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Polymeric NanoParticles: Production, Applications and Advantage

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Abstract

There is no accepted international definition of a nanoparticle, but one given in the new PAS71 document developed in the UK is: "A particle having one or more dimensions of the order of 1000nm or less". Nanoencapsulation of drugs involves forming drug load particles with diameters ranging from 1 to 1000 nm. Nanoparticles are defined as solid, submicron-sized drug carriers that may or may not be biodegradable. nanoparticle variesinmanufacturing methods and in this paper we focus on polymeric nanoparticle particulary chitosan /Alginate nanoparticle and charactristic and advantage .

Introduction

There is no accepted international definition of a nanoparticle, but one given in the new PAS71 document developed in the UK is: “A particle having one or more dimensions of the order of 1000nm or less”. There is a note associated with this definition: “Novel properties that differentiate nanoparticles from the bulk material typically develop at a critical length scale of under 100nm”.Many of these nanomaterials are made directly as dry powders, and it is a common that these powders will stay in the same state when stored. In fact, they will rapidly aggregate through a solid bridging mechanism in as little as a few seconds. Whether these aggregates are detrimental will depend entirely on the application of the nanomaterial. If the nanoparticles need to be kept separate, then they must be prepared and stored in a liquid medium designed to facilitate sufficient interparticle repulsion forces to prevent aggregation.[1,2]

Nanoencapsulation of drugs involves forming drug load particles with diameters ranging from 1 to 1000 nm. Nanoparticles are defined as solid, submicron-sized drug carriers that may or may not be biodegradable .The term nanoparticle is a collective name for both nanospheres and nanocapsules. Nanospheres have a matrix type of structure. Drugs may be absorbed at the sphere surface or encapsulated within the particle. Nanocapsules are vesicular systems in which the drug is confined to a cavity consisting of an inner liquid core surrounded by a polymeric membrane [1]. In this case the active substances are usually dissolved in the inner core but may also be adsorbed to the capsule surface .

Nanoparticles are receiving considerable attention for the delivery of therapeutic drugs.The literature emphasizes the advantages of nanoparticles over microparticles and liposomes The submicron size of nanoparticles offers a number of distinct advantages over microparticles, including relatively higher intracellular uptake compared with microparticles. In terms of intestinal uptake, apart from their particle size, nanoparticle nature and charge properties seem to influence the uptake by intestinal epithelia. Uptake of nanoparticles prepared from hydrophobic polymers seems to be higher than that of particles with more hydrophilic surfaces. The nanoparticle surface is also a very important consideration in targeting drug delivery, in this article we study about Polymeric nanoparticle, particularly chitosan/Alginate and their advantage and recent research about it.[1,2,3]

Nanoparticles obtained from preformed polymers

With the exception of alkyl cyano acrylates and poly(dialkyl methylidenemalonate), most of the monomers suitable for a micellar polymerization process in an aqueous phase lead to slowly biodegradable or nonbiodegradable polymers. In addition, residual molecules in the polymerization medium (monomer, oligomer, surfactant, etc.) can be more or less toxic, requiring meticulous purification of the colloidal material. To avoid these limitations, methods using preformed polymers instead of monomers have been proposed.[1,2]

