Review Article

Transferosome:ANovelTransdermalDrugDeliverySystemfortheTreatmentofHyperlipidemia

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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. Transfersomes are ultradeformable nanovesicles made of lipid bilayer of phospholipids in conjugation with edge activator that surrounds an aqueous core. Transfersomes are mainly prepared by film hydration method, reverse-phase evaporation method, modified handshaking method, vortexing–sonication method, and ethanol injection method.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 arespecifically 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: *Transferosomes, Transdermal delivery system, Vesicular carrier, High Entrapment Efficiency,Bioavailability,Cerebral strokes,Hyperlipidemia.*

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1. INTRODUCTION

A chronic condition known as Hyperlipidemia is defined with elevated levels of total cholesterol (TC), totalglycerides(TG),low-densitylipoproteincholesterol(LDL-C),andinadequatelevelsofhigh-densitylipoprotein cholesterol (HDL-C). In both advance and developing nations, Hyperlipidemia has becomeprevalent 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 heartattacks, strokes, liver damage, along with kidney failure. The disorder is typically without symptoms, whilean individual learns about it through standard tests for blood. When Hyperlipidemia attains its final phase,peoplecan getnumerousconsequencessuch hypertension andangina[1].

The two main forms for Hyperlipidemia include as follows. The primary form of Hyperlipidemia usually avery 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 kidneydamage,drinking,medications(B-blockers),even thyroid problems. [2].

1.1 PathophysiologyofHyperlipidemia

ThePathophysiologyof HyperlipidemiacanbestudiedunderthetwoclassificationsofHyperlipidemia.

1.1.1 Exogenouspathway:routeofdietarylipidabsorption

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 alongwith muscle, lipoprotein lipase breaks down chylomicrons. The remaining Chylomicrons migrate towardsthe Hepatocytes once TG is removed forstorage.Dietary TG is the outcome, which is deposited withinthemusclesalong withfattytissue.

1.1.2 Endogenous pathway: Cholesteryl esters (CE) transport pathway from liver to target cells MostofthetriglyceridesareremovedfromtheVLDLfromlipoproteinlipaseafterthis is producedthroughliverandtransportedviaplasmatowardsmuscularandfattissue.Wheneveralltriglyceridesarecompletelyremoved,remainingIDLmaybeabsorbedviatheHepatocytesandtransportedtillthatischangedintocholesterol-richLDLmolecules.PlasmaLDLiseliminatedviaendocytosis,whichisregulatedwithLDLreceptors.Consequently,TGalongwithCEaretransportedtowardtheintendedcellsby liver-derived VLDL and LDL,correspondingly. [3,4].

