLS or PCS. Moreover, the DLS method-associated computerized inspection system by Malvern Zetasizer can be used for the determination of the vesicle size and size distribution, whereas the structural changes are observed by transmission electron microscopy (TEM). The zeta potential is measured by the electrophoretic mobility technique using Malvern Zetasizer. The visualization of transfersome vesicles can be done by using phase contrast microscopy or TEM[30,31,32].

3. Turbidity Measurements:

The turbidity measurements were diluted with distilled water to give a total lipid concentration of 0.312m. sonicate for 5 min. Measure turbidity at 274 nm with a UV visible spectrophotometer [33].

4. NUMBER OF VESICLE PER CUBIC mm

Unsolicited transpersonal formulations are diluted five times using 0.9% sodium chloride. A hemocytometer with an optical microscope is used to study this sample. The transfersomes with a vesicle size of more than 100 nm can be observed by optical microscope[34,35]. The number of transfersomes in small squares are counted and calculated using the following formula:

Total number of transfersomes per cubic mm=

$$\frac{\text{(Total number of transfersomes counted} \times \text{dilution factor} \times 4000)}{\text{Total number of squares counted}}$$

5. Drug content

The drug content can be determined using one of the instrumental analytical methods such as modified high performance liquid chromatography method (HPLC) using a UV detector, column oven, auto sample, pump, and computerized analysis program [36,37].

6. *In vitro* drug release

In vitro drug release study is performed to determine the permeation rate. Time needed to attain steady state permeation and the permeation flux at steady state and the information from *in vitro* studies are used to optimize the formulation before more expensive *in vivo* studies are performed. For determining drug release, transfersomes suspension is incubated at 32°C and samples are taken at different times and the free drug is separated by minicolumn centrifugation. The amount of drug released is then calculated indirectly from the amount of drug entrapped at zero times as the initial amount (100% entrapped and 0% released).

7. *In vitro* skin permeation studies

The skin of an animal is utilized in a phosphate buffer with a pH of 7.4. The hair on the skin is removed, and the skin is moisturized with regular saline. The cotton swab should be used to remove fat tissues. A modified franz diffusion cell with a 50 mL column and a receiver compartment effective area of 2.50 cm2. Skin can be kept at a low temperature in IPA. with a 100rpm stirring speed and the stratum corneum towards the donor compartment A 1mL aliquot is drawn and replenished with fresh phosphate buffer regularly [38].

8. Stability of Transfersomes

The stability of transfer some vesicles can be determined by assessing the structure and the size of vesicles with respect to time. DLS and TEM can be used for the determination of the mean size and structural changes, respectively. The optimized transfersomal formulations can be stored in tightly sealed amber vials at different temperature conditions. According to ICH (International Conference on Harmonization) guidelines, under the stability testing of new drug substances and products, the general case for the storage condition is described as, for the long term, 25 ± 2 °C/60% relative humidity (RH) ± 5% RH or 30 ± 2 °C/65% RH ± 5% for 12 months and, for accelerated testing, 40 ± 2 °C/75% RH ± 5% for six months. Drug products intended for refrigeration should be subjected to long-term storage at a condition of 5 ± 3 °C for 12 months and accelerated study for 25 ± 2 °C/60% RH ± 5% RH for six months. A significant change for the drug product is defined as the failure to meet its specifications.

APPLICATIONS [39-45]

1. Delivery of insulin

Transfersome is one of the successive ways to deliver such large molecular weight drugs on the skin. Insulin is generally administered by a subcutaneous route that is inconvenient for the patient. Encapsulation of insulin in transfersome (transfersulin) overcomes all problems arises with conventional insulin delivery. After application of transfersulin on the intact skin, therapeutic effect was observed after 90-180 min, depending on the carrier composition.

2. Delivery of corticosteroids

Problems arise with corticosteroids delivery is masked by incorporation it into transfersomes. Site specificity and overall drug of corticosteroid delivery into skin by optimizing the epicutaneously administered drug dose safety is achieved by transfersome encapsulation. Dose required for the biological activity of corticosteroids is less by use of transfersomes technology.