Synthetic preformed polymers

1.Emulsification /solvent evaporation

Emulsification-solvent evaporation involves two steps. The first step requires emulsification of the polymer solution into an aqueous phase (see Figure 1). During the second step polymer solvent is evaporated, inducing polymer precipitation as Nanospheres. A polymer organic solution containing the dissolved drug is dispersed into nanodroplets, using a dispersing agent and high-energy homogenization, in a nonsolvent or suspension medium such as chloroform (ICH,class 2) or ethyl acetate (ICH, class 3). The polymer precipitates in the form of Nanospheres in which the drug is finely dispersed in the polymer matrix network. The solvent is subsequently evaporated by increasing the temperature under pressure or by continuous stirring The size can be controlled by adjusting the stir rate, type and amount of dispersing agent ,viscosity of organic and aqueous phases, and temperature .Even though different types of emulsions may be used, oil/water emulsions are of interest because they use water as the nonsolvent; this simplifies and thus improves process economics, because it eliminates the need for recycling, facilitating the washing step and minimizing agglomeration . However, this method can only be applied to liposoluble drugs, and limitations are imposed by the scale-up of the high energy requirements in homogenization .Frequently used polymers are PLA ,PLGA , ethylcellulose (EC) , cellulose acetate phthalate , poly(E-caprolactone) (PCL) , and poly(h-hydroxybutyrate) (PHB). Drugs or model drugs encapsulated were albumin, texanus toxoid, testosterone, loperamide, prazinquantel, cyclosporin A, nucleic acid, and indomethacin.[1]

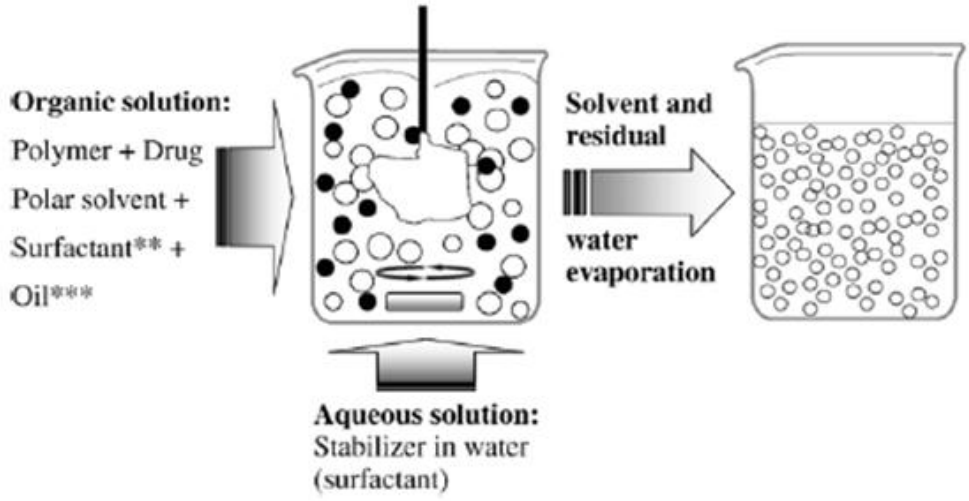


Fig 2. Schematic representation of the solvent displacement technique. **Surfactant is optional. ***In interfacial deposition method, a fifth compound was introduced only on preparation of nanocapsules.

Solvent displacement and interfacial deposition

Solvent displacement and interfacial deposition are similar methods based on spontaneous emulsification of the organic internal phase containing the dissolved polymer into the aqueous external phase (see Figure 2). However, solvent displacement forms Nanospheres or nanocapsules, whereas interfacial deposition forms only nanocapsules. Solvent displacement 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 surfactant. 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. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the instantaneous formation of a colloidal suspension. To facilitate the formation of colloidal polymer particles during the first step of the procedure, phase separation is performed with a totally miscible solvent that is also a nonsolvent of the polymer. The solvent displacement technique allows the preparation of nanocapsules when a small volume of nontoxic oil is incorporated in the organic phase considering the oil-based central cavities of the nanocapsules, high loading efficiencies are generally reported for lipophilic drugs when nanocapsules are prepared. The usefulness of this simple technique is limited to water-miscible solvents, in which the diffusion rate is enough to produce spontaneous emulsification. Then, even though some water-miscible solvents produce a certain instability when mixed in water, spontaneous emulsification is not observed if the coalescence rate of the formed droplets is sufficiently high . Although, acetone/dichloromethane (ICH, class 2) are used to dissolve and increase the entrapment of drugs, the dichloromethane increases the mean particle size and is considered toxic. This method is basically applicable to lipophilic drugs because of the miscibility of the solvent with the aqueous phase, and it is not an efficient means to encapsulate water-soluble drugs. In fact, it seems difficult to choose a drug/polymer/solvent/nonsolvent system in which particles would be formed and the drug efficiently entrapped, because the solvent and the nonsolvent of the polymer must be mutually Miscible. The progressive addition of the polymer solution to the nonsolvent generally leads to the

