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Influence of chitosan/clay in drug delivery of glucantime from PVP membranes

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HIGHLIGHTS

- Hydrogels from PVP and chitosan were processed by radiation.
- Addition of organoclay caused decrease of swelling.
- The system PVP/chitosan/clay has slower kinetic for glucantime drug delivery.

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ABSTRACT

Polymeric hydrogels are receiving much attention in the past few years, as intelligent materials due to their properties for biomaterials. In this work, hydrogels of poly(N-2-vinil-pirrolidone) (PVP) containing chitosan and clay nanoparticles were obtained and characterized for glucantime drug delivery. The matrixes were crosslinked by gamma irradiation process with doses of 25 kGy. Hydrogels morphologies were observed by a Scanning Electron Microscope (SEM). The structural properties of the network were determined by gel fraction and swelling kinetic at 22 °C to study the capacity of water retention and, finally, drug delivery tests were performed "in vitro". The system showed higher gel fraction for the matrix with 1.0% of clay. In this case, besides the interactions of clay ions with PVP, there were interactions of chitosan with PVP. The results of glucantime delivery at the chitosan/PVP and clay system were discussed.

1. Introduction

Hydrogels are a crosslinked network of hydrophilic polymers, the development of which has been increasing in scientific areas for a long time (Jagur-Grodzinzki, 2010). Hydrogels are a further example of modified drug release devices. Examples of that were hydrogels used for controlled release of drugs made through nanogels and microgel (Julien et al., 2008; Rosiak et al., 2003). The use of radiation processes to polymeric crosslinking of those hydrogels was reported (Jagur-Grodzinzki, 2010). Recently, hydrogels of nanocomposites with clays have been the focus of interest of many researchers (Peng et al., 2009). These represent a rational alternative to conventional polymeric materials, employing a small percentage of clay to improve mechanical properties, good transparency, thermal stability, low gas permeability (Imran et al., 2010; Oliveira et al., 2012), including the high capacity of clays to adsorb different substances (Norma et al., 2005).

This new class of polymeric materials was designed to modify the drug function of the dosage form and to control the release of active ingredient (Cole et al., 1995). The majority of controlled-release dosage forms can be categorized as matrix, reservoir or osmotic systems (Vermani et al., 2002). In matrix systems, the drug is embedded in the polymer matrix and the release takes place by partitioning of the drug into the matrix and the release medium (Efentakis and Politis, 2006). It may be characterized as a mass transport phenomenon. In contrast, reversion systems have a drug core surrounded by a rate controlling membrane such as coated products and implants. An increase in hydrostatic pressure drives osmotic devices and forces the drug solution or suspension out of the device through a small delivery pore (Thombre et al., 2004).

Investigations have been made using the laponite RD in hydrogel membranes for treatment of injuries caused by

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Leishmania. The cutaneous Leishmaniasis, caused by a protozoan of the genus Leishmania transmitted by mosquitoes *Phlebotomine*, is clinically characterized by prolonged fever, paleness, weight loss and difficult healing wounds of the skin. In the urban area, dogs are the main source of infection. Man is included in the epidemiological cycle as a possible host, but in epidemic areas he can be considered a reservatory or a vector of transmission (Amato et al., 2007).

Pentavalent antimonials, such as meglumine antimoniate (Glucantime®) or sodium stibogluconate (Pentostam®), are the main drugs recommended in the treatment of all forms of Leishmaniasis (Singh and Sivakumar, 2004). Other alternative drugs used in the treatment are pentamidine and amphotericin B, but their use has been limited by high toxicity and cost (Murray, 2001). Despite several gaps in the knowledge of action, toxicity and pharmacokinetic parameters, pentavalent antimonials have been used for over 60 years (Roberts et al., 1998). The definition of its pharmacokinetic profile may suggest a better therapeutic protocol for doses, administration interval and duration of the antimonial therapy reducing the severe side effects (Borborema et al., 2005).

In this work, hydrogels were formulated with polyvinyl alcohol (PVAl)/chitosan and nanostructured with clays in order to enable controlled release systems of high efficiency.

2. Materials and methods

Poly(N-2-vinyl-pyrrolidone) (PVP), K-90 by BASF, agar by Oxoid, chitosan and clay laponite RD coding S/1116/10 provided by Buntech were used. The membranes were processed according to IPEN protocol of hydrogel crosslinking by gamma irradiation in ^{60}Co source using 25 kGy dose.

2.1. Swelling

Hydrogels membranes previously dried were immersed in distilled water and weighed periodically until 30 h. The swelling was calculated according to

$$S(\%) = (ms - md)/md \times 100(\%\ H_2O \text{ per g hydrogel}) \quad (A)$$

where ms is the mass of swelled polymer and md is the mass of the hydrogel.

