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TRANSDERMALDRUG DELIVERY SYSTEM:NIOSOMESA MAGICAL MISSILE FOR NEOTERIC DRUG

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ABSTRACT

In the past, the most affordable way of drugdelivery systemwas oral. Traditionaldosage forms such as capsules, pills, and tablets have been followed for ages, but they present various challenges such as intermittent dosing frequency, first-pass metabolism,poor absorption and bioavailability, poor patient compliance, and swallowing difficulties in geriatrics and pediatrics. To avoid these problems, an improved method of administering the drug to the body was introduced. TDDS aims to transport a drug molecule through the skin and has several advantages such as neglecting first-pass metabolism, delivery of the drug when oral administration is not appropriate, avoiding absorption of thedrug from the gastrointestinaltract, and ease of use and removal. Transdermaldrug delivery isaskin barrier provided by itsouter layer beforeitreachesthesystemiccirculation. This review covers new drug carriers, such as niosomes, which can effectively encapsulate various drugs and can be used in transdermal drug delivery systems to improve drug specificity and help overcome the drug's barrier function for better absorption through the skin.

KEYWORDS:Niosomes,Transdermaldelivery,Patientcompliance,improvedabsorption,Better bioavailability

INTRODUCTION

Unlike injectable and oral methods, transdermal delivery has the significant advantage of patient acceptance and avoidance offirst-pass metabolism, allowing continuous infusion of drugs with short half-lives into the body avoiding pulsatile entry into the bloodstream. they usually have negative side effects[1]. Thus, several innovative drugs havebeen developed, including transdermal, controlled release, and transmucosal drugs. Transdermal drug delivery has several important advantages, including limitinghepatic first-passmetabolism, improving therapeutic efficacy and maintaining constant plasma drug levels[2]. Deposit patches work in a very simple way. A patch that is used on the skin for a long time will receive a significant dose.The drug is carried directly into the blood vessels of the skin by a diffusion process [3,4]. Interest in transdermal therapy has increased in recent years due to several variables, such as new clinical data from technology companies and pharmaceutical companies looking for new ways to extend drug patents[5]. Advantages of TDDS- Better bioavailability,longer duration of action resulting in reduced dosing frequency[6]. TDD is a good alternative to a short half-life drug. Flexibility to stop drug therapy by simply withdrawing.With these systems it is possible to self-regulate [7,8]. They are not invasive; they avoid interruption of parenteral therapy and maintain plasma concentrations of powerful drugs [9].

AdvantagesofTDDS

1. Betterbioavailability
2. Prolongeddurationofactionleadingtoreduceddosingfrequency.
3. Transdermaldrugdeliveryisagoodalternativetoadrugwithashorthalf-life.
4. Flexibilitytostoptakingmedicationbysimplyremovingthespotfromtheskinwithoutdiscomfort.
5. Fewersideeffects.
6. Self-regulationispossiblewiththesesystems.
7. Theyarenotinvasive;theyavoidinterruptionofparenteraltreatment
8. Theymaintaintheplasmaconcentrationofeffectivedrugs.

DisadvantageofTDDS

1. Drugsensitivityorskinsensitivityisnotsuitablefortransdermaltreatment.Manydrugs,especiallythosewithhydrophilic properties, penetrate the skin very slowly and cannot be effective in all possibilities of an allergic reaction [10].
2. When administering an ionic drug, drugs of high molecular weight cannot be taken at a therapeutic level. There is a significant delay in [11,12] .
3. LimitationsofTDDSSkinpenetrationlimitations,useofonlypotentdrugsandincompatibilitywithlargemolecules(molecules above 500 Daltons)
4. Highly soluble drugs cannot be delivered by this methoddue to their limited fat and water content. Medicines can break down in the skin. Ionic drugs cannot be delivered by this mechanism [13].

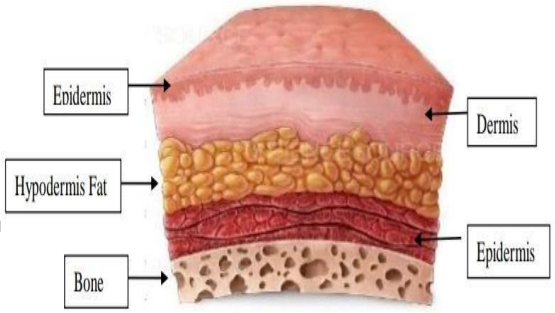
LimitationsofTDDS

1. Limitsofskinpermeability,useofonlypotentdrugsandincompatibilitywithlargemol

ecules(moleculesabove500Daltons)
2. Verysolubledrugscannotbeadministeredbythismethodbecausetheyarebothwaterandfatsoluble.
3. Notacceptediftheycauseskinirritation.
4. Adhesionofthepatchtotheskin.
5. Thedrugcanbreakdownintheskin.
6. Ionicdrugscannotbedeliveredbythismechanism.
7. TDDSonlyworkswitheffectivedrugs[14].

