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Cyclodextrin-functionalized polyethylene and polypropylene as biocompatible materials for diclofenac delivery

Cesar A.B. Nava-Ortíz[a], Carmen Alvarez-Lorenzo[b], Emilio Bucio[a], Angel Concheiro[b], Guillermina Burillo[a,*]

[a] Departamento de Química de Radiaciones y Radioquímica, Instituto de Ciencias Nucleares, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, México DF 04510, Mexico
[b] Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

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ABSTRACT

Polyethylene (PE) and polypropylene (PP) were surface functionalized with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD) with the aim of providing PE and PP with the capability of behaving as drug delivery systems. Functionalization was carried out according to a two-step procedure: (i) glycidyl methacrylate (GMA) was grafted by means of gamma radiation and (ii) the epoxy groups of GMA reacted with the hydroxyl groups of CDs forming ether bonds. For a fix radiation dose and GMA concentration, grafting yield (ranging from 1 to 100 μmol GMA cm^{-2}) depended on the time during which the preirradiated PE and PP films and slabs were immersed in the GMA solution. CD grafting (from 0.013 to 0.734 μmol cm^{-2}) was confirmed by infrared analysis, DSC and the organic compound approach (using 3-methylbenzoic acid as a probe). Functionalization with CDs rendered as highly cytocompatible materials as the starting ones, did not cause relevant changes in the water contact angle and the friction coefficient of PE and PP, but remarkably improved their capability to uptake diclofenac through formation of inclusion complexes with the CDs. Furthermore, the functionalized materials released the drug for 1 h, which could be useful for management of initial pain, inflammation at the insertion site as well as adhesion of certain microorganisms if these materials are used as medicated medical devices.

1. Introduction

The use of medical devices or prosthesis usually leads to injury, inflammation and wound healing response caused by the implantation event and by the foreign body nature of the material (Anderson, 2001). Friction with the biological tissues during insertion, physiological stress and removal causes damage that prompts the cellular cascade of wound healing, which in turn leads to inflammation, granulation tissue formation and fibrosis or fibrous capsule development. The dimensions of the medical device, its surface properties and the release of leachable substances determine the intensity and time duration of the (acute and/or chronic) inflammatory and wound healing processes (Anderson et al., 2008). Furthermore, the adhesion of macrophages and foreign body giant cells to the medical device reduces the bactericidal capability of these cells and induces their apoptosis, which contributes to the persistence of infections associated to the use of medical devices (Brodbeck et al., 2002). Local inflammation of the tissues results in redness, swelling and pain on pressure at the insertion site and discomfort of the patient (Neuburger et al., 2007). Despite inflammation has received less attention than infection, the deleterious effects of adherent inflammatory cells on the medical devices entails the risk of biomaterial degradation and clinical failure (Anderson et al., 2008). Polyethylene (PE) and polypropylene (PP) undergo surface oxidation by reactive oxygen intermediates released by macrophages and foreign body giant cells when used in artificial joints or as suture material (Anderson et al., 2008). Histology analysis of epidural space tissues during chronic catheterization with PE tubes usually evidences inflammatory responses at the catheter insertion place and, in some cases, the catheter tip is occluded by granulation tissues (Nishiyama and Hanaoka, 1999). The catheter obstruction results in a decrease in the flow of substances with a detriment of the catheter performance.

The design of anti-inflammatory and immunosuppressive drug-eluting devices appears as a feasible way of preventing the initial host immune-inflammatory response (Schneider et al., 2003). Stents coated with anti-inflammatory drugs stay open longer and the treated blood vessels are less likely to restenose (Muller et al., 2002; Pendyala et al., 2009). Similarly for catheters, the anti-inflammatory agent can be provided as a coating, bonded onto the outside or integrally compounded in the matrix of the device (Snorradottir et al., 2009). Catheters with antimicrobial or

* Corresponding author. Tel.: +52 5556224674; fax: +52 5556162233.
E-mail address: burillo@nucleares.unam.mx (G. Burillo).

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antithrombotic coatings have already been clinically tested with satisfactory results (Dwyer, 2008). Those catheters are mainly impregnated with the drug compounds or covered with drug molecules chemically attached to the device surface.

Custom-made design of drug-releasing devices should try to optimize the affinity of the surface towards the drug without prejudice of the bulk properties and performance of the medical device. The aim of this work was to functionalize with cyclodextrins (CDs) the surface of PE and PP, which are common components of biomedical devices (e.g. catheters, meshes, artificial joints or sutures) with a wide range of applications (Cosson et al., 2003). In such a way, any drug capable of forming inclusion complexes with CDs is a potential candidate to be loaded at the surface of the medical device (Loftsson and Duchene, 2007; Temtem et al., 2009). The drug-CD affinity constant may determine the amount loaded as well as the delivery rate when entering into contact with the physiological medium, as observed for hydrogels made with CDs (Siemoneit et al., 2006; Salmaso et al., 2007; Santos et al., 2009). This approach resembles, to some extent, recent attempts to modify natural fibers and synthetic fabrics with CDs in order to load them with odorizants or antifungal agents or to be used as reactive filters (Martel et al., 2002; Hirotsu, 2006). In the present work, CDs were grafted to the surface of PE and PP substrates through a two-step reaction that involves first the radiation grafting of glycidyl methacrylate (GMA) and then the covalent bonding of the CDs. Since information available about this functionalization process is quite limited (Schofield et al., 2006; Nava-Ortiz et al., 2009), the effect of the reaction variables on the yield of grafting of GMA by gamma radiation and on the anchorage of two CDs, β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD), was evaluated in detail using PE and PP sheets of different thickness. The incidence of having pendant CDs on the wettability, the thermal stability and the friction coefficient of the novel materials, as well as on the biocompatibility and the performance as carriers of diclofenac was evaluated in detail. Diclofenac is a widely used non-steroidal antinflammatory drug (NSAID) that can form inclusion complexes with CDs (Dias et al., 2003; Mehta et al., 2008). Thus, a high local proportion of CDs can create a favorable microenvironment for the uptake of the drug and for sustaining its release. Diclofenac has been shown to reduce the number of macrophages and neutrophils found at the implant site (Hunt and Williams, 1992) and to prevent bacterial adsorption on polymer surfaces (Bandare et al., 2004). The information obtained should serve to gain insight into the potential of CD-functionalized materials as components of medical devices.

