



Pseudo-thermosetting chitosan hydrogels for biomedical application

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Abstract

To prepare transparent chitosan/ β -glycerophosphate (β GP) pseudo-thermosetting hydrogels, the deacetylation degree (DD) of chitosan has been modified by reacylation with acetic anhydride. Two methods (I and II) of reacylation have been compared and have shown that the use of previously filtered chitosan, dilution of acetic anhydride and reduction of temperature in method II improves efficiency and reproducibility. Chitosans with DD ranging from 35.0 to 83.2% have been prepared according to method II under homogeneous and non-homogeneous reacylation conditions and the turbidity of chitosan/ β GP hydrogels containing homogeneously or non-homogeneously reacylated chitosan has been investigated. Turbidity is shown to be modulated by the DD of chitosan and by the homogeneity of the medium during reacylation, which influences the distribution mode of the chitosan monomers. The preparation of transparent chitosan/ β GP hydrogels requires a homogeneously reacylated chitosan with a DD between 35 and 50%.

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1. Introduction

Chitosan is a copolymer of β -(1 \rightarrow 4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose (Fig. 1). This polycationic

biopolymer is generally obtained by alkaline deacetylation from chitin (Fig. 1), the main component of the exoskeleton of crustaceans, such as shrimps (Muzzarelli, 1973). The main parameters influencing its characteristics are molecular weight (MW), crystallinity and morphology. Moreover, the degree of deacetylation (DD), which represents the percentage of deacetylated monomers (Fig. 1), and the distribution mode of the monomers are other essential parameters of chitosan

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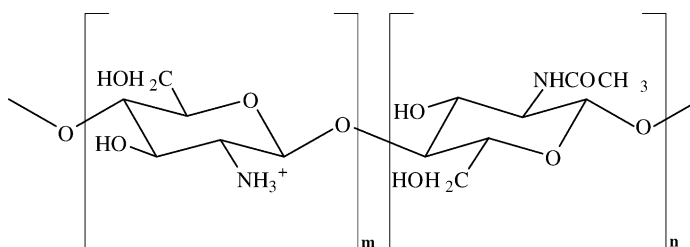


Fig. 1. Structure of chitosan (degree of deacetylation is given by $[m/(m+n)] \times 100$) and of chitin ($m \ll n$).

(Domard, 2000) influencing important properties such as solubility (Baumann and Faust, 2001; Sashiwa et al., 2002) and viscosity (Mucha, 1997). Consequently, modification of the DD and of the distribution mode of the chitosan monomers is a common way to modulate the properties of chitosan hydrogels. Ideally, this modification should be easy to perform without the addition of toxic reactants, in order to avoid a decrease of the intrinsic biocompatibility of chitosan. In addition, chitosan should not be degraded and the process should be reproducible and efficient. The DD of commercial chitosan (generally about 80%) can be increased by further deacetylation using concentrated NaOH solutions at temperatures above 100 °C. However, this process generally induces degradation that lowers the chitosan MW (Knaul et al., 1998). In order to avoid degradation, deacetylation by enzymatic methods has been suggested (Martinou et al., 1995). More common than deacetylation is the modification of DD by reacetylation, which results in a reduced DD. Reacetylation is generally performed by the addition of acetic anhydride to re-functionalise the amine of chitosan deacetylated monomers with an acetyl group. Consequently, the ratio of the acetylated monomers on the deacetylated monomers is increased, which favours the hydrophobicity of polymeric chains and contributes to the formation of secondary interchain interactions, leading to gelation (Vachoud et al., 2000). As reacetylation is performed in solution, the addition of acid is required to solubilise chitosan. Since the reaction of acetic anhydride with chitosan induces the formation of acetic acid, this latter is generally used (Hirano et al., 1993; Vachoud et al., 2000; Baumann and Faust, 2001). Reacetylation is not an amine specific reaction and the hydroxyl groups of chitosan are generally acetylated at the same time, which decreases the efficiency and reproducibility of the reacetylation process. Therefore,

if a large proportion of *O*-acetyl groups are not desired, they have to be removed, for example by treatment with methanolic KOH solution for 6 h (Ogawa and Yui, 1993). However, a simpler method is the use of scavenger groups during the reacetylation reaction in order to minimise *O*-acetylation. For example, an alcohol can be added to the acidic solution of chitosan (Hirano and Yamaguchi, 1976b). In addition to the protective effect, alcohol favours reacetylation by decreasing the dielectric constant of the medium, but on the other hand minimises polymeric chain repulsion and enhances hydrophobic interactions, which increases the viscosity of the solution during reacetylation and often leads to gelation (Aiba, 1994). However, this does not disturb reacetylation, which is a fast reaction step that has been shown to be completed before gelation starts (Domard, 2000). Nevertheless, attention must be paid to the fraction of alcohol added. If this fraction is too high, gelation is favoured and combined with a high proportion of reacetylated monomers this can lead to the formation of an irreversible chitin gel (Vachoud et al., 2000), from which chitosan cannot be precipitated. On the other hand, if the proportion is too low, the efficiency of the reacetylation of amino groups decreases due to the acetylation of hydroxyl groups. The alcohol generally used is methanol (Hirano et al., 1993; Baumann and Faust, 2001). It has been shown that a concentration of 80% (vol/vol) of methanol allows the best reacetylation efficiency and that a higher concentration only favours gelation (Aiba, 1994). Propanediol (Vachoud et al., 2000) can also be used, but methanol has approximately the same dielectric constant and therefore the same protective effect. In addition, methanol has the advantage of a lower boiling point, which favours final drying of the reacetylated chitosan.

Chitosan/ β -glycerophosphate (β GP) pseudo-thermosetting hydrogels were first described by

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