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Silicone Rubber Films Modified by Ethylenoxy Moieties: Characterization and Drug Delivery Properties

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ABSTRACT: We present a comparative study between two different types of modification applied on a highly hydrophobic, yet biocompatible polymer, aiming to increase its hydrophilicity. More specifically, silicone rubber (SR) was modified by the introduction of low-molecular weight poly(ethylene glycol), through either (a) blending or (b) addition-grafting reaction. The modifications were first evaluated in neat films with respect to their water sorption capacity, stability of ethylenoxy groups' embedment, mechanical and thermal properties. The results from this series of tests showed that blending offered better results in terms of hydrophilicity, both surficial and in the bulk, while the films maintained better mechanical properties. Subsequently, the release kinetics of a relatively hydrophilic drug (theophylline) along with the concurrent water uptake was examined in drug-loaded, pure and modified SR films. As in the case of the drug-free films, blending appeared to offer better possibilities in controlling the drug's release rate through increased water sorption. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 129: 874–883, 2013

KEYWORDS: drug delivery systems; crosslinking; mechanical properties

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INTRODUCTION

Materials based on silicone rubber (SR) elastomers [e.g., crosslinked poly(dimethylsiloxanes) (PDMS)], because of their attractive properties of biocompatibility,[1,2] good mechanical and thermal properties and chemical inertness, have drawn significant interest over the past years since they can be used in numerous applications. Relevant examples involve tissue engineering,[3] bioelectrodes,[4] microfluidic[5,6] as well as various medical devices,[7–9] contact lenses[10] and drug delivery systems.[11–17] Although advantageous in many areas, PDMS is by nature an inherently hydrophobic material which limits markedly its range of applications. Thus significant research efforts aim at the modification of PDMS to improve its wettability and/or its bulk water sorption capacity. Many works point out the necessity for increased wettability of PDMS-based materials since they present poor cell adhesion[18] or appear as poor candidates for microfluidics since they are not easily filled with aqueous solutions.[19] Furthermore, the need of water absorption in the bulk is also important since PDMS-based materials appear to have reduced permeability in hydrophilic bioactive molecules, such as steroids,[20] and they may irreversibly adsorb cells and/or small hydrophobic molecules,[5,21] which is detrimental in biomedical devices.

A common approach for improving the overall hydrophilicity is blending with various compounds of mild osmotic action such as poly(ethylene glycols).[22–26] However, in principle, these systems are often characterized by mechanical failure, leaching phenomena and present limitations in the incorporation of larger amounts of osmotically active compounds. Chemical modification of PDMS has been chosen as a means of overcoming these problems. One method of improving the surficial wettability of PDMS is the introduction of various polar groups through plasma treatment,[18,27] which although is promising sometimes leads to loss of biocompatibility and/or leads to deterioration of the mechanical properties, especially on the surface of PDMS. To overcome these problems, many works report the modification of PDMS through the attachment of various moieties by covalent bonding,[28] aiming to increase water sorption in the bulk of the polymer or its surficial hydrophilicity. Since silicone crosslinking can be achieved through different reactions, the nature and degree of crosslinking can affect the properties of the end-use material (mechanical properties, leaching, etc.). Peroxide curing for instance, could lead to by-products and post curing effects,[29] which are undesirable for biomedical applications. Other means of crosslinking involve addition-cure mechanism through tin-catalyzed crosslinking

reaction and condensation-cure mechanism by the use of hydroxy-terminated PDMS of low-molecular weight and tetra(alkyloxysilane) as the crosslinking agent.[21,28] Examples of PDMS modification through an addition-cure mechanism involve the grafting of hydrophilic poly(ethylene glycol) (PEG) on the hydrophobic PDMS either on the surface[30] or in the bulk.[19–21,31] Depending on the different types of crosslinking mechanisms, the findings of the aforementioned works exhibited a variety of properties with respect to the degree of crosslinking, the functionality of the crosslinking groups and hence a diversity in the observed mechanical properties, level of leaching, the hydrophilicity and water sorption capacity of the bulk polymer.

In this work, we chose an addition-type SR obtained through Pt-catalyzed addition reaction as the basis for the preparation of thin films where low-molecular weight PEG was incorporated either as a physical mixture or through covalent bonding. Our main objective was to proceed in a detailed study of the effect that the two types of ethylenoxy moieties embedment has on the mechanical and thermal properties of the end-use films, on their stability in aqueous environment and on their water sorption capacity and hydrophilicity. These properties are of great importance since they affect the performance of many applications, such as controlled release devices where the release of a drug may be activated and controlled by the ingress of water.[11–17,32,33] The films, where the ethylenoxy groups were covalently grafted, were prepared in analogy to the reaction mechanisms proposed by Zhou et al.[19] and Mc Bride et al.[21] Finally, to give a practical example on the potential use of such systems on drug delivery, we have prepared films loaded with theophylline, a model drug of negligible osmotic action and narrow therapeutic window, used in the therapy of respiratory diseases such as asthma. The study on the release kinetics was supplemented with data on the concurrent water uptake by the matrix, to gain further insight on the release process.

EXPERIMENTAL

Materials

Poly(dimethylsiloxane) (PDMS) (RTV 615 type), kindly supplied by Momentive (USA) as a two-component silicone kit, consisted of a vinyl-terminated prepolymer (part A) and a crosslinker, containing shorter PDMS chains with several hydride groups (part B). According to the GPC analysis,[34] both part A and B materials have a bimodal character of molecular weight (part A: 4000 and 67,000 g mol^{-1}, part B: 1500 and 60,000 g mol^{-1}). Curing of the PDMS films occurs via Pt-catalyzed hydrosilylation reaction to form a densely crosslinked polymer network, leading to free-standing SR films. PEG 400 (Merck, Hohenbrunn, Germany) with average number-molecular weight 400 g mol^{-1} was used for preparing physical mixtures with SR. PEG allyl methyl ether (AMPEG) (Clariant, Frankfurt, Germany) with average number-molecular weight 350 g mol^{-1}, was used as a grafting reagent. Theophylline $C_7H_8N_4O_2$ (1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurine, of 99% purity, M_w = 180.14 g mol^{-1} and 11 mg/cm^3 solubility in water at 37°C) in the form of granules of size 2−8 μm, was purchased from Acros Organics (Belgium).