formation of nanospheres close to 200 nm in size. Nanoparticles seem to be formed by a mechanism comparable to the diffusion and standingQ process found in spontaneous emulsification. This phenomenon has been explained by local variations of the interfacial tension between the two immiscible liquids due to the mutual diffusion of the third liquid. This method has been applied to various polymeric materials such as PLA, PLGA, PCL, and poly(methyl vinyl ether-comaleic anhydride) (PVM/MA) . This technique was well adapted for the incorporation of cyclosporine A, because entrapment efficiencies as high as 98% were obtained. Highly loaded Nanoparticulate systems based on amphiphilic h-cyclodextrins to facilitate the parenteral administration of the poorly soluble antifungal drugs bifonazole and clotrimazole were prepared according to the solvent displacement method Interfacial deposition is a process used for the production of nanocapsules; however, this is not a polymerization technique but an emulsification/solidification technique. In interfacial deposition, a fifth compound is introduced, of oil nature, miscible with the solvent of the polymer but immiscible with the mixture. The polymer deposits on the interface between the finely dispersed oil droplets and the aqueous phase, forming nanocapsules. An aqueous solution is used as the dispersing medium. The main difference is that polymers such as PLA are dissolved together with the drug in a solvent mixture (eg, benzyl benzoate, acetone, and phospholipids). This mixture is injected slowly into a stirred aqueous medium, resulting in the deposition of the polymer in the form of nanoparticles of about 230 nm in size. Polymer deposition occurs at the interface between water and benzoyl nanodroplets, forming nanocapsules with a shell-like wall.[1]

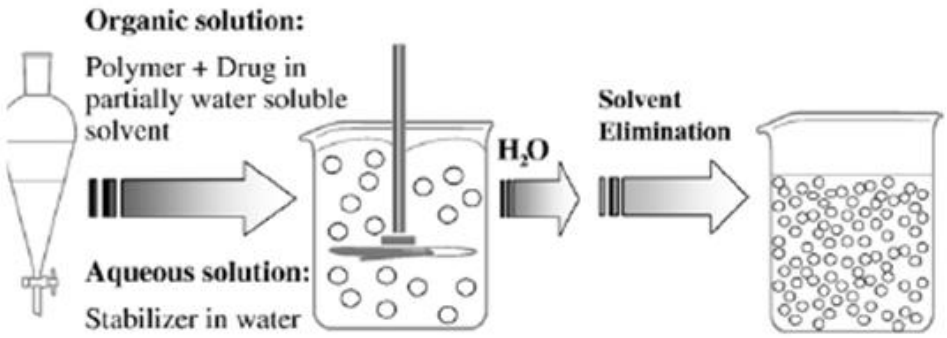


Fig 3. Schematic illustration of the ESD technique.

Emulsification/solvent diffusion

Emulsification/solvent diffusion (ESD) was proposed in the literature based on the use of organic solvents, and then it was adapted to the following salting-out procedure. The encapsulating polymer is dissolved in a partially water soluble solvent such as propylene carbonate (ICH not given) and saturated with water to ensure the initial thermodynamic equilibrium of both liquids. In fact, to produce the precipitation of the polymer and the consequent formation of nanoparticles, 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. Finally, the solvent is eliminated by evaporation or filtration, according to its boiling point. The procedure is illustrated in Figure 3.This technique presents several advantages, such as high encapsulation efficiencies (generally N70%), no need for homogenization, high batch-to-batch reproducibility, ease of scale-up, simplicity, and narrow size distribution. Disadvantages are the high volumes of water to be eliminated from the suspension and the leakage of water-soluble drug into the saturated-aqueous external phase during emulsification, reducing encapsulation efficiency. As with some of the other techniques, this one is efficient in encapsulating lipophilic drugs.

