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Radiation-grafting of acrylamide onto silicone rubber films for diclofenac delivery

Hector Magaña [a,1], Kenia Palomino [a,1], Jose M. Cornejo-Bravo [a,*], Carmen Alvarez- Lorenzo [b], Angel Concheiro [b], Emilio Bucio [c,*]

[a] Facultad de Ciencias Químicas e Ingeniería, Universidad Autónoma de Baja California, Calzada Universidad 14418, Parque Industrial Internacional Tijuana, 22390 Tijuana, Baja California, 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 DF 04510, México

HIGHLIGHTS

- SR–g-AAm depends on dose, monomer concentration, and reaction time and temperature.
- Diclofenac sodium salt is loaded and released in a sustained way from SR–g-AAm films.
- SR–g-AAm films are cytocompatible and have potential as components of drug–device.

GRAPHICAL ABSTRACT

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ABSTRACT

This work focuses on the pre-irradiation grafting of acrylamide (AAm) onto silicone rubber films (SR) and evaluates the effect of gamma-ray radiation conditions on the grafting yield, which in turn may influence the performance of the grafted materials as components of drug-eluting devices. Pristine and modified SR were characterized using FTIR-ATR, DSC, TGA, swelling, and water contact angle analysis in order to elucidate the effects of AAm grafting onto SR. Grafted films with content in AAm ranging from 0.81% to 22.20% showed excellent cytocompatibility against fibroblasts, and capability to uptake the anti-inflammatory drug diclofenac. Amount of drug loaded directly correlated with the grafting degree of the films. Drug release studies were performed at pH 7.4 and 37 °C (physiological conditions). Most grafted films released the drug in a sustained way for at least three hours.

1. Introduction

Drug–device combination products find a wide range of applications, either for avoiding adverse reactions associated to the use of implantable medical devices or for making it possible the local delivery of drugs to hardly accessible sites (Couto et al., 2012;

* Corresponding authors. Fax: +52 55 56224707.
E-mail addresses: jmcornejo@uabc.edu.mx (J.M. Cornejo-Bravo), ebucio@nucleares.unam.mx (E. Bucio).
[1] These authors contributed equally to this work.

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Shaikh et al., 2013). Possibility of obtaining synergic therapeutic effects has prompted an intense research on methods of loading sufficient amount of drugs and of controlling their release from the medical device (Alvarez-Lorenzo et al., 2010; Concheiro and Alvarez-Lorenzo, 2013; Vazquez-Gonzalez et al., 2014). In addition to compounding, surface modification of materials commonly used to prepare the medical devices is attracting increasing attention as a way to provide binding points to drugs and to regulate protein and cell adsorption (Elbert and Hubbell, 1996; Burt and Hunter, 2006). Antimicrobials, anti-inflammatory and anti-proliferative drugs, and anticoagulant agents are suitable candidates for delivery by means of medical devices for both prophylactic and therapeutic purposes (Mao et al., 2004). Once in the target site, drug release can occur by simple diffusion (Nava-Ortíz et al., 2009), in response to environmental stimuli such as temperature (Li et al., 1999) and/or pH (Muñoz-Muñoz et al., 2012), or can be triggered by the presence of microbes (Segura et al., 2014).

Radiation-induced graft polymerization is a convenient and powerful technique for surface modification of polymer-based medical devices, with important advantages over other conventional methods, such as chemical and photochemical grafting (Meléndez-Ortiz et al., 2009; Alvarez-Lorenzo et al., 2010). This technique is applicable for many polymer/monomer combinations and, unlike chemically initiated grafting; there is no contamination from initiators (Chapiro, 1977; Vahdat et al., 2007). When polymers are exposed to ionizing irradiation, trapped radicals and peroxides or hydroperoxides are formed and remain ready for initiating grafting copolymerization reactions (Bucio and Burillo, 2009; Contreras-García et al., 2010; Ramírez-Jiménez et al., 2012). In previous works, copolymers of N-isopropyl acrylamide (NIPAAm) and N-(3-aminopropyl) methacrylamide hydrochloride (APMA) or N,N′-dimethylaminoethylmethacrylate (DMAEMA) were grafted on polypropylene (PP) films by means of a γ-ray preirradiation method in order to provide a surface layer suitable to load non-steroidal anti-inflammatory drugs (NSAIDs) and to control their release under physiological conditions (Contreras-Garcia et al., 2011; Meléndez-Ortiz et al., 2014). Cationic nitrogen groups in APMA and DMAEMA strongly interacted with diclofenac anionic groups; however, difficulties for grafting of positively charged monomers and concerns on cell compatibility prompt the search of alternative monomers that exhibit other mechanisms of interaction. In this sense, it has been previously shown that NSAIDS having C–X bonds (X being a halogen) exhibit affinity to polymers having C=O bonds, mimicking a common type of interaction in Nature (Kamer et al., 2013; Yañez et al. 2011).

