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A Review on Advance Nano Sponge as Emerging Drug Delivery System

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ABSTRACT
In recent years, drug targeting to the site of impact is a big problem, to overcome this problem, several new targeted drug delivery methods have been invented. Nano sponges are one such invention, these sponges are smaller in size than viruses and contain voids filled with various drugs. This sponge can enter the systemic circulation and travel all over the body until it interacts with a specific target site and binds to the surface and begins to release the drug in a controlled manner. An important feature of these sponges is their ability to dissolve in water and exert an effect on drugs with low solubility. This review focuses on preparation methods and applications of nanosponges in the field of drug delivery. Efficient, targeted drug delivery systems have been a long-standing dream, but have largely been frustrated by the complex chemistry involved in developing new systems. The invention of nano sponges has become an important step towards solving these problems.
Keywordsnano-sponge, controlled release, poorly soluble drug, scaffold.

I. INTRODUCTION

In the recent year's identification of novel chemical entities as well as its application to the detection and treatment of a wide range of diseases, nanotechnology has recently attracted a lot of researcher's attention. There has been significant advancement in the field of nanomedicine, including the development of novel drug delivery systems like nano-emulsion, nanoparticles, nanosponges, and nanosuspension. Nano-sponges, one such novel drug delivery system, offers a multiple benefit over competing approaches, including improved drug bioavailability. As a by-product known as nanomedicine, it has also had a favourable impact on the healthcare industry. As a result of advances in nanotechnology, specialised drug delivery systems have been created to achieve specific goals. Nano-sponges are similar in size to viruses. Due to the small size it quickly penetrates the skin. It's a brand-new kind of material with nanometer-wide cavities comprised of incredibly tiny particles. Drugs catagorised under BCS class II and IV that are poorly water soluble could potentially be placed into nano-sponges along with lipid-soluble drug molecules, improving their solubility [1,2]. One of the benefits of nano-sponge is that it is a three-dimensional scaffold (backbone) or network of polyester that can naturally decay. These polyesters are mixed with a cross-linker in a solution to create nano-sponges.Biodegradable polyester is frequently utilised in this condition, as it breaks down gradually in the body. They will distribute through a matrix of additives, lubricants, diluents, and anti-caking agents when taken orally, where they will be more effectively utilised to tablet and capsule formulation [3].

Difference between Nanoparticles and Nanosponge

The thin line separating nanoparticles from nanosponges is the difference in size and porosity. While nanosponges' overall size can range from micrometre to micrometre and is normally less than 5 m, nanoparticles have holes that are nanometer in size. Nanoporous nanoparticles/microparticles have been described as nanosponges on a number of occasions. The hydrophobic and hydrophilic groups that are present provide nanosponges a structure with a variety of domains. [5]

Advantages of Nanosponges

- Improve solubility of lipophilic drugs in water.
- Protection of molecules and development of drug delivery systems for different routes of administration.
- They mix with water and serve as fluid carriers.
- To mask unpleasant tastes.
- Chemical linkers allow NS to bind specifically to the target site.
- NS engineering originates from the availability of relatively simple chemistry of polyesters and linker peptides.

Disadvantages of nanosponges

- Nanosponges have the ability to encapsulate small molecules that are not suitable for larger molecules.

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Special Properties of Nanosponges

- Nanosponges have a range of sizes (1 µm or less) with tunable polarization of the voids. Nanosponges of specific size and tunable polarity can be synthesized by varying the ratio of coupling agent to polymer. [4]
- Depending on the process conditions, they can be either para-crystalline or crystalline. The crystal structure of nanoparticles plays a very important role in their complexation with drugs. The drug loading capacity of nanosponges depends on the degree of crystallization. Para-crystalline nanosponges have shown different drug loading capabilities. [5]
- They are non-toxic, porous particles that are insoluble in most organic solvents and stable at high temperatures up to 300°C. [6]
- Nanosponges because the formulations are stable in the pH range from 1 to 11 and temperatures up to 130 °C. [7]
- They form clear, impure suspensions in water and can be recovered by simple thermal desorption.

