Incorporation of Theophylline in a hydrogel based on polyelectrolyte complex of chitosan/chondroitin sulfate: mechanical properties and release profiles at different pH conditions

Edvani C. Muniz*, Laís C. Lopes, Juliana F. Piai, André R. Fajardo and Adley F. Rubira
Grupo de Materiais Poliméricos e Compósitos, GMPC - Universidade Estadual de Maringá, UEM - Av. Colombo, 5790
CEP 87020-900, Maringá, Paraná, Brazil. *e-mail: ecmuniz@uem.br

Statement of Purpose: The idea of using hydrogels based on natural polymers for obtaining vehicles to be applied as controlled drug release has grown fastly[1]. The mixture of polymers with high charge density due to opposite charged functional groups can form compact hydrogels, allowing the formation of polyelectrolyte complexes (PEC)[2]. The chitosan (CHI), a linear polymer obtained from the deacetylation of chitin[3], has cationic nature and unique properties. The chondroitin sulfate (CS), a glycosaminoglycan, is a water soluble biopolymer with anionic nature and easily do complex with CHI[3]. Theophylline (TH) is a bronchus-dilator drug but its use in the treatment of asthma has been restricted due to its short half-life. One way to minimize such limitation is the encapsulation of the TH in an appropriate vehicle. This work studies: i) the incorporation of TH in a hydrogel formed by PEC of CHI/CS; ii) the CS and TH release profiles; and iii) the effect of pH the network when the hydrogel is swelled on different conditions of pH.

Methods: *Materials:* CHI was supplied by Golden-Shell Biochemical (China) with 15% acetylated. CS was supplied by Solabia (Brazil). Crystalline TH was purchased from Sigma-Aldrich (USA). *Hydrogel Preparation:* Acetic acid aqueous solution of CHI (1.75 wt-%) was mixed with a CS (25 wt-%) / TH (1 wt-%) aqueous solution. The resultant suspension was kept in resting by further 24 hours. The hydrogel formed was collected and purified in distilled water. After, it was cut in small pieces and dried at room temperature (25 °°C). *Release profile of CS and TH:* The samples were previously weight and left to swell in vessels containing pH 2 or 8 buffers at 37 °C. To quantify the fraction of CS and TH released, aliquots of buffers were removed in different time intervals. The aliquots were analyzed by HPLC technique. *Mechanical Properties:* The samples were swelled in buffers with wide pH range (2 to 10) during different time intervals. After this, they were collected and their compression elastic modulus (*E*) was determined through a Texturometer equipment. *WAXS profiles:* After the *E* determination the samples were crushed and then lyophilized. Powders of dried hydrogels samples were characterized by WAXS technique.

Results: HPLC was used for building the release profiles of CS and TH that are strongly pH-dependent. Comparing the results concerned to the hydrogel of CHI/CS with and without TH and also with those from previously developed in our research group[3], it can be inferred that the presence of TH in CHI/CS hydrogel does not affect the profile of CS release. The fraction of CS released from samples swollen at pH 8 is higher than from samples swollen at pH 2. Unlike, the fraction of TH released at pH 2-buffer is higher than at pH 8. This difference between CS and TH release profile was explained as: when swollen at pH 2-buffer the amino groups of CHI are protonated and the sulfate groups of CS are negatively charged. This enables the formation of strong electrostatic interactions among the CHI/CS chains[3]. So, the CS chains are kept entangled with CHI and no CS release occurs. However the TH entrapped within hydrogel is easily released by diffusion. When swelled at pH 8-buffer the amino groups of CHI are not protonated. So, the negatively charged groups of CS are not stabilized and cause destabilization of network due to anion-anion repulsion. This allows the CS chains get some mobility and are released. Also, the increase of CS released prevents the TH release. Thus, the TH fraction released from CHI/CS PEC swelled at pH 8-buffer decrease.

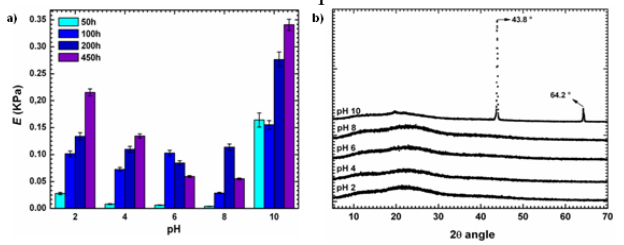

Figure 1. (a) Compression elastic modulus (*E*) of CHI/CS samples swelled in buffers with different pH values and time intervals. (b) WAXS profiles of CHI/CS samples swelled in different pH values by 400h.

According to Fig. 1a the samples swelled at pHs 2 and 10-buffers shows higher *E* values compared to pH 4, 6 and 8. It was inferred that at pH 4, 6 and 8 the network is lesser stabilized which allows the hydrogel became softer. For those hydrogels swelled at pH-10-buffer the network stabilization is enhanced due to the H-bonding[3] interaction among amino groups of CHI and groups of remaining CS, concomitant to the self-organization of matrix[3]. Due to the more reorganized state at pH 10, the chains stay closer and the hydrogel became more compact. The formation of more ordered regions were clearly characterized by the signal at 64.2° and 43.8° on WAXS profile obtained for after-dried sample previously swelled at pH 10-buffer.

Conclusions: The synthesis of pH-sensitive hydrogel formed by PEC of CHI/CS with TH encapsulated was performed. The pH of media of swelling influences the release profiles of both CS and TH in an opposite way. The values of elastic compression modulus, *E,* are influenced by the pH of swelling media. If the hydrogel is swelled at pH 10-buffer more ordered regions are formed within the network, clearly observed through WAXS profile. The PEC of CHI and CS can be an interesting vehicle to be used for controlled release of CS and TH.

References:

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