3. Delivery of proteins and peptides

Transfersomes have been widely used as a carrier for the transport of proteins and peptides also safely given by means of transfersome technology. Proteins and peptide has problem is it is difficult to transfer into the body, are large biogenic molecules, GI tract degradation is

problem arise when given orally. That's reasons why these peptides and proteins still given by means of injectables. Several approaches have been developed to improve this condition. Transfersome is somewhat identical to that resulting from subcutaneous injection of protein suspension in terms of bioavailability. On repeated epicutaneous application, transfer some preparation of protein also induced a strong immune response. For example, the adjuvant immunogenic serum albumin in transfersomes, after several dermal challenges, is as active immunologically as is the corresponding injected proteo-transfersomes preparations.

4. Delivery of interferon (INF)

INF also delivered using transfersome as a carrier, for example, leukocyte-derived INF-α is a naturally occurring protein having antiviral, antiproliferative, and some immunomodulatory effects. Transfersomes as drug delivery systems have the potential for providing controlled release of the administered drug and increase the stability of labile drugs. Hafer *et al*. studied the formulation of transfersome containing interleukin-2 (IL-2) and INF-α for potential transdermal application. They reported delivery of IL-2 and INF-α promising by transfersomes insufficient concentration for immunotherapy.

5. Delivery of anticancer drugs

Transfersome technology provides a new approach for cancer treatment, especially skin cancer. The result found to be favorable when methotrexate was tried for transdermal delivery using transfersome technology.

6. Delivery of anesthetics

Application of transfersome containing anesthetics induces topical anesthesia, under suitable conditions, within 10 min. The effect when we said in case of pain in sensitivity is nearly as strong (80%) as of a comparable subcutaneous bolus injection, but transpersonal anesthetics preparation has last longer effect.

7. Delivery of non-steroidal anti-inflammatory drugs (NSAIDs)

Problems that arise with most of NSAIDs are several GI side effects. This can be overcome by transdermal delivery using transfersome. Studies have been carried out on diclofenac and ketoprofen. Ketoprofen in a transfersome formulation gained marketing approval by the Swiss regulatory agency (Swissmedic) in 2007; the product is expected to be marketed under

the trademark "Direction." Further therapeutic products based on the transfersome technology, according to IDEA AG, are in clinical development.

CONCLUSION

The transdermal delivery system generally shows better regulation of blood levels, decreased occurrence of systemic toxicity, no first pass hepatic metabolism, and higher compliance as compared with conventional formulations. However, being selectively permeable restricts the permeation of many delivery systems. Transferosomes are specially designed vesicles capable of responding to external stress by squeezing themselves through skin pores that are many times narrower than they are leading to increased transdermal flux of therapeutic agents. Transferosomes shows more benefits compared to other vesicular systems in terms of high penetration ability and high degree of deformability. Therefore, ensuring effective transcutaneous drug transport .Since, Transferosomes are composed of both hydrophobic and hydrophilic moieties, and these can accommodate drug molecules with wide range of solubility.

REFERENCES:

1. Vijaya Shanti B., Mrudula T.P.K.V. An Imperative note on Novel Drug delivery Systems. J Nanomed Nanotechnol. 2011;2(7) doi: 10.4172/2157-7439.1000125. [CrossRef] [Google Scholar] [Ref list]
2. Jain S., Jain V., Mahajan S.C. Lipid-based Vesicular Drug delivery Systems. Adv. Pharm. 2014;2014:1–12. doi: 10.1155/2014/574673. [CrossRef] [Google Scholar] [Ref list]
3. Namdeo G.S., Nagesh H.A., Ajit S.K. Recent advances in Vesicular Drug delivery System. *Res J Pharm Dos Forms Technol.* 2014;6(2):110–120. [Google Scholar]
4. Rai S., Pandey V., Rai G. Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: The state of the art. Nano Rev. Exp. 2017;8:1325708. doi: 10.1080/20022727.2017.1325708. [PMC free article] [PubMed] [CrossRef] [Google Scholar].
5. Shilakari G., Singh D., Asthana A. Novel vesicular carriers for topical drug delivery and their application's. Int J Pharm Sci Rev Res. 2013;21(1):77–86. [Google Scholar] [Ref list]
6. Sachan R., Parashar T., Singh V., Singh G., Tyagi S., Patel C. Drug carrier transfersomes: a novel tool for transdermal drug delivery system. Int J Res Dev Pharm LIFE Sci. 2013;2(2):309–316. www.ijrdpl.com (Accessed May 22, 2019) [Google Scholar] [Ref list]
7. Sarmah Prasurjya Jyoti. Bhupen Kalita AKS. Transfersomes based transdermal drug delivery: an overview. Int J Adv Pharm Res. 2013;4(12):2555–2563. [Google Scholar] [Ref list]
8. Garg V., Singh H., Bimbrawh S. Ethosomes and Transfersomes: Principles, Perspectives and Practices. *Curr Drug Deliv.* 2016;14(5):613–633. doi: 10.2174/1567201813666160520114436. [PubMed] [CrossRef] [Google Scholar] [Ref list]
9. Sarmah Prasurjya Jyoti. Bhupen Kalita AKS. Transfersomes based transdermal drug delivery: an overview. *Int J Adv Pharm Res.* 2013;4(12):2555–2563. [Google Scholar]
10. Modi C., Bharadia P. Transfersomes: New dominants for transdermal drug delivery. *Am. J. PharmTech. Res.* 2012;2:71–91. [Google Scholar] [Ref list]
11. 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 J. Pharm. Sci.* 2015;10:81–98. doi: 10.1016/j.ajps.2014.09.004. [CrossRef] [Google Scholar] [Ref list]

