Experimental Investigation of the Release Mechanism of Proxyphylline from Silicone Rubber Matrices

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ABSTRACT: The release process of a water soluble, model drug (proxyphylline) with small, yet not negligible osmotic action, from silicone rubber (SR) matrices is presented. The kinetics of release for different initial loads of the drug is supplemented by measurements of the kinetics of the concurrent water uptake. To gain insight on the relevant non-Fickian transport mechanisms, the morphology, the diffusion, and sorption properties of the drug-depleted matrices are studied. In addition, both drug-loaded and drug-depleted matrices are characterized with respect to their mechanical properties. The combined information derived from these techniques support—at least below the percolation threshold—the operation of a release mechanism occurring through a uniformly swollen polymer matrix without formation of cracks, in contrast to the release observed in the case of water soluble, inorganic salts where release takes place through a network of microscopic cracks. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 120: 821–830, 2011

Key words: silicones; drug delivery systems; diffusion; films

INTRODUCTION

Materials based on silicone rubber (SR) elastomers [crosslinked polydimethylsiloxanes (PDMSs)], because of their chemical inertness, good mechanical properties, and ease of processing, have been widely used over the past years in drug delivery systems of lipophilic drugs in an aqueous environment.[1–5] In these cases, the release takes place by the diffusion of the drug through the hydrophobic, polymeric phase of the matrices and thus follows square root release kinetics, usually characterized by a constantly declining release rate. Furthermore, it has also been demonstrated that any restrictions posed by the intrinsically hydrophobic environment of these matrices can be overcome by the use of silicone rubber and hydrogel-based composite materials[6–8] or by the presence of water-soluble excipients.[9]

Since many hydrophobic polymers are widely accepted as materials with excellent biocompatibility properties, their use as carriers of hydrophilic drugs, such as hydrophilic proteins,[10] has gained significant interest during the last years. However, the release profiles of the water-soluble excipients and of hydrophilic organic molecules, although present similarities, are governed by different release mechanisms. In the former case, the osmotic action of the water-soluble excipients causes excess sorption of water, which in turn may give rise to non-Fickian release kinetics because of the formation of a microscopic crack network that allows the release of these water-soluble excipients. This mechanism was proposed by Schirrer et al.[11] and Amsden et al.[12–14] and was further supported experimentally by our previous report,[15] where we have presented results on the release process of three inorganic salts of various osmolalities from silicone rubber elastomeric matrices.

On the other hand, the release of a drug from a matrix follows $t^{1/2}$ (t = time) kinetics and two distinctive cases are reported, depending on whether the drug's initial concentration in the matrix is above or below its solubility in the polymer. When the solvent's influx is very rapid compared with the drug's release and the drug's initial concentration is below its solubility in the polymer, the release profile of the drug is diffusion-controlled, following Fickian release kinetics.[16] On the other hand, if the drug's initial concentration C_{D0} is substantially above its solubility in the polymer C^o_{DS} and if we assume that: (a) the presence of the dispersed solute has no material effect on the transport properties of the matrix and (b) instantaneous equilibrium exists between dissolved (mobile) and dispersed (immobile) solute then the release follows Higuchi kinetics.[17,18] In the latter case, the fractional amount of drug release $Q_{D,t}/Q_{D,\infty}$ ($Q_{D,t}$ and $Q_{D,\infty}$: amounts of drug released at times t and at $t\rightarrow\infty$ respectively) is given by eq. (1):

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$$\frac{Q_{D,t}}{Q_{D,\infty}} \cong 2\sqrt{\frac{2D_D C^o_{DS} t}{L^2 C_{D0}}} \quad (1)$$

for $C_{D0} \gg C^o_{DS}$, where D_D is the diffusion coefficient of the drug through the polymer and L is the matrix thickness. Following eq. (1), we expect a more prolonged linear part on the drug's release curve versus a $t^{1/2}$ scale compared to Fickian release kinetics. When the solute's release rate is comparable with that of the solvent penetration, the fractional amount of release versus $t^{1/2}$ tends to become sigmoidal and the corresponding $Q_{D,t}/Q_{D,\infty}$ versus t plot exhibits a quasi-linear middle portion, indicating that a nearly constant release rate can be approached.[19–21]

In this work, we report the experimental study on the release kinetics of a uniformly dispersed, hydrophilic model drug (proxyphylline) from SR monolithic matrices to gain further insight on its kinetic behavior and compare it with the previously reported results on inorganic salts. The study is supplemented by parallel measurements of: (i) the concurrent variation of the water content of the matrices, (ii) the permeation properties of the drug-depleted matrices, and (iii) the mechanical properties of loaded and depleted matrices.

EXPERIMENTAL METHODS

Materials

Poly(dimethylsiloxane)-PDMS (RTV 615 type) was kindly supplied by General Electric (Leverkusen, Germany). The silicone kit was a two component system, consisting of a vinyl-terminated prepolymer with high molecular weight (part A) and a crosslinker containing several hydride groups on shorter PDMS chains (part B). The curing of the PDMS-membrane occurs via Pt-catalyzed hydrosilylation reaction to form a densely crosslinked polymer network.

The drug used was 7-(β-hydroxy-propyl)theophylline ($C_{10}H_{14}N_4O_3$), also known as proxyphylline (Sigma-Aldrich, Germany) with $M_w = 238.24$ g/mol. The drug's particle size was below 1 μm and was evaluated by means of optical and SEM microscopy of the loaded matrices. Proxyphylline's density and solubility in water at 25°C, c^o_{DS} were 1.36 g/cm^3 and 2.31 mol/L respectively. The corresponding osmotic pressure, Π of the drug's saturated solutions at 25°C was found to be ~ 14 atm. It was calculated according to the methodology described in detail in Ref. 9 by the use of the experimentally determined freezing point depression of the saturated drug solution [$\Delta T_f = 1.10°C \pm 0.17°C$], by means of a model 2920 Modulated Differential Scanning Calorimeter-MDSC (TA Instruments, New Castle, DE), with a modulated signal of ± 0.796°C every 60 s and a 5°C/min heating rate from −50°C to 40°C.