ANATOMYANDPHYSIOLOGYOFSKIN

The blood circulating in the body is received by the largest organ of the body, the skin, which covers an area ofabout 20 square feet. It increases the body's sensitivity to cold and heat and helps control key messages. The skin acts as a barrier that prevents sweat and excess water from leaving the body.The purpose of skin, the multi-layered outer layer of our body, is to protect it from natural hazards, including chemical heat and toxins[15]. Each of its skin layers has properties that prevent transdermal spread, including the epidermis, which acts as a barrier between us and the environment, and the dermis, which has blood vessels and produces skin cells [16].



Figno.1 -Anatomyoftheskin

The complex web-like structure of the skin acts as the body's first line of defense against infection, UV rays, toxins andmechanical damage. The stratum corneum (dead epidermis) and the active epidermis are complementary parts of the epidermis. Stratum Lucidium, Stratum Granulosum, Stratum Spinosum, and Stratum Germinativum are the four layers that make up theactive epidermis. The stratum corneum, the outer layer of the skin, which acts as a barrier to external objects, is where the protective quality of the epidermis is first observed. The inhibitory effect is crucial for the transport of drugs of high molecular weight [17]. For high molecular weight substances, the intracellular approach is used and is more commonly used than the intercellular approach. However, this is because the skin component known as lipid, which contains cells as well as hydrophilic and hydrophobic chemicals, did not develop during skin formation on a completely normal but normal surface [18,19].

Routesofpermeationthroughskin[20,21].

1. Intercellularroute
2. Intracellularroute

BasicelementsofTDDS[22,23].

i. Polymermatrix
ii. API
iii. Permeationenhancers
iv. Differentexcipient

1) PolymerMatrix:

Thischemicalingredientregulateshowquicklythemedicationisreleasedontothewire.Thepolymercannotbeusedin transdermal patches unless the following requirements are satisfied. The polymer must exhibit the following pre-requisites:

- Stability
- Non-toxicandeaseofmanufacture.
- Thepolymershouldbereasonablypriced[24].

Thefollowingpolymersaresuitableforstratumdevices:

- NaturalPolymers:GelatinfromCellulose,Wax,NaturalRubber,Starch,etc.
- Synthetic elastomers include,for example,polybutadiene, hydrationrubber, polysiloxane,nitrile, propenonitrile, styrene-butadiene rubber, and others.
- Synthetic polymers, such as PVC, polyvinyl alcohol, polyamide, polyurea, polyvinyl pyrrolidone, polymethylmethacrylate, epoxy, etc.[25].

2) Drug

The medicine should be carefully chosen for the effective development of a TDDS. The following are some characteristics of amedicine that are ideal for transdermal distribution:

1. AMWoflessthan1000Daltonisrequired.
2. Thedrugshouldhaveaffinityforbothlipophilicandhydrophilic.
3. Thedrugshouldhavealowmelting point.

Biologicalproperties:

1. Themedicationshouldbeeffectiveatadoseofonlyafewmilligramsperday.
2. Thehalf-lifeneedstobe brief.
3. Themedicationmustnotcauseanallergicorirritatingreactionontheskin.
4. Transdermaladministrationisappropriatefordrugsthatbreakdowninthedigestive tract.
5. Drugsthatmustbetakencontinuouslyoveranextendedlengthoftimecanbedesignedfortransdermaldelivery[26].

3) PermeationEnhancers:

These chemicals increase skin porosity by modifying the skin's barrier function to the flow of desired product. To promote skin penetration, the dehydrator is supposed to have touched one or more of these layers. Many computers have been studied for their capacity to increase stratum corneum permeability [27].

Chemical enhancer: Chemicals that promote the penetration of topically applied drugs are commonly referred to as accelerants, absorption promoters, or penetration enhancers.

Classificationofchemicalenhancers:

1. Terpenes:e.g.menthol,carvone,etc.
2. Pyrrolidone's:e.g.N-methyl-2pyrrolidone,azone,etc.
3. Fattyacid:e.g.oleicacid,lauricacidetc.
4. Sulfoxides:e.g.dimethylsulfoxide.
5. Alcohols:e.g.ethanol,octylalcohol, etc.
6. Miscellaneousenhancer:e.g.Phospholi

pids,aminoderivatives,etc[28].

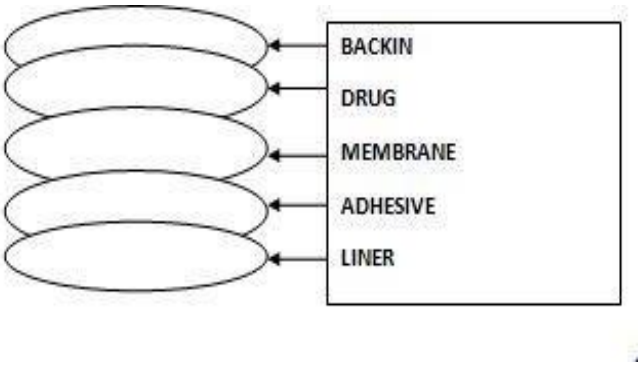


Fig.no.2IllustrationofdifferentlayersofTransdermalpatch

a) Dissolution in the preparation and release of the preparation.

