Transferosomes a New Transformation in Research:  
A Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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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. In order 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
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 thereby devoid of systemic toxicity 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 | VOLTAREN 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) | soypshiphotidylcholine,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 lipopholic | 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/cm²/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 |
|------|---------------------------------------------|---------------|----------------------|-----------------|-----------------------------|-------------------|
| 4.   | Itraconazole [6] 705.6 g/mol 5.66, lipophillic | Antifungal | sporanox film dispersion method | Nano-transfersomes 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 ratio 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, 1:2 ratio 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 antagonist | timolol XE-gel. | timolol maleate loaded transfersomes were prepared, to check the deformability properties of unlike timolol prepared by extrusion technique. | tween-20, egg L-α phosphotidylcholine, sodium deoxycholate, stearylamine. | From the results TM-loaded transfersomes 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 |
|------|---------------------------------------------|---------------|---------------------|-----------------|-----------------------------|------------------|
| 6.   | piroxicam [8] 331.3 g/mol logp= 3.06 slightly lipophilic drug | NSAID         | PX-TRS GEL          | 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 coefficient was 15.68X10⁻³(cm²h⁻¹) and flux of 23.53(µg·h⁻¹·cm⁻²), got good result 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 |
|------|-----------------------------------------------|---------------|----------------------|----------------|-------------------------------|------------------|
| 8.   | ketoprofen [10] 254.28 g/mol 3.12 moderately lipophilicity | NSAID         | fastumgel            | They compared the effect of ketoprofen in three different formulations ketoprofen loaded in transfersomes, oral ketoprofen, and drug free sequessome vesicles in reducing pain arisen 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. | transdermal application compared with the oral route. | the results clearly indicated that ketoprofen in transfersomes 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 protein expression and upregulation of ATGL protein expression of adipose tissue collaborate/coactions joint work to reduce the obese rats body weight. transfersomes loaded |
| S.No | Drug, molecular weight, nature and log p value | Drug category | Marketed Formulation | Study conducted | Lipid and edge activator used | Result/Observation |
|------|---------------------------------------------|---------------|---------------------|----------------|------------------------------|-------------------|
| 10.  | capsaicin [12] 305.4 g/mol log p= 3.04 hydrophillic antiarthritic agent zostrix cream | prepared capsaicin loaded transfersomes were tested for antiarthritic efficacy in rat models. the results of the capsaicin transfersomes were compared against marketed gel, therma gel (standard reference formulation) | phosphotidylcholine, ethanol, tween80 | 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. |
| 11.  | diclofenac sodium [13] 318.1 g/mol 0.7 hydrophillic NSAID Cambic | diclofenac sodium, a poorly water soluble drug loaded into transfersomes, 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, ethanolic carbopol-914. | results clearly indicated that out of all vesicular systems transfersomes 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 |
|------|---------------------------------------------|-------------|---------------------|----------------|-------------------------------|-------------------|
| 12.  | terbinafine [14] 291.4 g/mol logp=6         | antifungal  | lamisil dermgel     | in this investigation researcher studied about the mechanism involved 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. | phosphotidylcholine, sodium deoxycholate | 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/mol logp=2.13     | anti-inflamatory antioxidant | | | 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 $C_{\text{max}}$ 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. Transfersomal TDT 067 is only the therapy to treat onychomycosis. 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 onychomycosis 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 onychomycosis by phase-III trial. |
| 15. | ketoconazole [17] 531.4 g/mol logp=4.35 | antifungal agent nizoral topical | researcher prepared ketoconazole loaded transfersomes 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 |
|------|------------------------------------------------|---------------|----------------------|----------------|-----------------------------|--------------------|
| 16.  | curcuma longa 368.4 g/mol logp=3.29 | photoprotective | researcher prepared | suitable essential oils to determine the potential of transfersome for transdermal delivery. Transfersomes were incorporated into gel base and evaluated for gel characteristics such as drug content, viscosity, pH, spreadibility, extrudability, homogeneity etc. | ethylalcohol, soyaphosphatidylcholine, cholesterol, ethanol, sodium deoxycholate. | barrier to penetration present in skin without itself undergoing any change and also showed better release and permeation of ketoconazole. |
| 17.  | Meloxicam 351.4g/mol logp= 3.43 | NSAID Meloxicam 3% gel | researcher prepared | researcher concluded from the results that curcuma longa extract loaded in transfersomes showed better skin permeation properties when compared to ethosomes and liposomes. | | |

