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Transferosomes a New Transformation in Research: A Review

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Author's contribution

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The drugs mostly present are available with less bioavailability and the problem arises with less permeation or solubility so extensive work is done to enhance these mechanisms. Not only that drugs should pass hepatic metabolism, Inorder to improve its bioavailability they are formulated as transferosomes which can improve the patient compliance by delivering the drug through the transdermal-route. Soya lecithin is used as a phospholipid whereas Tween 60, Tween 80, Span 60 and Span 80 are used as edge activators. These formulations usually showed more entrapment efficiency. The reason behind this is due to the presence of more phospholipids and as the surfactant concentration increases drug release will be rapid. As our main aim is to enhance the bioavailability this can be achieved by optimizing the concentrations of phospholipid and surfactant one can attain a controlled release of drug through this drug delivery system.

Keywords: Transferosomes; methods; scope soya lecithin; Tween 60; Span80.

1. INTRODUCTION

1.1 Scope of Transferosomes

Presumptuous delivery of various drug molecules through/across open biological carriers is well suited by ultra-deformable vesicle technology [1].

Too bigger molecules also can be crossed easily in the form of transferosomes. Different therapeutic molecules like insulin, interferon can

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be delivered into systemic circulation easily across the intact mammalian skin.

Small molecule drugs can also be formulated in the form of transferosomes, which have certain physicochemical properties which would otherwise prevent them from diffusing across the barrier. one more application of transferosomes is the ability to deliver the drug to peripheral subcutaneous tissue.

1.2 Advantages of Transferosomes [2]

1. Direct availability of the drug to the target site.
2. Increase patients compliance by painless administration and Non-invasive delivery.
3. Bypassing the hepatic metabolism there by devoid of systemic toxixcity when compared to commercially available products.
4. Lower-drug plasma fluctuation.
5. Localised site specific delivery.
6. At higher temperatures these are in a liquid crystal state and have low transition temperature.

1.3 Disadvantages

Disadvantages of liposomes and niosomes are the following:

a. They are not suitable for transdermal delivery because they cannot reach the deeper layers of the skin as they are trapped in the superior layers of stratum-corneum.
b. Though vesicular systems assure targeted delivery, in most cases the liposomal or niosomal category vesicles do not achieve the desired transdermal penetration.

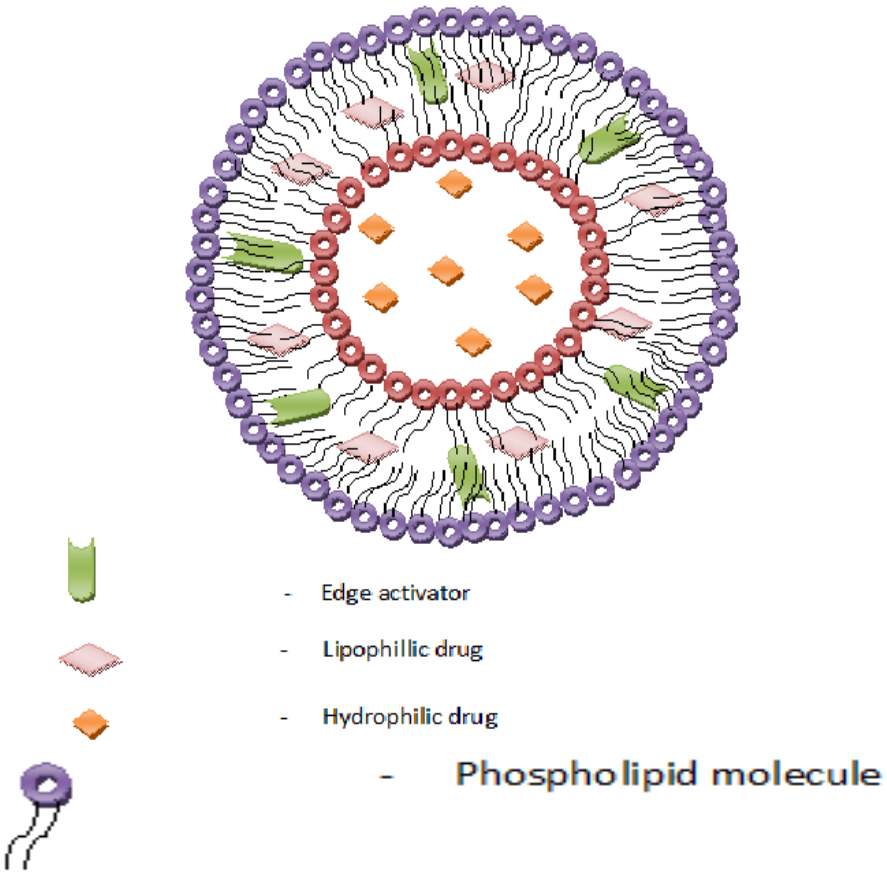

Table 1. Literature on transferosomes

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
1.	ovalbumin and saponin [3] ovalbumin-45 KDa, saponin- 1223.3 g/mol KDa, lipophilic , log p value of ovalbumin= saponin=1.17	Anti-ova antibody titre in serum	-	formulated various vesicular formulations including liposomes, transferosomes and ethosomes of saponin and albumin. Best formulation was selected based on protein encapsulation, for their transdermal immunisation in mice and stability studies.	Soya phosphotidyl choline, cholesterol, tween-20, sodium cholate, serum albumin.	From the results they concluded that from all vesicular formulations ethosomal formulation had showed greater concentration of specific antibody in the serum sample. Based on the zeta potential , particle size and PDI over a 2-month storage ethosomal formulation was more stable.
2.	Diclofenac sodium [4] 318.1 g/mol 0.7 hydrophillic	NSAID	VOLTARE N GEL	developed liposomes and transferosomes of diclofenac sodium , tested for controlled release properties and integrity (structural and functional) after administration by using liquid jet injector (subcutaneous route)	soyphosphotidylcholine,polysorbate-80, ethanol	In particular improvement of bith the efficacy and safety of localised therapy ,having characteristic performace of painless liquid injection diseases.
3.	osthole [5] 244.28g/mol 3.95 lipophillic	anti-fibrotic , anti-inflammatory	-	osthole loaded vesicular formulations like liposomes, ethosomes and transferosomes were prepared, tested for their characteristic properties	Soya phosphotidyl choline, tween 80, methanol	results clearly indicated that osthole loaded ethosomes showed enhanced transdermal flux of 6.98±1.6 µg/cm^2/h and a decreased lag time

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation		Study conducted	lipid and edge activator used	Result/Observation
					and for invitro , invivo permeation studies.		of 2.45 hours across porcine ear skin. Pharmacokinetic parameters AUC & Cmax were increased in ethosomes, when compared with other vesicles.
4.	Itraconazole [6] 705.6g/mol 5.66, lipophillic	Antifungal	sporanox	film dispersion method	Nano-transferosomes loaded with itraconazole were prepared by using three different types of edge activators in varying concentration and characterised. From that best formulation was selected, co-spray dried with mannitol, further , tested for aerodynamic properties and aerolisation efficiency of dry powders.	lecithin,span-80	Results showed that narrow distribution pattern was found with lecithin:span80 in the ration of 90:10. Particle size did not significantly influenced by different types of surfactants upon evaluation of co-spray dried formulations with different concentrations of mannitol, 1:2ratio of transferomes ;mannitol(w:w)showed the best aerolisation efficiency.
5.	timolol maleate [7] 432.5 g/mol log p=1.44 lipophillic	non-selective, β-adrenergic receptor antagoni	timolol XE-gel.		timolol maleate loaded transferosomes were prepared, to check the deformability properties of unlike timolol prepared by extrusion technique.	tween-20, egg L-α phosphotidyl choline, sodium deoxycholate, stearylamine.	From the results TM-loaded transferosomes may have improved transmittance through cornea and better /improved bioavailability compared to

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation		Study conducted	lipid and edge activator used	Result/Observation
		st.					conventional TM therapy.
6.	piroxicam [8] 331.3 g/mol logp= 3.06 slightly lipophilic drug	NSAID	PX-TRS GEL	Rotary – evaporation sonication method/thin film hydration technique	double loaded transferosomes with non-complexed piroxicam as well HP-βCD piroxicam were developed and characterised. Invitro and ex-vivo tests were performed to assess the permeation and lipid peroxidation studies. *Invivo* studies were performed in rat paw edema model to assess % inhibition of paw edema.	phospholipoin 90G ,sodium deoxycholate, phosphotidyl choline	Results clearly indicated that double loaded piroxicam transferosomes showed at the site of inflammation maximum localisation of drug , in comparison to conventional dosage forms. from ex-vivo results permeability co efficient was $15.68X10^{-3}$(cmh^{-1})and flux of 23.53($\mu gh^{-1}cm^{-2}$),got good result in comparison in comparison to marketed gel.
7.	asenapine maleate [9] 401.8 g/mol log p=4.9 lipophillic	antipsychotic drug	saphris	thin film hydration technique.		Soy phosphotidyl choline,sodium deoxycholate, triethanolamine	greater skin permeation enhancement was shown by transferosomes with ethanol(20%v/v) due to the individual effect of ethanol(chemical enhancer) transferome asenaline maleate permeated after 24h(Q24). Invivo pharmacokinetic study proved increase in bioavailability on

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						transdermal application compared with the oral route.
8.	ketoprofen [10] 254.28g/mol 3.12 moderately lipophilicity	NSAID	fastumgel	They compared the effect of ketoprofen in three different formulations ketoprofen loaded in transferosomes, oral ketoprofen, and drug free sequessome vesicles in reducing pain arised due to muscle twinge in the young ones of cow healthy individually after exercise involving getting down from the steps. the selected design was randomised, double – blind controlled phase-II study.		the results clearly indicated that ketoprofen in transferosomes form and sequessome form was more effective in comparison with oral ketoprofen. Joint pain associated with osteoarthritis was effectively treated by the ketoprofen and drug free sequessome vesicles.
9.	emodin [11] 270.24 g/mol log =3.82 hydrophillic	purgative , laxative	film ultrasonic dispersion technique.	in this study they have taken 60 male rats.blood parameters like fasting blood glucose and serum blood levels were determined after an 8-week treatment . By light microscopy technique they evaluated adipose tissue section, cellular diameter and quantity of adipocytes. Reverse	lecithin,deoxycholic acid,sodium salt,cholesterol	From the results they concluded that mutually antagonistic effects, down regulation of GOS2 protien expression and upregulation of ATGL protein expression of adipose tissue collaborate /coactions joint work to reduce the obese rats body weight. transferosomes loaded

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				transcription polymerase chain reaction assay method was used to determine the m-RNA expression of ATGL and GOS2 from peri-renal fat tissue.		with nano emodin might decrease body weight peripheral fat content, increase serum HDL-Cholesterol, pathological change of fatty liver, reduce TG-levels and adipocyte mass.
10.	capsaicin [12] 305.4 g/mol log p= 3.04 hydrophillic	antiarthritic agent	zostrix cream	prepared capaicin loaded transferosomes were tested for antiarthritic efficacy in rat models.the results of the capsaicin transferosomes were compared against marketed gel, therma gel (standard reference formulation)	phosphotidylcholine, ethanol,tween80	
11	diclofenac sodium [13] 318.1 g/mol 0.7 hydrophillic	NSAID	Cambic	diclofenac sodium , a poorly water soluble drug loaded into transferosomes, liposomes and ethosomes to enhance the permeation through the skin. Gel was prepared with these vesicular systems using 1%carbopol gel 914 gel.	soyalecithin,span-80,cholesterol,ethanoland carbopol-914.	results clearly indicated that out of all vesicular systems transferosomes and ethosomes showed a greater amount of cumulative permeation ,flux in steady state , permeability coefficient and residual drug into skin compared with conventional gel, conventional liposomes or hydro-ethanolic

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						solution. upon stability tests these vesicular formulations were stable over 3months of period.
12.	terbinafine [14] 291.4 g/mol logp=6	antifungal	lamisil dermgel	in this investigation researcher studied about the mechanism inviolved in invitro activity of terbinafine in conventional form and transferosome on the morphology of T.rubrum (the main element of onchomycosis) using white light microscopy, scanning –electron microscopy , transmission electron microscopy and got invitro results.		Results clearly stated that terbinafine transferosomes showed effective rapid and extensive ultra strucutal change in T.rubrum hyphae, and complete destruction of hyphae after 24 hrs against conventional terbinafine. after exposure of T. rubrum hyphae to TDT 067 for 30min,terbinafine transferosomes enter the intracellular space of hyphae after 24 hrs. Invivo Studies observed in subungual debris from onchomycosis patients, who went with topical application of TDT 067.
13.	cinnamic acid [15] 148.16g/mollogp= 2.13	anti-inflammatory antioxidant		In this present investigation the researcher compared the release of drug into skin which are loaded in liposomes and transferosomes by using	phosphotidylcholine, sodium deoxycholate	from the results they concluded as concentration of drug on debris from transferosomes are lower when compared to conventional liposomes.