2. Materials and methods

2.1. Materials

Low density PE (LDPE, 100 μm thickness) and PP (50 μm thickness) films were from PEMEX (Mexico), and high density PE (HDPE) and PP slabs (1 mm thickness) were from Goodfellow (UK). Glycidyl methacrylate (GMA) and 3-methylbenzoic acid (3-MBA) were from Aldrich Chemical Co. USA, and used without further purification. β-Cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD; M.S. 5.6) were supplied by Roquette Laisa España (Barcelona). Diclofenac sodium was from Vorquimica, S.L. (Spain). Ultrapure water (resistivity > 18.2 MΩ cm) was obtained by reverse osmosis (Milli-Q®, Millipore, Spain). Analytical grade solvents such as methanol, acetone, and dimethylformamide (DMF) were used as received.

2.2. Graft polymerization reaction

GMA was polymerized onto PE and PP films (1.2 cm × 4 cm) and slabs (1 cm × 4 cm) by applying an oxidative preirradiation grafting technique. PE and PP were washed with methanol, dried under vacuum at 40 °C for 5 h, and exposed to a ^{60}Co gamma source (Gamma-Beam 651-PT, Nordion Co., Canada) with activity of 63,000 Ci, at a dose rate of 11.3 kGy h^{-1}, at room temperature in the presence of air. The preirradiated films and slabs were placed in glass ampoules which contained 8 ml of 20% GMA in methanol/water (8:2, v/v). The ampoules were degassed by repeated freeze–thaw cycles and vacuum sealed. Then they were heated in a water bath at 60 °C from 0.5 to 14 h. Grafted films and slabs were extracted in methanol for 24 h under stirring in order to remove unreacted monomers and the homopolymer. They were then dried under vacuum at 40 °C. The grafting yield was calculated as follows:

$$Y_g(\text{mg cm}^{-2}) = \left[\frac{W_g - W_0}{\text{area}}\right] \quad (1)$$

W_0 and W_g being the weight of the film or slab before and after grafting, respectively. Grafting determination was carried out in triplicate with typical error ranging from 3% to 7%.

2.3. Immobilization of β-CD and HP-β-CD

Grafted copolymer films and slabs were swollen in 10 ml of DMF for 2 h and then immersed in a mixture of DMF (2 ml) and 0.5 M NaCl aqueous solution (8 ml) that contained β-CD or HP-β-CD. The amount of CD in the medium was equimolar to the GMA content of each piece of film or slab. The systems were kept under stirring at 70 °C for 24 h. The films and the slabs were successively washed with hot water, acetone, methanol and water, and dried under vacuum at 40 °C. Total content in grafted β-CD or HP-β-CD (micromoles per gram) was calculated as follows:

$$Y_{CD} = \frac{W_{CD} - W_g}{W_{CD} \times \text{Mw}_{CD}} \times 10^6 \quad (2)$$

where W_g and W_{CD} represent, respectively, the weight of the GMA-grafted film or slab before and after attachment of CDs, and Mw_{CD} corresponds to the molecular weight of the CD used.

2.4. Content in functional CDs

The number of CD cavities available for complexation was quantified using the typical organic compound (TOC) approach (Fundueanu et al., 2003). Dried films or slabs were immersed in 10 ml of 3-methylbenzoic acid (3-MBA) aqueous solution (0.2 mg ml^{-1}) and kept for 48 h in the dark. The concentration of 3-MBA was spectrophotometrically determined (Agilent 8453, Germany) at 281 nm. The total amount of 3-MBA taken up by the films or the slabs was calculated as the difference between the initial and the final amounts in the solution. The experiments were carried out in triplicate.

2.5. Infrared analysis

FTIR spectra of non-modified films, GMA-grafted films and CD-functionalized films were recorded in ATR mode over the range 500–4000 cm^{-1}, in a MB102 spectrometer (ABB Bomem Inc., Quebec, Canada).

2.6. Thermal analysis

DSC runs of 5–10 mg dried samples were carried out from 30 to 250 °C at 10 °C min^{-1} using a DSC Q100 (TA Instruments, New Castle, DE, USA) fitted with a refrigerated cooling accessory. Nitrogen was used as the purge gas at a flow rate of 50 ml min^{-1}. The calorimeter was calibrated for baseline using no pans, for cell constant and temperature using indium (melting point 156.61 °C,

enthalpy of fusion 28.71 J g^{-1}), and for heat capacity using sapphire standards. The degree of crystallinity was calculated using the following equation:

$$X_C = \frac{\Delta H_m}{\Delta H_m^+} \quad (3)$$

where ΔH_m is the specific enthalpy of melting, and ΔH_m^+ is the specific melting enthalpy for 100% crystalline PE or PP (288 and 209 J g^{-1}, respectively) (Krupa and Luyt, 2001; Adem et al., 2005).

2.7. Scanning electron microscopy

PE and PP films, before and after grafting of GMA and anchorage of β-CD and HP-β-CD, were swollen in water for 48 h at room temperature, frozen by immersion in liquid nitrogen, fractured to an adequate size, freeze-dried for 24 h and covered with Au. The micrographs of the surface were obtained using a SEM at 20 kV (LEO-435VP Microsystems, Cambridge, UK).

2.8. Contact angle

Drop shape analysis system (Krüss DSA 100, Germany) was used to measure water/slab contact angle at room temperature (25 °C). All the slabs were dried under vacuum at 40 °C for 1 day before measurements. Water drops were deposited onto the PE, PP and CD-functionalized slabs surface, and the measurement of the contact angles was directly carried out, in triplicate, using a microscope.

