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Design of novel PVA-based hybrid composites for drug delivery

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The aim of this study was to synthesize and characterize a new poly(vinyl alcohol) (PVA) hybrid composite with a basic drug content, e.g., 2-[4-(2-methylpropyl)phenyl]propanoic acid (ibuprofen). Through sol-gel approach of the polymeric matrix (chloro-propyltriethoxysilane) with a PVA precursor that contains a fluorescent dye (lissamine rhodamine-B sulphonyl chloride), a new kind of hybrid material was obtained in which clusters of micrometric dimensions were dispersed in PVA organic matrix. The incorporation of ibuprofen within sol-gel derived matrix is expected to lead to compounds that allow a sustained and controlled release of the drug.

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Keywords: Poly(vinyl alcohol), Ibuprofen, Sol gel, Drug delibery

1. Introduction

Hybrid inorganic-organic composites obtained through sol-gel reaction are materials that can potentially be designed for a wide range of applications. Structural diversity is achieved by controlling the ratio between organic and inorganic components, structural complexity and chemical nature of the organic component, chemical composition of the inorganic precursor molecule, and the reaction conditions used to synthesize the hybrid compounds. Composite materials based on biodegradable polymers associated with inorganic compounds are of particular interest for biomedical applications since they offer an excellent balance between strength and toughness and also improved mechanical properties when compared to their individual components [1-3]. Among several choices of biodegradable polymers, poly(vinyl alcohol) (PVA) play an important role in the design of pharmaceutical and biomedical devices such as drug delivery systems, dialysis membranes, wound dressing, artificial skin, cardiovascular devices and surgical repairs due to its special properties (good chemical resistance, processability, mechanical strength, biocompatibility and biodegradability, non-toxicity) [4-7].

In this paper, a hybrid composite with randomly oriented microfibers network obtained through sol-gel reaction between a chloro-functional silane, e.g., chloro-propyltriethoxysilane and a dye-based PVA compound, in the presence of a non-steroidal anti-inflammatory drug insoluble in water, e.g. 2-[4-(2-methylpropyl) phenyl]propanoic acid (ibuprofen), was prepared in order to evaluate the compound as platform for controlled drug delivery. For monitoring the structural changes and the microenvironment surrounding the drug, a fluorescent dye (lissamine rhodamine-B sulphonyl chloride) (LRSC) with a high quantum yield was incorporated into the material during the early stage of the sol-gel process.

2. Experimental

2.1 Synthesis of PVA precursor (PVA-SO_2R)

2 g of PVA (M = 2200) (0.000909 mol) were dissolved in 20 ml of anhydrous dimethylformamide (DMF), and then KOH (0.028 g, 0.0005 mol) was added in order to obtain a pH value of 9, followed by the addition of 0.104 g (0.000181 mol) of LRSC. The final reaction was performed at 0 - 4ºC for 2 h.

2.2 Synthesis of hybrid composite with PVA units (PVA-SO_2R-IB)

The hybrid composite (PVA-1) was obtained starting from the reaction between 1 g PVA-SO_2R (0.000365 mol), 1.177 g chloro-propyltriethoxysilane (0.00488 mol), 0.9 g (0.00436 mol) of ibuprofen, and the stoichiometrically amount of water in ethanol (pH = 5), at room temperature for 72 h.

2.3 Measurements

FTIR spectrum was performed on a Bruker Vertex 70 instrument, in the 400–4000 cm^{-1} region, 64 scans, at room temperature, using the KBr pellet technique and the Opus 5 FTIR Software. The SEM micrographs were obtained with a Quanta 200 scanning probe microscope, the specimen being fixed with adhesive past on Al conducting support of cylindrical shape and then sputter-coated with gold. The fluorescence spectra were obtained at room temperature (without correction) with an equipment containing a double monochromator with diffraction network of the GDM-1000 type, a compensatory printer of the K-201 type and a selective amplifier. The absorbance measurements were made using a UV/vis Specord M42 spectrophotometer.

3. Results and discussion

Through sol-gel reaction between chloro-propyltriethoxysilane and PVA modified with a fluorescent dye (LRSC), in the presence of ibuprofen, a new type of hybrid composite was obtained. In a first step, the synthesis of the precursor starting from PVA and LRSC (20 % w/w) was established, process followed by the sol gel reaction of chloro-propyltriethoxysilane with PVA precursor, in the presence of ibuprofen, at pH = 5.