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				dermal microanalysis sampling technique inspray gue-dawley rats.		Pharmacokinetic parameters C_{max} of cinnamic acid from conventional liposomes was found to be 3.21±0.25mg/ml and that from the transferosomes was 0.59 0.02mg/ml after application of cinnamic acid liposomes and transferosomes on abdominal skin region of rats for a period of 10hrs.
14.	terbinafine [16] 307.4 g/mol logp=6 hydrophillic	antifungal agent	nizoral topical	transferosomes facilitates the release of terbinafine to the nail and surrounding tissue. Transferosomal TDT 067 is only the therapy to treat onchomycosis . they reviewed published pre-clinical and clinical studies on the formulation.	TDT067	the study revealed effective mycological cure and clinical effect in a study involving patients with onchomychosis for a period of 12 weeks,TDT067 administered twice daily. A study involving 700 patients treated with TDT067 for a period of 48 weeks may reveal the effectiveness of terbinafine against onchomycosis by phase-III trial.
15.	ketoconazole [17] 531.4 g/mol logp=4.35	antifungal agent	nizoral topical	researcher prepared ketoconazole loaded transferosomes using	lipid film hydration technique.	Investigation revealed that permeation enhancers modify the

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				suitable essential oils to determine the potential of transferosome for transdermal delivery. Transferosomes were incorporated into gel base and evaluated for gel characteristics such as drug content, viscocity, pH, spreadibility, extrudability, homogeneity etc.		barrier to penetration present in skin without itself undergoing any change and also showed better release and permeation of ketoconazole.
16.	curcuma longa [18] 368.4 g/mol logp=3.29	photoprotective		researcher prepared curcuma longa loaded vesicular systems (transferosomes, liposomes, ethosomes), finally prepared cream formulations from these vesicular systems studied for their photoprotective effect by assessment of sebum content(sebumeter) and skin hydration.(cutometer).	ethylalcohol, soyaphosphotidylcholine, cholesterol, ethanol, sodium deoxycholate.	researcher concluded from the results that curcuma longa extract loaded in transferosomes showed better skin permeation properties when compared to ethosomes and liposomes.
17.	Meloxicam [19] 351.4g/mo log p= 3.43	NSAID	Meloxicam 3% gel	researcher prepared meloxicam loaded vesicular systems liposomes, transferosomes studied the effect of different	phosphotidylcholine, cholesterol, sodium cholate, sodium oleate dicetylphosphate	Researchers concluded that as transferosomes with medium length c-carbon chain containing surfactants showed higher entrapment

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				surfactant having varying C-chain length used in preparation of transferosomes.		efficiency, when compared with liposomes and MX-Suspension, transferosomes exibhits better skin permeation.
18.	ketoprofen [20]	NSAID	orudis	ketoprofen loaded in ultradeformable vesicles for epicutaneous application, in aqueous, viscous formulation known as Diractin (formly IDEA-033). It was earlier reported that many NSAIDS were used for long term effects ,safety and efficacy.	sodium heparin	researcher investigated and concluded that as use of Diractin for pain relief upto 18 months provided a good safety and tolerability profile.
19.	ketoprofen [21]	NSAID	vopac	In this research investigator compared the invivo transport and biodistributionof ketoprofen through oral route (oruvail), in transferosomes(diractin) or conventional topical gel.	carbomer, methylparaben, benzylalcohol, ethanol, glycerol, phosphotidylcholine	ketoprofen loaded in transferosomes that was Diractin showed effective /desirable biodistribution and clearance, when compared with others. transport of drug from transferosomes to skin involves carrier mediated drug transport , which gives long acting drug effect periphery.
20.	Tashinone [22] 294.3 g/mol log p= 6.31	Antihyper tensive	film ultrasonic dispersion technique	transferosomes loaded with tashinone were formulated and evaluated for parameters	lecithin, sodium cholate	Results proved that transferosomes showed good entrapment efficiency ,stability and

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				like morphology, content, entrapment efficiency, particle size, polydispersity, and Zeta potential ,stability and deformability.		also highly deformable nature in relation to the molar ration of sodium cholate to lecithin and the external pressure.
21.	18-β-glycerrhetic acid [23] 470.7 g/**mol** **log p=**6.574	dermatitis		prepared 18-β-glycerrhetic acid (poorly water-soluble drug)loaded transferosomes for the treatement of dermatitis. researcher conducted invivo studies in mice.	soyabean phospholipid, sodium deoxycholate, cholesterol.	From *Invivo* – studies they concluded as GA elastic vesicles has showed a better anti-inflammatory activity that is reduction in ear thickness and mass is (25.52& 49.23%)($p<0.05$) when compared with cream available in market.(triamcinolone acetonide &econazole nitrate) which are acted as positive control group. Pharmacokinetic parameters obtained upon application of transferosomal preparation on to mice ear skin were C max at 3hours was and had it effects for 16 hrs even after its removal.
22	catechin [24] 290.27 g/mol logp=1.8	antioxidant	veregen	In this research , they compared catechin loaded liposomes,	L-α-phosphotidylcholine choline,cholesterol,	results concluded as prolonged catechin release was exibhited by

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				conventional transferosomes, transferosomes prepared by reverse phase evaporation (REV) method.	sodium deoxycholate	all liposomal formulation where as transferosomes prepared by REV method showed a best deposition of catechin when compared to normal transferosomes. catechin solution did not exhibited any permeation into ear skin of porcine.
23.	Dipotassium glycyrrhizinate [25] 899.1 g/mol log p value=3.13	anti-inflammatory agent		prepared dipotassium glycyrrhizinate loaded elastic liposomes and observed the release of the KG into the skin for the treatment of acute and chronic dermatitis.	soyalecithin(PC)or hydrogenated soyalecithin	Skin deposition of KG formulated in liposomes was 4.5- fold ore whaen compared to aqeous solution of KG.
24.	ketoprofen [26]	anti-histaminic	zaditor ketoprofen	researcher prepared liposomes and ethosomes of ketoprofen to understood about the possible mechanism of penetration into the skin under non-occlusive condition.	phosphotidylcholine, tween -80	transdermal delivery of drugs by transferosomes might influenced by intact vesicle permeation into stratum corneum and penetration –enhancing effect under non-occlusive conditions , where as incase of ketotifen , penetration enhancing effect was of signifantly important factor.
25.	Quercetin& resveratrol [27]	to reduce subcutan	-	studied to dissolve the subcutaneous fat by	soyaphosphotidylcholine, cholesterol,	result concluded as prepared elastic

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
	poorly water soluble, 302.2 Da log p=1.48	eous fat		using quercetin and resveratrol containing SDC-elastic liposomes as a novel approach.	sterylamine, sodium deoxycholate	liposomes loaded with elastic quercetin and resveratrol, showed suitable characteristic properties and suitable pharmacokinetic parameters when administered through subcutaneous route.
26.	tetanus [28] 3051.6g/mol	vaccine	adacel	Investigator focused on determination of capacities of different vesicular systems loaded with tetanus toxoid in non-invasive delivery.	Soya phosphotidylcholine, sodium deoxycholate span-85	from the invivo results they stated that transferosomes with TT might exhibit an immune response(anti-TT-IgG) that was equivalent to TT administered through IM route for immunisation. when compared to liposomes and niosomes transferosomes produced a greater immune response. So, transferosomes were effective way of delivery of antigen in non-invasive topical delivery.
27.	Metronidazole [29] -0.46	Anti-ameobic	metrolotion	In this study transferosomes with and without metronidazole , liposomes with drug were prepared for administered through	egg phosphotidylcholine, sodium deoxycholate span-80, tween-80.	From the results (epithelial barrier as invitro model) researcher concluded that as permeability of metronidazole in

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				vaginal route .To increase vesicular systems liposomes and ultra deformable liposomes and to improve its trapping tendency and these were characterized in terms of zeta potential,PDI, Particle size distribution and permeability through CaC0-2 cell monolayer.		transferosomes was more effective than with conventional liposomes.
28.	repaglinide [30] 5.9	oral anti hyperglycemic agent	modified hand shaking method	repaglinide transferosomes were prepared by using various concentrations of tween 80 and span80.these transferosomes were incorporated into carbopol 930 gel base stability studies were performed on optimized gel formulation.	soyalecithin,tween-80,span-80	In view of the research data they conclude that RT-6 formulation which contains lecithin:span-80in the ratio 85:15(%w/w),incorporated in 2%carbopol gel had showed best drug release and good entrapment efficiency.
29.	mefenamic acid [31] 5.12	NSAID	modified hand shaking method, thin film hydration technique	Researcher prepared transferosomes loaded with mefenamic acid by using varying concentrations of phospholipids to surfactant and compared its characteristic properties and invitro	soyalecithin, span-60	among all the formulations T10 formulation showed greater drug content, entrapment efficiency, and invitro diffusion, with the composition of phospholipid :surfactant 2:1 ratio with the T10

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				release from the optimised formulation they prepared by incorporation into carbopol gel base of 1% & evaluated and compared with plain marketed gel.		formulation ,prepared gel and composition of transferosomal gel with marketed gel ,best results were observed with transferosomal gel.They also revealed that with increase in concentration of surfactant effective increase in entrapment efficiency of lipophillic drug has taken place.At last they concluded that repaglinide was efficiently permeated through skin, prolong the drug release and improve site specificity.
30	Isotrenetoin [32] 5.66	retinoid		transferosomes were prepared with isotrenetoin a poorly water soluble drug by varying concentration of surfactant span80.optimised formulation was incorporated into gel base .gel was evaluated for its evaluation like ph, viscosity, skin irritation study, spreadability and	phospholipoin 90 H	study revealed that transferosomal gel prepared was stable with all desired properties and complied within the range of results.

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				skin permeation study.		
31.	Thiocolchiside [33]	anti-inflammation analgesic		Investigator prepared various vesicular systems loaded with thiocolchicide by different methods and determined the entrapement efficiency , zetapotential ,vesicular size, invitroskin permeation and stability. these vesicular systems were compared with marketed thiocolchicide gel.	phospholipoin90 tween80 ethanol methanol chloroform	Investigation concluded the thiocolchiside ethosomes had performed greater entrapement efficiency, higher cumulative release of drug permeation (90±5%) after 24hrs.when compared to other liposomal and transferomal formulations. thiocolchicoside loaded ethosomes had effective treatement to musclerelaxant activity and this was concluded from pharmacodynamic studies.
32	miconazole nitrate [34]	antifungal drug	thinfilm hydration technique	researcher prepared 8 miconazole loaded transferosomal formulation using the multilevel 3-factorial design. studied the effect of indepent variables i.e., type of surfactant, total lipids and phospholids on dependent variables i.e.,vesicle size ,		out of all 8 formulations,f6 showed high transdermal flux of105.42±1.08, vesicle size of 84.5±0.684, entrapment of 67.98±0.66. Zone of inhibition for (55mm) MIC transferosomal gel was found to be greater than daktarin cream2%(50mm)

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				entrapement efficiency and flux. optimised formulation was selected and incorporated into carbopol 934 gel base. This transferosomal gel was compared against marketed cream2% i.e.,daktarin using model disease candidiasis. Invivo studies were conducted onimmunosupressed albino rats. histopathological studies were performed to characterize inflammation symptoms.		antifungal activity of the miconazole nitrate loaded transferosomal gel was found to be effective in comparison to marketed cream. from the above studies researcher concluded that in optimisation of miconazole nitrate formulation multilevel design had played a key role and antifungal activity was effective with miconazole transferosomal gel in comparison to marketed cream.
33.	lornoxicam [35] 2.62	NSAIDS	thin film hydration technique	research aimed at preparation of lornoxicam loaded transferomes for better therapy by varying concentration of sodium deoxycholate and soyalecithin by thin film hydration technique further , transferosomes were tested for invitro diffusion ,particle size analysis, zetapotential.	soyalecithin,sodium deoxycholate, chloroform,methanol .	from the results they concluded that as drug release from all formulation, followed first order kinetics with mathematical modelling higuchi mechanism respectively. high stability was observed with f8 formulation having the particle size of 106.7mm & zetapotential of -

