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Chitosan: A promising agent for formulation of nano particle

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ABSTRACT:

Nanoparticles have emerged as a next-generation drug delivery system with potential applications in pharmaceutical field, cosmetics, research, clinical medication and alternative allied sciences. Recently, increasing attention has been targeted on these SLN as mixture drug carriers for incorporating deliquescent or lipotropic medication. Proteins and antigens supposed for therapeutic functions could also be incorporated or adsorbate onto SLN, and more administered by epithelial duct routes or be various routes like oral, nasal and respiratory organ. The biodegradable and bioacceptable nature of SLNs makes them less cytotoxic as compared to polymeric nanoparticles. Chitosan is one in all the biodegradable and bioacceptable polymer. Chitosan could be a natural polysaccharide ready by the N-DE acylation of chitin. Chitosan is a remarkable polymer that has been used extensively within the medical field. It's either partly or absolutely deacetylated polysaccharide. Chitosan could be an absolutely biodegradable and biocompatible natural chemical compound, and might be used as an adhesive and as an antibacterial and antimycotic agent. Chitosan is soluble in acidic conditions - in solution the free amino teams on its polymeric chains will protonate, giving it a positive charge. Chitosan nanoparticles is fashioned by incorporating a poly anion like tripolyphosphate (TPP) into a chitosan solution beneath constant stirring.

Keywords: Chitosan, Nanoparticles, Biodegradable, SLNs, Polymeric nanoparticles, chitin

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INTRODUCTION: [1, 2, 3, 4, 5]

Today, nanoparticles is found in a very big selection of applications within the pharmaceutical industry. Owing to new advances in nanotechnology, it's currently doable to provide drug nanoparticles that may be used in a very sort of innovative ways in which. Injectable nanoparticulate carriers have necessary potential applications even supposing typical carriers will usually be accustomed cut back the number of administration doses and improve delivery potency whereas decreasing the adverse effects of drug toxicity. Nanoparticles are ready from biocompatible and biodegradable polymers in size between 10-1000 nm wherever the drug is dissolved, entrapped, encapsulated or hooked up to a nanoparticle matrix. Relying upon the strategy of preparation nanoparticles, nanospheres or nanocapsules will be obtained.

Nanoparticle are promising vehicles for drug delivery by straightforward manipulation to organize carriers with the target of delivering the medication to specific target, such a plus improves the drug safety. Polymer-based nanoparticles effectively carry medication, proteins, and DNA to target cells and organs. Their nanometer-size promotes effective permeation through cell membranes and stability within the blood stream. Polymers are terribly convenient materials for the manufacture of nuolecular styles that may be integrated into distinctive nanoparticle

constructs with several potential medical applications. Many strategies have been developed throughout the last 20 years for preparation of Nanoparticles, these techniques are classified in step with whether or not the particle condition involves a polymerization reaction or nanoparticles form directly from a macromolecule or preformed polymer or ionic gelation methodology.

Advantages of polymeric nanoparticles [1,2,6,7]

Increases the stability of any volatile pharmaceutical agents, simply and cheaply fictitious in giant quantities by a large number of strategies. They provide a significant improvement over ancient oral and intravenous strategies of administration in terms of potency and effectiveness. Delivers a higher concentration of pharmaceutical agent to a desired location. The selection of polymer and therefore the ability to change drug release from polymeric nanoparticles have created them ideal candidates for cancer therapy, delivery of vaccines, contraceptives and delivery of targeted antibiotics. Polymeric nanoparticles are often simply incorporated into different activities associated with drug delivery, like tissue engineering.

Formulation components: [8, 9]
Chitosan:

Viscosity	20-300 cP, 1 wt. % in 1% acetic acid (25 °C, Brookfield) (lit.)
Solubility	Dilute aqueous acid: soluble
Physical form	75-85% deacetylated
Application	Flocculent, protein precipitation, encapsulating agent and aqueous thickener.
Molecular weight	40,000 -150,000

Polymers used in preparation of nanoparticles: [10, 11, 12, 13]

The polymers should be compatible with the body in the terms of adaptability (non-toxicity) and (non-antigenicity) and should be biodegradable and biocompatible.

