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Research on Nanoparticle

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I. INTRODUCTION

The polymeric nanoparticles (PNPs) are prepared from biocompatible and biodegradable polymers in size between 10-1000 nm where the drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsulesare systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed 1,2. The field of polymer nanoparticles (PNPs) is quickly expanding and playing an important role in a wide spectrum of areas ranging from electronics, photonics, conducting materials, sensors, medicine, biotechnology, pollution control and environmental technology 3–11. PNPs are promising vehicles for drug delivery by easy manipulation to prepare carriers with the objective of delivering the drugs to specific target, such an advantage improves the drug safety12. Polymer-based nanoparticles effectively carry drugs, proteins, and DNA to target cells and organs. Their nanometer-size promotes effective permeation through cell membranes and stability in the blood stream. Polymers are very convenient materials for the manufacture of countless and varied molecular designs that can be integrated into unique nanoparticle constructs with many potentialmedicalapplications13.Severalmethodshave beendevelopedduringthelasttwo decades for preparation of PNPs, these techniques are classified according to whether the particle formation involves a polymerization reaction or nanoparticles form directly from a macromolecule or preformed polymer or ionic gelation method .

❖ Definition:

Nanoparticles are colloidal particle ranging from1to1000nmsizeandthey contain micromolecules materials in which the A.P.I dissolved and entrapped/attach.

❖ Advantages

1. Nanoparticlesdrugcarriershavehigherstabilities
2. Nanoparticleshavehighercarriercapacity.
3. Feasibilityofincorporationofbothhydrophilicandhydrophobicsubstance. 4.Feasibility of varies routes of administration . 5.Nanoparticlesarebiodegradablenon-toxicandcapableofbeingstoredforlonger periods . Nanoparticlescanalsobeusedforcontrolleddeliveryof drug. 7.Nanoparticles reduce dosing frequency and have higher .

❖ **Disadvantages**

1. Polymericnanoparticlespossesslimiteddrug–loadingcapacity
2. Onrepeatedadministrationtoxicmetabolitesmaybeformedduringthe biotransformation of Polymeric carrier .
3. ThePolymericnanoparticlesarerelativelyslowlybiodegradablewhichmightcause systemic toxicity .

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Applications

Application	Purpose	Material
Cancertherapy	Targeting, Reducing toxicity,enhanceuptakeof anti-tumor agent	Polyalkylcyanoacrylate with anticancer agent
Intra cellularTargeting	Targetreticuloendothellal system forIntra cellular infection	Polyalkylcyanoacrylate
Vaccineadjuvant	Prolong systemic drug effect.Enhanceimmune response	Poly methyl metha acrylate nanoparticleswithvaccines
DNAdelivery	Enhancedbioavallability and significantly higher expression level.	DNA gelatin nanoparticles, DNAchitosannanoparticles
Ocular delivery	Improved retention of the drugandreducedwashed out	Polyalkylcyanoacrylate nanoparticles, anti-inflammatoryagent

Classification of nano materials

Typically,NPsaredefinedasanagglomeration ofatomsand moleculesintherangeof1– 100 nm. They can be composed of one or more species of atoms (or molecules) and can exhibit a wide range of size-dependent properties. Within this size range, NPs bridge the gap between small molecules and bulk materials in terms of energy states [17]. NPs are generally classified based on their dimensionality, morphology, composition, uniformity and agglomeration .

1. Dimensionality

1Dnanomaterials.

- Thinfilmshavebeendevelopedandusedforde cadesinMaterialswithonedimension in the nanometre scale are typically thin films various fields including electronics, informationstoragesystems,chemicalandbiologicalse nsors,fibre-opticsystems,and magneto-optic and optical devices. Thin films can be deposited by various methods and can be grown controllably at the atomic level (a monolayer) [20].

2Dnanomaterial

- 2D nanomaterials have two dimensions in the nanometre scale. These include for example,nanotubes,dendrimers,nanowires,fibresandf ibrils.Freeparticleswitha large aspect ratio with dimensionsin thenanoscale range arealsoconsideredtobe 2D nanomaterials. The properties of 2D systemsare less wellunderstood and their manufacturing capabilities are less advanced.

3Dnanomaterials.