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						27.6m2 indicating good stability.
34	sumatriptine succinate [36] 0.74	anti-migraine property		research focused on preparation of sumatriptan succinate loaded transferosomes and incorporated it into gel base,for the treatement of migraine.gel was formulated using Placket-burmann series and studied the effect of sonication on size of transferosomes. The gel was tested for irritancy on animals.	phospholipid-soyalecithin,propylene glycol,ethanol.	out of all formulations F5 formulation was found to be the best, with vesicle size of 3048.80nm, polydispersity index 2.316nm, zetapotential 1.9mv, spherical vesicle shape, 92.71%drug entrapement efficiency and 97.65%cumulative drug release.
35.	sildenafil citrate [37] 1.8	vasodialator	rotary evapouration &sonication method,vertexing and sonication technique.	In this researcher prepared ultra deformable vesicles loaded with sildenafil citrate by using three different categories of surfactants i.e., anionic, cationic, non-ionic at varying concentrations and studied about physicochemical properties invitro, exvivo drug release characteristics and release kinetics,	phospholipoin 90G,soyabean lecithin, phospholipid, chloroform, cetrimide, SLS,Tween80, Span80	from the result they revealed that when compared to span80, tween80, performed better results in aspects of EE%,PS, PDI, invitro and exvivo permeation might be due to physicochemical properties of drug and edge activator employed. outof T80 containing SC loaded transferosomes, SC-TS3 permeated 99%of drug over 6hour

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				permeation studies and stability studies of best selected formulation from the three different categories of SC transferosomal formulations at 25^0C& 4^0 C		invitro condition&9hours of exvivo permeation studies. out of spa 80 containing SC loaded transferosomes,SC-TS7 permeated 93.62% of drug in 6hours duration and invitro 76.29% of drug permeated in exvivo condition over 9hrs duration/period. In SC-transferosomes containing anionic surfactant S C-Ats2 permeated 69.03% of drug over a 6hours invitro&99.90% of the containing drug during exvivo permeation studies. Improved flux was observed through male Sprague dawley hairless rat skin were 152.68%,117.6%114.6%, 149.39%&143.68% respectively by SC-TS3, SC-TS7,SC-Ats2& SC-CTS1 when compared to drug solution. from the stability data they

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						concluded as prepared formulae were generally stable.
36	Doxorubicin hydrochloride [38] 0.53	anti-cancer	DOXIL	In this research delivery of drug to lymphatics by a novel hyaluronic acid modified transferosomes were studied on tumour cells. Improved uptake of transferosomes by tumour cells was because of the hyaluronic acid.	sodium deoxycholate,lecithin	study showed that enhanced absorption and penetration of DOX-loaded HA-GMS-T into deep skin tissue and decreased organ toxicity. A new approach for metastatic tumour therapy through lymphatic drug delivery with transdermal nanomedicine.
37.	5-flourouracil [39] -0.89	cytotoxic	fluroplox	in this study transferosomes loaded with 5-fu were prepared by using two different edge activator. these 5-FU transferosomes were incorporated in 1% carbopol940 to compare its anticancer activity with marketed gel formulation available for treatment of skin cancer.	Tween-80,span-80,edge activator	on the basis of vesicle size and entrapment efficiency ,tween-80 performed better results, when compared with span-80. compared with marketed formulation ,transferosomal gel was able to perform greater invitro skin permeation and skin deposition of 5-FU.comparable transdermal flux was 21.46mg/cm2/h and maximum skin deposition was found to be 81.3%

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						by transferomes.
38.	raloxofene hydrochloride [40]	treatement of osteoporosis/selective estrogen receptor modulator		for this study researcher selected drug which is having poor bioavailability for preparation of transferosomes. Box-Behnken experimental design was implemented for optimisation of best formulation.	phospholipoin 90G, Sodium deoxycholate	Raloxifene hydrochloride loaded ultradeformable vesicles showed relevance increase in terms of concentrations of drug permeated &deposited in the skin with increment ratios of 6.25 1.50&9.25 2.40 respectively when compared with conventional liposomes & as an ethanolic solution of raloxifene hydrochloride. Ex-vivo results concluded as there was a clear change in skin structure from DSC-results compared with control sample. CSLM study confirmed permeation to a depth of approximately 160µm , by coumarin 6-loaded transferosomes, as compared with rigid liposomes.
39	celecoxib [41]	NSAID	celecoxib topical	researcher developed celecoxib loaded transferosomes,	tween-20,ethanol	penetration of drug into the skin through these vesicular systems

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				liposomes &ethosomes with suitable edge activator and surfactant respectively.		significantly more with respect to aqueous suspension, from
40	vinblastine [42]	neoplastic		In this study vinblastine liposomes and transferosomes were prepared by thin film hydration technique by using lipids dimiristoyl phosphotidyl choline with cholesterol and the same lipids with sodium cholate respectively.	dimiristoylphosphatidylcholine, dipalmitoylphosphatidylcholine,cholesterol, sodium cholate	encapsulation of drug into these vesicular systems were found to be 98% in liposomes when they used drug/phospholipid ratio from 0.17 to 0.18, where as with transferosomes encapsulation was found to be 50-80% when they used drug/phospholipid molar ratio from 0.05 to 0.09.however retention of drug in liposomes and transferosomes was found to be dependent on time term. from cell line study results they also stated that free vinblastine showed 2-fold high activity as compared to vinblasin liposomes.
41	pergolide [43]	dopamine agonist		pergolide transferosomes were prepared by using bilayer forming surfactant L-595(sucrose laurate ester), micelle forming surfactants, stabilisers.	sucrose larylester, octaoxyethylene laurate ester,sulfosuccinate.	Investigation revealed that there was 6.2 fold increase in steady state flux of pergolide transferosomes with that of rigid vesicles.

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				series of elastic vesicles were visualised using cryo-TEM and characterised for size, stability & invitro release studies. These elastic vesicles were compared against saturated buffer solution.		Research also concluded that because of these ingredients bilayer forming surfactant, micelle forming surfactant and stabilizer there was the best balance observed between the drug solubility, stability, elasticity. These ingredients had a major effect on physicochemical properties of the transferosomes.
42	loratadine [44]	antihistaminic drug	conventional thin film hydration technique	loratadine loaded transferomes were prepared and incorporated to mucoadhesive gel. For optimisation of transferosomes they used QBD approach that involves placket-burmann design for screening of formulation followed by constrained simplex centrid design for optimization of twwen-80/span-60/span-80 mixture.	Phosphotidyl choline, sodium cholate, sodium deoxycholate, poloxamer-188, Isopropyl myristate ,span-80, tween-80, tween-20,carbopol-940.	LTD transferosomes proved to be superior to control interms of permeation , percentage release , mucoadhesive time.

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation		Study conducted	lipid and edge activator used	Result/Observation
43	curcumin [45]	aromatic stimulant		rotary evaporation sonication mehod	In present study curcumin loaded transferosomes were prepared by using rotary evaporation sonication mehod, and compared it against pure curcumin ointment.	soyalecithin,tween-80,chloroform, ethanol	Tensile strength of pure curcumin ointment and curcumin transferosomes were found to be 665g and 654 g respectively. Hydroxyproline content was observed higher with group treated with transfeosomal curcumin in comparison to pure curcumin ointment. Epithelialisation period results in incision wound model in rats was found to be 16.13 ±0.4773& 17.33± 0.4944 for curcumin in transferosomes and pure curcumin ointment respectively.
44	enrolfloxacin [46]	synthetic anti bacterial agent			enrofloxacin loaded transferosomes were prepared to treat leishmaniosis. This was compared against enrofloxacin in solution over leishmanial Mexicana promastigotes. these transferosomes were characterized in terms of size, PDI ,zetapotential,		Enrofloxacin transferosomes had greater leishmanicidal activity than other flouroquinolones moxifloxacin, ciprofloxacin ,levofloxacin. concentration of flouroquinolones used for effective leishmanicidal effect were found to be

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				entrapment percentage, dissolution profile & physical stability.		20.00µm to 19, 5µ,50.000µM to 781 µM, 616.425 µM to 1.203 µM for enrifloxacin, ciprofloxacin, moxifloxacin and meglumine antimonite.
45	ketoconazole [47]	solvent evaporation method		ketoconazole loaded transferosomes were formulated and best formulation was found out from those formulation by using Box-behnken design. These optimized transferosomes were incorporated into gel base and gel was characterised for invitro, exvivo and antimicrobial evaluation.		Cumulative release of drug was found to be 97% and 74% respectively for transferosomal gel and suspension of ketoconazole. transdermal flux of ketoconazole suspension gel was found to be 3 times lesser with that of ketoconazole transferosomal gel. Minimum inhibitory concentration of ketoconazole transferosomal gel was found to be 4.57-4.6 µg/ml against candida albicans. from the overall studies transferosomal gel of ketoconazole had showed better antimicrobicidal activity,

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						negligible sign of toxicity and irritation.
46	sertraline [48]	antidepressant	rotary evapouration sonication method	researcher selected drug poorly soluble drug sertraline for preparation of transferosomes to overcome the problems in oral drug delivery. different transferosomes were prepared by varying concentrations of drug & edge activator optimized formulation was selected incorporated into gel base. Transferosomes were tested for highest entrapment efficiency and for appearance of crystals over of period of 14days. Transferosomal gel was compared against control gel, transferosomal suspension and drug solution. Invivo studies were performed using modified forced swim model test. Exvivo studies were also performed on transferosomal gel, transferosomal suspension.	soyalecithin,span-80,ethanol.	Investigation revealed that presence of ethanol in transferosomes increases the entrapement efficiency ,fluidity and EL-SP4 optimised formulation containing gel showed asignificantly higher ($p<0.05$) cumulative amount of drug permeation and transdermal flux. transferosomal gel had shown better effect owing to the higher viscosity imported by the gel. Hence they concluded as that transferomal sertraline can be used as a substitute for oral sertraline with no side effects. transferosomal gel (EL-SP-4) decreased the time immobility /depression, it was found to 0.323 min. immobility. transdermal flux for ELSP4 was found to be

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						0.119±2.67µg /h/cm2 had for transferosomal gel was found to be 0.114±2.5767µg /h/cm2 .
47	bifinazole [49]	antifungal drug		In this study researcher selected class-4 drug bifinazole for preparation of transferosomal gel to cure /treat the superficial fungal infections.by using various concentrations of various surfactants ,transferosomes were prepared .cholesterol was added to increase the stability of transferosomes.	soyalecithin,span-60,span-80,tween-80.	out of five formulations of bifonazole transferosomes , transferosomes with span-60 showed best results with high entrapment efficiency of 94.8% for formulation F2. The same f2 formulation had showed best invitro drug release ,permeability and stability(upon addition of cholesterol.)
48	pentoxyfilline [50]	anticoagulant	modified vertexing sonication method	researcher selected the drug pentoxyfilline which has poor oral bioavailability and short half life for preparation of transferosomes by using varying concentrations of edge activators SC,tween21, tween 20, span80, span 20 with different lipid components. Also performed invitro & invivo evaluation and	sodium cholate , phospholipoin 90G, egg yolk L-α phosphotidylcholine , soybean L- α phosphotidylcholine.	From the results researcher stated that out of 16 formulations F4 had showed good entrapement efficiency of 74.9±1.6 % vesicle elasticity of 146±0.6(mg/s/cm2), zetapotential of 34.9±2.2, average vesicle diameter of 0.69±0.049µm with PDI of 0.11±0.037& permeation flux of 56.28±0.19 µg/cm2/h and

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				characteristic tests on transfersomes.		drug release was found to be 79.1± 2.1% after 10 hours of run. Ex vivivo & in vivo studies proved that F4 transfesomes had showed increased PTX-absorption& prolonged its half-life comparing to commercial oral-SR-tablets.
49	azathioprine [51]	. immunosupressant	rotary evapouration technique/thin film hydration technique	Research optimised azathioprine loaded transferosomes by trial and error design .stability studies were performed at different storage conditions and studied about effect of surfactant on experimental results.	phospholipoin90G ,span80, tween 80,hloroform, ethanol.	They concluded that increasing the concentration of edge activator increases the deformability of transferosomes optimised transferosomes were suitable for transdermal delivery of azathioprine and they also stated prepared transferosomes were stable at refrigeration condition.
50	papaverine hydrochloride [52]	vasodialator		In this study , researcher focus on preparation of papaverine hydrochloride loaded vesicular system that is ultradeformable vesicle transferosomes for the diagnosis and	soyabean phosphotidylcholine, cholesterol, sodium deoxycholate,sorbitan monosterate	From the overall results out of 9 formulations T3 had showed best effects in all its characteristic properties like entrapement efficiency particle size,

