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Regulation of proxyphylline's release from silicone rubber matrices by the use of osmotically active excipients and a multi-layer system

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ABSTRACT

In this work we present results on the modification of the release kinetics of a water-soluble model drug (proxyphylline) from silicone rubber (SR) matrices by either: (i) the incorporation of inorganic salts acting as osmotically active excipients in single-layer matrices, containing a uniform concentration of proxyphylline or (ii) by the use of three-layer matrices with distributed proxyphylline load. In relation to (i) our data show that the incorporation of inorganic salts, of varying water solubilities and in different initial loads, accelerated the release of proxyphylline and helped to the stabilization of its declining release rate. Drug release kinetics is supplemented by measurements of concurrent water uptake, and salt release, kinetics. In addition, in order to further investigate the release mechanisms of the drug and the salts, we studied the diffusion and sorption properties of the depleted polymeric matrix along with the morphology and the mechanical properties of the matrices either in the presence or after the depletion of the solutes. The combined information, derived from these techniques, supports a drug release mechanism occurring through an excessively swollen polymer matrix and accelerated by the formation of microscopic cracks generated by the osmotically active excipients. In relation to (ii) we studied a multi-layer device with proxyphylline-loaded inner layer and drug-free outer layers which practically diminished the initial burst effect and allowed the release of about 60% of the drug at a constant rate.

1. Introduction

Controlled release systems consisting of a polymer matrix incorporating a bioactive solute are known as monolithic or matrix-controlled release (MCR) devices. Research on such polymeric systems primarily aims at alleviating the pronounced initial burst effect and the continuously declining release rate, usually occurring in practice when solute release from monolithic matrices is mainly diffusion-controlled. These problems can be reduced by the use of multi-layer systems where the burst effect is diminished and the achievement of a constant release rate becomes more feasible (Abdul and Poddar, 2004; Papadokostaki et al., 2008). Another line of research focuses on extending the successful practical use of hydrophobic, biocompatible polymers as matrices for lipophilic bioactive substances, such as in Norplant™ (Venkatraman et al., 2000), to substances of a relatively hydrophilic nature. In this case, permeation of the solute through the polymer matrix can be markedly facilitated, and its release rate may be regulated, by the presence of osmotically active excipients, a methodology which has been applied to systems based on silicone elastomers. In particular, Carelli et al. (1989) have demonstrated the release of bovine serum albumin (BSA) in the presence of NaCl from silicone rubber (SR) matrices, Dash and Suryanarayanan (1992) have studied the enhancement that glycerol offers on the release of tobramycin, Kajihara et al. (2000) have studied the release of interferon in the presence of human serum albumin while Woolfson et al. (2006) have demonstrated the regulation of dapivirine through the use of lactose. Moreover, other relevant examples involve the release of interferon-gamma (Gu et al., 2005) and interleukin-2 or vascular endothelial growth factor (Gu et al., 2007) from degradable elastomers, synthesized from photo-cross-linked prepolymers of ω,ω,ω,-triacrylate [star-poly(ε-caprolactone-co-D,L-lactide)], by the use of an osmotic pressure delivery mechanism, produced by embedded excipients such as trehalose. Furthermore, quite recently, Chapanian and Amsden (2010a,b) demonstrated the release of BSA and two growth factors from poly(trimethylene carbonate) based elastomeric rods, in the presence of either trehalose or trehalose combined with NaCl as osmotigens.

The release mechanism of osmotically active solutes has been studied in detail in the case of hydrophobic matrices containing inorganic salts. Various models have been proposed to account for the observed kinetic behaviour of such systems taking into account both the properties of the osmotic solute and of the polymeric matrix (Amsden, 2003; Papadokostaki et al., 1998; Schirrer et al., 1992). According to these references, the particles, initially

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surrounded by the polymeric walls, upon their hydration are first dissolved to form an aqueous saturated solution. Due to the lower, compared to the outer surrounding solution, water activity of these solutions an activity gradient is created causing further imbibition of water in the particle-containing cavities. The imbibition of water is continued until the solution is diluted enough so that the resistive pressure of the surrounding polymeric wall equalises the osmotic pressure of the particle-containing pores. If the critical pressure, for the rupture of the polymer, is higher than the equilibrium pressure, then the particle-containing pore will swell to reach equilibrium without crack formation. In this case, the solute will either remain permanently trapped inside the matrix (as is the case of an inorganic salt) or, if it is able to diffuse through the polymer (as may be the case of an organic molecule), its release will be facilitated through the hydrated polymeric matrix following a $t^{1/2}$ kinetics (diffusion-controlled). If the pressure in the particle-containing cavity exceeds the resistance of the polymeric walls, microscopic cracks are formed (Schirrer et al., 1992; Soulas et al., 2009) and solute release is accelerated, through hydrated pathways, resulting in significant deviations from $t^{1/2}$ kinetics and leading to release rates approaching constancy for a substantial part of the release curve.

Evidently, the release of relatively hydrophilic organic molecules from hydrophobic matrices, containing strongly osmotic inorganic salts as excipients, is affected by the presence of these excipients. In previous work in our lab, the release mechanism from SR matrices containing as solute, either an inorganic salt (Soulas et al., 2009) or the water-soluble model drug proxyphylline (Soulas and Papadokostaki, 2011), has been studied in detail. It has been found that, in contrast to the crack-formation mechanism governing the release of salts, release of proxyphylline is mainly diffusion-controlled, although the particular drug presents a weak osmotic action of its own.

The main objective of the present work is to proceed to a detailed study of the release of proxyphylline from single-layer crosslinked poly(dimethylsiloxane) (PDMS) matrices in the presence of three different inorganic salts of varying osmotic pressure. Parallel to the kinetics of drug release, the kinetics of salt release and of water uptake was simultaneously monitored. In order to gain a more comprehensive view on the drug's release process, the results are combined with the study of the diffusion and sorption properties of the depleted matrices, supplemented by information on the morphology and the mechanical properties of the loaded and depleted matrices and discussed in the light of our previous findings concerning the release mechanisms of each one of the two solutes (proxyphylline and salt) independently of each other.

An alternative possibility of regulating a drug's release from polymeric controlled release systems is the use of multi-layer matrices with distributed load of the drug. Among the design strategies aiming at modulating the release rate [e.g. altering of the releasing surface of the matrix through its chemical modification (Wu and Brazel, 2008) or partial coating with a polymeric layer (Abdul and Poddar, 2004; Conte et al., 1993; Kajihara et al., 2001)], multi-layer matrices are attractive as they provide choice from a variety of parameters (permeability properties of the polymeric materials employed, distribution of solute load and the relative thicknesses of the layers) in order to achieve stabilization of the overall rate of release (Papadokostaki et al., 2008, 2009). In previous works, multi-layered systems made of cellulose acetate (Charalambopoulou et al., 2001) or PHEMA (Lu and Anseth, 1999) were loaded to different concentrations of model dyes and presented fine examples of composite matrices with uniform material properties that exhibited improved release performance compared to the respective monolithic system. In addition, multi-layer systems consisting of an inner loaded layer and coated with thin, solute-free layers (Bodmeier and Paeratakul, 1990; Huang et al., 1999, 2010; Nauman et al., 2010; Schulze Nahrup et al., 2004) have also been studied with promising results. In the present study, within the frame of regulating the release rate of proxyphylline, the results from single-layer matrices are complemented by an example of a multi-layer SR system, comprised of an inner drug-loaded and two drug-free outer layers.