2.2. Gel fraction

The gel fraction was obtained by immersion of the sample in water at around 100 °C, for 12 h until the extraction, under stirring. The water was replaced after every 4 h. After that the samples were dried in oven (100 °C) and the gel fraction was calculated by

$$\text{Gel fraction} = mf/ms \times 100 \quad (B)$$

where ms is the mass before extraction and mf is the mass of the dried sample after extraction.

2.3. Scanning electron microscopy (SEM)

For morphological investigation, Scanning Electron Microscopy (SEM) was done using an EDAX PHILIPS XL 30. In this work, gold sputter-coated layer was deposited onto the samples of nonconducting materials.

3. Results and discussion

3.1. Swelling

A very important characteristic of a hydrogel is swelling; the rate of swelling is determined by various physical and chemical parameters and the type of porous structure formed by molecular interactions during crosslinking. During the process intramolecular crosslinking of ether and OH chitosan molecule and the intermolecular interaction between the amino group of chitosan and the hydroxyl PVP as reported previously were favored (Srivastava et al., 2010). Generally the swelling of hydrogels depends on the rearrangement of the molecules and is related to the functional groups present along the polymer chain. It can be seen from Fig. 1 that swelling of hydrogel decreased in the order: PVP/chitosan/clay < PVP/clay < PVP/chitosan, showing that the clay other than chitosan interferes directly in the swelling.

3.2. Gel fraction

Comparing the systems PVP/clay, PVP/chitosan and PVP/chitosan/clay, higher gel fraction for PVP/chitosan and clay was observed. It corroborates with the results of swelling and showed that clay directly interferes with the crosslinking mechanism, Table 1. It is assumed that the radicals formed by irradiation have favored intramolecular bonds of chitosan with higher rearrangement of the molecules during the crosslinking and also have influenced the intermolecular interactions between the amine groups of chitosan and the amine groups of PVP, as shown in Fig. 2.

3.3. Scanning electron microscopy (SEM) and energy dispersive spectroscopy (EDS)

The hydrogels can be categorized into five classes: non-porous, nanoporous, microporous, macroporous and superporous (Fariba

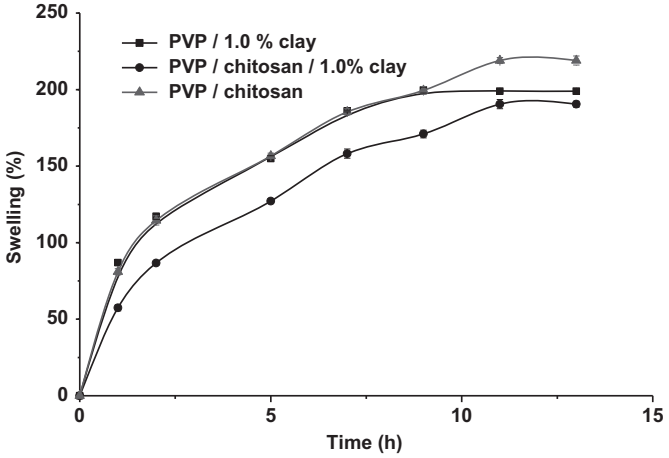

Fig. 1. Swelling curves of hydrogels PVP/clay, PVP/chitosan/clay and PVP/chitosan, obtained by gamma irradiation at 25 kGy dose.

Table 1
Gel fraction mean content and standard deviation of dried hydrogels PVP/chitosan/clay laponite RD obtained by gamma irradiation.

Samples	Gel fraction (%)
PVP/clay 1.0%	67.0 ± 0.5
PVP/chitosan	67.8 ± 1
PVP/chitosan 0.5%/clay 1.0%	72.5 ± 2

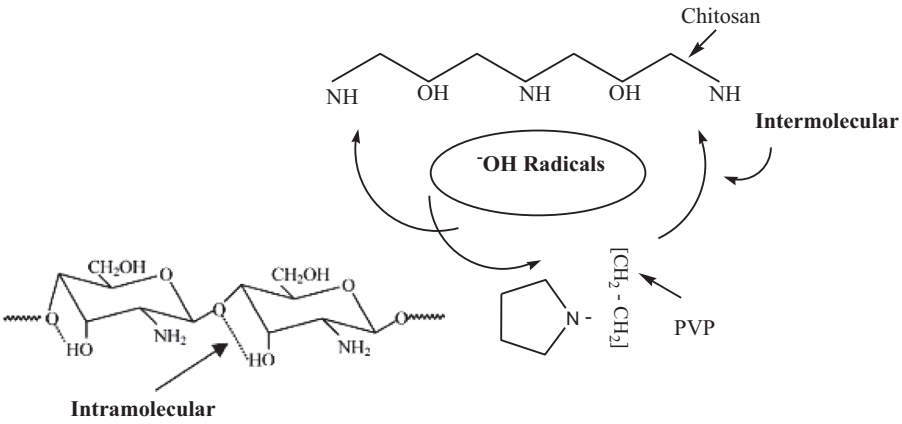

Fig. 2. Simulation of molecular interactions after crosslinking of N-vinyl-2-pyrrolidone with chitosan.

