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A REVIEW ON THE METHODS FOR THE SYNTHESIS OF NANOPARTICLES OF CHITOSAN

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ABSTRACT
Naturally occurring polymers, particularly of the polysaccharide type, have been used pharmaceutically for the delivery of a wide variety of therapeutic agents. Chitosan, the second abundant naturally occurring polysaccharide next to cellulose, is a biocompatible and biodegradable mucoadhesive polymer that has been extensively used in the preparation of micro- as well as nanoparticles.

KEYWORDS: Naturally occurring polymers, mucoadhesive polymer micro- as well as nanoparticles.

INTRODUCTION
Drug delivery is a general term that refers to formulation and administration of a pharmacologically active compound for the purpose of providing an efficient drug plasma concentration, as well as bringing the drug to the specific site of action. Different strategies have been employed to overcome some drug stability issues in the gastrointestinal tract (GIT), control the drug release, enhance the transmucosal absorption, as well as get the drug into its site of action. Microfabrication is a technique that creates materials in the micrometer scale feature and has been reported to significantly improve diagnosis and biomedical applications. Modification of the material shape, surface characteristics, and release kinetics is a consequence of this micronization.[1] Nanotechnology has been utilized as one of these strategies in the development of novel drug delivery systems through entrapment of the drug in nanoparticulate systems.[2] In general, the potential applications of nanotechnology render this field an area of interest to many researchers and scientists. These applications have covered different scientific areas that extend from electronics to cosmetics.[1-5]

Polymers obtained from natural origins have been extensively employed not only in the food industry but also in pharmaceutical technology. Polysaccharide polymers have emerged as being one of these because they are less toxic, biocompatible and biodegradable.[6-7] Incorporation of the therapeutic agent into a polymeric matrix, particularly of a natural origin, might potentiate the protection of the biologically active compound from degradation, control drug release, improve absorption, enhance the therapeutic effect and lead to the consequential decrease in the frequency of administration. Chitosan, alginate and carrageenan are the most commonly used polysaccharide polymers in various pharmaceutical applications.[8-9] Chitosan is a polymer of interest that has been widely used for delivery of different therapeutic agents, particularly those based on chitosan micro- and nanoparticles, owing to its unique properties. Preparation of mucoadhesive formulations, enhancing the dissolution rate especially for poorly water-soluble drugs, utilization in drug targeting and improvement of protein absorption are common therapeutic applications of this naturally occurring polymer.[10-12]

In this review, the importance of chitosan, as a naturally occurring polysaccharide polymer and its derivatives in drug delivery are illustrated. The different methods of preparation and characterization of chitosan micro- and nanoparticles are addressed. The usefulness of these particles in parenteral and nonparenteral drug delivery is demonstrated. Finally, a very specific application of chitosan in the preparation of metal-based nanoparticles is clarified, establishing the advantages of chitosan metal nanoparticles over the metal nanoparticles.

Chitosan as a polymeric drug carrier
Chitosan is a molecule with a carbohydrate backbone structure similar to cellulose, which consists of two types of repeating units, *N*-acetyl-d-glucosamine and d-glucosamine, linked by (1-4)-β-glycosidic linkage.[13-15] It is a biopolyaminosaccharide cationic polymer that is obtained from chitin by alkaline deacetylation and characterized by the presence of a large numbers of amino groups on its chain. Although chitosan is obtained from chitin, the applications of the latter compared to chitosan are limited because it is chemically inert. A

common method for chitosan synthesis is the deacetylation of chitin, usually derived from the shells of shrimp and other sea crustaceans, using excess aqueous sodium hydroxide solution as a reagent. Chitosan is insoluble in water but soluble in dilute acidic solutions of acetic, citric and tartaric but not phosphoric or sulfuric at pH less than 6.5[16] In dilute aqueous acidic solution, the free amino groups of chitosan glucosamine units that have an apparent pK_a of 6.5 undergo protonation and convert into the ionizable soluble R-NH_3^+ form.[16] Usually, dilute aqueous acetic acid solution in concentrations 1%–3% is used to make a soluble chitosan solution. Chitosan is available in low and high molecular weights.

