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# Review on niosomalstructure Through nasal Route

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***Abstract:*** *Nanotechnology has created one of the most dynamic science and technology domains at the confluence of physical sciences, molecular engineering, biology, biotechnology and medicine. There has been a considerable research interest in the area of developing drug delivery using nanoparticles (NP's) as carriers for small and large molecules. Targeting delivery of drugs to the diseased lesions is one of the most important aspects of drug delivery system especially brain. They have been used in-vivo to protect the drug entity in the systemic circulation, restrict access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to this site of action. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Various polymers have been used in the formulation of niosomes for drug delivery research to increase therapeutic benefit, while minimizing the side-effects. It is obvious that niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, antiinfective agents.Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome.Niosomes represent a promising drug delivery module. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical and parenteral.*

***Key Words:*** *Nanotechnology, niosomes, nasal route, targeting.*

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## I. Introduction

Thedrugdeliverybynasalroutegeneratedtheinterestofthewidespreadamongthecommunityofthescientistsasitisagoodalternativerouteofadministrationthatcanavoidthefirstpasseffectofsomedrugsthataresusceptiblefortheenzymaticallydegradabledrugs.Intranasalroutealsoallowsbetterabsorptionofthedrugthroughthevascularityandpermeabilityofthenasalmucosa.(1)Thebarriersthatfacethedrugthroughtheintranasalrouteistheenzymesthatlocatedinthenasalmucosallining.Despitethat,largenumbersofthedrugsthatincludepeptides,protein,vaccinesandhormonescanbedeliveredtothepatientthroughthenasalroute.Intranasalrouteofadministrationhasseveraladvantagesanddisadvantagesasshowedintable(2).

**Table ( 1):** The advantages andlimitations of intranasal route(1).

| Advantages | Limitations |
|---|---|
| 1. Avoid the enzymaticallydegradation in GIT.<br>2. Avoid firstspasseffects.<br>3. Rapidonset of the drug.<br>4. Uselower dosesbecauseofhigherbioavailability.<br>5. Theroute is noninvasive.<br>6. Easilyself-medication.<br>7. Transporttherequireddosedirectlytothesystemiccirculationa nd to the brain<br>8. Avoid over-doses.<br>9. Not complex. | 1. Therequiredvolumetobedeliveredintothenasalroute is20-200 ml.<br>2. Thecomponentsthathavehighmolecularweightcannotbedeliver ed.<br>3. Enzymesbarriersinthenasalmucosa.<br>4. Nasalirritation.<br>5. Limitmechanisms understanding.<br>6. Largevariability.<br>7. Sideeffectsbypathologicalactivities. |

Toovercomesomelimitationoftheintranasalroutewecanformulatethedrugintoniosomes,proliposomesandfilmsthatenhancethedrugpermeabilitythatisshowedtobebetterthansuspensions,solutions,sprays,emulsions,snuffsandointments.Thecauseisthatniosomes,proliposomesandfilmsallowprolongedcontact with the mucusmembrane (1).

**Nasalcavityfunctionalfeature:**

Thenasalmucosaisrichlysuppliedwiththebloodtoachievethefunctionsofthecavityofthenosethatincludehumidification,heating,mucocilliaryclearance,olfactionandimmunologicalfunctions.Thesurfaceareaofthecavityisabout150160cm²;thatistheresultofpresenceabout400microvilli/cellthevolumeofthesecretionsofthenoseabout15ml/day.

Allofthesecondition sfavorthelargepermeabilityof thedrugsthrough the nose.(1)

**Drug permeationmechanism**(2):

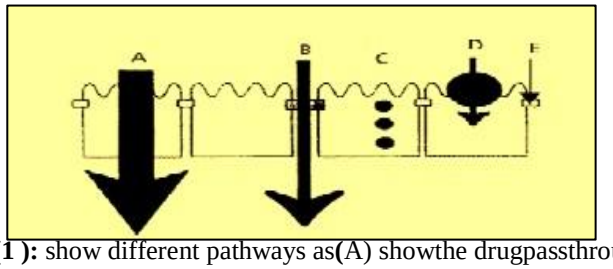



**Figure (1 ):** show different pathways as**(**A) showthe drugpassthrough epithelium, (B) paracellulartransport, (C)transcellular transport, (D)carriermediated transportand(E)intracellulartightjunction

Thepermeation through the nasal cavitywhile administration of the drugcanbecarriedoutbyeitherpa racellularpathwayasshowedinfigure1passivelyoractivelyandpassivelyviatranscellularpathway.Inwhichitdependsm ainlyonthelipophilicityof thedrug**.**(1)

## II. Factors That Affect The Drug Permeability Through Nasal Route

**Mucocilliary Clearance:**

It involves the combined actions of the mucus layer and the cilia and is an important factor in the physiological defence of the respiratory tract against inhaled hazardous particles. The composition, function and clinical aspects of nasal mucus have been widely reviewed. It is assumed that the speed of mucocilliary clearance in healthy humans is about 5 mm/ min;although this is easily influenced by pharmaceutical excipients, airborne irritants or diseases. The tips of the cilia are in contact with and transport the superficial viscoelastic mucus layer towards the nasopharynx, while the less viscous lower layer of the mucus is relatively stationary. Several workers, using various in vitro or in vivo methods, have investigated ciliary beat frequency in order to evaluate the effects of drugs or formulation additives or of infections in the upper airways on the mucocilliary system. The cilia beat in a coordinated fashion, with a frequency of approximately 10 Hz, when measured in in - vitro studies on human nasal cilia (2).