Several drug-loaded nanoparticles were produced by the ESD technique, including mesotetra (hydroxyl phenyl) porphyrin-loaded PLGA (p-THPP) nanoparticles , doxorubicin-loaded PLGA nanoparticles ,plasmid DNA-loaded PLA nanoparticles , coumarin-loaded PLA nanoparticles , indocyanine , cyclosporine (Cy-A)-loaded gelatin and cyclosporin (Cy-A)-loaded sodium glycolate nanoparticles .[1,4]

Salting out with synthetic polymers

Salting-out is based on the separation of a water miscible solvent from aqueous solution via a salting-out effect. The salting-out procedure can be considered as amodification of the emulsification/solvent diffusion. Polymer and drug are initially dissolved in a solvent such as acetone, which is subsequently emulsified into an aqueous gel containing the salting-out agent (electrolytes, such as magnesium chloride, calcium chloride, and magnesium acetate, or non- electrolytes such as sucrose)

and a colloidal stabilizer such as poly vinyl pyrrolidone or hydroxyl ethyl cellulose. This oil/water emulsion is diluted with a sufficient volume of water or aqueous solution to enhance the diffusion of acetone into the aqueous phase, thus inducing the formation of nanospheres. The selection of the salting out agent is important, because it can play an important role in the encapsulation efficiency of the drug. Both the solvent and the salting-out agent are then eliminated by cross-flow filtration. This technique used in the preparation of PLA, poly-(methacrylic) acid, and EC nanospheres leads to high efficiency and is easily scaled up .The main advantage of salting out is that it minimizes stress to protein encapsulants. Salting out does not require an increase of temperature and, therefore, may be useful when heat sensitive substances have to be processed. The greatest disadvantages are exclusive application to lipophilic drugs and the extensive nanoparticle washing steps. The preparative steps of this procedure are described in Figure 4.[1]

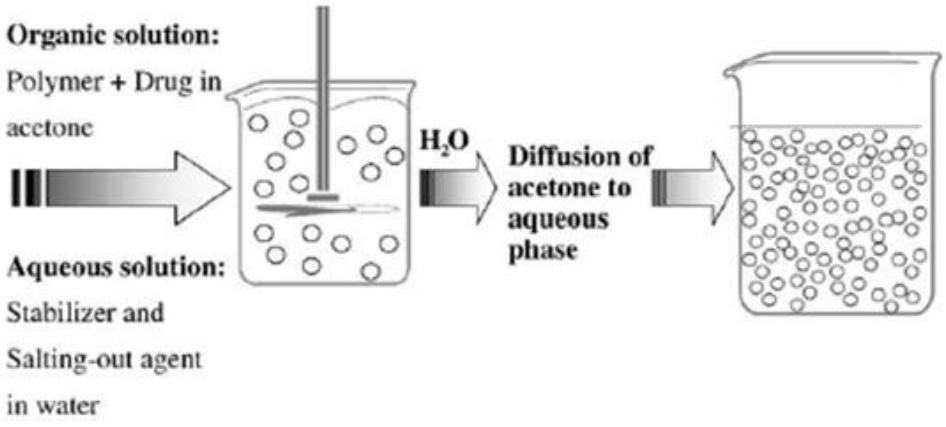


Fig 4. Schematic of the salting-out technique.

