

Transfersome: A Novel Transdermal Drug Delivery System for the Treatment of Hyperlipidemia

UNDER PEER REVIEW

ABSTRACT:

Hyperlipidemia describes a group of genetic along with medical conditions which raise cholesterol levelsthroughout the bloodstream. Many individuals suffer from this illness. It puts the patient at risk for majorproblems such heart disease,brain strokes,hepatic malfunction, and renal dysfunction. The barrierfunction of the skin usually restricts Transdermal drug delivery, although it has evolved into a helpfulstrategy for therapeutic pharmacological compound administration. By using an extremely deformablevesicular carrier to transfer bioactive chemicals through the skin more effectively, new potential anddifficulties for the creation of innovative, enhanced therapeutics are presented. Since transfersomes are specifically optimized vesicles with the ability to respond to an external stress via quick and energy-efficient shape changes, it can solve all the issues with Transdermal administration. Transfersomes havehigh entrapment efficiency and increase bioavailability. The use of Transfersomes as a Transdermaldelivery system for drugs with hyperlipidemia-active medication is part of an efficient treatment regimen forthehyperlipidemiadisease.

Key words: *Transfersomes, Transdermal delivery system, Vesicular carrier, High Entrapment Efficiency, Bioavailability, Cerebral strokes, Hyperlipidemia.*

UNDER PEER REVIEW

1. INTRODUCTION

A chronic condition known as Hyperlipidemia is defined with elevated levels of total cholesterol (TC), total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and inadequate levels of high-density lipoprotein cholesterol (HDL-C). In both advanced and developing nations, Hyperlipidemia has become a prevalent disorder where blood cholesterol level is increased over the typical range. Increased lipid (cholesterol, fat, and triglyceride) levels put individuals vulnerable for significant problems such as heart attacks, strokes, liver damage, along with kidney failure. The disorder is typically without symptoms, while an individual learns about it through standard tests for blood. When Hyperlipidemia attains its final phase, people can get numerous consequences such as hypertension and angina [1].

The two main forms for Hyperlipidemia include as follows. The primary form of Hyperlipidemia usually a very common kind and was brought through inherited defects. Another kind is secondary Hyperlipidemia, a condition brought upon by circumstances such as being overweight, hypothyroidism, persistent kidney damage, drinking, medications (B-blockers), even thyroid problems. [2].

1.1 Pathophysiology of Hyperlipidemia

The Pathophysiology of Hyperlipidemia can be studied under the two classifications of Hyperlipidemia.

1.1.1 Exogenous pathway: route of dietary lipid absorption

Triglycerides, Cholesteryl esters, and apoprotein make up the mixture known as the Chylomicron (CM). While removing triglycerides, Chylomicron residues develop. On the endothelial cells of fat tissue along with muscle, lipoprotein lipase breaks down chylomicrons. The remaining Chylomicrons migrate toward the Hepatocytes once TG is removed for storage. Dietary TG is the outcome, which is deposited within the muscles along with fatty tissue.

1.1.2 Endogenous pathway: Cholesteryl esters (CE) transport pathway from liver to target cells Most of the triglycerides are removed from the VLDL from lipoprotein lipase after this is produced through liver and transported via plasma toward muscular and fatty tissue. Whenever all triglycerides are completely removed, remaining IDL may be absorbed via the Hepatocytes and transported till that is changed into cholesterol-rich LDL molecules. Plasma LDL is eliminated via endocytosis, which is regulated with LDL receptors. Consequently, TG along with CE are transported toward the intended cells by liver-derived VLDL and LDL, correspondingly. [3,4].

