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# Rheological characterisation of a novel thermosensitive chitosan/poly(vinyl alcohol) blend hydrogel

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**Abstract**

Thermosensitive hydrogels that are triggered by changes in environmental temperature thus resulting in in situ hydrogel formation have recently attracted the attention of many investigators for biomedical applications. In the current work, the thermosensitive hydrogel was prepared through the mixture of chitosan (CS), poly(vinyl alcohol) (PVA) and sodium bicarbonate. The mixture was liquid aqueous solutions at low temperature (about 4 °C), but a gel under physiological conditions. The hydrogel was characterized by FTIR, swelling and rheological analysis. The effect of hydrogel composition and temperature on both the gel process and the gel strength was investigated from which possible hydrogel formation mechanisms were inferred. In addition, the hydrogel interior morphology as well as porosity of structure was evaluated by scanning electron microscopy (SEM). The potential of the hydrogels as vehicles for delivering bovine serum albumin (BSA) were also examined. In this study, the physically crosslinked chitosan/PVA gel was prepared under mild conditions without organic solvent, high temperature or harsh pH. The viscoelastic properties, as investigated rheologically, indicate that the gel had good mechanical strength. The gel formed implants *in situ* in response to temperature change, from low temperature (about 4 °C) to body temperature, which was very suitable for local and sustained delivery of proteins, cell encapsulation and tissue engineering.


*Keywords:* Chitosan; Poly(vinyl alcohol); Hydrogel; Thermosensitivity

## 1. Introduction

Hydrogels that are hydrophilic three-dimensional polymeric networks capable of absorbing large quantities of water have become increasingly important in the biomedical field. One of the recent trends in hydrogel research is *in situ*-forming systems for various biomedical applications, including drug delivery (Gariepy, Chenite, Chaput, Guirguis, & Leroux, 2000; Hsiue, Chang, Wang, & Lee, 2003) and tissue engineering (Anseth et al., 2002; Shu, Liu, Palumbo, Luo, & Prestwich, 2004). *In situ*-forming systems are liquid aqueous solutions before administration, but gel under physiological conditions. There are several possible mechanisms that lead to in situ gel formation (Gariepy & Leroux, 2004): solvent exchange, UV-irradiation, ionic cross-linkage, pH change, and temperature modulation. These approaches, which do not require organic solvents, copolymerization agents, or an externally applied trigger for gelation, have gained increasing attention, such as a thermosensitive approach for in situ hydrogel formation (Jeong, Kim, & Baeb, 2002). The temperature responsive hydrogel, which is triggered by changes in environmental temperature thus resulting in in situ hydrogel formation, has caused the interest of many investigators for biomedical applications.

Recently, polysaccharides have been extensively studied for the development of thermosensitive *in situ*-forming hydrogel systems because they are suitably biodegradable, a quality not possessed by most synthetic polymers. Chitosan, a polysaccharide derived from naturally abundant chitin, is currently receiving a great deal of interest. Chenite,

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Chaput, Wang, Combes, and Buschmann (2000) developed a novel approach to produce thermosensitive neutral hydrogel based on chitosan/polyol salt combinations that could undergo sol–gel transition at a temperature close to 37 °C. Other researchers also evaluated the hydrogel for use in pharmaceutical applications (Gariepy, Leclair, Hildgen, Gupta, & Leroux, 2002; Gariepy et al., 2004) and cartilage repair (Hoemann et al., 2001, 2003). Many modified chitosan copolymers also have thermosensitive characteristics. Bhattaraim, Ramay, Gunn, Matsen, and Zhang (2005) found the aqueous solution of the PEG-grafted chitosan, which is an injectable liquid at low temperature and transforms to a semisolid hydrogel at body temperature, has a broad range of medical applications, particularly for sustained *in vivo* drug release and tissue engineering. Dang et al. (2006) have shown that a 3.8% w/w hydroxybutyl chitosan solution forms a gel within 60 s when it is exposed to a 37 °C environment, which indicates the potential of hydroxybutyl chitosan gel as an injectable carrier for future applications of delivering therapeutics to encourage a biologically relevant reconstruction of the degenerated disk. Chung, Bae, Park, Lee, and Park (2005) prepared two kinds of water soluble thermosensitive chitosan copolymers by graft polymerization of *N*-isopropylacrylamide and by coupling monocarboxy Pluronic® with chitosan. The resulting copolymers formed thermally reversible hydrogels with a lower critical solution temperature of 34 °C, and they could be used as injectable cell-polymer complexes.