Table 1
Drug and salts densities, solubilities in water (at 25 °C) and osmotic pressures of saturated solutions.

Solute	Density (g/cm^3)	Solubility, c_S^0 (mol/L)	Osmotic pressure, Π (atm)
Proxyphylline	1.36	2.31	14
NaCl	2.17	6.10	346
$CsNO_3$	3.69	1.43	53
CsCl	3.97	11.0	551

2. Experimental methods

2.1. Materials

Poly(dimethylsiloxane) (PDMS) (RTV 615 type) was kindly supplied by General Electric (Leverkusen, Germany). The two-component silicone kit consisted 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 film occurs via Pt-catalysed hydrosilylation reaction to form a densely crosslinked polymer network, leading to SR films.

The drug used was 7-(β-hydroxy-propyl)theophylline, $C_{10}H_{14}N_4O_3$ (Sigma–Aldrich, Germany) with M_w = 238.24 g/mol, also known as proxyphylline. The drug's particle sizes were below 1 μm and were evaluated by means of optical and SEM microscopy of the loaded matrices.

The salts we used were: NaCl (Riedel-de Haën Fine Chemicals), $CsNO_3$ (Ventron Chemicals Ltd.) and CsCl (Aldrich–Chemie), all of analytical grade. Salt particles (in the range of 7–8 μm for NaCl and $CsNO_3$ and ca. 11 μm for CsCl) were obtained by addition of acetone to stirred saturated aqueous solutions. The precipitate was dried and then ground in a vibrating mill (Grindex-MK II) for about 24 h to dissociate aggregates formed upon drying. Finally, the retrieved salt particles were passed through a fine sieve to eliminate any remaining aggregates as far as possible. The particle sizes were also evaluated by the means of optical and SEM microscopy of the loaded matrices. The densities, the solubilities in water at 25 °C, c_S^0 and the osmotic pressures Π of saturated solutions of the drug and the three salts are given in Table 1. The corresponding osmotic pressures Π (Table 1), were calculated according to the works of Gu et al. (2005) and Soulas et al. (2009).

2.2. Preparation of matrices

The loaded single-layer films were obtained by mixing simultaneously, the prepolymers A and B (10:1, w/w) with the drug and salt particles by means of a mechanical stirrer at 400 rpm. The whole mixture was degassed in vacuum and then cast 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. The films' thickness, L, was measured by means of a micrometer, reading to 1 μm, at several areas of each dry film and was found to be ranging from 380 to 410 μm with a standard deviation of ±5 μm for each specimen.

All single-layer films contained proxyphylline at the same volume fraction v_D (=0.11), while they contained NaCl at two volume fractions v_N: 0.04 and 0.07 (matrices will be designated henceforth as P-I-4 and P-I-7 films, respectively) and $CsNO_3$ or CsCl at

Table 2
Composition of drug and salt loaded films (each mean value and standard deviation is derived from six samples).

Film	Salt	Initial drug content		Initial salt content	
		% (w/w)	v_D	% (w/w)	v_N
P-11[a]	–	16.57 ± 0.09	0.111 ± 0.001	–	–
P-22[a]	–	37.79 ± 0.08	0.221 ± 0.000	–	–
P-I-4	NaCl	18.17 ± 0.07	0.115 ± 0.001	10.87 ± 0.39	0.043 ± 0.001
P-I-7	NaCl	18.26 ± 0.09	0.112 ± 0.000	18.30 ± 0.11	0.070 ± 0.000
P-II-7	$CsNO_3$	18.14 ± 0.04	0.112 ± 0.000	29.46 ± 0.08	0.067 ± 0.000
P-III-7	CsCl	18.24 ± 0.15	0.112 ± 0.001	32.10 ± 0.49	0.068 ± 0.001

% (w/w): g/100 g of neat polymer.
v_D, v_N: volume fractions of drug and salt, respectively, in PDMS matrix.
[a] Data from Soulas and Papadokostaki (2011).

one volume fraction $v_N = 0.07$ (designated as P-II-7 and P-III-7, respectively). The composition of all matrices studied (expressed in volume fractions and in g per 100 g of neat polymer) is summarized in Table 2. It should be noted that in order to check the reproducibility of the results, at least two films corresponding to each initial concentration, were prepared.

The multi-layer films, consisting of an inner drug-loaded layer and two outer drug-free layers, were prepared by casting, successively, on top of an already cured neat film, the drug-containing polymer fluid, followed by curing and then a second drug-free polymer mixture, followed by a new curing. The thickness of the outer layers was 105 ± 10 μm, while the thickness of the inner layer, loaded at $v_D = 0.22$, was 400 ± 5 μm and were all measured by means of SEM microscopy. In this case the results were compared to the results of single-layered matrices with $v_D = 0.22$ (Soulas and Papadokostaki, 2011) (designated as P-22 films).

2.3. Characterization of the matrices

The morphology of the SR matrices was evaluated in cross-sections of the films, both for the loaded and the depleted matrices by the use of a scanning electron microscope (Leo 440 SEM, Leo, Germany).

The glass-transition temperatures (T_g) of the matrices were obtained by means of a model 2920 modulated differential scanning calorimeter (TA Instruments, New Castle, DE). Samples were initially cooled at −150 °C and then heated with a non-modulated signal and a 5 °C/min heating rate up to 20 °C.

The degree of swelling of loaded films was determined gravimetrically by immersing specimens in n-hexane (Stafie et al., 2005) and following the procedure described in detail in previous work (Soulas et al., 2009). Moreover, specimens of lateral dimensions 1 cm × 0.1 cm and of thickness varying from 380 to 410 μm were cut from both the loaded films and the dried, depleted ones, in order to test their mechanical properties and acquire comparative values of the tensile modulus of elasticity. The instrument used, was the TENSILON UTM-II-20 (Toyo Baldwin, Co. Ltd., Japan) and the stress–strain tests were performed with a strain rate of 20 mm/min at room temperature and 70% relative humidity.

2.4. Drug release experiments

2.4.1. Release experiments from drug and salt loaded matrices

Three samples, of 2 cm × 2 cm lateral dimensions, were cut from each of the loaded films and mounted on stirring rods, rotating at 50 rpm in frequently renewed, 100 mL of distilled water, thermostatted at 25 ± 0.1 °C. The particular temperature was selected for reasons of comparison with previous works (Soulas et al., 2009; Soulas and Papadokostaki, 2011) and in order to minimize any errors due to evaporation, since the gravimetric measurements were conducted manually. 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. At the same time intervals the amount of salt released (denoted as $Q_{N,t}$ at time t and $Q_{N,\infty}$ at $t \to \infty$) was also monitored by means of a conductivity meter (Consort K911: cell constant 1 cm^{-1}, conductivity reading accuracy 0.5%). The small but not negligible conductivity of the drug was also taken into account and hence appropriate corrections were made in the measurement of the amounts $Q_{N,t}$ and $Q_{N,\infty}$.