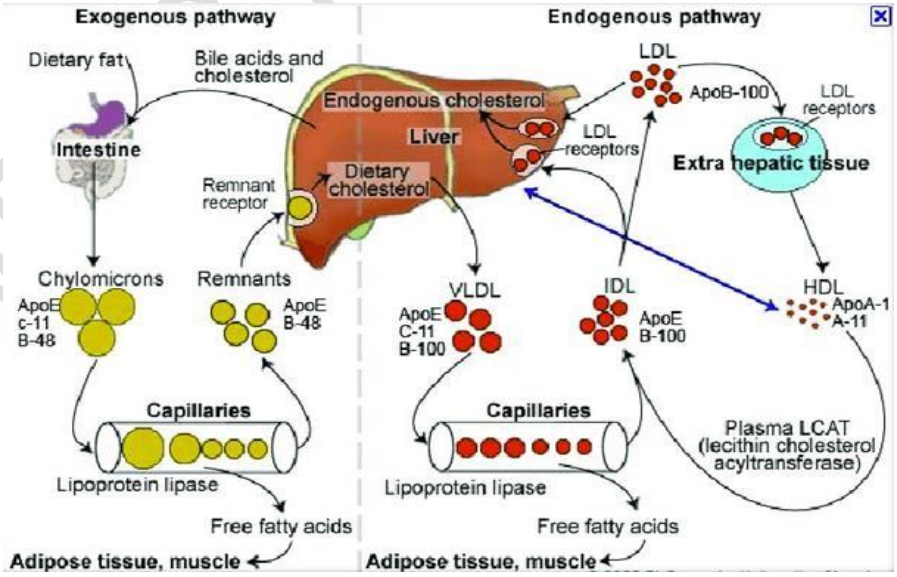

Figure1:PathophysiologyofHyperlipidemia

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In overall, hyperlipidemia has little overt consequences. Nevertheless, unless it leads to atherosclerosis /coronaryheartdisease(CHD),patientstobedetectedafterregularchecksandwhenindividualspersistat the risky stages before a stroke or heart attack. Persons having hereditary types ofthis condition aswellthose having high blood cholesterol levels mightgetaccumulation ofcholesterol beneath theirdermis, particularly around their eyes. [5] Individuals may have the following warning signs: Angina (chestdiscomfort/ tightness), blockage ofheartand brain blood arteries,elevated arterialpressurestrokes,heart attack, and when triglyceride levels rise, lumps develop around the knees. The pancreas along withlivermightbecome enlarged.Heartalongwith brainvesselsmighthave been obstructed[2].

1.2 Treatment

(HMG-CoA)Reductaseinhibitors(Statins)3-Hydroxy-3-methylglutarylcoenzymeA
It involves the following medications: Lovastatin, simvastatin, Pravastatin, Fluvastatin, atorvastatin, alongwith Rosuvastatin. These medications have been shown for managing hypercholesterolemia and maydecreasecholesterollevelsby20%to 50%.[6].

Bileacidsequestrants

Cholestyramine,Cholestipol,Colestimide,alongwithColesevelamwasbileacidsequestrants.Cholestyramine along with Cholestipol remains both bile acid sequestrants known to be presently on themarket. Forintestine, bile acids get released that play an essential function in making it simpler to digestlipidsthrough diet. [7,4].

Fibricacidderivatives(Fibrates)

Fibrates,acategoryoffrequentlyprescribedAntihyperlipidemicdrugsthatalsoincludeClofibrate,Gemfibrozil,Fenofibrate,andBezafibrate,significantlylowerplasmatriglycerideswhileonlymildlyloweringLDL cholesterol.ThelevelofHDL cholesterolrisessomewhat.

Nicotinicacidderivatives(Niacin)

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

Selectivecholesterolabsorptioninhibitor (Ezetimibe)

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

2. TRANSFEROSOMES

An artificial vesicle called a Transferosomes transporter is made to resemble a cell vesicle or a cell that isexocytosing,makingitappropriateforregulatedalongwithselectivemedicationadministration.Transferosomes comprise a highly flexible and stress-sensitive complex aggregation. Its primary form hasan extensive lipid bilayer that encasing an aqueous core in an ultra-deformable vesicle. Because of theinterdependence of the localized content and form of the bilayer, the vesicle is self-regulating and self-optimizing. As a result, the Transferosomes can pass through a variety of transportation obstacles alongwith serve as drug carriers for non-invasive selective medication administration along with sustainedrelease of medicinal chemicals. One of the greatest divisive methods to deliver medicament through theskinincludesthe utilization ofvesicleformation[9].

The SC (Stratum Corneum), a thin layer of skin, serves as durable, malleable barriers along with iswater-resistant. It consists of the keratinized, flattened remains of growing epidermal cells. Numerousmethodswereinvestigatedtogetbeyondthisbarrier,involvingelectrophoresis,chemicalpermeation

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enhancers,iontophoresis,microemulsions,alongwithnovelvesicularcarriersfacilitatingcarryingmedicationsthroughtheskin,which includeliposomes,noisome,Twosomes,andtransferosomes[10].

Auniquetypeofliposomecalledatransfersomecontainsbothphosphatidylcholineplusanedgeactivator. They're pliable, spongy vesicles designed to more efficiently convey active substances [11]. TheGerman company IDEA AG owns the trademarks and uses them to identify their distinct medicationdelivery technology. The term "carrying body" is derived from the Latin verb "transfere," which means "tocarry across,"and the Greekword"soma,"whichmeans"body."

Transferosomes are self-aggregates with an incredibly flexible membrane that transfer drugs into orthrough the skin in a consistent manner. Compared to typical liposomes, these vesicular vesicles are anumber of orders of magnitude more elastic. Transferosomes circumvent the obstacle of skin penetrationby squeezing along the stratumcorneum'sinternal sealinglipids.
Transdermaldrug delivery is evolving towards a replacementwith the traditionaloraldrug delivery,especially besides serving as an alternative for hypodermic injections [12]. Particularly, transdermal drugdelivery works better than oral drug delivery in a variety of manners, like preventing first-pass metabolism,thathasa negativeimpactondrugbioavailabilityalongwith producesafastdrug metabolism[13].

