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Modification of medical grade PVC with N-vinylimidazole to obtain bactericidal surface

H. Iván Meléndez-Ortiz [a,*], Carmen Alvarez-Lorenzo [b], Angel Concheiro [b], Víctor M. Jiménez-Páez [c], Emilio Bucio [c]

[a] Departamento de Materiales Avanzados, Centro de Investigación en Química Aplicada, Blvd. Enrique Reyna Hermosillo, # 140, Saltillo, Coahuila 25294, México

[b] Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

[c] Departamento de Química de Radiaciones y Radioquímica, Instituto de Ciencias Nucleares, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, México D.F. 04510, México

HIGHLIGHTS

- Grafting of poly(N-vinylimidazole) onto medical grade poly(vinylchloride) catheters.
- Determination of reaction conditions to carry out the grafting with gamma rays.
- Modified PVC catheters show antimicrobial activity.
- PVC-g-VIm catheters may be suitable for the development of new medical devices.

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ABSTRACT

N-vinylimidazole (VIm) was grafted onto medical-grade poly(vinyl chloride) (PVC) catheters in order to provide a bactericidal surface that make them less susceptible to microbial colonization. The grafting of VIm was carried out by means of gamma rays using the direct method, which demonstrated to be an efficient and fast procedure for obtaining PVC-g-VIm copolymers. These copolymers could be quaternized in a second step using methyl iodide (CH_3I). The effects of solvent nature, absorbed dose, and monomer concentration on the grafting yield were investigated. Modified PVC catheters were characterized by means of Fourier transform infrared spectroscopy (FT-IR), thermogravimetry (TGA), and swelling studies. PVC-g-VIm copolymers both before and after quaternization showed good hemocompatibility, while quaternization was required to inhibit the growth of *Staphylococcus aureus*.

1. Introduction

Poly(vinyl chloride) (PVC) has been extensively used for the fabrication of biomedical devices and is employed in applications including urinary catheters, blood storage bags, and blood tubing in extracorporeal circuits (Lafarge et al., 2013; Zhong et al., 2013; Rahman and Brazel, 2004; Lamba et al., 2000). However, the extensive use of biomedical devices has led to an increased concern on the morbidity associated to biomaterial-related infections. Various strains of bacteria are capable of adherence and proliferation on the biomaterial which may result in a focus of infection while inserted or implanted in the body (Zilberman and Elsner, 2008; Triandafillu et al., 2003). Catheter-associated urinary tract infections affect around of 450,000 patients each year in the United States (Klevens et al., 2007). Hence, there is a definite need for materials with antimicrobial activity able to prevent microbial cell adhesion and consequently biofilm formation.

The most common strategy for preventing or reducing pathogen colonization and further biofilm formation involves the incorporation of antimicrobial drugs into polymer bulk or adsorption onto the surface (Islas et al., 2015; Li et al., 2014; Asadinezhad et al., 2010; Gupta et al., 2007). Nevertheless, this method has some drawbacks such as difficulties in the incorporation of drugs into the polymer matrices, the occurrence of burst during the drug-release process or the microbial colonization when the drug is exhausted. A different approach is the coating of the biomaterial with antimicrobial polymers such as those bearing imidazolium groups (Ng et al., 2014; Siedenbiedel and Tiller, 2012; Anderson

* Corresponding author. Fax: +52 844 438 9839.
E-mail address: hector.melendez@ciqa.edu.mx (H.I. Meléndez-Ortiz).

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and Long, 2010). In this case, the biocide effect is obtained without releasing antimicrobial drugs to the surrounding cells of the host. Also, the use of antimicrobial polymers reduces the probability of generating microbial resistance. However, a careful balance between antimicrobial features and biocompatibility should be attained; in this context, covalent grafting of the antimicrobial polymer to the substrate is preferred as it can provide permanent protection without migration to surrounding tissues.

Polymers containing imidazole rings have potential use in biomedical applications not only due to their biocompatibility but also their antimicrobial activity (Ng et al., 2014; Anderson and Long, 2010; Soykan et al., 2005). Previous works have reported the modification of chitosan derivatives with N-vinylimidazole (VIm) and the resulting copolymers showed certain antimicrobial features (Yalinca et al., 2013; Sabaa et al., 2010; Caner et al., 2007). On the other hand, radiation-induced graft polymerization enables the tuning of desirable properties into biomaterials (Higa et al., 2014; Munoz-Munoz et al., 2014, Vázquez-González et al., 2014). The attractive feature of gamma radiation technique is that the grafting percentage can be modulated by proper selection of radiation conditions. Also, this technique does not require the use of initiators or additives which may be harmful and difficult to remove. In a previous work, PVC catheters were modified with poly (N-isopropylacrylamide) (PNIPAAm) by a pre-irradiation method using gamma rays (Arenas et al., 2007). The resulting copolymer showed to be temperature responsive. Gupta et al. (2007) grafted VIm onto polypropylene monofilaments using the direct method in order to immobilize ciprofloxacin in the imidazole units. The influence of various parameters on the grafting yield of simultaneous grafting of VIm and acrylic acid onto polypropylene and poly(vinyl alcohol) with gamma rays has been also reported, but the antimicrobial activity was not explored (Aji and Alib, 2005; Naguib et al., 2003). As far as we know, there is no report about the grafting of VIm onto PVC. Therefore, the main aim of the present work was to identify the adequate conditions for the grafting of VIm onto medical-grade PVC catheters via γ-ray irradiation. Hemocompatibility and antimicrobial activity against *Escherichia coli* (Gram-negative bacteria) and *Staphylococcus aureus* (Gram-positive bacteria) were evaluated for the obtained PVC-g-VIm copolymers and their quaternized analogues.