SKINBARRIERSTHATNEEDTOBEOVERCOMEI NDELIVERINDRUGTRANSDERMALLY

A) STRATUMCORNEUM

The outer layer of the skin is primarily a rate-limiting barrier that tends to limit the entry and exit of chemical substances into the skin. The stratum corneum is also called the stratum corneum and its protective function depends on the components from whichitismade, i.e.75-80%proteins,5-15%lipidsand5-10%ondansetron,calculated on thedryweightofthelayer.corneaofmaterial. The cornea is relatively impermeable but also flexible, while the stratum corneum is composed of coenocytes embedded in a lipid matrix that is crucial for the protective barrier function of the skin. The absorption of drugs and the ability to reach the systemic circulation involves several steps, for example:

b) Distribution in the outer layerofthe skin,stratum corneum.
c)Diffusion mainlythrough the stratum corneum (SC) through intercellular lipid pathways
d)Diffusion into the aqueous solution of the epidermis coming from the SC, diffusion through the incoming epidermis and into the upper dermis, and adsorption into the papillary dermis [29].

B) TIGHTJUNCTIONS

Tightjunctionsactasabarrierinepidermalgranulosis.Atightjunctionusuallyformsabarriertoparticlesormoleculesof different sizes. Tight junctions, especially claudins, can prevent the charge-selective transport of compounds[30].

c) Hyaluronicacidmatrix:

Gel-likematrixofdermiscomposedofhyaluronicacidandothergly cosaminoglycans.Thismatrixlimitsthediffusionof molecules, especially large molecules, through the skin[31].

Conventionaldrugdeliverysystem	Targetedpolymericdrugdeliverysystem
Affecthealthytissue/organs	Donotaffecthealthy tissue/organs
Bioavailabilityislow	Highbioavailabilityandbiocompatibility
Non specific	Specific
Lowerefficacyandtherapeuticeffect	Higherefficacyandtherapeuticeffect
Toxicitylevelishigher	Toxicitylevelislower
Highdoserequired	Lowdoserequired
Highersideeffect	Lowersideeffects

Table1.COMPARISONOFCONVENTIONALANDPOLYMERICDRUGDELIVERYSYSTEM

TRANSDERMALDELIVERYOFDRUGSVIANOVELCARRIER:NIOSOMES

Niosomal formulations are believed to have several advantages over standard topical formulations, including better solubility, better pharmaceutical activity, stability, resistance to toxicity, and absorption. Many disease models have recently been applied to study TDDS using niosomes, and current research focuses on protocol optimization and innovative formulation[32]. Transdermal delivery of drugs contained in niosomes increased the rate of penetration, as the slow penetration of the drug through the skin is a major limitation. Disadvantage of transdermal administration to other dosage forms. The local distribution of erythromycin from several formulations, including niosomes, was studied in hairlessmice, and confocal microscopy showed that anionic vesicles can be engineered to target sebaceous glands. nanocarriers, which have been an immediate drug delivery strategy due to their undoubted advantages. They have amphiphilic molecular lamellar structures enclosed in a fluid compartment. Surfactants are amphiphilic and have hydrophobic and hydrophilic groups that can self-assemble into various geometric shapes, such as micelles or planar lamellar bilayers. Sorbitan esters and

analogs based on polyoxyethylene, polyglycerol, sometimes in combination with membrane additives such as cholesterol, can be used as potential drug delivery methods [34] .

MERITS

1. Alowerdoseisneededtoachievethecorrecteffect.
2. Cancapturebothlipophilicandhydrophilicdrug.
3. Canincreasetheabilityofthedrugtoreachthe skin.
4. Ifnecessary,thepropertiesofthedruginthebubble,suchassizeandlamellarity,canbechanged.
5. Vesiclescanactasreservoirsthatallowcontrolledreleaseofdrugsovertime.
6. Canbeusedforseveraldrugsbecausetheirstructureslowstheentrapmentofbothhydrophilicandlipophilicdrugs.

DEMERITS

1. Fusion
2. Aggregation
3. Leakageofencapsulateddrug[35].

FORMULATIONCOMPONENTSOFNIOSOMES

Thetwomainingredientsutilizedtopreparenniosomesarenon-ionicsurfactantsandcholesterol.
Rigidity and the right form are provided by cholesterol.The Niosome production is significantly influenced by surfactants. For the manufacture of niosomes non-ionic surfactants such as:

a) spans(span20,40,60,85,80)
b) tweens(tween20,40,60,80)
c) Brij(Brij30,35,52,58,72,76)[36].