2.9. Friction coefficient

The friction coefficient of slabs was measured, in duplicate, at 25 °C using a Rheolyst AR1000N rheometer (TA Instruments, Crawley, UK) equipped with an AR2500 data analyzer and a Peltier plate. The slabs were cut as disks (10 mm diameter) and glued (Loctite® Super Glue-3, Henkel, Barcelona, Spain) to a 4 cm steel plate geometry. 1 ml of water was put on the surface of the Peltier plate and the geometry was moved towards the plate to an initial gap of 1.3 mm. The experiment consisted of a conditioning step applying 5 ± 0.01 N normal force (W) for 15 min and a peak hold step with an angular velocity of 0.05 rad s^{-1} for other 15 min (Gong et al., 1999). Since the velocity changes with the distance from the center of the axis, the obtained torque, T, is a total value over the velocity range from 0 to ωR, where R is the radius of the disk. Thus, the total friction, F, and the coefficient of friction, μ, were determined as follows (Gong et al., 1999):

$$F = \frac{4T}{3R} \quad (4)$$

$$\mu = \frac{F}{W} \quad (5)$$

2.10. Cytocompatibility

Pieces of 1.2 cm × 0.5 cm of surface-modified and non-modified PP and PE films were immersed in phosphate buffer pH 7.4 and autoclaved. Then, the pieces were added to wells (24 wells plates) containing Balb/3T3 clone A31 cells (200,000 cells per well, 2 ml in Dulbecco's modified eagle medium DMEM F12 HAM, Sigma–Aldrich, USA) and kept in humidified incubator at 5% CO_2 and 37 °C. After 24 h, aliquots (100 μl) of medium were taken and mixed with 100 μl of the reaction medium contained in the Cytoxicity Detection Kit^{PLUS} (LDH, Roche). Blank (100 μl of medium), negative (50 μl of cells and 50 μl of medium) and positive (50 μl of cells and 50 μl of medium with 5 μl of lysis factor) controls were also prepared. The plates were incubated 10 min at 15–25 °C protected from light. 50 μl of stop solution were added to each well and the absorbance at 490 nm immediately measured using an ELISA reader.

The cytotoxicity was estimated as follows:

$$\text{Cytotoxicity}\,(\%) = \frac{\text{Abs}_{\text{exp}} - \text{Abs}_{\text{negative control}}}{\text{Abs}_{\text{positive control}} - \text{Abs}_{\text{negative control}}} \times 100 \quad (6)$$

2.11. Drug 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 (Agilent Technologies 8453, Germany). 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 without stirring under *sink* conditions. The volume of the medium was enough to cover the films and to make the changes in UV–vis absorbance quantifiable. Samples of the release medium were withdrawn at regular intervals (after being gently hand-shaken to ensure a homogeneous concentration in the medium) and returned to the vial immediately after measurement of absorbance at 276 nm. After 48 h in the release medium, the films were washed in water under stirring for 3 h at room temperature. Finally, the films were dried at 40 °C and then reloaded by immersion in diclofenac sodium solution (1 mg ml^{-1}). The release experiments were carried out as described above. All experiments were made in triplicate.

3. Results and discussion

3.1. Grafting of GMA and functionalization with CDs

PE and PP surfaces were functionalized with CDs applying a two-step procedure: (i) GMA was grafted onto the surface by means of gamma radiation and (ii) the epoxy groups of GMA reacted with the hydroxyl groups of CDs forming ether bonds (Fig. 1). Different from the method proposed by Schofield et al. (2006) which involves the use of pulsed plasma polymerization, we used gamma radiation for the grafting polymerization of GMA.

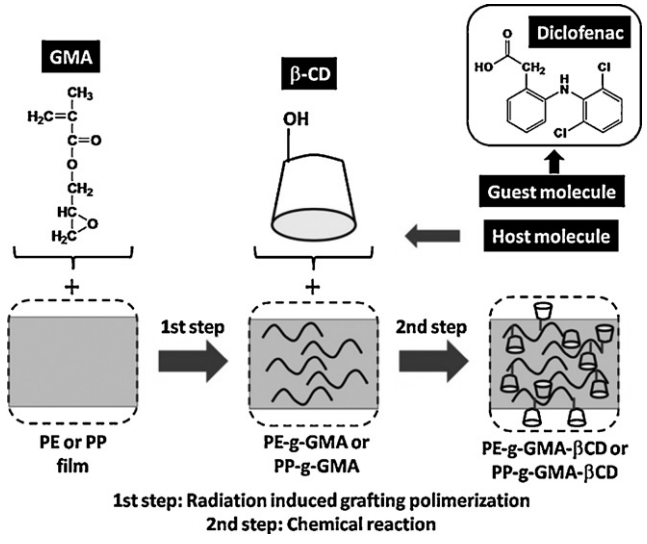

Fig. 1. Steps followed to functionalize PE and PP surfaces with cyclodextrins.

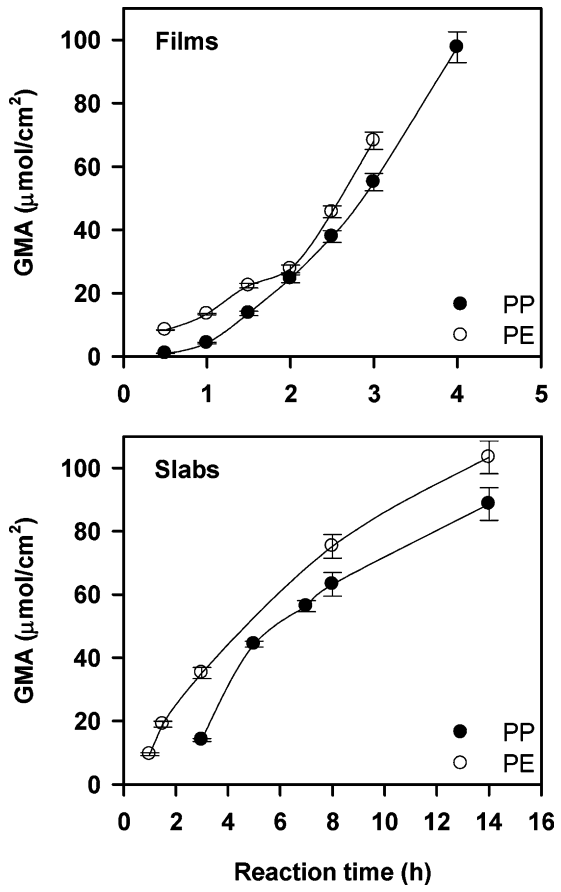

Fig. 2. Yield of GMA grafting onto PE and PP films and slabs as function of reaction time at 60 °C.