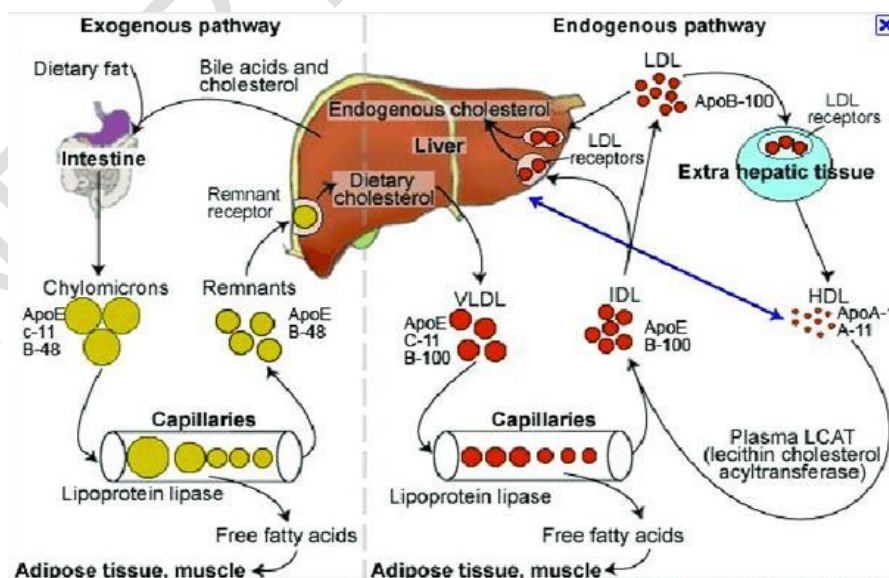


Figure 1: Pathophysiology of Hyperlipidemia

In overall, hyperlipidemia has little overt consequences. Nevertheless, unless it leads to atherosclerosis /coronary heart disease (CHD), patients to be detected after regular checks and when individuals persist at the risky stages before a stroke or heart attack. Persons having hereditary types of this condition as well as those having high blood cholesterol levels might get accumulation of cholesterol beneath their dermis, particularly around their eyes. [5] Individuals may have the following warning signs: Angina (chest discomfort/tightness), blockage of heart and brain blood arteries, elevated arterial pressure strokes, heart attack, and when triglyceride levels rise, lumps develop around the knees. The pancreas along with liver might become enlarged. Heart along with brain vessels might have been obstructed [2].

1.2 Treatment

(HMG-CoA) Reductase inhibitors (Statins) 3-Hydroxy-3-methylglutaryl coenzyme A

It involves the following medications: Lovastatin, simvastatin, Pravastatin, Fluvastatin, atorvastatin, along with Rosuvastatin. These medications have been shown for managing hypercholesterolemia and may decrease cholesterol levels by 20% to 50%. [6].

Bile acid sequestrants

Cholestyramine, Cholestipol, Colestipol, along with Colesevelam was bile acid sequestrants. Cholestyramine along with Cholestipol remains both bile acid sequestrants known to be presently on the market. For intestine, bile acids get released that play an essential function in making it simpler to digest lipid through diet. [7,4].

Fibric acid derivatives (Fibrates)

Fibrates, a category of frequently prescribed anti-hyperlipidemic drug that also include Clofibrate, Gemfibrozil, Fenofibrate, and Bezafibrate, significantly lower plasma triglycerides while only mildly lowering LDL cholesterol. The level of HDL cholesterol rises somewhat.

Nicotinic acid derivatives (Niacin)

Earliest medication for lowering lipids utilized for treating hyperlipidemia was niacin, a type-B water-soluble vitamin that has been shown to lessen heart disease along with overall mortality. This lowers triglycerides, LDL cholesterol, and total cholesterol.

Selective cholesterol absorption inhibitor (Ezetimibe)

The initial medication of a kind which prevents cholesterol along with phytosterols from being absorbed through the intestine, Ezetimibe, was created in order to treat hypercholesterolemia. It stops the small intestine against accumulating cholesterol irrespective of the levels of fat-soluble vitamins in blood plasma [2,8].