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				treatment of erectile dysfunction. Different deformable liposomes were formulated using varying concentrations of sodium deoxycholate,span60 &Brij35. Best formulation was selected and incorporated into 2% w/v hydroxypropylmethylcellulose hydrogel base. clinical investigation was performed on nine men (age between 32-60years) for 11day period. Results were determined using color flow Doppler ultrasound model.		zetapotential 72% ,220nm& -33.4mV respectively, T3 released 73% of total drug content with 2hrs. Clinical evaluation results were found to be as increase in peak systolic flow velocity from 5.95cm/sec to 12.2 cm/sec, increase in cavernous artey diameter from 0.53 mm to 0.78mm. Atleast from the above results , research concluded that PH transferosomal gel could be used successfully in treatment of erectile dysfunction .
51.	Insulin [53]	antidiabetic	conventional rotary evapouration technique	In this present study researcher focused on formulation of insulin loaded nanocarriers for hypoglycaemic effect to overcome the problems trelated with its subcutaneous delivery. pluronic F-127 was used as gel base and iodophor as chemical enhancer.	soyalecithin,sodium cholate, methanol,chloroform	From the research study researcher concluded that insulin was successively entrapped and cumulative percent drug release was found to be 83.11±3.782) . The use of chemical enhancer iodhophor could be helpful in

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				Invitroand invivo studies were carried out by using cellophane membrane ,animal models rats and hairless goat abdomen skin by franz-difussion cell.		moderate delivery and enhance transport of large peptide insulin by its peculiar action on vessel wall. At last they concluded that insulin transferosomes were also potential carrier for transport of insulin through skin when compared to insulin injection.
52	methotrexate-entrapped oleic acid containing deformable liposomes [54]	psoriasis	conventional rotary evapouration technique	In the study, the physico-chemical properties and in vitro release characteristics of this formulation have been investigated	phosphotidylcholine, oleic acid	Investigator reported that penetration of methotrexate ultradeformable liposomes was due to elastic nature of oleic acid.
53	Imperatonin [55]	multipurpose Chinese medicinal plant	conventional rotary evapouration technique	researcher formulated transfeosomes of imperatonin (cationic – UDL s, anionic- UDL s and conventional liposomes by conventional rotary evapouration technique.	phosphotidylcholine, dicetyl phosphate, stearylamine.	Researcher concluded that cationic transferosomes of imperatonin has shown desired therapeutic effect for treating skin inflammation or bacterial infection with low quantity of drug, that could be due to positive charge modification of UDL s.

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation		Study conducted	lipid and edge activator used	Result/Observation
54	Indinavir sulphate [56]	Anti HIV drug		conventional rotary evapouration technique	researcher prepared indinavir sulphate loaded transferosomes by using different edge activators and investigated certain characterization parameters.	phosphotidylcholine, sodium deoxycholate, sodium cholate, tween80, span80.	Researcher observed enhanced transdermal flux(8.91± 0.9 µg/cm^2/hr) and decline in lag time(0.9hr) for indinavir sulphate. Researcher also concluded that as sodium deoxycholate has shown equivalent effect as that of span80,tween80 and sodium cholate.
55	caffeine [57] -0.55/-0.24	CNS stimulant		conventional rotary evapouration technique	here, researcher formulated caffeine vesicular systems and compared the ability 0f these vescular systems to deliver hydrophilic drug caffeine into and through excised skin.	dilauroyl-L- α – phosphotidylcholine) oleic acid, eucalyptol, ethanol and cholesterol .	Here researcher checked all characterisation parameters like PDI,PSD, zeta potential, encapsulation efficiency, skin permeation studies and concluded as penetration enhancer is not an important operating factor in the vesicle component.
56	tacrolimus [58]	immunosuppresant		thin film hydration and dispersion technique	researcher formulated tacrolimus loaded transfersomes and compared that with commercial tacrolimus ointment and liposomal gel of tacrolimus gel invitro and invivo.	Lipoid E80, sodium cholate, Tween80,vitamin E	Investigator concluded that transferosomes loaded with tacrolimus has shown to be proved better skin permeation results hence confirmed better in comparison to liposomes.

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation		Study conducted	lipid and edge activator used	Result/Observation
57	buspirone hydrochloride [59]	anxiolytic		thin-layer evapouration technique	formulated trasfersomes with hydrophilic drug ,buspirone hydrochloride by using tween 80 and oleic acid as a transdermal permeation enhancer and for hydration of dry film had used distilled water or hydroalcoholic solution.	egg phosphotidylcholine, tween80,oleic acid	has shown better permeation physical stability,and precise dosing of hydrophilic drug.
58	eprosartan mesylate [60]	anti hypertensive		thin film hydration technique	eprosartan mesylate loaded ultradeformable vesicles were formulated ,evaluated and compared against liposomes in wistar rat skin.	phospholipoin 90G, span80, sodium deoxycholate	The optimized nano-transfersomes formulation showed vesicles size of 108.53 ± 0.06 nm and entrapment efficiency of 63.00 ± 2.76%. The optimized nano transfersomes provided an improved transdermal flux of 27.22 ± 0.29 mg/cm2 /h with an enhancement ratio of 16.80 over traditional liposomes through Wistar rat skin.here from this research study researcher stated that as concentarion and nature of edge activator has direct effect on characeristic properties of transfersomes and

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
						confirmed that transfersomal application of eprosartan mesylate was proved to be better route.
59	embelin [61]	antineoplastic and antimalarial	thin-film hydration technique	emnelin loaded transferosomes were formulated by using span 80 and tween80 and optimized formulation was incorporated into carbopol934 gel base.	span80,tween80	researcher projected that as emnellin transferosomes were potential vesicular systems for treatment of skin cancer.
60	telmisartan [62]	anti hypertensive	conventional rotary evapouration technique	telmisartan transferosmes were formulated by taking 64mg of soyaphosphotidylcholine and 4mg of sodium cholate	soyaphosphotidylcholine , sodium cholate	Results obtained from transferosomal gel has shown a flux of 0.478 ± 0.001 mg/cm^2/h and permeability coefficient of 7.982 ± 0.15 × 10^{-2}cm/h with 8 folds increase in transdermal flux. histology and DSC of rat abdominal skin were carried to know mechanism of enhancement and elucidated .. Pharmacodynamic study performed on albino Wistar rats projected prolonged release of drug through transferosomal gel.

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation		Study conducted	lipid and edge activator used	Result/Observation
61	doxorubicin loaded hyaluronic acid modified transfersomes [63]	anti cancer		thin-film hydration technique		lecithin, sodium deoxycholate	results concluded that transferosomes were efficiently absorbed by lymphatics and shown improved uptake by cancer cells.
62	Tamoxifen [64]	anti psoriatica and treatement of breast malignancies		thin-film hydration technique	*formulator encapsulated tamoxifen in the new generation* phospholipid-based vesicular and micellar systems, i.e. flexible membrane vesicles (fmvs) and pluronic lecithinized organogels (plos).	span80,	Results revealed that.antipsoriatic activity on mice tail significantly higher ($p < 0.01$) efficacy of TAM–FMV gel (i.e. 35.8%) and TAM–PLO (i.e. 24.6%) vis-à-vis the conventional TAM–hydrogel (i.e. 10.2%) and also projected that tamoxifen can be used effectively for treatment of psoriasis along with treatment of breast malignancies.
62	vincristine [64,65]	cytotoxic		thin-film hydration technique		lecithin, sodium deoxycholate	Has shown good targeting at lymphatics and increase in skin permeation.
63	zinc phthalocyanine (ZnPc) and the nitrosyl ruthenium complex $[Ru(NH.NHq)(tpy)NO]^{3+}$ (RuNO) [66]	photosensitizers			Investigator formulated zinc phthalocyanine (ZnPc) and the nitrosyl ruthenium complex $[Ru(NH.NHq)(tpy)NO]^{3+}$ (RuNO)loaded transferosomes by using	dioleylphosphocholine (DOPC),tween80, dimyristoylphosphocholine (DMPC)	Results concluded that transfersomes showed 6 times better in vitro permeation through fresh pig ear skin than liposomes. Atleast formulator projected as

S .No	Drug ,molecular weight ,nature and log p value	Drug category	Marketed Formulation	Study conducted	lipid and edge activator used	Result/Observation
				unsaturated and saturated phospholipids DOPC ,DMPC respectively ,compared with liposomal formulation in all characteristic parameters.		novel topical UDLs formulation developed is a suitable delivery vehicle for photodynamic therapy.

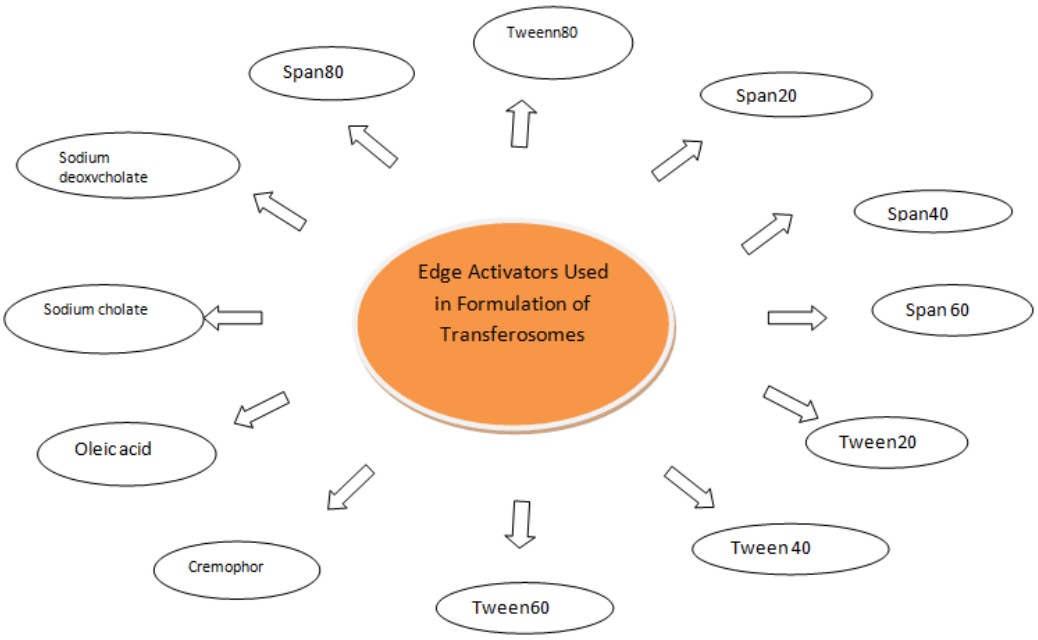

Fig. 1. Edge activators used in formulation of transferosomes

1.4 Ingredients Used in Formulation of Transferosomes[66-69]

For preparation of transferosomes following ingredients are used:

1. lipid polymers
2. Edge activators
3. solvents
4. buffering agents

2. MECHANISM OF PENETRATION

For all topical formulations [70], skin is the most eminent first-line barrier for many drugs. Many researchers have suggested for delivery of drugs into skin transferosomes with or without physical methods.

After application of transferosomal formulation on to skin, it will interact with the skin ,show several sequential steps.

↓

After application of transferosomal formulation, water present in formulation evaporates immediately.

↓

Increase in concentration of non-volatile excipients on skin

↓

Establishment of hydration gradient between skin and transferosomal vesicles after reaching saturation level.

↓

Water present in uppermost layer of skin increases to 10-30% and in epidermis it is75%

↓

Hence there is a development of trans epidermal hydration gradient between upper layer and inner viable epidermis.

↓

Due to the high elasticity of vesicle towards water increases , which acts as a driving force to pull the vesicle towards the inner layer of skin, until it has reached the water –rich viable epidermis.

↓

One more interesting /notable sentence about transferosomal vesicles is that without trans-eopidermal hydration gradient vesicles cannot penetrate SC layer and it should be applied only under non-occlusive conditions which helps in increase of hydration gradient.

2.1 Challenges of Transferosomes [71]

Even though transferosomes are having several applications in delivery various categories of drugs to the targeted sites , still researchers are facing some challenges in case of these transferosomes development [72,73].

1. Delivery of hydrophilic drugs and high molecular weight complexes is becoming a big challenge because the outer most layer of skin is of hydrophobic nature

which creates a problem of delivering drug to the inner starta of skin.