Preparation of SR Films

Pure SR films were prepared by mixing prepolymers A and B at a ratio 10 : 1 (w/w) by means of a mechanical stirrer at 400 rpm at room temperature for 1 h. The viscous mixture (~ 4.4 cm^3) was degassed *in vacuo* and then cast onto a poly(propylene) (PP)-coated glass plate with dimensions 60 cm × 35 cm, by means of an adjustable knife blade running on rails parallel to the plate, and cured at 100°C for 1 h.

For the modification of SR films, through grafting of ethylenoxy moieties by addition reaction,[19,21] proper amounts of part B and AMPEG were mixed for 1 h at 40°C. Then part A was added at a 10 : 1 (w/w) ratio to part B, followed by a second stirring for 30 min at 25°C. Finally the mixture was degassed *in vacuo*, and the curing procedure applied for pure SR films was followed. Films of this type will be designated as SR/AMPEG.

Blends of SR with PEG-400 were obtained by mixing, at 400 rpm, at room temperature, appropriate amounts of PEG-400 first with prepolymer B, to be consistent with the methodology followed for the chemical modification described above. After stirring for 1 h prepolymer A was added and the whole mixture was stirred for another 30 min and subsequently the same procedure as above was followed. Films of this type will be designated as SR/PEG.

For the preparation of drug-loaded films, we followed the same methodology as above up to the stage of part A addition. After this stage, theophylline was added, the final mixture was stirred for 1 h at 25°C and curing was effected as described above. The drug-loaded matrices will be designated as SR/PEG/T and SR/AMPEG/T films to distinguish them from the corresponding drug-free ones.

All types of neat and drug-loaded films are summarized in Table I along with nominal amounts of incorporated ethylenoxy groups and theophylline and their thicknesses *L*. The latter was measured at five points on each film with a micrometer reading to 1 μm.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy (FTIR) in the mid-IR range (4000–500 cm^{-1}) was performed in as-prepared neat films, as well as in dried films, previously extracted with chloroform. The instrument used was a Nicolet 6700 FTIR (Thermo Scientific) equipped with an ATR with diamond (Smart Orbit). The samples were scanned at a resolution of 4 cm^{-1} and 32 scans per sample were analyzed using the Omnic Software (version 7.3).

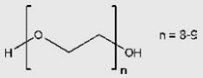
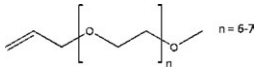
Differential Scanning Calorimetry

The thermal properties of pure and modified SR films were determined by means of a 2920 Modulated Differential Scanning Calorimeter-MDSC (TA Instruments). Samples of 5–10 mg, were first quenched to −160°C and then heated with a non-modulated signal at a 5°C/min heating rate up to 30°C in a nitrogen environment.

Extraction/Swelling in Chloroform

Since chloroform is a good solvent for PEG and a swelling agent for SR,[35] neat films were equilibrated in chloroform to first extract PEG-400 or any unreacted AMPEG, as well as non-crosslinked

Table I. Characteristics of the Studied Films

Film	Ethylenoxy moiety used	Nominal ethylenoxy content (% w/w)	Range of total thickness, L (μm)	Theophylline content (% w/w)
SR	–	–	202-222	–
SR/T 6	–	–	225-229	6.58
SR/T 13	–	–	95-307	13.04
SR/PEG-2		1.96	235-245	–
SR/PEG-4		3.92	247-251	–
SR/PEG-6		5.66	216-222	–
SR/PEG-2/T 6		1.76	228-241	6.49
SR/PEG-2/T 13		1.70	252-257	13.05
SR/PEG-4/T 6		3.64	232-238	6.56
SR/AMPEG-2		1.92	240-252	–
SR/AMPEG-4		3.83	252-266	–
SR/AMPEG-6		5.63	206-214	–
SR/AMPEG-2/T 6		1.74	217-218	6.40
SR/AMPEG-2/T 13		1.60	210-217	12.82

PDMS, and then estimate the degree of PDMS crosslinking through the swelling degree q of the films. At least three samples from each type of film, with lateral dimensions 2 cm × 2 cm, were immersed in chloroform, inside stoppered bottles at 25°C, and were periodically weighed until constant weight, reached in approximately 7 days. Then the samples were dried under vacuo. The degree of swelling q (volume ratio of swollen film to dry film) was calculated by taking into account the densities of pure PDMS and of chloroform (1.02 and 1.48 g/cm^3 at 25°C, respectively).

Mechanical Properties

The tensile properties of neat films were determined by a TENSILON UTM-II-20 (Toyo Baldwin, Co. LTD, Japan) apparatus. Each specimen had lateral dimensions 2 cm × 0.4 cm and thickness within the range 210–270 μm. Stress–strain tests were performed with a strain rate of 20 mm/min at 25°C and 70% relative humidity, while the grip separation was 1 cm.

Static Contact Angles and Water Sorption Capacity

Static contact angle measurements on the surface of neat films were performed at ambient temperature with a drop of ca. 1-μL deionized water on at least five points on each surface of the films i.e. the surface that was attached to the PP-coated plate and the surface that was exposed to air. The angles were determined by means of a Cam 100 Optical Contact Angle Meter array (KSV Instruments Ltd., Finland).

The water sorption capacity of pure and modified films was determined as follows: At least three samples from each type of films with lateral dimensions 2 cm × 2 cm and of thicknesses in the range 210–270 μm, were immersed in deionized water at 25°C and periodically weighed until constant weight was reached. Then they were dried under vacuo and finally weighed to obtain the dried specimen mass.