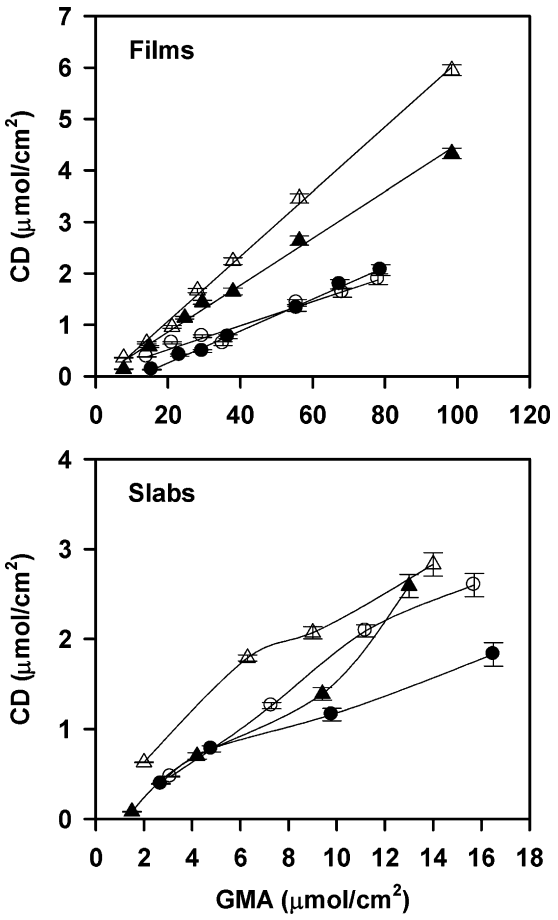

Fig. 3. Amount of β-CD (open symbols) or HP-β-CD (full symbols) immobilized onto PE-g-GMA (circles) and PP-g-GMA (triangles) films and slabs.

When PE and PP are exposed to ionizing radiation in air, trapped peroxy radicals are formed. The greater the radiation dose, the higher the likelihood of creating radicals capable of serving as reactive sites in the polymer structure. In a previous paper, the effects of radiation dose and GMA concentration on the amount of GMA grafted to PE were studied (Nava-Ortiz et al., 2009). For a fix dose rate of 11.3 kGy h^{-1}, radiation doses between 50 and 200 kGy were adequate for the grafting of GMA. Furthermore, 20% GMA was shown as the concentration that enables the highest yield of grafting with the lowest loss by homopolymerization. Therefore, 100 kGy and 20% GMA were chosen to carry out the present work. There was no cross-linking of PP or PE, nor of GMA chains, at this radiation dose.

The time during which the preirradiated PE and PP films and slabs were immersed in the GMA solution remarkably determined the grafting yield (Fig. 2). The degree of grafting was higher for PE than for PP, owing to the higher crystallinity of PP which makes the copolymerization reaction more difficult. In the case of the films, the grafting yield of GMA increased up to 4 h. Nevertheless, for the slabs the grafting increased up to 14 h and then leveled. Taking into account the amount of monomers in the reaction ampoule, the maximum amount of GMA that could be grafted would be 1170 μmol cm^{-2}. Thus, the highest values plotted in Fig. 2 indicate that the grafting efficiency was around 10%. This finding is due to the fact that active species created during oxidative preirradiation were gradually consumed until they became exhausted. Moreover, grafting onto the slab was controlled by the diffusion of GMA solution through the layers of the grafted GMA, and thus the slabs required more time than the films to reach a similar yield of grafting. Due to different polarity and poor miscibility between the monomer solution and PP or PE; the grafting reaction mainly takes place in surface.

Films and slabs of PE and PP with a yield of grafting ranging from 1 to 100 μmol cm^{-2} were prepared with the purpose of achieving various degrees of CD functionalization (Fig. 3). As expected, the greater the content in epoxy groups, the greater the amount of CD immobilized. For both grafted polymers (PE-g-GMA and PP-g-GMA), the immobilization yield of β-CD was higher than that of HP-β-CD which is explained by the greater molecular size of this derivative. A HP-β-CD molecule covers a greater surface than a β-CD one and, therefore, less HP-β-CD molecules were attached per unit of surface. DMF improved the wettability of the hydrophobic grafted polymers and, thereby, enhanced the reaction yield. After the reaction, the films and slabs were extensively washed for the complete removal of DMF. This is an important issue since the CD cavities have to be empty to fully develop their complexation capability and, on the other hand, the leakage of DMF during clinical use could cause cytotoxicity problems.

The ATR infrared spectrum of PE film (Fig. 4) exhibited signals at 2916 and 2848 cm^{-1} due to symmetrical bending vibration of CH_2 groups (Adem et al., 1998). Characteristic absorption bands of PP at 1375 and 1452 cm^{-1} corresponded to symmetrical and asymmetrical bending vibration of CH_3 groups, respectively (Ramírez-Fuentes et al., 2007). The spectra of PE-g-GMA and PP-g-GMA, compared with that of PE and PP, showed additional absorbance bands due to the ester carbonyl group (1725 and 1180 cm^{-1}) and to the epoxy group (1256, 900 and 845 cm^{-1}). Moreover, the absence of the characteristic absorption bands of unsaturated C=C group of the GMA monomer (3140, 1640 and 940, 815 cm^{-1}), clearly proved that graft polymerization occurred (Kunita et al., 2005; Ao et al., 2007). Func-