Chemicals used for the synthesis of nanosponges
Polymers

Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β- Cyclodextrins and Copolymers like Poly(valerolactoneallylvalerolactone) & Poly(valerolactoneallylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA

Cross linkers

Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles) Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2bis(acrylamido) Acetic acid

Factors affecting the formulation of NanoSponge Polymer Type

The formation as well as the performance of nanosponge depends on the selection of the appropriate polymer. The cavity or pore size of the nanosponge must be able to accommodate drug molecules of the appropriate size. [13]

Drugs

• Molecular weight must be between 100 and 400 Daltons.
• The structure of the drug molecule should not contain more than five condensate rings.
• Water solubility should be less than 10 mg/ml.
• The melting point must be below 250°C. [15]

Temperature

Temperaturevariationscanaffectdrugcomplexation.IncreasingtemperaturereducesthestabilityofNanoSpongecomplexwhichisclearlypossible becauseNanoSpongedruginteractionforce,VanderWaalsforceandhydrophobicforcecanbereducedwithincreasingtemperature.[14]

METHOD OF PREPARATION

Nanosponges made from hyper cross-linked β-cyclodextrins

super-crosslinked Nanospongeismadefromamaterialthatgeneratesnon-porousmoleculesasacarriercalledcyclodextrinfordrugdelivery.Thesecyclodextrinsareasuper-crosslinkingagentthatformsmanynetworksinthenanonetwork,orcanevenbesphericalwithmanyproteinchannelnetworks,pores,etc.Thesecrosslinkingagentsstabilizespongeswithspecificsurfacechargedensities,porosity,andporesizesof basedonthemoleculestheycontain.Crosslinkingagentshelpkeep Nanospongesatdifferentacidicandevenneutral pH values[8]

Solvent emulsification method

Main polymers used in this method are ethyl-cellulose and polyvinyl alcohol in variable proportions. The dispersed phase was formed by adding ethyl cellulose and the available drug was dissolved in 20 ml of dichloromethane. The continuous phase dropwise addition was prepared by dissolving polyvinyl alcohol in 150 ml of distilled water. The mixture was then stirred at 1000 rpm for about 2 h. The obtained Nano sponges will be collected, filtered and dried in an oven for about 1 day and then stored in a desiccator. [9]

Solvent method

The polymers used above can be used with suitable polar aprotic solvents such as dimethylformamide, dimethyl sulfoxide and mixed in proportion. Then, to this mixture, available crosslinkers are added in a ratio of 4:16. The temperature was maintained from 10 °C for the reaction of the polymers for 2 days. Most carbonyl crosslinkers (dimethyl carbonate and carbonyl diimidazole) are used. When the reaction was complete, the product was kept cooled to room temperature, then the mixture was added with distilled water for recovery and filtration in an air

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furnace and purification was performed using a Soxhlet apparatus with the addition of water. add ethanol for additional extraction. Again, opt for vacuum drying and mechanical beating to obtain a uniform white powder. [10]

Ultrasonic-assistedsynthesis

Inthisprocess,nanospongescanbeobtainedusingpolymerswithcarbonylcross-linksundersolvent-freeconditionsandstoredforsonication.TheseNano-developedspongeswillhaveauniformsphericalsize.Mixpolymerandcrosslinkingagentinsufficientquantityandcollectinbottle.Theflaskwasfilledwithwaterandheatedto90°Cforsonication.Themixturewaskeptfor5hforcontinuousnegatives.Themixturewasthencooled,andtheproductwaswashedwithdistilledwaterandpurifiedusingaSoxhchletextractorusingethanol.Thefinalproductobtainedwasdriedat25°Candthewhitepowderwasrecoveredandstoredawayfrommoisture.[11]

NanoSpongedrugloading

Nanospongesformulatedfordrugdeliverymustfirstbepretreatedtoachieveanaverageparticlesizeoflessthan500nm.TheNanospongesarethensuspendedinwaterforaperiodoftimeandtreatedwithultrasonicwavestoavoidtheformationofagglomerates.Theproductsuspensionobtainedwascentrifugedtoobtainthecolloid.Theobtainedsupernatantwasseparatedandthesamplewasdriedbylyophilization.[12]

Alternatively,aqueoussuspensionsofNanospongesarepreparedanddispersedwithcontinuousstirringforaspecificperiodoftime.NanoSpongesolidcrystalsareobtainedbyevaporatingthesolventorbylyophilization.Thecrystallinestructureofthenanoporousfoamplaysaveryimportantroleinthedrugcomplexationprocess.Thedrugloadingcapacityincrystallinenanospongesishigherthanincrystallineforms.Innanospongescontainingpoorcrystallinestructure,drugloadingoccursasmechanicalmixingratherthanformationofaninclusioncomplex.