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, taking into account the amount of drug and salt that was released. At the end of the release experiments, the films were dried and weighed in order to check the amounts of permanently trapped drug and/or salt particles.

2.4.2. Release experiments from multi-layer matrices

In the case of the multi-layer matrices, three samples, of 2 cm × 2 cm lateral dimensions were cut from the drug-loaded multi-layer film. Each sample's perimeter was covered with silicone Sista Silicone 5 (Henkel, Düsseldorf, Germany) in order to avoid leakage of the drug from the rims of the samples. The methodology of the previous paragraph was followed except from the part of weighing the matrices. The amount of drug released was monitored by means of the UV/vis spectrophotometer.

2.5. Determination of transport properties in depleted single-layer matrices

At least six dried, drug and salt-depleted matrices (i.e. three matrices per film of the same initial load) were immersed into a 10% (w/v) proxyphylline aqueous 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.

The diffusion coefficients D_D of proxyphylline, were obtained from the initially linear part of the $Q_{D,t}/Q_{D,\infty}$ vs. $t^{1/2}/L$ plots by the use of Eq. (1) (Crank, 1975):

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

Partition coefficients K_D were calculated according to Eq. (2):

$$K_D = \frac{C_{DS}(\text{in g of drug/cm}^3 \text{ of hydrated matrix})}{c_{DS}(\text{in g of drug/cm}^3 \text{ of equilibrating solution})} \quad (2)$$

The experiments were repeated in the same depleted, dried matrices, but this time they were equilibrated in a 2% (w/v) NaCl solution. The same methodology with the previous paragraph was followed and the NaCl desorption kinetics was monitored by means of the conductivity meter. In analogy to the above, the diffusion

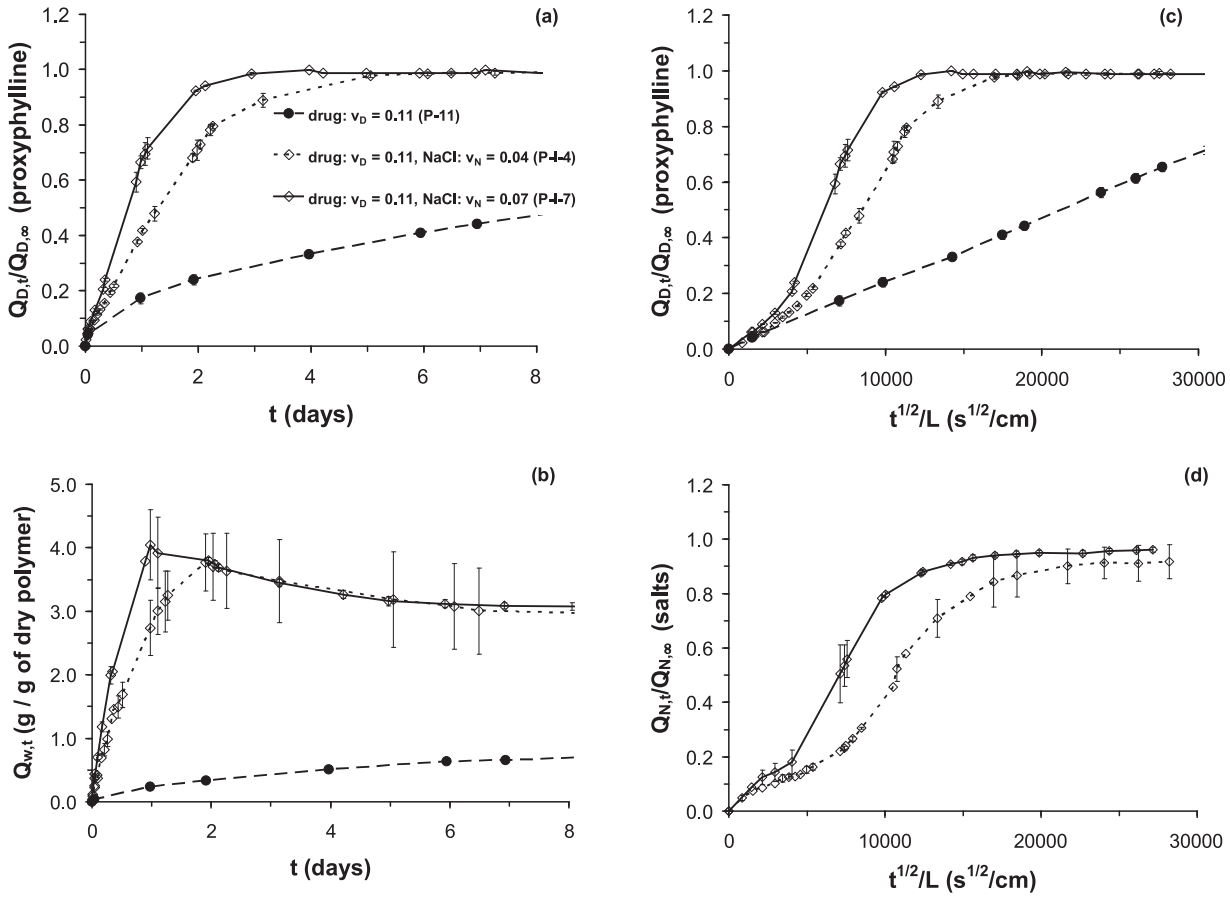

Fig. 1. Effect of NaCl initial load on the release of proxyphylline at 25 °C. In all cases proxyphylline's volume fraction is $v_D = 0.11$. (a) Drug release kinetic curves on a t scale, (b) corresponding variation of osmotically induced water uptake, (c) drug release kinetic curves on a $t^{1/2}/L$ scale, where L is the initial thickness of the matrix and (d) corresponding NaCl release kinetic curves.

coefficients D_N and the partition coefficients K_N of NaCl were obtained.

Finally, in order 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 $Q_{w,t}/Q_{w,\infty}$ vs. $t^{1/2}/L$ plots, by the use of Eq. (1).

3. Results and discussion

3.1. Single-layer matrices

3.1.1. Drug release and concurrent water uptake experiments, in loaded matrices

The effect of NaCl's concentration on the release of proxyphylline is shown in plots of the fractional amount $Q_{D,t}/Q_{D,\infty}$ of proxyphylline from P-I-4 and P-I-7 matrices vs. time t (Fig. 1a). The aforementioned films contained, initially, the drug in volume fraction $v_D = 0.11$ and NaCl in $v_N = 0.04$ and 0.07 (see Table 2). The graphs are compared with the release of proxyphylline, at the same initial volume fraction, in the absence of salt (P-11 films) (Soulas and Papadokostaki, 2011). Each plot represents the average of at least six samples coming from the two films of the same load. The corresponding variation of the concurrent water uptake is shown in Fig. 1b while in Fig. 1c and d, the fractional amount of proxyphylline or NaCl released is plotted vs. the square root of time, reduced over the initial dry film thickness L, so as to point out the deviations from Fickian release kinetics. The effect of the salts' solubility on the release of proxyphylline is shown in Fig. 2a–d, where plots come from matrices P-I-7, P-II-7 and P-III-7, containing proxyphylline at $v_D = 0.11$ and the different salts at $v_N = 0.07$ and are compared with the corresponding graph in the absence of salts (P-11 matrices).

