ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

Current Status and Future Perspective of Transferosomes- an Effective Vesicular Carrier for Delivery of Drugs

Received: 17 August 2022**, Revised:** 24 September 2022**, Accepted:** 28 October 2022

Kaur Kiranjeet
Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, India

Kaur Gurpreet
Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, India

Sharma Hanum
Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, India

Nanda Ravika
Department of Pharmacy, Global Group of Institutes, Amritsar

Narang Jasjeet Kaur
Department of Pharmaceutics, Khalsa College of Pharmacy, Amritsar, India (Corresponding author)
jasjeet2975@yahoo.com

Keywords
Vesicular, Transferosome, Topical, Transdermal

Abstract: **Transferosomes, a vesicular carrier has evolved as a very effective carrier for the delivery of therapeutics, both for topical application as well as for transdermal application. It has been utilized for the delivery of enumerable drugs both herbal and synthetic. The present review provides a detailed account of transferosomes, which includes their constitution, the mechanism by which they enhance the permeation of drugs and their advantages. Besides this, the review entails a compilation of the various applications of transferosomes in topical and transdermal delivery of drugs. The present review also supplements the current status of trnsferosomes with the future perspectives surrounding their use.**

1. Introduction

Transdermal delivery is another suitable and feasible method instead of intravenous and oral routes for delivery of drugs. It saves the patients from the suffering caused by intravenous injections and it is specifically essential in those conditions which are associated with emesis, motion sickness and nauseousness[36-37].

Encapsulating the drug in vesicular system is a novel technique which has been utilized to conquer the stratum corneum barrier without doing any destruction to it. From the structural point of view, vesicles consist of internal hydrophilic core enveloped by bilayer wall of phospholipids or surfactants. Many researchers have introduced different types of alterations to make a novel vesicles which have significantly improved their penetration across the entire skin. A few examples of such modified vesicles include transferosomes, invasomes, flexosomes, ethosomes, menthosomes & niosomes[34].

In 1980, transdermic delivery with the aid of vesicular transporters was reported for the first time, after which many investigators and

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

researchers utilised them for the delivery of drugs[17].

In 90's Cevc and co authors formulated ultra adaptable vesicles (transferosomes) in contrast with the typical liposomes. The word transfersomes is a Latin word made of two words "transferred" and "soma" which means "carrying" and "body" respectively. Transferosomes in contrast to their conventional counterparts were extra stretchy, additionally adjustable & stress respondent, due to the presence of edge activator. The transferosomes were composed of blend of phosphatides or non lipids amphiphytes[19].

2. Constitution Of Transferosomes

A schematic representation of the constitution of transferosomes is given in fig 1.

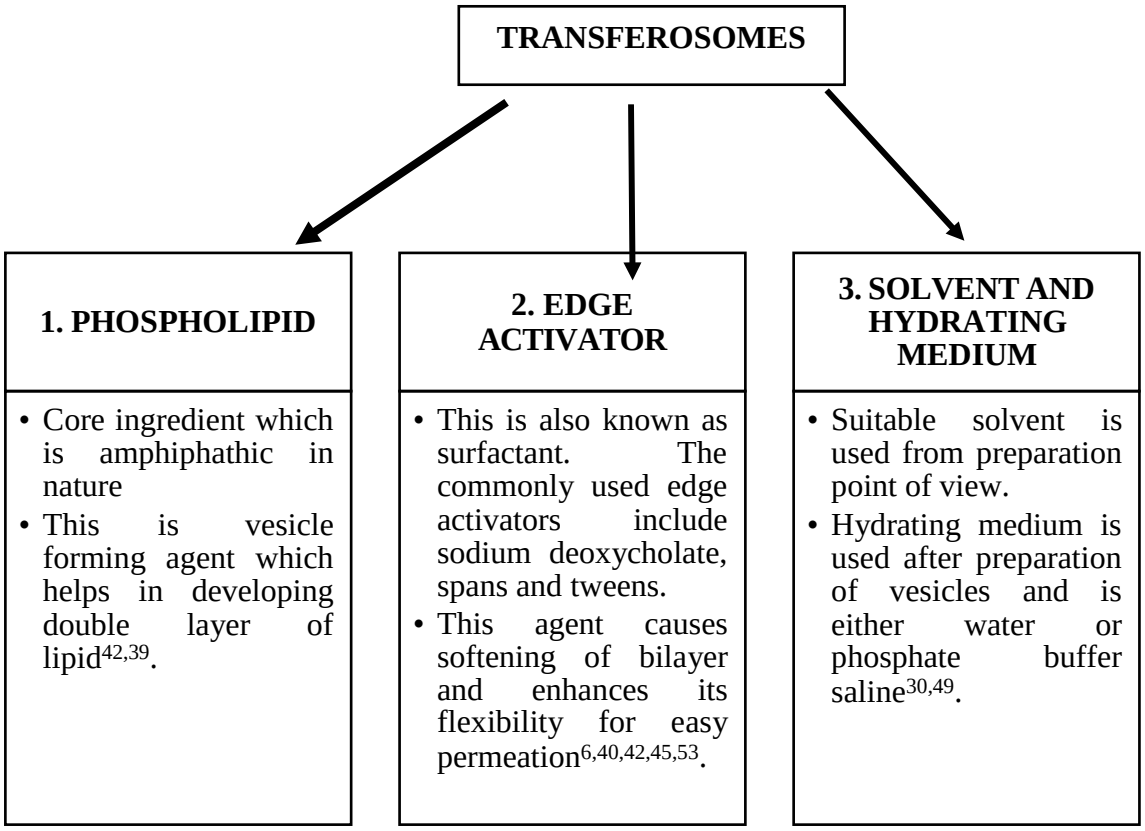

Figure 1: Composition of transferosomes

Tansferosomes are progressively being utilized for transdermal and topical delivery of drugs[59]. The adaptability of these vesicles is attributed to their ultra adjustable double layer membrane[62], by virtue of which they can easily permeate across the phospholipid route of the hypodermis[23,28,38,42,50,52].