The FTIR spectrum of PVA-SO_2R-IB derivative is shown in Fig. 1. As follows, a characteristic strong and broad band appeared at around 3434 cm^{-1} corresponding to O–H stretching vibrations of the hydroxyl groups due the strong hydrogen bond of intramolecular and intermolecular type [8]. Moreover, one peak around 3800 cm^{-1} attributed to silanol (isolated and geminal) groups can be distinguished, while the vicinal ones and the physical adsorbed water are characterized by adsorption bands in the range 3000-3800 cm^{-1}. The C-H alkyl stretching band can be observed between 2854-2954 cm^{-1}. The absorption peak from 1708 cm^{-1} may be attributed to the stretching vibration of C = O of pure ibuprofen. The shift of the carbonyl band (from 1732 cm^{-1} – molecularly dispersed ibuprofen) to the lower wavenumber region is caused by the complexation *via* hydrogen bonding between carboxyl from ibuprofen and the OH group of PVA-SO_2R-IB derivative, leading to the formation of a stable complex. The typical OSO_2 bands appeared at 1344 and 1115 cm^{-1}.

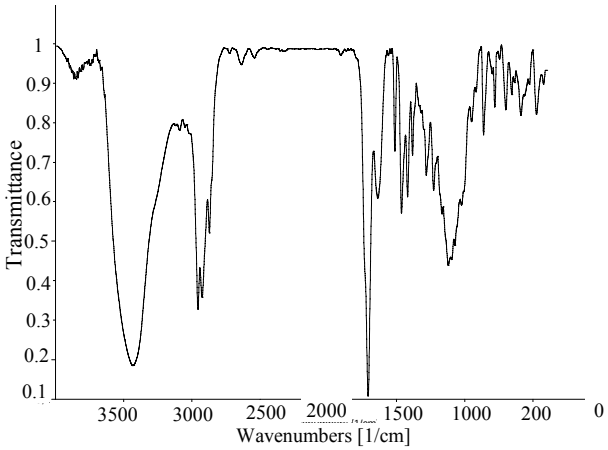

Fig. 1. FTIR spectrum of PVA-SO_2R-IB hybrid composite.

The γ_{as}(Si-O-Si) modes (1096 cm^{-1}) are the result of condensation reaction between hydrolyzed silanol Si-OH groups. At the same time, Si-O-C groups (1043 cm^{-1}) may be originated from the condensation reaction between Si-OH groups from hydrolyzed chloro-propyltriethoxysilane and C-OH groups from PVA. Hence, the presence of Si-O-C and Si-O-Si bonds confirmed the existence of covalent linkage between the organic groups and the silica, which led to better compatibility and crosslinking network between organic and inorganic components.

In the silica structure, three types of particles organization can be distinguished. At the smallest size scale, quasi-spherical primary particles are found ranging from 3-500 nm in diameter, these ones controlling the specific surface area of the powder. Under the effect of colloidal forces, the primary particles are clustered to form disordered aggregates at the 0.1 μm size scale. Typically, aggregates are further linked to form agglomerates that extend up to hundreds of μm in size. The dimension of the primary particles, as well as the density and the aggregation and agglomeration degrees influence the porosity and the specific surface of the silica. SEM characterization was conducted in order to evaluate the morphology of the hybrid composites. SEM micrographs of PVA-SO_2R-IB hybrid composite at different resolutions are presented in Fig. 2. SEM analysis showed a randomly oriented fibers network without interconnected pores in the diameter range 1-2 μm. The morphology is best described by the presence of silica clusters of micrometric dimensions dispersed in PVA organic matrix.

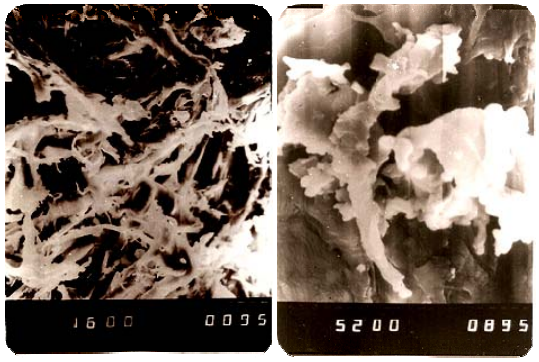

Fig. 2. SEM images of PVA-SO_2R-IB hybrid composite at different resolutions: (a) X 1600, (b) X 5200.