**Enzymes:**

While nasal administration of drugs does avoid first pass hepatic metabolism, there is a broad range of metabolic enzymes situated in the nasal mucosa which can limit the bioavailability of some drugs, especially those containing peptides or proteins Among the enzymes present are the oxidative phase I enzymes (e.g. cytochrome P-450 enzymes), non-oxidative enzymes, conjugative phase II enzymes and proteolytic enzymes such as endo-and exo-peptidases .The nasal enzyme population and/ or activities vary extensively among different species .However, the level of activity seems to be lower for nasal enzymes than for those in the gastrointestinal tract or liver, on the basis of the amount of tissue involved .(3)

**Nasal pathophysiology various pathophysiological changes:**

Such as the common cold, seasonal rhinitis, nasal polyps and cancer, may also alter absorption from the nasal cavity in different ways, although this has not yet been thoroughly investigated; While it has been demonstrated that a rhinovirus infection in vitro causes sloughing of epithelial cells and destruction of the epithelial layer, microscopy studies of mucosal biopsies from otherwise healthy patients with colds didn't show any abnormalities in ciliated cells.(2)

**Physico-chemical characteristics of the substance:**

The physicochemical characteristics of the administered drug, which can influence nasal absorption, include molecular weight, solubility, dissolution rate, charge, partition coefficient, pKa, particle size and the presence of polymorphism.(4)

**Solubility of the drug in nasal secretion:**

As the drug needs to be solubilized in the nasal secretion before its permeation.Diurnal variation as diurnal rhythm affects the nasal secretions. As the secretion and clearance rates are reduced at night which affects the drug permeation.

**Ph Of The Nasal Cavity:**

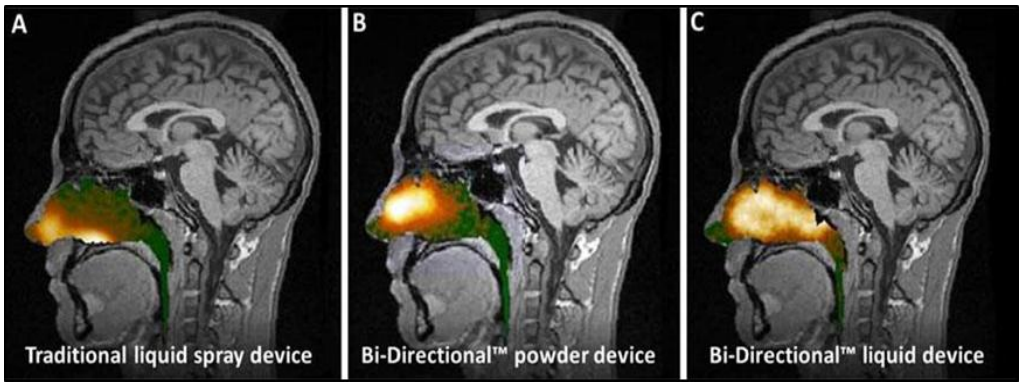
As it is varied from 5.5 to 6.5 in adults and from 5 to 7 in infants. Usually drug permeation increased when the nasal pH is lower than the drug pKa because under this condition the drug molecules present as unionized species. Change in nasal pH affects the ionization of the drug molecules that affect the drug permeation.(1)

**Molecular weight:**

An inverse relationship between molecular weight and percent absorption has been reported; data are supported by the results of rat studies compiled with literature data, which indicate good bioavailability for compounds with molecular weights up to 1000 kDa in formulations without adjuvants). (10) However, contrary to the findings of Donovan et al. (1990) no difference in absorption characteristics between gastrointestinal and nasal mucosae was found in rats (6) Accordingly, mechanisms other than the suggested aqueous pores between cells of the nasal mucosa) might be involved in the absorption of large molecules. Other studies have demonstrated that hydrophobicity is an important factor in nasal drug delivery in contrast to studies on quaternary ammonium compounds where a decrease in absorption was found with increased lipophilicity and molecular weight .(3)

**Thedrugadministratedthroughnasalroutetakenbydifferentmethods:**

**Figure (2 ):** show thedrug depositiontwo minutesafterdrug deliveryusing(A)traditional liquid spray, (B) breathpoweredBi-directionalpowder device and (C)breathpowered Bi-directional liquid device incorporating spraypum




**Devices for liquid formulations:**

Liquid formulations include emulsion, aqueous solutions and suspensions. Liquid formulation considered to be good method as it does humidification in which counteract the dryness of the nose that usually accompany the chronic diseases of nose.The devices used with liquid formulations mainly spray pump systems as showed in figure (2) usually require preservatives which is mainly benzalkonium chloride that may cause reduction in ciliary movement and irritation also recent studies proved that the use of benzalkonium chloride in long term use is well tolerated and safe for the long-term use.(11)

**Drops delivered with pipette:**

It is the oldest method for the nasal delivery in which the breast milk has been dripped for the treatment of nasal congestion in infants, methanol vapors have been used to wake fainted people and both vapors and drops are still present in the market till now. Drops are administrated by liquid sucking into glass dropper; the dropper is inserted into the nostril with extended neck then squeezing the rubber top to allow the drops to be emitted. For the purposes of multiple use drops have been replaced by metered dose spray pump.(11)

**Liquid delivery by rhinyle catheter and squirt tube:**

It is a simple way in which physicians used to insert the drug into the nose by inserting a tip of catheter to the required area under visual control then squirt the required drug to the desirable location. This method mainly used in the studies that include the use of animals. But this method has a dangerous disadvantage that it cannot be used for self-medication.(12)