Because several mechanisms have been proposed to account for niosomes' ability to enhance transdermal drug transport, but a single mechanism is not sufficient. Suggestions include: a change in the protective function of the stratum corneum fromreversible disruption of lipid organization and a reduction in trans epidermal water loss leading to hydration of the stratumcorneum and relaxation or absorption/fusion of its tightly packed cell structures. alternatively, niosomes can fuse with the cell membrane,whichwouldresult in acomplete mixingofthecytoplasm andniosomes contentsif thematerial enteringtheniosomes cavity is released into the culture medium by lysozymes; ispresent in the cytoplasm and degrades or can disrupt the membrane of niosomes [38,39]. Many studies have shown significant contributions to the evaluation of Niosome vesicles as a permeabilityenhancer.The goal of the researcher was to find out if the structural sequenceof the niosomes used to transfer the active molecule determines the greater penetration of hydrophilic drugs through the skin, which is always seen in vesicular systems, or if itdepends only on its binary nature of surfactant used to make Niosomal molecule[40].

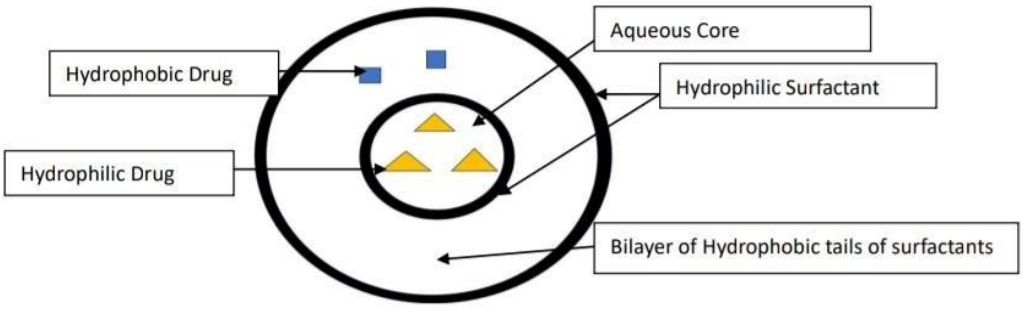


Figure3-StructureofNiosome

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Here'showniosomeshelpintransdermaldrugdelivery:

1. **Improved penetration:** niosomes can encapsulate drugs in their aqueous compartments or lipid bilayers formed by surfactant molecules. This capsule protects the drug from degradation and improves its penetration through the layers of the skin. The lipid bilayers of niosomes can fuse with the lipids of the stratum corneum (the outermost layer of the skin), which facilitates the transport of drugs into the deeper layers of the skin[41].
2. **Targeted delivery:** Niosomes can be designed to deliver drugs to specific skin layers or even target skin cells (e.g., keratinocytes or fibroblasts).This targeted delivery reduces systemic exposure and can improve treatment efficacy while minimizingsideeffects. Controlledrelease:Thelipidbilayer structureofniosomesallowscontrolledreleaseofdrugsover a long period of time. This long-lasting profile may result in a prolonged therapeutic effect and reduced frequency of administration.
3. **Biocompatibility:** Niosomes are generally biocompatible and biodegradable, reducing the risk of toxicity or irritation when applied to the skin. This property is crucial for the development of safe transdermal drug delivery

systems.

4. **Stability:** Niosomes help protect drugs from degradation due to enzyme activity or changes in the pH of the skin environment. This stability ensures that a sufficient amount of the active drug reaches the target intact.
5. **Versatility:** Niosomes can encapsulate both hydrophilic and hydrophobic drugs, making them versatile for transporting various pharmaceutical compounds across the skin barrier[42].

Together, niosomes improve transdermal drug delivery by improving drug penetration through the skin, providing targeted delivery to specific skin layers, enabling controlled release, ensuring drug stability and maintaining biocompatibility. These properties make niosomes promising carriers for the development of efficient and safe transdermal drug delivery systems.

METHODOFTRANSDERMALDRUGDELIVERYTHROUGHNIOSOMES

- **BilayerFusion**:Niosomescanfusewiththelipidbilayersoftheskin,releasingthedrugdirectlyintotheskin layers[43].
- **Endocytosis**:Niosomescanbetakenupbyskincellsthroughendocytosis,deliveringthedrugintothecytoplasm[44].
- **FluidizationofLipidMatrix**:Niosomescanfluidizethestratumcorneumlipidmatrix,whichincreasesthe permeability of the skin to the encapsulated drug[45].

