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Design and characterization of chitosan/zeolite composite films — Effect of zeolite type and zeolite dose on the film properties

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ABSTRACT

Chitosan films can be used as wound dressings for the treatment of chronic wounds and severe burns. The antimicrobial properties of these films may be enhanced by the addition of silver. Despite the antimicrobial activity of silver, several studies have reported the cytotoxicity as a factor limiting its biomedical applications. This problem may, however, be circumvented by the provision of sustained release of silver. Silver zeolites can be used as drug delivery platforms to extend the release of silver. The objective of this study was to evaluate the addition of clinoptilolite and A-type zeolites in chitosan films. Sodium zeolites were initially subjected to ion-exchange in a batch reactor. Films were prepared by casting technique using a 2% w/w chitosan solution and two zeolite doses (0.1 or 0.2% w/w). Films were characterized by thermal analysis, color analysis, scanning electron microscopy, X-ray diffraction, and water vapor permeation. The results showed that films present potential for application as dressing. The water vapor permeability is one of the main properties in wound dressings, the best results were obtained for A-type zeolite/chitosan films, which presented a brief reduction of this property in relation to zeolite-free chitosan film. On the other hand, the films containing clinoptilolite showed lower water vapor permeation, which may be also explained by the best distribution of the particles into the polymer which also promoted greater thermal resistance.

1. Introduction

Silver compounds have been used for medicinal purposes for centuries [1], but it has recently emerged as a viable compound for the management of infections in burns, open wounds and chronic ulcers [2]. Silver sulfadiazine (SD-Ag) is the most used silver compound in the treatment of burns because of its antibacterial properties [3]. However, it has been reported that SD-Ag slows down the process of wound healing and silver can have a severe cytotoxic activity [4].

The current difficulties encountered in topical administration of silver are related to low levels of silver released, the lack of penetration, rapid consumption of silver ions and the presence of nitrate or ointment cream bases which are pro-inflammatory and negatively affect wound healing [5]. Other problems include color which silver promotes over the skin, electrolyte imbalance and patient discomfort. Many of these problems could be circumvented by the use of controlled release platforms, such as particles and films or even both together.

The antimicrobial mechanism of silver ions is not well understood, but the effect of silver ions on bacteria can be verified by the morphological changes. It seems that when DNA molecules are in the relaxed state the replication of DNA can be effectively performed. Otherwise, when the DNA is in condensed form, it reacts with the thiol group proteins and loses its replication ability that is what happens when the silver ions penetrate inside the bacterial cell, leading to cell death [6].

According to Ismaiel and Tharwat [7], the antifungal mechanisms of silver ions are also not fully understood but it seems like the antibacterial mode of action. Then the interaction between silver and the constituents of the bacterial membrane changes the structure and damages the membranes and metabolic activity, leading to the bacteria death.

Zeolites are crystalline aluminosilicates widely used in chemical industry as catalysts, adsorbents or ion exchangers [8]. The studies about using zeolites as drug delivery systems have increased over the years, mostly due to its adsorption and ion exchange capacities that enable their interaction with many molecules, and also due to their porous structure with channels and cavities with molecular dimensions enabling the transfer of molecules within the crystal to the environment and vice versa [9].

The application of zeolites as drug delivery systems is well documented in recent literature, using either the Y-type [10,11], the X-type

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[12–14], the A-type [13,15], the BEA-type [12], the ZSM5-type [16], the P-type [17] or the mordenite [16]. Zeolite Y and X are the most commonly used zeolites, because of their market availability, diversity, microporosity and well-defined composition. Examples of drugs loaded in zeolites include ketoprofen [15], famotidine [16], 5-fluorouracil [10,12], ibuprofen [11,13], chloroquin [18], tramadol hydrochloride [14], and indomethacin [11].

Clinoptilolite, a natural zeolite, has also been studied as drug delivery systems for drugs like cephalexin [19], fat-soluble vitamins [20], aspirin [21,22], metronidazole [22–24], sulfamethoxazole [22,24], and diclofenac sodium [25].

One of the problems of using natural zeolites is the impurities with potential toxicity, although literature does not show zeolite toxicity results for skin or skin lesions, most of which are related to pulmonary or oral toxicity.

Adamis et al. [26] carried out in vitro and in vivo tests for determination of the pathogenicity of Hungarian clinoptilolite and other minerals. The mineralogical composition of the clinoptilolite was: clinoptilolite 50%, cristobalite 15–20%, quartz 5–20%, and small quantities of chalcedony, montmorillonite, kaolinite and feldspar. Clinoptilolite was previously incubated with peritoneal macrophages from male rats and the extracellular LDH activity was evaluated. Clinoptilolite induced moderate LDH extracellular release, but caused significant human hemolysis against human erythrocytes. This is a characteristic aluminosilicate type reaction in the course of in vitro experiments. For the in vivo tests, the suspension of clinoptilolite in sterile isotonic saline was injected directly into the trachea of the rats. On the basis of the pulmonary damage via bronchoalveolar lavage results, clinoptilolite was innocuous.