**N Squeeze bottles:**

This method used to deliver OTC drugs as topical decongestant. As the air filled plastic bottle is partly squeezed

in which the drug is ionized while delivering from a jet outlet. The size and particles of the dose varied according the applied force. While releasing the pressure the nasal secretions and micro-organisms are sucked into the bottle so the use of the squeeze bottles is not recommended for children.(11)

**Spray pumps metered dose:**

Which offers high reproducibility of the dose that emitted and plume geometry in tests applied in vitro. The size of the particles and the plume geometry varied within limits and depend on the pump properties, the orifice of the actuator, formulation and the force applied. In the traditional spray pump the air is replaced by emitted liquid so preservatives are required to prevent contamination. Pump manufacturers are developing other methods to avoid the use of preservatives.(11)

**Single and due dose spray devices:**

It is preferred to be used for narrow index drugs and used also for vaccines and other drugs that need single accurate dose.(11,13)

**Nasal pressurized metered dose inhalers:**

Most of the drugs used for the local action delivered using spray pumps but some other drugs as nasal aerosols taken by inhalers (11.12)

**Devices for powder formulations:**

Powder sprayers with compressible compartment to supply pressure in which when it is released it make a plume of powder particles which is like that produced by liquid spray.(11)Breath actuated inhalers in which the human use his own breath for the powder inhalation into the nostril from a capsule or blister.(11)Nasal insufflator describes the devices that contain nosepiece and mouthpiece which are connected. The drug delivery carried out while exhalation of the drug into the mouthpiece to close the velum, then the airflows carries the particles of powder into nose through the nosepiece of the device.(11)

**Nasalphysiologythataffect the drugdelivery**

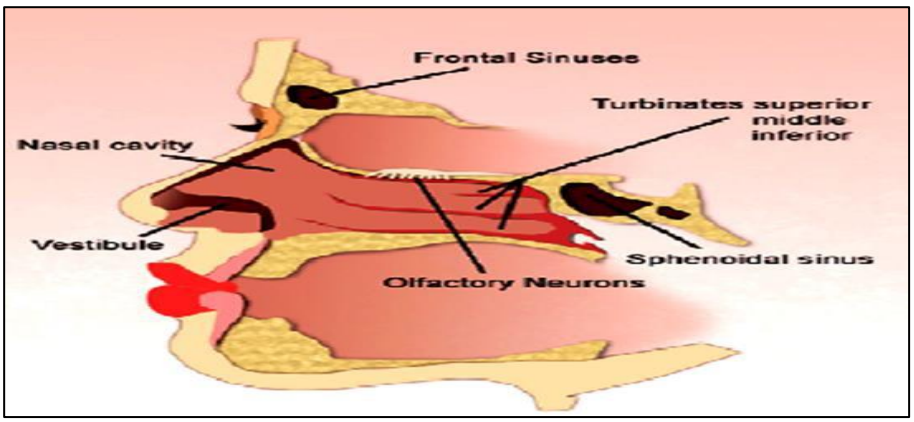



**Figure ( 3):** Nasalanatomy

**Aerodynamic andnasalvalve:**

Thedynamicsegmentofnarrowanteriortriangularofthenasalanatomycallednasalvalvewhichisthelimitingsegmentprimaryflowandextendsanteriorandposteriortotheinferiorturbinateheadapproximately23cmfromtheopeningofnostril.Thenarrowtriangularslitplaysaroleofdynamicvalveforthemodificationofthe rateand the direction ofthe airflow during the respiration.(12)

**Thenasal mucosaclearance and filtration:**

Theanteriorregiontothevalveiscalledvestibulewhichislinedbynonciliatedsquamousepitheliumthenthevalveisgraduallyconvertedintociliatedepitheliumwhichistypicalofciliatedrespiratoryepitheliumposteriortotheregionofthevalve.Behindthevalveofthenose,theturbinateofthenosedividedthenasalcavityintoslitlikepassageswithlargersurfaceareaandcrosssectionalarea.thespeedofthelaminarairflowisloweddownto23m/sanddisruptwitheddiesthatpromotedepositionoftheparticlesthatarecarriedwithairandbehindtheregionofthevalve.Theciliatedrespiratorymucosawhichisposteriorto thenasalvalve,coveredbyablanket designedprotective mucosathattrapsparticlesandmicro-organisms.(11).

**Thenasal cycle:**

Thephysiologyofthealternationbetweencongestionanddecongestionobservedhasbeenobservedinabout80 %ofthehumansthatarehealthyiscalledthenasalcycle.Theautonomiccycleischangedduringairflowresistancewhichma inlydependsonbloodcontentofsubmucosalcapacitancevesselswhichconstitutetheerectilecomponentatsiteswhichare critical,notablytheregionofnasalvalve.Theerectiletissueofseptalandlateralwallsandturbinateareresponding tostimulu sincludingsexualandphysicalactivityandthestateoftheemotionsthatcanoverrideandcausemodificationtobasiccyclicr hythm.Becauseofthecycleonenostrilmorecongestedtotheothermostoftimeandmajorairflowispassingfromonenostril whiletheotheroneisremainingnarrow.(14)