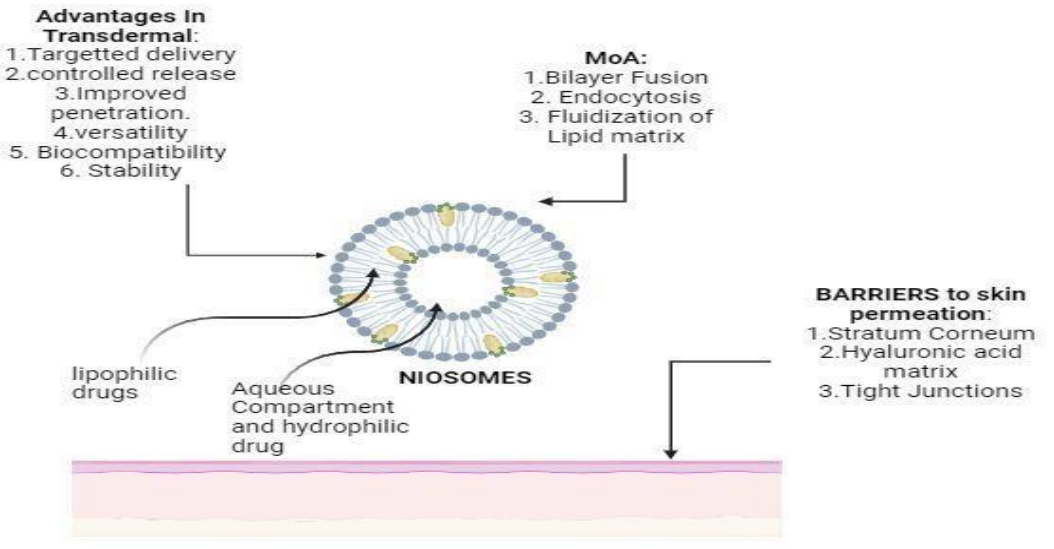

Fig.4 Mode of action (MoA)

andstructuralcompartmentsofNiosomes

METHODOFPREPARATIONOFNIOSOMES

1) HANDSHAKINGMETHOD

The surfactant and cholesterol mixture are dissolved in 10ml of diethyl ether in an RBF. The ether is evaporated under vacuum at room temperature in a rotary evaporator. Upon hydration, the surfactant swells and detaches from the substrate to form a membrane, as in lipids in lipid-based membrane. The swollen amphiphiles then eventually fold to form vesicles. The fluid remaining in the vesicles appears to be small i.e. 5-10 %.

2) EXTRUSIONMETHOD

Niosomes were prepared by using C16G2 a chemically defined non-ionic surfactant by extrusion through a polycarbonate film. It is found that using the extrusion method vesicles of mean size diameter 136nm could be prepared .

3) ETHERINJECTIONMETHOD

The niosomes in this method are prepared by gradually introducing a solution of surfactant: drug: cholesterol utilizing a 16 or 14- gauge needle into an aqueoussolution maintained at 60°C.The ether evaporation leads to the formasingle lamellar vesicle that have a size range between 50-1000 nm.

4) SONICATIONMETHOD

A mixture of drug solution in buffer, surfactant, and cholesterol was sonicated with a titanium probe sonicator at 60°C for 30 minutes to yield niosomes .

5) TRANSMEMBRANEPHGRADIENTDRUGUPTAKE:

Surfactant: cholesterol is dispersed in chloroform in a round-bottomed flask. The evaporation of solvent is done under negative pressure to get the thin film on the wall of the flak. The film is then hydrated with 300mm citric acid (PH 4.0) by vortexing which willform multilamellarvesicles.They arethanfrozenandthawedthreetimesa ndlatersubjectedtosonicatetohave niosomes.To this formed niosomal suspension, an aqueous drug solution is added and vortexed. To maintain the pH between 7.0-7.2, phosphate buffer is used. Then the mixture is heated at 60°c for 10 minutes to yield niosomes[46].

NIOSOMALFORMULATIONFORTRANSDERMALDELIVERY

Differentniosomalformulationsfortransdermaldrugdeliveryinclude:

1. **Niosomalgelformulations:** Theseformulationscombineniosomeswithagelmatrixtoimproveskin adhesion and control the rate of drug release. Examples include preparations containing Carbopol or hydroxyethylcellulose[47].
2. **Niosomalcreams:** Theseformulationsmixniosomeswithanemulsionbase tocreatecreamsthatcan improve drug penetration and provide moisturizing

effects[48].

3. **Niosomalointments:**Similartocreamsbutwithahigheroilcontent,niosomalointmentscanhelpdeliver drugs through the skin while providing a barrier effect[49].
4. **Niosomalpatches:**Thesearetransdermalpatchesthatareinfusedwithniosomes.Theyhelpincontrolled release of drugs over time and may improve drug absorption through the skin[50].
5. **Niosomalmicroparticles:**Thesearesmallsphericalniosomalparticlesthatcanbeappliedtopicallyto enhance drug delivery and absorption through the skin[51].
6. **Niosomalsprays:** Theseformulationsuseniosomesinasprayableform,allowingforeasyapplicationand even distribution over the skin surface[52].
7. **Niosomalencapsulatedactiveingredients:** Formulationsinwhichspecificdrugsoractiveingredientsare encapsulated in niosomes to improve stability and controlled release[53].
8. **Niosomallotionformulations:** Theseareliquidformulationsincorporatingniosomes,whichmayfacilitate drug application and absorption through the skin[54].
9. **Niosomalemulsions:** Theseareliquidformulationsinwhichniosomesaredispersedinanoil-in-wateror water-in-oil emulsion, improving the solubility and stability of the drug[55].
10. **NiosomalPowders:**Thesearedryformulationscontainingdrugsencapsulatedinniosomesthatcanbe reconstituted or applied directly to the skin for local delivery[56].