- Materials that are nanoscale in all three dimensions are considered to be 3D nanomaterials.Theseincludequantumdotsornanocryst als,fullerenes,particles, precipitates and colloids. Some 3D systems, such as natural nanomaterials and combustion products, metallic oxides, carbon black, titanium oxide (TiO_2) and zincoxide(ZnO)arewellknown,whileotherssuchasfull erenes,dendrimersand quantum dots represent the greatest challenges in terms of production and understanding of properties.
- Figure 1.1shows examples of nanomaterials with different dimensions. All the samplesweredepositedonaSi(111)substrateusingthe magnetron-sputtering- based inert-gas-condensation (MS-IGC) method as described in figures2.1and2.2.Thematerialsshowninfigures1.1(*a*) and(*b*)canbeclassified as 1D nanomaterials, while theCu NPs shown in figure 1.1(*c*) are classified as 3D nanomaterials. The iron nanorods shown in figure 1.1(*d*) can be classified as 2D nanomaterials

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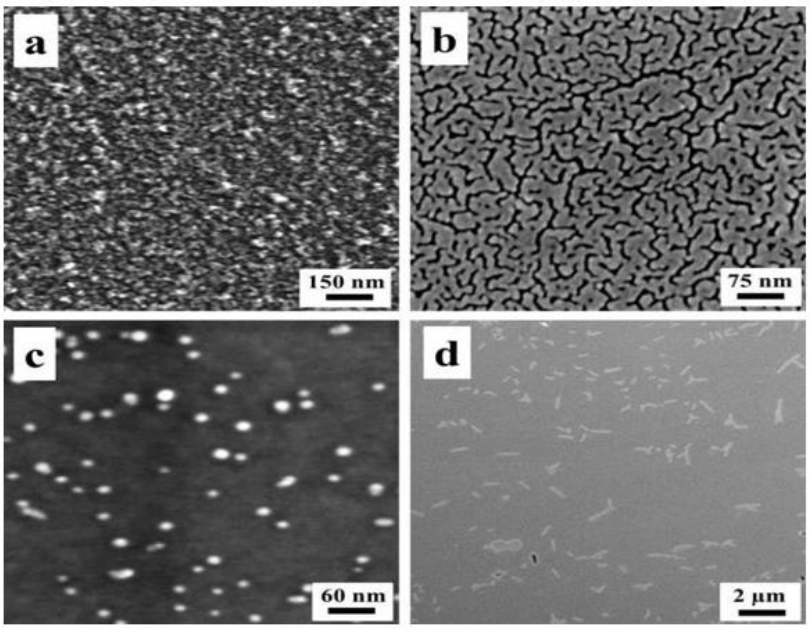

2.ThemorphologyofNPsandnanocomposites

- The morphological characteristics to be taken into account are the flatness, aspect ratio and spatial position of each element in the case of hybrid NPs (HNPs). Ageneral classification exists between high and low aspect ratioparticles.
- High aspect ratio NPs include nanotubes and nanowires. Small aspect ratio morphologiesincludespherical,oval,cubic,prism,helical andpillarshapes. Figure 1.2shows examples of different morphologies of NPs and nanocomposites.
- Transmission electron microscopy (TEM) images of monodispersed Cu NPs, Fe nanorods and Cu core–Si shell NPs are shown in figures 1.2(*a*), (*b*) and (*c*), respectively.
- The details of the preparation methods for these NPs are presented in chapter 2. The TEM images in figures.(*d*) and (*e*) show a porous magnetite NP and magnetite cubes decorated with Ni nanocrystals, respectively. These NPs were designed and synthesized using the hydrothermal process for purification of histidine-tagged proteins.
- TEM images of examples of NPs with different morphologies and compositions. (a) Monodispersed CuNPs,(b)Fe nanorods, (c)Cu–Si core–shellNPs, (d) porous Fe3O4 NPs, (e) Fe3O4 cubes decorated with Ni NPs, (f) porous silica spheres with γ-Fe2O3 NPs adsorbed on their surfaces and (g) γ-Fe2O3 NPs embedded in porous silica spheres.
- Formoredetailsaboutthepreparationandcharacterizationofthesecomposites seen. Withregardtonanocomposites,substantialprogresshasbeenmadeinrecentyears in developing technologies in the fields of magnetic microspheres, magnetic nanospheres and ferrofluids.
- Nanospheresandmicrospherescontainingamagneticcoreembeddedina nonmagnetic matrix are used in numerous biological applications.