Determination of Theophylline Partition Coefficients

At least three dried neat films (2 cm × 2 cm and of thickness shown in Table I) were immersed in 25 mL of a theophylline solution of concentration c_{DS} = 6 mg/cm^3, thermostatted at 37°C and shaken periodically for 15 days. To ensure that drug sorption equilibrium was attained, equilibration times were much longer than those required for the depletion of the drug in the release experiments, described in the following section. A periodic gravimetric control was also performed just to make sure that water uptake equilibrium was attained as well. After equilibration, the water content of the films was determined gravimetrically, and subsequently the films were immersed in distilled water until the total amount of sorbed drug was eluted and estimated by the UV/Vis Spectrophotometer at 271 nm. Partition coefficients, K_D, were calculated according to the expression: $K_D = C_{DS}/c_{DS}$, where C_{DS} and c_{DS} are the drug's concentration inside the matrix and in water, respectively (expressed in g/cm^3 of hydrated matrix and in g/cm^3 of equilibrating solution, respectively).

Release Experiments

In vitro release experiments were conducted in a 21 CFR Part 11 compliant, Dissolution System (DT-810, Jasco, Japan) coupled with an automatic fraction collector and sampler (FC-812AS, Jasco) and a UV/Vis spectrophotometer (V-630, Jasco) equipped with a peristaltic sipper (NPF-721, Jasco) with a flow cell unit. The release medium was in all cases deionized water which had been previously degassed. All release experiments were performed in triplicate at 37 ± 0.2°C. Sampling and circulation was carried out by means of an eight-channel peristaltic pump (LH-PV3, Jasco). Samples of 3 × 3 cm^2 lateral dimensions were suspended by custom made holders rotating at 100 rpm in the dissolution vessels containing 700 mL of release medium. The UV absorbance of the drug solution in the flow cell was measured at 271 nm and recorded at suitable time

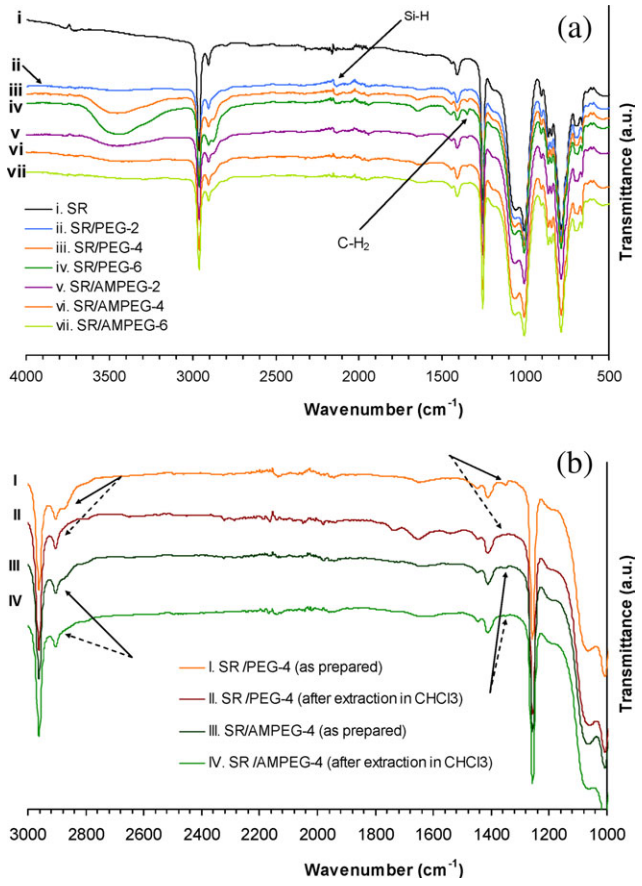


Figure 1. (a) FTIR spectra for drug-free SR/PEG blends and SR/AMPEG-modified films. (b) Comparison between selected spectra of as-prepared films and of the respective films after their extraction with chloroform. In the case of SR/PEG blends, the peaks at 1335 cm^{-1} vanish (dashed arrows) after the chloroform extraction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

intervals. The concurrent variation of the water uptake by the films during the release process was measured independently, also in triplicate, in samples of lateral dimensions 2 × 2 cm^2 that were immersed in deionized water at 37°C. The water uptake was measured by weighing the blotted films at suitable time intervals ($Q_{w,t}$ at time t and $Q_{w,\infty}$ at $t \rightarrow \infty$) by taking into account the amount of drug that was released. In all cases, the water was frequently renewed to ensure the required sink conditions.

RESULTS AND DISCUSSION

FTIR Spectroscopy

Results from FTIR spectroscopy are given in Figure 1(a,b) for pure and modified neat SR films. The strongest band, in all cases, is a double peak at 1064 and 1008 cm^{-1} corresponding to the stretching vibration of Si—O—Si. The asymmetric and symmetric stretching vibrations of C—H_3 can be found at 2962 and 2906 cm^{-1} respectively, while the sharp single peak at 1257 cm^{-1} corresponds to the deformation vibration of C—H_3 in Si-Me_2 group.[30,34,36] In some cases, a broad vibration peak of 3440 cm^{-1} appears due to the —OH group of PEG or its H-bonding forming.

As pointed out by arrows in Figure 1(a,b), the characteristic vibration peaks of PEG appear as a new vibration peak of 1335 cm^{-1} which is attributed to the C—H_2 bending vibration of PEG molecules; its symmetric stretching vibration at 2866 cm^{-1} shoulders the symmetric stretching vibration peak[30,37] of C—H_3 at 2909 cm^{-1} and its asymmetric stretching vibration at 2953 cm^{-1} greatly strengthens the asymmetric stretching vibration of C—H_3 at 2962 cm^{-1}.

To check the grafting of AMPEG on the PDMS chains of SR we focus on two characteristic vibrations at 912 and 2160 cm^{-1} which are attributed to the stretching and bending vibrations of Si—H bond. As pointed out in Figure 1(a) the bands at 912 and 2160 cm^{-1} appear in the spectra of the SR/PEG films since it is expected, that several Si—H groups remain unreacted in the presence of PEG 400. In the corresponding SR/AMPEG spectra, the bands at 912 cm^{-1} become significantly weakened and the corresponding bands at 2160 cm^{-1} practically vanish. This is an indication that some of the hydride groups located in part B of the two-component RTV 615, have reacted with the vinyl groups of AMPEG.

