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## Review Article

# Impact of chitosan composites and chitosan nanoparticle composites on various drug delivery systems: A review

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## ARTICLE INFO

## Article history:

Received 2 May 2014

Received in revised form

28 September 2014

Accepted 22 October 2014

Available online 4 December 2014

## Keywords:

chitosan

drug delivery system

nanoparticle composite

wound healing

## ABSTRACT

Chitosan is a promising biopolymer for drug delivery systems. Because of its beneficial properties, chitosan is widely used in biomedical and pharmaceutical fields. In this review, we summarize the physicochemical and drug delivery properties of chitosan, selected studies on utilization of chitosan and chitosan-based nanoparticle composites in various drug delivery systems, and selected studies on the application of chitosan films in both drug delivery and wound healing. Chitosan is considered the most important polysaccharide for various drug delivery purposes because of its cationic character and primary amino groups, which are responsible for its many properties such as mucoadhesion, controlled drug release, transfection, *in situ* gelation, and efflux pump inhibitory properties and permeation enhancement. This review can enhance our understanding of drug delivery systems particularly in cases where chitosan drug-loaded nanoparticles are applied.

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## 1. Introduction

Chitosan is a natural polysaccharide and is considered the largest biomaterial after cellulose in terms of utilization and distribution [1]. It is produced from chitin—the structural element found in the exoskeleton of crustaceans such as shrimps, lobsters, and crabs. The shells of these crustaceans

are first removed and then ground into powder, which is further processed to produce chitosan. Chitosan also occurs naturally in some microorganisms such as fungi and yeast [2]. Although chitosan is structurally similar to cellulose, it contains, in addition to hydroxyl groups, acetamine or free amino groups, which display very different properties from those of cellulose [3]. Chitosan has attracted attention because

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<http://dx.doi.org/10.1016/j.jfda.2014.10.008>

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of its biological properties and effective uses in the medical field, food industries, and agricultural sector [4]. It shows a variety of biological activities such as phytoalexin elicitor activity, activation of immune response, cholesterol lowering activity, and antihypertension activity [5,6]. Similarly, mesoporous silica nanoparticles (NPs) have the ability to efficiently entrap cargo molecules because of their unique characteristic of having a huge pore size. They have already been recognized as a promising drug carrier and have recently become a new area of interest in the field of biomedical applications [7]. For instance, Zhu et al [7] focused on the stimuli-responsive controlled-release systems that responded to tumor cell environmental changes, such as pH, glucose, adenosine-50-triphosphate, glutathione, and  $H_2O_2$ .

Chitosan's therapeutic properties have also been reported by other researchers, such as inhibition of growth of microorganisms and pain alleviation [8,9] and promotion of hemostasis and epidermal cell growth [10]. However, some researchers are interested in the potential applications of chitosan for medical and pharmaceutical purposes. The increased interest in chitosan, particularly its use in the pharmaceutical field, is attributed to its favorable properties such as biocompatibility, ability to bind some organic compounds, susceptibility to enzymatic hydrolysis, and intrinsic physiological activity combined with nontoxicity and heavy metal ions [11–13]. These properties are particularly amenable to a wide variety of biomedical applications in drug delivery and targeting, wound healing, and tissue engineering, as well as in the area of nanobiotechnology. Chitosan has attracted attention as a material for drug delivery biomedical applications in the past few years because of its biological and physicochemical properties, leading to the recognition of chitosan as a drug delivery element and a promising material specifically for the delivery of macromolecules [14–16]. In this regard, chitosan-based delivery systems range from microparticles to NP composites and films. However, there are several drawbacks in the use of chitosan for drug delivery systems. The main drawback is its poor solubility at physiological pH owing to the partial protonation of the amino groups, thereby causing presystemic metabolism of drugs in intestinal and gastric fluids in the presence of proteolytic enzymes. To overcome these inherent drawbacks, various derivatives of chitosan such as carboxylated, different conjugates, thiolated, and acylated chitosan have been used in drug delivery systems [17,18]. Researchers reported on the goals of using chitosan as an excipient for drug delivery systems [19–23]. Therefore, the main objective of this review is to highlight and investigate the application of chitosan and chitosan-based NP composites in drug delivery systems and to provide some insight for its future potential.