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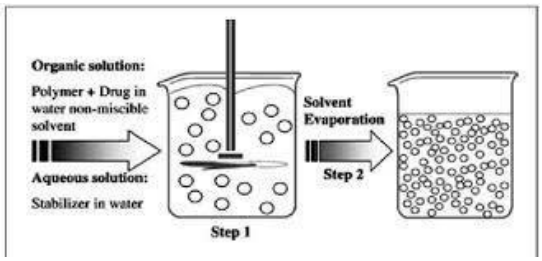
Techniquesofpreparationofnanoparticles

Methods for preparation of nanoparticles from solvent evaporation ,

Nanoprecipitation,Emulsification/solventdiffusion,saltingout,Dialysis.

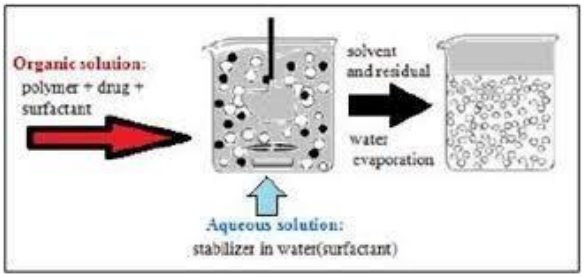
1.Solventevaporation

- Solvent evaporation was the first method developed to prepare PNPs from a. In this method, polymer solutions are prepared in volatile solvents and emulsions are formulated



2. Nanoprecipitation

- Nanoprecipitation is also called solvent displacement method. It involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant35-38.
- The polymer generally PLA, is dissolved in a water-miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. This phase is injected into a stirred aqueous solution containing a stabilizer as a surfactant.



3. Emulsification/solventdiffusion(ESD)

- it is necessary to promote the diffusion of the solvent of the dispersed phase by dilution with an excess of water when the organic solvent is partly miscible with water or with another organic solvent in the opposite case.
- Subsequently, the polymer-water saturated solvent phase is emulsified in an aqueous solution containing stabilizer, leading to solvent diffusion to the external phase and the formation of nanospheres or nanocapsules, according to the oil-to- polymer ratio

4. Saltingout

- Salting out is based on the separation of a water miscible solvent from aqueous solutionviaasaltingouteffect.Thesaltingoutprocedure canbeconsideredasa modification of the emulsification/solvent diffusion

5. Dialysis

- Dialysisoffersasimpleandeffectivemethodforthepreparationofsmall,narrow- distributed PN31,35,60-62. Polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cut off.

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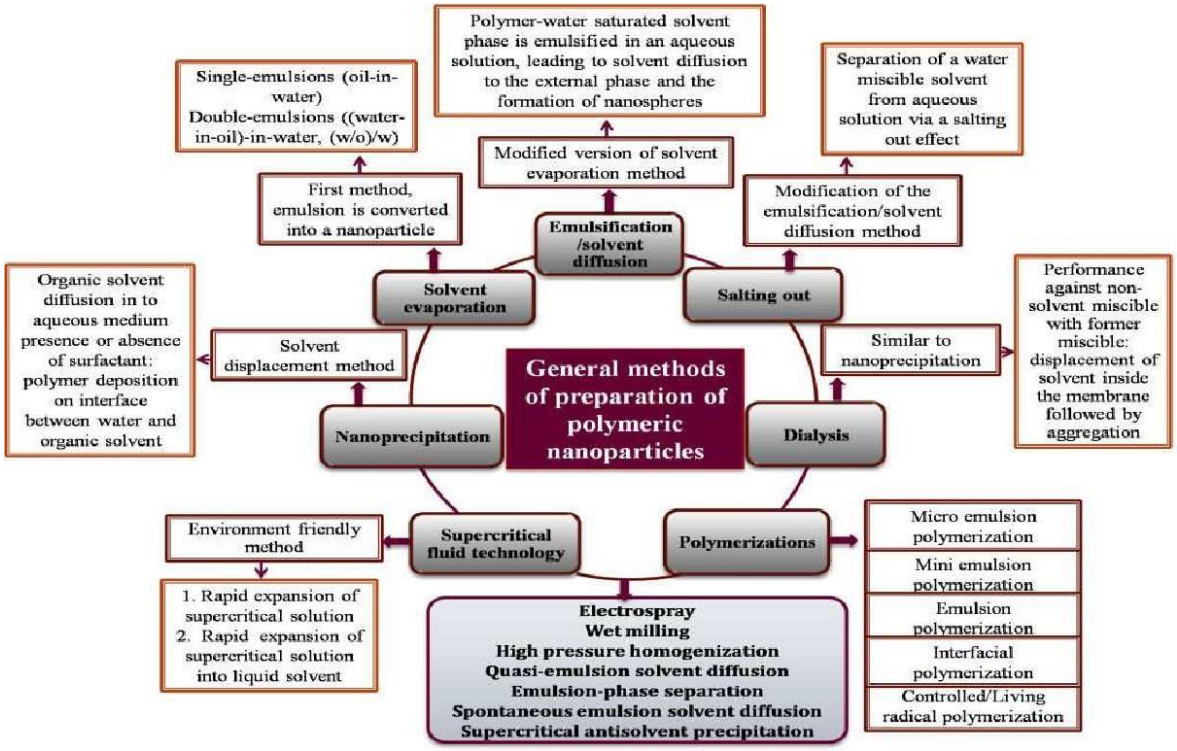
Method of preparation nano particles