2. Stability of transferosomes during their storage

2.2 Salient Features of Transferosomes [74-77]

- Some 20 years ago the only larger than pore aggregates are highly deformable and elastic mixed bilayer vesicles with phospholipids were launched. Penetration of non-ionic synthetic amphiphiles were found to be better when compared to conventional liposomes, but no confirmation regarding crossing across the skin barrier in full.
- Under non-occlusive conditions, transferosomes will rapidly penetrate the stratum corneum and are visible at least down to the stratum corneum viable epidermis junction. These vesicles were found in the channel like structures between keratinocytes.
- Ultradeformable can cross skin barrier completely and with great stability ,overcome the problems with artificial barriers which are with relatively narrow pores without serenity.
- These deformable liposomes can pass through a pore (having a diameter 5-10 times less than their own diameter) due to presence of surfactants in it and will release the drug in controlled rate to the subcutaneous tissue and peripheral tissue. Ultradeformable vesicles have size range of 300nm typically and 5-8 times higher elastic in comparison to conventional liposomes.
- As tranferosomes are having both hydrophobic and hydrophilic moieties there by it can accomdate the drugs with widerange of solubility.log P value is undefined.
- Transferosomes are defined as ultradeformable vesicles (lipid bilayered vesicles) distantly related to liposomes , but they are differed in functionality, as these are highly flexible and adaptable. These are special designed vesicular particles consisting of inner aqueous compartment enclosed by lipid vesicles.
- Vesicles will be formed after spontaneous addition of oils (lipids), edge activator ,organic solvent and drug in polar solvents(including of water).
- Easy transport of transferosomes through the skin is because of presence of edge activator.

2.3 Characterisation of Transfersomes

Vesicle size, size distribution and Diameter of vesicle – Transmission electron microscope technique is generally used to visualise transferosomes [78]. Vesicle size and size distribution can be determined by dynamic light scattering technique.(DLS technique). Vesicle diameter can be measured using photon correlation spectroscopy (or) dynamic light scattering (DLS Technique).

Methods of preparation of transferosomes:

➢ **Rotary film evaporation technique [79]**:

Bangham,invented this method ,employed mostly in the research of multilamellar vesicles. A mixture of phospholipids and edge activator is put together to a solvent mixture (which contains chloroform and methanol) ,pour this mixture into a spherical flask with a narrow neck, which revolved at a thermostatically controlled temperature(above the lipid transition temperature) and reduced pressure.

A thin film of lipids and edge activator is performed on the walls of RBF, is then hydrated with drug solution . this gives rise to formation of bilayered vesicles. By the expulsion of these vesicles through polycarbonate membrane (or) by sonication entreat size vesicles.

➢ **Modified hand shaking method/modified thin film method[80]**:

This modified thin film involves the same basic principle as that of rotary film evapouration technique, but here instead of using rotary evapourator, hand shaking will be done for evaporation of solvent. this method involves the addition of mixture of phospholipids, edge activater(surfactant-non-ionics/biosurfactants)and lipophillic drug to round bottomed flask containing organic solvents. After the formation of clear solution , by hand shaking evaporation of organic solvent takes place concurrently the place the round bottomed flask on water bath maintained at a temperature of range 40-60^0 C. After allowing for complete evaporation of organic solvent for overnight formation of thin film takes place.

Incorporation of hydrophilic drug can be done at this step. Above transition temperature, buffer solution is then added with gentle shaking.

- **Reverse phase evapouration technique[81]**:

Transferosomes were formed by dissolving drug , phospholipids and surfactants(edge activator)in ethylalcohol. At a temperature of 40-45 ^{0} can under reduced pressure in rotary evaporator, the organic solvent is evaporated ; followed by residual solvent removal under vacuum. At room temperature the formed lipid thin film is hydrated with buffer by rotation at 60 rpm for 1 hour.

Multilamellar vesicles are then formed , followed by extrusion , low shear mixing (or) high shear mixing .By centrifugation (or) dialysis membrane we cannot differentiate non-encapsulated material & residual solvents. Addition of edge activator aqueous solution to the lipid organic solution, should be done under nitrogen purging.

- **Vertexing sonication method[82]-**

In phosphate buffer, add surfactant, phospholipids and the therapeutic agent/drug and vertexed until the formation of milky suspension takes place. This milky suspension is exposed to sonication, then suspension is expulsed through polycarbonate membrane. DOTMA cationic transferosomes were prepared by this method followed by extrusion through a polycarbonate (100nm) filter.

- **Ethanol injection method [83]:** This method offers miscellaneous advantages over other, includes simplicity, simplicity, reproducibility and scale up. At constant temperature, aqeous solution of drug is prepared with heating and simultaneous stirring of the solution.

Organic solution is injected into aqueous solution dropwise with precipitation of lipid molecules takes place as the organic solution comes in contact with aqeous solution and form vesicles.

- **Freeze thaw method [84]**:

Involves cycling of formed multilamellar vesicles between very low temperature followed by very high temperature. The prepared suspension should be collected in a tube and in a nitrogen bath (-30^{0} C) for 30sec. About 8-9 times this cycling process must be repeated.

- **Centrifugation technique [85]:**

Basic principle involved in this method is solvent will be evaporated by rotary evaporator and traces of solvent removed under vacuum. Formed thin film is then hydrated in centrifuging at room temperature followed by incorporation of drug at this step. After swelling of vesicles sonication is done at room temperature.

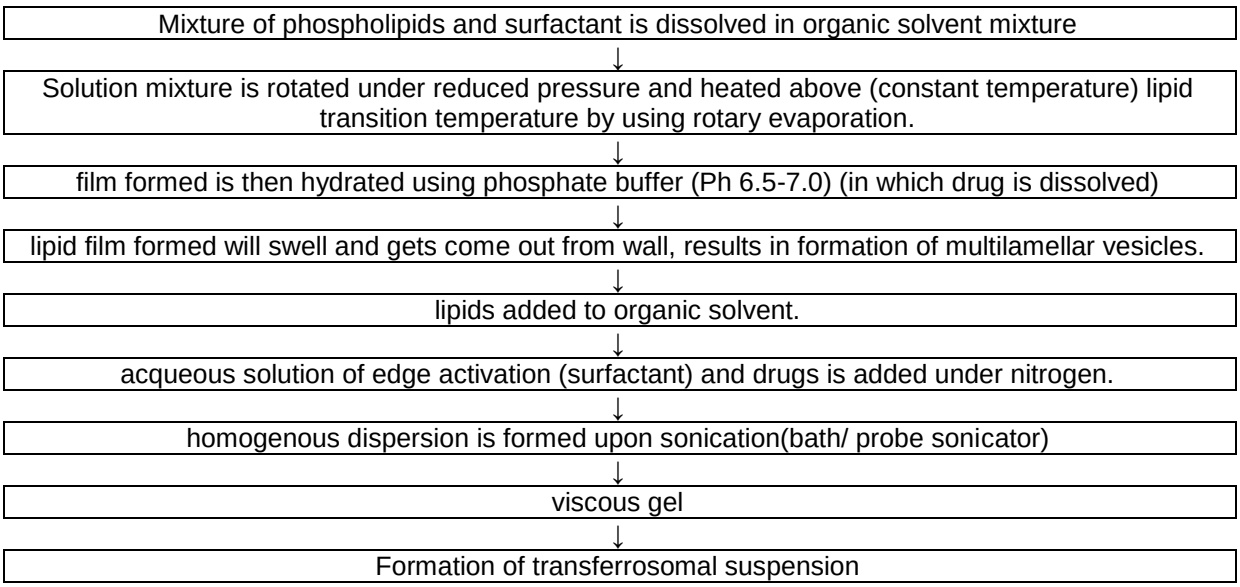

Fig. 2. Reverse phase evaporation technique

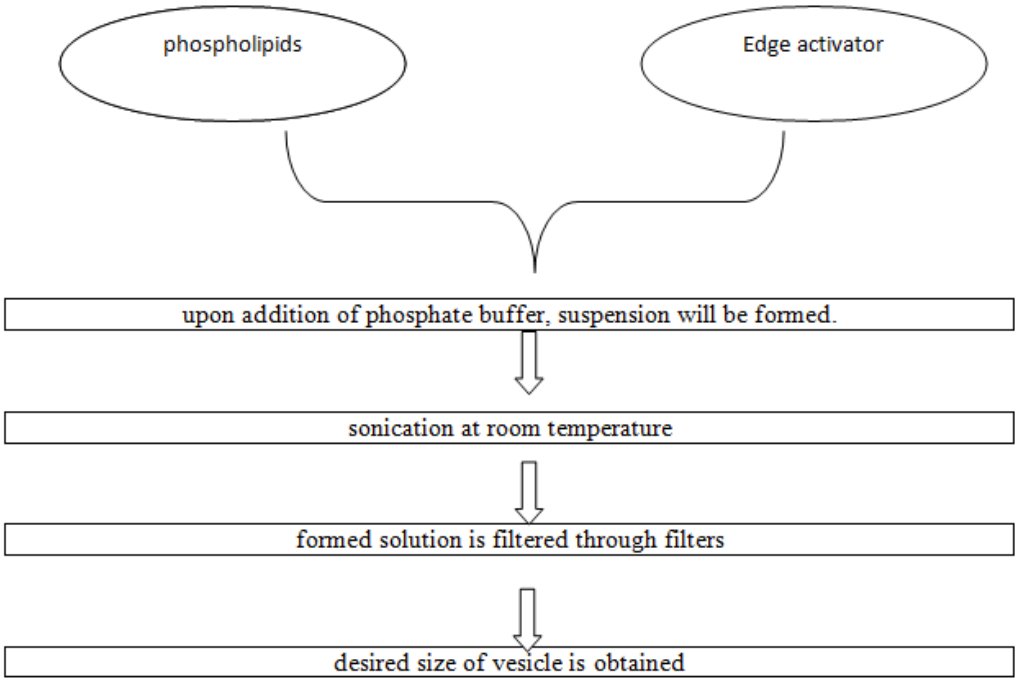

Fig. 3. Vortex sonication method

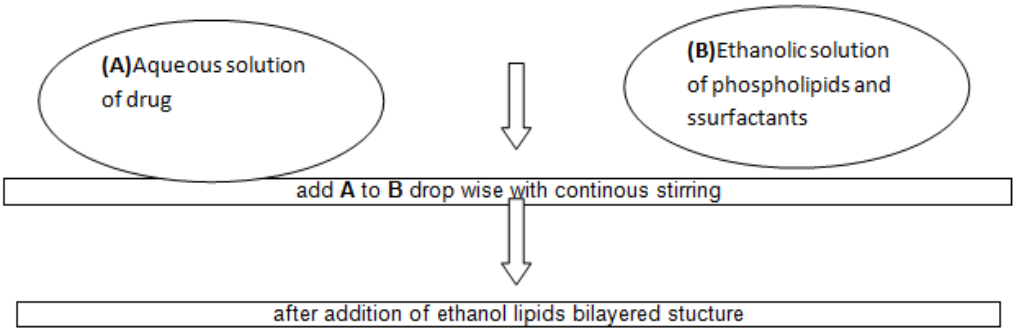

Fig. 4. Ethanol injection method

2.4 In vitro Skin Permeation Studies [86]

Franz-diffusion cell is used for this study .selected membranes are placed horizontally on the receptor compartment .Ideal membrane that is suitable for study of these permeation characteristic of a transferosomal formulation is human skin but its unlimited availability ethical problems make it less attractive for carrying out permeation studies. Even though, there is a significant difference between the results (*In vitro* skin permeation studies) obtained from various skin models such as snake skins, primates, porcine, rat, mouse, guinea pig and human skin are used for *in vitro* skin permeation studies.

Many research reports revealed that the porcine skin and human skin are of the same order of magnitude in terms of fluxes through the skin and concentrations in skin [87] and One more option to carryout invitro skin permeation studies is synthetic membranes (eg: Strat M R) also can be used as it is being more homogenous in permeability, as well as responsiveness in comparison with human and animal skin [8]. Optimum conditions to carryout this invitro skin permeation studies should be compatible with human skin conditions .Here for this inorder mimic blood circulation beneath the skin and temperature receptor fluid of volume 50ml is usually maintained at a temperature 37 ± 0.5^0[9,10].