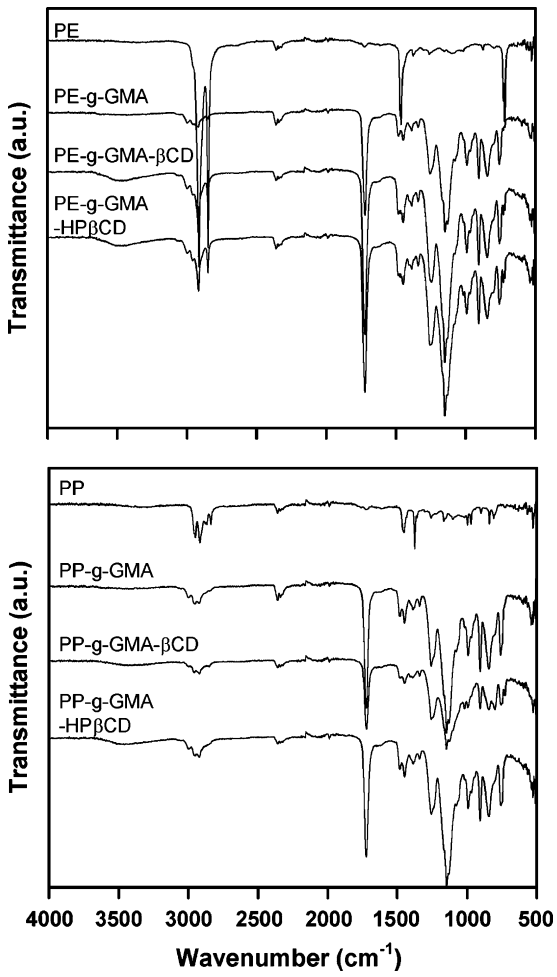

Fig. 4. FTIR-ATR spectra of PE-, PP-, GMA-grafted and CD-functionalized films.

tionalization of PE-g-GMA and PP-g-GMA with β-CD and HP-β-CD was confirmed by the appearance of a broad strong absorption band at 3457 cm^{-1} due to vibrational stretching of the –OH groups. The decrease of the epoxy signals and the appearance of broad bands in the 1100 and 1200 cm^{-1} region (because the stretching of C–O ether bonds) indicated that the CDs were indeed bonded to PE and PP through ether bonds that resulted from the chemical reaction of the GMA epoxy groups with some hydroxyl groups of the CDs.

Melting temperature (T_m) and enthalpy (ΔH_m) of unmodified, GMA-grafted and CD-functionalized PE and PP are summarized in Table 1. Since structural changes caused by grafting are more relevant at the surface level and at a short length under the surface, thin films (with a high surface-to-mass ratio) were chosen to evidence the effect of such changes. The melting temperatures of pure PE and PP films were 108.8 and 164.7 °C, respectively, which is in agreement with the values reported in literature (Pracella and Chionna, 2003; Ishihara et al., 2004). GMA-grafted and β-CD-functionalized films exhibited slightly lower T_m but markedly smaller crystallinity degree (X_C) than the parent polymers. This means that GMA grafting caused some amorphization of PE and PP.

After grafting of GMA and functionalization with CDs, the thickness of the films and slabs increased in a range from 100 to 200 μm and from 1 to 1.3 mm, respectively. As the film is very thin, the contribution of the grafting to the final thickness is greater than in the case of the slabs. SEM micrographs of the surface of pure PE and PP, grafted polymers (PE-g-GMA and PP-g-GMA) and β-CD- and HP-β-CD-functionalized polymers are shown in Fig. 5. The surface of PE and PP was smooth with no observable discontinuities. At ~30 μmol cm^{-2} graft, the surface showed some discontinuities for both grafted polymers, which may reflect the preferential grafting of GMA onto the amorphous regions of the polymers. Similarly, CD-functionalized films exhibited a discontinuous surface.

3.2. Wettability and friction coefficient

Both the wettability and friction coefficient determine the easiness of insertion and removal of medical devices. This information was only obtained with the thicker samples (slabs) due to methodological constrains that prevent an accurate test of the thin films. Contact angle measurements of water droplets on PE and PP slabs were carried out before and after functionalization with CDs. Water was carefully dropped onto slabs and contact angles were quickly measured before the beginning of the swelling. The water contact angles of grafted PP and PE slabs ranged from 91° to 112° and from 112° to 120°, respectively (Table 2). These values are slightly greater than those of the unmodified PP (104°) and PE (108°), meaning that the grafting of GMA and the functionalization with CDs slightly decreased the surface hydrophilicity.

The friction coefficients of the slabs were estimated using rheometry, which is an advantageous approach compared to tribometry mainly because of the greater sensitivity and the more precise control of the temperature of the sample and of the liquid trapped between the geometry and the solid surface (Peltier plate) (Gong et al., 1999; Yañez et al., 2008). The values of friction coefficient, μ, against the Peltier plate (surface of chrome-plated copper) ranged between 0.23 and 0.72 (Table 2). The greater values corresponded to the slabs with a higher degree of functionalization. This finding may correlate with the increase in surface roughness as the grafting progresses, as observed in SEM images. Nevertheless, all μ values are in range of those recorded for commercially available catheters (Katarzyna et al., 2008) and are similar to those found for soft contact lenses (Yañez et al., 2008) and synthetic articular cartilage (Freeman et al., 2000). These results indicate that CD functionalization did not cause detriments of practical relevance on the wettability and sliding of PE and PP.

Table 1
Melting temperature, melting enthalpy and degree of crystallinity (%) of PE (100 μm) and PP (50 μm) films before and after undergoing gamma irradiation for the grafting of GMA and functionalization with β-CD (n = 2; error below 1%).