Finally, in Figure 1(b), we compare the spectra coming from samples of the same films before and after the extraction process in chloroform. Focusing on the characteristic peaks at 1335 cm^{-1} and the shouldering at 2866 cm^{-1} [marked by arrows in Figure 1(b)], we observe that although they appear in all spectra of the as-prepared films, they vanish as expected, in the spectra of the chloroform treated blends SR/PEG. In contrast, the peaks are present in the chloroform treated SR/AMPEG films [line IV in Figure 1(b)]. This is another indication that, even after extensive exposure of the chemically modified films to chloroform, at least part of AMPEG remains attached to PDMS.

Differential Scanning Calorimetry

The differential scanning calorimetry (DSC) results are shown in the thermographs of Figure 2(a,b) and in Table II. The heating run thermograms were obtained after quenching (at a rate of ca. 40°C/min) the samples at −160°C.

The thermograph of pure SR film [Figure 2(a,b)] shows the presence of a glass transition (T_g) at −125.5°C and two peaks: an exothermic one at T_c, corresponding to the cold crystallization of PDMS followed by an endothermic one at T_m, corresponding to the crystalline melting of PDMS.[38,39] As shown in Table II, the glass transition temperature T_g both in blends and in the chemically modified films is lowered by 2°C compared to that of the neat SR films. This finding points to imperfect cross-linking of the PDMS network due to the obstructive effect of the ethylenoxy moieties during the curing process, as also indicated by the extraction-swelling experiments and the mechanical tests presented below.

Compared to the pure SR films, the PEG-modified films exhibited systematically lower T_c and at the same time, higher T_m values, especially in the case of SR/AMPEG (Table II) indicating better crystal quality. The heat of melting of pure SR films ($\Delta H_m = \sim 10$ J/g) is the same as the heat of cold crystallization

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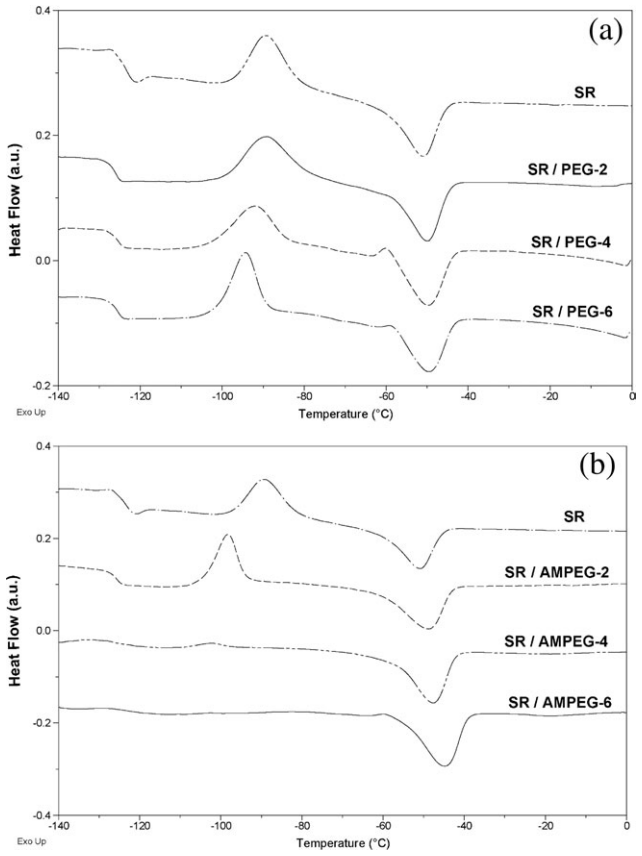

Figure 2. Thermographs coming from (a) SR/PEG blends and (b) SR/AMPEG modified films.

(ΔH_c) indicating that PDMS does not crystallize during cooling. The same is true for SR/PEG blends. However, in the case of the chemically modified SR/AMPEG films, the results of Table II show that: (a) ΔH_m increases ($\sim$ 15 J/g for all SR/AMPEG films) showing higher ease of crystallization at the expense of the amorphous phase[39,40] and (b) ΔH_c values are significantly lower than ΔH_m, the former ranging from $\sim$ 9.0 J/g for SR/AMPEG-2 to negligible for the two higher AMPEG contents, indicating that crystallization occurred during quenching of the samples; this is also verified by the lower values of ΔC_p (variation in heat capacity at T_g). These differences in the thermal behavior reflect structural differences attributable mainly to the presence of dangling PDMS chains[19,41] formed due to the occupation of several crosslinking sites by AMPEG.

Table III. Results from Extraction-Swelling in Chloroform

Film	q (chloroform)	Weight loss (% g/g)
SR	2.62 ± 0.04	2.59 ± 0.11
SR/PEG-2	3.13 ± 0.02	4.31 ± 1.09
SR/PEG-4	3.44 ± 0.02	7.36 ± 0.17
SR/PEG-6	3.64 ± 0.01	9.01 ± 0.00
SR/AMPEG-2	4.35 ± 0.16	10.4 ± 1.10
SR/AMPEG-4	4.75 ± 0.11	14.2 ± 2.54
SR/AMPEG-6	9.75 ± 0.02	27.2 ± 1.08

Extraction-Swelling in Chloroform

The results of the extraction/swelling experiments in chloroform are summarized in Table III. The observed weight losses arise from two sources: (a) loss of PEG-400 or unreacted AMPEG and (b) loss of non-crosslinked PDMS. The corresponding q values of the extracted films reflect mainly changes in the degree of crosslinking of the PDMS network. Some enhancement of q in the case of SR/AMPEG films, due to swelling of the covalently bonded AMPEG cannot be excluded, but must be of limited extent due to the small amounts of AMPEG used for the modification of SR.

