



## Review

# Glycerophosphate-based chitosan thermosensitive hydrogels and their biomedical applications



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## ABSTRACT

Chitosan is non-toxic, biocompatible and biodegradable polysaccharide composed of glucosamine and derived by deacetylation of chitin. Chitosan thermosensitive hydrogel has been developed to form a gel in situ, precluding the need for surgical implantation. In this review, the recent advances in chitosan thermosensitive hydrogels based on different glycerophosphate are summarized. The hydrogel is prepared with chitosan and  $\beta$ -glycerophosphate or  $\alpha\beta$ -glycerophosphate which is liquid at room temperature and transits into gel as temperature increases. The gelation mechanism may involve multiple interactions between chitosan, glycerophosphate, and water. The gelation behavior, rheological and physicochemical properties, and gelation process of the hydrogel are affected not only by the molecule weight, deacetylation degree, and concentration of chitosan, but also by the kind and concentration of glycerophosphate. The properties and the three-dimensional networks of the hydrogel offer them wide applications in biomedical field including local drug delivery and tissue engineering.

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## 1. Introduction

Hydrogels are composed of three-dimensional polymer networks that have a high number of hydrophilic groups. The hydrogels can absorb large quantities of water and will neither disintegrate nor dissolve. Fully swollen hydrogels are soft, pliable, and low interfacial tension with water or biological fluids. The high water content of hydrogel renders it compatible with most living tissue and the viscoelastic nature of hydrogel minimizes damage to the surrounding tissue when it is implanted in the host. These characteristics make hydrogel an ideal candidate in biomedical applications such as remedying injuries to living systems (Bhattacharai, Gunn, & Zhang, 2010). In addition, hydrogels can serve as a supporting material for cells during tissue regeneration as well as drug delivery system because the hydrogel's physicochemical properties are similar to the native extracellular matrix both compositionally and mechanically (Lee & Mooney, 2001; Tessmar & Gopferich, 2007). The hydrogel will become responsive to environmental stimulation if the polymer network of hydrogel is endowed with functional groups (Buenger, Topuz, & Groll, 2012). The stimulation may be temperature, pH, biomolecules, electric field, magnetic field, light rays and so on. When the environment stimulation is changed, the hydrogels undergo a volume-phase transition due to molecular interactions resulting in abrupt changes in the network such as swelling, collapse or sol-to-gel transition.

Glycerophosphate is an organic compound naturally found in the body which is usually used as a source of phosphate in the treatment of unbalance of phosphate metabolism and its venal administration has been approved by FDA.  $\beta$ -Glycerophosphate has been shown as an osteogenic supplement when added to cultures of human bone marrow stem cells.  $\alpha\beta$ -Glycerophosphate is the mixture of  $\alpha$ -glycerophosphate and  $\beta$ -glycerophosphate, and  $\alpha$ -glycerophosphate has linear chain structure and shows less steric hindrance than  $\beta$ -glycerophosphate. Glycerophosphate also has been used as a catalyst to cause a sol-to-gel transition in chitosan solutions at physiological pH and temperature.

Chitosan, the cationic (1-4)-2-amino-2-deoxy- $\beta$ -D-glucan, partly acetylated to the typical extent close to 0.25 is industrially produced in medical/pharmaceutical grade from marine chitin (Jayakumar, Menon, Manzoor, Nair, & Tamura, 2010; Jayakumar, Prabakaran, Nair, & Tamura, 2010; Jayakumar et al., 2010; Muzzarelli, 2009; Muzzarelli, 2010; Muzzarelli, 2012; Muzzarelli et al., 2012). The development of chitosan hydrogel has been an area drawing intensive investigation and a large amount of works have been reported on chitosan hydrogel and its potential use in various applications (Lee et al., 2009; Nagahama et al., 2009; Sung et al., 2010; Tang, Du, Hu, Shi, & Kennedy, 2007; Zhou et al., 2012).

Chitosan hydrogels have been prepared with a variety of different geometries and formulations including liquid gels, beads, films, tablets, capsules, microspheres, microparticles, sponges, and textile fibers (Denkbas, 2006; Hamidi, Azadi, & Rafiei, 2008; Khan, Tare, Oreffo, & Bradley, 2009; Ladet, David, & Domard, 2008). In each preparation, the polymer binding is accomplished either by non-covalent physical association, such as secondary forces (hydrogen, ionic, or hydrophobic bonding) and physical entanglements, or by covalent cross-linked chemical association (Hoffman, 2002). Physical associated networks can often be obtained by simply mixing the components which make up the gel under the appropriate conditions. Furthermore, the gelation, requiring no toxic covalent linker molecules, is always safe for clinical applications.