Preparation of matrices

Neat (i.e., drug-free) films (thickness, $L = 400$ μm) were prepared by mixing prepolymers A and B (10 : 1 w/w) with a mechanical stirrer at 400 rpm, degassing *in vacuo*, and then casting onto a poly(propylene)-coated plate by the means of a doctor's knife. The cast films were cured at 100°C for 1 h according to the supplier's instructions to accelerate the crosslinking reaction.

Since there weren't any common solvents between the prepolymers and proxyphylline, the drug-loaded films ($L = 390$–410 μm) were obtained by dispersing the drug particles in the fluid prepolymer mixture (10 : 1 w/w) prior to degassing and curing. The films contained proxyphylline in three different concentrations 7.38, 15.03, and 30.05% w/v : g of drug per 100 cm^3 of matrix, corresponding to volume fractions v_D: 0.054, 0.110, and 0.221 respectively, comparable with the volume fractions used for the preparation of salt-loaded matrices of Ref. 15. It should be noted that to check the reproducibility of the results at least two matrices corresponding to each concentration were prepared.

Drug release and concurrent water uptake experiments in drug-loaded matrices

Three samples of 2 × 2 cm^2 lateral dimensions were cut from each of the drug-loaded films and mounted on stirring rods, rotating at 37 rpm in frequently renewed, known volumes of distilled water, thermostatted at 25°C ± 0.1°C. The amount of drug released was measured at suitable times t and at $t \to \infty$ ($Q_{D,t}$ and $Q_{D,\infty}$ respectively) by means of a UV/Vis Spectrophotometer (V-630 Jasco, Japan) at 275 nm. The concurrent variation of the water content of the films ($Q_{w,t}$ at time t and $Q_{w,\infty}$ at $t \to \infty$) was monitored by weighing the blotted films at suitable time intervals by taking into account the amount of drug that was released. At the end of the release experiments, the films were dried and weighed to check the amounts of any permanently trapped drug particles.

Morphology, mechanical properties, and estimation of the degree of crosslinking

The morphology of the SR membranes was evaluated in the cross sections of the films, both for the drug-loaded and the drug-depleted matrices, by the use of a scanning electron microscope (Leo 440 SEM, Leo, Germany) and an optical microscope (Pol U-Amplival, Jena, Germany) equipped with a camera.

Furthermore, specimens of lateral dimensions 1 × 0.1 cm^2 and of thickness varying from 390 to 410 μm were cut from the neat films and from both the drug-loaded matrices and the dried, drug-depleted ones to test their mechanical properties and acquire the tensile modulus of elasticity. The instrument used, was the TENSILON UTM-II-20 (Toyo Baldwin, C.O. Ltd., Japan), and the stress–strain tests were performed with a strain rate of 20 mm/min at room temperature and 70% relative humidity.

Finally, the degree of crosslinking of the neat and the drug-loaded films was estimated by measuring the degree of swelling q ($q = 1 + V_{n\text{-hex}}/V_{SR}$, where $V_{n\text{-hex}}$ is the volume of the imbibed n-hexane and V_{SR} is the polymer volume that corresponds to each dry matrix) and correlating it with the mean molecular weight by number between two consecutive crosslinks $\overline{M}_c$, through the following equation:

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

which is an approximated expression derived from the Flory-Rehner theory.[22] In eq. (2), υ is the specific polymer volume (0.98 cm^3/g for silicone rubber), χ is the Flory-Huggins parameter for the linear PDMS and solvent system ($\chi = 0.4$ for the linear PDMS[23]), and $\overline{V}_S$ is the molar volume of the solvent (132 cm^3/mol). The experiments were performed[24] at room temperature by immersing the films in n-hexane containing stoppered bottles as a precautionary measure to avoid evaporation of n-hexane and weighing them until they had reached constant weight.

The results were correlated with the measured T_g values of the neat and the drug-loaded matrices, obtained by means of the 2920-MDSC, in which the samples were originally cooled at −150°C and then heated with a nonmodulated signal and a 5°C/min heating rate up to 20°C.

Determination of drug and water transport properties in drug-depleted and neat SR matrices

At least six dried, drug-depleted matrices (i.e., three matrices per film of the same initial load) were immersed into a 0.1 g/cm^3 proxyphylline solution for a time period of 30 days. During this period, the samples were periodically removed from the solution, blotted, and weighed until they had reached a constant weight. Then they were blotted, rinsed with distilled water and placed into a known volume of distilled water. The proxyphylline desorption kinetics was monitored by the means of the UV/Vis Spectrophotometer. After proxyphylline's desorption was concluded, the films were removed from water, blotted, weighed, and then dried again to obtain the weight of the dry polymer and compare it with the corresponding values obtained after the release experiments.

The diffusion coefficients D_D of proxyphylline were obtained from the initially linear part of the $Q_{D,t}/Q_{D,\infty}$ versus $t^{1/2}/L$ plots by use of eq. (3)[16]:

$$\frac{Q_{D,t}}{Q_{D,\infty}} = 4\left(\frac{D_D t}{\pi L^2}\right)^{1/2} \tag{3}$$

Partition coefficients K_D ($= C_{DS}/c_{DS}$, where C_{DS} and c_{DS} are the drug's concentration inside the matrix and in water respectively) were calculated according to eq. (4):

$$K_D = \frac{C_{DS}\ (\text{in g of drug/cm}^3\ \text{of hydrated matrix})}{c_{DS}\ (\text{in g of drug/cm}^3\ \text{of equilibrating solution})} \tag{4}$$

The permeability coefficient P_D was calculated as the product of the corresponding values of D_D and K_D. Finally, the intrinsic partition coefficients $k_{s,D}$ were calculated according to eq. (5):

$$k_{s,D} = \frac{\text{g of drug/cm}^3\ \text{of imbibed water}}{\text{g of drug/cm}^3\ \text{of equilibrating solution}} \tag{5}$$