The swelling degree in chloroform, q, of pure SR was $\sim$ 2.6, while the corresponding weight loss was $\sim$ 2.6% g/g. The swelling degrees of the SR/PEG films are not significantly higher, attaining a value of 3.6 for SR/PEG-6, pointing to a minimum hindrance of the reaction between part A and part B components of RTV 615 due to the presence of PEG 400 in the initial preparation mixture. In line with this, is the fact that the leached out polymer fraction is not materially different from that of pure SR, taking into account the weight loss due to the extraction of PEG 400. However, in the case of SR/AMPEG films, q values and total weight loss are considerably higher, pointing to imperfect crosslinking especially in the case of SR / AMPEG-6 films where the value of q is three times higher than that of pure SR. The limited degree of crosslinking may be attributed to reaction between the silyl groups located in part B prepolymer and the vinyl groups of AMPEG, which in turn would lead to less available silyl groups for crosslinking with vinyl groups located in part A.

Table II. Thermal Properties of the Studied Films

Film	T_g (°C)	ΔC_p (J/g °C)	T_c (°C)	ΔH_c (J/g)	T_m (°C)	ΔH_m (J/g)
SR	−125.5	0.565	−89.0	10.3	−51.0	10.2
SR/PEG-2	−127.7	0.404	−89.1	12.2	−49.8	12.2
SR/PEG-4	−127.3	0.346	−92.2	10.3	−49.4	10.1
SR/PEG-6	−127.4	0.348	−94.4	9.3	−49.2	9.4
SR/AMPEG-2	−127.3	0.343	−98.4	9.0	−48.9	15.9
SR/AMPEG-4	−127.7	0.135	−102.1	0.8	−47.8	15.0
SR/AMPEG-6	−127.5	0.141	-	-	−44.8	13.5

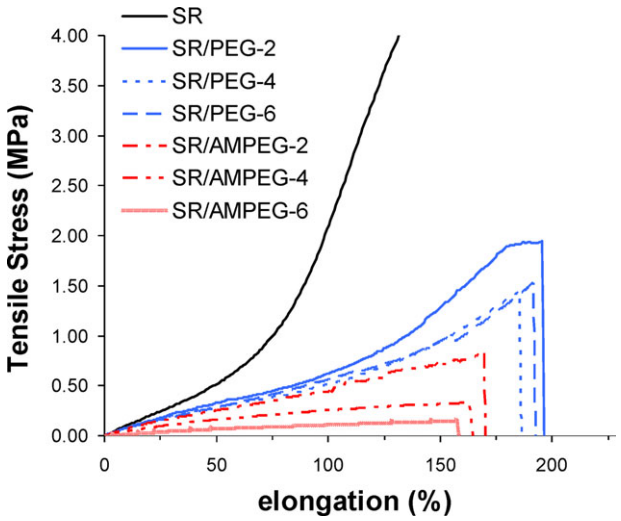

Figure 3. Stress–strain curves for pure SR, SR/PEG, and SR/AMPEG films. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

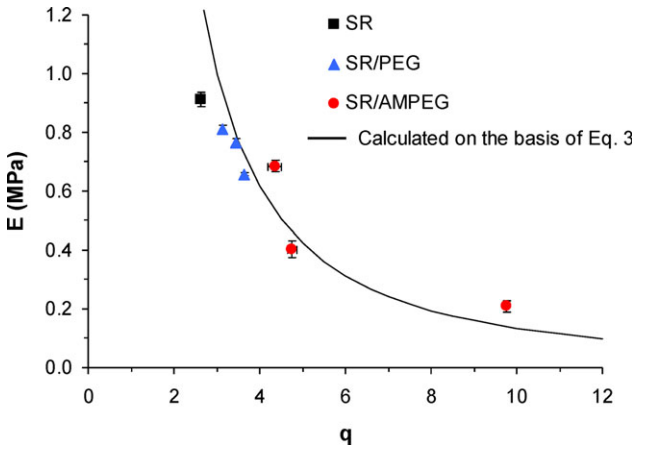

Figure 4. Correlation of Young's modulus to the degree of swelling in chloroform q. Points correspond to experimentally determined values, while the continuous line was calculated on the basis of eq. (3). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Mechanical Properties

Results of the mechanical properties are given in representative stress–strain curves in Figure 3 and in Table IV. The stress–strain curve of pure SR films is typical[42] for addition-type hydrosilylated PDMS, in terms of ultimate strength and elongation at break. As shown in Table IV, pure SR films have a Young's modulus E of $\sim$ 1 MPa, which is similar to the values reported elsewhere in literature.[43,44]

With increasing amounts of ethylenoxy content, the Young's modulus in each type of films (blends or grafted) decreases systematically (Table IV), with SR/PEG-6 and SR/AMPEG-6 films having E values of 0.66 and 0.21 MPa, respectively. The same holds for the ultimate stress values (Figure 3). The more intense effect in the case of SR/AMPEG samples is in line with the conclusion drawn above on the higher interference of AMPEG in the crosslinking reaction of PDMS. In this case, it is expected that more dangling chains are produced which in turn reduce the extensibility of the samples[45] and since longer chains between crosslinks are present, the Young's modulus of the films is reduced.[46,47]

The E values of Table IV have been plotted in Figure 4 vs. the corresponding swelling degree q in chloroform (Table III). The theoretical correlation of E and q for a particular crosslinked polymer, can be derived by combining the expressions of the functional dependence of E and q on the mean molecular weight by number between two consecutive crosslinks, $\overline{M}_c$. The latter dependence is derived from the Flory–Rehner theory[48]:

$$q^{5/3} \cong (\upsilon \cdot \overline{M}_c)\frac{(1/2-\chi)}{\overline{V}_s} \quad (1)$$

where υ is the specific volume of the polymer (0.98 cm^3/g for SR), $\overline{V}_s$ is the molar volume of the solvent, and χ is the Flory–Huggins interaction parameter for the polymer-solvent system.