Table 2. Various lipids that can be used for preparation of transferosomes are represented in following table

S.no	Lipid polymer name	Molecular weight of lipid	Molecular formula	Degree of unsaturation and double bond at c -number	Charge	T_m
1	L-αphosphotidylcholine	313.24	C_{10} H_{20} NO_8 P	Saturated	neutral	$<0^0$C
2	hydrogenated soy(HSPC)	783.77	C_{44} H_{88} N O_8 P	Saturated	neutral	$<0^0$C
3	Phosphotidylserine(PS)	385.304	$C_{13}H_{24}N0_8P$	Saturated	neutral	$<0^0$C
4	Phosphotidylinositol(PI)	886.56	$C_{47}H_{83}0_{13}P$	unsaturated	Anionic	$<0^0$C
5	1,2-doleoyl-3-trimethyl ammonium propane (DOTAP)	698.55	$C_{42}H_{80}CIN0_4$	unsaturated	cationic	$<5^0$C
6	1,2-dioleoyl-sn-glycero-3-phosphate(DOPA)	722.95	$C_{39}H_{72}0_{80}Na$	unsaturated	cationic	$-^{20}$C
7	1,2-dipalmitoyl-sn-glycero-PC(DGPC)	734.1	$C_{40}H_{80}NO_8P$	Saturated	Neutral	41^0C
8	DL-α PC (DPC)	790.15	$C_{44}H_{89}NO_8P$	Saturated	cationic	
9	1,2-dilauryl-sn-glycero-3-phosphocholine(DLPC)	621.437	$C_{32}H_{64}NO_8P$	Unsaturated	cationic	-2^0C
10	1,2-dioleoyl-sn-glycero-3-phosphocholine(DOPC)	786.59	$C_{44}H_{84}NO_8P$	Unsaturated	cationic	-17^0C

Now a selected membrane are usually mounted on the receptor compartment in such a way that stratum corneum should face upwards towards donor compartment.

On donor compartment an appropriate amount of testing formulation is placed on the selected membrane into each donor compartment and top of the donor compartment is opened to mimic non-occluded condition .At appropriate time intervals sample is withdrawn from receptor compartment and examined / analyzed by HPLC or spectroscopic method [88,89] and an equal volume of sample is replaced by fresh receptor medium.

By performing these studies we can calculate transdermal flux [90] of the drugs which is generally expressed in units µg /cm^2/h and can come to know about the factors that increase transdermal flux of the drugs.

We can also predict the information from invivo studies and also for optimisation of the formulation prior to performing more expensive invivo studies [91]**.** Skin retention studies are usually carried at the end of skin permeation studies experiments involves the following steps:

1st step: Skin was washed for five times with ethanol: PBS pH 7.4 (1:1) followed by water to remove drug from the skin surface.

2nd step: skin was cut into small pieces and keep it for homogenisation in same solution composition of 1:1 ratio of ethanol: PBS and left for 6hr at room temperature .now allow the solution for 5min. shaking and centrifugation process at 500 rpm.

3rd step: The drug content was analysed by making appropriate dilutions with buffer solution (pH7.4) using t-test the results are compared with control group.

3. FACTORS AFFECTING PROPERTIES OF TRANSFEROSOMES [92-95]

In order to get optimized formulation of transfersosomes, there is a need to control number of process parameters that could affect the properties of transferosomes.

3.1 Effect of Phospholipid: Surfactant Ratio

As entrapment efficiency, size of vesicle and penetration ability of vesicle is directly affected by lipid and surfactant, so, there is a need to maintain optimized ration of lipid:surfactant. Many researchers reported that the entrapment efficiency gets decreased upon increasing the concentration of surfactant. This may be due to leakage of drug from vesicles, that could be due to increased membrane permeability (structurally membrane contains surfactant molecules)inturn generate pores.

3.2 Effect of Various Solvents

Commonly used solvents are methylalcohol and ethyl alcohol. choice of solvent mainly depends on solubility of formulation ingredients and compatability with the solvent. For formation of film with good stability after hydration there should be a formation of clear transparent solution. solvent added will also contribute penetration enhancement effect by improving drug flux through the membrane. Williams and barry [15] projected and reported that ethylalcohol has shown an increase in flux of different drugs like hydrocortisone, 5-flourouracil, estradiol and levonorgestrol through rat skin Improved drug partitioning in membrane, modification of solubility properties of targeted tissue, enhancement of solubility of drug by acting as solvent and penetration of drug into stratum corneum are these added advantages are contributed by ethyl alcohol. Consequently, By increasing the concentration of ethanol in formulation there will be decrease in entrapement efficiency of drug in vesicle which could be contributed to the increased permeability of phospholipid bilayer. further increase in concentration of drug leakage of entrapped drug takes place.

3.3 Effect of Different Surfactants

Due to change in chemical structure of surfactants, deformability and entrapment efficiency of these transfersomal vesicular systems will vary increase in HLB value, carbon chain length, hydrophilicity of head groups of surfactant, surfactant concentration in formulation certainly decrease the size of the vesicle formed. The most commonly used surfactants were tween80, span80, sodium deoxycholate, and sodium cholate in the formulation of transfersomes loaded with different categories of drugs and decrease in vesicle size was reported with increase in concentration of surfactant, but not above 15%, as this might be due to the fact that the higher

concentration of surfactants will forms the micelles instead of vesicles.

Pathomthat [96] formulated methotrexate loaded transfersomes by using oleic acid as penetration enhancer and had observed good penetration through the stratum corneum and reported that enhanced permeability of these elastic liposomes is due to the elastic nature of oleic acid.

Low PDI(<0.3) value for a transfersomal suspension was recommended because it indicates higher stability to the formulation , this might be due to increase in charge on the surface of vesicles, which would further reduces the interfacial tension and aggregation of vesicles and thus leads to formation of homogenous population(more uniform size vesicles).

For entrapment of hydrophobic drugs or lipophillic drugs an edge activator with low HLB value is required and inorder to get more number of vesicles you need to add more quantity of edge activator, but if concentration of lipophillic drug crosses the loading capacity of vesicle leading to leakage of drug from vesicle disruption which could be due to higher volume of the hydrophobic bilayer domain that is not available for drug loading .

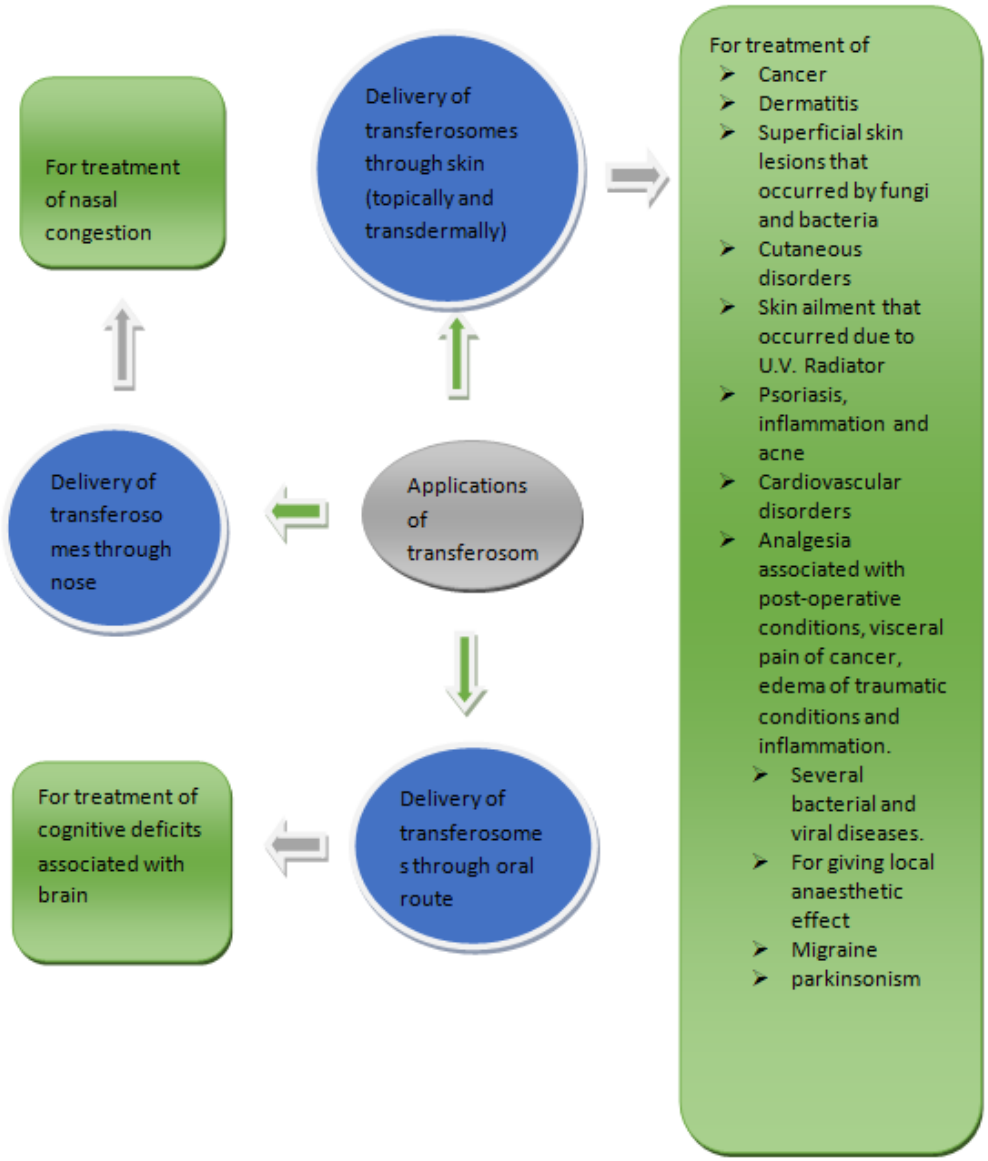

Fig. 5. Applications of transferosomes

Membrane permeability depends on carbon chain length and transition temperature of the edge activator and quantity of edge activator to be taken to formulate a optimum formulation depends on packing density of lipid polymer used and the edge activator –lipid polymer interaction.

Cipolla [97] confirmed that presence of edge activator significantly increases the releases of drug ciporofloxacin which was formulated by using tween 80 as edge activator.

Abdul Rasool [98] also reported that characteristic parameters of transfersomes were mainly affected by type and amount of edge activator used.

3.4 Effect of Hydrating Medium

Most probably for hydration of film we can use either water or saline phosphate (pH 6.5-7), in such a way that it should be compatible to pH of applied body part as well as route of administration. The unionised form of drug will go and bind to phospholipid bilayer and penetrate through intracellular route and also it is most important to use suitable pH buffer for hydration of film, to maintain unionised form of the drug to increase the entrapement and permeation of the drug [99,100].

4. CHARACTERIZATION OF TRANSFEROSOMES [101-105]

In SEM, the main principle involved here is that by beam of electrons, the surface of samle is “scanned” & we can get image with the detection of secondary electrons that are released from electrons that are released from the specimens. These secondary electrons are emitted from sample being examined because, it was earlier scanned by primary electrons those are emitted from the electron “gun” which is the source of electrons in the SEM technique.

TEM- involves the principle of transmission of beam of electrons through the sample and interacts with it as long as the beam of electrons passed through this ultrathin sample.

4.1 Stability of Transferosomes [106-109]

For determining stability of transferosomes, vesicular suspension is transferred to glass ampoules and sealed and expose these formulations to different temperatures 4^0 C, 25^0 C and 37^0 C for atleast 3 months.Samples were tested for drug leakage after 30days [110] , by considering 100% of drug is entrapped initially.

5. FUTURE PROSPECTIVE

Transdermal drug delivery system is frequently used due to its several advantage over other routes drug delivery but the penetration of drug via the stratum corneum is a rate limiting step. the elastic vesicles deform themselves to penetrate the skin through pores.it is more safe and efficient in composition than others. the high tolerability and efficiency of these vesicular systems open vast potential therapeutic uses[111-114].

6. CONCLUSION

New methods for drug delivery through transdermal route are continuous under process for efficient therapeutic response. The development of transfereosomes by the use of vesicles plays a crucial role in the new era of research. They allow enhanced permeation of drug through skin. In this type of delivery, drug release can also be controlled according to the requirement. Thus, this approach can overcome the problems that are faced in conventional techniques.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Garg V, Singh H, Bimbrawh S, Kumar Singh S, Gulati M, Vaidya Y, Kaur P. Ethosomes and transferosomes: Principles, perspectives and practices. Current Drug Delivery. 2017;14(5):613-33.