Transferosomes are vesicular transporters with potential of enhancing drug penetration through the skin[25,27,69]. From the composition point, these ultraflexible nanocarriers are generally constituted of surfactant, which is also known as edge activator and imparts flexibility to the vesicles as well as phospholipids which are responsible for the formation of double layer membrane[10].

mechanism by which transferosomes improve permeation

The main mechanism by which transferosomes act and enhance the permeation of drugs topically and transdermally is given in fig 2.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

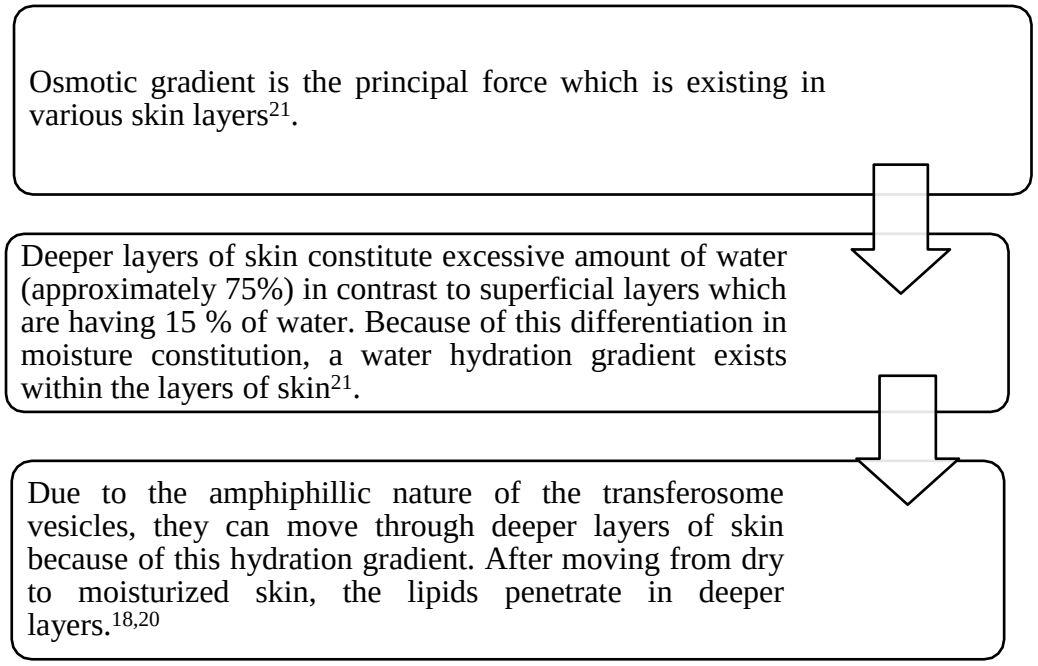

Figure 2: Mechanism of improvement of permeation by transferosomes

The presence of edge activators / surfactants plays a pivotal role in the enhancement of permeation of transferosomes topically & transdermally. Several researchers have reported the mechanism by which the edge activators/ surface active agents enhance the penetration of these vesicles[43,48,66]. It has been reported that existence of particular molecular inclination of surfactants, supports the vesicles to pervade the SC and in due course upsurge the drug's transdermal permeation[66].

3. Advantages Of Transferosomes

The presence of edge activator makes the vesicle much more elastic and flexible and enables them to deform their size and shape because of which they can easily permeate across skin barrier[11,12,18]. The delivery of medications to deeper skin layers provides better therapeutic efficacy[16]. Furthermore, vesicular carriers are having biomimetic nature because of the presence of the edge activator and phospholipid and thus are biocompatible. Transferosomes can deliver both hydrophilic as well as lipophilic molecules[7,13,42,48]. They are also responsible for protecting the drug against enzymatic and other biological degradation by enclosing it in phospholipid. A number of drugs have been delivered using transferosomes bilayer.

4. Application Of Transferosomes

Transferosomes are used for painless delivery of a variety of therapeutics, some of them are presented in fig 3.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

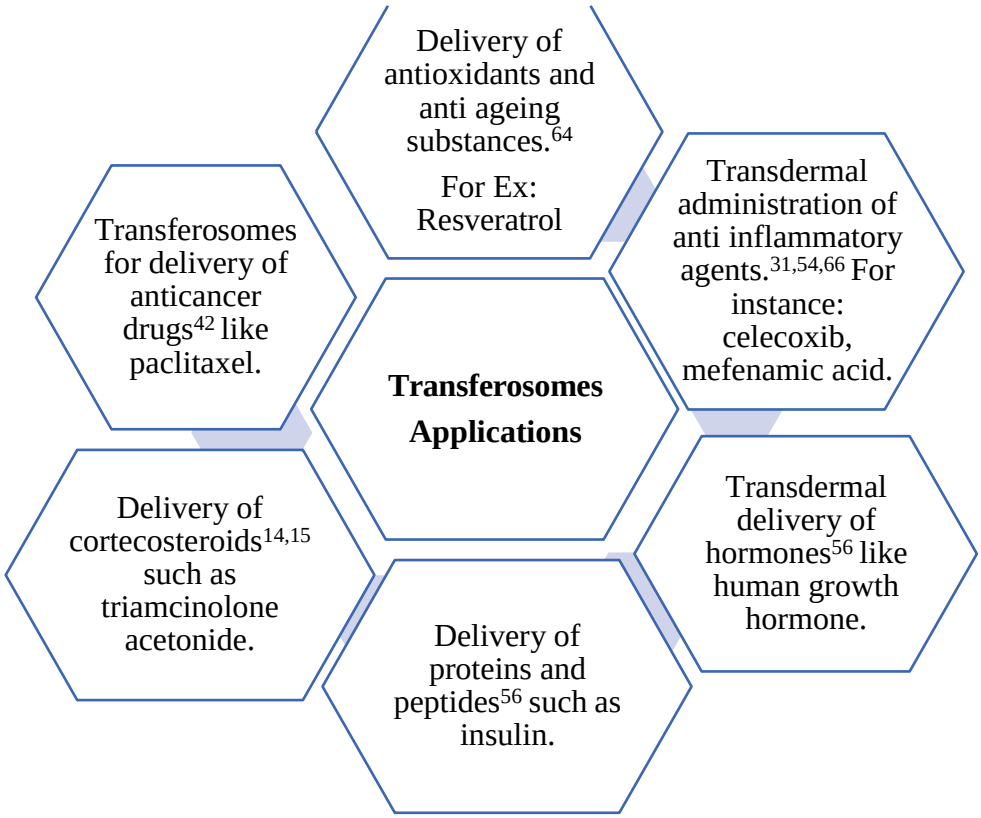

Figure 3: Applications of transferosomes

Mahmood and co- workers formulated raloxifene hydrochloride (RXN) loaded transferosomes and studied the effect of different surfactants such as span 85, span 80 on the permeation of RXN through the skin. The authors further evaluated & optimized the prepared transferosomes for size, transdermal flux, drug entrapment efficacy and other physicochemical properties. After all the studies, the authors reported a considerable enhancement in flux and bioavailability with acceptable zeta potential and particle size (90-140 nm) when transferosomes were formulated using a combination of span 80 and span 85 as compared to other transfersome formulations. The investigators stated that a combination of surfactants can be used for the formulation of ultradeformable vesicles loaded with imperfectly solubilised and excessively metabolised drugs such as raloxifene hydrochloride to improve their dermal delivery as well as systemic availability[46].