❖ ROLEOFNANOPARTICLESINPHARMACOTHERAPY

- The term ‘nanoparticle’ is not usually applied to individual molecules. Itusually refers to inorganic material. The reason for the synonymous definition of nanoparticles and ultrafine is that during the 1970s and 80s, when the first thorough fundamental studies with ‘nanoparticles’ were underway in the USA (byGranqvistandBuhrmann)andJapan,(withinanERATOproject)theywerecalledultrafineparticles.Nanoparticleareparticlesbetween1and100 nanometer (nm) insize.

- Innanotechnologyaparticlesisdefinedasasmallobjectthatbehavesas awholesunitrespecttoitstransportandproperties.Particlesarefurther classified according to diameter.

A. Ultrafineparticlesarethesameasnanoparticlesand between1tn100nmin size.
B. Fineparticlesaresizedbetween100and2,500nm.
C. Andcoarseparticlescoverarangebetween2,500and 10,000.

❖ **ROLEOFNANOPARTICLESINCANCERTHERAPHY**

EnhancedthepotentialofintracellularTaxanedeliveryroleofnanoparticlesalbumin-blood paclitaxel in the treatment of advanced breast cancer.

1] Docetaxelandpaclitaxelareamongthemostactiveagentsforthetreatmentofbreast cancer.
2] Thesefirst–generationTexansareextremelyhydrophobictherefore,solventsare needed for its parenteral administration.
3] Albuminnanoparticlestechnologyallowsforthetransportation.Ofsuchhydrophobic drugs without the need of potentially toxic solvents.
4] Nab-paclitaxelcanbeadministeredwithoutpremedication,inashorterinfusiontime and without the need for a special infusion set.
5] Thebioavailabilityoforallydelivereddrugsisinfluencedbythephysico-chemical properties of the drugs (i.e. solubility, pKa, size, etc.).
6] Theabsorptionofdrugsandparticlesingastrointestinaltract(GIT)occursthrough various sites depending upon their size.
6] Particleswith1µmdiameterareabsorbedviaphagocytosisbyintestinalmacrophages while particles <10 µm in diameter are transported

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through payer's patches (lymphatic islands present on GIT). Nanoparticles (<200 nm) are absorbed through endocytosis by enterocytes .
7] The efflux transporters such as P-glycoprotein (Pgp) and enzymes, expressed on enterocytessurface,alsorenderthelowsystemicbioavailabilityofdrugsaffectingthe absorption and excretion of drugs.
8] Nanotechnologyrevealstheapplicationofsizescalecomplexsystemsinvariousfields due to their unique properties.
9] Oneoftheextensivelystudiedareasofnanotechnologyisdeliveringsystemsforthe active ingredient of the medicine.