**Nasal sinus vasculature and lymphatic system:**

Thesiteofdepositionaffectstherouteandextendsofadministrationinwhichthetargetedorgandistributesassho wedinfigure(3).Thebranchesofthemaxillaryandophthalmicarteriessupplythemucusmembranethatcoverthesinus,me atuses,septumandturbinate.Wherethesuperiorlabialbranchoffacialarterywhichsupplythepartofseptuminthevestibul eregion.Theturbinateislocatedinthelateralnosewallthatishighlyvascularizedwithabloodflowandthenactsasaradiator totheairway.(12)Substancesthatareabsorbedfromtheregionoftheanteriorseemstodrainbyjugularveins,wheredrugsar eabsorbedfrommucousbehindthevalveofnoseseemstodrainbyveinsthatarereachedtosinuscavernousasthevenousblo odbecomeindirect contact with the carotidarteries walls.(12)

**Targetednasaldelivery:**

Inmostcasesthebroaddistributionoftheactiveconstituentsofthedrugonthesurfaceofthemucosaappearsgoodf orThedrugsthatrequiredforthelocalaction,Vaccinationorsystemiccirculation.Incaseofnasalpolyposisandchronicsin usitisthedeliverytargetedtosuperiorandmiddlemeatuseswherethepolypsoriginateappearsdesirableandsinusopening present.Anotherexceptionisthedrugsthataredeliveredfromnosetothebrainaremoretargetedtotheupperpartofthenose whereth eolfactorynervesarepresent.(20)

**Braintargetingthroughintranasalroute:**

Whenthedrugpassesthebarriersofthenasalepitheliumandentersthenosesubmucousspace.Thedrugmolecule diffusedacrossthearachnoidmembranethenenterstheCSFcompartmentofolfactoryregionandthendistributedwiththef lowofCSFandabsorbedintothecirculation.Thedrugsthatarelipophilicwithmolecularweight<400Dawillpasstheblood brainbarriersbylipidmediationandalsopassingthenasalepitheliumbarrierandarachnoidmembrane.Andtheotherdrugs thatarewatersoluble(hydrophilic)orhavemolecularweightabout>400Da,thenthedrugpass the membranespoorlybyf ree diffusion so in this case it is essential to disrupt theepithelialbarriers to completedrugtransportation.(16,25) Thedrugsthatdonotpassthebloodbrainbarriersbylipidmedicationthatisapproximatelyabout%ofthepresentdrugsinthe market,canpasstheBBBbycarryingittobetransportedontheendogenoustransporters.Smallandlargemoleculesofthedr ugsmustbeformulatedtoallowthetransportationonthebloodbrainbarriersendogenoustransporters.TheBBBendogeno ustransportersdividedintothreecategoriescarriermediatedtransport,receptormediatedtransportandactiveeffluxtransp ort.(16,25)

**Nano-technologybaseddrugdeliverysystem:**

Nanotechnology is changing the perception of drug administration using conventional dosage forms. The term of nanoparticles refer to a particulate drug delivery system where particle size is in nanometer range (1-1000 nm). Nano particles are being investigated extensively in order to develop drug delivery systems capable of allowing penetration through physiological barriers.(24)Over the past decades, there has been considerable research interest in the area of developing nano technology by using nano particles as carriers for small and large molecules. Various polymers have been used in the formulation of nano particles. This review presents the most outstanding contributions in the field of nanotechnology. The word 'Nano' is derived from Latin word, which means dwarf. Nano size refers to one thousand millionth of a particular unit thus nanometer is one thousand millionth of a meter (i.e. 1n=109m).The term nanotechnology has been most commonly used in the fields of science like electronic, physics and engineering since many decades. However, bio medical and pharmaceutical fields remain yet to be explored. (24)

**Major advantages of nano sizing include:**

[1] Increase surface
[2] Enhanced solubility
[3] Increase rate of dissolution and oral bio availability
[4] Rapid onset of action
[5] Less amount of dose required in the field of pharmacy.

For applications to medicine and physiology these materials and devices can be designed to interact with a high degree of functional specificity, thus allowing a degree of interaction between technology and biological systems not previously attainable. (18 )

## III. Typesof Nanotechnology-Baseddrugdeliverysystems

**Polymeric Nanoparticles (Nps)**

Nanoparticlesaredefinedasparticulatedispersionsorsolidparticleswithdiameterrangesfrom1to1,000nm.By usingseveralmethodsnanoparticleshavebeenprepared,thesemethodsincludeionicgelationorcoacervation,polymerpo lymerizationandemulsionsolventevaporation(24),solventdiffusionorspontaneousemulsification,supercriticalfluidte chnologyspraydrying,Nanoprecipitation,andparticlereplicationinnonwettingtemplates(10).Themechanismbywhic htransportation ofnanoparticles can pass theBBBcanbeexplainedbytheimprovedadsorptionofthenanoparticlesto thecapillarywallsduetotheincreasedretentionofthenanoparticlesinthebrainbloodcapillaries.Thisresultedinahigherco ncentrationgradient,whichincreasesthetransportacrosstheendothelialcelllayerandenhancesthedeliverytothebrain.U singpolysorbate80asthecoatingagentcausedInhibitionoftheeffluxsystemwhichcanalsofacilitatethetransportofdrug. Nanoparticlesmayleadtoalimitedpermeabilizationofthebrainendothelialcellsduetoinducementoflocaltoxiceffectson thebrainvasculature.EnhancementofpermeabilityofdrugacrosstheBBBcanbeimprovedbysolubilizethelipidsoftheen dothelialcellmembranebytheuseofsurfactant.ThroughthetightjunctionsnanoparticlescouldpermeatetheBBB,which areopenbetweentheendothelialcellsofthebrainbloodvessels.Anothermethodtofacilitatesthedrugdeliverytothebrainis throughEndocytosisbytheendothelialcellsfollowedbythedrugreleasewithinthesecells.Inordertoimprovethedelivery ofdrugtothebrainnanoparticlescanbeadministeredthroughintranasalroute.Othermethodstoimprovethedeliveryinclu deantibodiesorpolymerstoimprovenasalabsorption,coatingnanoparticleswithpolyethyleneglycol.Theretentiontime ofnanoparticlesdeliveredthroughtheintranasalroutecanbeincreasedby SurfacemodificationoftheNPswithmucoadhesivepolymers.(17,18)