Polymers divided in two sub types.

Natural Polymers	Synthetic polymers
Chitosan	Poly(methacrylic acid)
Gelatin	Poly acrylamide
Sodium alginate	Polylactides(PLA)
Albumin	Polyglycolides(PGA)

Poly(lactide co-glycolides) (PLGA)
Poly malic acid
Polyorthoesters
Poly(vinyl alcohol)
Polycaprolactones
Poly(methyl methacrylate)
Polyanhydrides
Poly(N-vinyl pyrrolidone)
Poly(acrylic acid)
Poly(ethylene glycol)
Poly glutamic acid

Mechanisms of Chitosan Nanoparticles drug release: [14, 15]

With the swelling of the Chitosan nanoparticles by hydration followed by release through diffusion. With AN enzymatic reaction leading to rupture or cleavage or degradation of the polymer at site of delivery, there by releasing the drug from the entrapped inner core. Dissociation of the drug from the polymer and its de-adsorption/release from the swelled nanoparticles.

Chitosan Nanoparticle preparation Techniques: [16]

The properties of Chitosan Nanoparticle got to be optimized depending on the actual application. So as to achieve the properties of interest, the mode of preparation plays a significant role. Thus, it's extremely advantageous to own preparation techniques at hand to get Chitosan Nanoparticle with the required properties for a specific application. Totally different techniques like polymerization, preformed polymers or ionic gelation are used.

Ionic Gelation method: [17]

The Chitosan nano particles were prepared following the procedure described by Calvo et al. (1997). A 7.5 mg/mL chitosan solution was prepared by dissolving LMW or VLMW chitosan in a 1% (v/v) acetic acid solution and leaving it under stirring for 24hr. The pH was adjusted to 5.5 with a 0.5 M sodium hydroxide solution and diluted in deionized water to the final desired concentrations. TPP was dissolved in deionized water to a final concentration of 2.5 mg/ml. TPP and chitosan solutions were filtered through a 0.45 μm membrane. Then TPP solution was added to the chitosan solution drop wise (1 mL/min) at different TPP-chitosan ratios under vigorous magnetic stirring at room temperature. The resulting suspension

was then left 30 min. After centrifuge the solution get separate nano particle at bottom site.

Reverse Micellar Method: [18, 19]

1>Ultrafine polymer nanoparticles with a slim size vary are often ready with this technique. The surface-active agent is dissolved in associate organic solvent to arrange reverse micelles. A solution of chitosan is side with constant agitation to avoid any murkiness. The liquid section is regulated in such the simplest way on keep the whole mixture in Associate in an optically clear micro emulsion section. Additional water ought to be side if nanoparticles of a bigger size get. **Brunel et al. (2008) used a reverse micellar method to prepare chitosan nanoparticles. 2>**The lower the molar mass of chitosan, the higher the management over particle size and size distribution, most likely as a results of either a discount within the body of the interior binary compound section or a rise within the freeing of the compound chains throughout the method. **Mansouri et al. (2010) prepared Bovine Serum Albumin (BSA)-loaded chitosan nanoparticles using the reverse micellar method.** Particles were obtained within the size vary of 143 to 428 nm. The FTIR spectrum indicated that BSA was with success encapsulated into the chitosan nanoparticles. The chitosan concentration and BSA loading compete a very important role within the unleash of BSA. Increasing the chitosan answer concentration shrunken the discharge of BSA, each with a BSA loading of 100% and two hundredth, whereas decreasing the BSA loading accelerated the discharge of BSA at either a chitosan concentration of 0.1% and 0.2%. Magnetic chitosan nanoparticles were ready by a reversed section suspension methodology exploitation Span-80 as associate degree wetter and glutaraldehyde as cross-linking chemical agent **(Fang et al., 2009).** Laccase was immobilized on the chitosan nanoparticles. The immobilized laccase exhibited a considerable chemical action capability and had smart storage stability and operation stability. The metric linear unit of immobilized and free laccase were 140.6 and 31.1 µM in phosphate buffer (0.1 M, pH 3.0), respectively. The immobilized laccase could be a smart candidate for the analysis and development of biosensors supported laccase. **Emulsification and cross-linking:** [20, 21, 22]