The common observation in all the above cases was that, in the presence of salts, the release rate of the drug was significantly enhanced and was comparable to the release rate of salts in the case of NaCl and $CsNO_3$. The maximum release rates of the drug and the salts (corresponding to portions of the graphs with the maximum slope) along with the maximum rates of water uptake are given in Table 3, where mean values of six samples (three samples per film with the same initial load) are given for each of the four studied cases. Comparison of the drug release rates between matrices containing NaCl, shows that by increasing the amount of salt, higher release rates were achieved, while the enhancement of proxyphylline's release in the presence of different salts followed the order NaCl > $CsNO_3$ > CsCl. As shown in Fig. 2d, the highly hydrophilic CsCl is rapidly released due to the formation of aggregates in the hydrophobic environment of SR at the preparation stage (Soulas et al., 2009), and as a result the osmotic action inside the matrices is markedly diminished. Furthermore, as shown in Figs. 1c and 2c, the release kinetics of the drug turns from diffusion-controlled in the absence of salts, to non-Fickian. As a result, linear parts can be seen in the graphs of both Figs. 1a and 2a, corresponding to constant release rates. The extent of the linear parts, along with the acceleration of the drug's release, is affected both by the initial volume fraction of the salts and their solubility in water. In general, the more prolonged constant release rates were recorded

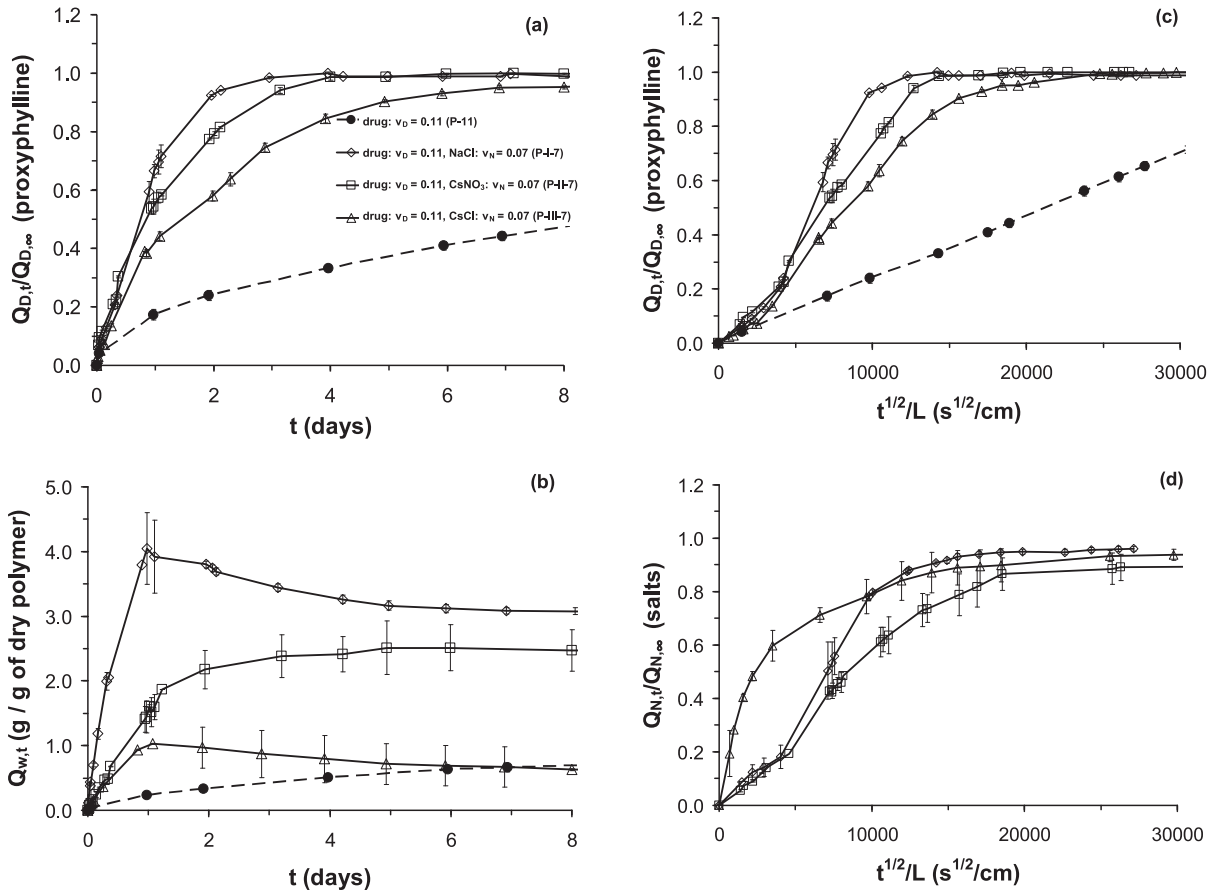

Fig. 2. Effect of salts' osmotic action on the release of proxyphylline at 25 °C. In all cases proxyphylline's volume fraction is $v_D = 0.11$ and each salt's volume fraction is $v_N = 0.07$. (a) Drug release kinetic curves on a t scale, (b) corresponding variation of osmotically induced water uptake, (c) drug release kinetic curves on a $t^{1/2}/L$ scale, where L is the initial thickness of the matrix and (d) corresponding salt release kinetic curves.

in the presence of NaCl corresponding to approximately 60% of the amount of drug released for a time period of ~24 h.

The osmotically driven water (Figs. 1b and 2b) appears to follow an initial steep rise to a maximum value $Q_{w,max}$, followed by a decline to a final value $Q_{w,final}$ in the depleted matrices. In Table 3, $Q_{w,max}$ and $Q_{w,final}$ are given along with the amount of salt, permanently remaining in the matrix. Note that, in all cases, the total of amount of the drug was released and that $Q_{w,final}$ values, given in Table 3, are several days after the completion of the release experiments, which is not shown in Figs. 1b and 2b. In the case of $CsNO_3$ containing matrices, declining of $Q_{w,t}$ is not observed due to the large amount of permanently trapped $CsNO_3$ particles, that allowed the matrices to remain highly hydrated.

Both $Q_{w,max}$ and $Q_{w,final}$ values exceed the corresponding amounts of imbibed water by P-11 matrices (compare corresponding values in Table 3). This is mainly due to two reasons: (a) the higher osmotic action of the salts compared to proxyphylline (see Table 1) and (b) the significant amounts of permanently trapped salt particles that allowed for the matrices to be more hydrated at the end of the experiments.