In contrast to the depleted matrices, the neat SR matrices could not sorb any measurable amounts of proxyphylline from the equilibration solution. Hence, to measure the corresponding values of P_D, D_D, and K_D, a permeability apparatus consisting of two side by side cells with volume capacity of 3 cm^3 each was used. The two cells were at all times thermostatted at 25°C and contained proxyphylline solution 0.1 g/cm^3 (donor cell) and distilled water (receptor cell), respectively. Matrices were placed between the two cells (each with an opening of 0.78 cm^2), and at frequent time intervals the solution of the receptor cell was removed and replaced by distilled water. The concentration of proxyphylline was measured by means of the UV/Vis spectrophotometer as above. Permeation data were treated in the basis of eq. (6)[16]:

$$\frac{1}{A}\cdot\frac{dQ_{D,t}}{dt} = P_D\frac{(c_o - c_L)}{L} \tag{6}$$

where $(dQ_{D,t}/dt)$ $(1/A)$, the permeation flux, is the slope of the linear portion of the cumulative amount permeated per unit surface area versus time plot, L is the matrix thickness, A is the matrix surface, and c_o, c_L are the drug's concentrations in the donor and receptor cells respectively. The diffusion coefficient D_D of the drug was estimated from the lag time t_L ($t_L = L^2/\ 6D_D$) of the corresponding graphs of $Q_{D,t}$ versus t.

Finally, to estimate the water sorption kinetics by dried, drug-depleted matrices, the said matrices were immersed in distilled water at room temperature. Consequently, they were periodically removed from water, blotted, and weighed until constant weight was reached. The apparent diffusion coefficients of water D_w in the depleted matrices were estimated from the initial linear part of the $Q_{w,t}/Q_{w,\infty}$ versus $t^{1/2}/L$ plots, by the use of eq. (3).

RESULTS AND DISCUSSION

Drug release and concurrent water uptake experiments in drug-loaded matrices

Representative plots of the fractional amount $Q_{D,t}/Q_{D,\infty}$, of proxyphylline release from drug-loaded matrices with various amounts of drug versus time t are shown in Figure 1(a). For every initial load two plots are given, corresponding to each of the two films prepared with the same initial loads.

As shown by the extended linear part on a $t^{1/2}$ scale, in Figure 1(c), the release of proxyphylline for the two lower initial loads (i.e., $v_D = 0.054$ and 0.110) is diffusion controlled. Increasing the initial load to $v_D = 0.221$ caused a significant increase of the release rates.

As shown in Figure 1(b), the concurrent variation of the water content of the films $Q_{w,t}$ (g of imbibed water per g of dry polymer) appeared to follow an initial rise to a maximum value $Q_{w,\max}$, followed by a decline to a final value $Q_{w,\text{final}}$ in the drug-depleted films, which is noteworthy since it showed that proxyphylline appeared to have a small —compared with inorganic salts—but not negligible osmotic action ($\sim$ 14 atm) compared with 346, 53, and 551 atm of NaCl, $CsNO_3$, and CsCl, respectively.[15]

The results of $Q_{D,\infty}$, $Q_{w,\max}$ and, $Q_{w,\text{final}}$ are summarized in Table I, where mean values of six samples (three samples per film with the same initial load) are given for each of the three different studied loads.

Matrices with $v_D = 0.054$ appeared to have comparable release rates to those with $v_D = 0.11$. On the other hand, the concurrent water uptake was significantly higher in the latter case (Table I). It appears thus that proxyphylline's diffusion does not take place exclusively through the water filled cavities, but through the polymeric phase as well. To interpret this behavior, we approached the studied system by the use of Higuchi's model, although osmotically driven water was imbibed inside the matrices and therefore not all the criteria of the model were met. Since C^o_{DS} was unavailable, by replacing D_D in eq. (1) with P_D/K_D [$= P_D \cdot (c_{DS}/C_{DS}) = P_D \cdot (c^o_{DS}/C^o_{DS})$], where c^o_{DS} is the drug's solubility in water (0.55 g/cm^3 at 25°C), the said equation transforms to[18]:

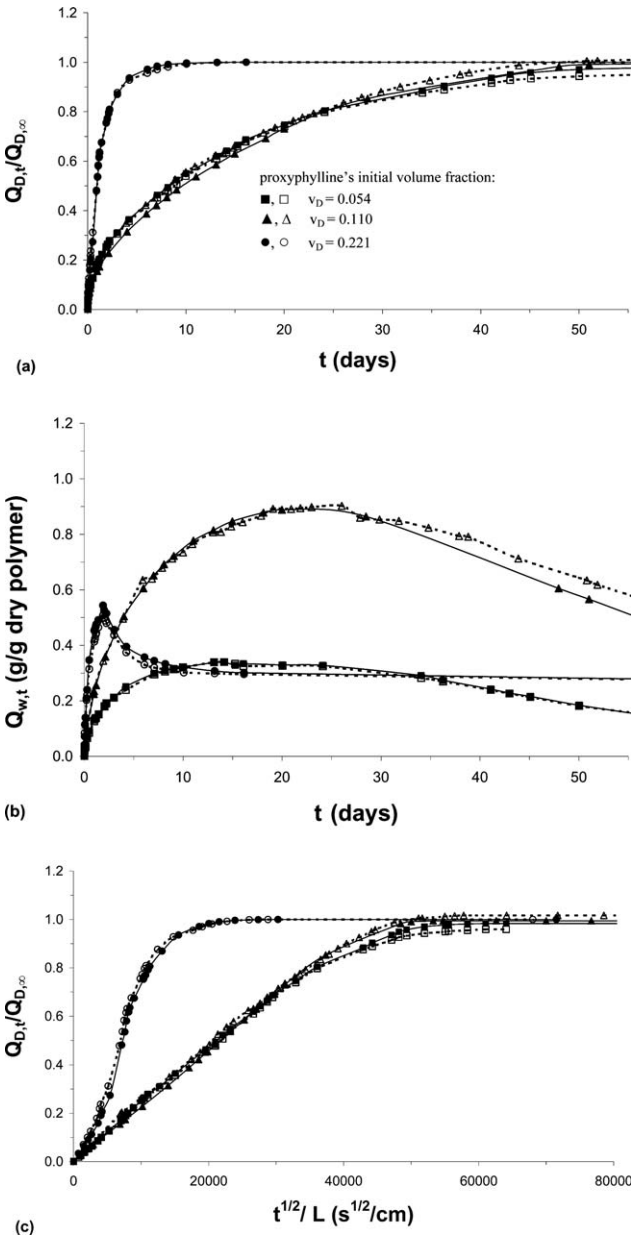

Figure 1 (a) Fractional proxyphylline release kinetic curves plotted on t-scale for initial volume fractions v_D = 0.054–0.221. (b) Corresponding variations of osmotically induced water uptake during the drug's release. (c) Data of Figure 1(a) replotted on a normalized $t^{1/2}/L$ scale. Matrices' thickness L = 390–410 μm. Two curves are given for each load.