10] Effectivenanomedicinemustbestable,biodegradable,non-toxic,noninflammatory, non-thrombogenic, nonimmunogenic and should escape by reticuloendothelial system.
11] Moreover,nanomedicineshouldbeapplicabletodifferentmoleculessuchassmall drugs, proteins, vaccines or nucleic acids.

12] Ithasbeenprovedexperimentallythat,fortherapeuticandimagingapplications, nanoparticles may range from 2 to 1000 nm.

Targeteddeliveryforbreastcancertherapy.

1] **Roleofnanoparticle-albumin-boundpaclitaxel**

Paclitaxel is hydrophobic, and available formulations require polyoxyethylated castor oil, Cremphor EL® (CrEL) and an ethanol vehicle to allow parental administration.Taxanes are agentsforthetreatmentofbreastcancer.Nanoparticlealbumin-boundpaclitaxel(nab-P)isa CrEL-free formulation of paclitaxel.The human albumin-stabilized paclitaxel particles have a size of approximately 130 nm, which allows intravenous infusion without capillary blockage othereceptorsonepithelialcell surface.

Amongvariouslimitationsoforaldeliveryofcertaindrugsistheirpoorabsorptionfromthe GIT.

ROLEOFNANOPARTICALINDIABETICTHERAPY

- Nanotechnologyin diabetes researchhas facilitated thedevelopmentofnovel glucose measurementandinsulindeliverymodalitieswhichholdthepotentialtodramatically improve quality of life for diabetics.
- Recentprogressinthefieldofdiabetesresearchatitsinterfacewithnanotechnologyis our focus.
- Inparticular,weexamineglucosesensorswithnanoscalecomponentsincludingmetal nanoparticles and carbon nanostructures.
- Theadditionofnanoscalecomponentscommonlyincreasesglucosesensorsensitivity, temporalresponse, andcanleadtosensorswhichfacilitatecontinuousinvivoglucose monitoring.
- Additionally, we survey nanoscale approaches to 'closed-loop' insulin delivery strategies which automatically release insulin in response to fluctuating blood glucose levels(BGLs).'Closingtheloop'betweenBGLmeasurementsandinsulinadministration by removing the requirement of patient action holds the potential to dramatically improve the health and quality of life of diabetics.
- Advantagesandlimitationsofcurrentstrategies,aswellasfutureopportunitiesand challenges are also discussed.

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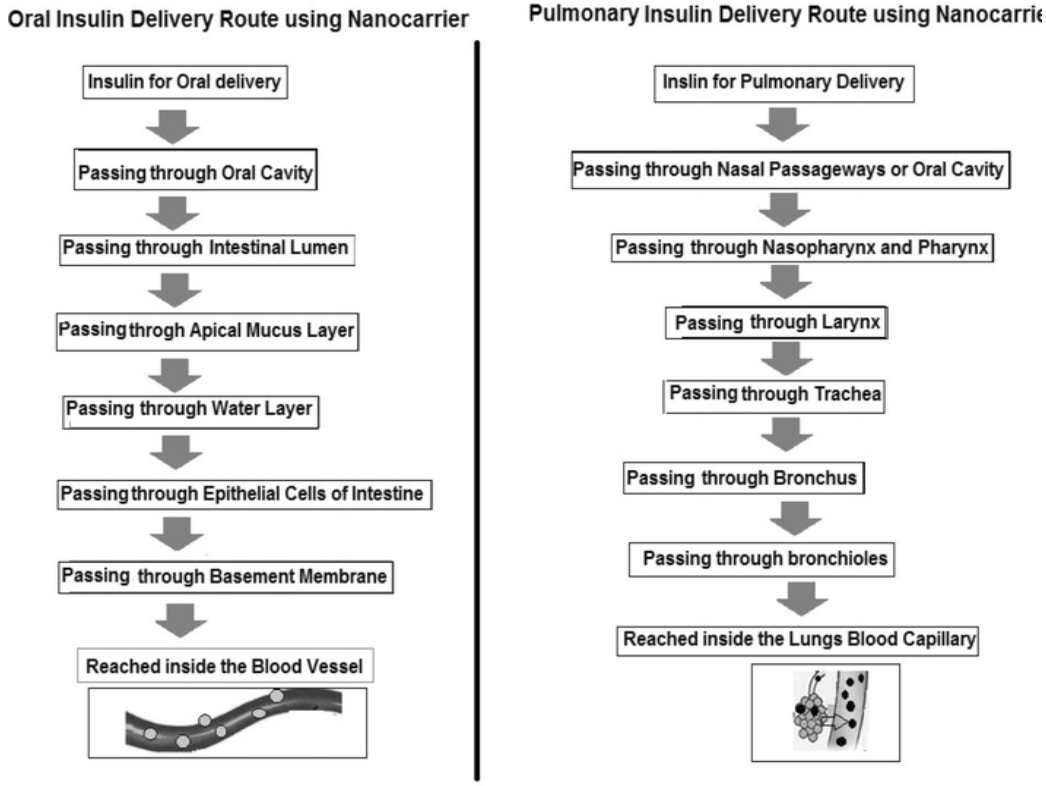