Maji R and the investigators aimed to deliver extremely hydrophilic and high molecular weight drug vancomycin hydrochloride through trasferosomal two phase gel system. Vancomycin loaded transferosomes & transferosomes loaded bigel were evaluated by various techniques such as biosafety assay, size, zeta potential, entrapment efficiency, prolonged release profile, *ex vivo* permeation and flux. The results indicated that prepared transferosomes had particle size of 63.02 ± 5.34 nm, zeta potential − 20.93 ± 6.13 mV and entrapment efficiency 84.48 ± 1.22% with better results for transferosomal bigel as compared to transferosomes. After conducting all these studies the authors concluded that, transferosomal loaded bigel is a potential drug delivery system for highly water soluble & high molecular weight drugs[47].

A study was conducted by Surini, S. and co-workers who aimed to deliver andrographolide via transdermal delivery. After the development of andrographolide transfersomes, the authors converted them into gel. Further, the authors evaluated the developed formulation for various characteristics such as *in vitro* permeation studies, penetration flux, entrapment efficiencies & other parameters. The results revealed that the andrographolide transferosomes had a particle size of 524.02 nm, entrapment efficiency of

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

97.02±0.01% penetration flux of 1.28±0.82 µg/cm^2/h. Based on the results the authors concluded that that andrographolide encapsulated gel exhibited better effect in comparison to transferosomes thereby ensuring that ultradeformable vesicular based gel is a formulation with potential for improving transdermal delivery of drugs[61].

In an another study, Zhang, ZJ. and coworkers prepared polymer based aqueous gel encapsulated with meloxicam for application to skin. Meloxicam was loaded into flavosomes, typical liposomes, and elastic liposomes. Furthermore, the developed ultraflexible nanocarriers were assessed for stability, zeta potential, size & entrapment efficiency. After that, meloxicam encapsulated transferosomes were further incorporated into polymer based gel and evaluation was done for viscosity, penetration studies & stability studies. The results of the evaluation studies showed that the vesicle size was less than 120 nm with higher entrapment efficiency. Based on the results the authors concluded that a successful delivery of meloxicam through transdermal route is possible by formulating it as an ultradeformable gel[68].

Sundralingam, U. and co authors developed and assessed the tamoxifen loaded ultradeformable vesicles, with the help of animal model for breast cancer with inclusion and exclusion of emu oil. The authors investigated the blood plasma concentration after administration of the formulation. Furthermore, they have performed the test for evaluation of irritation on skin which showed that emu oil alone as well as prepared formulations with inclusion and exclusion of emu oil did not cause any harmful effects to skin of animals. Thus the authors sum up with the conclusion that the capability of emu oil in ultraflexible formulation[60].

Balata, G.F. and collaboratives prepared dermal film of ivabradine (IVB) loaded transferosomes which is applied one time in a day and used for effective healing of cardiovascular diseases. After the preparation of transferosomes by ethanol injection method they were evaluated for different physicochemical properties for instance, Fourier transform infrared spectroscopy (FTIR), optical and transmission electron microscopy imaging, differential scanning calorimetry (DSC), zeta potential, entrapment efficiency and particle size. After that the best selected vesicle formulation which showed optimised outcomes was chosen for further assessment and a drug loaded transdermal film was formulated using it and investigated for further studies. Furthermore, transferosomal film's pharmacokinetic parameters were compared with extravascular solution of the drug. The IVB loaded transferosomal films showed the best outcomes in terms of entrapment efficiency of 82.03%, size of 206.7 nm, zeta potential of -88.3 mv and permeability, skin retention and other evaluated parameters from which the authors concluded that transferosomal film was suitable drug delivery system for delivery of drugs by transdermal route[9].

Fernández-García, R. and associates encapsulated poorly soluble and high molecular weight drug like amphotericin B in transferosomes. Amphotericin B is efficient in treatment of infections caused by Leishmania spp. parasites. The authors formulated ultradeformable vesicles loaded with amphotericin B. Further, characterization of vesicles was done by authors which showed the favourable results (physicochemical stability, flux of 4.91 ± 0.41 µg/cm^2/h across mouse skin and *in vivo* efficacy which showed that the parasite load was decreased. Eventually, the reasearchers claimed that the transferosomes can efficiently enhances the topical bioavailability of the entrapped drug[29].

Zyl, L.V. and co-workers selected different drugs as a polytherapy for the effective healing of cutaneous tuberculosis (T.B). The authors developed transferosomes and evaluated the incompatibility between all the active pharmaceutical ingredients via various calorimetric methods. In addition, ultradeformable vesicles were further investigated for entrapment efficiency, stability study, size, skin permeation studies and activity against Mycobacterium tuberculosis H37Rv laboratory stain. All three formulations illustrated defined effect with entrapment efficiencies of higher than 85%. At the end the optimized formulation was selected for the treatment of T.B[70].

Abd El-Alim, SM, and collaboratives prepared and evaluated the vesicular carrier for encapsulatin of diflunisal. Ethosomes and transferosomes were two

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

types of nanovesicles that were compared with traditional liposomes. Furthermore, transferosomes revealed optimized drug encapsulation of 46.73 - 65.99%, zeta potential was -45.40 to -86.90 mV & vesicle size was 453.10 - 796.80 nm. Apart from this, 30% ethanol containing ethosomes and optimized ultradeformable vesicles were incorporated into hydrogel and assessed for drug release outside the body as well as an assessment of penetration was done. Moreover, in contrast to conventional liposomes, these two vesicles showed sustained drug release, best penetration, consistent flux and anti-inflammatory effects. In conclusion, the researchers stated that the developed vesicles of diflunisal delivered by dermal administration have good potential for management of pain and inflammation[26].

Alhakamy, N.A. and co-authors enhanced the bioavailability of raloxifene by encapsulating it in nano lipid carriers. The authors have used surfactant based transferosomes. After the formulation of vesicles, characterization was done by evaluating different parameters and all the investigations showed the potential of prepared vesicles in delivery of drug with an average vesicle size of 96.05 nm and zeta potential of 39.4 mV. Therefore, the formulated vesicular system was successfully considered for transdermal delivery of raloxifene[5].