2. TRANSFERSOMES

An artificial vesicle called a Transfersome transporter is made to resemble a cell vesicle or a cell that is exocytosing, making it appropriate for regulated along with selective medication administration. Transfersomes comprise a highly flexible and stress-sensitive complex aggregation. Its primary form has an extensive lipid bilayer that encasing an aqueous core in an ultra-deformable vesicle. Because of the interdependence of the localized content and form of the bilayer, the vesicle is self-regulating and self-optimizing. As a result, the Transfersomes can pass through a variety of transportation obstacles along with serve as drug carriers for non-invasive selective medication administration along with sustained release of medicinal chemicals. One of the greatest divisive methods to deliver medication through the skin includes the utilization of vesicle formation [9].

The SC (Stratum Corneum), a thin layer of skin, serves as a durable, malleable barrier along with is water-resistant. It consists of the keratinized, flattened remains of growing epidermal cells. Numerous methods were investigated to get beyond this barrier, involving electrophoresis, chemical permeation

enhancers, iontophoresis, microemulsions, along with novel vesicular carriers facilitating carrying medication through the skin, which include liposomes, niosomes, Twosomes, and transfersomes [10].

A unique type of liposome called a transfersome contains both phosphatidylcholine plus an edge activator. They're pliable, spongy vesicles designed to more efficiently convey active substances [11]. The German company IDEA AG owns the trademarks and uses them to identify their distinct medication delivery technology. The term "carrying body" is derived from the Latin verb "transfere," which means "to carry across," and the Greek word "soma," which means "body."

Transfersomes are self-aggregates with an incredibly flexible membrane that transfer drugs into or through the skin in a consistent manner. Compared to typical liposomes, these vesicular vesicles are a number of orders of magnitude more elastic. Transfersomes circumvent the obstacle of skin penetration by squeezing along the stratum corneum's internal sealing lipids.

Transdermal drug delivery is evolving towards a replacement with the traditional oral drug delivery, especially besides serving as an alternative for hypodermic injections [12]. Particularly, transdermal drug delivery works better than oral drug delivery in a variety of manners, like preventing first-pass metabolism, that has a negative impact on drug bioavailability along with producing a fast drug metabolism [13].

The disadvantages of hypodermic injections, especially irritation near the injection site, substantial unease, along with the grave worry of medical waste including illness spread upon reusing syringe are all eliminated via transdermal delivery. Affordably priced and easily administered transdermal medication delivery systems were available. The few drugs which can be altered with transdermal distribution is a disadvantage of this form of treatment [14].

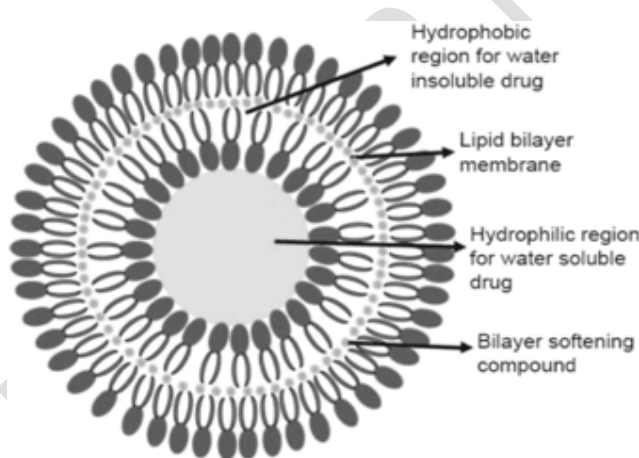


Figure 2 Structure of Transfersome

A bilayer of lipids surrounds the aqueous core to create ultra-deformable vesicles with the ability to regulate.