**Solid lipidcarriers**

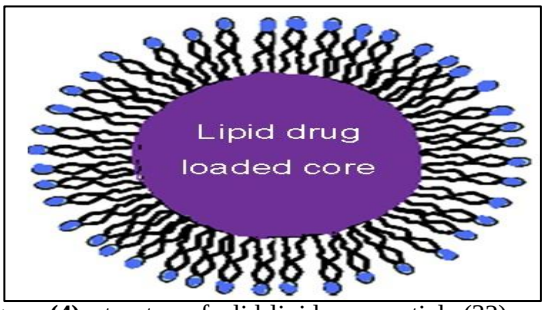



**Figure (4)**: structureofsolid-lipid nanoparticle (32)

Solidlipidnanoparticles(SLNs)asshowninfigure10aretypicallysphericalarticles,withaveragediametersbet ween10and1,000nmwhendispersedinwater.SLNshaveacore matrixofsolidlipidthatcansolubilizelipophilicmolecul es(Müller etal2002).Thelipidcore,typicallyconsistingofsteroids(eg,cholesterol),monoglycerides(eg,glycerolmonost earate),diglycerides(eg,glycerylbehenate),triglycerides(eg,tristearin),waxes(eg,cetylpalmitate)orfattyacids(eg,stea ricacid),is stabilized bysurfactants though thecombination of emulsifierswhich help inpreventingagglomeration ofparticles(30).Solidlipidnanoparticlesarepreparedfromanemulsifier,lipidsandwaterorsolventbyusingdifferentmet hodswhichinclude:thesolventevaporationmethod,ultrasonication/highsheartechnique,highpressurehomogenization ,thesupercriticalfluidmethod,thespraydryingmethod,theMEbasedmethod,thesolventemulsificationdiffusionmetho d,theprecipitationtechniqueorthedoubleemulsionmethod.TheuseofSLNsornanocarrierslipidsforthedrugdeliverytot hebraincanfacilitatetheproblemofcrossingtheBBB,astheseformulationscanbeusedintranasallytobypasstheBBBorp enetratedirectlytheBBB.Promotingelectrostaticinteractionswithmucusinadditiontomediatingtheadsorptive-mediatedtranscytosiscationicNPsacrosstheBBBcanbedonethroughtheuseofcationiclipidsthatimprovemucoadhesio ninthenasalcavity.ThetransportofnanoparticlescoatedwithsurfactantacrosstheBBBtakesplacethroughendocytosism ediatedbytheendothelialcells of thebrain capillaries(30).

**Surfactant-basedsystems:**

Drugdeliverysystemsinwhichmoleculesofsurfactantareself-aggregatedwhichtakes placein present of waterandlead to formation of structureswithdifferentparametersthatdifferwithrespecttoconcentrationthesedrugd eliverysystemsarecalledSurfactantbaseddrugdeliverysystems.Theselfaggregatedsurfactantsbecomemoreorganized evenwhenothercomponentssuchasoilsorothersurfactantsareaddedtothesystemofsurfactantandwater.Thus,microem ulsion(MEs)andnanoemulsions(NEs)canbproduced.Microemulsionsareusuallythermodynamicallystableisotropicl iquidsformedbywater,mixingoil,andsurfactantsalltogether.Incontrast,nanoemulsionsareconventionalemulsionsthat containverysmallparticles.Thesizesofdropletsofmicroemulsionrangesbetween10and140nm,whichleadstoformatio nofsystemsthatareopticallytransparentandthermodynamicallystable.Nanoemulsionsarenottransparentwithdiameter rangesupto140nmalsotheyarelessthermodynamicallystablethanmicroemulsion(29).Thetwosystemsareverydiffere ntbecauseMEphasesareformedbyselfassemblyandNEsareformedbymechanicalshearing.Otherparameterscandistin

guishMEsfromNEs:MEsaremorestableinlongtermstoragethanNEs;MEscanbeagitated,cooled,orheatedandthenreturnedtotheiroriginalconditions,whereasNEscannotreturntotheiroriginalconditions(29);Microemulsionresultedfromspontaneousmixturesofwater,oilsandsurfactants,howeverinordertotofacilitatetheformationofmicroemulsionitisrecommendedtoapplyheatingorstirringbecauseofkineticenergybarriersthatmustbeovercome.Nanoemulsionscanbeformedbyusesinputofsomeexternalenergyprovidedbymicrofluidizers,highpressurehomogenizersandsonicationmethodstoconvertthemixtureintoacolloidaldispersionorphaseinversion.Nanoemulsionformedfromcurcuminundergonedevelopmentfordrugdeliverythroughintranasalroute,andtheresultsfrombehavioralexperimentsshowedimprovedlearningandmemoryinthegrouptreatedwithcurcumin-loadednanoemulsioncomparedwith the grouptreatedwith thepuredrug. (34 )

**Vesicular drugdelivery system:**

Systemsthathavebeenpresentedascarriersfordeliveryofdrugformanyyearsarecalled Vesiculardrugdeliverysystems.Theyweresupposedtoachievemanygoalswhichincluded:enhancementofthetransportofdrugthroughdifferentbiologicalmembranes,targeteddrugdeliveryandcontrollingthereleaseofdrugaswellasprolongingthisreleaseifneeded.Thesesystemsincludeliposomes,transfersomes,niosomes,vesosomes,ethosomes,andcolloidosomes(15).Onlyvesicles employed in thenasal drug deliverywill be discussedsuch as