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| 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 exhibit better skin permeation. |                    |
| 18.  | ketoprofen [20]                               | NSAID          | orudis               | ketoprofen loaded in ultradeformable vesicles for epicutaneous application, in aqueous, viscous formulation known as Diractin (formerly 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 use of Diractin for pain relief up to 18 months provided a good safety and tolerability profile. |
| 19.  | ketoprofen [21]                               | NSAID          | vopac                | In this research investigator compared the in vivo transport and biodistribution of 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 294.3 g/mol log p = 6.31            | Anti hypertensive | 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. | soyabean phospholipid, sodium deoxycholate, cholesterol. | also highly deformable nature in relation to the molar ratio 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 transfersomes for the treatment 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 transfersosomal preparation on to mice ear skin were C max at 3 hours was and had it effects for 16 hrs even after its removal. |
| 22  | catechin 290.27 g/mol \[log p\]=1.8         | antioxidant    | veregen              | In this research, they compared catechin loaded liposomes, L-α-phosphotidylcholine choline, cholesterol, | results concluded as prolonged catechin release was exhibited by |                                                                                                                   |
| S.No | Drug, molecular weight, nature and log p value | Drug category | Marketed Formulation | Study conducted | Lipid and edge activator used | Result/Observation |
|------|-----------------------------------------------|----------------|----------------------|-----------------|------------------------------|-------------------|
| 23.  | Dipotassium glycyrrhizinate [25] 899.1 g/mol log p value=3.13 | anti-inflammatory agent | transferred, 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. |
| 24.  | ketoprofen [26] | anti-histaminic ketoprofen | researcher prepared liposomes and ethosomes of ketoprofen to understood about the possible mechanism of penetration into the skin under non-occlusive condition. | phosphatidylcholine, 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 significantly important factor. |
| 25.  | Quercetin & resveratrol [27] | to reduce subcutaneous fat | studied to dissolve the subcutaneous fat by soyaphosphatidylcholine, cholesterol, | prepared elastic | result concluded as |
| 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   | metrolotio         | 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 |
|-------|---------------------------------------------|---------------|----------------------|-----------------|------------------------------|-------------------|
| 28.   | repaglinide 5.9 [30] 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-80 in the ratio 85:15(%w/w), incorporated in 2% carbopol gel had showed best drug release and good entrapment efficiency. |
| 29.   | mefenamic acid 5.12 [31] 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 |
|------|---------------------------------------------|---------------|----------------------|----------------|-----------------------------|-------------------|
| 30   | Isotrenetoin [32] 5.66 retinoid             |               |                      | release from the optimised formulation they prepared by incorporation into carbopol gel base of 1% & evaluated and compared with plain marketed gel. | formation .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. |  |