The aqueous core is encased in a bilayer of lipids to produce ultra-deformable vesicles having regulatory capabilities. Edge activator increases a vesicle membrane's capacity for deformation, while mixed with incorrect proportion with a sufficient quantity of lipids; this increases the flexibility and penetrating the transfersomes. By adding edge activators, hydrophobic medications become more soluble, increasing the drug's ability to be captured [15]. According to research, vesicles having size >600 nm permeate deeply through skin layers compared to those having sizes <300 nm, while those having sizes <70 nm exhibit highest content of accumulation in the epidermis along with dermis skin layer [16]. It happens by the vesicle structure's inclusion both hydrophilic and lipophilic components.

Being projected to be smaller than 300 nm, transfersomes have highly ultra-deformable vesicles which may squeeze via the SC which enter the skin as fully formed vesicles. Medicines with a hydrophilic

remain within the aqueous middle cavity, while those that have hydrophobic are encased within the phospholipid bilayer. With diameter under 300 nm, transfersomes have greater flexible and elastic than liposomes [9,17,18].

2.1 Mechanism of Transfersomes

Transfersomes may transmit about 0.1 mg of lipids every hour and cm² via healthy skin if applied appropriately. Compared to what is generally established by the gradient of transdermal concentration, this quantity is significantly larger. The actual explanation for this higher flow rate is due to the "Transdermal osmotic gradient". The skin permeation barriers inhibit transpiration of water throughout the skin by maintaining its water content at 75% in the epidermis and at 15% in the stratum corneum, that is positioned close towards the skin's surface. Almost every polar lipid absorbs a little water as a result of the interaction between hydrophilic lipid residues with the adjacent water. Lipid vesicles strive to bridge the "osmotic gradient" they encounter if a lipid transfersome suspension is put to partially dried skin in an effort to prevent complete dryness. In contrast to liposomes, that possess hydrating and surfactant properties that have the capability of significant deformation, they can do only if they're enough bendable to squeeze via the skin's microscopic openings.

As pushing down the lipids of SC, transfersomes circumvent the challenge to skin penetration. It is yet unclear how to enhance medicinal component delivery through the skin. Two methods which were suggested are as follows:

1. Since transfersomes withstand penetration of the skin intact, these are used as medication vectors.
2. Transfersomes function as penetrating boosters, improving the passage of drug molecules across the stratum corneum by rupturing the closely bonded intercellular lipids within the SC [9,15].

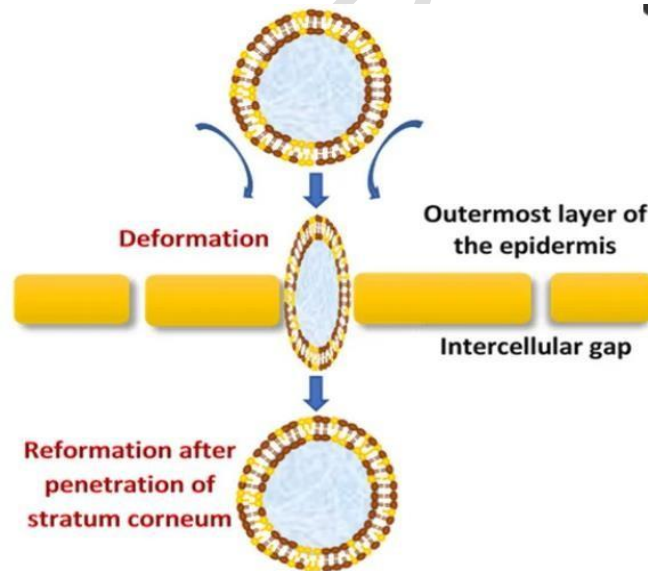


Figure 3 Mechanism of Transfersome

2.2 Composition of Transfersomes

Transfersomes typically consist of

1. To begin with, the primary element, an amphipathic substance (such as soy phosphatidylcholine, egg phosphatidylcholine, etc.), is what creates a vesicle that creates the lipid bilayer [19,20].
2. Surfactants like sodium cholates, sodium deoxycholate, Tweens along with Spans (Tween 20, Tween 60, Tween 80, Span 60, Span 65, and Span 80), or dipotassium glycyrrhizinate, known to be biocompatible bilayer-softening substances which enhance vesicles' bilayer flexibility and enhance

permeation, have been most frequently used edge activators in transfersomes formulations [9, 19, 21, 22, 23].