2. Experimental section

2.1. Materials

Poly(vinyl chloride) (PVC) urinary catheters (diameter 3 mm, thickness 0.5 mm; Biçakcilar, Turkey) were washed with ethanol for 24 h and then dried under reduced pressure. N-vinylimidazole (VIm; Aldrich, St. Louis MO, USA) was distilled under reduced pressure before use. The solvents used were acetone, dioxane, and methanol (MeOH) from J.T. Baker (Mexico) and distilled water (H_2O). Methyl iodide (CH_3I) was obtained from Aldrich (St. Louis MO, USA).

2.2. Synthesis of PVC-g-VIm

PVC-g-VIm was prepared via the direct method by placing pieces of 2.5 cm PVC catheters (previously weighed) in glass ampoules containing a solution of VIm in a range of concentration from 25 to 100 (vol%). In the preparation of these solutions, different solvents were chosen according to the solubility of both PVC and VIm. An appropriate solvent is that able to solubilize VIm but not PVC catheter. In this way, solvent or solvent mixtures of MeOH, dioxane, acetone, or H_2O were used.

Then, the solution was degassed by bubbling argon during 15 minutes and the ampoule was sealed. After that, ampoules were irradiated with a ^{60}Co γ-source (Gammabeam 651 PT, Nordion International) at irradiation doses from 20 to 100 kGy and a dose rate of 10.5 kGy h^{-1}. The grafted catheters were extracted with MeOH and then with H_2O in order to remove the residual monomer and the homopolymer generated during grafting process. Then, the grafted PVC catheters were dried under reduced pressure and the grafting percentage was calculated as follows:

$$\text{Grafting percentage (\%)} = 100\left[(W_g - W_0)/W_0 \right] \quad (1)$$

where W_g and W_0 are the weights of the grafted and pristine PVC catheters, respectively.

Preparation of PVC-g-VIm via the pre-irradiation method was also attempted. To do that, pieces of PVC catheters (2.5 cm length) were placed in glass ampoules which were then irradiated in the presence of air at 50 kGy and a dose rate of 10.5 kGy h^{-1}. After that, a solution of VIm in the appropriate solvent (50% v/v) was added into the ampoules. After that, the ampoules were degassed by bubbling argon during 15 min and then sealed. The ampoules were heated at 60 °C to carry out the grafting process. Finally, the grafted catheters were extracted as mentioned above.

2.2.1. Quaternization of PVC-g-VIm copolymers

The grafted PVC catheters were immersed in CH_3I solution in MeOH (5 and 10% v/v) and kept from 15 to 300 min under stirring and protected from light at room temperature. Then, quaternized PVC-g-VIm catheters were washed with MeOH and H_2O in turn in order to remove the unreacted CH_3I (Contreras-García et al., 2011). The quaternized PVC catheters were dried under vacuum to constant weight and the degree of quaternization (DQ) was estimated as follows:

$$\text{DQ(\%)} = 100\left[(W_3 - W_2)/(W_2 - W_1)(94.1/141.9) \right] \quad (2)$$

where W_1, W_2, and W_3 represent the weights of pristine PVC, PVC-g-VIm and PVC-g-VIm quaternized catheters, respectively while 94.1 and 141.9 correspond to the molecular weight of VIm and CH_3I, respectively.

2.3. Characterization of PVC-g-VIm

FTIR-ATR (attenuated total reflection) spectra were recorded using a Perkin-Elmer Spectrum 100 spectrometer (Perkin Elmer Cetus Instruments, Norwalk, CT, U.S.A.). For determination of equilibrium water uptake, the graft copolymers were immersed into distilled water for various periods of time. Equilibrium water uptake was achieved after 10 h. The pH-responsiveness was determined by measuring the degree of swelling of PVC-g-VIm catheters in citric acid (0.05 M) and boric acid (0.2 M)/$Na_3PO_4 \cdot 12H_2O$ (0.1 M) buffer solutions of pH ranging from 2 to 12 during 10 h. Swelling study started at the highest pH value finishing at the lowest one. At certain pH values, the surface of the copolymers was wiped with filter paper to remove the free buffer solution and then the swollen samples were weighed. Swelling percentages were determined from the weights of the swollen (W_s) and dried (W_d) modified PVC catheters as follows:

$$\text{Swelling(\%)} = 100\left[(W_s - W_d)/W_d \right] \quad (3)$$

TGA studies were carried out to know the effect of the grafting process on the thermal stability of the PVC catheters. TGA studies were determined under nitrogen atmosphere using a Q50 (TA Instruments, New Castle, DE) from 25 to 800 °C at 10 °C min^{-1}