❖ **Roleofnanoparticlesoninsulindelivery**

- Majortworoutesofnanocarrierbasedinsulindelivery.
- Theusesofbiodegradablepolymericnanoparticleshaveevolvedasabetter alternative for oral/pulmonary delivery of proteins and peptide drugs.
- Furthermore, the stability and functional abilities of the nanoparticles can be modulatedbysomeofthepharmaceuticallyacceptedexcipientsabletoregulatepH responsivelyandPgpeffect

PLGA-insulinnanoparticles

- PLGAisFDAapprovedbiodegradablesynthe ticpolymerusedfrequentlyfordrug delivery.
- Usingcomputationalanalysis,Lassallaetal.showedthepresenceofhydrophobic and hydrophilic interactions between insulin and PLGA polymer.
- PLGAnanoparticleswereformulate dbyamodifiedsolventdiffusiontechniqueas model nanocarriers for insulin and potential oral drug delivery system.
- nsulin loaded PLGA (PNP) and PLGA-Hp55 nanoparticles (PHNP) nanoparticles werealsoinvestigatedasaneffectivemethodofreducing serumglucoselevels,in vivo.
- The relative bioavailabilityofPNP and PHNP compared with subcutaneous (s.c.) injection(1IU/kg)indiabeticratsobservedwas3.68±0.29and6.27±0.42%, respectively.
- Hp55 was used as a pH sensitive cellulose coating to resist high acidic pH of gastric fluidsforlongertimesimultaneouslydissolvinginlower acidicpHofsmallintestine.
- Double emulsion solvent evaporation method was also used to design PLGA encapsulatedinsulinnanoparticlesandthenembedded withinPVAhydrogels.
- This composite system showed a reduction in both the release rate and the total amount of insulin released. Attempts have been made to modify the slight negative surface charge of PLGA by using polyatomic polymer, chitosan. Because of the positive surface charge, chitosan reverses the effect of negative charge on PLGA furthersupportingendocytosisofnanoparticlesthrough theirincreasedinteraction with the cell membrane.
- Previously, chitosan has been known as one of the Pgp modulator which may decreasethePgp-

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mediatedeffluxofdrugloadednanoparticlesfromthelu minal surface of cells.

- As a result, chitosan modified PLGA nanoparticles exhibited strong bioadhesive potencyandincreasedpharmacologicalavailabilitywit hregardtoorallydelivered insulin.
- PLGAnanoparticlesharboringinsulin-S.O(sodiumoleate)complexwasprepared via an emulsion solvent diffusion method and was evaluated for their pharmacological effects via oral administration to diabetic rats.