Khatoon, K. et al., delivered the BCS class 3 drug cilnidipine via vesicular system. For that purpose, the authors designed a quadratic model of Box Behnken design as QbD approach to analyse the consequence of variables on methodology quality (example: drug encapsulation, size range of vesicles and transdermal flux). The functional formulation exhibitted the best outcomes of all the tests conducted with particle size of 206.24 ± 5.94 nm, polydispersity index of 0.302 ± 0.034, entrapment efficiency of 96.45 ± 1.92 % and transdermal flux value 27.72 ± 3.55 µg/cm^2 /h. Furthermore, the results of histopathology and skin irritancy study showed the formulation which was incorporated in gel was much tolerable, safe and effective with higher drug release (81.52 ± 9.01%) than the drug suspension (20.29 ± 3.78 13%). Moreover, pharmacokinetic study also showed that the formulation exhibited results with enhanced bioavailability. Thus, it was confirmed that cilnidipine transferosomes can be successfully used as transdermal vehicle to treat hypertension[44].

Shamshiri, MK. and co-workers aimed to deliver human growth hormone through a non invasive route by incorporating it in ultradeformable vesicles via transdermal delivery. The authors prepared two formulations using sodium deoxycholate and sodium lauryl sulfate as different surfactants. Furthermore, both of the formulations were investigated for various evaluation parameters such as vesicle size range, release of drug outside the body as well penetration into dermal layers. The authors have reported that transferosomes showed more prominent release of growth hormone from rat skin in contrast to hormone administered alone. Therefore, the investigators concluded that the vesicular system was the best way to encapsulate & deliver the hormones through transdermal route[56].

Habib, B.A. and co- authors formulated and evaluated the transferosomes and other different nanocarriers of ondansetron by 23 full factorial design. The optimized formula exhibited favourable outcomes for *ex vivo* penetration studies[35].

Ahad, A. et al., targeted to design and illustrate the ultraflexible vesicles of eprosartan mesylate by using different compositions of phospholipids and surfactants. Furthermore, the formulated transferosomes were characterized for physicochemical properties like zeta potential, entrapment study, particle size, polydispersity index, vesicle shape, confocal laser scanning microscopy, release *in vitro* release and penetration inside the tissue. All the results were in desired range with particle size of 71.18 nm to 85.66 nm, entrapment efficiency between 83.00% to 88.19% and flux of 1.78 µg/cm2 /h to 5.02 µg/cm2 /h. The authors concluded that the transferosomes were suitable carriers for the delivery of eprosartan mesylate through dermal route[4].

Wang, J. and co-workers designed and characterized mixture of monoterpenes and edge activated pegylated transfersomes (MMPTs) with sinomenine hydrochloride as drug. Orthogonal design was used for optimization of the formulation. Drug release studies were conducted

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

which revealed the best penetration of transferosomes. Eventually, it was observed that transferosomes were good carrier for delivering sinomenine[63].

Das. B et al, formulated and evaluated the transferosomal gel containing risperidone. The formulation of ultradeformable vesicles was done which was further converted into methyl cellulose gel. Characterization was done by evaluating steady state flux which was 0.2387 ± 0.0245 µg/cm^2 /h, average vesicle size which was 589.50 nm, entrapment efficacy which was found to be 61.54 ± 2.14 % and zeta potential was – 20.90 mV. The results revealed that transferosomes were a much better alternative than conventional liposomes[24].

AL Shuwaili, A.H. et al., formulated transdermal transferosomes of pentoxifylline for treatment of diseases associated with chronic arteries. *In vitro* release, *in vivo* evaluation, vesicle shape, vesicle elasticity and zeta potential were evaluated. The results showed that vesicle diameter was 0.69 ± 0.049 nm, zeta potential was 34.9 ± 2.2 mv, entrapment efficiency was 74.9 ± 1.6%, flux was 56.28 ± 0.19 cm^2/ h, vesicle elasticity was found to be 145 ± 0.6 45 and all the evaluated results were compared with the conventional oral sustained release tablets. It was concluded that elastic liposomes of pentoxifylline exhibited enhanced bioavailability and sustained release[1].

Ahad, A. et al., formulated and characterized novel soft lipid-based nanoparticles which were nano-transfersomes for dermal delivery of eprosartan mesylate (EM). After the preparation of these vesicles these were further evaluated by vesicle size and shape and other parameters. The results of evaluation showed that vesicle size was 108.53 ± 0.06 nm, flux of 27.22 ± 0.29 µg/cm2 /h, entrapment efficiency was 63.00 ± 2.76%. Moreover, confocal laser scanning microscopy was done which confirmed the permeation of ultraflexible vesicles into internal layers of skin. The authors concluded that the composition of surfactants influenced the nature of nanotransferosomes. In conclusion, the investigators claimed that nanotransferosmes were the best alternative to deliver eprosartan mesylate via skin[3].

Shivani, S.S and Srujan, K.M. prepared and evaluated flexible liposomes of tramadol hydrochloride. The preparation was done by commercial rotary evaporation method using different compositions of lipids and surfactants. After the formulation of vesicles they were incorporated into gel and evaluated for different physicochemical parameters. Moreover, SEM analysis was done for vesicle size range. Furthermore, skin penetration was evaluated. All the assessed characters were in favour of formulated transferosomes with entrapment efficiency of 92.71±0.56 % which confirmed that transferosomes are efficient delivery system[57].

Abdellatif, A.A.H and Tawfeek, H.M. encapsulated clindamycin phosphate into ultraadjustable vesicles known as transferosomes. After the formulation of vesicles these were characterized by various evaluation parameters and further the formulation was incorporated in Carbopol 934 gel. Furthermore, the gel was evaluated for its viscosity, spreadability, stability, skin irritation, homogenous nature. The evaluation outcomes showed that clindamycin phosphate had significantly higher encapsulation efficiency (93.3±0.8%) and *in vitro* release as compare to the control Carbopol gel. Apart from this, it also showed higher steady state flux and cumulative amount of drug release in contrast to other two control formulations. Therefore, outcome of the study showed that transferosomes of clindamycin phosphate were a hopeful vesicular delivery system for the transdermal delivery of drugs[2].

Shreya, A.B. et al encapsulated Asenapine maleate (ASPM) into transdermal transferosomes to enhance its bioavailability, which otherwise exhibits poor bioavailability due to extensive metabolism via oral route. Moreover, collaborative approach was employed by combination of chemical and nano carrier methods. Furthermore, after the preparation of transferosomes they were evaluated for different physicochemical parameters and different penetration promotors were selected for increasing dermal permeability of asenapine maleate. After the selection of optimized permeation enhancer they were further evaluated for skin penetration in animals for assessing bioavailability against oral route. After all the tests conducted the results showed that entrapment

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

efficiency of 54.96%, average vesicle size was 126.0 nm, polydispersity index was 0.232 and zeta potential was 43.7 mV and it was noticed that combined technology using both chemical and nano carrier approach significantly enhanced the drug permeation. The authors concluded that it was the best approach to increase bioavailability of ASPM[58].