Pavelić et al. [27] carried out a wide study to assess the toxicity and anticancer activity of clinoptilolite. They found evidence that orally administered natural clinoptilolite is nontoxic and useful in cancer treatment in animal models. Additional in vitro tissue culture experiments with various cancer cell lines indicated that clinoptilolite treatment modifies intracellular signaling pathways leading to inhibition of survival signals and induction of tumor suppressor genes. Repeated-dose dermal tolerance testing was performed on male rats and mices, and the results showed that clinoptilolite was not toxic or allergenic for the skin. Clinoptilolite treatment of mice and dogs suffering from a variety of tumor types led to improvement in the overall health status, prolongation of life-span, and decrease in tumors size. The best results in animal models were observed in the treatment of skin cancer in dogs by local application of clinoptilolite, suggesting that adsorption of some active components is responsible for clinoptilolite activity.

Purification of clinoptilolite usually begins with the crushing of the rock and then the sieving. Afterwards, the purification is usually performed under mild conditions by suspending the zeolite in water during about 24–72 h and successive washing with water [28,29]. The suspending and washing steps may remove water-soluble mineral salts and also magnetic impurities. On the other hand, the purification of clinoptilolite may also be performed by acid leaching like nitric acid [30].

Ion exchange capacity is one of the most exploited properties of zeolites. Zeolites are usually synthesized with sodium and then these ions are exchanged by other ions, which contribute to the different properties of zeolite. The antibacterial capacity of the zeolites can be established when sodium ions are exchanged by silver ions [17,31]. When applied onto the wound, the silver ions present in the zeolite are exchanged with calcium and sodium ions existing in the wound. The released silver is then responsible for the antibacterial activity in the affected tissue. In recent years, there has been an increase in the number of commercial dressings containing silver, such as Acticoat (Smith & Nephew Healthcare Limited), Actisorb Silver 220 (Johnson & Johnson Medical Ltd), Aquacel AG (ConvaTec), and Mepilex Ag (Mölnlycke Health Care) [32].

The company Z-Medica Corp (Wallingford, USA) has also commercialized a zeolite product – QuickClot – for hemostatic applications. This product was approved by FDA for bleeding soldier in the battlefield. QuikClot consists of high surface porous aluminosilicate that acts as molecular sieve. When QuickClot contact the blood, it quickly adsorbs water molecules of the blood, thus the protein concentration and other substances increases in the wound and this catalyzes the clot formation. Otherwise, the increase of temperature to about 70 °C is one of the challengers to get over because the adsorption of water molecules is an exothermic process [33].

Zeolites can be incorporate into biopolymeric films in order to facilitate the topical application to wounds and burns. Biopolymers such chitosan, alginate, and carboxymethylcellulose have been widely used in the production of dressing films, however, chitosan noteworthy specially for presenting antifungal activity. In the present scenario, the antimicrobial activity of chitosan has been extensively reported in many applications like foodstuffs and medical devices. Chitosan appears as good candidates for further development not only as antifungal but also an antibacterial agent [34]. Moreover, chitosan stimulates cell proliferation and histoarchitectural reorganization of the tissue [35], promotes activation and proliferation of inflammatory cells in granular tissues [36], and accelerates the healing process [37].

The aim of this work was the production of ion-exchanged zeolites, namely, the synthetic one (A-type zeolite) and the natural one (clinoptilolite zeolite) for incorporating in chitosan films. The choice of these zeolites was based on the availability and low cost, in addition to their good capacity of ion exchange. The availability of A-type zeolite is due to the wide application in the detergent industry and its high ion exchange capacity. On the other hand, the clinoptilolite is the most abundant species among the approximately 40 natural zeolites [38]. The films were evaluated by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), color analysis, X-ray diffraction analysis (XRD) and water vapor permeability.

2. Materials and methods

2.1. Materials

Commercial chitosan (deacetylation degree of 82% and molar mass of approximately 1.47×10^5 g/mol) was supplied by Polymar (Fortaleza, Brazil) without prior purification and acetic acid (Synth, Brazil) was used as the acid medium. Two different types of zeolites were tested: 4A-type and clinoptilolite. The 4A-type zeolite and clinoptilolite was kindly supplied by Oxanyl (Sorocaba, Brazil) and CeltaBrasil (Cotia, Brazil), respectively. Both the zeolites had the same mean particle size (44 μm), and were used as received from the suppliers without further purification.

2.2. Preparation ion-exchanged zeolite

As it was described in the Introduction, the purification of clinoptilolite can be performed by suspending the zeolite in water during about 24–72 h and successive washing with water. Although the purification was not performed in this work, the long term ion-exchange methods and the successive washings probably provide such purification. Twenty-five grams of the zeolite were dispersed in 1 L of 0.025 mol/L $AgNO_3$ solution. The dispersion was kept at room temperature with stirring (IKA, RW20, Germany) for 24 h. The recipient was covered with aluminum foil in order to protect against the light. After centrifugation (Marconi, MA1815, Brazil) at 5000 r/min for 15 min, the sediment was washed with distilled water (800 mL) for two times, dried at 105 °C for 24 h (Tecnal, TE-393/1-MP, Brazil).

2.3. Chitosan solution

Chitosan (2.0%, w/w) was dissolved in acetic acid aqueous solution. The acetic acid content applied was the excess in 50% of stoichiometric