APPLICATIONSOFNANOSPONGES

Nanospongesassustainedreleasesystem

Acyclovirisoneofthewidelyusedantiviralagentsforthetreatmentofherpessimplexvirusinfections.Itsabsorptioninthe GITisslowandincompleteandveryvariable.Theinvitroreleaseprofileofacyclovirfromdifferent Nanospongesindicatessustainedrelease.Thepercentageofacyclovirrelease fromNanocarbspongeandNanosponge after3hoursofuseisabout22%and70%.Thedrugwasnotabsorbedonthesurfaceofthe NanoSpongeasnoinitialexplosiveeffectwasobserved.[16]NanospongesinSolubilityEnhancement

ItraconazoleisaBCSdrugwithlimitedsolubilityandlowbioavailability.Therefore,theapplicationofnanospongesimprovedthedrugsolubilitybymorethan27-fold.Solubilitywasfoundtobeinexcessof55-fold,whencopolyvidonumwasaddedasacarriercomponent.Eitherbymaskingthehydrophobicgroupsofitraconazole,increasingdrugwetting,orreducingdrugcrystallinity,nano-slitsimprovedrugsolubility.[17]

Nanosponges in solubility enhancement

Itraconazole is a BCS class Ⅱdrug which has a dissolution rate limited poor bioavailability. Thus the application ofnanosponges improved the solubility of the drug more than 27-fold. The solubility was found to be exceeded to 55fold, whencopolyvidonum was added as a Supporting component. Eitherby masking the hydrophobic groups of itraconazole, by increasing the wetting ‘of the drug or by decreasing the crystallinity of the drug nanosponges improve the solubility of the drug. [17]

NanoSpongesinDrugDelivery

Nanospongescanbeformulatedindifferentdosageformssuchastopical,injection,aerosol,tabletsandcapsules.Telmisartan(TEL)isadrugwithlimitedbioavailability.TELwasincorporatedintothenanospongeformulation.Thesaturationsolubilityandinvitrosolubilityofthe TELβ-CDcomplexwerecomparedwiththatoftheconventionalTELandTELnanospongecomplexes.Thehighestinvitrodrugsolubilityandreleasewereobservedininclusioncomplexespreparedfromnanospongeand NaHCO3.Paclitaxelisapoorlywater-solubleantineoplasticdrug.β-CD-basednanospongesareanalternativetotheclassicalcremophoreformulationbecausecremophorereducesthetissuepenetrationofpaclitaxel.Thebiologicaleffectsofpaclitaxelinvitroaresignificantlyenhancedbythenanospongeformulation.Econazolenitrateisanantifungalagentusedforskininfectionsandfungalskindiseases.Absorptionisnegligiblewheneconazoleisappliedtotheskin.Therefore,econazolenitratenanofoamsweregeneratedbysolventdiffusionandloadedashydrogels.[18].

NanospongesinEnzymeImmobilization

Nanospongeshavebeenwidelyusedforenzymestabilization.CD-NSexhibitsamuchhigherintegrationconstantthanCDandissuitableforsupportingenzymeimmobilization.Theyhelpmaintainthecatalyticcapacityandstabilityofimmobilizedenzymes.Enzymeimmobilizationisimportantforenzymerecyclingandfacilitatesseparationandrecoveryoftheformedproductsaswellasincreasesthermalstabilityandbiocatalystactivity.Boscolaetal.alsoinvestigatedthehighcatalyticefficiencyofsomePseudomonasflurescenslipasesadsorbedoncyclodextrin-

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basednanosponge.Lipasesarewidelyusedtocatalyzetriacylglucerolhydrolysisandtransesterificationreactions,withmanyindustrialapplications.[19]