Thedisadvantagesofhypodermicinjections,especiallyirritationneartheinjectionsite,substantialunease, along with the grave worry of medical waste including illness spread upon reusing syringe are alleliminated via transdermal delivery. Affordably priced and easily administered transdermal medicationdelivery systems were available. The few drugs which can be altered with transdermal distribution is adisadvantageofthisformoftreatment [14].

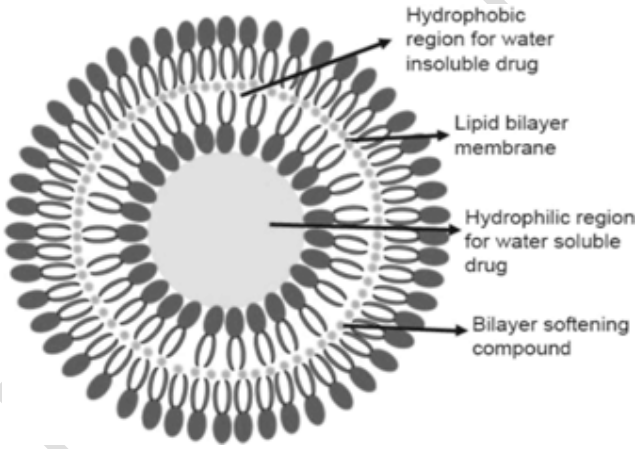

Figure2Structure ofTransfersome

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

The aqueous core is encased in a bilayer of lipids to produce ultra-deformable vesicles having regulatorycapabilities. Edge activator increases a vesicle membrane's capacity for deformation, while mixed withincorrect proportion with a sufficient quantity of lipids; this increases the flexibility and penetrating thetransferosomes. By adding edge activators, hydrophobic medications become more soluble, increasing thedrug's ability to be captured [15]. According to research, vesicles having size >600 nm permeate deeplythrough skin layers compared to those having sizes <300 nm, while those having sizes <70 nm exhibithighest content of accumulation in the epidermis along with dermis skin layer [16]. It happens by thevesiclestructure'sinclusion both hydrophilicand lipophiliccomponents.

Being projected to be smaller than 300 nm, transferosomes have highly ultra-deformable vesicles whichmaysqueezeviatheSCwhichentertheskinasfullyformedvesicles.Medicineswithahydrophilic

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

2.1 MechanismofTransferosomes

Transferosomes may transmit about 0.1 mg of lipids every hour and cm2 via healthy skin if appliedappropriately. Compared to what is generally established by the gradient of transdermal concentration,thisquantityissignificantlylarger.Theactualexplanationforthishigherflowrateisduetothe"Transdermal osmoticgradient". The skin permeation barriers inhibits transpiration ofwaterthroughoutthe skin by maintaining its water content at 75% in the epidermis and at 15% in the stratum corneum, thatis positioned close towards the skin's surface. Almost every polar lipid absorb a little water as a result ofthe interaction between hydrophilic lipid residueswith the adjacentwater.Lipid vesicles strive to bridgethe "osmotic gradient" they encounter if a lipid transferosome suspension is put to partially dried skin in aneffort to prevent complete dryness. In contrast to transferosomes, that possess hydrating and surfactantproperties that have the capability of significant deformation, they can do only if they're enough bendableto squeezevia the skin'smicroscopicopenings.

As pushing down the lipids of SC, transferosomes circumvent the challenge to skin penetration. It is yetunclearhow to enhance medicinal componentdeliverythrough the skin. Twomethods which weresuggestedare asfollows:
1. Sincetransferosomeswithstand penetratetheskinintact,theseare usedasmedicationvectors.
2. Transferosomes functions as penetrating boosters, improving the passage of drug molecules across thestratumcorneumbyrupturingthe closelybonded intercellularlipidswithinthe SC[9,15].