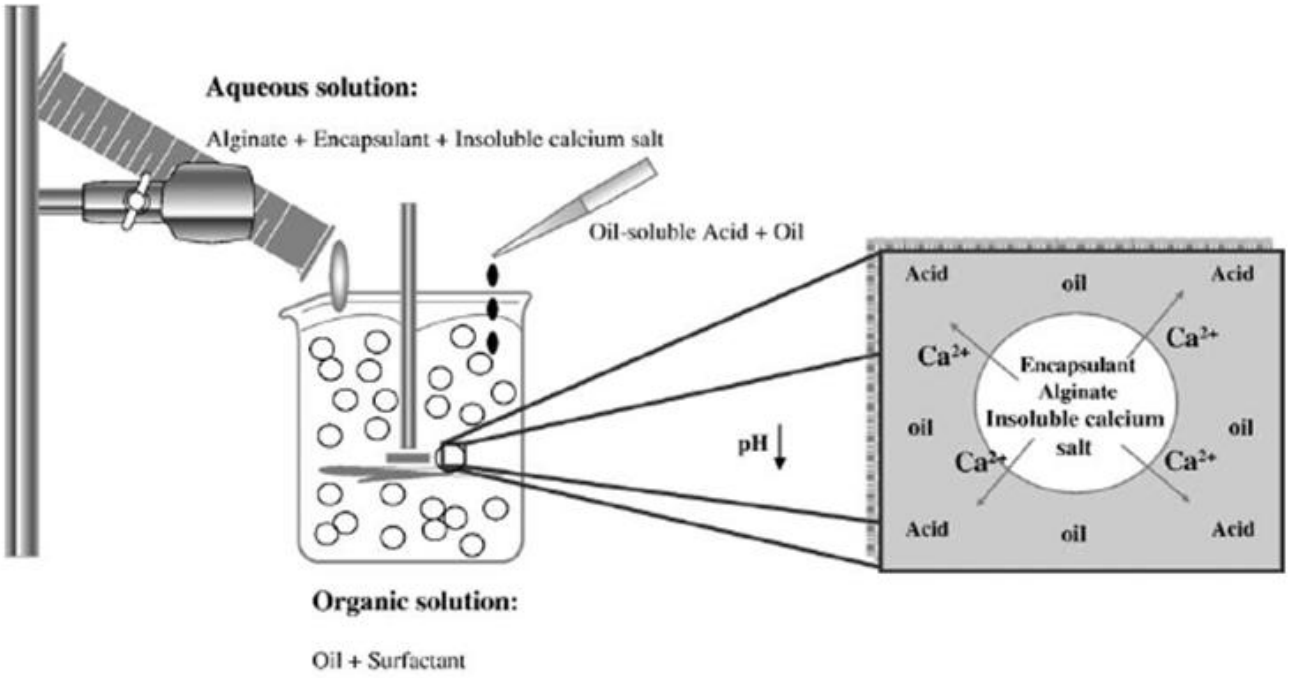


Fig 5. Schematic representation of the emulsification–internal gelation technique using alginate.

Chitosan

Chitosan is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine and can be derived by partial deacetylation of chitin from crustacean shells. (Figure 1) .It is also naturally present in some microorganism and fungi such as yeast .The term chitosan is used to describe a series of chitosan polymers with different molecular weights (50kDa-2000kDa), Viscosity (1% chitosan in 1% acetic acid <2000mpa) and degree of deacetylation (40%-98%). Chitosan is a natural nontoxic biopolymer derived by deacetylation of chitin, a major component of the shells of crustacean such as crab, shrimp, and craw fish. It has received considerable attention for its commercial applications in biomedical, food, and chemical industries .[8,9]

Alginate

Among polymers, alginate has several unique properties that have allowed using it as a matrix for the entrapment and/or delivery of a variety of biological agents . Alginate is a co-polymer extracted from some types of brown algae and it is made up of two uronic acids: D-mannuronic acid and L-guluronic acid. Polyvalent cations are responsible for interchain and intrachain reticulations because they are tied to the polymer when two guluronic acid residuals are close. The reticulation process consists of the simple substitution of sodium ions with calcium

ions .The relatively mild gelation process has enabled not only proteins, but also cells and DNA to be incorporated into alginate matrices with retention of full biological activity.[5,7]