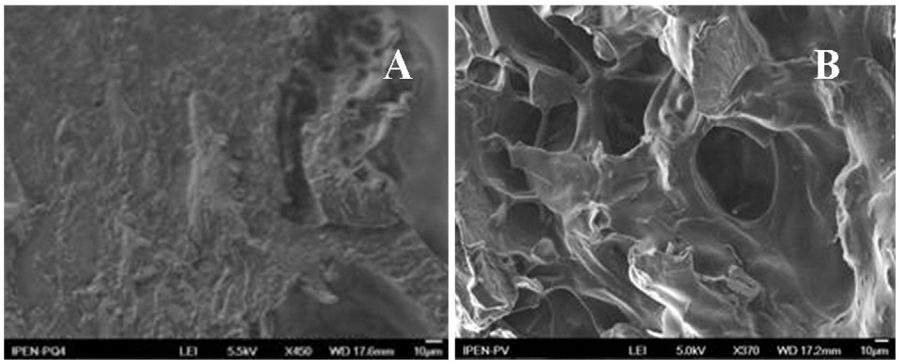

Fig. 3. SEM images (A) of dried PVP/chitosan hydrogel and (B) dried PVP/chitosan hydrogel with 1.0% of clay laponite RD obtained by gamma irradiation at 25 kGy dose.

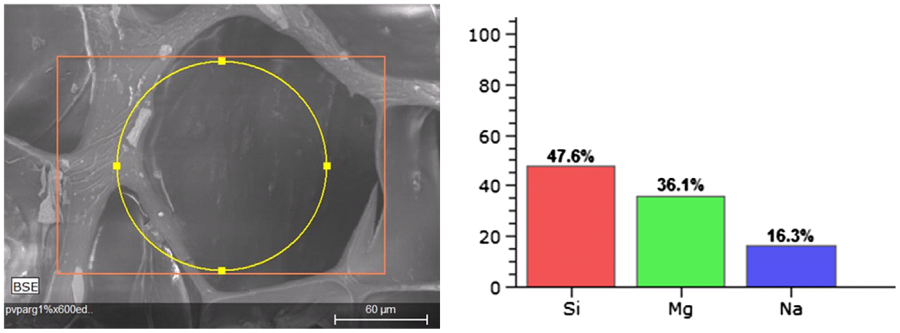

Fig. 4. Microscopy and EDS of lyophilized hydrogel PVP/1% clay obtained by gamma irradiation at 25 kGy dose.

et al., 2010). In Fig. 3, a micrograph of hydrogel PVP/clay with homogeneous regions and few disorganized porous PVP/chitosan/clay hydrogel presenting superporous structure, followed by macroporous structure, and microporous structure which was more organized with homogeneous regions, is observed.

Figs. 4 and 5 present the EDS with percentages of silicon ions, sodium and magnesium in the samples of PVP/clay and PVP/chitosan/clay. Different distributions in accordance with the matrix composition confirmed the presence of clay in the matrix.

3.4. FTIR

FTIR spectra in Fig. 6 show two strong peaks at 3390 cm^{-1} and 1641 cm^{-1} attributed to OH stretching vibration and C=O vibration, respectively. It was observed that the spectra of PVP/clay and PVP/chitosan/clay showed variations in the intensity of the OH and NH stretching vibrations. The peak at 1580 cm^{-1}, characteristic of chitosan NH, disappeared due to the increase of the stretching vibration peak intensity in the region 1641 cm^{-1}, indicating the participation of hydroxyl groups and amino groups in the chemical reaction. The crosslinking of the hydrogel matrix is confirmed by absorption peak of 1641 cm^{-1}, due to vibration and elongation of characteristic C=O peak. The peak at 1066 cm^{-1} is characteristic of COC. The peak at 964 cm^{-1} is characteristic of Si–O–Si and did not change.