**Liposomes**

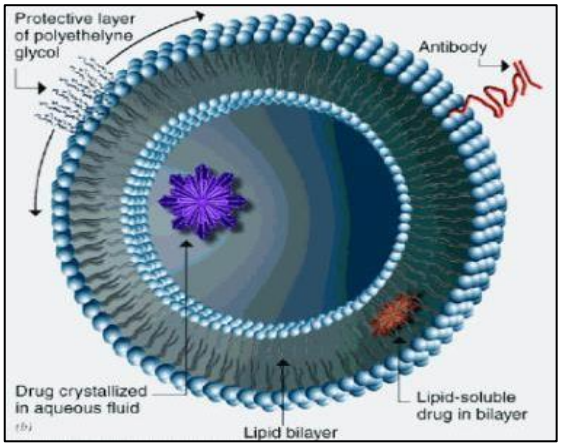



**Figure (5):** structureofliposome (17)

Liposomesasshowninfigure11aremicroscopicvesiclessphericalinshapecomposedofoneormorebilayersoflipids,arrangedaroundacentralcoreaqueousinnature(21).Theyaremadeofnontoxic,biodegradable,andnaturalconstituents suchasphospholipidsLiposomesmayincludeintheircompositionmembranestabilizerascholesterolaswellassmallamountsofchargingagentsandbecauseofthisdesirablecompositionliposomeshavetheabilitytoencapsulatedrugswithwidelydifferencesinthelipophilicfeatureofdrugswhereasthelipophilicportionbeinglocatedinthebilayeroflipidandtheportionwhichishydrophilicislocatedthecentralaqueouscore.Liposomescanchangethepharmacodynamicsandpharmacokineticsoftheentrappeddrugsanditisconsideredefficientdrugdelivery system.Theactivityofliposomesascarriersfordrugsdependsupondifferentfactorssuchasreleaserates,stability,andefficiencyofencapsulation,distributioninbodyafteradministration,rigidityandsizesurfacecharge.Thepropertiesofliposomescanbevariedandcontrolledbychangingthe preparation methods and using differenttypes oflipids.Poorstabilityofliposomesisconsideredthemainproblemintheresearchofliposomesandthisproblemresultedfromthechemicaldegradationofcomponentsofliposomesaswellastheproblemsofphysicalstability(28),thatcanincludethesizechangeuponstorageandthelossofentrappeddrug.Increasingtherigidityofthebilayercandecreasetheentrappedmaterialmembranealsoreducingthewatercontentofliposomeformulationsproducingtheso-calledproliposomescanhelp inimproving the physical stabilityof liposomes.(30)

**Proliposomes:**

Proliposomesarefreeflowing,dryparticlesthatuponadditionofwaterformvesiculardispersionsinstantly.Their freeflowingparticulatepropertiesallowthefabricationofthesenanoaggregatesintosoliddosageforms,whichtheniscon vertedtoliposomesoncontactwithwaterorbiologicalfluids.Proliposomesarepreparedbypenetratingasolutionofdrugsandphospholipidsinvolatileorganicsolventsintothemicroporousmatrixofwatersolublecarrierparticles,thenevaporationoftheorganicsolventstakesplace.Phospholipidsanddrugsarethusdepositedinthemicroporousstructureofthecarriermaterials,thuskeepingthefreeflowingsurfacecharacteristicsofthecarriermaterials.proliposomes have someadvantageswhichincludedecreasingtheproblemsofphysicalinstabilitysuchasleakage,fusionandaggregation.Inaddit,proliposomescharacterizedbyeaseofstorage,distribution,transportationanddosage.(19)

**Niosomes**

Niosomes are multilamellervesicular structureofnonionicsurfactants as showninfigure12,similartoliposomes howeverinsteadofphospholipidsthatarecomponentsofliposomestheyarecomposedofnon-ionicsurfactants.(22)

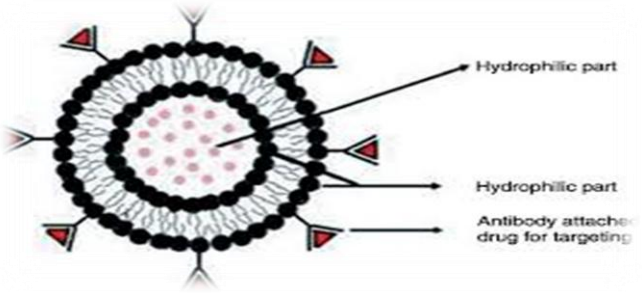



Figure (6 ): structureofniosomes (26)

**AdvantagesofNiosomes**(11)

- Niosomeshavetheabilitytoentraplipophilic,hydrophilicandamphiphilicdrugssotheycanbeusedtodeliverwiderangeofdrugswithdifferentproperties.
- Niosomeshavebettertherapeuticeffectwhencomparedtootherconventionaloilyformulationsand betterpatientcompliance.
- Composition,size,shape and fluidityof niosomes drug can becontrolled.
- Niosomesduetodepotformationcanprovidecontrolledandsustainedreleaseof drugs.
- Niosomes has theadvantage ofdrugstargeting todifferentorgans.(6)
- Niosomescharacterizedbyhigherbioavailabilitythanotherconventionaldosage forms.
- Niosomescanbeadministratedthroughdifferentroutessuchastopical,oral ,parenteral and intranasal.
- Niosomeshavetheabilityofincreasingthepermeationofdrugsthroughtheskin.
- Niosomesprotectstheactiveconstituentfromacidandbiologicalenzymesthatlead to increase the stabilityof theactiveconstituent.
- Niosomesarestableastheyarecomposedofnonionicsurfactants(morethanliposomes that composed of phospholipids).
- Transportation,handlingandstorage ofniosomes iseasy.
- Niosomescanimprove Oral bioavailabilityof thedrug.
- Niosomesarenon-immunogenic (safe)to the body,biodegradableandbiocompatible.(10)

