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Research review paper

Advances in self-assembled chitosan nanomaterials for drug delivery

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ABSTRACT

Nanomaterials based on chitosan have emerged as promising carriers of therapeutic agents for drug delivery due to good biocompatibility, biodegradability, and low toxicity. Chitosan originated nanocarriers have been prepared by mini-emulsion, chemical or ionic gelation, coacervation/precipitation, and spray-drying methods. As alternatives to these traditional fabrication methods, self-assembled chitosan nanomaterials show significant advantages and have received growing scientific attention in recent years. Self-assembly is a spontaneous process by which organized structures with particular functions and properties could be obtained without additional complicated processing or modification steps. In this review, we focus on recent progress in the design, fabrication and physicochemical aspects of chitosan-based self-assembled nanomaterials. Their applications in drug delivery of different therapeutic agents are also discussed in details.

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Introduction

Chitosan and its derivatives are natural polysaccharides derived from chitin. They have been demonstrated to be nontoxic in both animal models and humans (Kanauchi et al., 1994; Maezaki et al., 1993; Roy et al., 1999). In addition, chitosan has a special feature of adhering to mucosal surfaces and is capable of penetrating the tight junctions between epithelial cells, which make it ideal material for drug delivery. Therefore, chitosan and its derivatives have attracted significant interests as carriers for drug (Lee et al., 2000; Ruel-Gariepy et al., 2002; Wang et al., 2008a) or gene (Büyüktimkin et al., 2012; Kim et al., 2001; Roy et al., 1999) delivery due to their excellent biocompatibility, biodegradability, biological activities, and adsorption properties (Hirano, 1999; Hu et al., 2011; Molinaro et al., 2002; Park et al., 2003; Williams et al., 2009). There is no doubt that chitosan is a very promising material for drug delivery.

Presently, a variety of chitosan-based drug delivery materials in the forms of gels, tablets, films and particle have been developed and studied (Gupta and Ravi Kumar, 2000; Hari et al., 1996; Hu et al., 2002; Wang et al., 2003). Mini-emulsion (Samuels, 1981), chemical or ionic gelation, coacervation/precipitation and spray-drying are the commonly used methods to prepare chitosan carriers. However, the challenges involving the use of high cost materials, large amount of chemical agents, and the tedious and time-consuming process prevent the real-world large scale applications of chitosan drug carriers.

Recently, an increasing number of publications have appeared that explore self-assembly as a feasible and cost-effective strategy to prepare chitosan drug carriers. Compared to the traditional top-down fabrication methods, self-assembly is a bottom-up process. During the fabrication of self-assembled materials, molecules associate into well-defined, functional geometries through simple interactions with each other. The self-assembly process of chitosan and its derivatives is similar to many other biological molecules (DNA, RNA and proteins) that occur in water phase under normal conditions to generate materials with a wide range of properties and functions. Moreover, some structure that is difficult or impossible to be achieved by conventional ways can be obtained by self-assembly method. In the mean time, the rich functional groups in chitosan molecule provide the opportunity for further functionalization of the self-assembled structures to endow them specific stimuli-responsive properties for drug targeting and controlled release.

Till now, self-assembled chitosan nanomaterials have demonstrated tremendous potential for drug delivery applications. However, there is no relevant review on this. Here, we reviewed the recent advancements of self-assembled chitosan nanomaterials in drug delivery. In particular, we focused on the preparation and physicochemical aspects of the synthetic self-assembled nanomaterials based on chitosan and its derivatives. We further discussed the application of self-assembled chitosan nanomaterials in drug delivery, such as delivery of proteins and peptides, genes, small molecules, and combinational drugs. By presenting self-assembled chitosan nanomaterials from theory to application, we wish that this review will provide a broad overview of this promising new material in drug delivery.

Properties of chitosan and its advantages in drug delivery

Chitosan is a natural polysaccharide consisting of varying amounts of (1–4)-glycosidic bonds linking N-acetyl-2-amino-2-deoxy-D-glucopyranose (glucosamine) and 2-amino-2-deoxy-D-glucopyranose (N-acetyl-glucosamine) (Agrawal et al., 2010; Ravi Kumar, 2000). As shown in Fig. 1, rich functional groups, such as hydroxyl groups, amino groups, and acetylamino groups are present in the molecule chain endowing chitosan with versatile chemical properties (Yi et al., 2005). Moreover, the amino groups make chitosan a natural polyelectrolyte that readily dissolves in acidic solution. The charge density of chitosan molecules depend on the degree of acetylation (DA) and the pH of the solution. Due to the inter- and intra-molecular hydrogen bonds between the $-OH$ and $-NH_2$ groups, chitosan possesses a crystalline structure. Although the main molecular chain is hydrophilic, chitosan also shows a slight degree of hydrophobic behavior due to the presence of N-acetyl groups. As a result of the combined effects of hydrogen bonds and hydrophobic interaction, chitosan tends to form aggregates and is difficult to dissolve in the neutral media. However, chitosan can easily dissolve in dilute acid solution because of the ionization of amino groups. Generally, the molecular weight and degree of deacetylation (DD) are key factors influencing the charge density, hydrophobicity and solubility of chitosan.

Recent advances in chitosan research have revealed the potential of chitosan-based materials in drug delivery (Bernkop-Schnürch and Dünnhaupt, 2012). Like most other polysaccharides, chitosan has excellent biodegradability, biocompatibility and non-immunogenicity (Bhattarai et al., 2010; Duceppe and Tabrizian, 2010). As the only natural positive polysaccharide, chitosan is especially advantageous in forming stable complex with negative compounds, which makes chitosan a good candidate for the drug encapsulation and controlled release. In addition, chitosan has mucoadhesive and absorption-enhancing properties. It had been reported that chitosan can interact with mucus and epithelial cells resulting in opening of cellular tight junctions (Illum et al., 1994, 2001). These properties make chitosan also an ideal candidate for the delivery of macromolecular therapeutics, like protein and peptides.

Self-assembly of chitosan

Molecular design

The molecular structure of chitosan and its derivatives plays an important role in the self-assembly. As discussed above, the chemical

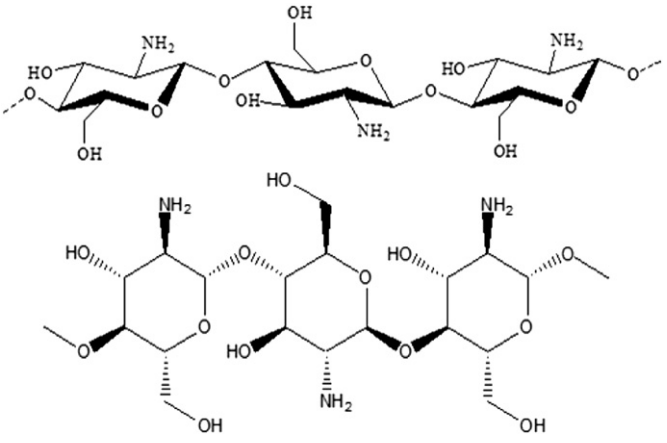

Fig. 1. Chemical structure of chitosan.