Poly(vinyl alcohol) (PVA), a water-soluble polyhydroxy polymer, has been frequently explored as implant material for drug delivery systems and surgical repairs because of its excellent mechanical strength, biocompatibility and nontoxicity (Martien, 1986). Therefore, it is promising to blend chitosan with PVA to produce a new biosynthetic polymer applicable for a variety of purposes. Koyanoa, Koshizakib, Umeharab, Nagurac, and Minourab (2000) and Minoura et al. (1998) prepared a blend of chitosan with PVA to study the surface properties and elucidate the relationship between these properties and the cell attachment/growth behavior. Many researchers explored such blends to determine the properties changes in response to the external stimuli such as pH change (Wang, Turhan, & Gunasekaran, 2004) and the electrical charges (Kim, Park, Kim, Shin, & K, 2002). In addition, a blend of chitosan with PVA has been evaluated as a drug delivery agent (Kurkuri & Aminabhavi, 2004; Sugimoto, Yoshida, Yata, Higaki, & Kimura, 1998).

In the previous study, the introduction of PVA to make blend fibers of chitosan and PVA improved tensile strength and water retention properties of the blend formations compared to those of pure chitosan (Zheng, Du, Yu, Huang, & Zhang, 2001). These properties are interesting for further study of the properties of blends of chitosan and PVA. Though some blends of PVA with chitosan have been prepared, there are scarcely any reports about the thermosensitive hydrogel nature of chitosan and PVA blends. This study aimed to develop an injectable and thermosensitive system based upon the blend of chitosan and PVA, and which can serve as a therapeutic drug-delivery system promoting tissue repair and regeneration through controlled release of loaded drugs. As Gariepy and Leroux (2004) reported, the system will be a solution that is a injectable liquid at ambient temperature and gel at body temperature. Moreover, loading with drugs or cells should be achieved by simple mixing. When administered parenterally, the system should exhibit a pH close to neutrality and should be biodegradable.

## 2. Materials and methods

### 2.1. Materials

Chitosan was obtained from Yuhuan Ocean Biochemistry Co. (Zhejiang, China). The DD as determined by elemental analysis was 92%, and the molecular weight calculated from the GPC method was about $2.7 \times 10^5$. Standard pullulans for GPC were purchased from Showa Denko, Tokyo, Japan. Poly(vinyl alcohol) with an average degree of polymerization of 2400–2500 were purchased from Shanghai Chemical Reagent Co. (Shanghai, China). All other chemicals were of analytical grade.

### 2.2. Preparation of chitosan/PVA hydrogel

A clear solution of chitosan was obtained by dissolving chitosan (200 mg) in 0.1 M HCl (10 mL) and chilled in an ice bath for 15 min. PVA was added to deionized water and heated at 80 °C for 1 h to make solutions containing 2, 5 and 10% w/w PVA. 1.0 M $NaHCO_3$ (1 mL), and 2% w/w PVA solution (10 mL) were mixed and similarly chilled for 15 min. Then the PVA was slowly added to the chitosan solution in an ice bath under magnetic stirring for 10 min. The solution was degassed by centrifugation of samples at 3500*g* for 3 min at 5 °C. The gel was then formed in 30 min by keeping it at 37 °C.

### 2.3. Characterization of the gel by FTIR

FTIR spectra were recorded on an FTIR spectrometer (Nicolet, Model Impact 410, WI) at room temperature. Chitosan, PVA and the dried gel were triturated with KBr in the ratio of 1:100 and pressed to form pellet samples 400–4000 $cm^{-1}$.

### 2.4. Rheological measurement

The rheological properties were performed on a strain-controlled ARES rheometer (TA. Inc., New Castle, USA). The rheometer was equipped with two sensitive force transducers for torque measurements ranging from 0.004 to 100 g cm. A Couette (two concentric cylinders) cell geometry was used for monitoring the steady-state shear flow and dynamic rheology of the samples modulus. The rheometer is equipped with a thermo-bath with circulating