Chitosan micro-/nanoparticles as drug delivery system

Among the novel drug delivery systems investigated, chitosan micro-/nanoparticles have offered great promise in oral, parenteral, topical and nasal applications.[17-19] In these systems, the drug is either confined and surrounded by a polymeric membrane or is uniformly dispersed in the polymer matrix. The size and surface characteristics of the prepared particles play an important role in their transport across the biological cell membranes. These particles could be used to deliver the pharmaceutically active agent in a controlled and, sometimes, site-specific manner. The mucoadhesive nature of chitosan renders the prepared particles the ability to improve both drug absorption and bioavailability because of extended drug contact with the mucosal layer and the high surface-to-volume ratio of nanoparticles that might also enhance this effect. Drug release at a specific site and for an extended period of time could also be achieved by mucoadhesion where chitosan adhere to specific mucosal surfaces in the body such as buccal, nasal and vaginal cavities.[20-23] Chitosan microparticles have shown varied applications in the delivery of a range of compounds owing to particle size reduction by micronization and their mucoadhesive properties. Dastan and Turan[24] developed chitosan–DNA microparticles and reported a sustained-release profile of DNA from the prepared microparticles with a potential transfer of the DNA into Human embryonic kidney, Swiss 3T3 and HeLa cell lines. Another research group prepared chitosan–DNA microparticles that have demonstrated suitable in vitro characteristics for mucosal vaccination in simulated intestinal fluid and simulated gastric fluid.[55] Their role in protein and peptide delivery has been illustrated by Chua et al[56] after developing luteinizing hormone-releasing hormone chitosan-based microparticles as a vaccine delivery vehicle. Successful delivery of hormones by these particles extends their application for induction of immunity against some tumor antigens and microorganisms such as bacteria and viruses.[25] Insulin delivery via the nasal route using chitosan microparticles was demonstrated by Varshosaz et al[26] who showed that the insulin-loaded microspheres exhibited a 67% lowering in the blood glucose level compared to insulin administered by the intravenous route (with absolute insulin bioavailability of 44%). Many research groups have thus described the applicability of chitosan microparticles in drug delivery. Encapsulation of diclofenac sodium, 5-flurouracil, cisplatin, felodipine and hydroquinone[27-31] into these carriers has been reported and the designed microparticles generally exhibited a controlled-release effect. Chitosan magnetic microparticles (CMM) are a special class of chitosan microparticles that have been developed and find wide applications in the delivery of anticancer drugs or radionuclide atoms to a targeted tissue[63] by binding the drug or the radioactive atom to a magnetic compound, which is then injected into the blood and stopped at the targeted tissue by an externally applied magnetic field.[64]

Methods of preparation

Top–down and bottom–up are the two techniques used to develop micro- and nanoparticle drug carriers. In the latter, the particulate system is prepared from a state of molecular dispersion type and is allowed to associate with subsequent formation of solid particles. Bottom–up techniques, therefore, seek to arrange smaller components into assemblies of complex structure, While the former starts with large size materials and breaks these down into smaller particles. Conventional nanoparticle synthesis usually depends on bottom–up techniques.[32]

Different methods have been utilized in the preparation of chitosan micro- and nanoparticles. The particle size, stability of the active constituent and the final product, residual toxicity present in the final product and the kinetic of the drug-release profile are factors that should be considered during selection of the method.[33] During the preparation of chitosan particulate systems, the size of the prepared particles is greatly dependent on chitosan molecular weight, chitosan chemical structure, particularly the degree of deacetylation and on the method of preparation. As a general rule, higher molecular weight chitosan produces larger-size particles.[34] Different methods are available to prepare chitosan micro-/nanoparticles in which the drug is mostly bound to chitosan by hydrogen bonding, electrostatic interaction, or hydrophobic linkage. Generally, loading the therapeutic agent into chitosan micro-/nanoparticles may be achieved either during the preparation process or after the particles have been formed. In the former, the therapeutic agent is incorporated and embedded in the chitosan matrix, whereas in the latter the therapeutic agent is adsorbed on the particle surface. Usually, the aim is to achieve high entrapment efficiency, which could be accomplished by incorporation into the matrix, but the therapeutic agent could be affected by the preparation method, additives, etc. Generally, selection of the method is greatly dependent on the nature of therapeutic agent and the type of device utilized in the delivery.[13] A list of methods used in the preparation of these particles is given in. All these methods involve the bottom–up production process, in which assembly of the

dissolved molecules is achieved to form a definite micro- or nanoparticulate structure.[35-39]

The techniques used in the preparation of chitosan micro-/nanoparticles loaded with thermosensitive or less stable substances such as proteins, peptides, hormones, vaccines, plasmid DNA and antigens may be broadly classified into cross-linking techniques and drying techniques. Cross-linking could be achieved chemically or physically. The stability of these thermosensitive or less stable substances are strongly affected by the organic solvent and the cross-linking agent used, with the consequence of denaturation or chemical modification.[98] So, physical cross-linking and drying techniques, such as spray drying, are preferred and widely used for these substances. Recently, reverse micellar method has been introduced. These aforementioned techniques – cross-linking, drying, and reverse micellar – in addition to sieving and solvent evaporation were used in the preparation of other drugs of different pharmacotherapeutic groups. An insight on these methods is described in the following sections.[40-43]

CONCLUSION

This review shows that extensive research activities have been focused on the applications of chitosan-based micro- and nanoparticles. Successful loading and delivery of different molecules, including low-molecular-weight drugs and macromolecules, such as proteins, peptides, vaccines, hormones and genes by these systems via different routes of administration, find potential therapeutic applications. The development of chitosan derivatives has extended these applications due to the enhancement of bioavailability accomplished by an increase in the stability, solubility, mucoadhesiveness, cellular permeability, absorption, biodistribution and tissue targeting achieved when particulate carriers are based on these derivatives.