The dependence of E on $\overline{M}_c$ is given by the rubber-elasticity theory[43]:

$$E = 3RTd/\overline{M}_c \quad (2)$$

where R is the universal gas constant, T is the temperature (298 K here), and d is the polymer density (1.02 g/cm^3). From eqs. (1) and (2), we get:

$$E \cong \frac{3RT(1/2-\chi)}{\overline{V}_s} q^{-5/3} \quad (3)$$

The line in Figure 4 has been calculated on the basis of eq. (3) with $\overline{V}_s = 81.1$ cm^3/mol for $CHCl_3$ using the value of $\chi = 0.43$, which is close to that for the pure PDMS-chloroform system.[49,50] Although our experimental data refer to E values of modified PDMS, containing different amounts of PEG moieties, they follow closely the theoretical trend of E with increasing q, showing that the Young's modulus decreases due to imperfect crosslinking. The good correlation between the Young's moduli and the swelling ratios is a verification of the assumption made in the previous paragraph that the swelling degrees mainly correspond to the crosslinking density of the modified films.

Table IV. Mechanical Properties of the Studied Films

Film	Modulus of elasticity, E (MPa)	Elongation at break (%)
SR	0.91 ± 0.02	233 ± 8
SR/PEG-2	0.81 ± 0.02	192 ± 11
SR/PEG-4	0.77 ± 0.03	195 ± 20
SR/PEG-6	0.66 ± 0.02	191 ± 12
SR/AMPEG-2	0.69 ± 0.01	164 ± 6
SR/AMPEG-4	0.40 ± 0.01	164 ± 13
SR/AMPEG-6	0.21 ± 0.02	162 ± 12

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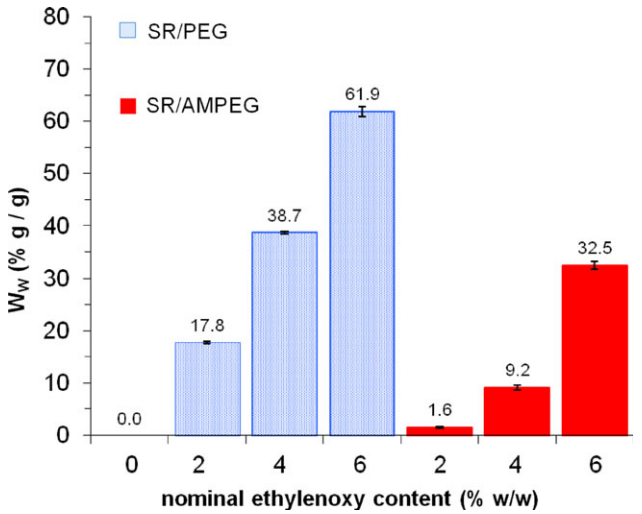

Figure 5. Water sorption W_W, by as-prepared, drug-free pure SR, SR/PEG, and SR/AMPEG films at 25°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Water Sorption and Static Contact Angles

Water sorption experiments, conducted on the as-prepared films, are of particular interest, since regardless of the chosen path of modification the desired outcome was to increase the hydrophilicity of the films. Weight losses, after one month of contact with water were small, in all cases, ranging from negligible (for pure SR) to ca. 1.0% (g/g) for SR/AMPEG-6 films.

The water uptake W_W (%), expressed in g of water per g of dried polymer, is shown in Figure 5 vs. the nominal ethylenoxy moieties content. Blends of SR with PEG-400 presented significant capability of water absorption (from negligible, for pure SR films, to ~ 62% g/g for SR/PEG-6 films) which increased with increasing PEG content. The water sorption by the chemically modified films was more limited (up to 32.5% g/g for SR/AMPEG-6 films). This difference in water sorption is attributed to the distribution of PEG inside the films. In the blends, PEG-400, being incompatible with PDMS, may aggregate forming discrete regions where water is osmotically driven. In SR/AMPEG films, the ethylenoxy moieties are more finely distributed in the hydrophobic matrix and thus less accessible to water.

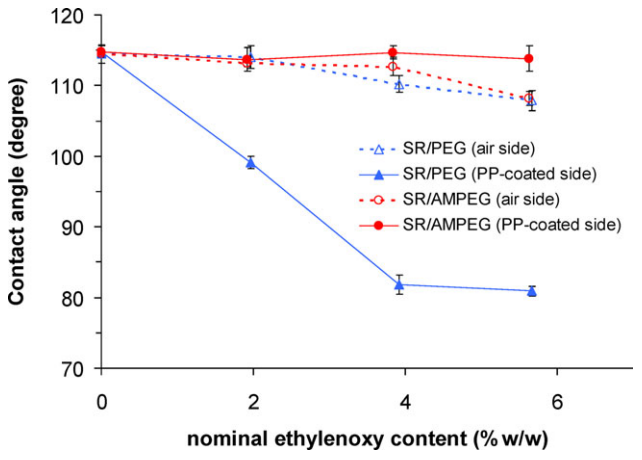

Figure 6. Contact angles measured in both surfaces of each of the studied films. (a) Films produced through blending and (b) films produced through chemical modification. Air side (open points) and PP-coated side (closed points) correspond to the two surfaces of the films upon their casting on the PP-coated plate. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

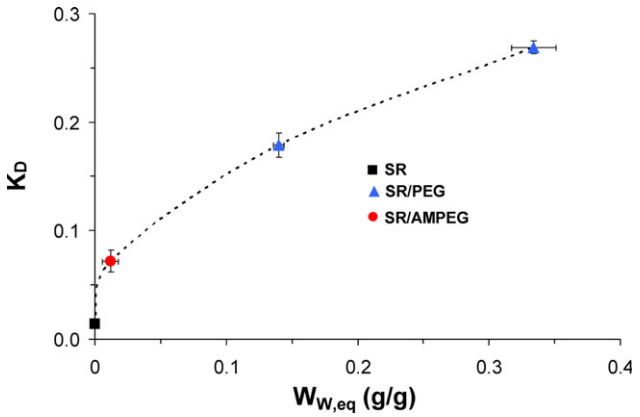

Figure 7. Partition coefficients K_D of theophylline, for pure SR (square), SR/AMPEG-2 (circle), and SR/PEG-2 and 4 (triangles) correlated with the amount of sorbed water at equilibrium at 37°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The measured contact angles were in line with the water uptake results since the decrease of the relevant values, as compared to pure SR, was more intense upon blending (Figure 6). Another interesting observation in the case of blends, was that the contact angles corresponding to the side exposed to air were higher compared to the side attached to the poly(propylene) coated plate used for casting the films. This finding points to precipitation of PEG-400, occurring during casting the films. The opposite trend was observed in the case of the chemically modified films where some hydrophilic dangling chains have been driven away from the side adjacent to the hydrophobic PP-coated plate, making thus the air-exposed side of the films more hydrophilic.[41]

Determination of the Drug Partition Coefficients

Partition coefficients K_D, derived as described in the experimental section, are shown in Figure 7, together with the corresponding water uptake at equilibrium $W_{W,eq}$.