$$\frac{Q_{D,t}}{Q_{D,\infty}} = 2\sqrt{\frac{2P_D c^o_{DS} t}{L^2 C_{D0}}} \tag{7}$$

Then, from the slopes of the release curves versus $t^{1/2}$ [Fig. 1(c)], we were able to estimate the drug's apparent permeability coefficients P_D (Table I). The said coefficients appear to increase with increasing initial load. Concerning the matrices with the two lower initial loads, the increase of P_D for matrices with $v_D = 0.110$ compared with that of $v_D = 0.054$ is

TABLE I
Results from Proxyphylline's Release and Concurrent Water Uptake Experiments in Drug-Loaded Matrices: Total Amount of Released Drug, Maximum, and Final Water Uptake

v_D	Total amount of released drug $Q_{D,\infty}$ (g of drug/g of dry polymer)	Water uptake at maximum $Q_{w,max}$, (g/g of dry polymer)	Final water uptake $Q_{w,final}$, (g/g of dry polymer)	Permeability, P_D[a] (10^{-10} cm^2/s)
0.054	0.073 ± 0.003	0.345 ± 0.011	0.067 ± 0.004	0.08 ± 0,00
0.110	0.161 ± 0.002	0.889 ± 0.011	0.154 ± 0.002	0.18 ± 0,00
0.221	0.381 ± 0.001	0.499 ± 0.031	0.263 ± 0.003	4.52 ± 0,02

[a] Permeability coefficient calculated through eq. (7).

not so intense (just twofold) and is attributable to the excess osmotically induced water uptake. Thus in this case, the expected by eq. (7) depression of the release rate, because of the larger C_{D0} values, is compensated by the contribution of water.

A rather different picture emerges for matrices with $v_D = 0.221$. In this case, P_D increases sharply and the diffusion release kinetics deviate from $t^{1/2}$ release kinetics although the water uptake is not the highest among the other two cases. As shown in previous works,[18,25] when the initial load of a solute exceeds the percolation threshold, it enables the particles to interconnect and/or allows the facile formation of microscopic cracks because of thin polymeric walls. This in turn, leads to the formation of an intraconnected pore network through which the solute may be rapidly released. The rapid release of the drug consequently led to the quick reduction of the osmotic action inside the matrices and ultimately to the lower water uptake maximum [Fig. 1(b)].

Morphology, mechanical properties, and estimation of the degree of crosslinking (of neat, drug- loaded and drug-depleted matrices)

Representative SEM micrographs of neat, drug-loaded and the corresponding drug-depleted film are given in Figures 2(a–c). As shown, the drug is homogeneously dispersed in the matrices and small cavities are formed after the release. In Figure 2(d) the same drug-loaded film is photographed by means of an optical microscope while swollen, during the release process.

The experimentally determined values of the swelling degree of neat and drug-loaded matrices in *n*-hexane q were correlated to the mean molecular weight by number between two consecutive crosslinks $\overline{M}_c$, through eq. (2), in analogy to Refs. 15 and 22. Results are shown in Table II, where values of $\overline{M}_c$, are normalized to $\overline{M}_{c,SR}$, referring to the neat SR matrices of standard crosslinking.

In all cases, the $\overline{M}_c/\overline{M}_{c,SR}$ ratio exceeded unity, pointing to a lower crosslinking degree, despite the fact that the mixing ratios of parts A and B were the same in all cases (i.e., 10 : 1 w/w). Although the increase of q, especially at the two higher loads, may be partially because of the solvent filling any gaps between the polymer and the embedded drug particles, it is also plausible to assume that at the molecular level the drug might have hindered the extent of the vinyl-to-(Si—H) reaction and ultimately led to a lower degree of crosslinking. It should also be noted that the occurrence of any reaction between the drug and the fluid prepolymer mixture was excluded, since no peak corresponding to any reaction, was detected by DSC in the corresponding thermographs of the said mixture. The same effect was observed in the case of NaCl-loaded matrices at salt loads[15] above 0.07, but the phenomenon was less pronounced. In line with these results are the T_g values. As shown in Table II, all matrices exhibited a small, but not negligible, decrease of the T_g compared with the T_g values of the neat SR samples, verifying thus a lower degree of crosslinking.

To further verify the above results, stress–strain tests were performed for all concentrations of drug-loaded matrices and of the corresponding dried, drug-depleted ones, along with this of neat SR. Typical curves for all the aforementioned cases are shown in Figure 3(a), where f is the exercised stress and ε is the strain ($\varepsilon = \Delta L/L_o$, ΔL elongation, L_o initial sample length). The Young's modulus is calculated from the slope of the initial linear part of the aforementioned curves and for the neat SR matrices it was found to be $E_{SR} = 0.91 \pm 0.02$ MPa, in line with literature values (0.92 MPa,[26] $\sim$ 1 MPa[27]).

As shown in Figure 3(b), the presence of the drug reduced the Young's modulus of the matrices with $v_D = 0.054$ below 0.91 MPa, whereas the corresponding values of the other two films were higher than that of the SR matrices. After the drug's release, the corresponding values of E reduced below E_{SR} (corresponding to the neat SR matrix) to an almost constant value $\sim$ 0.61 MPa.