As mentioned on top of, this method was 1st to be used to type chitosan nanoparticles and involves the preparation of a W/O emulsion (this first report represented the emulsification of chitosan solution in methylbenzene, exploitation Span 80® as emulsifier), with resultant addition of a cross-linking agent that has the Operate of hardening the fashioned droplets. The reactive amino teams of chitosan undergo a covalent cross-linking with the aldehyde groups of glutaraldehyde that is further when the emulsion formation and, consequently, when nanoparticle production **(Ohya et al. 1994).** Those authors pioneered the assembly of chitosan nanoparticles that were accustomed deliver 5-fluorouracil. Alternative authors used the method for an equivalent purpose of drug delivery, however changed the oil part composition to liquid paraffin and petroleum ether **(Songjiang and Lixiang 2009).** The ultimate particle size was incontestable to be extremely keen about stirring speed, also as on the extent of cross-linking **(Agnihotri et al. 2004, Prabaharan and Mano 2005).** Many drawbacks are more and more known for this technique, as well as the necessity of tedious procedures and therefore the application of harsh cross-linking agents **(Agnihotri et al. 2004).** In fact, cross-linkers like glutaraldehyde were found to cause obvious toxicity and to compromise drug integrity, causative to a progressive shift of interest towards less aggressive procedures **(Janes et al. 2001).** Consequently, the applying of this methodology to get chitosan nanoparticles was restricted to a number of works.

Emulsion droplet coalescence: [17, 19, 22]

This method is a derivation of the emulsification and cross-linking method described above and was first reported for micro particles preparation **(Tokumitsu et al. 1999a).** The same authors later adapted the method to prepare chitosan nanoparticles loaded with gadolinium, as a strategy for neutron-capture therapy of cancer **(Tokumitsu et al. 1999b).** Chitosan is dissolved in the aqueous solution of gadolinium and a small aliquot (1 mL) of this is added to 10 mL of liquid paraffin containing Sorbian sesquiolate (Span® 83). The mixture is stirred with a high-speed homogenizer, thus forming and W/O emulsion. In parallel, another W/O emulsion is prepared by adding 1.5 mL NaOH to 10 mL of a similar outer phase. Both emulsions are then mixed using a high-speed homogenizer, leading to droplet coalescence. This results in the solidification of chitosan particles by action of NaOH, which acts as precipitating agent. Afterwards, a further set of washing and centrifugation steps is applied using toluene, ethanol and water **(Tokumitsu et al. 1999b).** A similar procedure was used in a different study

to encapsulate 5-fluorouracil **(Anto et al. 2001)**. This method exploits the fact that, when two emulsions with equal outer phase are mixed together, droplets of each collide randomly and coalesce, resulting in final droplets with uniform content. The nanoparticles are formed within the emulsion-droplets **(Ichikawa et al. 2006)**. Decreasing chitosan DE acetylation degree was shown to increase particle size and to reduce nanoparticle capacity for drug association, as a consequence of the diminished capacity of ion-pair formation and de-swelling **(Tokumitsu et al. 1999b)**. It was also found that varying chitosan concentration between 0.5 and 2.5% did not affect 5-fluorouracil encapsulation efficiency (around 70%) or release profile, which extended over 13 hours **(Anto et al. 2011)**. To our knowledge, no other works report the application of this method to produce chitosan nanoparticles.