2. Umalkar D, Saudagar RB, Patel D, Rajesh KS. Formulation and Evaluation of Transferosomal gel of Isotretinoin for severe Acne. Research Journal of Topical and Cosmetic Sciences. 2014;5(2):39.
3. Zhang Y, Ng W, Feng X, et al. Lipid vesicular nano-carrier: quick encapsulation efficiency determination and transcutaneous application. INT J Pharm. 2017;516:225-230.
4. Sch lich M, Lai F, Murgia S, et al .needle free jet injection of intact phospholipid vesicles across the skin: a feasible study. Biomed micro devices. 2016;18:67.
5. Meng S, Zhang C, Shi W, et al. Preparation of osthole-loaded nano-vesicles for skin delivery: characterization, in vitro skin permeation and preliminary in vivo pharmacokinetic studies. Eur J Pharm Sci. 2016;92:49–54.
6. Hassanpour AM, Ghanbarzadeh S, Javadzadeh Y, et al. Aggregated nano transfersomal dry powder inhalation of itraconazole for pulmonary drug delivery. Adv Pharm Bull. 2016;6:57–64.
7. González-Rodríguez ML, Arroyo CM, Cózar-Bernal MJ, etal. Deformability properties of timolol-loaded transfersomes based on the extrusion mechanism, statistical optimization of the process. Drug Dev Ind Pharm. 2016;42:1683–1694.
8. Garg V, Singh H, Bhatia A, et al. Systematic development of transethosomal gel system of piroxicam: formulation optimization, in vitro evaluation, and ex vivo assessment. AAPS Pharmscitech. 2017;18:58–71.
9. Shreya AB, Managuli RS, Menon J, et al. Nano-transfersomal formulations for transdermal delivery of asenapine maleate: in vitro and in vivo performance evaluations. J Liposome Res. 2016;26:221–232.
10. Seidel EJ, Rother M, Regenspurger K, et al. Arandomised trial comparing the efficacy and safety of topical ketoprofen in Transfersome(®) gel (IDEA-033) with oralketoprofen and drug-free ultra-deformable Sequessome™ vesicles (TDT 064) for the treatment ofmuscle soreness following exercise. J Sports Sci. 2016;34:88–95.
11. Lu K, Xie S, Han S, et al. Preparation of a nano emodin transfersome and study on its anti-obesity mechanism in adipose tissue of diet-induced obese rats. J Transl Med. 2014;12:72.
12. Sarwa KK, Mazumder B, Rudrapal M, et al. Potential of capsaicin-loaded transfersomes in arthritic rats. Drug Deliv. 2015;22:638–646.
13. Ghanbarzadeh S, Arami S. Enhanced transdermal delivery of diclofenac sodium via conventional liposomes, ethosomes, and transfersomes. Biomed Res Int. 2013;2013:1–7.
14. Ghannoum M, Isham N, Henry W, et al. Evaluation of the morphological effects of TDT 067 (terbinafine in Transfersome) and conventional terbinafine on dermatophyte hyphae in vitro and in vivo. Antimicrob Agents Chemother. 2012;56:2530–2534.
15. Zhang YT, Xu YM, Zhang SJ, et al. In vivo microdialysis for the evaluation of transfersomes as a novel transdermal delivery vehicle for cinnamic acid. Drug. 2014;40:301–307.
16. Sigurgeirsson B, Ghannoum M. Therapeutic potential of TDT 067 (terbinafine in Transfersome): a carrierbased dosage form of terbinafine for onychomycosis. Expert Opin Investig Drugs. 2012;21:1549–1562.
17. Rajan R, Vasudevan DT. Effect of permeation enhancers on the penetration mechanism of transfersomal gel of ketoconazole. J Adv Pharm Techno lRes. 2012;3:112–116.
18. Kaur CD, Saraf S. Topical vesicular formulations of Curcuma longa extract on recuperating the ultraviolet radiation-damaged skin. J Cosmet Dermatol. 2011;10:260–265.
19. Duangjit S, Opanasopit P, Rojanarata T, et al. Characterization and in vitro skin permeation of meloxicam-loaded liposomes versus transfersomes. J Drug Deliv. 2011;2011:418316.
20. Rother M, Seidel EJ, Clarkson PM, et al. Efficacy of epicutaneousDirractin (ketoprofeninTransfersome gel)for the treatment of pain related to eccentric muscle contractions. Drug Des Devel Ther. 2009;3:143–149.
21. Cevc G, Mazgareanu S, Rother M. Preclinical characterisation of NSAIDs in ultradeformable carriers or conventional topical gels. Int J Pharm. 2008;360:29–39.
22. Zheng Y, Hou SX, Chen T, et al. Preparation and characterization of transfersomes of three drugs in vitro. Zhongguo Zhong Yao Za Zhi. 2006; 31:728–731.

23. LiS, Qiu Y, Zhang S, etal. Enhanced transde rmal delivery of 18β-glycyrrhetica cidviaelasticvesicles: Invitroandin vivo evaluation. Drug Dev Ind Pharm. 2012;38:855–865.
24. Chen G, Li D, Jin Y, et al. Deformable liposomes by reverse-phase evaporation method for an enhanced skin delivery of (+)-catechin. Drug Dev Ind Pharm. 2014;40:260–265.
25. Trotta M, Peira E, Debernardi F, et al. Elastic liposomes for skin delivery of dipotassium glycyrrhizinate. Int J Pharm. 2002;241:319–327.
26. Elsayed MM, Abdallah OY, Naggar VF, et al. Deformable liposomes and ethosomes: mechanism of enhanced skin delivery. Int J Pharm. 2006;322:60–66.
27. Cadena PG, Pereira MA, Cordeiro RBS, et al. Nanoencapsulation of quercetin and resveratrol into elastic liposomes. Biochim Biophys Acta. 2013;1828:309–316.
28. Gupta PN, Mishra V, Rawat A, et al. Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: a comparative study. Int J Pharm. 2005;293:73–82.
29. Vanic Z, Hafner A, Bego M, et al. Characterization of various deformable liposomes with metronidazole. Drug Dev Ind Pharm. 2013;39:481–488.
30. Viyalakshmi M, Zafaruddin MD, Vijay kunchana design and characterization of transferosomal gel of repaglinide. International research journal of pharmacy. 2015;6(1):38-42.
31. Sailaja K, Supraja R. Formulation of mefenamic acid loaded transfersomal gel by thin film hydration technique and hand shaking method. Nanomed J. 2017;4(2):126-134.
32. Watanabe M, Tagami H, Horii I, Takahashi M, Kligman AM. Functional analyses of the superficial stratum corneum in atopic xerosis. Arch Dermatol. 1991;127(11):1689–1692.
33. Bundela, Ragini; Bhardwaj, Rita; Khan, Mohd.Faarooq; Gupta, Revathi A. Formulation and Characterization of Lipid Vesicles Containing Thiocolchicoside for Transdermal Delivery. International Journal of Pharmacy & Life Sciences. 2018;9(2):30-30.
34. Mona Qushawy, Ali Nasr, ID, Mohammed Abd-Alhaseeb 4 ID and Shady Swidan 5,* Design, Optimization and Characterization of a Transfersomal Gel Using Miconazole Nitrate for the Treatment of Candida Skin Infections Pharmaceutics 2018;10:26. DOI:10.3390/pharmaceutics10010026.
35. Karanki Pavani, M. Kishore Babu Formulation and evaluation of Lornoxicam transferosomes as carriers for effective transdermal drug delivery Indian Journal of Research in Pharmacy and Biotechnology. 2015;3(6).
36. Srujan Kumar M, Anna Balaji Formulation And Evaluation of Transfersomal Gel of Sumatriptan Succinate Indo American Journal of Pharmaceutical Research. 2015;5(11)35.
37. Maged K El Sayyad, Alaa A Zaky, Ahmed M. Samy Fabrication and characterization of sildenafil citrate loaded transfersomes as a carrier for transdermal drug delivery. Pharmacy & Pharmacology International Journal. 2017;5(2).
38. Martina Di Francesco, Christian Celia, Maria Chiara Cristiano, Nicola d'Avanzo, Barbara Ruozi, Constantin Mircioiu, Donato Cosco, Luisa Di Marzio and Massimo Fresta Doxorubicin Hydrochloride-Loaded Nonionic Surfactant Vesicles to Treat Metastatic and Non-Metastatic Breast Cancer. 2021;6(4):2973–2989.
39. Alvi IA, Madan J, Kaushik D, et al. Comparative study of transfersomes, liposomes, and niosomes for topical delivery of 5-fluorouracil to skin cancer cells: preparation, characterization, in-vitro release, and cytotoxicity analysis. Anticancer Drug. 2011;22:774–782.
40. Mahmood S, Taher M, Mandal UK. Experimental design and optimization of raloxifene hydrochloride loaded nanotransfersomes for transdermal application. Int J Nanomedicine. 2014 12;9:4331–4346.
41. Bragagni M, Mennini N, Maestrelli F, et al. Comparative study of liposomes, transfersomes and ethosomes as carriers for improving topical delivery of celecoxib. Drug Deliv. 2012;19:354–361
42. Maswadeh H, Demetzos C, Dimas K, et al. Accumulation of vinblastine into transfersomes and liposomes in response to a transmembrane ammonium sulfate gradient and their cytotoxic/cytostatic activity in vitro. Anticancer Res. 2001;21:2577–2583.
43. Honeywell-Nguyen P. Loan, J. A. B The in vitro transport of pergolide from surfactant-based elastic vesicles through human

skin: A suggested mechanism of action. Journal of Controlled Release. 2003;86:145–156.

44. Mohammed H, Elkomy, Shahira F. El Menshawe, Heba A. Abou-Taleb & Marwa H. Elkarmalawy. Loratadine bioavailability via buccal transferosomal gel: formulation, statistical optimization, invitro/invivo characterization, and pharmacokinetics in human volunteers, Drug Delivery. 2017;24:1:781-791.
45. Preeti Sharma, Fedelic Ashish Toppo, R. S. Pawar Comparative studies on pure curcumin ointment and curcumin loaded transferosomes for wound healing potential, Asian Journal of Biomaterial Research. 2015;1(1):23-26.
46. Lissette Esteves,Gina Loachamin, Karen Tufiño,Javier Santamaría enrofloxacin transferosomes as alternative leishmaniasis nanotherapy IPAP Salamanca Project: Development of innovative therapeutic approaches against leishmaniasis;2018.
47. Reshmy Rajan, Deepa T. Vasudevan Effect of permeation enhancers on the penetration mechanism of transfersomal gel of ketoconazole Journal of Advanced Pharmaceutical Technology & Research. 2012;3 (2).
48. Gupta A, Aggarwal G, Singla S, Arora R. Transfersomes: A novel vesicular carrier for enhanced transdermal delivery of sertraline: Development, characterization, and performance evaluation. Sci. Pharm. 2012;80:1061–1080.
49. Sumaiya Parveen, Sirisha Mittapally Formulation and In-vitro evaluation of topical transferosomal gel of bifonazole for fungal infectionsThe Pharma Innovation Journal. 2018; 7(7):711-720.
50. Ahmed H. AL Shuwaili, Bazigha K.Abdul Rasool, Alaa Abdulrasool. Optimisation of elastic transferosomes formulations for transdermal delivery of pentoxyfilline. Europian Journal of Pharmaceutics and Biopharmaceutics; 2016.
51. Penn I. Kaposi's sarcoma in organ transplant recipients: report of 20 cases. Transplantation. 1979;27:8–11.
52. Maha Fadel M, Ali Heba F, Salem Hany F ,Abdelmohsen, Sameh K Attia Preparation and clinical evaluation of nanotransferosomes for treatment of erectile dysfunction, Drug Design, Development and Therapy. 2015;9:2431–2447.
53. Gregor cevc. Transdermal drug delivery of insulin with ultradeformable carriers, Clin Pharmacokinet. 2003;42(5):461-74.
54. Alam Zeb, Omer Salman Qureshi, Hyung-Seo Kim, Ji-Hye Cha, Hoo-Seong Kim, and Jin-Ki Kim improved skin permeation of methotrexate via nano sized ultradeformable liposomes. International Journal of Nanomedicine. 2016;11:3813–3824.
55. Sheo Datta Maurya ,Vijay kumar Tilak, Ram Chand Dhakar, Aklavya Singh, Shweta Aggarwal, Ghanshyam Maurya Enhanced transdermal delivery of indinavir sulphate via transfersomes. International journal of comprehensive medicine. 2010;1(06).
56. Michael S, Roberts, Eman Abd, Jeffrey E.Grice A Comparison of the penetration and permeation of caffeine into and through human epidermis after application in various vesicle formulations .Skin Pharmacology and Physiology. 2016;29:24-30
57. Abd E, Grice JE, Roberts JA. A comparison of the penetration and permeation of caffeine into and through human epidermis after application in various vesicle formulations. Ski. Pharmacol. Physiol. 2015;22:24–30.
58. Parkash V, Maan S, Chaudhary V, Jogpal V, Mittal G, Jain V. Implementation of design of experiments in development and optimization of transfersomal carrier system of tacrolimus for the dermal management of psoriasis in albino wistar rat. J. Bioequiv. Availab. 2018;10:98–105.
59. Shamma RN, Elsayed I. Transfersomal lyophilized gel of buspirone HCl: Formulation, evaluation and statistical optimization. J. Liposome Res. 2013;23:244–254.
60. Ahad A, Al-Saleh AA, Al-Mohizea AM, Al-Jenoobi FI, Raish M, Yassin AEB, Alam MA. Formulation and characterization of novel soft nanovesicles for enhanced transdermal delivery of eprosartan mesylate. Saudi Pharm. J. 2017;25:1040–1046.
61. Jain S, Jain N. PUB040 formulation and evaluation of embelin loaded transfersome for effective treatment of skin cancer. J. Thorac. Oncol. 2017;12:S2378.
62. Amin S, Sarfenejad A, Ahmad J, Kohli K, Mir SR. Nanovesicular transfersomes for enhanced systemic delivery of telmisartan. Adv. Sci. Eng. Med;2013, 5:299–308.