Film	GMA (μmol cm^{-2})	β-CD (μmol cm^{-2})	T_m (°C)	ΔH_m (J g^{-1})	X_C (%)
PE alone	–	–	108.8	97.2	33.8
PE-g-GMA	31	–	108.4	69.5	24.1
PE-g-GMA-β-CD	31	0.096	107.8	57.9	20.1
PE-g-GMA	56	–	108.6	63.8	22.1
PE-g-GMA-β-CD	56	0.100	107.9	52	18.1
PP alone	–	–	164.7	113	54
PP-g-GMA	29	–	160.4	96.4	46.1
PP-g-GMA-β-CD	29	0.197	161.3	78.5	37.5
PP-g-GMA	56	–	161.0	82.5	39.5
PP-g-GMA-β-CD	56	0.312	162.3	67.7	32.4

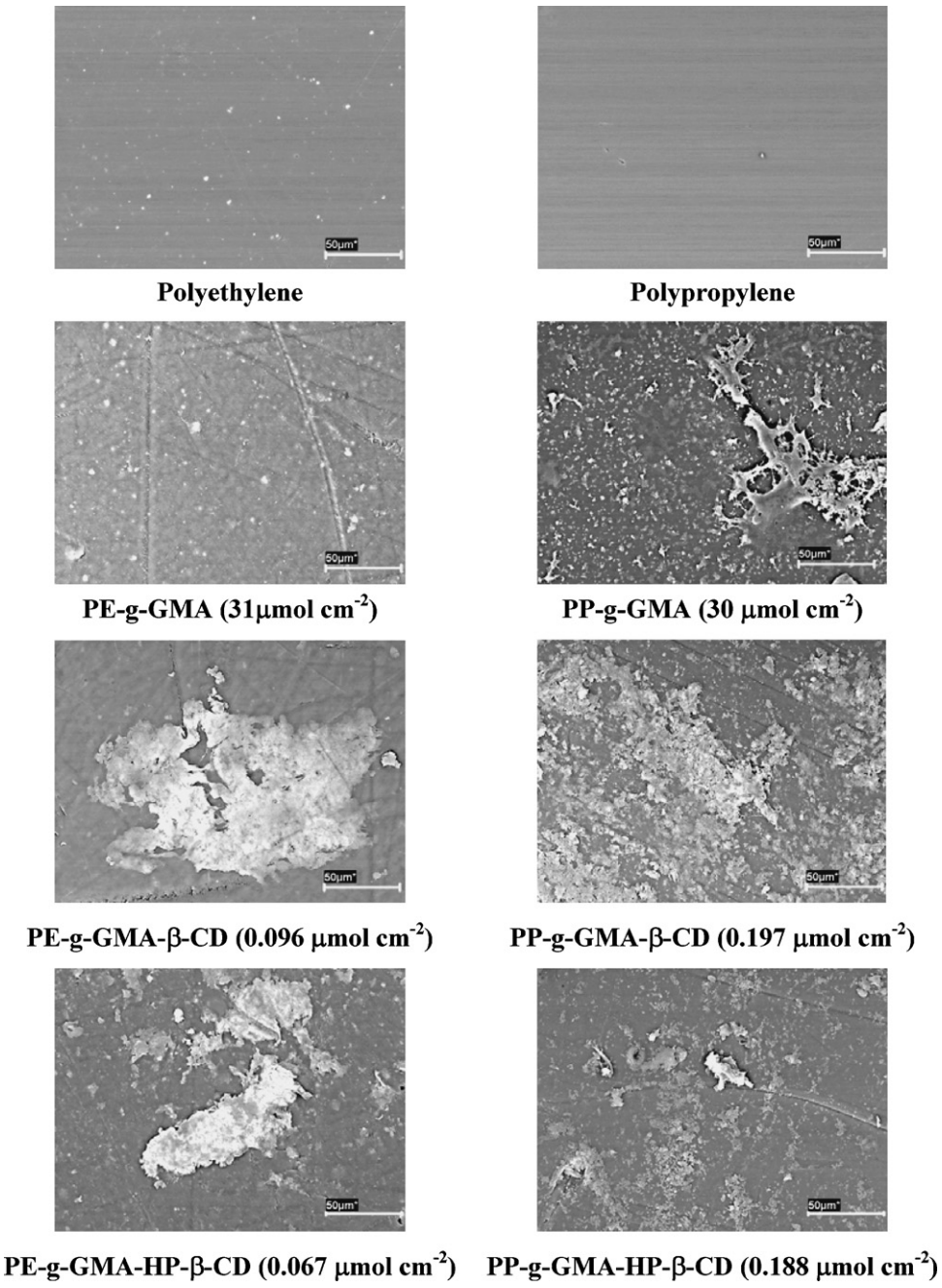

Fig. 5. SEM images from free surface of PE-, PP-, GMA-grafted and CD-functionalized films.

Table 2
Contact angle and friction coefficient of PE and PP slabs before and after undergoing gamma irradiation for the grafting of GMA and functionalization with cyclodextrins ($n = 3$; error below 1%).

Slab	GMA (μmol cm^{-2})	CD (μmol cm^{-2})	Contact angle (°)	Friction coefficient
PP	–	–	104	0.33
PP-g-GMA-β-CD	42	1.17	91	0.41
	98	2.85	109	0.57
PP-g-GMA-HP-β-CD	28	0.80	112	0.57
	91	2.60	95	0.64
PE	–	–	108	0.23
PE-g-GMA-β-CD	21	0.47	120	0.32
	112	2.70	112	0.57
PE-g-GMA-HP-β-CD	35	0.78	116	0.34
	112	1.83	115	0.72

Table 3
Amount of GMA and cyclodextrin grafted onto PP films (50 μm thickness) and capability of uptake 3-methylbenzoic acid (3-MBA) ($n = 3$; error below 5%).