3. The hydrating medium can either water or a saline phosphate buffer (pH 6.5-7), whereas the solvent used includes 3 to 10% alcohol (ethanol or methanol) [15, 24].

2.3 Advantages of Transfersomes as a Carrier

1. Transfersomes enhance bioavailability, adherence among patients, overall adverse reaction reduction [17].
2. High entrapment of 90% transfersomes can boost the efficiency of lipophilic medicines. If entrapment efficiency is poor, lipophilic encapsulation may be improved through adding a surfactant having a low HLB scale [18].
3. It serves as a storage facility and delivers the medication gradually [25].
4. Transfersomes are biocompatible and biodegradable since they contain native phospholipids, which are also present in liposomes. Transfersomes are used for topical as well as systemic delivery of drugs.
5. Transfersomes are simple to build as they do not require time-consuming processes or the unintended utilization of pharmaceutical ingredients. They have high entrapment efficiency, especially in the case of lipophilic drugs, nearly 90%.
6. They can bend or squeeze over the epidermal barrier due to its elastic properties without wasting any drugs.
7. Because of its mixture of lipophilic along with lipophobic moieties, this is capable of accepting drugs having a wide range of solubility [21].
8. These are employed to transport a variety of substances, including protein, peptides, insulin, corticosteroids, NSAIDs, analgesics, even anesthetics [26].

2.4 Limitations of Transfersomes

1. Transfersomes are chemically unreliable because they're susceptible to oxidative degradation.
2. Another aspect that goes toward the utilization of transfersomes as drug delivery systems is their purity of their natural phospholipids.
3. Transfersome preparations are expensive [27, 28, 29, 30].

3. THERAPEUTIC POTENTIAL OF HERBAL AND XENOBIOTIC MEDICINE FOR MANAGEMENT OF HYPERLIPIDEMIA

3.1 Atorvastatin calcium (ATV)-loaded transfersomes

The rate-limiting stage for cholesterol production, when HMG-CoA breaks down into mevalonate, it is hindered by a particular inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, atorvastatin calcium (ATV) [31]. This is employed for treating people who have high cholesterol in order to reduce plasma levels of total cholesterol and specifically, low-density lipoprotein cholesterol (LDL-C), by raising the number of LDL receptors on Hepatocytes. Thereby quickens the process of LDL-C absorption and oxidation [32]. Upon an oral dose, ATV has a maximum bioavailability of 14% [33]. Reduced systemic availability is related to presystemic clearance in the gastrointestinal mucosa and substantial hepatic first-pass metabolism [34]. Furthermore, ATV's liver-related adverse reactions generally manifest as elevated plasma transaminase activity as well as appear to be regulated by a number of variables, which involve both pharmacokinetic along with physicochemical properties.

According to the thin film hydration approach, several ATV Transfersomal vesicles developed [35]. The anti-hyperlipidemic activity of the nanotransfersomal formulation T8 has been investigated. It was picked for the purposes of the present study then transformed into gel by adding 1% (w/w) carbopol 971P while contrasting to the hyperlipidemic group (P-407 only) or the group administered using a conventional ATV gel, overall cholesterol, triglyceride, along with LDL-C levels were substantially reduced in the two groups administered with either oral ATV or the transdermal ATV nanotransfersomal gel in poloxamer 407-

induced Hyperlipidemia rats. In all treated groups when compared with one another or the control group, there wasn't any discernible decrease in HDL-C levels. This study's six-week duration of therapy using nanotransfersomal ATV formulations resulted in a notable improvement in the lipid profile without having any adverse impacts on the liver. It has shown that the ATV nanotransfersomal gel was efficient for treating hyperlipidemia without harming the liver.