REFERENCES

1. Chirra HD, Desai TA. Emerging microtechnologies for the development of oral drug delivery devices. Adv Drug Deliv Rev. 2012; 64(14): 1569–1578.
2. Des Rieux A, Fievez V, Garinot M, Schneider YJ, Preat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. J Control Release. 2006; 116(1): 1–27.
3. Sahoo SK, Parveen S, Panda JJ. The present and future of nanotechnology in human health care. Nanomedicine. 2007; 3(1): 20–31.
4. Park JH, Lee S, Kim JH, Park K, Kim K, Kwon IC. Polymeric nanomedicine for cancer therapy. Prog Polym Sci. 2008; 33(1): 113–137.
5. Sumer B, Gao J. Theranostic nanomedicine for cancer. Nanomedicine. 2008; 3(2): 137–140.
6. Dass CR, Choong P. The use of chitosan formulations in cancer therapy. J Microencapsul. 2008; 25(4): 275–279.
7. Prabaharan M. Review paper: chitosan derivatives as promising materials for controlled drug delivery. J Biomater Appl. 2008; 23(1): 5–36.
8. Augst AD, Kong HJ, Mooney DJ. Alginate hydrogels as biomaterials. Macromol Biosci. 2006; 6(8): 623–633.
9. Gombotz WR, Wee SF. Protein release from alginate matrices. Adv Drug Deliv Rev. 1998; 31(3): 267–285.
10. Piyakulawat P, Praphairaksit N, Chantarasiri N, Muangsin N. Preparation and evaluation of chitosan/carrageenan beads for controlled release of sodium diclofenac. AAPS Pharm Sci Tech. 2007; 8(4): E97.
11. Santo VE, Frias AM, Carida M, et al. Carrageenan-based hydrogels for the controlled delivery of PDGF-BB in bone tissue engineering applications. Biomacromolecules. 2009; 10(6): 1392–1401.
12. Grenha A, Gomes ME, Rodrigues M, et al. Development of new chitosan/carrageenan nanoparticles for drug delivery applications. J Biomed Mater Res A. 2010; 92(4): 1265–1272.
13. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. J Control Release. 2004; 100(1): 5–28.
14. Roberts GAF. Structure of chitin and chitosan. In: Roberts GAF, editor. Chitin Chemistry. Houndmills, Basingstoke: Macmillan; 1992; 1–53.
15. LeHoux JG, Grondin F. Some effects of chitosan on liver function in the rat. Endocrinology. 1993; 132: 1078–1084.
16. Chandy T, Sharma CP. Chitosan – as a biomaterial. Biomater Artif Cells Artif Organs. 1990; 18(1): 1–24.
17. Sugano M, Watanabe S, Kishi A, Izume M, Ohtakara A. Hypocholesterolemic action of chitosans with different viscosity in rats. Lipids. 1988; 23(3): 187–191.
18. Azad AK, Sermsintham N, Chandrkrachang S, Stevens WF. Chitosan membrane as a wound-healing dressing: characterization and clinical application. J Biomed Mater Res B Appl Biomater. 2004; 69(2): 216–222.
19. Felt O, Buri P, Gurny R. Chitosan: a unique polysaccharide for drug delivery. Drug Dev Ind Pharm. 1998; 24(11): 979–993.
20. Rabea EI, Badawy ME, Steurbaut W, et al. Fungicidal effect of chitosan derivatives containing an N-alkyl group on grey mould Botryti77s cinerea and rice leaf blast Pyricularia grisea. Commun Agric Appl Biol Sci. 2005; 70(3): 219–223.
21. Kockisch S, Rees GD, Young SA, Tsibouklis J, Smart JD. Polymeric microspheres for drug delivery to the oral cavity: an in vitro evaluation of mucoadhesive potential. J Pharm Sci. 2003; 92: 1614–1623.

