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Antifungal vanillin–imino-chitosan biodynameric films†

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Vanillin–chitosan biodynamers have been prepared and structure–morphology correlations revealed the pathway of progressive incorporation of the aldehyde onto chitosan backbones. Such dynamic biopolymers or *biodynamers*, generated from reversibly interacting components, offer the possibility to address the dynamic covalent behaviour of the reversible imine-bond formation/hydrolysis equilibria between vanillin and chitosan polymeric backbones. The reaction takes place with very low conversion in acidic aqueous solutions (7–12%), but the imine bond formation is amazingly improved (~80%) when the reaction takes place while solution–solid state transition and solid state phase-organization events occur. The chitosan–vanillin biopolymeric films described here present interesting *Candida albicans* antifungal activity compared with other common bacterial strands, which suggests the implementation of these biocompatible materials as thin layer protecting systems for medical devices.

Introduction

Due to its therapeutic, haemostatic, depressant, immuno-adjuvant and antitumor properties and its non-toxic behaviors[1,2] chitosan (**C**), the natural polymer obtained from deacetylation of chitin, has become a biomaterial of expanding interest in biomedical, cosmetics, food or agricultural applications. *De novo* design of synthetic chitosan-based materials as films,[3] fibers,[4] nanoparticles[5] and gels[6] further increases its applicative value. The main challenge in the large scale use of chitosan is its low solubility in water. To overcome this, different chitosan modification reactions have been explored.[7–14] Among them, the reversible reaction of amino groups of chitosan with aldehydes bearing Schiff base–chitosan received much attention because the functional moieties, reversibly grafted onto the chitosan backbone, disrupt the H-bonding network of chitosan, thus improving its solubility.[7] Moreover, it represents a simple synthetic strategy, yielding modified chitosan with improved antimicrobial, antifungal, antitumor activity or for the delivery of insoluble therapeutic agents, *etc.*[8,9] Ultrasound,[10] microwave,[11] plasma[12] or enzymatic[13] activated synthetic methods have been used to obtain Schiff base–chitosan derivatives. The yield of imine formation in water is very low, due to imine exchanging or hydrolysis reactions occur very fast in acidic aqueous solutions.[14,15] We previously answered this challenge by reporting[14] that the very low conversion degrees (1–12%) obtained in acidic aqueous solutions can be amazingly improved to 80–90% if concentrated hydrogel/solid state irreversible vitrification processes occur or if aldehydes of low solubility react "out of water",[15a] when the components are in hydrophobic contact. With all these in mind, the further step was to implement these strategies to obtain such biodynamers[16] of high applicative interest. Within this context, our attention was attracted by vanillin (**V**), a natural product used as a food flavoring agent, which presents improved antifungal properties when forming Schiff bases,[17a] or incorporated onto chitosan as a vanillyl unit.[17b] Moreover, recent studies demonstrated that vanillin is an efficient inhibitor of cancer cell migration and metastasis in a mouse model.[17c] One should expect that these premises promise the chitosan–vanillin imine (**CV**) biopolymers to be a potentially valuable system for different applications. In the present work, chitosan–vanillin Schiff-base biopolymers were synthesized *via* imine-bond formation between chitosan and vanillin at different molar ratios ($\mathbf{C_{0.5}V}$, **CV**, $\mathbf{C_{1.5}V}$, $\mathbf{C_2V}$, $\mathbf{C_3V}$, $\mathbf{C_4V}$, $\mathbf{C_5V}$), in acidic water–acetone mixtures, in toluene used as a non-solvent for both components (**CVT**) or by grinding in the absence of solvents (**CVM**) (Scheme 1). Two aspects were preferentially followed: (1) the chemical investigation of the reaction evolution by spectroscopic and morphological analyses of resulted materials and (2) the antibacterial and antifungal properties of the synthesized biodynameric films. We have tested these materials against the most common bacterial agents, while they present interesting activity against *Candida albicans* fungus strain.

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