Furthermore, this amount of sorbed water appeared to exceed the cumulative amount that was sorbed by matrices that contained solely either the drug or NaCl in the same amounts (Fig. 3). This phenomenon is attributable to the synergistic osmotic action of proxyphylline and the salts. The fact that the amount of sorbed water exceeds the sum of the respective amounts of sorbed water is attributable on the one hand to the smaller degree of crosslinking; as shown by Soulas and Papadokostaki (2011) and verified by the results of Section 3.1.2, the presence of the drug in the prior to curing mixture hinders the crosslinking of the matrices which makes SR less brittle and hence more eligible for swelling before rupturing. On the other hand, it is attributable to the fact that in the

Table 3
Results from drug release experiments (each mean value and standard deviation is derived from six samples).

Film	Drug release rates (%/h)	Salt release rates (%/h)	Water uptake rates (g/g of dry polymer/h)	Amount of remaining salt (%)[a]	Water uptake at maximum, $Q_{w,max}$ (g/g of dry polymer)	Final water uptake, $Q_{w,final}$ (g/g of dry polymer)
P-11[b]	0.04 ± 0.00	–	0.0023 ± 0.0001	–	0.889 ± 0.011	0.154 ± 0.002
P-I-4	1.38 ± 0.05	1.22 ± 0.05 (NaCl)	0.1035 ± 0.0065	8.5 ± 4.2	3.802 ± 0.083	2.920 ± 0.061
P-I-7	2.75 ± 0.11	2.03 ± 0.10 (NaCl)	0.1515 ± 0.0061	4.1 ± 1.2	4.108 ± 0.092	2.603 ± 0.202
P-II-7	1.65 ± 0.18	1.44 ± 0.04 ($CsNO_3$)	0.0595 ± 0.0036	15.1 ± 1.9	2.491 ± 0.118	2.491 ± 0.118
P-III-7	1.06 ± 0.06	2.30 ± 0.67 (CsCl)	0.0408 ± 0.0043	6.0 ± 1.5	0.965 ± 0.022	0.625 ± 0.012

[a] Percentage of the initial salt load.
[b] Data from Soulas and Papadokostaki (2011).

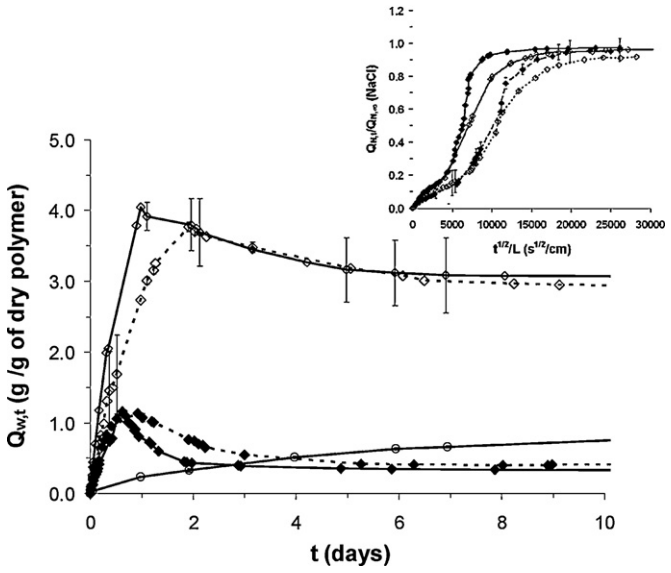

Fig. 3. Cumulative water uptake by P-I-4 (◊, dashed line) and P-I-7 (◊, continuous line) matrices compared to the amount of imbibed water by matrices that contained solitarily proxyphylline (○) at the same load ($v_D = 0.11$) and matrices that contained solitarily NaCl at $v_N = 0.04$ (♦, dashed line) and 0.07 (♦, continuous line). Inset: corresponding NaCl release from the same matrices in the presence or in the absence of drug (symbols as in main figure). All experiments were conducted at 25 °C.

presence of proxyphylline, the release of the salts is slowed down (see inset of Fig. 3) which prolongs the osmotic action inside the matrices.

The release kinetics of the salts is also characterized as non-Fickian (Figs. 1d and 2d) and is affected by the presence of the drug. The formation of microscopic cracks is a prerequisite for the release of a highly water-soluble solute from SR matrices; however since the films under study are crosslinked at a lesser degree, due to the concurrent presence of the drug (see Section 3.1.2), the polymeric walls around the salt containing pores are capable of extending to a higher degree before the formation of microscopic cracks. This in turn delays the crack formation and consequently allows the imbibition of higher amounts of water, as mentioned above. As a result, the release of the salts is somewhat slowed down compared to the corresponding release rates from films where the salts (i.e. NaCl at initial $v_N = 0.04$ and 0.07) were the only solutes (see inset of Fig. 3).

3.1.2. Characterization of loaded and depleted matrices

The single-layer matrices were characterized with respect to their morphology, mechanical properties and swelling degree in n-hexane. Representative SEM micrographs on the cross-section of a neat SR film and P-I-7 films are shown in Fig. 4. As shown in Fig. 4b, the drug and NaCl were homogeneously dispersed, something which was adequately achieved in the case of matrices containing NaCl or $CsNO_3$ but not in the case when CsCl was present. Furthermore, Fig. 4c gives a representative image of a dried, depleted matrix, where permanently formed pores are clearly shown.

The experimentally determined values of the swelling degree q, of neat and loaded matrices in n-hexane are shown in Table 4. The higher q values of loaded films point out that the latter are crosslinked to a lesser degree compared to the neat SR films, despite the fact that the mixing ratios of parts A and B were the same in all cases (i.e. 10:1, w/w). This finding was in line with the findings of Carelli et al. (1995) and Soulas and Papadokostaki (2011), where it was shown that the presence of the drug in the prior to curing mixture affects the degree of crosslinking, although an increase of q, may be partially due to the solvent filling any gaps between

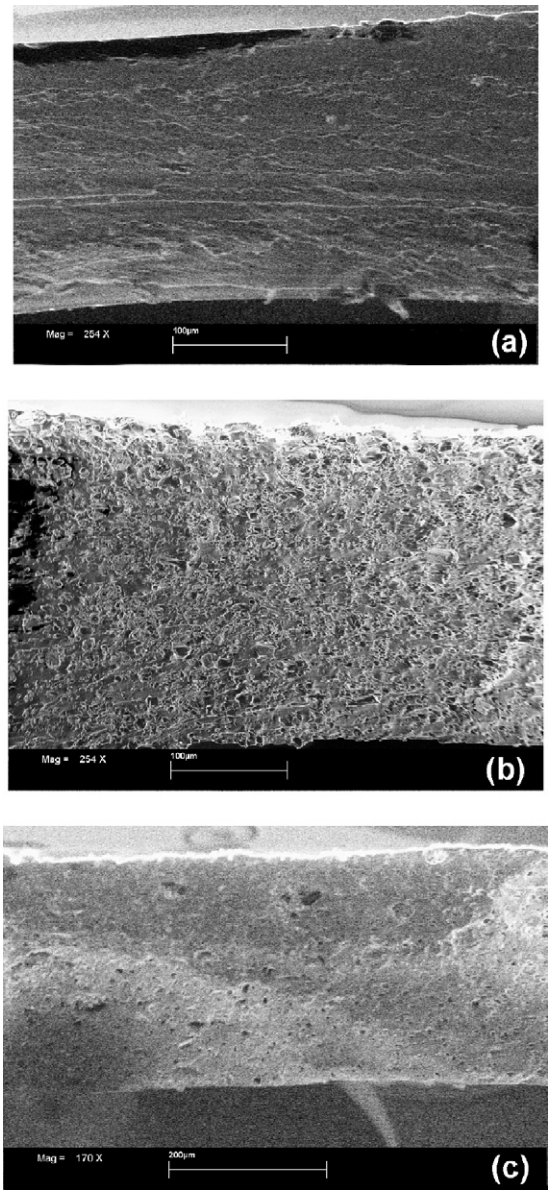

Fig. 4. Representative SEM micrographs from the cross-sections of: (a) a neat SR matrix, (b) a matrix containing proxyphylline at $v_D = 0.11$ and NaCl at $v_N = 0.07$ and (c) the previous matrix after the drug's and the salt's release.