Nanospongesforproteindelivery

Amajorobstacleinproteinformulationdevelopmentismaintainingtheoriginalproteinstructurebothduringformulationandduringlong-termstorage.Swaminathanetalinvestigatednovelexpandablepolynanospongesbasedoncyclodextrin.Throughwaterabsorptionstudies,theyobservedverygoodstableswellingfor72hours.Bovineserumalbuminwasusedasthetemplateproteinandincorporatedintotheprepared nanosponge.Improvedswellingpropertiesaswellasincreasedproteinstabilitywereobserved.AtphysiologicalpH,thelactoneringopensanddevelopsaninactivecarboxylateform.Thefusionofcamptothecininthenanospongesresultsinasustainedreleaseprofileintheactiveform,whichpreventshydrolysisofthelactoneformandleadstoimprovedstability.[20]

CancerTherapies[21]:

Nanospongescanbeusedasananti-tumordrugdeliverydeviceforcancerdrugs.Themethodwasthreetofivetimesmoreeffectivethandirectinjectionofthedruginreducingtumorgrowth,theresearcherssaid.Thesmallnanospongesareencapsulatedwithadoseofthedruganddisplayabindingpeptidethatbindstocellsurfacetargetsbyradiationtothetumor.Theysticktothesurfacewhenthespongecomesintocontactwithtumorcellsandarestimulatedtoexpeltheircharge.Thebenefitoftargeteddrugdeliveryallowsformoreaccuratediagnosisatthesamedoseandfewerhealthproblems.Studieshavebeenconductedasaspongefillerinanimalswithpaclitaxel.

Antiviralapplication[22]:

Inallcranial,nasal,pulmonarytherapeutics,nanospongesmaybebeneficial.TocaptureRTI-infectingviruses,includingrespiratorymembranecellviruses,influenzaviruses,andhinoviruses,nanocarrierscanselectivelydeliverantiviraldrugsorsmallinterferingRNAs.(siRNA)tothenasalandlungepithelium.TheycanalsobeusedforHIV,HBV,andHSV.Zidovudine,saquinavir,interferon-α,acyclovir(Eudragit-based)aredrugscommonlyusedonlyasanano-deliverysystem.

GasEncapsulation[22]:

Cyclodextrin-dependentNanospongeisusedtoformcomplexesconsistingof3separategases,namely1-methylcyclopropene,oxygenandcarbondioxide.Forsomebiomedicalapplications,complexationofoxygenorcarbondioxidecanbeuseful.Inparticular,oxygen-fillednanospongecandeliveroxygentohypoxictissuesinvariousdiseases.Duetoitshighnature,extremelyporous;Asanefficientgascarrier,Nanospongehasalsobeenexplored.Thecompositionofnanospongeshowstheabilitytomonitortheaccumulationandreleaseofoxygen.Theycouldbeavaluabletooltodeliversomeimportantgasesinthefuture.

Otherusesofnanosponges

Cyclodextrin-basednanospongescanstronglybindorganicmoleculesandextractthemevenattheselowwaterlevels.Thesameconceptcouldbebeneficialwhenselectivelycombiningapolymerandacrosslinkertoremovebittercomponentsfromgrapejuice.Three-dimensionalnanospongesforproteomicsapplicationscanplayanimportantroleinpeptidefractionation.Forgasessuchasoxygenandcarbondioxide,nanospongescanbeusedasatransportmedium.

Oraldistribution

Thiscomplexcanbedispersedinamatrixofdiluents,excipients,lubricantsandanti-cakingagentsfororaladministrationincapsuleortabletform.Acetylsalicylicacid,anonsteroidalanti-inflammatorydrug(NSAID)classifiedasaClassIIIBCSdrug,isusedtoformnanospongesforuseinanoraldrugdeliverysystem.[23]

Topicaluse

ThecomponentsofNanospongecanbeappliedtopicallyasagelorcream.Itisbelievedthatthenanoparticlesareloadedwithresveratrol[24]

Characterizationofthenanoparticles

Methodsforthecharacterizationofcomplexingdrugs/nanospongesarelistedbelow: Solubilitystudies Inclusioncomplexesareatechniquefordeterminingdrugsolubilityandbioavailability.Thistechniqueisthemostwidelydiscussedtechniquefortheanalysisofnanospongecomplexes.Thedegreeofcompletioncanbeknownbyplottingthesolubilityofthephases.Solubilitystudiesareperformedtoaccessthe pHofthedrug,outlinethesolubility,andtoevaluatethefactorsaffectingdrugsolubility[16].