In all cases the partition coefficients K_D were found to be below unity (by two orders of magnitude for pure SR films) showing low solubility of the drug in the polymer matrix. Moreover, the amount of water sorption is comparable to that shown in Figure 5 for films equilibrated in pure water. As shown in Figure 7, with increasing water sorption values, $W_{W,eq}$, due to the presence of the ethylenoxy moieties, the partition coefficients K_D increase.

Finally, it should be noted that the weight loss that occurred during the equilibration of the films and the consequent exposure in the deionized water was found to be comparable to the weight loss of the samples subjected to water sorption

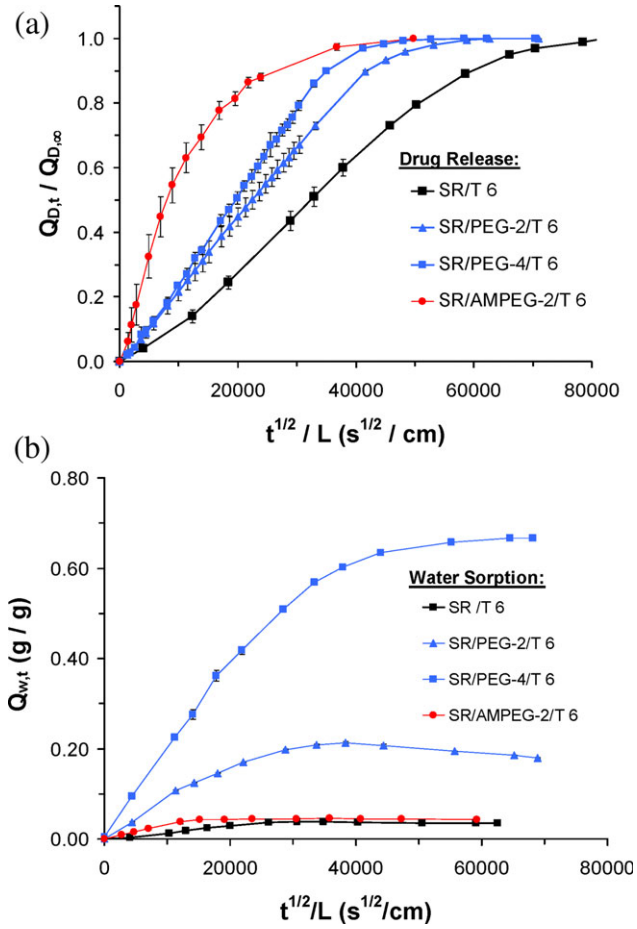

Figure 8. (a) Theophylline release kinetics and (b) concurrent water uptake from pure SR films, SR/PEG blends, and SR/AMPEG-modified films loaded at initial concentration 6.5% (w/w). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

experiments (described in the previous paragraph), ranging from negligible (for pure SR) to ca. 1.1% (g/g) for SR/PEG-4 films.

Release Experiments

As shown in previous work[16] the presence of xanthene derivatives in the prepolymer mixture interferes with the crosslinking reaction of SR. Controlled release matrices with acceptable film forming properties were prepared for pure SR, SR/PEG-2, and SR/AMPEG-2 loaded with drug at 6.5 and 13% (w/w) and for SR/PEG-4 loaded with drug at 6.5% (w/w) (Table I).

Release Kinetics and Concurrent Water Uptake. The results of the release kinetics of theophylline, and of the concurrent water uptake, from films loaded at 6.5% (w/w) are shown in Figure 8(a,b) and in Table V.

Since theophylline has a negligible osmotic action, the amount of sorbed water by pure SR/T 6 films is attributable to the filling of formed pores left behind by eluted drug particles. This hypothesis is supported by the similar values of the initial volume fraction of the drug in the film (0.047) and of the volume fraction of water at the end of the release (0.044). In the case of blends, with increasing PEG content the release rate increases, due to increasing water sorption. On the other hand, in the case of the chemically modified film, although the water sorption is comparable to that from SR/T 6 films, the release rate is accelerated. Based on the findings of the previous paragraphs for chemically modified films, the lower degree of crosslinking leads to a looser polymeric network, which in turn deteriorates the rate controlling properties of the SR/AMPEG films. The phenomenon was more intensified by the presence of the drug.

The effect of the drug's initial load on the release kinetics and on the concurrent water uptake is shown in Figure 9(a,b). In all cases the increase of the initial drug load led to increased water sorption. This may be attributed to: (a) the increased number of drug-containing pores that may be filled with water upon the elusion of the drug and (b) higher extensibility of the polymeric network, due to the interference of the drug in the crosslinking reaction.