3.5. Glucantime drug delivery

According to Ikada et al. (1994), the area available for diffusion of the solute is the free space that exists between the macromolecular chains. The more crosslinked is a hydrogel, the smaller are the spaces between them. When the spaces between the chains are filled with water or biological fluids, reaching swelling equilibrium, these chains lengthened and the smaller particles will

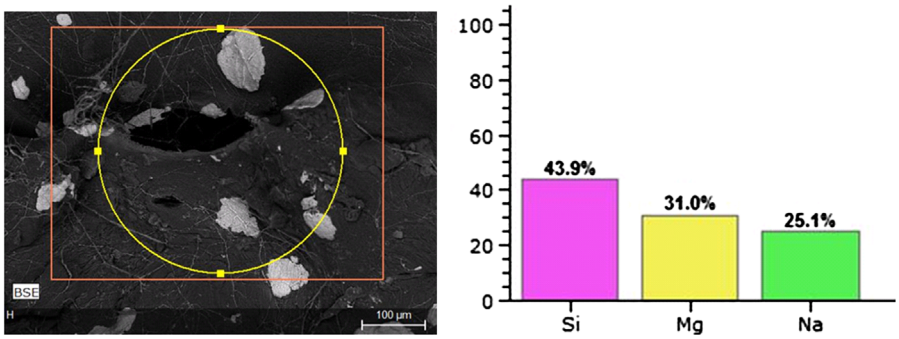

Fig. 5. Microscopy and EDS of lyophilized hydrogel PVP/chitosan/1% clay obtained by gamma irradiation at 25 kGy dose.

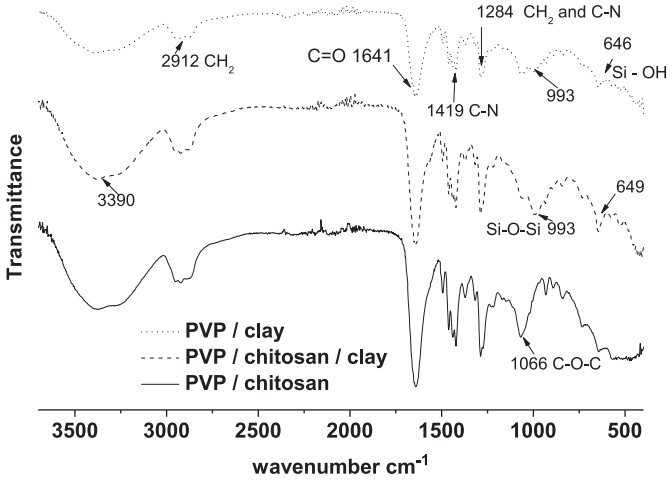

Fig. 6. FTIR spectra of PVP/clay, PVP/chitosan/clay and PVP/chitosan hydrogels, obtained by gamma irradiation, dose 25 kGy.

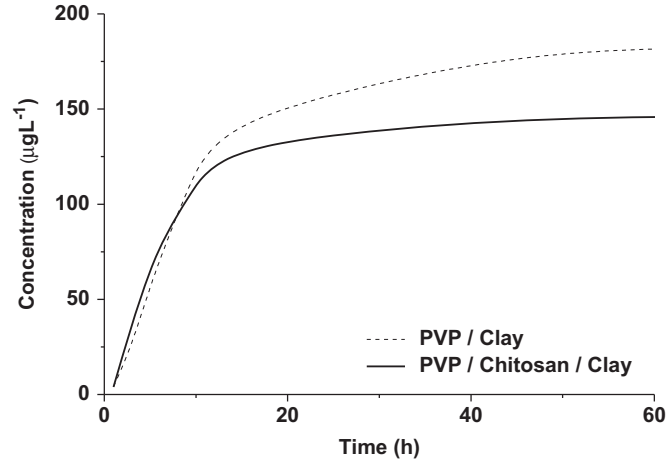

Fig. 7. Drug release of glucantime of hydrogels PVP/clay and PVP/chitosan/clay, obtained by gamma irradiation, dose 25 kGy.

diffuse out of the hydrogel matrix. It is observed in Fig. 7 that after 10 h the release is equilibrated in PVP/chitosan/clay, and is lower compared to the PVP/clay system. Between PVP/clay and PVP/chitosan/clay an increase in crosslinking is observed and probably the clay reduces the spaces between polymeric chains in the hybrid material of hydrogel nanocomposites.

4. Conclusion

As shown by swelling and the gel fraction, the highest crosslinking occurred for PVP/chitosan/1.0% clay. It was assumed that the drug release in the PVP/clay system and PVP/chitosan/clay depends on the swelling. Therefore, minor release is presented by PVP/chitosan/clay, which is associated to the crosslinking between PVP and chitosan, and is hampered by clay.

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