The aim of this work was to implement a pre-irradiation oxidative method to graft acrylamide (AAm) onto silicone-rubber films and to enhance the entrapment and release of the anti-inflammatory drug diclofenac, by exploiting the bioinspired interaction of the C=O groups of AAm with the C–Cl groups of diclofenac, while still exhibiting good cytocompatibility.

2. Experimental

2.1. Materials

Silicone rubber (SR; density 1.1–1.5 g cm^{-3}; thickness 1 mm) from Goodfellow (England) was washed with isopropyl alcohol (24 h) and then with dichloromethane (2 h) to remove impurities and finally dried under vacuum at 60 °C. Acrylamide (AAm), sodium chloride and diclofenac sodium salt were from Aldrich Chemical Co. (USA). Sodium phosphate dibasic anhydrous and sodium phosphate monobasic anhydrous were from Millinckrodt Pharmaceuticals (USA).

2.2. Grafting

SR films (1 cm × 2.5 cm) were irradiated with a ^{60}Co gamma source (Gammabeam 651 PT from Nordion Co., Canada) in air, at a dose rate of 13.5 kGy h^{-1} up to absorbed doses between 30 and 100 kGy. Solutions of AAm at various concentrations were prepared in methanol/dichloromethane (MeOH/DCM; 8 mL) and poured into glass ampoules to which the pre-irradiated SR films were added. The ampoules were degassed in a vacuum line by repeated freeze-thaw cycles for 1 h, and then sealed and placed in a water bath at constant temperature. At given time points, the grafted films (SR–g-AAm) were removed from the ampoules, washed with ethanol at room temperature 3 times for 3 h to remove non-grafted homopolymer and residual monomer. Finally, the graft films were dried under vacuum and then placed in an oven at 60 °C until constant weight. The degree of grafting was calculated as follows:

$$Grafting\ (\%) = \frac{w - w_o}{w_o} \times 100$$

where W_o and W are the weights of a SR film before and after grafting, respectively.

2.3. Characterization of SR film and SR graft film

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra of AAm, SR film and SR–g-AAm were recorded with a Perkin-Elmer Spectrum 100 spectrometer (Perkin Elmer Cetus Instruments, Norwalk, CT) with 16 scans, taken over the range of 4000–600 cm^{-1}. Differential scanning calorimetry analysis were carried out in a DSC 2010 (TA Instruments, New Castle, DE) from 25 °C to 400 °C, under nitrogen atmosphere at a flow rate of 60 mL min^{-1} and a heating rate of 10 °C min^{-1}. Thermogravimetric analyses were performed using a TGA Q50 (TA Instruments, New Castle, DE) at a heating rate of 10 °C min^{-1} in the temperature interval from 25 to 800 °C under nitrogen atmosphere. Pristine and grafted SR films were mounted on metal studs and then observed under high vacuum using a scanning electron microscope operated at 1.5 kV (SEM EVO LS 15; Zeiss, Germany), and energy distribution X-ray spectroscopy of the transversal sides was carried out using an EDS (FESEM ULTRA Plus; acceleration voltage of 4 kV). Water contact angle was recorded for 1 min after deposition of a small drop of bidistilled water onto dry films using a drop shape analyzer Kruss DSA 100 apparatus (Matthews NC, USA). Swelling of pristine and grafted films was recorded by placing pieces of the films in 20 mL of bidistilled water. The films were weighted at different times and the degree of swelling was calculated as:

$$Swelling\ (\%) = \frac{W_s - W_d}{W_d} \times 100$$

where W_s is the weight of the swollen film and W_d is the weight of the dry film.

2.4. Diclofenac loading and release

Dried pieces of films (10–20 mg; 1 cm × 0.5 cm) were placed in 5 mL of diclofenac sodium solution (0.5 mg mL^{-1} in water) and kept at 20 °C protected from light for 48 h. The amount of diclofenac sodium loaded by the films was calculated as the difference between the initial and final concentrations in the surrounding solution, from absorbance measurements at 276 nm (UV spectrophotometer Beckman Colter DU 520). Then, the films were dried in an oven at 40 °C. Drug-loaded films (10–20 mg) were transferred to test tubes containing 1 mL of phosphate buffer pH 7.4. The experiments were carried out in a temperature controlled shaker at