## IV. Factorsaffectingthe physiologicalpropertiesofniosomes

**Membrane Additives:**

Thenumberofadditivesaddedtoformulationofniosomesbesidesthenonionicsurfactantandthedrugcaninc reasethestabilityofniosomes,alsopermeabilityandmorphologyofvesiclesareinfluencedbynumbersofadditivessuc has:increasing therigidityand stabilityof niosomes byaddingcholesterol theformulation.(10)

**TemperatureofHydration:**

Hydrationtemperaturehasagreatinfluenceonsizeandshaeofniosomes.Compositionofvesiclesofniosomesi saffectedbythechangeintemperatureofthesystemofniosome.Thechangeintemperaturecanalsocausetransformation invesicleshape.Attemperatureof25°CPolyhydralvesiclesof$C_{16}G_2$:solulanC24(91:9)isformed,howeverattemperat ureof45°Cit is convertedintovesiclesspherical inshape.(39)

**Properties ofDrugs:**

Theentrapmentefficiencyofdrugsinniosomesisaffectedbylipophilicity,chemicalstructure,hydrophilicity, molecularweightandthehydrophiliclipophilicbalance(HLB)ofthedrug.Chargeonpolymermaybeincreasedasitisaff ectedbyinteractionbetweendrugparticlesandtheheadgroupofthenon-ionicsurfactantwhichinturncauserepulsionofthesurfactantbilayerthatfinallyleadstoincreaseinthe sizeofvesicle.(2 6)

**Amount and TypeofSurfactant:**

Themeansizeofniosomescanincreasewiththeincreaseof HLBvalueofsurfactants likespan20(HLB 8.6)tospan85(HLB1.8)indirectproportionalrelation,thisphenomenaisduetodecreaseofsurfacefreeenergythatassociatetheincreaseinHLBvaluethusincreaseinhydrophilicityofsurfactant.Thestructureofbilayerismoredisorderedintheliquidstate,whileinthegelstatealkylchainispresentinwell-orderedstructure.Thephasetransitiontemperatureofthegel–liquidisusedtocharacterizethelipidsandsurfactant,alsotheefficiencyofdrugentrapmentisaffectedbyphasetransitiontemperature,forexamplespan60providebetterentrapmentefficiencyduetohighervalueof.HLBvalueofsurfactantshasagreateffectonefficiencyofentrappingthedruginniosomesforexampleatHLBvalue8.6niosomeshavehighentrapmentefficiencybutatHLBvalue14to17thereisnosuitabilityfor formulation of niosomes (28).

**CholesterolContent and Chargeon the Surfactant:**

Thepresenceofcholesterolcontentintheniosomalbilayercanincreasetheentrapmentefficiencyandthediameterofnoisome.Cholesterolcanactbytwowayseitherbydecreasingthechainorderofthegelstatebilayerorincreasingthechainorderofliquidatedbilayer.Ithasbeenfoundthatrigidityofbilayerincreasesandthe drugreleaseratedecreasesbecauseofthehighconcentrationofcholesterol.(28)

**Method ofPreparation of niosomes**

MethodofpreparationscanalsoaffectpropertiesofniosomesforexampleReversephaseevaporationaswellasmicrofluidizationmethodcanbeusedtoproduce vesicles that aresmaller in size and with greaterstability.(32)

**Hand Shaking Method**

Initially surfactant and cholesterol are dissolved in some organic solvent such as benzene, chloroform and ether then the solvent is evaporated under decreased pressure in a rotary evaporator in a round bottom flask that leaves the mixture of cholesterols and solid surfactant on the walls of round bottom flask then using aqueous solution containing drug with continuous shaking, this layer was then rehydrated which cause swelling of the surfactant layer. Swelled amphiphiles eventually folds and form vesicles which entrap the drugs. (26).

**Ether Injection Method:**

A slowly injection of a solution containing a certain ratio of surfactant and cholesterol in ether into aqueous solution of the drug that is preheated and maintained at 60 °C through the specified gauze needle. Formation of unilameller vesicles of the surfactants containing the drug takes place due to vaporization of ether. Ether cannot be used in case of thermolabile drugs so in this case fluorinated hydrocarbons have been used as an alternative, because their vaporization takes place at a much lower temperature. The size of niosomes that result from this method ranges from 50 to1000mm, which mainly depend on the experimental conditions and formulation variables. (36)

**Sonication Method:**

In this method initially in the aqueous phase the cholesterol-surfactant mixture is dispersed, then at temperature at 60 °C this dispersion is probe sonicated for 10 minutes that leads to the formation of multilameller vesicles (MLV). Which are further ultrasonicated either by bath sonicator or probe sonicator, which finally resulted in the formation of unilamellervesicles. (26).