PP-g-GMA-β-CD				PP-g-GMA-HP-β-CD			
GMA (μmol cm^{-2})	β-CD (μmol cm^{-2})	3-MBA (μmol cm^{-2})	CD/3-MBA mole ratio	GMA (μmol·cm^{-2})	HP-β-CD (μmol cm^{-2})	3-MBA (μmol cm^{-2})	CD/3-MBA mole ratio
7.7	0.045	0.062	0.714	7.7	0.014	0.153	0.094
14.1	0.080	0.057	1.407	14.8	0.058	0.180	0.319
21.1	0.119	0.104	1.137	24.6	0.114	0.241	0.472
28.1	0.206	0.130	1.593	29.5	0.144	0.237	0.607
38.0	0.276	0.214	1.292	38.0	0.165	0.211	0.783
56.3	0.426	0.211	2.020	56.3	0.264	0.246	1.072
98.5	0.734	0.247	2.970	98.5	0.433	0.298	1.457

Table 4
Amount of GMA and cyclodextrin grafted onto PE films (100 μm thickness) and capability of uptake 3-methylbenzoic acid (3-MBA) ($n = 3$; error below 5%).

PE-g-GMA-βCD				PE-g-GMA-HPβCD			
GMA (μmol cm^{-2})	β-CD (μmol cm^{-2})	3-MBA (μmol cm^{-2})	CD/3-MBA mole ratio	GMA (μmol cm^{-2})	HP-β-CD (μmol cm^{-2})	3-MBA (μmol cm^{-2})	CD/3-MBA mole ratio
14.1	0.047	0.081	0.581	15.5	0.013	0.083	0.152
21.1	0.081	0.125	0.646	23.2	0.041	0.080	0.511
29.5	0.097	0.111	0.875	29.5	0.049	0.062	0.792
35.2	0.079	0.094	0.840	36.6	0.077	0.072	1.065
55.6	0.176	0.097	1.822	55.6	0.133	0.055	2.425
68.2	0.201	0.101	1.992	67.5	0.179	0.056	3.195
78.1	0.233	0.098	2.386	78.8	0.207	0.079	2.633

3.3. Cytocompatibility

Although β-CD and HP-β-CD are approved as pharmaceutical excipients and are not expected to induce adverse reactions (Irie and Uekama, 1997) and hydrogels with epoxy groups (such as those of GMA) have a low toxicity (Lee et al., 1991), the cytocompatibility of the novel materials was tested to ensure that the steps followed for the functionalization did not render toxic products. The cytocompatibility studies were carried out following the direct contact test of the ISO 10993-5:1999 standard, which enabled an evaluation of the toxicity of both the modified PE and PP materials themselves and of the substances that could have been leached to the culture medium. Before the test, the films were immersed in phosphate buffer pH 7.4 and autoclaved. The films withstood this thermal treatment without breaking or undergoing changes in their texture. Both starting films and CD-functionalized films were found to be highly cytocompatible, with cell viability above 95%.

3.4. Content in functional CDs

The data shown in Tables 1 and 2 and Fig. 3 regarding the content in CD refer to the total amount of CDs on the surface of the films and slabs, estimated as increases in weight. From the point of view of the performance of the modified PE and PP materials as drug delivery systems, a key parameter is the content in CDs which can certainly host guest molecules. For this purpose, 3-MBA was used as a probe with a high affinity for β-CD and HP-β-CD (Fundueanu et al., 2003; Santos et al., 2008). The amount of 3-MBA sorbed, correlated with the content in β-CD and HP-β-CD (Tables 3 and 4), although the increase in 3-MBA uptaken was smaller for the films with higher CD grafting. The results obtained indicate that there is some adsorption of 3-MBA onto the unmodified surface of PE and PP, which is particularly evident at low degrees of grafting. Therefore, as the functionalization with CD increases, 3-MBA can also form inclusion complexes with the CD units, but steric hindrance among CDs too close may also occur. Consequently, not all CDs are capable of hosting 3-MBA. In general, the amounts up-taken were higher for the CD-functionalized PP films, compared to the PE films. This suggests a better arrangement of the CDs onto PP for forming inclusion complexes.

3.5. Diclofenac loading and release

Unmodified PE and PP surfaces were not capable of loading diclofenac and thus functionalization with CDs was needed to promote drug uptake. When the CD-functionalized films were

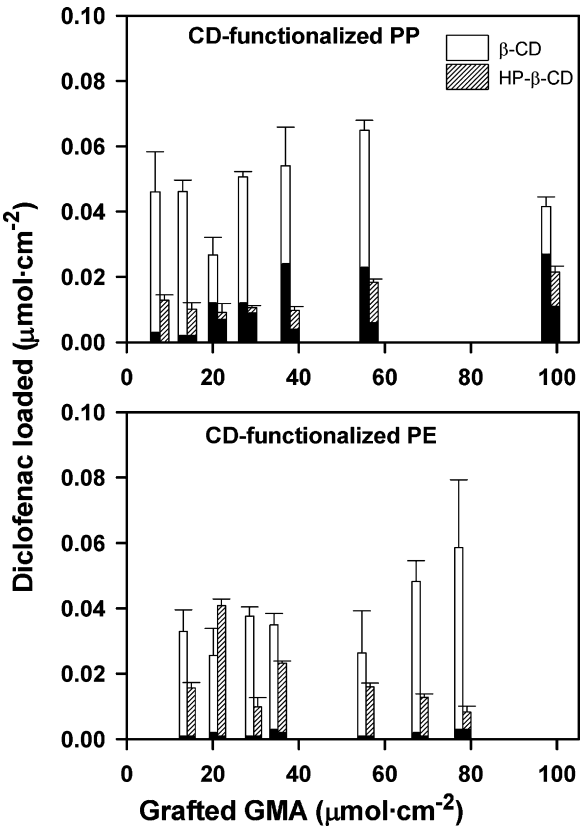

Fig. 6. Diclofenac loaded by CD-functionalized PP and PE films as a function of the amount of GMA initially grafted. Loading solutions were 0.5 mg ml^{-1} (black fills) and 1.0 mg ml^{-1} (white fills). Functionalization was carried out with β-CD (no pattern) and HP-β-CD (striped pattern).