Study demonstrates the potency of the ATV nanotransfersomal formulation. Both oral along with nanotransfersomal ATV formulations were successful in reducing the increased amounts of atherogenic lipids generated by P-407. Because of the prevention of first-pass metabolism plus the direct administration of ATV to the bloodstream, transdermal ATV nanotransfersomal gel seemed successful in the current study in decreasing Hyperlipidemia without increasing the activity of liver enzymes [36].

3.2 Nano Emodin transfersomes (NET)

Another of the ingredients of Chinese traditional medicines is Emodin, having the chemical formulae $C_{15}H_{10}O_5$. Amongst other factors, it seems to possess significant impacts on liver fibrosis, Hepatocytes damage, including inflammation. Latest investigations indicated Emodin can dramatically decrease the body weight accumulation associated with high-fat diets in rats, regulate problems with blood lipid along with glucose metabolism, improve anti-lipid peroxidation, and safeguard the functioning of the liver [37]. Emodin is believed to have a key role in the management of weight gain by increasing lipolysis and inhibiting adipocytes growth.

The high fat diet induced model was implemented in the present study to assess NET's anti-hyperlipidemic activities. Comparison to other groups, the body weight, blood TC, TG, LDL, and HDL all significantly decreased shortly after 8 weeks of NET treatment. During this investigation, the results of external usage demonstrated its capacity to alleviate the pathological changes of fatty liver, lower the peripheral fat percentage, raise serum HDL-C, and lower TG levels.

The current investigation offered thorough evidence that NET might aid in losing weight within obese rats via lowering overall body weight and abdominal fat. Likewise the biochemical evaluations indicated that external NET therapy reduced TG and increased HDL-C. Equal fat cell diameter, circumference, and area were all considerably reduced in the treatment group compared to the experimental group. Histopathological analysis revealed healthy liver tissue, which raises the possibility of NET emulsion might be having an effect upon what amount of energy is expended throughout fat metabolism. The research found that NET exhibited excellent entrapment efficiency and remained stable, which helped to decrease Hyperlipidemia [38].

4. CONCLUSION

Since Hyperlipidemia is growing more widespread worldwide and affects nations that are both developed and developing. Since there are numerous treatments available for Hyperlipidemia, such as statins, liver damage is a common adverse effect. The Transfersomes are more effective at treating Hyperlipidemia than orally administered medications without causing severe liver adverse reactions; being one of the non-invasive routes of treatment, it provides a suitable and perfect substitute for the conventional oral route of administration for several reasons, including avoiding gastrointestinal adverse reactions and hepatic first-pass metabolism. Therefore, transfersomes may have therapeutic relevance for hyperlipidemic individuals who need to stop taking their medications because of liver toxicity. In the end, transfersomes might create an opening of access for the carefully monitored Transdermal distribution of medication that cause adverse reactions when taken orally.