Emulsion solvent diffusion: [23, 24, 25]

The emulsion solvent diffusion methodology of preparing chitosan nanoparticles is an adaptation of the first procedure developed to provide PLGA-based nanoparticles **(Niwa et al. 1993)**, setting its basis on the partial miscibility of an organic solvent with water. the particular methodology for preparation of chitosan nanoparticles involves the addition of an organic part (e.g. dichloromethane and acetone) containing the hydrophobic drug, to an aqueous solution containing chitosan and a stabilizer (e.g. Poloxamer and lecithin), beneath stirring **(El-Shabo Uri 2002)**. This results in the formation of an O/W emulsion that is then subjected to homogenization blending. Dichloromethane is afterward removed beneath reduced pressure at room temperature. At this stage, dissolver diffuses to the binary compound part, decreasing chitosan solubility and, thus, nanoparticles are fashioned upon polymer precipitation. A further quantity of water is typically added so as to allow the entire diffusion of acetone. Finally, nanoparticles are isolated by centrifugation. This methodology incontestable to be appropriate for encapsulating hydrophobic medicine like cyclosporine, with high encapsulation efficiencies. In spite of the restricted range of studies accessible on the method, parameters like chitosan relative molecular mass, homogenization rate and time interval (period of evaporation and diffusion), are expected to affect the ultimate properties of the vehicles. The presence of acetone was additionally reportable as essential **(El-Shabo Uri 2002)**, since its fast diffusion disturbs the

organic/aqueous part interface, that ad libitum produces a bigger area and, thus, results in the formation of abundant smaller droplets. Particles made while not acetone conferred sizes outside the submicron range (above 1.2 µm). Notwithstanding the power of this methodology to provide effective vehicles, it's vital to focus on the necessity for harsh preparation conditions, like organic solvents and high shear forces, that are absent in many alternative methods that may be delineated in subsequent sections.

De solvation: [5, 6]

The method of desolation is additionally frequently noted as easy coacervation or part Separation and involves a macromolecular aggregation led to by partial desolation of absolutely solvated molecules **(Kissel et al. 2006)**. The utilization of desolating agents to provide chitosan particles was reported for the first time for the preparation of micron-sized carriers **(Berthold et al. 1996)** but, nowadays, this procedure section applied to the assembly of chitosan nanoparticles. Substances like sulphate **(Mao et al. 2001, author et al. 2005, Atyabi et al. 2009)** and non-solvents miscible with water, like acetone **(Agnihotri and Aminabhavi 2007)**, are projected as precipitating agents, though the former has been used additional frequently. The preparation of chitosan nanoparticles by this methodology is incredibly easy and mild because it involves the drop wise addition of the solvent competitive agent of greater hydrophilicity (e.g. sodium sulfate) into a previously fashioned chitosan solution. Because the salt enters in contact with the aqueous environment of chitosan solution, a progressive elimination of association water surrounding chitosan happens as a consequence of the upper affinity of water for the salt. Eventually, this method results in the polymer insolubilisation and its subsequent precipitation **(Alonso 1996, Janes et al. 2001, Poncelet 2005)**. This impact is determined as a result of water-salt interactions are additional favorable than those occurring between the water and therefore the chemical compound, causation the partial desolation of chitosan. This, in turn, results in increased interactions between chitosan molecules, forming the Nano carriers **(Kissel et al. 2006).** It's very frequent to incorporate a stabilizer like Polysorbate 80 within the preparation medium, to stabilize the nanoparticle suspension. A resultant method of cross-linking, for instance with glutaraldehyde, has been described, so as to harden the nanoparticles **(Alonso 1996)**. Factors like chitosan mass, chitosan

concentration, quantity of desolating agent and stirring rate have been found to powerfully have an effect on the final characteristics of nanoparticles. Therefore, it's necessary to endure an improvement of those parameters. Additionally, a correlation was known between the quantity of sulphate ions required and chitosan properties, just like the molecular weight and therefore the DE acetylation degree **(Borges et al. 2005)**.

CONCLUSION

Chitosan nano particle drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility and high toxicity. The oral, Parenteral etc., delivery of hydrophobic and hydrophilic drugs can be made possible by polymeric nano particle, which have been shown to substantially improve oral bioavailability and reduce toxicity and thus the dose of the drug can be reduced. With future development of this chitosan nano particle, will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs low, high Toxicity.

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