X-raydiffractionstudies

Forthesolidstate,X-raypowderdiffractionmeasurementcanbeusedtodetermine thecomplexityofimpurities.Whenthedrugmoleculeisliquidandtheliquiditselfhasazero-diffractionpattern,thediffractionpatternofanewlyformedsubstancewillbemarkedlydifferentfromthediffractionpatternofanincompletenanosponge.Thisdifferenceinthediffractionpatternindicatestheformationofa

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complex.Whenthedrugcompoundisasolid,itisnecessarytocomparethediffractionpatternofthecomplexandthatofthemechanicalmixtureofdrugmoleculesandpolymers.Thediffractionpatternofaphysicalmixtureisusuallythesumoftheformsofeachcomponent,whilethediffractionpatternsofacomplexareobviouslydifferentforeachcomponentandresultinanewsolidphasewithdifferentdiffractionpatterns.together.Thediffractionpeaksformixturesofcompoundsareusefulindeterminingchemicaldecompositionandcomplexformation.Complexformationofthedrugwithnanospongechangesthediffractionpatternandalsochangesthecrystallinenatureofthedrug.Thecomplexformationleadstotheemphasisofexistingpeaksandthedisplacementofcertainpeaks.

Microscopicstudies

Microscopicstudiesofdrug/nanofoamcanbeperformedusingscanningelectronmicroscopyandtransmission electronmicroscopy.Theinclusioncomplexformation representedbythedifferencebetweenthecrystallizationandproductstateswasobservedundertheelectronmicroscope.

Thermodynamicmethod

Ifthechangesoccurinthedrugmoleculeortheparticleschangeearlierthanthethermaldecompositionofthenanofoam,itcanbedeterminedbythermochemicalmethod.Thedrugparticlechangescanbemelting,evaporation, oxidationanddecompositionandmacromolecularchanges.Changesinthedrugmoleculesuggesttheformationofagoodcomplex.

ParticlesizeanddispersionPolydispersity

Particlesize wasdeterminedbydynamiclightscatteringusing90Plusparticlesizedeterminationsoftware.Dynamiclightscattering(DLS)isdefinedasatechniqueusedtoknowthesizedistributionprofilesofnanoparticles.Finally,thefinalparticlediameteranddispersionindex(PDI)canbefound.

Thinlayerchromatography(TLC)

TLCcanbedefinedasatechniquethatcanbeusedtoseparatenon-volatileorvolatilemixtures.Inthistechnique,iftheRfvalueofaparticulardrugmoleculeiswithinanacceptablerange,itisusefulinrecognizingtheformationofacomplexbetweenthedrugandthenanosponges.

InfraredSpectroscopy

Interactionsbetweennanoslitsandsolid-statedrugscanbedeterminedbyinfraredspectroscopy. Thenanospongebandsmaychangeslightlyuponcomplexformation.Fewguestmoleculesareboundinthecomplexwithafractionlessthan25%,sothedrugspectrumcanbeeasilymaskedbythenanospongespectrum.Thistechniqueisnotsuitablefordeterminginclusioncomplexescomparedtoothermethods[17].

Chargingefficiency

TheloadingefficiencyofnanospongecanbedetermineddbyestimatingthedrugloadedintothenanospongeusingUVspectrophotometerandhigh-performanceliquidchromatographyfornanoparticles. Thechargingefficiencyof nanospongescanbecalculatedusingthefollowingformula.

$$\mathbf{LE} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \text{ X } 100$$

II. CONCLUSION

Nanospongescandeliverbothhydrophilicandhydrophobicdrugs,andtheyaredrugdeliverysystemsthatenablecontrolledandpredictabledrugreleasetoanefficienttargetsite,therebyimprovingefficiencyandbioavailability.Theycanbeformulatedinmanydifferentformulationssuchastopical,oralandsystemic.

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