the polymer and the embedded salt and drug particles. Note that, since the presence of NaCl at such loads (0.07, v/v) does not materially affect the degree of crosslinking (Soulas et al., 2009), the main reason for the low crosslinking degrees appears to be the drug.

In line with these results are the T_g values (Table 4). P-I type matrices exhibited a small, but not negligible decrease of the T_g compared to the values of the neat SR samples, verifying a lower degree of crosslinking.

In order to further verify the above results, stress–strain tests were performed to P-I-4 and P-I-7 matrices and to the corresponding dried, depleted ones and the results were compared to those for the neat SR matrix. The Young's modulus was calculated from the slope of the initial linear part of graphs of exercised stress f vs. ε ($\varepsilon = \Delta L/L_0$, ΔL elongation, L_0 initial sample length) and was compared to that of the neat polymer ($E_{SR} = 0.91 \pm 0.02$ MPa) (Soulas et al., 2009). The corresponding Young's modulus of the loaded P-I-4 and P-I-7 (Table 4), as expected, was above this value. However, as shown by Soulas and Papadokostaki (2011), the contribution of

Table 4
Degrees of swelling in n-hexane q, glass transition temperatures T_g, and Young's modulus for neat matrices and matrices initially containing proxyphylline and NaCl (each mean value and standard deviation is derived from six samples).

Film	q	T_g (°C)	E_{SR} (MPa)	E (loaded matrices) (MPa)	E (depleted matrices) (MPa)
Neat SR	2.46 ± 0.03	−125.2	0.91 ± 0.02	–	–
P-I-4	3.57 ± 0.06	−127.1	–	0.98 ± 0.02	0.84 ± 0.06
P-I-7	3.83 ± 0.04	−127.2	–	1.28 ± 0.05	0.65 ± 0.02

Table 5
Sorption and diffusion parameters of proxyphylline in depleted matrices (each mean value and standard deviation is derived from six samples).

Film	$Q_{D,eq}$ ($\times 10^{-3}$ g/g dry polymer)	$Q_{w,eq}$ (g/g dry polymer)	K_D ($\times 10^{-3}$)	D_D ($\times 10^{-10}$ cm^2/s)
P-I-4	201.0 ± 30.4	2.121 ± 0.339	596.6 ± 24.4	2.1 ± 0.1
P-I-7	172.0 ± 7.9	1.953 ± 0.134	553.7 ± 37.3	2.4 ± 0.2
P-II-7	188.0 ± 5.8	2.163 ± 0.112	564.3 ± 35.4	2.2 ± 0.0
P-III-7	43.0 ± 12.7	0.301 ± 0.060	309.0 ± 77.6	2.7 ± 0.2

interspersed proxyphylline particles to the increase of the Young's modulus of SR films is less, compared to the contribution of interspersed NaCl particles. If we compare the Young's modulus of P-I-4 and P-I-7 matrices (containing in total 15 and 18% (v/v) of interspersed particles, respectively) to the value 1.41 ± 0.05 MPa (Soulas et al., 2009), corresponding to matrices containing 12% (v/v) NaCl we may realize that the increase is not as high as expected and that the discrepancy is attributed to the lower modulus of SR, crosslinked in the presence of the drug. After the release of the solutes, the measured Young's modulus was below the value of 0.91 MPa due to the formation of permanent pores filled with air. However comparison of these values with the corresponding values of the salt-depleted matrices in the work of Soulas et al. (2009) (e.g. 0.88 MPa for matrices with initial NaCl volume fraction 0.12) shows that the reduction of the Young's modulus is not only attributable to the release of the salt [the drug does not leave permanently formed pores at $v_D < 0.11$ (Soulas and Papadokostaki, 2011)] but also to the lower degree of crosslinking, verifying thus the above results.

3.1.3. Transport parameters in depleted matrices

The results of drug and NaCl sorption–desorption experiments in depleted matrices are summarized in Tables 5 and 6, respectively. As shown, upon their equilibration with proxyphylline solution, the matrices were able to sorb significant amounts of water. The sorption of water is attributable to the permanently trapped salt particles and is mainly accommodated into the salt and drug-containing cavities and also in the crack network that was formed during the release process and which may reopen during the equilibration of the matrices (Soulas et al., 2009). The amounts of sorbed water $Q_{w,eq}$ however, were somewhat lower compared to the amounts of water measured at the end of the release experiments $Q_{w,final}$ (Table 3). On the other hand, when the same depleted matrices were equilibrated with the NaCl solution, the sorbed amount of water was 3–5 times lower than in equilibrium with the drug solution (Tables 5 and 6) which is attributable to the lower water activity of the NaCl solution.

In turn, the amounts of solute sorbed at equilibrium ($Q_{D,eq}$ and $Q_{N,eq}$) as well as the partition coefficients of both solutes (K_D and K_N) were directly affected by the water sorption at equilibrium, i.e. higher amounts of sorbed water resulted in higher partition coefficients. However, the significantly lower – by three orders of magnitude – partition coefficients of NaCl compared to those of proxyphylline, were not only due to the lower water sorption, but mainly to the fact that NaCl is practically excluded from SR (Soulas et al., 2009), while proxyphylline appears to have an affinity towards the polymer (Soulas and Papadokostaki, 2011). It should also be noted that K_D values calculated here (Table 5) are much higher compared to the corresponding coefficients calculated in previous work (Soulas and Papadokostaki, 2011) for matrices that contained solitarily the drug (amounting to ∼0.04) and this is also attributable to the high water uptake observed here (in comparison to $Q_{w,eq} \approx 0.04$ g/g for the latter ones).

Moreover, the diffusion coefficients of proxyphylline D_D, calculated from the first linear part of desorption curves plotted vs. $t^{1/2}/L$, according to Eq. (1), were found to be three orders of magnitude lower than those of NaCl, calculated for the same, depleted SR matrices (Tables 5 and 6). Since the diffusion coefficient of NaCl in water (ca. 1.6×10^{-5} cm^2/s) (Chang and Myerson, 1985) is of the same order of magnitude compared to the corresponding diffusion coefficient for the drug (ca. 0.9×10^{-5} cm^2/s) (Papadokostaki et al., 2009), 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, which is the rate determining phase and as shown in previous works, the diffusion of the salt is carried out exclusively through the water phase (Soulas et al., 2009). However, D_D values characterize the drug's diffusivity in the depleted matrices and do not correspond to the diffusivity observed during the release experiments. In the latter case, the formation of microscopic cracks allows the release of the drug, on a comparable rate with that of the salt.