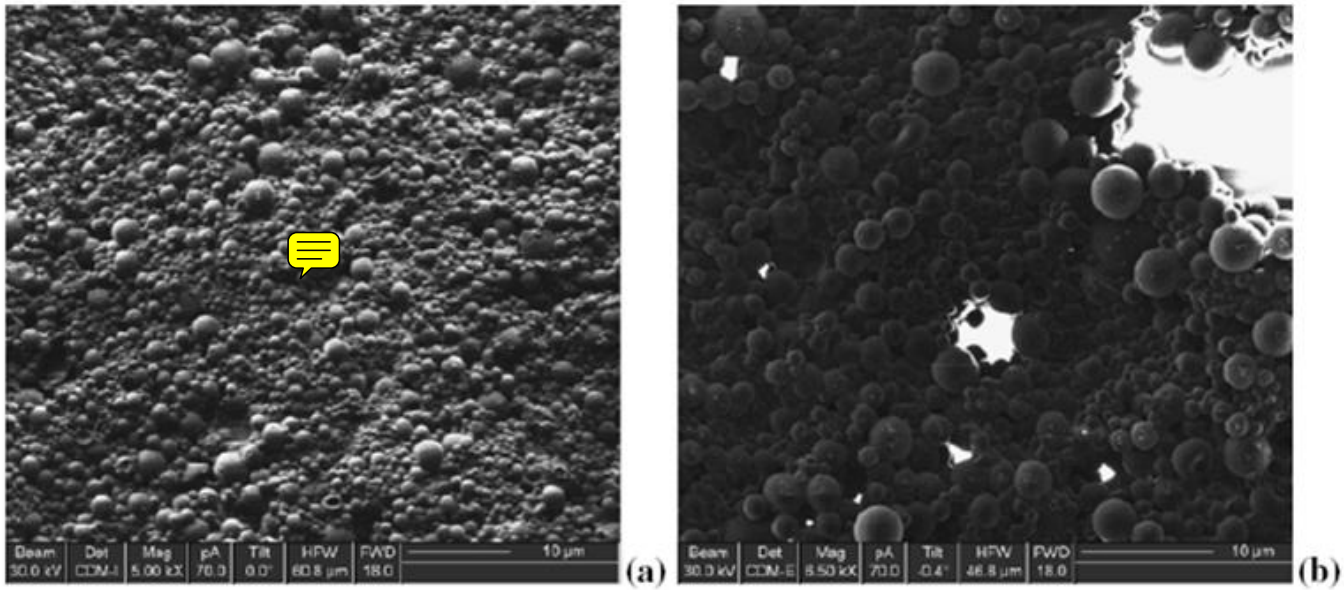
Alginate nanoparticles

Sodium alginate is a water-soluble polymer that gels in the presence of multivalent cations such as calcium .Alginate particles are usually produced by drop wise extrusion of sodium alginate solution into calcium chloride solution. Alginate particle size depends on the size of the initial extruded droplet. The smallest particles produced had a minimum size of 1 to 5 nm, obtained by air atomization. The preparation of alginate nanoparticles was first achieved in a diluted aqueous sodium alginate solution in which gelation was induced by the addition of a low concentration of calcium. This leads to the formation of invisible clusters of calcium alginate gels. In an additional advance, alginate particles have been produced by using a modified emulsification/internal gelation method as illustrated in Figure 5. The preparation of alginate nanoparticles via this method does not require specialized equipment and can be performed at ambient temperature. The main difficulty of this method is the nanoparticle washing step to eliminate the residual oil droplets, but new strategies have been devised.[5]