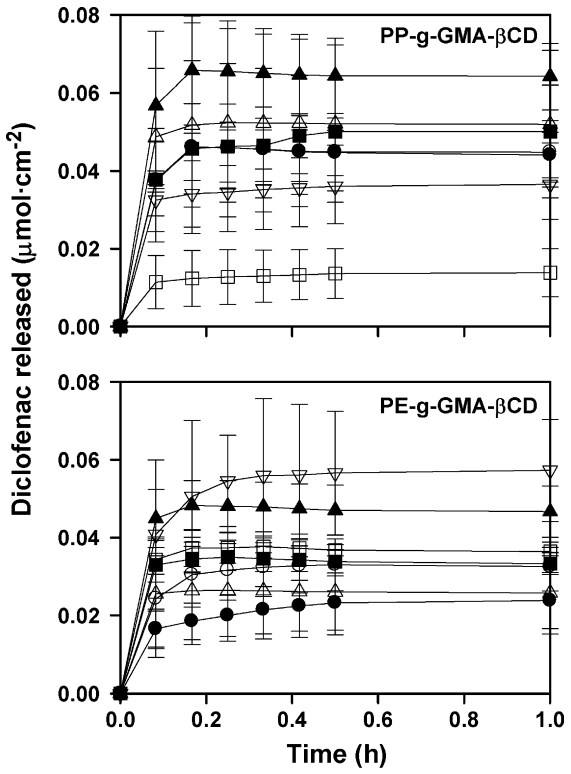

Fig. 7. Diclofenac release profiles from β-CD-functionalized PP and PE films. Legend: PP-g-GMA-β-CD: 7.4 (○), 14.1 (●), 21.1 (□), 28.1 (■), 38.0 (△), 56.3 (▲), 98.5 (▽) μmol cm^{-2} of GMA grafted, and PE-g-GMA-β-CD: 14.1 (○), 21.1 (●), 29.5 (□), 35.2 (■), 55.6 (△), 68.2 (▲), 78.1 (▽) μmol cm^{-2} of GMA grafted.

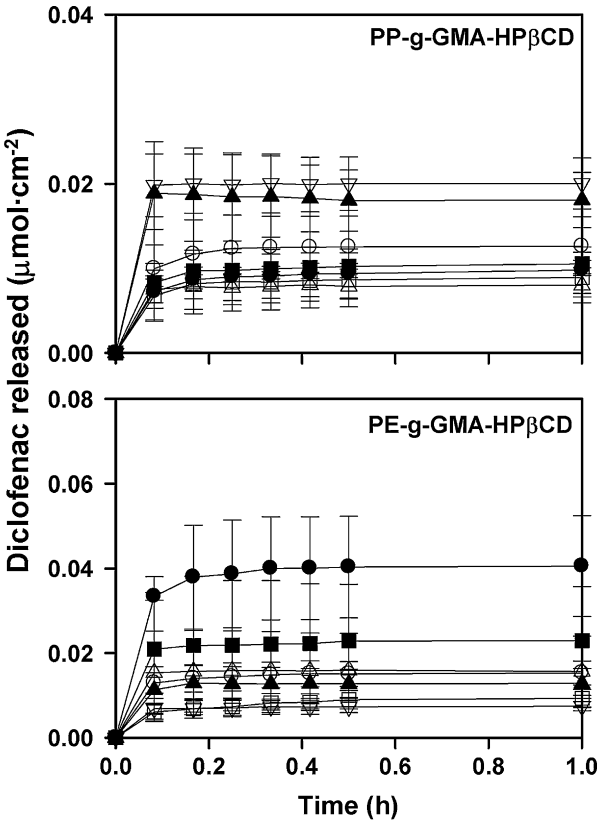

Fig. 8. . Diclofenac release profiles from HP-β-CD-functionalized PP and PE films. Legend: PP-g-GMA-HP-β-CD: 8 (○), 14.8 (●), 24.6 (□), 29.5 (■), 38.0 (△), 56.3 (▲), 98.5 (▽) μmol cm^{-2} of GMA grafted, and PE-g-GMA-HP-β-CD: 15.5 (○), 23.2 (●), 29.5 (□), 36.6 (■), 55.6 (△), 67.5 (▲), 78.8 (▽) μmol cm^{-2} of GMA grafted.

immersed in 0.5 mg ml^{-1} diclofenac aqueous solutions, the drug sorption was quite poor (Fig. 6), but an increase in the amount of diclofenac loaded as a function of the degree of functionalization was observed. Comparing the lowest functionalized films with the most functionalized ones, the increase in diclofenac loaded was 10-fold for PP functionalized with β-CD, 20-fold for PP functionalized with HP-β-CD, 5-fold for PE functionalized with β-CD and 4-fold for PE functionalized with HP-β-CD. These drug-loaded films released the whole dose within 1 h when immersed in buffer phosphate pH 7.4. With the aim of increasing the amount of diclofenac loaded, in a second set of experiments the films were immersed in 1.0 mg ml^{-1} drug solutions. As can be seen in Fig. 6, the higher the drug concentration in the loading solution, the greater the amount loaded. In fact, a remarkable increase (several orders of magnitude in some cases) was observed. This finding was not unexpected since loading prompted by complex formation with CDs depends on the concentration of free drug in solution. The higher the number of drug molecules available, the greater the shift of the equilibrium towards complex formation (Uekama et al., 1994; Stella et al., 1999). It is interesting to note that, as in the case of 3-MBA, a low degree of functionalization is sufficient to enhance the capability of PE and PP films to uptake diclofenac. Steric hindrance may be the reason the films functionalized with greater amounts of CDs could not load more diclofenac. In general, films functionalized with β-CD loaded more diclofenac than those with HP-β-CD, which confirms that the yield of β-CD grafting was greater and reveals a more favorable interaction of diclofenac with β-CD. Furthermore, the drug-loaded films sustained the delivery for 1 h (Figs. 7 and 8).

4. Conclusion

Gamma irradiation grafting of GMA onto PE and PP enabled the surface functionalization of these polymers with CDs rendering novel materials with potential as components of medicated medical devices. The functionalized materials maintain their bulk properties as well as their wettability and friction coefficient, but also exhibit the capability of CDs to form inclusion complexes. Therefore, any drug able to be hosted by the CD cavities, such as diclofenac, may be loaded by the CD-functionalized PE and PP.

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