The experimental results of the Young's modulus may be correlated to theoretical predictions if we regard the drug-loaded matrices as binary systems consisting of: (a) a neat polymer continuum of Young's modulus E_{SR} (neat SR in our case), occupying volume fraction $v = 1 - v_D$ and (b) of

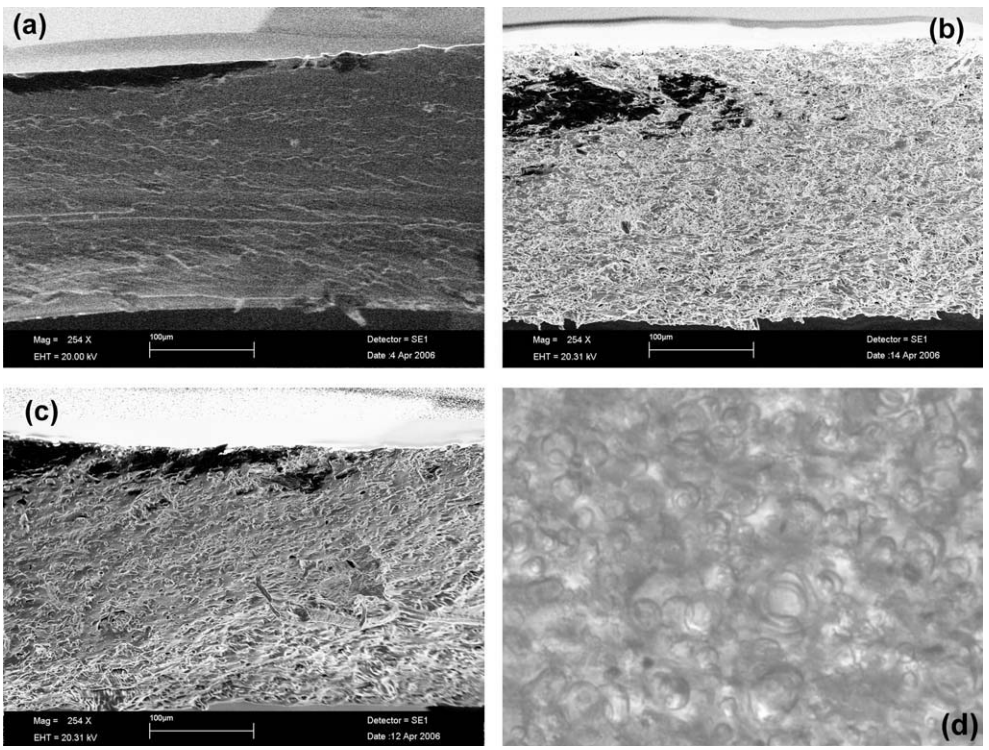

Figure 2 SEM micrographs of (a) SR matrix, (b) matrix containing proxyphylline at $v_D = 0.221$, (c) same matrix after the drug's release, and (d) same matrix while swollen by osmotically imbibed water (photo taken by means of optical microscope).

interspersed drug particles of volume fraction $v_{D,}$ with an infinite Young's modulus E_D and use the appropriate formula describing the dependence of E/E_{SR}, from the volume fraction of the drug.[28] The formula introduced by Maxwell is:

$$\frac{E}{E_{SR}} = 1 + 3v_D\left(\frac{a+2}{a-1} - v_D\right)^{-1} \quad (8)$$

where $a = E_D/E_{SR}$. For high values of E_D ($a \rightarrow \infty$) eq. (8) reduces to:

$$\frac{E}{E_{SR}} = 1 + \frac{3v_D}{1 - v_D} \quad (9)$$

Regarding the drug-depleted matrices, we can assume that the volume previously occupied by the drug particles is now occupied by air, with $E_D \ll E_{SR}$. Thus, for $a \rightarrow 0$, eq. (8) reduces to:

$$\frac{E}{E_{SR}} = 1 - \frac{3v_D}{2 + v_D} \quad (10)$$

The dashed lines shown in the E versus v_D graph of Figure 3(b) are calculated from eqs. (9) and (10) using the experimentally determined value E_{SR} (0.91 MPa).

The experimental E data, for both the drug-loaded and the drug-depleted matrices, follow the same trends with v_D as the corresponding theoretical curves but are vertically transposed. In fact, they fit fairly well (on the overall) to the theoretical predictions of eqs. (9) and (10) with $E_{SR} = 0.71$ MPa [continuous lines in Fig. 3(b)]. These results point to a lower crosslinking degree of loaded matrices, as compared with neat ones, and are in line with results of the swelling in *n*-hexane experiments (see above). They are also in line with the findings of other works,[29] where the addition of a hydrophilic drug caused the deterioration of the SR mechanical properties.

It should also be noted in the case of drug-depleted matrices, although the experimental E values are lower than 0.71, they show positive deviation from the theoretically predicted (especially at $v_D = 0.221$), indicating that in this case the volume left

TABLE II
Degrees of Swelling in *n*-Hexane (q), Molecular Weight Ratios ($\overline{M}_c/\overline{M}_{c,SR}$), and Glass Transition Temperatures T_g for Neat Matrices and Matrices Containing Proxyphylline at Volume Fraction v_D

v_D	q	$\overline{M}_c/\overline{M}_{c,SR}$	T_g (°C)
0	2.46 ± 0.03	1	−125
0.054	3.05 ± 0.09	1.44 ± 0.03	−128
0.110	3.55 ± 0.04	1.86 ± 0.02	−128
0.221	3.69 ± 0.08	1.96 ± 0.02	−128