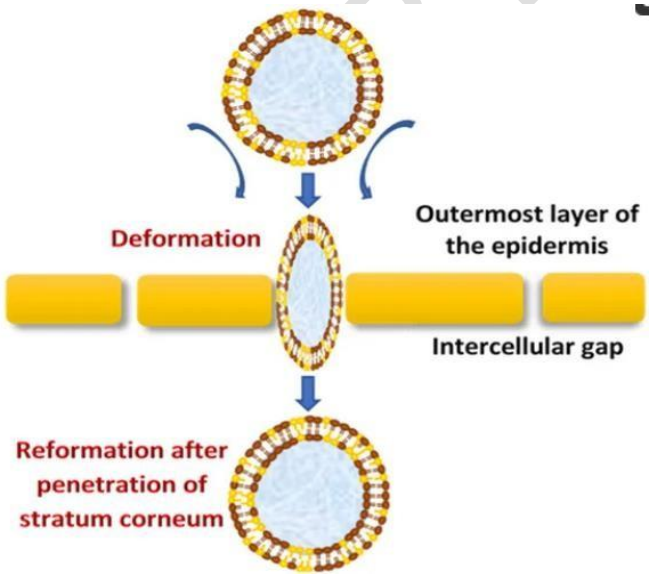

Figure3MechanismofTransfersome

2.2 CompositionofTransferosomes

Transferosomestypicallyconsist of
1. To begin with, the primary element, a amphipathic substance (such as soy phosphatidylcholine, eggphosphatidylcholine,etc.),iswhatcreatesavesiclethatcreatesthelipid bilayer[19,20].
2. Surfactants like sodium cholates, sodium deoxycholate, Tweens along with Spans (Tween 20, Tween60,Tween80,Span 60,Span65,and Span80), ordipotassiumglycyrrhizinate,knowntobebiocompatiblebilayer-softeningsubstanceswhichenhancevesicles'bilayerflexibilityandenhance

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permeation,havebeenmostfrequentlyusededgeactivatorsintransfersomeformulations[9,19,21,22,23].

3. The hydrating medium can either water or a saline phosphate buffer (pH 6.5-7), whereas the solventusedincludes3 to 10%alcohol(ethanolormethanol)[15,24].

2.3 AdvantagesofTransferosomesasaCarrier

1. Transferosomes enhance bioavailability, adherence among patients, overall adverse reaction reduction[17].
2. HighEntrapmentof90%Transferosomescanboosttheefficiencyoflipophilicmedicines.Ifentrapment efficiency is poor, lipophilic encapsulation may be improved through adding a surfactanthaving alowHLBscale[18].
3. Itservesasa storagefacilityand deliversthemedication gradually[25].
4. Transferosomes are biocompatible and biodegradable since they contain native phospholipids, whichare also present in liposomes. Transferosomes are used for topical as well as systemic delivery ofdrugs.
5. Transferosomesaresimpletobuildastheydonotrequiretime-consumingprocesses ortheunintended utilization of pharmaceutical ingredients. They have high entrapment efficiency, especiallyinthecase oflipophilicdrugs,nearly90%.
6. Theycanbendorsqueezedovertheepidermalbarrierduetoitselasticpropertieswithoutwastingany drugs.
7. Because of its mixture of lipophilic along with lipophobic moieties, this is capable of accepting drugshavinga wide range ofsolubility's[21].
8. Theseareemployedtotransportavarietyofsubstances,includingprotein,peptides,insulin,corticosteroids,NSAIDS,analgesics,even anesthetics[26].

2.4 LimitationsofTransferosomes

1. Transferosomesarechemicallyunreliablebecausethey're susceptibletooxidative degradation.
2. Anotheraspectthatgoestowardstheutilizationoftransferosomesasdrugdeliverysystemsistheirpurityoftheirnatural phospholipids.
3. Transfersomepreparationsareexpensive[27,28,29,30].