Chitosan nanoparticles

Chitosan nanoparticles have been developed to encapsulated proteins such as bovine serum albumin, tetanus and diphtheria toxoid, vaccines, anticancer agents, insulin , and nucleic acids . Chitosan considerably enhanced the absorption of peptides such as insulin and calciton in across the nasal epithelium ,The methods proposed to prepare chitosan nanoparticles are based on the spontaneous formation of complexes between chitosan and polyanions or the gelation of a chitosan solution dispersed in an oil emulsion .Various methods for producing chitosan nanoparticles are described in the literature Chitosan nanoparticles obtained by formation of a spontaneous complex between chitosan and polyanions such as tripolyphosphate have small diameters (200–500 nm)and show a quasi spherical shape under transmission electron microscopy. Chitosan nanoparticles produced by a promoting gelation in an emulsification-based method as illustrated in Figure 6, results in a diameter of 400 nm. Compared with the previously described method,

this technique has a major disadvantage of involving organic solvents during the isolation of the particles; these are difficult to remove and may cause toxicity.[8,9]



(a) FIB imaging of alginate particles; (b) FIB imaging of chitosan particles;

Recent studies in Alginate/chitosan Nano Particle

Tao Li et al. (2007) studies Quaternized chitosan/alginate nanoparticles for protein delivery and found that the diameter of the nanoparticles with a positive surface charge was about 200 nm. The load of bovine serum albumin (BSA) was affected by the concentration and the molecular parameters, i.e. degree of substitution (DS) and weight-average molecular weight.(11) B. Sarmento et al. (2007) attained that Alginate/Chitosan nanoparticles are effective for oral insulin delivery and found nanoparticles were negatively charged and had a mean size of 750 nm, suitable for uptake within the gastrointestinal tract due to their nanosize range and mucoadhesive properties. The insulin association efficiency was over 70% and insulin was released in a pH-dependent manner under simulated gastrointestinal conditions. Olga Borges et al. (2008), study on Alginate coated chitosan nanoparticles are an effective subcutaneous adjuvant for hepatitis B surface antigen and found The enhancement of the immune response observed with the antigen-loaded nanoparticles demonstrated that chitosan is a promising platform for parenteral HBs Ag delivery and, when co-administered with the CpGODN, resulted in a mixed Th1/Th2 type immune response.(3) Gazori et al (2008) Chitosan-

Alginate nanoparticles for antisense delivery and found that these nanoparticles are good candidate for antisense delivery. EGFR antisense used in the treatment of breast cancer, was successfully loaded in the CS-ALG nanoparticles and the formulation was optimized by statistical screening design considering the alginate/Chitosan ratio, calcium chloride/ sodium alginate ratio, pH and N/P ratio. The optimized formulation according to size and loading efficacy was chosen, this optimized nanoparticles have positive zeta potential which can be a stable nanoparticles and help the antisense molecules to pass cross cell membrane. Also the suitable size of the nano particles (189nm) can ease passing through cells. [60]

Advantage this system in comparison with other polymer nanoparticles:

Polymers such as alginate and chitosan have been described as biocompatible, biodegradable and mucoadhesive, enabling numerous pharmaceutical and biomedical applications (including the design of controlled release devices.[10]

Alginate/chitosan Nano Particle Preparation Method

Solutions of chitosan were prepared in acetic acid, adjusted their pH at 5.2 and alginate solutions in ddH2O at pH 5.4. A certain amount of the drug solution was added to alginate working solution mixed for a certain time at room temperature. Then chitosan solution was added to the mixture stirred for further time. The solution was centrifuged to remove the large aggregates. The supernatant was used for further microscopic analysis [9].

Nanoparticle Characterization

Particle size was determined by photon correlation spectroscopy at 25-C with a detection angle of 90- and zeta potential by laser doppler anemometry by using a Malvern Zetasizer and Particle Analyzer 5000 (Malvern Instruments).Measurements were made on aqueous dilute nanoparticle suspension (n Q 6).The association efficiency (AE) was determined by calculating the difference between the total amount used to prepare the particles and the amount of insulin present in the

supernatant after nanoparticle removal by centrifugation. The difference between the total insulin initially used to prepare the particles and the amount of residual unassociated insulin after particle separation as a percent of total nanoparticle dry mass is referred to as loading capacity (LC). Insulin was measured by high-performance liquid chromatography (HPLC).[9]

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