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 |
|------|-----------------------------------------------|----------------|----------------------|-----------------|-------------------------------|---------------------|
| 31.  | Thiocolchiside [33]                           | anti-inflammation analgesic |                     | Investigator prepared various vesicular systems loaded with thiocolchiside by different methods and determined the entrapment efficiency, zetapotential, vesicular size, invitro skin permeation and stability. These vesicular systems were compared with marketed thiocolchiside gel. | phospholipoin90 tween80 ethanol methanol chloroform | Investigation concluded the thiocolchiside ethosomes had performed greater entrapment efficiency, higher cumulative release of drug permeation (90±5%) after 24hrs. when compared to other liposomal and transferosomal formulations. Thiocolchiside loaded ethosomes had effective treatment to muscle relaxant 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 independent variables i.e., type of surfactant, total lipids and phospholipids on dependent variables i.e., vesicle size, | out of all 8 formulations, f6 showed high transdermal flux of 105.42±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 cream 2%(50mm) |
| S.No | Drug, molecular weight, nature and log p value | Drug category | Marketed Formulation | Study conducted | Lipid and edge activator used | Result/Observation |
|------|---------------------------------------------|---------------|----------------------|----------------|-------------------------------|-------------------|
| 33.  | lornoxicam 2.62 [35]                         | 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 106.7 mm & 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 |
|------|---------------------------------------------|----------------|---------------------|-----------------|-------------------------------|------------------|
| 34   | sumatriptine succinate [36] 0.74            | anti-migraine property |                    | research focused on preparation of sumatriptan succinate loaded transfersomes and incorporated it into gel base, for the treatment of migraine. Gel was formulated using Placket-burmann series and studied the effect of sonication on size of transfersomes. The gel was tested for irritancy on animals. | phospholipid-soyalecithin, propylene glycol, ethanol. | 27.6m² indicating good stability. |
| 35   | sildenafil citrate 1.8                      | vasodilator      | rotary evaporation & sonication method, vortexing 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, soybean 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. out of T80 containing SC loaded transfersomes, 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°C & 4°C | invitro condition & 9 hours of ex vivo permeation studies. Out of spa 80 containing SC loaded transferosomes, SC-TS7 permeated 93.62% of drug in 6 hours duration and invitro 76.29% of drug permeated in ex vivo condition over 9 hours duration/period. In SC-transferosomes containing anionic surfactant S C-Ats2 permeated 69.03% of drug over a 6 hours invitro & 99.90% of the containing drug during ex vivo 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 |
|-------|-----------------------------------------------|---------------|---------------------|----------------|-------------------------------|-------------------|
| 36    | Doxorubicin hydrochloride [38] 0.53            | anti-cancer   | DOXIL               | In this research delivery of drug to lymphatics by a novel hyaluronic acid modified transfersomes were studied on tumour cells. Improved uptake of transfersomes 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 transfersomes loaded with 5-fu were prepared by using two different edge activator. these 5-FU transfersomes 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, transfersomal 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 |
|------|-----------------------------------------------|---------------|----------------------|-----------------|-------------------------------|--------------------|
| 38.  | raloxofene hydrochloride [40]                | treatment of osteoporosis/sele<br>ctive 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 |
|------|--------------------------------------------|--------------|----------------------|----------------|-------------------------------|-------------------|
| 40   | vinblastine [42]                           | neoplastic   |                      | liposomes &ethosomes with suitable edge activator and surfactant respectively. | dimiristoylphosphatidylcholine, dipalmitoylphosphatidylcholine, cholesterol, sodium cholate | significantly more with respect to aqueous suspension, from |
|      | vinblastine [42]                           | neoplastic   |                      | In this study vinblastine liposomes and transferosomes were prepared by thin film hydration technique by using lipids dimiristoyl phosphatidyl 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, whereas 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 vinblastin liposomes. | |
| 41   | pergolide [43]                             | dopaminergic antagonist |                      | pergolide transferosomes were prepared by using bilayer forming surfactant L-595 (sucrose laurate ester), micelle forming surfactants, stabilisers. | sucrose laurylster, 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]                             | antihistaminc drug | conventio nal thin film hydration technique | loratadine loaded transferomes were prepared and incorporated to mucoadhesive gel. For optimisation of transferomes they used QBD approach that involves placket-burmann design for screening of formulation followed by constrained simplex centroid 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 interns 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 method | In present study curcumin loaded transferosomes were prepared by using rotary evaporation sonication method, 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   | enrofloxacin [46]                           | synthetic antibacterial 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 fluoroquinolones moxifloxacin, ciprofloxacin ,levofloxacin. concentration of fluoroquinolones 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 |
|------|---------------------------------------------|---------------|---------------------|----------------|--------------------------|--------------------|
| 45   | ketoconazole [47]                            | solvent evaporation method | ketoconazole loaded transfersomes were formulated and best formulation was found out from those formulation by using Box-behnken design. These optimized transfersomes were incorporated into gel base and gel was characterised for invitro, exvivo and antimicrobial evaluation. | 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. | Cumulative release of drug was found to be 97% and 74% respectively for transfersosomal gel and suspension of ketoconazole. transdermal flux of ketoconazole suspension gel was found to be 3 times lesser with that of ketoconazole transfersosomal gel. Minimum inhibitory concentration of ketoconazole transfersosomal gel was found to be 4.57-4.6 µg/ml against candida albicans. from the overall studies transfersosomal 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 |
|------|-----------------------------------------------|---------------|---------------------|----------------|----------------------------|-------------------|
| 46   | sertraline [48]                               | antidepressant| rotary evaporation  | 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 14 days. 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. | negligible sign of toxicity and irritation. |