Shaji. J and Lal, M. targeted to incorporate poorly water soluble drug Piroxicam into transdermal transferosomes. After the formulation of transferosomes they were evaluated by different methods. Furthermore, the optimized formulation was converted into gel and showed significantly higher release ($p<0.05$) as compared to conventional gel. The study concluded that transferosomal gel formulation of piroxicam had better anti-inflammatory activity and higher drug permeation across the skin as compared to conventional formulations of piroxicam[55].

Zhang, Y.T. et al., prepared the transferosomes by delivery through transdermal route by encapsulating cinnamic acid. After the formulation of transferosomes all the characterization parameters were performed and results compared to conventional liposomes. The entrapment profile, *in vitro* release and permeation across the skin of transferosomes were observed to be significantly high as compared to the simple liposomes. So, from these results the investigators concluded that transferosomes of cinnamic acid were a promising nano lipid carrier for better drug permeation into skin[67].

Yusuf, M. et al., formulated felodipine loaded transferosomes. For the preparation, rotary evaporation method was used and distinct methods were used for assessing vesicles for zeta potential, size and structure of vesicle, homogenity, drug encapsulation etc. The results showed that zeta potential was −49.8 mv, deformability index was 119.68 and particle size was found to be 75.71 ± 5.4 nm. Moreover, pharmacokinetic study depicted the sustained release of formulation with maximum release into skin layers. The authors concluded that difference in ratios and preparation method had prominent influence on vesicles nature[65].

Chaudhary, H. and co-workers designed and characterized nanocarriers i.e transferosomes of diclofenac diethylamine and curcumin. For construction of contour and reponse surface plots box Behnken factorial design was used to obtain a polynomial equation. The influence of independent and dependent variables, size range, encapsulation capability, flux were studied. From the polynomial equation, 2D and 3 D plots the compositions of formulation was optimized[22].

Ghanbarzadeh, S. and Sanam Arami, S. formulated and assessed the transdermal transferosomes, ethosomes, liposomes of diclofenac sodium which is a poorly solubilised drug. After the formulation, the formulated nanocarriers were assessed for particle size, shape and amount of drug entrapped. After preparation, the formulation which was optimal was further constituted into gel by using Carbopol 914 and characterized for retention of drug in skin, spreadability and skin irritation. The cumulative drug release, steady state flux of ethosomes and transferosomes were much better than conventional liposomes with entrapment efficiency of 42.61% and 51.72% respectively with particle size between 145 to 202 nm. Furthermore, all the results revealed that transferosomes and ethosomes are best nanovasicular carriers for transdermal release of diclofenac sodium[32] .

Gupta, A. encapsulated the poorly soluble drug sertraline by nano transferosomes so that the difficulties related to sertraline could be resolved. After the preparation of vesicles with rotary evaporation, the vesicles were investigated for different physicochemical properties, entrapment efficiency which was found to be 90.4±0.15% and compatibility of drugs with excipients was checked. The optimized formulation was converted into gel. Transferosomal gel showed significant release of drug (73.8%) and *ex vivo* penetration as compared to the transfersomal suspension, control gel, and drug solution. No skin irritation and stability issues were observed in transferosomal gel in contrast to conventional gel. Therefore, the study supported that the trasferosomal gel of sertraline is best approach for its transdermal delivery[33].

Patel R, et al., prepared and evaluated the elastic liposomes of curcumin for delivery through skin. After the preformulation studies the formulation of

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

elastic liposomes were done and characterization was carried by zeta potential, entrapment efficiency, particle size and vesicle shape. All the outcomes were in favourable range and showed the maximum drug entrapment (89.6±0.049%). At the end it was concluded that the optimized formulation was effective to deliver curcumin via transdermal route[51].

Jain, S. et al., targeted the formulation of dexamethasone transferosomes for promoting administration via dermal route. After the preparation of vesicles the prepared transferosomes were further evaluated for size, shape, deformability, entrapment efficiency. Fluorescence microscopy was performed. The release of drug was a significant as compared to the traditional liposomes. Therefore, it was concluded that transferosomes were efficient vesicular approach for improvement of dexamethasone delivery through skin[41].

The applications of transferosomes are summarized in Table 1.

Table 1: Applications of transferosomes

Sr. no.	Drug	Application	Method of preparation	Formulation	Reference
1.	Raloxifene hydrochloride	To improve dermal delivery and bioavailability	Thin film formation	Transferosomes	46
2.	Vancomycin hydrochloride	To enhance transdermal and antibacterial activity	Reverse phase evaporation method	Transferosomal bigel	47
3.	Andrographolide	To improve its bioavailability	Thin film hydration method	Transferosomal gel	61
4.	Meloxicam	To improve its solubility & lipophilicity	Thin film hydration method	Liposomal hydrogel	68
5.	Tamoxifen	Breast cancer	Thin film hydration method	Transferosomes	60
6.	Ivabradine	To improve bioavailability	Ethanol injection method	Transdermal film	09
7.	Amphotericin B	For treating cutaneous leishmaniasis	Thin film hydration method	Transferosomes	29
8.	Diflunasil	For improve skin permeation	Thin film hydration method	Vesicular hydrogel	26
9.	Raloxifene	To improve bioavailability	Thin film hydration	Transferosomes	05
10.	Cilnidipine	Hypertension	Thin layer evaporation	Transferosomes	44
11.	Human growth hormone	For painless administration of hormone through skin	Modified thin film hydration method	Nanotransferosomes	56
12.	Ondansetron	To improve bioavailability	Thin film hydration	Nanovesicular transferosomes	35
13.	Sinomenine hydrochloride	To enhance systemic availability	Ethanol injection method	Pegylated transferosomes	04
14.	Risperidone	To improve	Reverse phase	Transferosomal	24

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

		bioavailability	evaporation method	gel	
15.	Pentoxifylline	For treatment of arterial diseases	Modified vortex sonication method	Transferosomes	01
16.	Eprosartan mesylate	Hypertension	Thin film hydration method	Transferosomes	04
17.	Tramadol hydrochloride	Effective agent for moderate tosevere chronic pain	Rotary evaporation method	Transferosomal gel	57
18.	Clindamycin phosphate	To improve the skin permeation of antibiotic drug	Thin film hydration method	Transferosomal nanoparticles	02
19.	Asenapine maleate	Schizophrenia treatment	Thin film hydration method	Transferosomal gel	58
20.	Piroxicam	NSAID for improving its deeper skin permeation	Rotary evaporation method & vortex sonication method	Transferosomal gel	55
21.	Cinnamic acid	To improve skin penetration	Film dispersion method	Transferosomes	67
22.	Felodipine	To enhance bioavailability	Vortex sonication method	Nanovesicle transferosomes	65
23.	Diclofenac diethylamine & curcumin	For enhancing skin penetration	Rotary evaporation sonication method	Transferosomes	22
24.	Diclofenac	NSAID for improving its penetration inside skin	Rotary evaporation method	Transferosomes	32
25.	Sertraline	Depression	Conventional rotary evaporation sonication method	Transferosomes	33
26.	Curcumin	To improve bioavailability	Modified hand shaking, lipid film hydration method	Transferosomes	51
27.	Dexamethasone	Enhanced skin penetration	Conventional rotary evaporation and sonication method	Transferosomes	41