The kinetics of water uptake in drug-depleted matrices were approached by assuming Fickian kinetics. The estimation of the apparent diffusion coefficients of water D_w, was made by the use of Eq. (1) and they were found to be of the order of 10^{-10} cm^2/s. Although smaller, compared to the D_w of water vapor in neat SR (Favre et al., 1994; Watson and Baron, 1996), by four to five orders of magnitude, they appear to be in line with the D_w coefficients in saturated by water SR matrices (Barrie and Machin, 1969). The amount of sorbed water was comparable to the amount of water at the end of the release experiments $Q_{w,final}$ as also seen in the work of Soulas et al. (2009). The common observation between this work and our previous work is that the remaining, permanently

Table 6
Sorption and diffusion parameters of NaCl in depleted matrices (each mean value and standard deviation is derived from six samples).

Film	$Q_{N,eq}$ ($\times 10^{-3}$ g/g dry polymer)	$Q_{w,eq}$ (g/g dry polymer)	K_N ($\times 10^{-3}$)	D_N ($\times 10^{-7}$ cm^2/s)
P-I-4	0.124 ± 0.006	0.433 ± 0.047	4.3 ± 0.2	4.6 ± 0.2
P-I-7	0.108 ± 0.005	0.378 ± 0.014	3.9 ± 0.2	2.5 ± 0.1
P-II-7	0.090 ± 0.005	0.453 ± 0.031	3.1 ± 0.1	5.4 ± 0.2
P-III-7	0.074 ± 0.004	0.097 ± 0.024	3.4 ± 0.2	3.2 ± 0.2

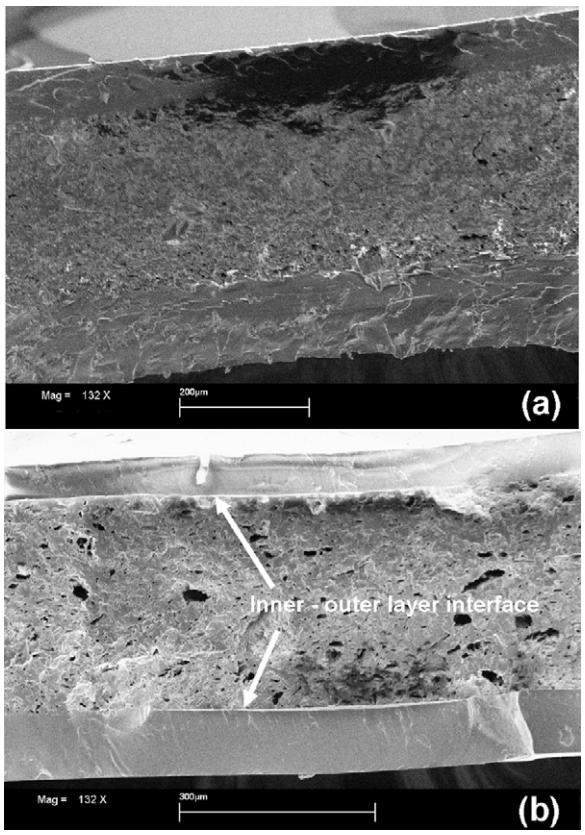

Fig. 5. Representative SEM micrographs from the cross-sections of: (a) the multi-layer matrix before the release of the drug and (b) the same matrix after the release of the drug.

trapped salt particles lead to the formation of an intra-connected pore network that exists in the depleted matrices and is capable of accommodating the total amount of sorbed water. The low D_w are in line with the existence of this secondary mechanism, possibly corresponding to the reopening of the pore network that took place during the water sorption by the depleted matrices and may partially heal upon drying of the films.

3.2. Drug release experiments from multi-layer matrices

Representative SEM micrographs on the cross-section of the multi-layer matrices before and after proxyphylline's release are shown in Fig. 5a and b, where arrows show the interface between the inner and outer layers. The layers are glued by the formation of covalent bonds between the vinyl and (Si–H) groups of the layers and thus remain intact after the conclusion of the release.

The release of proxyphylline from single-layer matrices loaded at $v_D = 0.22$ and multi-layer matrices with drug-free outer layers and inner layer loaded at the same v_D (=0.22) is shown in plots of $Q_{D,t}/Q_{D,\infty}$ on t and $t^{1/2}/L$ scales in Fig. 6a and b, respectively. In Fig. 6a, it is clear that the release of proxyphylline from the multi-layer matrix is significantly prolonged, compared to single-layer matrices, from a matter of hours to a matter of days and the release curve vs. $t^{1/2}$ becomes prominently sigmoidal (Fig. 6b). This is due to the fact that the rate-controlling layer is the drug-free layer; hence migration of the drug through this layer is delayed. However, it should be noted that any diffusion of the drug from the inner layer to the outer drug-free layers during the casting of the layers should not be excluded, due to the dissolution of the drug in the polymer. This is evident from the rather limited time-lag shown in Fig. 6a. Although limited, the delay produced by the outer layers,