Investigation revealed that presence of ethanol in transferosomes increases the entrapment efficiency, fluidity and EL-SP4 optimised formulation containing gel showed significantly 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 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 |
|------|---------------------------------------------|---------------|---------------------|----------------|-------------------------------|-------------------|
| 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. | 0.119±2.67µg /h/cm² had for transferosomal gel was found to be 0.114±2.5767µg /h/cm². 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 entrapment 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 |
|------|---------------------------------------------|---------------|----------------------|----------------|-------------------------------|-------------------|
| 49   | azathioprine [51]                           |                | rotary evaporation technique/ thin film hydration technique | Research optimised azathioprine loaded transfersomes by trial and error design. Stability studies were performed at different storage conditions and studies about effect of surfactants on experimental results. | phospholipoin90G, span80, tween 80, chloroform, ethanol. | drug release was found to be 79.1± 2.1% after 10 hours of run. Ex vivo & in vivo studies proved that F4 transfesomes had showed increased PTX-absorption & prolonged its half-life comparing to commercial oral-SR-tablets. |
| 50   | papaverine hydrochloride [52]               |                |                      | In this study, researchers focus on preparation of papaverine hydrochloride loaded vesicular system that is ultradefomable vesicle transfersomes for the diagnosis and | soyabean phosphotidylcholine, cholesterol, sodium deoxycholate, sorbitan monostearate | From the overall results out of 9 formulations, T3 had showed best effects in all its characteristic properties like entrapment 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 |
|------|-------------------------------------------------|---------------|----------------------|----------------|-------------------------------|-------------------|
| 51.  | Insulin [53]                                     | antidiabetic   | conventional rotary evaporation technique | In this present study researcher focused on formulation of insulin loaded nanocarriers for hypoglycaemic effect to overcome the problems related 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 iodophor 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 |
|------|-----------------------------------------------|---------------|---------------------|----------------|-----------------------------|------------------|
|      |                                               |               |                     | Invitro and invivo studies were carried out by using cellophane membrane, animal models rats and hairless goat abdomen skin by franz-diffusion 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   | Imperatoin [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 evaporation technique | researcher prepared indinavir sulphate loaded transfersomes 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/cm²/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 evaporation technique | here, researcher formulated caffeine vesicular systems and compared the ability of these vesicular 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]                             | immuno suppressant | thin film hydration and dispersion technique | researcher formulated tacrolimus loaded transfersomes and compared that with commercial tacrolimus ointment and liposomal gel of tacrolimus gel invtro and invivo. | Lipoid E80, sodium cholate, Tween80, vitamin E | Investigator concluded that transfersomes 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 evaporation technique | formulated transfersomes 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 phosphatidylcholine, tween 80, 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 ultradisperse 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 concentration and nature of edge activator has direct effect on characteristic 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 |
|------|-------------------------------------------------|---------------|----------------------|-----------------|------------------------------|---------------------|
| 59   | embelin [61] antineoplastic and antimalarial thin-film hydration technique | emnelin loaded transfersomes were formulated by using span 80 and tween80 and optimized formulation was incorporated into carbopol934 gel base. | span80,tween80 | confirmed that transfersomal application of eprosartan mesylate was proved to be better route. researcher projected that as emnelin transferosomes were potential vesicular systems for treatment of skin cancer. |
| 60   | telmisartan [62] anti hypertensive conventional rotary evapouration technique | telmisartan transfersomes were formulated by taking 64mg of soyaphosphatidylocholine and 4mg of sodium cholate | soyaphosphatidylocholine , sodium cholate | Results obtained from transferosomal gel has shown a flux of 0.478 ± 0.001 mg/cm²/h and permeability coefficient of 7.982 ± 0.15 x 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 transfersomal 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 transfersomes were efficiently absorbed by lymphatics and shown improved uptake by cancer cells. |
| 62   | Tamoxifen [64]                                  | anti psoriatica and treatment of breast malignancies | thin-film hydration technique | 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. |
| 63   | zinc phthalocyanine (ZnPc) and the nitrosyl ruthenium complex [Ru(NH,NHq)(tpy)NO]$^{3+}$ (RuNO) [66] | cytotoxic     | thin-film hydration technique | lecithin, sodium deoxycholate | Has shown good targeting at lymphatics and increase in skin permeation. |
|      | Investigator formulated zinc phthalocyanine (ZnPc) and the nitrosyl ruthenium complex [Ru(NH,NHq)(tpy)NO]$^{3+}$ (RuNO)loaded transfersomes by using dioleylphosphocholine (DOPC), tween80, dimyristoylphosphoholine (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. |
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.