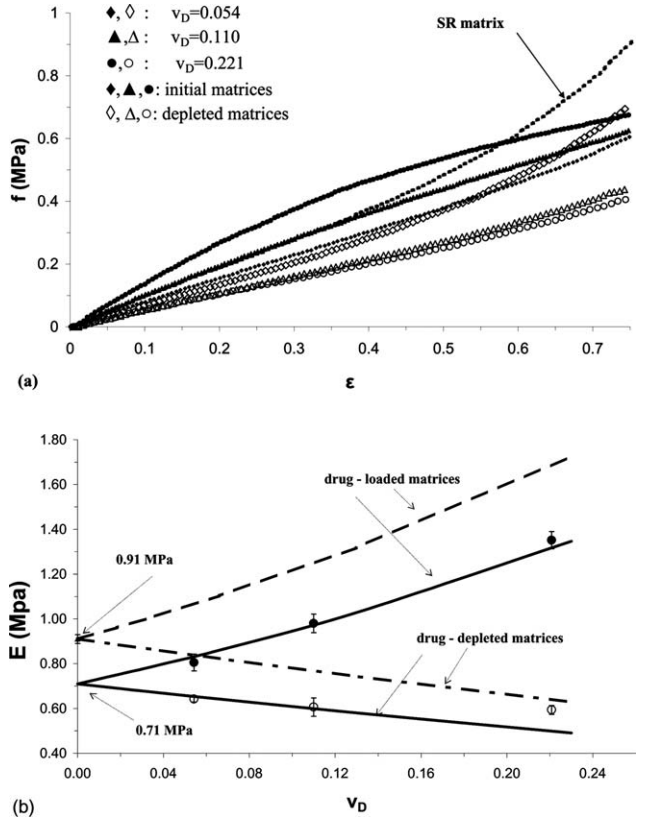

Figure 3 (a) Stress–strain curves for drug-loaded matrices (closed points) and the corresponding drug-depleted ones (open points) with proxyphylline at $v_D = 0.054$ (◆,◇), 0.110 (▲,Δ), and 0.221 (●,○). (b) Experimental (points) and theoretically predicted (lines) Young's moduli E. Lines were produced by setting $E_{SR} = 0.91$ MPa (dashed lines) and $E_{SR} = 0.71$ MPa (continuous lines) in eqs. (9) and (10) for drug-loaded and drug-depleted matrices, respectively.

after the drug's release is reduced because of partial healing of the remaining pores in the polymeric matrices, which was further verified by water sorption experiments (see below).

Finally, we reach the conclusion that the Young's modulus of the drug-loaded matrices is a combination of two antagonistic factors related to the drug's presence: (a) the reduction of the degree of crosslinking because of hindrance of the crosslinking reaction and (b) the formation of a binary polymer-drug system, which leads to the increase of the Young's modulus. It appeared that for initial loads below 0.11, the predominant factor is the reduction of the crosslinking degree, which explains the lower than 0.91 MPa E values, which progressively increases with increasing initial loads and eventually allow the drug particles to have a more substantial contribution to the total Young's modulus.

Determination of drug and water transport properties in drug-depleted and neat SR matrices

The results of drug sorption–desorption experiments are summarized in Table III. The partition coefficients K_D were found to be two orders of magnitude below unity, showing low solubility in the polymer matrix. Although small, K_D was found to be one order of magnitude above the corresponding K_N values derived from NaCl sorption experiments in SR matrices,[15] showing greater affinity of the drug molecule toward the polymer. Finally, by the use of the values of K_D (Table III) and the drug's solubility in water (experimentally found 0.55 g/cm^3 at 25°C), we were able to calculate the saturation concentration of proxyphylline in the depleted SR matrices (assuming constant K_D). The said concentration ranged between 0.017 g/cm^3 for depleted matrices initially with $v_D =$ 0.054 to $\sim$ 0.024 g/cm^3 for the matrices with the other two higher loads. This showed that the initial concentrations were at least five times higher than the drug's solubility and hence the approach of the release kinetics by Higuchi's model is justified.

Furthermore, from the estimated intrinsic partition coefficients $k_{s,D}$, it is deduced that proxyphylline's concentration in the sorbed, by the matrices, water was comparable with that of the equilibrating solution, pointing to the greater affinity of the drug towards water than the polymer. Results also show no exclusion of the drug from the polymer compared to inorganic salts, where the corresponding $k_{s,N}$ values were substantially below unity (of the order of 10^{-2}).[15]

Moreover, the diffusion coefficients of proxyphylline D_D that were calculated from the first linear part of desorption curves plotted versus $t^{1/2}/L$ were found to be three orders of magnitude lower than those of NaCl calculated for salt-depleted SR matrices,[15] and were practically not dependant on the initial volume fraction of the drug (v_D). This was because of the fact that the matrices, regardless of the initial v_D, sorbed practically the same amounts

TABLE III
Results from Sorption–Desorption of Proxyphylline Experiments in Drug-Depleted Matrices Initially Loaded at v_D

v_D	$Q_{D,eq}$ (10^{-3} g/g dry polymer)	$Q_{w,eq}$ (g/g dry polymer)	$Q_{w,final}$ (g/g dry polymer)	$k_{s,D}$	D_D (10^{-10} cm^2/s)	K_D (10^{-3})	P_D (10^{-10} cm^2/s)
0.054	3.4 ± 0.1	0.028 ± 0.001	0.035 ± 0.002	1.19 ± 0.03	10.3 ± 0.3	32.6 ± 0.9	0.348 ± 0.008
0.110	4.8 ± 0.1	0.041 ± 0.001	0.061 ± 0.002	1.16 ± 0.04	7.3 ± 0.1	45.8 ± 0.7	0.334 ± 0.010
0.221	4.7 ± 0.2	0.041 ± 0.004	0.053 ± 0.004	1.16 ± 0.06	13.9 ± 1.2	44.5 ± 2.1	0.614 ± 0.041

TABLE IV
Results from Permeability Experiments in Drug-Depleted Matrices Initially Loaded at v_D

v_D	D_D (10^{-10} cm^2/s)	K_D (10^{-3})	P_D (10^{-10} cm^2/s)
0	15.3 ± 1.0	22.1 ± 1.5	0.338 ± 0.004
0.054	10.8 ± 0.5	33.4 ± 4.1	0.361 ± 0.017
0.110	7.3 ± 0.1	46.7 ± 1.6	0.341 ± 0.011
0.221	12.9 ± 1.1	68.4 ± 6.1	0.883 ± 0.023

of water $Q_{w,eq}$ (Table III) because of shrinkage of the drug-containing pores, which in turn left the diffusion coefficients practically unaffected. In the case of the salt-depleted matrices, the corresponding D_N coefficients for NaCl were significantly larger compared with D_D because the diffusion of the salt was carried out exclusively through the water phase. Since the diffusion coefficient of NaCl in water ($\sim 1.6 \times 10^{-5}$ cm^2/s)[30] is of the same order of magnitude compared with the corresponding diffusion coefficient for the drug ($\sim 0.9 \times 10^{-5}$ cm^2/s),[31] the difference between D_N and D_D can only be interpreted by considering that the drug diffuses both through the water and the polymeric phase.