5. Future Perspective

Nano lipid carriers are exceedingly investigated and practiced applied science for transdermic and transcutaneous delivery system across the horny layer. Ultradeformable vesicles such as transferosomes have prominent effect that overcomes the shortcomings of traditional liposomes and therefore easily penetrates reaches to the deepeer layer of skin. The deformability characteristic is due to the exixtence of a surfactant in transferosomes which aids in providing elasticity for permeation. There is still a need to work in the area of formulating these nanovesicles and developing them from pilot scale to large industrial scale to make certain that finished product sustain their encapsulatioin, constitution, firmness and particle dimensions. The clinical experimentation that have been conducted till now assure suitability of transferosomes, but still examination is required to evolve novel techniques of integrating these methods with other technologies used for enhancing interpenetration like microneedles, electropermeabilization and to ease delivery of drugs in deeper layers of dermis.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

The collaboration of electroporation and transferosomes can be one more feasible option for amplifying the permeation by reversibly opening skin pores after the application of electric energy.

6. Conclusion

Transferosomes are the novel lipid based nanocarrier that are excessively deformable in nature and help in delivering the therapeutic agent into deeper layers of skin in a more efficient manner in contrast to traditional liposomes. The action of edge activator and osmotic gradient are the main driving forces to administer the medication across the internal layers of skin. Superiorly, transferosomes are particularly formulated nanolipid carrier that have to upgrade in line with specific cases of drugs of significance to attain the most constructive formulation and eventually therapeutic response. Moreover, advancements in transferosomes may support in treating variety of disorders.

References

[1] A.L Shuwaili A.H., Rasool B.K.A., Alaa A. and Abdulrasool A.A., Optimization of elastic transfersomes formulations for transdermal delivery of pentoxifylline, *Eur J Pharm Biopharm*, **(2016)**

[2] Abdellatif A.A.H. and Taleb H.A.A., Transfersomal nanoparticles of keratolytic and antibacterial agents for enhanced transdermal delivery, *J. nanotech adv materials*, **(2015)**

[3] Ahad A., Al Saleh A.A., Al Mohizea A.M., Al Jenoobi F.I., Raish M., Yassin A.E.B. and Alam M.A., Formulation and characterization of novel soft lipid-based nanoparticles for enhanced transdermal delivery of eprosartan me mesylate, *Saudi Pharmaceutical Journal*, (**2016**)

[4] Ahad A., Saleh A.A, Al Mohizea A.M., Al-Jenoobi F.I., Raish M., Yassin A.E.B. and Alam MA., Formulation and characterization of Phospholipon® 90 G and Tween® 80 based transfersomes for transdermal delivery of eprosartan mesylate, *IJPDT*, **(2017)**

[5] AlhakamyI N.A., Fahmy U.A. and Ahmed O.A.A., Vitamin E TPGS based transferosomes augmented TAT as a promising delivery system for improved transdermal delivery of raloxifene, *Plos One*, (**2019)**

[6] Ascenso A., Batista C., Cardoso P., Mendes T., Praça F.G., Bentley M.V.L.B., Raposo S. and Simões S., Development, characterization, and skin delivery studies of related ultradeformable vesicles: Transfersomes, ethosomes, and transethosomes, *Int J Nanomedicine*, **10**, 5837–5851 **(2015)**

[7] Ascenso A., Salgado A., Praça E.F.G, Bentley M.V.L.B., Marques HC., Santos O.C. and S Simoes., In vitro and in vivo topical delivery studies of tretinoin loaded ultradeformable vesicles, *Eur J. Pharma and Biopharm*, **88 (1),** 48–55 **(2014)**

[8] Avadhani K.S, Manikkath J., Tiwari M., Chandrasekhar M., Godavarthi A., Vidya S.M, Hariharapura R.C, Kalthur G., Udupa N. and Mutalik S., 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 Deliv*, **24**, 61–74 **(2017)**

[9] Balata G.F., Faisal M.M., Elghamry H.A. and Sabry S.A., Preparation and Characterization of Ivabradine HCl Transfersomes for Enhanced Transdermal Delivery, *J. Drug Delivery Sci Technol*, (**2020)**

[10] Bhasin B. and Londhe V.Y, An overview of transfersomal drug delivery. *Int. J. pharm sci res*, **9(6),** 2175-2184 **(2018)**

[11] Bjorklund S., Engblom J., Thuresson K. and Sparr E.A., Water gradient can be used to regulate drug transport across skin, *Journal of Control Release (JCR)*, **143(2),** 191-200 **(2010)**

[12] Bouwstra J.A. and Honeywell Nguyen P.L., Skin structure and mode of action of vesicles, *Adv. Drug Deliv. Rev*, **54**, S41-S55 **(2002)**

[13] Carter P., Narasimhan B. and Wang Q., Biocompatible nanoparticles and vesicular systems in transdermal drug delivery for various skin diseases, *Int J. Pharm*. **555**, 49–62 **(2019)**

[14] Cevc G. and Blume G., Biological activity and characteristics of triamcinolone-acetonide formulated with the self-regulating drug carriers, Transfersomes®, *BBA. Biomembranes*, **1614**, 156–164 **(2003)**

[15] Cevc G. and Blume G., Hydrocortisone and dexamethasone in very deformable drug carriers have increased biological potency,

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

prolonged effect, and reduced therapeutic dosage, *BBA. Biomembranes*, **1663**, 61–73 **(2004)**

[16] Cevc G. and Vierl U., Nanotechnology and the transdermal route: a state of the art review and critical appraisa, *Journal Control Release (JCR)*, **141 (3),** 277–299 **(2010)**

[17] Cevc G., and Chopra A., Deformable (Transfersome®) vesicles for improved drug delivery into and through the skin, in: Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement, *Education and Information Technologies Springer*, 39–59 **(2016)**

[18] Cevc G., Gebauer D., Stieber J., Schätzlein A. and Blume G, Ultraflexible vesicles, Transfersomes, have an extremely low pore penetration resistance and transport therapeutic amounts of insulin across the intact mammalian skin. *BBA*, **1368(2),** 201-215 **(1998)**

[19] Cevc G., Rational design of new product candidates: the next generation of highly deformable bilayer vesicles for noninvasive, targeted therapy, *JCR*, **160 (2),** 135–146 **(2012)**