In Fig. 3 the fluorescence spectra of LRSC and both rhodamine derivatives (PVA-SO_2R and PVA-SO_2R-IB) in buffer solution (pH = 7.2) can be observed. Fluorescence spectra were recorded at λ = 568 nm (absorption maximum of LRSC in UV spectrum). All spectra appear to be red-shifted (more than 15 nm) compared with the corresponding LRSC absorption maximum. Such Stokes shift for structures of rhodamine type can be ascribed to the onset of fluorescence resonant-energy transfer (FRET) between the LRSC molecules distributed along PVA chains, a similar process being observed for rhodamine 6G molecules in poly(vinyl alcohol) [9]. FRET is a process by which excitation energy is transferred from an excited donor to an acceptor (due to long-range dipole–dipole interactions between the donor and acceptor - similar or dissimilar molecules) and takes place without appearance of photon. The process is generally experimentally manifested in simultaneous quenching of the donor fluorescence and electronic excitation of the acceptor

[10,11]. All spectra appear to be blue-shifted (3-7 nm) compared with the corresponding LRSC emission maximum, thus evidencing the presence of rhodamine dimers. The „sholder" appeared at arround 570 nm can be assigned to rhodamine maximum absorbance.

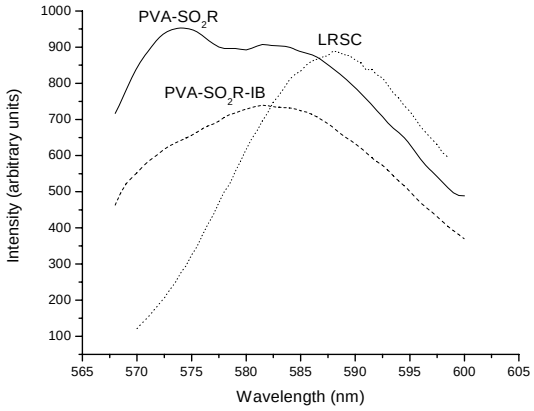

Fig. 3. Fluorescence spectra of LRSC and rhodamine derivatives (PVA-SO_2R, PVA-SO_2R-IB) in buffer solution (pH = 7.2).

The monitoring of 221 nm ibuprofen absorbance in the UV spectrum (Figure 4) evidence the increase of this value after 144 hours of immersion in buffer solution (pH = 7.2), this behavior being attributed to the increase of the molar extinction coefficient of ibuprofen in solution as comparative to the value in solid state; as a consequence, the ibuprofen release can be taken into account, being known that complexation of a drug often results in a small shift of UV absorption maximum and modification of molar extinction coefficient.

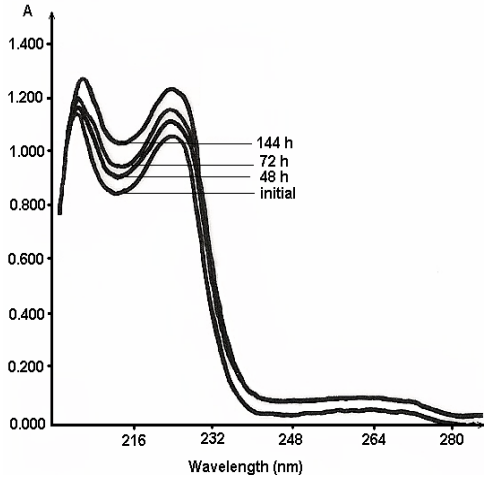

Fig. 4. Variation in time of ibuprofen absorbance in the UV spectrum (221 nm) in buffer solution (pH = 7.2).

4. Conclusions

The technique based on sol-gel polymerization described in this paper represented a versatile synthetic approach to obtain hybrid composites with tailor-made composition of both the organic core and the silica or organo-silica shell. Thus, were obtained silica clusters of micrometric dimensions dispersed in PVA organic matrix. Due to rhodamine content, much information may be obtained concerning the structural changes and the microenvironment surrounding the drug in the macromolecules. The resulting PVA-based compound allowed a sustained drug delivery for a longer period of time (144 hours), therefore such type of hybrid composites could function as platforms for controlled drug delivery.

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