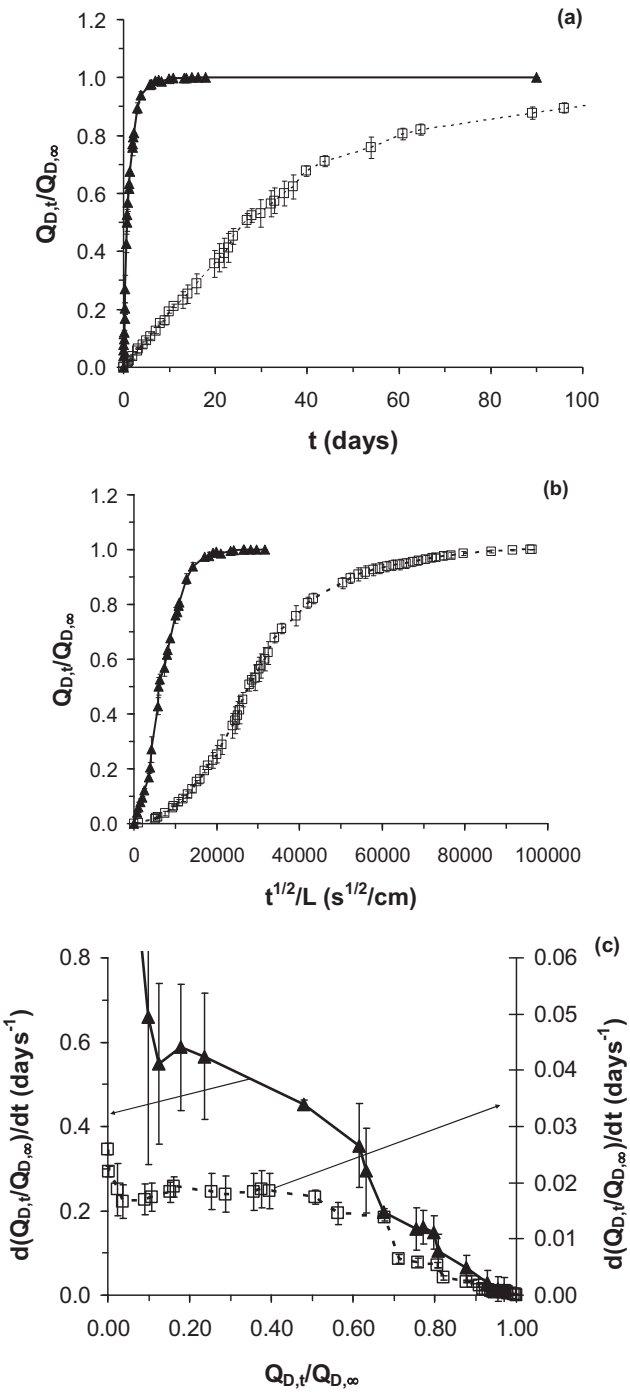

Fig. 6. (a) Proxyphylline release plots from multi-layer matrix (open points) and from single-layer matrix (closed points) both loaded at $v_D = 0.22$, vs. time t, (b) same graphs plotted on a $t^{1/2}/L$ scale, where L is the initial thickness of the matrix and (c) drug release rates plotted vs. the fractional amount of drug released. All experiments were conducted at 25 °C.

is adequate enough to suppress the initial burst effect as shown in Fig. 6c. After this stage, a constant release rate is achieved up to 60% of the total drug load.

The main picture emerging from the comparison between the single and the multi-layer system is that by the use of a rather simple experimental methodology in the preparation of the multi-layer system: (a) the initial burst effect is sufficiently suppressed and (b) for the same amount of released drug, the constant release rate is prolonged from several hours to 30 days.

3.3. Discussion on the release mechanism

The release experiments of the hydrophilic model drug from single-layer, monolithic matrices, in the presence of inorganic salts with osmotic action, showed that:

i. The drug's release was significantly enhanced and by the addition of larger amounts of salt the enhancement became even more significant.
ii. The drug's release kinetics is altered from $t^{1/2}$ release kinetics (observed in the absence of salts) to sigmoidal vs. $t^{1/2}$, non-Fickian release kinetics. This change stabilized the continuously declining release rate of the drug.
iii. Due to the concurrent presence of the drug and the inorganic salts, the matrices could sorb vast amounts of water exceeding the amount of water that the matrices would sorb when the solutes were incorporated solitarily at the same amounts.
iv. Although the incorporation of salts, with varying osmotic actions, had a significant impact on the water uptake, the drug's release kinetics was not significantly affected.

As indicated in the Section 2, the transport parameters of proxyphylline, NaCl and water determined in depleted silicone rubber matrices, support the allegation that the drug can diffuse through the polymeric matrix while diffusion of inorganic salts can be performed only through water-filled channels. Moreover, as shown in our previous work (Soulas and Papadokostaki, 2011), the release of proxyphylline, despite its non-negligible osmotic action follows $t^{1/2}$ release kinetics in the absence of salts and is considerably slowed down. The presence of inorganic salts with a considerable osmotic action, on the other hand, leads to the imbibition of excess amount of water which in turn enhances the drug's release rates, as clearly shown by the positive deviations of the drug's release from $t^{1/2}$ kinetics. As a result, in the presence of salts, the drug's release rate approaches linear vs. t kinetics.

This excess amount of water imbibed by the matrices is attributable to two factors: (a) the synergistic osmotic action of the drug and the salts and (b) to the limited degree of crosslinking as compared to neat SR matrices, verified by swelling and modulus of elasticity measurements. In the case studied here, the lower degree of crosslinking due to the presence of the drug makes the films less susceptible to cracking and therefore more prone to the imbibition of large amounts of water. However, as mentioned in Section 3.1.1, the existence of a network of microscopic cracks should not be disregarded, since otherwise the release of the inorganic salts would not have been possible.

At this point we should also point out the impact of the salts' solubility on the drug's release rates. The results indicated that NaCl appeared to be the best osmotigen, since for a given initial load it produced the more uniform release rate for the drug. Although CsCl could produce the higher osmotic pressure inside a cavity, due to its hydrophilicity, it appeared to have poor distribution in the prior to curing mixture. As a result, ~50% of its initial load was rapidly released reducing the osmotic action inside the matrices and therefore producing the lower rates of drug release. On the other hand, $CsNO_3$ appeared to behave more satisfactorily as an osmotigen. However, in this case the imbibition of water was rather limited and delayed compared to NaCl, which in turn limited the extent of proxyphylline's constant release rate.

Regarding the multi-layer system, consisting of one drug-loaded inner layer and two drug-free outer layers, the main observations were that:

i. The release rate was significantly reduced in relation to the single layer matrix.
ii. The initial burst effect was sufficiently suppressed.
iii. A nearly constant drug release rate was achieved.

The results indicate that the release process is related to the different permeability properties of the inner and outer layers. As shown by (Soulas and Papadokostaki, 2011), since the initial volume fraction of the drug in the inner layer exceeds the percolation threshold, a wall rupture mechanism operating in parallel to the diffusion of the drug through the polymer is also plausible making the inner layer more permeable to the drug as compared to the outer layers. In fact, proxyphylline's permeability through neat SR, and loaded at $v_D = 0.22$, matrices was ca. 0.34 and 4.52×10^{-10} cm^2/s, respectively, indicating that the outer layers are less permeable and hence they act as rate-controlling barriers.

In conclusion, the two systems studied offered different aspects on the regulation of proxyphylline's release from SR matrices. The presence of salts accelerates markedly the drug's diffusion by invoking the imbibition of large amounts of water. What is more, by altering the diffusion towards non-Fickian release kinetics a constant release rate is approached. On the other hand the usage of the multi-layer system significantly slowed down the release rate, reduced the initial burst effect and increased the percentage of the drug released in a constant release rate.

4. 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 water-soluble, model drug at a load 11% (v/v), in the presence of inorganic salts of varying water solubilities, both initially dispersed in highly hydrophobic SR matrices.

In this case, the overall picture emerging by the study of the kinetics of drug release from single-layer matrices and the concurrent kinetics of water uptake is in line with a mechanism that follows non-Fickian release kinetics although, in the absence of salts, the release of the drug followed square root t kinetics. The acceleration of the release rate was found to be the result of the formation of microscopic cracks due to the osmotically induced water. Thus, a nearly constant release rate was achieved for more than 60% of the drug load.

Furthermore, a three-layer system comprising two drug-free outer layers and an inner drug-loaded layer at a load 22% (v/v), was also studied. The addition of drug-free outer layers to the single-layer matrix regulated the drug's release since it effectively suppressed the undesired initial burst effect, often occurring in monolithic systems and additionally prolonged the time and increased the percentage of the drug that was released at a constant rate. In this case, the release of the drug was regulated by diffusion through the drug-free layers of the device.

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