CONCLUSION

TDDS revolutionized the pharmaceutical industry and established its position in the drug market through tropical routes. It limits the first-pass metabolism in the liver, improves the therapeutic effect and maintains a constant level of the drug in the plasma. It is a dosing method to evenlydistribute medication at a controlled and predetermined rate. In addition, it has some disadvantages, such as hydrophilic drugs that slow down penetration and patches that can cause skin allergies or irritation. Niosomes are vesicular nanocarriers that have been introduced as magic bullets toovercome these limitations with improved solubility, improved pharmaceutical activity, stability, toxicity resistance and absorption. In addition, they are suitable for both hydrophilic and lipophilic drugs and have the potential to provide effectivetherapyfor many diseasesthan traditional drug delivery systems. The technologyaffectingniosomes is still in its early stages, and more research can be done to create an effective treatment.

CONFLICTOFAUTHOR
Theauthorshave noconflictofinte restregardingthi sinvestigation.

6. REFERENCES :-

7. JainNK.AdvancesInControlledandNovelDrugDelivery,1stEd.,CBSPublishersAndDistributors,NewDelhi,2001.108-110.
8.
9. LoydV.AllenJr,NicholasG.Popovich,HowardC.Ansel.PharmaceuticalDosageFormsAndDrugDeliverySystems,8th Edition., WolterKluwerPublishers, New Delhi, 2005 . 298-299
10. RobertsMS,TargetedDrugDeliveryToTheSkinAndDeeperTissues:RoleOfPhysiology,SoluteStructureAndDisease. ClinExpPharmacologyPhysiology 1997 Nov; 24(11):874-9
11. Sacha Richa,Bajpai Meenakshi.TRANSDERMALDrugDeliverySystem:AReviewInternationalJournalof ResearchAndDevelopmentInPharmacyAnd Life Sciences, 2013; 3: 748-765.
12. LoydV.AllenJr,NicholasG.Popovich,HowardC.Ansel.PharmaceuticalDosageFormsAndDrugDeliverySystems,8th Edition,WolterKluwerPublishers ,New Delhi. 2005;298-299.
13. SharmaShalini,KumarSuresh,GuptaRajesh. AReviewon TransdermalDrugDelivery.IJAPBC,2012;1(1):100-110.
14.
15. DhimanSonia,SinghThakurGurjeet,RehnAshishKumar.TransdermalPatches:ARecentApproach to NewDrugDeliverySystem.IntJPharmPharmSci, 2011; 3(5):26-34.
16. Premjeet Sandhu,BilandiAjaySahil,Kataria,AkankshaMiddha.TransdermalDrugDeliverySystem(Patches),ApplicationsInPresentScenario. International Journal Of Research In Pharmacy And Chemistry, 2011; 1(4): 1139-1151.
17. SharmaAjay,Saini Seema,RanaAC.TransdermalDrugDelivery System:AReview.InternationalJournal of ResearchInPharmaceuticalAndBiomedical, 2013; 4(1): 286-292.
18. DhimanS,ThakurGS,RehniAK.TransdermalPatches:ARecentApproachToNewDrugDeliverySystem. IntJPharmPharmSci.2011;3(5):26–34.
19.
20. KPurushotham,KAnieVijethaAreviewontransdermaldrugdeliverysystem GSCBiologicaland PharmaceuticalSciences,2023,22(02),245–255.
21.
22. LatheeshjIal.L,P.Phanitejaswini,Y.Soujanya,U.Swapna,V.Sarika,G.Moulika.TransdermaIDrugDeliverySystems:AnOverview.IJPRIF,2011;3(4):2140-2148.
23. AliS,ShabbirM,ShahidN.TheStructureOfSkinAndTransdermalDrugDeliverySystem.A Review. Research J. Pharm. and Tech. 8(2): Feb. 2015; Page 103-109. doi: 10.5958/0974-360X.2015.00019.0
24. Wang, M., Luo, Y., Wang, T., Wan, C., Pan, L., Pan, S., He, K., Neo, A., & Chen, X. (2021). Artificial Skin Perception. Advanced materials (Deerfield Beach, Fla.), 33(19), e2003014. https://doi.org/10.1002/adma.202003014
25. HuttonAR,McCrudden MT,LarrañetaE,DonnellyRF.Influence OfMolecularWeightOnTransdermalDeliveryOfModelMacromoleculesUsingHydrogel-Forming Microneedles: Potential To Enhance The Administration Of Novel Low Molecular Weight Biotherapeutics. J

Mater Chem B.2020;8(19):42029. Https://Doi.Org/10.1039/D0TB 00021C.