## 2. Preparation and physicochemical properties of chitosan

Fig. 1 shows the structures of chitin, cellulose, and chitosan. Chitosan is recognized as a linear binary heteropolysaccharide composed of  $\beta$ -1,4-linked glucosamine with various degrees of N-acetylation of glucosamine residues [24,25]. It is prepared from chitin by alkaline N-deacetylation [24,26] using

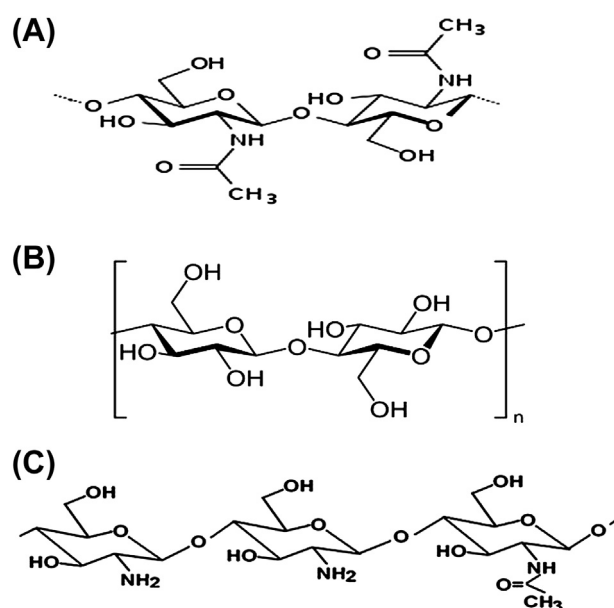


Fig. 1 – Structures of (A) chitin, (B) cellulose, and (C) chitosan.

concentrated sodium hydroxide (NaOH) solutions at high temperatures for a long period. Another method for the production of chitosan is N-deacetylation using enzymes under relatively mild conditions [27]. The commercially available chitosan is mostly derived from chitin of crustaceans by alkaline N-deacetylation because it is easily obtainable [28]. The production of chitosan involves a two-step process. The first step is extraction of chitin [a linear chain consisting of N-acetyl-D-glucosamine (2-acetamido-2-deoxy- $\beta$ -D-gluconopyranose) joined together by  $\beta$  (1 $\rightarrow$ 4) linkage] and removal of calcium carbonate ( $CaCO_3$ ) from crustaceans' shells using dilute hydrochloric acid and deproteination with dilute aqueous NaOH. In the second step, 40–50% aqueous NaOH at 110–115°C is used for deacetylation of chitin for several hours without oxygen. When the degree of deacetylation exceeds 50%, then chitosan is produced [29]. Chitin with a degree of deacetylation of  $\geq 75\%$  is also recognized as chitosan [28].

The degree of deacetylation and molecular weight are the two fundamental parameters that can affect the properties and functionality of chitosan [26,30]. These properties include solubility, viscosity, reactivity of proteinaceous material coagulation, and heavy metal ion chelation [31–33], and physical properties of films formulated using chitosan such as tensile strength, elasticity, elongation, and moisture absorption [34]. Chitosan is soluble in aqueous acidic solutions, but insoluble in both water and alkaline solutions [25]. The majority of polysaccharides are usually found neutral or negatively charged in an acidic environment. When dissolved, the amino groups ( $-NH_2$ ) of the glucosamine are protonated to  $-NH_3^+$  [35], and the cationic polyelectrolyte readily forms electrostatic interactions with other anionic groups [36]. Therefore, the cationic chitosan molecule interacts with negatively charged surfaces that modify its physicochemical characteristics [2,37]. These modifications of chitosan molecules are the source of its unique functional properties.

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