5. REFERENCES

1. NaserIH,AlkareemZA,MosaAU.Hyperlipidemia:pathophysiology,causes,complications,andtreatment.Areview.KarbalaJournalofPharmaceuticalSciences.2021Jan1;1(19).
2. ShattatGF.AreviewarticleonHyperlipidemia:types,treatmentsandnewdrugtargets.BiomedicalandPharmacologyJournal.2015 May3;7(1):399-409.
3. BarnhartJW,WagnerER,JacksonRL.InAntilipidemicDrugs:Medicinal,Chemical,andBiochemicalAspects.WitiakDT,Newman HAI,FellerDR.
4. JainKS,KathiravanMK,SomaniRS,ShishooCJ.ThebiologyandchemistryofHyperlipidemia.Bioorganic&medicinalchemistry.2007 Jul15;15(14):4674-99.
5. Tripathi,K.D.,2008.Essentials of medical pharmacology,6th edn.India:JPBrother's medical publishers, pp613-614.
6. BelayB,BelamarichPF,Tom-RevzonC.Theuseofstatinsinpediatrics:knowledgebase,limitations,andfuturedirections.Pediatrics.2007 Feb1;119(2):370-80.
7. RussellDW.Theenzymes,regulation,andgeneticsofbileacidsynthesis.Annualreviewofbiochemistry.2003 Jul;72(1):137-74.
8. NutescuEA,ShapiroNL.Ezetimibe:aselectivecholesterolabsorptioninhibitor.Pharmacotherapy:TheJournalofHumanPharmacologyandDrugTherapy.2003Nov;23(11):1463-74.
9. Rajan R, Jose S, Mukund VB, Vasudevan DT. Transfersomes-A vesicular Transdermal delivery system for enhanced drug permeation. Journal of advanced pharmaceutical Technology & Research. 2011 Jul;2(3):138.
10. Kodi SR, Reddy MS. Transfersomes: A Novel Topical Approach. Journal of Drug Delivery and Therapeutics. 2023 Feb 15;13(2):126-31.
11. Cevc G, Blume G. New, highly efficient formulation of diclofenac for the topical, Transdermal administration in ultra deformable drug carriers, Transfersomes. Biochimica et biophysica acta(BBA)-biomembranes.2001 Oct1;1514(2):191-205.
12. Talegaonkar S, Mishra P, Khar R, et al. Vesicular systems:an overview.Indian J Pharm Sci2006;68:141.<http://doi.org/10.4103/0250-474X.25707>
13. PrausnitzMR,LangerR.Transdermaldrugdelivery.Naturebiotechnology.2008Nov;26(11):1261-8.
14. Witika BA, Mweetwa LL, Tshiamo KO, Edler K, Matafwali SK, Ntemi PV, Chikukwa MT, MakoniPA. Vesicular drug delivery for the treatment of topical disorders: Current and future perspectives. Journal of Pharmacy and Pharmacology. 2021 Nov 1;73(11):1427-41.
15. Pawar AY. Transfersome: A novel technique which improves Transdermal permeability. Asian Journal of Pharmaceutics(AJP).2016Dec21;10(04).
16. Das B, Nayak AK, Mallick S. Transfersomes: a novel nanovesicular approach for drug delivery. In System of Nanovesicular Drug Delivery 2022 Jan 1 (pp.103-114). Academic Press.
17. Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for Transdermal drug delivery. Pharmaceutics. 2020 Sep;12(9):855.
18. Fernández-GarcíaR, LalatsaA, Statts L,Bolás-FernándezF,Ballesteros MP,SerranoDR.Transfersomes as nanocarriers for drugs across the skin: Quality by design from lab to industrial scale. International journal of pharmaceutics. 2020 Jan 5;573:118817.
19. Jiang T, Wang T, Li T, Ma Y, Shen S, He B, Mo R. Enhanced Transdermal drug delivery by transfersome-embedded oligopeptide hydrogel for topical chemotherapy of melanoma. ACS nano. 2018 Sep 5;12(10):9693-701.
20. RahmiAD,PangestiDM.Comparisonofthecharacteristicsoftransfersomesandprotransfersomes containing azelaic acid. Journal of Young Pharmacists. 2018;10(2s):S11.
21. JainAK, KumarF. Transfersomes: Ultra deformable vesicles for Transdermal drug delivery. Asian J. Biomater. Res. 2017;3:1-3.
22. KotlaNG,ChandrasekharB,RooneyP,SivaramanG,LarrañagaA,KrishnaKV,PanditRochevY.Biomimetic lipid-based nanosystems for enhanced dermal delivery of drugs and bioactive agents. ACS Biomaterials Science & Engineering. 2017 Jul 10;3(7):1262-72.
23. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, Bentley MV, Simões S. Development, characterization, and skin delivery studies of related ultra deformable vesicles:

transfersomes, ethosomes, and transethosomes. *International journal of nanomedicine*. 2015 Sep;18:5837-51.