The permeability coefficients P_D were also found to be smaller compared with the corresponding P_N coefficients for NaCl, which means that the diffusion of the drug molecule inside the matrices was not carried out exclusively through water but also through the polymer, which consequently hindered the drug's diffusion.

As mentioned above, the neat SR matrices were not able to sorb any measurable amounts of proxyphylline. Therefore, the corresponding diffusion, partition, and permeability coefficients were measured by the use of the permeability apparatus. The results, along with those corresponding to the matrices that initially contained proxyphylline, are summarized in Table IV. P_D was measured from the steady-state slope of the Q_t plot versus t and D_D from the lag time t_L ($t_L = L^2/ 6D_D$), as shown in Figure 4. whereas K_D was derived as the quotient of P_D and D_D.

The results showed that the drug molecule can diffuse through the neat SR matrix and the diffusion coefficients D_D are very close to those measured for the drug-depleted films, verifying thus the conclusion that proxyphylline may diffuse through the polymer practically in the absence of water.

Comparing D_D and P_D coefficients, obtained from sorption-desorption or permeability experiments (Tables III and IV respectively), it appears that they are in good agreement. The only discrepancy can be found in the case of the permeability coefficients P_D, of the matrices that initially contained proxyphylline at $v_D = 0.221$. This can be explained by taking into account that the presence of an intraconnected pore network could lead to sufficient pathways, which in turn lead to a higher directly measured permeability. Finally, the comparison of the permeability coefficients P_D calculated by eq. (7), (Table I) to those of Tables III and IV showed that, although different, they were of the same order of magnitude. Their different values are attributable to the fact that the apparent permeability coefficients refer to the drug-loaded matrices; however the fact that they are in the same order of magnitude confirms that regardless of the environment in which proxyphylline's diffuses (i.e., drug-loaded or depleted and then equilibrated matrices), the diffusion regime is the same.

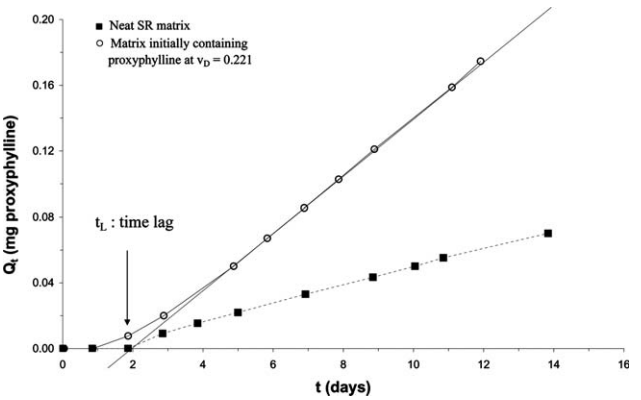

Figure 4 Representative graphs of proxyphylline's flux through a neat SR matrix (■) and a drug depleted matrix initially containing the drug at $v_D = 0.22$ (○). Thickness L = 390–410 μm.

The water sorption experiments showed that although the depleted matrices could sorb amounts of water, these were below the corresponding amounts at the end of the release experiments (Table V), leading to the assumption that the depleted drug-containing pores went under a permanent shrinkage, which reduced their original sizes and thus left only a limited volume for the sorption of water.

The kinetics of water uptake in drug-depleted were approached by assuming Fickian kinetics. The estimation of the apparent diffusion coefficients of water D_w was made by the use of eq. (3), and they were found to be of the order of 10^{-10} cm^2/s (Table V). Although smaller, compared with the D_w of water vapor in neat SR,[32,33] by four to five orders of magnitude, they appear to be in line with the D_w

TABLE V
Results from Water Sorption Experiments in Drug-Depleted Matrices, Initially Loaded at v_D

v_D	$v_{w,final}$ (release experiments)	$v_{w,final}$ (water sorption experiments)	D_w (10^{-10} cm^2/s)
0	0.00	0.00	
0.054	0.06	0.03	6.1
0.110	0.14	0.04	4.2
0.221	0.21	0.04	4.0