↓ Water present in uppermost layer of skin increases to 10-30% and in epidermis it is 75%.

↓ 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-epidermal 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 transfersomes 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, transfersomes 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 transfersomes are having both hydrophobic and hydrophilic moieties there by it can accomdate the drugs with widerange of solubility.log P value is undefined.
- Transfersomes 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 transfersomes 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 transfersomes [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 transfersomes:

- **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 evaporation technique, but here instead of using rotary evaporator, hand shaking will be done for evaporation of solvent. This method involves the addition of mixture of phospholipids, edge activator(surfactant-non-ionic/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°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 evaporation technique**[81]:

Transferosomes were formed by dissolving drug, phospholipids and surfactants (edge activator) in ethylalcohol. At a temperature of 40-45°C 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 expelled 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, aqueous 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 aqueous 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°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.

| Mixture of phospholipids and surfactant is dissolved in organic solvent mixture |
| Solution mixture is rotated under reduced pressure and heated above (constant temperature) lipid transition temperature by using rotary evaporation. |
| film formed is then hydrated using phosphate buffer (Ph 6.5-7.0) (in which drug is dissolved) |
| lipid film formed will swell and gets come out from wall, results in formation of multilamellar vesicles. |
| lipids added to organic solvent. |
| aqueous solution of edge activation (surfactant) and drugs is added under nitrogen. |
| homogenous dispersion is formed upon sonication(bath/ probe sonicator) |
| viscous gel |
| Formation of transferrosomal suspension |

**Fig. 2. Reverse phase evaporation technique**
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 carry out in vitro 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 carry out this in vitro skin permeation studies should be compatible with human skin conditions. Here for this in order mimic blood circulation beneath the skin and temperature receptor fluid of volume 50ml is usually maintained at a temperature 37±0.5°[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-α-phosphotidylcholine                     | 313.24                    | C_{10}H_{20}NO_{8}P | Saturated                                          | neutral    | <0°C |
| 2    | hydrogenated soy(HSPC)                       | 783.77                    | C_{44}H_{88}N_{8}O_{8}P | Saturated                                          | neutral    | <0°C |
| 3    | Phosphotidylserine(PS)                       | 385.304                   | C_{13}H_{24}N_{8}O_{8}P | Saturated                                          | neutral    | <0°C |
| 4    | Phosphotidylinositol(PI)                     | 886.56                    | C_{27}H_{53}O_{13}P  | unsaturated                                        | Anionic    | <0°C |
| 5    | 1,2-dioleoyl-3-trimethyl ammonium propane (DOTAP) | 698.55                  | C_{42}H_{82}ClNO_{4}  | unsaturated                                        | cationic   | <5°C |
| 6    | 1,2-dioleoyl-sn-glycero-3-phosphate(DOPA)    | 722.95                    | C_{39}H_{72}O_{60}Na | unsaturated                                        | cationic   | -20°C|
| 7    | 1,2-dipalmitoyl-sn-glycero-PC(DGPC)          | 734.1                     | C_{40}H_{80}NO_{6}P  | Saturated                                          | Neutral    | 41°C |
| 8    | DL-α PC (DPC)                               | 790.15                    | C_{34}H_{68}NO_{6}P  | Saturated                                          | cationic   | -2°C |
| 9    | 1,2-dilauryl-sn-glycero-3-phosphocholine(DLPC) | 621.437                  | C_{32}H_{64}NO_{6}P  | Saturated                                          | cationic   | -17°C|
| 10   | 1,2-dioleoyl-sn-glycero-3-phosphocholine(DOPC) | 786.59                   | C_{44}H_{84}NO_{6}P  | Unsaturated                                        | cationic   | -17°C|
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/cm²/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 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 transfersosomes.

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) turn generate pores.

3.2 Effect of Various Solvents

Commonly used solvents are methylic alcohol and ethyl alcohol. Choice of solvent mainly depends on solubility of formulation ingredients and compatibility 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, estradioi 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 entrapment 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 form micelles instead of vesicles.

Pathomthath [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 reduce 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 lipophilic 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 lipophilic 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 transfersomes
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 ciprofloxacin 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°C, 25°C and 37°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.

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