12. Moawad F.A., Ali A.A., Salem H.F. Nanotransfersomes-loaded thermosensitive in situ gel as a rectal delivery system of tizanidine HCl: Preparation, in vitro and in vivo performance. *Drug Deliv.* 2017;24:252–260. doi: 10.1080/10717544.2016.1245369. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]
13. Bnyan R., Khan I., Ehtezazi T., Saleem I., Gordon S., Neill F.O., Roberts M. Surfactant effects on lipid-based vesicle properties. *J. Pharm. Sci.* 2018;107:1237–1246. doi: 10.1016/j.xphs.2018.01.005. [PubMed] [CrossRef] [Google Scholar] [Ref list]
14. Sharma N, Agarwal G, Rana AC, Bhat Z and Kumar D: A Review: Transdermal drug delivery system: A tool for novel drug delivery system. International Journal of Drug Development and Research 2011; 3:70-84.
15. Patel RP and Baria AH: Formulation and evaluation considerations of transdermal drug delivery system. International Journal of Pharmaceutical Research, 2011; 3:1-9.
16. Vinod KR, Sarvani P, Banji D and Teja BB: Transdermal drug delivery system over coming challenges of popular drug delivery system. International Journal of Pharma World Research, 2010; 1:1-14.
17. Cevc G, Blume G, Sehatzlein A, Gebauer D, Paul A. The skin - A pathway for systemic treatment with patches and lipid-based agent carriers. Adv Drug Deliv 1996; 18:349-78.
18. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochim Biophys Acta 1992; 1104:226-32.
19. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. J Mol Biol. 1965;13:238–252.
20. Singh H, Utreja P, Tiwary A, et al. Elastic liposomal formulation for sustained delivery of colchicine: in vitro characterization and in vivo evaluation of antigout activity. Aaps J. 2009;11:54–64.
21. Abdallah M. Transferosomes as a transdermal drug delivery system for enhancement the antifungal activity of nyastatin. Int J Pharm Pharm Sci. 2013;5:560–567.
22. Sazoka F, Papahadjopoulos D. Procedure for preparation of liposomes with large internal aqueous space 16 S. RAI ET AL. and high capture by reverse-phase evaporation. Proc Natl Acad Sci. 1978;75:4194–4198
23. Rai K. Transfersomes: self-optimizing carriers for bioactives. PDA J Pharm Sci Technol. 2008;62:362–379.
24. Kumar A, Adde S, Kamble R, et al. Development and characterization of liposomal drug delivery system for nimesulide. Int J Pharm Pharm Sci. 2010;2:87–89.
25. Charcosset C, Juban A, Valour J, et al. Preparation of liposomes at large scale using ethanol injection method: effect of scale up and injection devices. Chem Eng Res Des. 2015;94:508–515.
26. Maestrelli F, Rodriguez M, Rabasco A, et al. Effect of preparation techniques on the properties of liposomes encapsulating ketoprofen- cyclodextrin complexes aimed for transdermal delivery. Int J Pharm. 2006;312:53–60
27. Sheo DM, Shweta A, Ram CD, Ghanshyam M, Girish K, Sunil KP, Transfersomes-A novel vesicular carrier for enhanced transdermal delivery of stavudine: Development, characterization and performance evaluation. J Scientific Speculations and Res 2010; 1(1):30-36.
28. Podili C, Firoz S. A review on transferases for transdermal drug delivery. J. Glob. Trends Pharm. Sci. 2014; 5(4):2118-27.
29. Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics. 2020 Sep 9; 12(9):855.
30. Chaurasiya P., Ganju E., Upmanyu N., Ray S.K., Jain P. Transfersomes: A novel technique for transdermal drug delivery. *J. Drug Deliv. Ther.* 2019;9:279–285. doi: 10.22270/jddt.v9i1.2198. [CrossRef] [Google Scholar] [Ref list]
31. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: Permeation enhancement, vesicle penetration, and transdermal drug delivery. *Crit. Rev. Ther. Drug Carr. Syst.* 1996;13:257–388. doi: 10.1615/CritRevTherDrugCarrierSyst.v13.i3-4.30. [PubMed] [CrossRef] [Google Scholar] [Ref list]
32. .Chauhan P., Tyagi B.K. Herbal novel drug delivery systems and transfersomes. *J. Drug Deliv. Ther.* 2018;8:162–168. doi: 10.22270/jddt.v8i3.1772. [CrossRef] [Google Scholar] [Ref list]
33. Walb JR, Bakliwalm SR, Rane BR, Pawar SP, “transferosomes A surrogated carrier for “transdermal drug delivery”, Der Pharmacia Letter, 2009, 1(2), 143-150.
34. . Singh S., Vardhan H., Kotla N.G., Maddiboyina B., Sharma D., Webster T.J. The role of surfactants in the formulation of elastic liposomal gels containing a synthetic opioid analgesic. *Int. J. Nanomed.* 2016;11:1475–1482. [PMC free article] [PubMed] [Google Scholar] [Ref list]