[20] Cevc G., Schätzlein A., and Blume G, Transdermal drug carriers: Basic properties, optimization and transfer efficiency in the case of epicutaneously applied peptides, *Journal Control Release (JCR)*, **36(1-2)**, 3-16 **(1995)**

[21] Cevc, G. and Blume G, Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force, *BBA*, **1104(1),** 226-232 **(1992)**

[22] Chaudharya H., Kohli K. and Kumar V., Nano-transfersomes as a novel carrier for transdermal delivery, *Int J. Pharm*, **454**, 367–380 **(2013)**

[23] Chaurasiya P., Ganju E., Upmanyu N., Ray SK. and Jain P., Transfersomes: a novel technique for transdermal drug delivery, *J. Drug Deliv. Ther*, **9 (1),** 279–285 **(2019)**

[24] Das B., Sen S.O., Maji R., Nayak A.K. and Sen K.K., Transferosomal gel for transdermal delivery of risperidone: Formulation optimization and ex vivo permeation, *J Drug Deliv Sci Technol*, **(2017)**

[25] Duangjit S., Opanasopit P., Rojanarata T., et al. Evaluation of meloxicam-loaded cationic transfersomes as transdermal drug delivery carriers, *AAP Sci*, **14(1),** 133-140 **(2013)**

[26] El Alim S.H.A., Kassem A.A., Basha M. and Salama A., Comparative study of liposomes, ethosomes and transfersomes as carriers for enhancing the transdermal delivery of diflunisal: In vitro and in vivo evaluation, *Int J. Pharm*, **(2019)**

[27] El Maghraby GM., Williams A.C. and Barry B.W. Oestradiol skin delivery from ultradeformable liposomes: refinement of surfactant concentration, *Int. J. pharm*, **196(1),** 63-74 **(2000)**

[28] Fern andezGarcia R., Lalatsa A., Statts L., BolasFern andez F., Ballesteros M.P. and Serrano D.R, Transferosomes as nanocarriers for drugs across the skin: Quality by design from lab to industrial scale, *Int J. Pharm*, 573, 118817 **(2020)**

[29] Fernández-García R., Sttats L., Jesus J.A., Dea-Ayuela M.A., Bolás-Fernández F., Ballesteros M.P., Laurenti M.D., Passero L.F.D., Lalatsa A. and Serrano DR. Topical Delivery of Amphotericin B Utilizing Transferosomes for the Treatment of Cutaneous Leishmaniasis, *Proceedings*, **78**, 26, **(2021)**

[30] Garg V., Singh H., Bimbrawh S., Singh S.K., Gulati M., Vaidya Y. and Kaur P., Ethosomes and transfersomes: Principles, perspectives and practices, *Curr. Drug Deliv*, **14**, 613–633 **(2016)**

[31] Ghanbarzadeh S. and Arami S., Enhanced transdermal delivery of diclofenac sodium via conventional liposomes, ethosomes, and transfersomes, *Biomed Res Inte*, 1–7 **(2013)**

[32] Ghanbarzadeh S. and Arami S., Enhanced Transdermal Delivery of Diclofenac Sodium via Conventional Liposomes, Ethosomes, and Transfersomes, *BioMed Res. Int*. **(2013)**

[33] Gupta A., aggarwal G., Aingla S. and Arora R., Transfersomes: A Novel Vesicular Carrier for Enhanced Transdermal Delivery of Sertraline: Development, Characterization, and Performance Evaluation, *Sci Pharm*, **80**, 1061–1080 **(2012)**

[34] Habib B.A., and AbouGhaly M.H.H., Combined mixture-process variable approach: a suitable statistical tool for nanovesicular

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

systems optimization, *Expert Opin. Drug Delivery*. **13**, 1–12 **(2016)**

[35] Habib B.A., Sayed S. and Elsayed G.M. Enhanced transdermal delivery of ondansetron using nanovesicular systems: Fabrication, characterization, optimization and ex-vivo permeation study-Box-Cox transformation practical example, *Eur J. Pharm Sci*, **(2018)**

[36] Habib B.A., Tag R. and Nour S.A., Factorial design approach for optimization of a gel formulation for in vitro iontophoretic transdermal delivery of granisetron, *Bulletin of Faculty of Pharmacy, Cairo University*, **49**, 305–313 **(2008)**

[37] Hu L., Damaj B.B., Martin R. and Michniak Kohn B.B., Enhanced *in vitro* transbuccal drug delivery of ondansetron HCl, *Int. J. Pharm*, **404**, 66–74 **(2011)**

[38] Hussain A., Singh S., Sharma D., Webster T.J., Shafaat K. and Faruk A, Elastic liposomes as novel carriers: recent advances in drug delivery, *Int J. Nanomedicine*, **12,** 5087 **(2017)**

[39] Iskandarsyah Rahmi A.D., and Pangesti D.M., Comparison of the characteristics of transfersomes and protransfersomes containing azelaic acid, *J Young Pharm*, **10**, S11–S15 **(2018)**

[40] Jain A.K., and Kumar F., Transfersomes: Ultradeformable vesicles for transdermal drug delivery, *Asian Journal of Biomaterial Research*, **3**, 1–13 **(2017)**

[41] Jain S., Jain P., Umamaheshwari R.B. and Jain N.K., Transfersomes—A Novel Vesicular Carrier for Enhanced Transdermal Delivery: Development, Characterization, and Performance Evaluation, *Drug Dev Ind Pharm*, **29**, 1013-1026 **(2003)**

[42] Jiang T., Wang T., Li T., Ma Y. and Shen S.B., Enhanced transdermal drug delivery by transfersome-embedded oligopeptide hydrogel for topical chemotherapy of melanoma, *ACS Nano*, **12(10),** 9693–9701 **(2018)**

[43] Khan M.A., Pandit J., Sultana., Sultana Y.S., Ali A., Aqil M. and Chauhan M., Novel carbopol-based transfersomal gel of 5-fluorouracil for skin cancer treatment: in vitro characterisation and in vivo study, *Drug Deliv*, **22(6),** 795802 **(2015)**

[44] Khatoon K., Rizwanullah M.D., Amin S., Mir S.R. and Akhter S., Cilnidipine loaded transfersomes for transdermal application: Formulation optimization, *in vitro* and *in vivo* study, *J Drug Deliv. Sci Technol*, (**2019)**

[45] Kotla N.G., Chandrasekar B., Rooney P., Sivaraman G., Larrañaga A., Krishna K.V., Pandit A. and Rochev Y., Biomimetic lipid-based nanosystems for enhanced dermal delivery of drugs and bioactive agents, *ACS Biomater. Sci. Eng*, **3**, 1262–1272 **(2017)**