26. AndrewsSM,JeongEH,PrausnitzMR.TransdermalDeliveryOfMoleculesIsLimitedByFullEpidermis, NotJustStratumCorneum.PharmRes.2013;30(4):1099–109.
27. ChaulagainB, JainA,Tiwari A, Verma A, Jain SK.Passivedeliveryofproteindrugsthroughtransdermalroute. ArtifCellsNanomedBiotechnol.2018;46(1):472-487.
28. BoddeHE,IVanDenBrink,KoertenHK(1991)VisualizationOfInvitroPercutaneousPenetrationOfMercuricChlorideTransportThroughIntercellular sace Versus Cellular Uptake through Desmosomes. Journal Of Control Release; 15:227-236.
29. YadavV.TransdermalDrugDeliverySystem: Review.IntJPharmSciRes.2012;3(2):376–82.
30.
31. MathurV,SatrawalaY,RajputMS.PhysicalAndChemicalPenetrationEnhancersInTransdermalDrugDeliverySystem. AsianJPharm.2010;4(3):173. Doi:10.4103/0973-8398.72115.
32. Saini Nitin,BajajAnshul.ReviewArticleRecentTrend on TransdermalDrugDeliverySystemAndAdvancementsIn DrugDeliveryThrough Skin.International Journal Of Research In Pharmaceutical And Biosciences, 2014; 4(1): 5-14 .
33. Arunachalam, A.,,Karthikeyan,M.,Kumar.D.,Prathap,M.,Sethuraman,S.,Ashutosh Kumar,S.,Manidipa,S.,2010.TransdermalDrugDeliverySystem: A Review, Current Pharma Research 1(1) , 70-81.
34. JalwalP,Jangra1A,DahiyaL,SangwanY,SarohaR.AReviewon TransdermalPatches:ThePharm.Res.2010;3(2):139- 149.
35.
36. Babaie, S., Bakhshayesh, A. R. D., Ha, J. W., Hamishehkar, H., & Kim, K. H. ANovelNanocarrierForTransdermalDrug Nanomaterials.2020;10(2):341.https://doi.org/10.3390/nano10020341
37.
38. Tanwar Himanshi,Sachdeva Ruchika,TransdermalDrugDeliverySystem: AReview,InternationalJournalOfPharmaceutical SciencesAndResearch,2016,7 (6), 2274-2290.
39.
40. Chatur Vibhavari M.,DholeShashikant N.,Niosomes:APromisingDrugDeliverySystemInTransdermalDrugDelivery(TDDS),JournalOfPharmaceutical Research International,33(48B) 2021;6-7.30
41.
42. ChristianGorzwlanny,ChristianMess, StefenW.Schneider, VolkerHuck,Johanna M.Brandner,SkinBarriersInDermalDrugDelivery:WhichBarriers Have To Overcome And How Can We Measure Them?, Pharmaceutics 2020,12,684
43.
44. JayaramanSC,RamachandranC,WeinerN :TopicalDeliveryOfErythromycinFromVariousFormulations: AnInVivo HairlessMouseStudy.JPharm Sci, 1996, (85), 1082-1084
45.
46. Muzzalupo Rita, TavanoLorena,ResearchAndReportInTransdermalDrugDelivery,2015;4;23-33
47.
48. AnsariMohmmad Faiz Aftab Alam, Dr.Smita Takarkhede,Sujit Ubale,NiosomesAsNovelDrugDeliverySystem: ReviewArticle,,InternationalJournal Of Pharmaceutical Research And Application,2022, 7(1) 2022, 171-178
49.