35. Al Shuwaili A.H., Rasool B.K.A., Abdulrasool A.A. Optimization of elastic transfersomes formulations for transdermal delivery of pentoxifylline. *Eur. J. Pharm. Biopharm.* 2016;102:101–114. doi: 10.1016/j.ejpb.2016.02.013. [PubMed] [CrossRef] [Google Scholar] [Ref list]
36. Priyanka Chaurasiya, Eisha Ganju, Neeraj Upmanyu, Sudhir Kumar Ray, Prabhat Jain. Transfersomes: a novel technique for transdermal drug delivery. Journal of Drug Delivery and Therapeutics. 2019;9(1):279-285.
37. Chauhan Pradeep, Tyagi Bharat Kumar. Herbal novel drug delivery systems and transfersomes. Journal of Drug Delivery & Therapeutics. 2018; 8(3): 162-168.
38. Pawar AY. Transfersome: A novel technique which improves transdermal permeability.Asian J Pharm. 2016;10(04).
39. Gregor C, Dieter G, Juliane S, Andreas S, Gabriele B. Ultra-flexible vesicles, transfer somes, have an extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin. Biophys Acta 1998; 1368:201-15.
40. El Maghraby GM, Williams AC, Barry BW. Skin delivery of oestradiol from lipid vesicles: Importance of liposome structure. Int J Pharm 2000; 204:159-69.
41. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. Int J Pharm 2004; 270:119-25.
42. Hofer C, Göbel R, Deering P, Lehmer A, Breul J. Formulation of interleukin-2 and interferon-alpha containing ultra deformable carriers for potential transdermal application. Anicancer Res 1999; 19:1505-7.
43. Benson HA. Transfersomes for transdermal drug delivery. Expert Opin Drug Deliv 2006; 3:727-37.
44. Dubey V, Mishra D, Asthana A, Jain NK. Transdermal delivery of a pineal hormone: Melatonin via elastic liposomes. Biomaterials 2006; 27:3491-6.
45. Modi CD, Bharadia PD. Transfersomes: A newdominants for transdermal drug delivery. Am J PharmTech Res 2012; 2:71-91.