22. Sinha VR, Singla AK, Wadhawan S, et al. Chitosan microspheres as a potential carrier for drugs. Int J Pharm. 2004; 274(1–2): 1–33.
23. Huo M, Zhang Y, Zhou J, et al. Synthesis and characterization of low-toxic amphiphilic chitosan derivatives and their application as micelle carrier for antitumor drug. Int J Pharm. 2010; 394(1–2): 162–173.
24. Dasha M, Chiellinia F, Ottenbriteb RM, Chiellini E. Chitosan – a versatile semi-synthetic polymer in biomedical applications. Prog Polym Sci. 2011; 36: 981–1014.
25. Calderón L, Harris R, Cordoba-Diaz M, et al. Nano and microparticulate chitosan-based systems for antiviral topical delivery. Eur J Pharm Sci. 2013; 48(1–2): 216–222.
26. Aiedeh K, Taha MO. Synthesis of chitosan succinate and chitosan phthalate and their evaluation as suggested matrices in orallyadministered, colon-specific drug delivery systems. Arch Pharm (Weinheim). 1999; 332(3): 103–107.
27. Florea BI, Thanou M, Geldof M, Meaney C, Junginger HE, Borchard G. Modified chitosan oligosaccharides as transfection agents for gene therapy of cystic fibrosis. Proc Int Symp Control Release Bioact Mater. 2000; 27: 846–847.
28. Sieval AB, Thanou M, Kotze AF, Verhoef JE, Brussee J, Junginger HE. Preparation and NMR characterization of highly substituted N-trimethyl chitosanchloride. Carbohydr Polym. 1998; 36: 157–165.
29. Verheul RJ, Amidi M, van der Wal S, van Riet E, Jiskoot W, Hennink WE. Synthesis, characterization and in vitro biological properties of O-methyl free N,N,N-trimethylated chitosan. Biomaterials. 2008; 29: 3642–3649.
30. Hamman JH, Stander M, Kotze AF. Effect of the degree of quaternisation of N-trimethyl chitosan chloride on absorption enhancement: in vivo evaluation in rat nasal epithelia. Int J Pharm. 2002; 232: 235–242.
31. Thanou M, Verhoef JC, Marbach P, Junginger HE. Intestinal absorption of octreotide: N-trimethyl chitosan chloride (TMC) ameliorates the permeability and absorption properties of the somatostatin analogue in vitro and in vivo. J Pharm Sci. 2000; 89: 951–957.
32. Thanou M, Nihot MT, Jansen M, Verhoef JC, Junginger HE. Mono-N-carboxymethyl chitosan (MCC), a polyampholytic chitosan derivative, enhances the intestinal absorption of low molecular weight heparin across intestinal epithelia in vitro and in vivo. J Pharm Sci. 2001; 90: 38–46.
33. Xu Y, Du Y, Huang R, Gao L. Preparation and modification of N-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride nanoparticle as a protein carrier. Biomaterials. 2003; 24: 5015–5022.
34. Bernkop-Schnurch A, Hornof M, Zoidl T. Thiolated polymers–thiomers: synthesis and in vitro evaluation of chitosan-2-iminothiolane conjugates. Int J Pharm. 2003; 260: 229–237.
35. Hornof MD, Kast CE, Bernkop-Schnurch A. In vitro evaluation of the viscoelastic properties of chitosan-thioglycolic acid conjugates. Eur J Pharm Biopharm. 2003; 55: 185–190.
36. Roldo M, Hornof M, Caliceti P, Bernkop-Schnurch A. Mucoadhesive thiolated chitosans as platforms for oral controlled drug delivery: synthesis and in vitro evaluation. Eur J Pharm Biopharm. 2004; 57: 115–121.
37. Yin L, Ding J, He C, Cui L, Tang C, Yin C. Drug permeability and mucoadhesion properties of thiolated trimethyl chitosan nanoparticles in oral insulin delivery. Biomaterials. 2009; 30(29): 5691–5700.
38. Ubaidulla U, Khar RK, Ahmad FJ, Sultana Y, Panda AK. Development and characterization of chitosan succinate microspheres for the improved oral bioavailability of insulin. J Pharm Sci. 2007; 96(11): 3010–3023.
39. Ubaidulla U, Sultana Y, Ahmed FJ, Khar RK, Panda AK. Chitosan phthalate microspheres for oral delivery of insulin: preparation, characterization and in vitro evaluation. Drug Deliv. 2007; 14(1): 19–23.
40. Rekha MR, Sharma CP. Synthesis and evaluation of lauryl succinyl chitosan particles towards oral insulin delivery and absorption. J Control Release. 2009; 135(2): 144–151.
41. Tomita M, Hayashi M, Horie T, Ishizawa T, Awazu S. Enhancement of colonic drug absorption by the transcellular permeation route. Pharm Res. 1988; 5(12): 786–789.
42. Le Tien C, Lacroix M, Ispas-Szabo P, Mateescu MA. N-acylated chitosan: hydrophobic matrices for controlled drug release. J Control Release. 2003; 93(1): 1–13.
43. Sonia TA, Sharma CP. Chitosan and its derivatives for drug delivery perspective. Adv Polym Sci. 2011; 243: 23–54.