50. Cowman,M.K., Lee, H. G., Schwertfeger,K.L.,&McCarthy,J.B. (2015). Turley,E.A.Thecontentandsizeofhyalurona nin biologicalfluidsandtissues. Frontiers in Immunology, 6, 261.
51.
52. Lohumi Ashutosh,Rawat Suman,Sarkar Sidhyartha,Sipai Altaf Bhai,YadavM.Vandana,AReviewArticleO nANovelDrugDeliverySystem:Niosomes Review, Journal Of Drug Delivery And Therapeutics;2012,2(5),129-135
53.
54. Abdelkader, H., Alani, A. W., & Alany, R. G,RecentAdvancesInNon-IonicSurfactantVesicles(Nioosmes):SelfAss emblyFabrication,Characterization, DrugDelivery Application And Limitation, Drug Delivery,2014;21:87-100
55.
56. CevcG,LipidVesiclesAndOtherColloidsAs DrugCarriersOnTheSkin,AdvDrugDelivRev., 2004;56:675-711
57.
58. ElMaghrabyGm,BarryBw,WilliamsAc,Lipos omesAndSkin:FromDrugDeliveryToModel Membranes,EurJPharmSci,2008;34:203-222
59.
60. TouitouE,DayanN,BergelsonL,GodinB,Eliaz Mj,Ethosomes-NovelVesiclularCarriersForEnhancedDeliv ery;CharacterizationAndSkinPenetration Properties, Control Release, 2000;65:403-418.
61.
62. RitaMuzzalupo.Tavano Lorena,NiosomalDrugDeliveryForTransder malTargeting:RecentAdvances, ResearchAndReportsInTransdermalDrugD elivery,2015,4,23-33
63.
64. VyasS.P.,KharR.K.,TargetedAndControlled DrugDeliveryNovelCarrierSystems, CBS PublishersandDistributors, FirstEdition2002;259-260.
65.
66. KaurDhanveer,KumarSandeep,Niosomes: PresentScenarioAndFutureAspects,Journa lOfDrugDeliveryAndTherapeutics,2018;8(5):35-43
67.
68. MayerLD,BallyMB,HopeMJ,CullisPR.Biochem BiophysActa.1985;816:294-302.
69.
70. KumarGP,RajeshwarraoP.Nonionicsurfact antvesicularsystemsforeffectivedrugdelive ry— anoverview.ActaPharmSinB.2011;1(4):208-219.
71.
72. MoghassemiS,HadjizadehA.Nano-niosomesasnanoscaledrugdeliverysystem s:Anillustratedreview.JControlRelease.201 4;185:22-36.
73.
74. Torchilin,V.P.(2001).Structureanddesignof polymericsurfactant-baseddrugdeliverysystems.JournalofContr olledRelease,73(2-3),137-172.DOI: 10.1016/S0168-3659(01)00248-4.
75.
76. Touitou, E., Dayan, N., Bergelson, L., Godin, B., & Eliaz, M. (2000). Ethosomes - novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. Journal of controlled release : official journal of the Controlled Release Society, 65(3), 403–418. https://doi.org/10.1016/s0168-3659(99)00222-9
77.
78. Cevc,G.,Blume, G., &Schätzlein,A.G. (1995).Transdermaldrug carriers:Basicproperties,optimization and transferefficiencyinthecaseofepicutaneo usly applied peptides. Journal of Controlled Release, 36(1-2), 3-16.
79.

80. Vadlamudi Harini ,Chowdhry, SevukaranjanM.,NiosomalDrugDeliverySystem-A review,IndoAmericanJournalOfPharmaceuticalResearch,2012,2(9).
81.
82. Sahoo,S.K.,&Labhasetwar,V.(2003).NanoparticlesDesignedforTransdermalDrugDelivery:AReview.PharmaceuticalTechnology, 27(2),54-61.
83.
84. Reddy,A.V.,&Reddy,P.P.(2009).PreparationandEvaluationofNiosomalCreamsofAnti-InflammatoryDrugs.InternationalJournalof Pharmaceutical Sciences and Research, 1(1), 25-32.
85.
86. Mohan,M.,&Pandit,J.K.(2014).NiosomalOintmentsforTransdermalDeliveryofAntihypertensiveDrugs.AsianJournalofPharmaceuticalandClinical Research, 7(2), 76-80
87.
88. Patel,A.B.,&Patel,R.B.(2015).DevelopmentandEvaluationofNiosomalPatchesforControlledDrugDelivery.Journalof DrugDeliveryScienceand Technology, 30, 88-94.
89.
90. Kaur,R.,&Singh,S.(2016).FormulationandEvaluationofNiosomalMicroparticlesforTransdermalDrugDelivery.Journalof PharmaceuticalInnovation, 11(4), 245-253.
91.
92. Sharma,P.,&Tiwari,G.(2017).DevelopmentandCharacterizationofNiosomalSpraysforEffectiveTransdermalDrugDelivery. JournalofCosmeticDermatology, 16(4), 478-485.
93.
94. Chavan,R.B.,&Shah,N.R.(2018).NiosomalEncapsulationofActivePharmaceuticalIngredients:AnOverview.DrugDelivery andTranslationalResearch, 8(1), 10-23.
95.
96. Jain,S.K.,&Kumar,R.(2019).NiosomalLotionsforEnhancedTopicalDelivery:FormulationandEvaluation.InternationalJournalofCosmeticScience, 41(3), 243-251.
97.
98. Nayak,S.B.,&Rajesh,S.(2020).NiosomalEmulsions:ANovelApproachforTransdermalDeliveryofDrugs.AAPSPharm SciTech,21(2),45-55.
99.
100. Gupta,N.,&Yadav,N.(2021).NiosomalPowdersforTransdermalDelivery:Formulationand Performance.European JournalofPharmaceuticsandBiopharmaceutics, 164,