3. THERAPEUTICPOTENTIALOFHERBAL ANDXENOBIOTICSMEDICINEFORMANAGEMENTOF HYPERLIPDEMIA

3.1 Atorvastatincalcium(ATV)-loadedtransferosomes

The rate-limiting stage for cholesterol production, when HMG-CoA breaks down into mevalonate, it ishinderedbyaparticularinhibitorof3-hydroxy-3-methylglutarylcoenzymeA(HMG-CoA)reductase,atorvastatin calcium (ATV) [31]. This is employed for treating people who have high cholesterol in order toreduce plasma levels of total cholesterol and specifically, low-density lipoprotein cholesterol (LDL-C), byraising the number of LDL receptors on Hepatocytes. Thereby quickens the process of LDL-C absorptionand oxidation [32]. Upon an oral dose, ATV has a maximum bioavailability of 14% [33]. Reduced systemicavailability 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 elevatedplasma transaminase activity as well as appear to be regulated by a number of variables, which involveboth,pharmacokineticalong withphysicochemicalproperties.

According to the thin film hydration approach, several ATV Transfersomal vesicles developed [35]. Theanti-hyperlipidemic activity of the nanotransfersomal formulation T8 has been investigated. It was pickedfor the purposes of the present study then transformed into gel by adding 1% (w/w) carbopol 971PWhilecontrasting to the hyperlipidemic group (P-407 only) or the group administered using a conventional ATVgel, overall cholesterol, triglyceride, along with LDL-C levels were substantially reduced in the two groupsadministeredwitheitheroralATVorthetransdermalATVnanotransfersomalgelinpoloxamer407-

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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 usingnanotransfersomal ATV formulations resulted in a notable improvement in the lipid profile without havingany adverse impacts on the liver. It has shown that the ATV nanotransfersomal gel was efficient fortreatinghyperlipdemiawithoutharming theliver.
StudydemonstratesthepotencyoftheATVnanotransfersomalformulation.Bothoralalongwithnanotransfersomal ATV formulations were successful in reducing the increased amounts of atherogeniclipidsgeneratedbyP-407.Becauseofthepreventionoffirst-passmetabolismplusthedirectadministration of ATV to the bloodstream, transdermal ATV nanotransfersomal gel seemed successful inthecurrentstudyin decreasingHyperlipidemiawithoutincreasing theactivity ofliver enzymes[36].

3.2 NanoEmodintransferosomes(NET)

Another of the ingredients of Chinese traditional medicines is Emodin, having the chemical formulaeC15H10O5. Amongst other factors, it seems to possess significant impacts on liver fibrosis, Hepatocytesdamage, including inflammation. Latest investigations indicated Emodin can dramatically decrease thebody weight accumulation associated with high-fat diets in rats, regulate problems with blood lipid alongwith 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 andinhibitingadipocytesgrowth.

ThehighfatdietinducedmodelwasimplementedinthepresentstudytoassessNET'santihyperlipidemic activities.Comparison to other groups, the body weight, blood TC, TG, LDL, and HDL allsignificantly decreased shortly after 8 weeks of NET treatment. During this investigation, the results ofexternal usage demonstrated its capacity to alleviate the pathological changes of fatty liver, lower theperipheralfatpercentage,raiseserumHDL-C,andlower TGlevels.

The current investigation offered thorough evidence that NET might aid in losing weight within obese ratsvia lowering overall body weight and abdominal fat. Likewise the biochemical evaluations indicated thatexternal NET therapy reduced TG and increased HDL-C. Equal fat cell diameter, circumference, and areawereallconsiderablyreducedinthetreatmentgroupcomparedtotheexperimentalgroup.Histopathological analysis revealed healthy liver tissue, which raises the possibility ofNET emulsionmight be having an effect upon what amount of energy is expended throughout fat metabolism. Theresearch found that NET exhibited excellent entrapment efficiency and remained stable, which helped todecreaseHyperlipidemia[38].

4. CONCLUSION

Since Hyperlipidemia is growing more widespread worldwide and affects nations that are both developedand developing. Since there are numerous treatments available for Hyperlipidemia, such as statins, liverdamage is a common adverse effect. The Transferosomes are more effective at treating Hyperlipidemiathan orally administered medications without causing severe liver adverse reactions; being one of thenon-invasive routes of treatment, it provides a suitable and perfect substitute for the conventional oralroute of administration for several reasons, including avoiding gastrointestinal adverse reactions andhepaticfirst-passmetabolismTherefore,transferosomesmayhavetherapeuticrelevanceforhyperlipidemic individuals who need to stop taking their medications because of liver toxicity. In the end,transferosomes might create an opening of access for the carefully monitored Transdermal distribution ofmedicationsthatcause adverse reactionswhen taken orally.

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