Dextran-insulinnanoparticles

- Earlierstudiessuggestthatthebestwaytotreat diabetesistoprovideexogenous insulin level according to the blood glucose level of the patient.
- Althoughthemethodsdescribedaboveenhanc einsulindeliveryprocess,stilltheir release mechanism is not proportional to the required physiological blood sugar concentration. To achieve the goal of glucose responsive release of insulin, the researchers have focused on novel nonmaterial's. Among these approaches, competitive binding is the most acceptable one.
- Synthesizingnanoparticleswithsuchglucoser esponsivematerialswouldcarrythe advantagesofnanosizedparticlesaswellasglucoseresp onsedependentreleaseof insulin in the body.
- Zion et al. (2003), synthesized a novel reverse micro emulsion (RM) mediated glucose-responsivedextran,poly(α-1,6glucose),nanoparticleswhichwasphysically cross linked with the tetrafunctional glucose-binding protein, Concanavalin A (Con A), for controlled insulin delivery.
- Uponcontactwithfreeglucose,ConAreleases polymericglucoseandfurtherbinds to free glucose, leading to disintegration of hydrogel. As discussed above, insulin is marginally stable and can easily break up during their formulation as drugs.
- Therefore, in order to achieve stable insulin formulation, aqueous insulin encapsulating nanoparticle delivery system was developed. This method utilized oppositelychargeddextransulfate(DS)andpolyethylen imine(PEI)alongwithzinc as a stabilizer and was tested for insulin stability.
- However,thissystemshowednosign ificantconformationalchangesin encapsulated insulin as compared to free insulin.
- Recently,fororaldeliveryofpeptide stheuseofsomenaturaluptakeprocessesof the intestine like vitamin B12 (VB12) transport system has also been highlighted whichutilizesVB12-IF-IFR(intrinsicfactorreceptor)mediatedendocytosisthro ugh intestinal ileocytes for targeting systemic circulation .
- VB12–dextran NPs conjugates, chemically coupling insulin, acting as an oral deliverysystemhasalsobeenattemptedtoprotectinsulin againstgutproteasesand to show a faster release profile..
- Thesenanoparticleconjugateswerefoundtob eviablecarrierforpersonalinsulin delivery to treat diabetes. A multilayered nanoparticle system consisting of mucoadhesivepolymers,sodiumalginateanddextransu lfate,aroundcalciumwas also developed to entrap insulin which enhances the residence time atabsorption site.
- Thissystemwasfurtherstabilizedbychitosanb oundtoploxamer188further coated with albumin A to protect insulin from enzymatic degradation.

Polyalkylcyanoacrylated-insulinnanoparticles

- Initially,PACAwereusedastissueglueinsurg erybecauseoftheirstableand biodegradable character.
- Recently,ithasbeenutilizedinthetransportati onofinsulinthroughintestinal epithelium polymeric insulin carrier for oral administration.
- According to MALDI ionization coupled tandem time-of-flight (TOF) mass spectrometryanalysis,insulinwasnotmodifiedduringc ovalentbondingwithPACA nanoparticles.
- Entrapment of insulin in PACA nanoparticles prepared from micro emulsions with the different microstructure containing isopropyl myristate, caprylocaproyl macro golglycerides,polyglyceryloleateandinsulinsolution wereinvestigatedforinvitro release and bioactivity.
- Moreover, insulin-loaded polybutylcyanoacrylate nanoparticles (IPN) were also tried for the hypoglycemic effect upon oral administration to streptozotocin (STZ) induceddiabetic rats inan oilymedium (soybeanoil containing0.5% (v/v) Tween-20and5%(v/v)VitaminE).ItwasconcludedthatIPNcan serveasaneffective and stable delivery system for oral insulin.

Solidlipidinsulinnanoparticles

- Asanalternativetopolymericnanoparticles,s olidlipidnanoparticles(SLN)were developed for drug

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delivery nanoparticulate system.

- SLNissubmicron,around50–1000nmindiameter,colloidalcarriersmadeupof lipids which are solid at room temperature. SLN can be dispersed in water or surfactant solution.

II. CONCLUSION:

Presently, nanoparticle-based drug deliverysystem is playing an essentialrole inthepharmaceuticalindustry.Anewdrugdeliverysystemofanexistingdrug can provide a new marketability which isthe important in theeconomic point of view. Thenextgenerationnanoparticle-basedinsulinmaybethefuturemedicinefor T1DM. In the near future, this nanocarrier-based insulin delivery could replace the traditional and most predictable subcutaneous insulin injections.
Possibly this next generation nanoparticle mediated insulin may improve efficacyofthismedicineandwillalsohelpthebetterqualityofthelivingof T1DM patients.
From thistopicwecanconclude:

When we use the nanoparticles in breast cancer therapy we can avoid the side effectofpalcitaxellikedrug.becausethesedrugrequired thespecialsolventfor its action so and its give toxic effect.
Ifweusethenanoparticalsinthediabetictherapywecanuseinsulinorallyso we avoid the tissue damage associated the regular insulin therapy.

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