This review focuses on the hydrogel based on different glycerophosphate including the preparation and applications, which is a temperature-sensitive physical associated network. There are several excellent reviews of hydrogel or chitosan-based hydrogel (Bhattacharai et al., 2010; Buenger et al., 2012; Hoffman, 2002; Lee & Mooney, 2001) and there is a review about

thermosensitive chitosan/glycerophosphate-based hydrogel and its derivatives (Supper et al., 2014), but an in-depth review on chitosan/glycerophosphate hydrogel based on the different glycerophosphate cannot be found ever. In this review, we will summarize the various categories of chitosan/glycerophosphate hydrogels prepared with chitosan and  $\beta$ -glycerophosphate or  $\alpha\beta$ -glycerophosphate, describe the preparation methods, introduce the properties and gelation mechanism, and present recent advances in biomedical applications.

## 2. Chitosan/ $\beta$ -glycerophosphate hydrogels

### 2.1. Development process and gelation mechanism

Chitosan dissolves in acidic environments via protonation of its amine groups. Once dissolved, chitosan remains in solution up to pH value in the vicinity of 6.2. Neutralization of chitosan aqueous solutions to pH value exceeding 6.2 systematically leads to the formation of a hydrated gel-like precipitate. Effort on chitosan neutral solution is first proposed by Chenite et al. (2000). They find that chitosan solutions remain liquid below room temperature, even with pH values within a physiologically acceptable neutral range from 6.8 to 7.2, in the presence of  $\beta$ -glycerophosphate salt. The system becomes thermally sensitive, which is liquid at room temperature and solidifies into gel as temperature increasing to body temperature (Fig. 1) (Ruel-Gariépy et al., 2004).  $\beta$ -glycerophosphate plays three essential roles in the system: (1) to increase the pH into the physiological range of 7.0–7.4; (2) to prevent immediate precipitation or gelation; and (3) to allow for controlled gel formation when an increase in temperature is imposed. The sol-to-gel transition temperature is pH-sensitive and gelling time is shown to be temperature-dependent.

The molecular mechanism of gelation may involve multiple interactions between chitosan,  $\beta$ -glycerophosphate, and water (Crompton et al., 2005; Ruel-Gariépy, Chaput, Guirguis, & Leroux, 2000). The effective interactions responsible for the sol/gel transition included: (1) the increase of chitosan interchain hydrogen bonding as a consequence of the reduction of electrostatic repulsion due to the basic action of the salt, (2) the chitosan-glycerol-phosphate electrostatic attractions via the ammonium and the phosphate groups, respectively, and (3) the chitosan–chitosan hydrophobic interactions which should be enhanced by the structuring action of glycerol on water.

The solution behavior of chitosan/ $\beta$ -glycerophosphate hydrogel is affected by the concentration of chitosan and  $\beta$ -glycerophosphate (Cho, Heuzey, Bégin, & Carreau, 2006a). The pH of chitosan solution is slightly increased with increasing of  $\beta$ -glycerophosphate concentration due to the neutralizing effect of the phosphate groups. The pH increase with polymer concentration is due to the consumption of  $H^+$  ions in solution by the protonation of the free amine groups. The relationship between gelation temperature and concentration of chitosan ( $C_C$ ) and  $\beta$ -glycerophosphate ( $C_{GP}$ ) is shown in Fig. 2. The region below the surface is the sol state, while that above is a gel.  $T_{gel}$  is gradually decreased with increasing of  $C_{GP}$  and  $C_C$ . However, a synergistic effect at high  $C_{GP}$  and  $C_C$  results in a sudden drop of the gelation temperature and a phase transition which is on the edge between concentration-induced and heat-induced gelation.

The rheological and physicochemical properties of the chitosan/ $\beta$ -glycerophosphate system in terms of temperature are investigated sequentially (Chenite, Buschmann, Wang, Chaput, & Kandani, 2001; Cho, André Bégin, & Carreau, 2005). Increasing temperature has no effect on the pH value of the chitosan/ $\beta$ -glycerophosphate system, while conductivity is increased. The results indicate that the decrease of potential ionic interactions

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