CROSSLINKED CHITOSAN NANOPARTICLES
AND CHEMICAL MODIFICATIONS FOR DRUG DELIVERY APPLICATIONS

Introduction

As a polysaccharide, chitosan can have a large density of reactive groups and a wide range of molecular weights ($M_w$). Chitosan is a linear heteropolymer of $N$-acetyl-$d$-glucosamine and $d$-glucosamine linked by $\beta$-(1→4)glycosidic bonds (Figure 1). It is obtained by partial deacetylation of chitin, the second largest and most abundant polysaccharide in nature after cellulose. The degree of acetylation (DA) represents the fraction of $N$-acetyl-$d$-glucosamine relative to the total number of units.

Figure 1. Chemical structure of chitosan

For many years chitosan was considered useful as a bioadhesive material because of its ability to form non-covalent bonds with biological tissues, mainly epithelia and mucous membranes. Bioadhesions formed using natural polymers have unique properties as a carrier because they can prolong residence time and, therefore, increase the absorbance of loaded drugs. Chitosan is hydrophilic and soluble in acidic solutions through the protonation of its amine groups. Modified and unmodified chitosan has been widely used, albeit with different molecular weights and chemical modifications, in biomedical, pharmaceutical, metal chelation, food additive, and other industrial applications. Chitosan is biocompatible and can be biodegraded by enzymes such as lysozymes, some lipases, and proteases. These properties, as well as its positive charge in physiological conditions, endow chitosan with a promising future as a biomaterial.

Nanoparticle drug delivery systems, including nanospheres, nanocapsules, nanomicelles, nanoliposomes, etc., are nanometric carriers used to deliver drugs or biomolecules by trapping active agents in their interior structures and/or adsorbing them onto their exterior surfaces. Presently, nanoparticles (NPs) have been widely used to deliver drugs, polypeptides, proteins, vaccines, genes, and nucleic acids. Recently, there has been increased interest in the use of NPs containing natural polysaccharides for drug delivery applications. A large number of studies have been conducted on polysaccharides and their derivatives for their potential application as NP drug delivery systems, and chitosan has been identified among the most promising candidates.

The following sections focus on the leading techniques for preparation and application of chitosan NPs, as well as chemical modification methods for self-assembly structures including nanoparticles and nanomicelles.

Chitosan NP Preparation Methods

Particulate chitosan structures are 3D crosslinked networks where polymeric chains are interconnected by crosslinkers. The main parameter, which determines the properties of a crosslinked NP, such as drug release and mechanical strength, is the crosslinking density. Depending on the desired chitosan structural characteristics, nanoparticles are prepared mainly by four mechanisms:

1. Covalent crosslinking
2. Ionic crosslinking
3. Polyelectrolyte complexation
4. Self-assembly of hydrophobically modified polysaccharide

In general, for mechanisms 1–3, chitosan NP preparation starts with the dropwise addition of the desired crosslinker to the chitosan solution with continuous stirring for 1–24 h, with or without slight heating depending on the crosslinking chemistry. However, the fourth mechanism of NP preparation, in addition to hydrophobic moiety chemistry, depends on two parameters: the percentage of hydrophobic substitution (Degree of Substitutions—DS%) and the final modified chitosan concentration (lower for nanoparticles and nanomicelles; higher within hydrogels). Table 1 summarizes and compares these four mechanisms as well as current delivery applications. Figure 2 represents illustrative photos on the crosslinked chitosan 3D structure formation highlighting internal interactions. Hydrophobic groups on chitosan confer new physicochemical properties, including the ability to self-associate in water or under sonication, to form different types of drug delivery systems (Figure 2).