[46] Mahmood S., Chatterjee B. and Uttam Kumar Mandal U.K., Pharmacokinetic evaluation of the synergistic effect of raloxifene loaded transfersomes for transdermal delivery, *J. Drug Deliv Sci Technol*, **63**, 102545 **(2021)**

[47] Maji R., Calvin A., Omolo C.A., Jaglal Y., Singh S., Devnarain N., Mocktar C. and Govender T., A transferosome-loaded bigel for enhanced transdermal delivery and antibacterial activity of vancomycin hydrochloride, *Int J Pharma*, **607**, 120990 **(2021)**

[48] Meng S., Zhang C., Shi W., Zhang X.W., Liu D.H, Wang P., Li J.X. and Jin Y. Preparation of osthole-loaded nano-vesicles for skin delivery: characterisation, *in vitro* skin permeation and preliminary *in vivo* pharmacokinetic studies, *Eur. J. Pharm. Sci*, **92**, 49–54 **(2016)**

[49] Pawar AY., Jadhav KR. and Chaudhari LH., Transfersome: A novel technique which improves transdermal permeability, *Asian J. Pharm. Sci*, **10**, 425–436 **(2016)**

[50] Piumitali B., Neeraj U. and Jyotivardhan J, Transfersomes—a nanoscience in transdermal drug delivery and its clinical advancements, *Int. J. Nanoscience*, 1950033 **(2020)**

[51] R Patel., Singh S.K., Singh S., Sheth N.R. and Gendle R., Development and Characterization of Curcumin Loaded Transfersome for Transdermal *Delivery, Int J Pharm Sci Res*, **14**, 71-80 **(2009)**

[52] Rai Shubhra., Pandey Vikas. and Rai Gopal, Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: the state of the art, *Nano Rev. Exp*, **8(1),** 1325708 **(2017)**

[53] Rajan R., Jose S., Mukund V.P.B. and Vasudevan D.T., Transferosomes—A vesicular transdermal delivery system for enhanced drug

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

permeation, *J. Adv. Pharm. Technol*, **2**, 138–143 **(2011)**

[54] Shabana S. and Sailaja A.K., Formulation and evaluation of diclofenac sodium transferosomes using different surfactants by thin film hydration method, *Der Pharmacia Lettre*, **7,** 43–53 **(2015)**

[55] Shaji J. and Lal M., Preparation, optimization and evaluation of transferosomal formulation for enhanced transdermal delivery of a cox-2 inhibitor, *Int J. Pharm Sci*, 467-477 **(2014)**

[56] Shamshiri M.K., Borojeni A.A.M., Shahraky M.K. and Rahimi F., Lecithin soybean phospholipid nano-transfersomes as potential carriers for transdermal delivery of the human growth hormone, *J cell biochem*, **2018**

[57] Shivani S.S. and Srujan K.M., Novel Vesicular Carrier for Enhanced Transdermal Delivery of Tramadol Hydrochloride Transfersomal Gel, *J Pharma Biomed Sci*, **06(03),** 139–144 **(2016)**

[58] Shreya A.B., Managuli R.S., Menon J., Kondapalli L., Hegde A.R., Avadhani K., Shetty P.K., Amirthalingam M., Kalthur G. and Mutalik S., Nano-transfersomal formulations for transdermal delivery of asenapine maleate: *in vitro* and *in vivo* performance evaluations, *J Liposome Res.*, **(2015)**

[59] Souto Eliana B., Baldim Iara., Oliveira Wanderley P., Rao Rekha., Yadav Nitesh., Gama Francisco M. and Mahant Sheefali, SLN and NLC for topical, dermal, and transdermal drug delivery, *Expert Opin. Drug Deliv*, **17 (3),** 357–377 **(2020)**

[60] Sundralingam U., Chakravarthi S., Ammu Kutty Radhakrishnan A.K., Saravanan Muniyandy S. and Palanisamy U.D., Efficacy of Emu Oil Transfersomes for Local Transdermal Delivery of 4-OH Tamoxifen in the Treatment of Breast Cancer, *Pharmaceutics*, **12**, 807 **(2020)**

[61] Surini S., Nastiti P.D., Putri A.R., Kurnia S. S. and Putri K.S.S. Formulation of andrographolide transfersomes gel for transdermal delivery: a preliminary study. *Int. J. Appl. Pharm*, 12, **(2020)**

[62] Verma P., Ram A., Jha A., Mishra A. and Thakur A, Phosphatidylcholine: a revolution in drug delivery technology, *Int J Pharm Sci Res*, **1**, 1–12 **(2010)**

[63] Wang J., Wei Y., Fei Y.R., Fang L., Zheng H.S., Mu C.F., Li F.Z. and Zhang Y.S., Preparation of Mixed Monoterpenes Edge Activated PEGylated Transfersomes to Improve the In Vivo Transdermal Delivery Efficiency of Sinomenine Hydrochloride, *Int J Pharm*, **(2017)**

[64] Wu P.S., Li, Y.S, Kuo Y.C., Tsai S.J.J. and Lin C.C., Preparation and evaluation of novel transfersomes combined with the natural antioxidant resveratrol, *Molecules*, **24,** 600 **(2019)**

[65] Yusuf M., Sharma V. and Pathak K,. Nanovesicles for transdermal delivery of felodipine: Development, characterization, and pharmacokinetics, *Int J. Pharm Investig*, **(2014)**

[66] Zaafarany G.M., Awad G.A., Holayel. and Mortada N.D., Role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery, *Int J. Pharm*, **397 (1-2),** 164–172 **(2010)**

[67] Zhang Y.T., Xu Y.M., Zhang S.J., Zhao J.H., Wang Z., Xu D.Q. and Feng N.P., In vivo microdialysis for the evaluation of transfersomes as a novel transdermal delivery vehicle for cinnamic acid, *Drug Dev Ind Pharm*, **40(3),** 301–307 **(2014)**

[68] Zhang Z.J., Osmałek T. and Michniak-Kohn B., Deformable Liposomal Hydrogel for Dermal and Transdermal Delivery of Meloxicam, *Int J. Nanomedicine*, **15**, 9319–9335 **(2020)**

[69] Zheng W., Fang X., Wang L., et al, Preparation and quality assessment of itraconazole transfersomes, *Int J. pharm*, **436(1-2),** 291 **(2012)**

[70] Zyl L.V., Viljoen J.M., Haynes R.K., Aucamp M., Ngwane A.H. and Plessis J.D., Topical Delivery of Artemisone, Clofazimine and Decoquinate Encapsulated in Vesicles and Their In vitro Efficacy Against Mycobacterium tuberculosis, *AAPS*, **20**, 33 **(2019)**