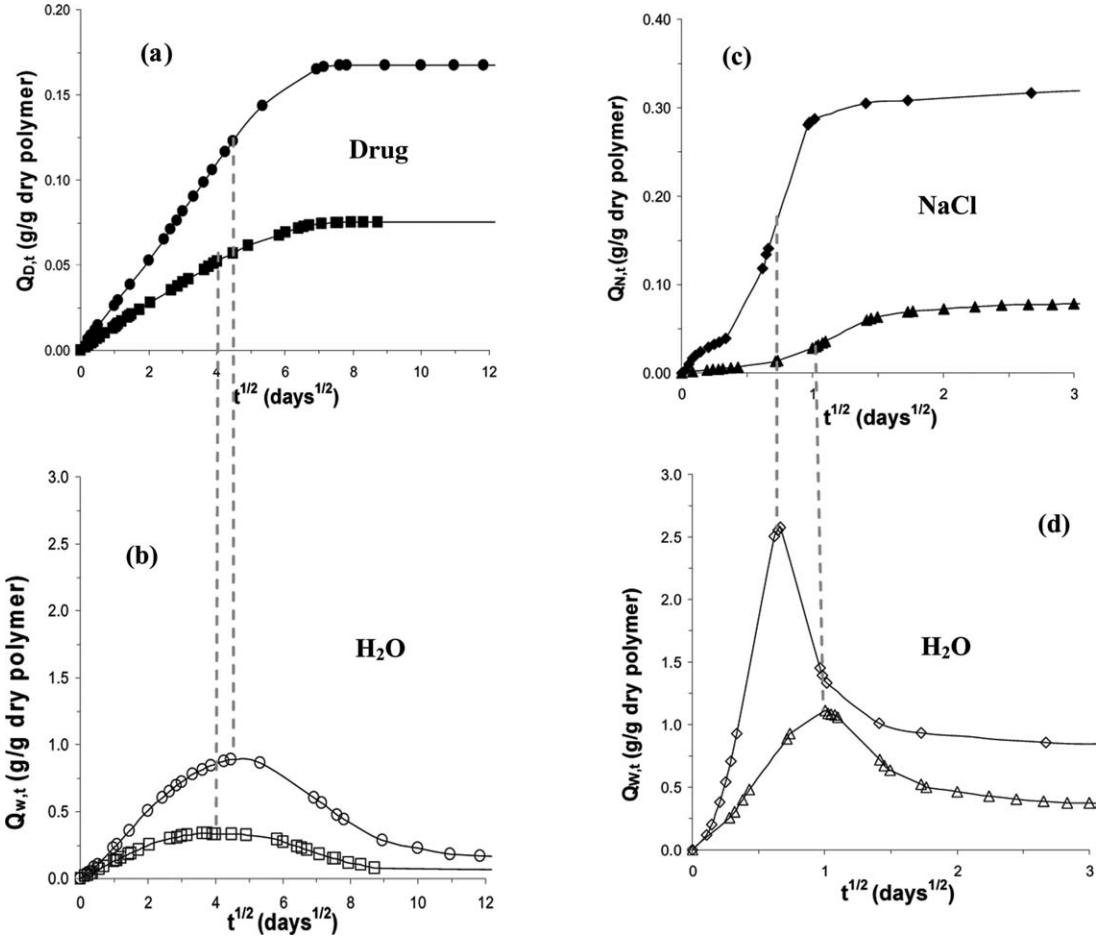

Figure 5 (a) Drug release kinetic curves on a $t^{1/2}$ scale for volume fraction 0.054 (■) and 0.110(●). (b) Corresponding variation of osmotically induced water uptake. (c) Salt release kinetic curves on a $t^{1/2}$ scale for volume fraction 0.036 (▲) and 0.130 (◆). (d) Corresponding variation of osmotically induced excess water uptake. Figures (c) and (d) are based on data from Ref. 15.

coefficients in saturated by water SR matrices.[34] Since no evidence supports the formation of an intra connected network analogous to the cases of the salt-loaded matrices,[11,15] it is plausible to assume that the observed water sorption could only be limited to superficial and/or easily accessible pores.

Discussion on the release mechanism

The overview of the release experiments of the hydrophilic, model drug studied above showed that:

i. The drug's release was not materially enhanced with increasing initial drug load v_D below the drug's percolation threshold. Only when the initial volume fraction v_D exceeded 0.22 the release rate was significantly enhanced.
ii. The water uptake reached a maximum during the release process, followed by a decline to the final value $Q_{w,\text{final}}$, which approached the volume v_D that the drug originally occupied inside the matrix.
iii. The release kinetics is complex when $v_D \geq 0.22$.

The above findings support a release mechanism carried out by the diffusion of the drug through both the polymeric and the water phase of the matrices. In all cases, the drug's initial loads are above its solubility in the polymer. Although part of the drug is dissolved in the polymer, the majority of the drug particles remain nondissolved, creating pores inside the matrices. Furthermore, the drug itself has an osmotic action, which provokes the influx of water inside these pores. As shown above, from sorption experiments, the drug's concentration inside the imbibed by the depleted matrices, water is almost the same as in the equilibration solution (i.e., 0.1 g/cm^3), since $k_{s,D}$ are practically equal to unity. Furthermore, although a number of pores remain after the drug's release, they heal to a volume fraction that is significantly lower than the drug's initial occupying volume. On the other hand, no evidence that would support the formation of microscopic cracks was supported by the mechanical properties of the matrices, the SEM micrographs, and the estimated diffusion coefficients (in the cases when $v_D \leq$

0.110). Therefore the presence of the drug created pores that consequently altered the inner environment through which the drug diffuses. On the one hand Higuchi's release mechanism is followed, supported by the extensive linear parts in the release curves versus the square root time scale [Fig. 5(a)], but on the other hand the presence of the osmotically induced water [Fig. 5(b)] alleviates the restrictions that the polymer itself would pose on the drug's diffusion. In contrast to what was found in the cases of the salt-loaded matrices,[15] where the excess water uptake [Fig. 5(d)] caused the acceleration of NaCl release kinetics, the release of the drug (in the cases when $v_D \leq 0.110$) appeared to have a continuously declining rate, practically unaffected by the presence of water. In this case the diffusion of the drug occurs by diffusion through a more uniformly and less extensively swollen polymeric matrix, in contrast to the release of highly-osmotically active salts where the excessive water uptake leads to the formation of a network of microscopic cracks. In the latter case the release follows non-Fickian release kinetics [Fig. 5(c)], which is characterized by more prolonged, constant release rates.

Finally, another interesting point is that although the osmotic pressure of a saturated NaCl solution is 25 times higher compared with the corresponding proxyphylline solution the respective ratio of imbibed water at maximum [Figs. 5(b,d)] is only 2.5 times higher. On a qualitative basis, this is attributable to the fact that the drug-loaded matrices, as mentioned above, are crosslinked at a lesser degree compared with the neat SR matrices and therefore present greater expandability, which in turn permits the imbibition of larger amounts of water without rupturing.[10]

CONCLUSIONS

A comparative study based on the combination of various experimental techniques allowed us to gain significant insight on the complex mechanisms operating during the release process of a hydrophilic model drug with osmotic action, initially dispersed in highly hydrophobic SR matrices.

The overall picture emerging by the study of the kinetics of drug release and concurrent water uptake in drug-loaded matrices is in line with a mechanism that follows square root t release kinetics, when the initial load is below the percolation threshold. In these cases, the mechanism followed the Higuchi model except for the observed water uptake. On the other hand, when the initial drug load exceeded the percolation threshold, the formation of an interconnected network of cavities during the release process is eminent, leading to the significant acceleration of the release kinetics. However, the relatively low degrees of hydration, combined with the drug's ability to diffuse through the polymer indicate that the predominant mechanism is diffusion. At sufficiently high loads a polymer wall rupture mechanism,[12] operating in parallel to the diffusion of the drug is also plausible.

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