Apparent Permeability Coefficients of Theophylline. The release kinetics curves of Figures 8(a) and 9(a), present extensive linear parts on a $t^{1/2}/L$ scale and under certain conditions may be approached by Higuchi release kinetics,[51,52] for supersaturated systems. The drug particles are uniformly dispersed in all films studied and their size is small (ca. 2–8 μm) compared to the diffusion path (ca. 230 μm, i.e., the average film thickness). The initial drug concentration, C_{D0}, is well above the saturation limit of the drug in the swollen matrix, C^o_{DS}. The latter can be estimated by the use of the K_D values and the drug's solubility in water c^o_{DS} (11 mg/cm^3 at 37°C), assuming constant K_D. The calculated C^o_{DS} values ranged between 0.15 mg/cm^3 for pure SR films to 3.0 mg/cm^3 for SR/PEG-4 films, i.e., at least 20 times lower than the drug loads C_{D0} studied here (~ 60 and 130 mg/cm^3). The Higuchi model is strictly applicable under conditions of fast water penetration (ensuring effectively uniform hydration of the matrix throughout the experiment). This condition is not totally fulfilled here, because osmotically driven water is imbibed during the release process. However, as an approximation, we may use eq. (4), describing Higuchi kinetics:

$$\frac{Q_{D,t}}{Q_{D,\infty}} \cong 2\sqrt{\frac{2D_D C^o_{DS} t}{L^2 C_{D0}}} \qquad (4)$$

Table V. Release Experiments Results

Film	Water sorption at the end of release (g/g)	Apparent permeability coefficient P_D (10^{-10} cm^2/s)
SR/T 6	0.05 ± 0.00	1.7 ± 0.2
SR/T 13	0.08 ± 0.01	2.9 ± 0.0
SR/PEG-2/T 6	0.18 ± 0.00	4.0 ± 0.7
SR/PEG-2/T 13	0.28 ± 0.01	8.6 ± 0.7
SR/PEG-4/T 6	0.67 ± 0.01	4.8 ± 0.2
SR/AMPEG-2/T 6	0.04 ± 0.00	29.0 ± 2.0
SR/AMPEG-2/T 13	0.09 ± 0.01	96.9 ± 5.5

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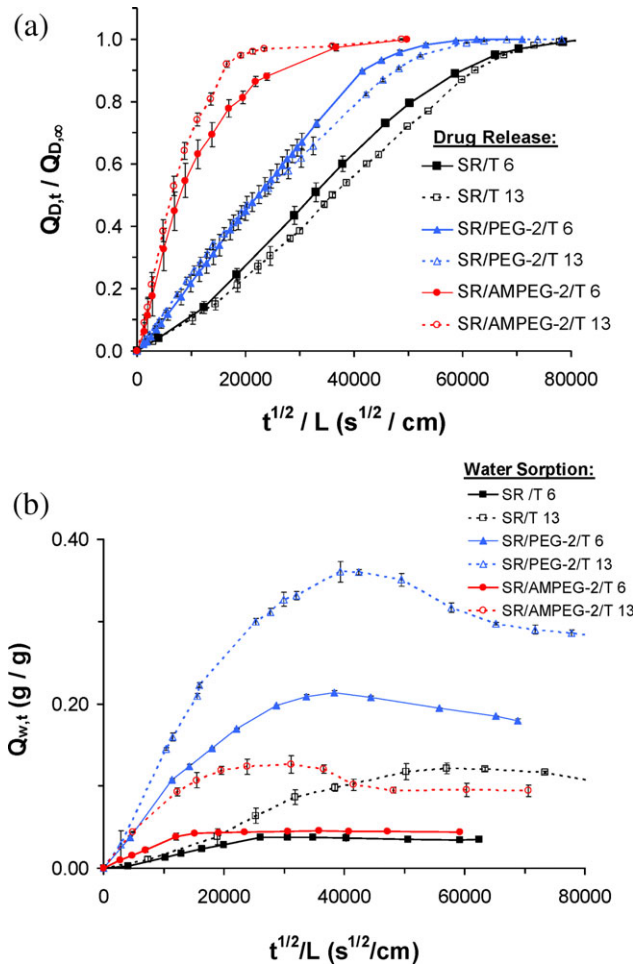

Figure 9. (a) Theophylline release kinetics and (b) concurrent water uptake from pure SR films, SR/PEG blends, and SR/AMPEG-modified films loaded at initial concentration 6.5 and 13% (w/w). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

where D_D is the diffusion coefficient of the drug. By replacing D_D in eq. (4) with P_D/K_D [$=P_D$ (c^o_{DS}/C^o_{DS})], the said equation transforms to eq. (5)[53]:

$$\frac{Q_{D,t}}{Q_{D,\infty}} = 2\sqrt{\frac{2P_D c^o_{DS} t}{L^2 C_{D0}}}. \quad (5)$$

The permeability coefficients derived from the slope of the linear parts of the release curves of Figures 8(a) and 9(a), on the basis of eq. (5), are given in Table V.

In the case of the blends loaded with 6.5% w/w drug, the apparent permeability coefficients of theophylline increase with increasing amounts of sorbed water, following the corresponding increase of the partition coefficients (Figure 7). Thus, in this case, the drug's permeability is directly affected by its enhanced affinity towards the matrix. Furthermore, as shown in Table V permeability coefficients increase with increasing initial drug concentration. This should be correlated with the corresponding enhanced water sorption of the matrices discussed above.

The permeability coefficients of SR/AMPEG films are higher than anticipated, given the small amounts of sorbed water. It appears that in this case, the rate controlling parameter is not exclusively the enhanced water uptake but also the lack of integrity in the polymeric network.

CONCLUSIONS

Hydrophilization of PDMS is sought in many medical applications. An effective modification should also retain, as much as possible, the mechanical properties of the material and the samples must be stable for the intended period of use.

In this work, we made a comparative study on the effect of the incorporation of ethylenoxy groups in PDMS networks through blending or chemical grafting. The simple method of blending with PEG 400 was found more effective than grafting of PEG moieties, both in terms of water swellability and wettability. Moreover, the blends exhibited limited interference with the curing reaction, and consequently with the mechanical properties, and minimal weight losses after one month of contact with water. The latter shows that leaching out of PEG was rather limited, at least for this period of use. In principle, however, the use of low-molecular weight compounds in blends may result to long-term migration and/or leaching phenomena. On the other hand, chemical modification seems less promising. Although covalent bonding was at least partially achieved, as evidenced by the FTIR spectra, the interference of the introduced AMPEG moieties with the crosslinking reaction leads to inferior mechanical properties and to poor drug release controlling properties.

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