24. Garg V, Singh H, Bimbrawh S, Kumar Singh S, Gulati M, Vaidya Y, Kaur P. Ethosomes and transfersomes: Principles, perspectives and practices. *Current drug delivery*. 2017 Aug;14(5):613-33.
25. Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: a novel technique for Transdermal drug delivery. *Journal of drug delivery and therapeutics*. 2019 Jan;9(1):279-85.
26. Rajkumar J, Kumar AS, Shahnawaz GJ, Sushmitha A. Recent Update on Transfersomes as Transdermal Drug Delivery System. *J Pharmacy and Drug Innovations*. 2021 Dec;10(3):2.
27. Modi CD, Bharadia PD. Transfersomes: new dominants for Transdermal drug delivery. *Am J Pharm Tech Res*. 2012;2(3):71-91.
28. Prajapati ST, Patel CG, Patel CN. Transfersomes: A vesicular carrier system for Transdermal drug delivery. *Asian Journal of Biochemical and Pharmaceutical Research*. 2011 Jan; 2(1):507-24.
29. Vinod KR, Kumar MS, Anbazhagan S, Sandhya S, Saikumar P, Rohit RT, Banji D. Critical issues related to transfersomes- novel vesicular system. *ACTA Scientiarum Polonorum Technologia Alimentaria*. 2012 Mar;11(1):67-82.
30. Sachan R, Parashar T, Soniya SV, Singh G, Tyagi S, Patel C, Gupta A. Drug carrier transfersomes: A novel tool for Transdermal drug delivery system. *International Journal of Research and Development in Pharmacy and Life Sciences*. 2013 Feb;2(2):309-16.
31. Hsiao SH, Chang HJ, Hsieh TH, Kao SM, Yeh PY, Wu TJ. Rhabdomyolysis caused by the moderate CYP3A4 inhibitor fluconazole in a patient on stable atorvastatin therapy: a case report and literature review. *Journal of clinical pharmacy and therapeutics*. 2016 Oct;41(5):575-8.
32. Zhou X, Mou Y, Shen X, Yang T, Liu J, Liu F, Dong J, Liao L. The role of atorvastatin on the restenosis process post-PTA in a diabetic rabbit model. *BMC Cardiovascular Disorders*. 2016 Dec;16:1-8.
33. Lennernäs H. Clinical pharmacokinetics of atorvastatin. *Clinical pharmacokinetics*. 2003 Nov;42:1141-60.
34. Lau YY, Okochi H, Huang Y, Benet LZ. Pharmacokinetics of atorvastatin and its hydroxymetabolites in rats and the effects of concomitant rifampicin single doses: relevance of first-pass effect from hepatic uptake transporters, and intestinal and hepatic metabolism. *Drug metabolism and disposition*. 2006 Jul;34(7):1175-81.
35. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Mol Biol*. 1965;13:238-25.
36. Mahmoud MO, Aboud HM, Hassan AH, and Ali AA, Johnston TP. Transdermal delivery of atorvastatin calcium from novel nanovesicular systems using polyethylene glycol fatty acid esters: ameliorated effect without liver toxicity in poloxamer 407-induced hyperlipidemic rats. *Journal of controlled release*. 2017 May;28:254:10-22.
37. Jiang HY, Chen Y, Zhang H. Determination of Emodin in different products of *radix sophoraeflavescens* [J]. *Chin Tradit Patent Med*. 2001;23(3):185-7.
38. Lu K, Xie S, Han S, Zhang J, Chang X, Chao J, Huang Q, Yuan Q, Lin H, Xu L, Shen C. Preparation of a nano Emodin transfersome and study on its anti-obesity mechanism in adipose tissue of diet-induced obese rats. *Journal of translational medicine*. 2014 Dec;12(1):1-4.