63. Bhatia A, Usha K, Wadhwa S, Raza K, Katare OP. Novel phospholipid-based topical formulations of tamoxifen: Evaluation for antipsoriatic activity using mouse-tail model. Pharm. Dev. Technol. 2013;19:160–163.
64. Yanzhong Chen ,Zhufen Lu , Hongwei Lin ,Qingchun Xie, et al. Increaser skin permeation efficiency of imperatonin via charged ultradeformable lipid vesicles for transdermal delivery. International Journal of Nanomedicine. 2018;13:831-842.
65. Lu Y, Hou SX, Chen T, Sun YY, Yang BX, Yuan Z.Y. Preparation of transfersomes of vincristine sulfate and study on its percutaneous penetration. China J. Chin. Mater. Med. 2005;30:900–903.
66. Lu Y, Hou SX, Zhang LK, Li Y, He JY, Guo DD. Transdermal and lymph targeting transfersomes of vincristine. Yao Xue Xue Bao Acta Pharm. Sin. 2007;42:1097–1101.
67. Montanari J, Maidana C, Esteva MI, Salomon C, Morilla MJ, Romero EL. Sunlight triggered photodynamic ultradeformable liposomes against Leishmania braziliensis are also leishmanicidal in the dark. J Control Release. 2010;147:368–376.
68. Maulvi FA, Dalwadi SJ, Thakkar VT, Soni TG, Gohe lMC, Gandhi TR. Improvement of dissolution rate of aceclofenac by soliddi spersion technique. Powder Technology. 2011Feb15;207(1-3):47-54.
69. Batlouni M. Non-steroidal anti-inflammatory drugs: cardiovascular, cerebro vascular and renal effects. Arquivos Brasileiros Decardiologia. 2010; 94(4):556-63.
70. Lain BM. Mechanisms of disease N Engl J Med. 2011;23:2205-19.
71. Patel R, Singh SK, SinghS, Sheth NR, GendleR.Development and characterization of curcumin loaded transfersome for transdermal delivery. J Pharm Sci Res. 2009;1(4):71-80.
72. ElMaghraby GM, Barry BW, Williams AC. Liposomes and skin: From drug delivery to model membranes. Eur. J. Pharm. Sci. 2008;34:203–222.[CrossRef][PubMed]
73. Haq A, Goodyear B, Ameen D, Joshi V, Michniak-Kohn, B. B. StratM®synthetic membrane: Permeability comparison to human cadaver skin. Int. J. Pharm. 2018;547:432–437.[CrossRef]
74. Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Characterization and invitro skin permeation of meloxicam-loaded Liposomes versus Transfersomes. J. DrugDeliv. 2010;2011:1–9.[CrossRef]
75. Singh S, Verma D, Mirza MA, Das AK, Dudeja M, Anwer MK, Sultana Y, Talegaonkar S, Iqbal Z, Mukharjee A Development and optimization of ketoconazole loaded nano-transfersomal gel for vaginal delivery using Box-Behnken design: *In vitro*, *ex vivo* characterization and antimicrobial evaluation. J. Drug Deliv. Sci. Technol.2017;39:95–103.[CrossRef]
76. Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: A novel technique for transdermal drug delivery. J. Drug Deliv. Ther. 2019;9:279–285. [CrossRef]
77. Pawar AY, Jadhav KR, Chaudhari LH. Transfersome: A novel technique which improves transdermal permeability. Asian J. Pharm. 2016;10:425–436.
78. Ruela ALM, Perissinato AG, Lino MEDS, Mudrik PS, Pereira GR. Evaluation of skin absorption of drugs from topical and transdermal formulations. Braz. J. Pharm. Sci. 2016;52:527–544. [CrossRef]
79. Skin deposit ion studies of optimised formulation: Prajapati ST, Patel CG, Patel CN. Transfersomes: A vesicular carrier system for trans-dermal drug delivery. Asian J Biochemical Pharma Res. 2011; 1(2):507-524.
80. Kikwai L, Babu RJ, Prado R, Kolot A, Armstrong CA, AnselJC, SinghM. Invitro and invivo evaluation of topical formulations of spantideII. American Association Pharmaceutical Science Pharmscitech. 2005;6(4):E565-72.
81. Kumar PM, Patel MR, Patel KR, Patel NM. Emulgels: a novel approach to topical drug delivery. International Journal of University Pharmbio Sciences. 2013;2(1):134-48.
82. Güngör S, Erdal MS, Aksu B. New formulation strategies in topical antifungal therapy. Journal of Cosmetics, Dermatological Sciences and Applications. 2013;3(01):56.
83. Michaels AS, Chandrasekaran SK, Shaw JE. Drug permeation through human skin: theory and *in vitro* experimental measurement. America lnstitute of Chemical Engineering Journal. 1975; 21(5):985-96.
84. Dudhipala N, Mohammed RP, Youssef AAA, Banala N. Effect of lipid and edge activator concentration on development of Aceclofenac loaded transfersomes gel for

transdermal application: *In vitro* and *ex vivo* skin permeation. Drug Dev. Ind. Pharm. 2020;46:1–28.[CrossRef]
85. N'Da DD. Prodrug strategies for enhancing the percutaneous absorption of drugs. Molecules. 2014;19:20780–20807. [CrossRef].
86. Sheo DM, Shwetha A, Ram CD, Ghanshyam M, Girish K, Sunil KP. Transferosomes-A novel vesicular carrier for enhanced Trans-dermal delivery of stavudine: Development, characterization and performance evaluation.J Sci Speculations Resea. 2010;130–6. [GoogleScholar]
87. Patel R, Singh, Singh S, Sheth NK, Gendle R. Development and characterization of curcumin loaded transferosomes for trans dermal Delivery. J Pharm Sci Res. 2009;1:271–80. [GoogleScholar]
88. Pandey S, Goyani M, Dev MV, Fakir J. Transferosomes: A novel approach of transdermal drug. Delivery Sch Res Libr. 2009;1:143–50. [GoogleScholar]
89. Boinpally RR, Zhou SL, Poondru S, Devraj G, Jasti BR. Lecithin vesicles for topical delivery of diclofenac. Eur J Pharm Biopharm. 2003;56:389–92. [PubMed] [GoogleScholar]
90. Cevc G. Material transport across permeability barriers by means of lipid vesicles. In Lipowsky R., Sackmann E, editors. Hand book of physics of biological systems. Amsterdam: Elsevier. 1995;1: 441–64.[GoogleScholar]
91. Singodia D, Gupta GK, Verma A, Singh V, Shukla P, Mishra P, et al. Development and performance evaluation of amphotericin B transferosomes again stresistant and sensitive clinical isolates of visceral leishmaniasis. J Biomed Nanotechnol. 2010;6:293–302. [PubMed] [GoogleScholar]
92. Jain S, Umamaheshwari RB, Bhadra D, Tripathi P, Jain P, Jain NK. Ultradeformable liposomes: Are cent tool for effective transdermal drug delivery. Indian J Pharm Sci. 2003;65:223–31. [GoogleScholar]
93. Barry B. Transdermal drug delivery. In: Aulton EM, editor. Pharmaceutics, The science of dosage forms design. Churchil lLivingstone, Newyork: Harcourt Publishers. 2002;499–33. [GoogleScholar]
94. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: Permeation enhancement, vesicle penetration and trans dermal drug delivery. Crit Rev The Drug Career Syst. 1996;13:257388.[PubMed][GoogleScholar]
95. Vyas SP, Khar RK. 1st Ed. Delhi: CBS Publishers. Targeted and Controlled Drug Delivery. 2002;219–43.[GoogleScholar]
96. Jain S, Uma Maheshwari RB, Bhadra D, Jain NK. Ethosomes: A novel vesicular carrier for enhanced transdermal delivery of an anti-HIV agent. Indian J Pharm Sci. 2004;66:72–81.[GoogleScholar]
97. Kumar R, Philip A. Modified Transdermal Technologies: Breaking the barriers of drug permeation via skin. Trop J Pharm Res. 2007;6:63344.[GoogleScholar]
98. Chien YW. Logics of transdermal controlled drug administration. Drug Dev Ind Pharm. 1983;9: 497520. [Google Scholar]
99. Nandha A, Nandha S, Dhall M, Rao R. Transferosomes: A novel Ultra deformable vesicular carrier for transdermal drug delivery. Pharma Info Net. 2005;395. [GoogleScholar]
100. Cevc G. Drug delivery across the skin. Exp Opin Investig Drugs. 1997;6:1887–973. [PubMed][GoogleScholar]
101. Langer R. Transdermal drug delivery: Past progress, current status, and future prospects. Adv Drug Deliv Rev. 2004;56: 5578. [PubMed][GoogleScholar]
102. Cevc G, Blume G. New, highly efficient formulation of diclofenac for the topical ,transdermal administration in ultra-deformable drug carriers. Transfersomes Biochem Biophys Acta. 2001;1514:191–205.
[PubMed] [GoogleScholar]
103. Jain NK. Advances in controlled and novel drug delivery. 1:426–51. [GoogleScholar]
104. Verma P, Ram A, Jha AK, Mishra A, Thakur A. Phosphatidylcholine :A revolution in drug delivery technology. Int J Pharm Sci Res; 2010. [GoogleScholar]
105. Jain CP, Vyas SP, Dixit VK. Niosomal system for delivery of rifampicin to lymphatics. Int J Pharma Sci. 2006; 68:5758. [GoogleScholar]
106. Chien YW. New York: Marcel DeckerInc; Novel drug delivery systems. 1982;149–215. [GoogleScholar]
107. Nanda A, Nanda S, Dhall M, Rao R. Transferosomes-A novel ultra-deformable vesicular carrier for transdermal. Drug Deliv. 2005;5:395. [GoogleScholar]

108. Chuanping N. College of pharmacy Liaoning medical university. Preparation and study on properties of ibuprofen transferosomes. J Math Med. 2010; 2. [GoogleScholar]
109. Shen Y, Zhang Y, Liao Ming. Preparation and quality evaluation of drug loading transferosomes. Med J Chin People's Liberation Army. 2007;10. [GoogleScholar]
110. Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Characterization and Invitro Skin Permeation of Meloxicam-loaded liposomes versus Transferosomes. J Drug Deliv. 2011;5:207–14. [PMCfreearticle] [PubMed] [GoogleScholar]
111. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the trans dermal osmotic gradients and hydration force. Biochem Biophys Acta. 1992;1104:226–32. [PubMed] [GoogleScholar]
112. Jain S, Jain P, Umamaheshwari RB, Jain NK. Transferosomes: A novel vesicular carrier for enhanced transdermal delivery: Development, characterization and performance evaluation. Drug DevInd Pharm. 2003; 29: 101326. [PubMed] [GoogleScholar]
113. Benson HA. Transdermal drug delivery: Penetration enhancement techniques. Curr Drug Deliv. 2005;2:23–33. [PubMed] [GoogleScholar]
114. Maurya SD, Agarwal S, Tilak VK, Dhakar RC, Singh A, Maurya G. Enhanced transdermal delivery of indinavir Sulfate via transferosomes. Int J Compr Pharm. 2010;1:1–7. [GoogleScholar]

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