**Reverse Phase Evaporation Method:**

The solution of cholesterol and surfactant is prepared in a mixture of chloroform and ether (1:1). Then the aqueous solution of drug is added and at temperature four and five °C sonication occurred. Phosphate buffer saline (PBS) is added to the solution obtained from sonication and the solution is subjected to further soniction which leads to the formation of gel. Thereafter pressure is reduced and temperature is raised to 40 °C for the solvent removal. For ten min, the PBS is added again and heated on water bath at 60 °C to produce niosomes. (39)

**Microfluidization Method:**

Two fluidized streams (one containing the surfactant and the other one containing drug) interact at ultra high speed, in certain micro channels within the chamber of interaction in such a way that the energy supplied to the system remains in the area of niosomes formations. This is called submerged jet principle. It leads to reproducibility in the formulation of niosomes, smaller size of niosomes and better uniformity (29).

**Extrusion Method:**

A mixture of diacetyl phosphate and cholesterol is prepared by the use of rotary vacuum evaporator the solvent is evaporated leaving a thin film. The thin film is then hydrated with aqueous drug solution and the

suspension thus obtained is extruded through the polycarbonate membrane which has mean pore size of 0.1mm and then placed in series up to eight passages that lead to formation of uniform size niosomes.(38 )

## V. Components Of Niosomes

**Non-ionic Surfactants:**

In bilayer lattice, non-ionic surfactants place themselves where the hydrophilic heads face the aqueous region while the lipophilic head orient themselves in such a way that the interaction with the aqueous media would be minimized (face the lipid bilayer). Every bilayer folds over itself as continuous membrane in order to achieve thermodynamic stability. Types of non-ionic surfactant include: Alkyl Esters such as Sorbitan esters which are the most preferred Surfactant used for the preparation of niosomes in this category, Alkyl Ethers such as monoalkyl glycerol ether, Fatty Acid and Amino Acid Compounds and Alkyl Amides such as glucosides have also been used to produce niosomal vesicles.(15)

**Cholesterol:**

Cholesterol is mainly used for the formulation of niosomes and it is a steroid derivative that is essential component of cell membrane and affects the permeability as well as fluidity of bilayer (10). Properties of niosomes such as encapsulation efficiency, rigidity, membrane permeability, ease of rehydration of freeze dried niosomes and their toxicity are affected by incorporation of cholesterol. Cholesterol prevents the vesicle aggregation by electrostatic forces or repulsive steric that leads to the conversion from the gel to the liquid phase in the system of noisome; hence the niosome becomes less leaky in nature.

**Charged Molecule:**

In order to increase the stability of niosomes, some charged molecules are added to niosomes which prevents aggregation of niosomes by electrostatic repulsion. The negatively charged molecules that are used include phosphotidic acid and diacetyl phosphate (DCP). Similarly, stearyl pyridinium chloride and stearylamine (STR) are the well-known positively charged molecules used in niosomal preparations.(1,16) Only 2.5—5 mol percentage concentration of charged molecules is tolerable because high concentration can inhibit the niosome formation.(39)

## VI. Types of Niosomes

**Proniosomes:**

This type of niosomes containing surfactant and carrier that requires to be hydrated before its usage, this hydration leads to the formation of dispersion of aqueous niosome. Proniosomes decreases the aggregation, leaking and fusion problem associated with niosomal formulation.

**Bola Surfactant Containing Niosomes:**

The surfactants that are made of omega-hexadecyl-bis-(1-aza-18 crown-6) (bola surfactant): span-80/cholesterol in 2: 3: 1 molar ratio.

**Niosomes in Carbopol Gel:**

In this type, niosomes prepared from cholesterol, drug and spans are then incorporated in carbopol-934 gel (1% w/w) base containing glycerol (30% w/w) and propylene glycol (10% w/w).

**Aspasomes:**

This type formed by Combination of highly charged lipid diacetyl phosphate, cholesterol and acorbyl palmitate.

**Vesicles in Water and Oil System (v/w/o):**

This type of niosomes can be created by. Adding of niosomes suspension that is formed from mixture of solulan C24, cholesterol and sorbitol monostearate to oil phase at temperature 60 °C that leads to the formation of vesicle in water in oil (v/w/o) emulsion which can be converted to vesicle in water in oil gel (v/w/o gel) by cooling to room temperature, This gel has the ability to provide controlled release as well as entrap /proteinous drugs and proteins also protect it from enzymatic degradation after oral administration.

**Niosomes of Hydroxyl Propyl Methyl Cellulose**

It the type of niosomes in which, a base including 10% glycerin of hydroxy propyl methyl cellulose was initially developed and then niosomes were incorporated in it.

**Table (2):** variation between niosomes and liposomes (Manda et al, 2014) on between niosomes and liposomes (28).

| Liposomes | Niosomes |
|---|---|
| Requiredspecial methodforstorage,handlingandpurificationofphospholipids | No special methods are required forsuchformulationscomparatively |
| Phospholipids are prone to | non-ionic surfactants arestable (Mahaleet |
| Moreexpensive | Lessexpensive |

## VII. Conclusion

Niosome are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Noisome are promising vehicle for drug delivery and being non-ionic; and Niosomes are biodegradable, biocompatible nonimmunogenic and exhibit flexibility in their structural characterization. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections and other microbial diseases. Niosomes can entrap both hydrophilic and lipophilic drugs and can prolong the circulation of the entrapped drug in body. Encapsulation of drug in vesicular system can be predicted to prolong the existence of drug in the systemic circulation and enhance penetration into target tissue, perhaps reduce toxicity if selective uptake can be achieved. This review article focuses on the advantages, Disadvantages, preparation methods, factors affecting, characterizations, invitro methods, drug release kinetics, and applications of noisome.

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