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Proxyphylline release kinetics from symmetrical three-layer silicone rubber matrices: Effect of different excipients in the outer rate-controlling layers

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ABSTRACT

In this work we present results on the release kinetics of a water-soluble model drug (proxyphylline) from symmetrical three-layer ABA matrices made from silicone rubber. The ABA matrices, consisting of an inner drug-containing layer, loaded at concentration near the percolation threshold, and two drug-free outer layers, were studied with respect to (a) the varying permeability properties of the outer layers achieved by the incorporation of either poly(ethylene glycol), a hydrophilic polymeric excipient, or NaCl, an inorganic salt with high osmotic action, and (b) the relative thickness of the inner to outer layers. In all cases, substantial uniformity of release rate was achieved and the initial burst effect, characterizing the corresponding single-layer system, was suppressed. The results are interpreted on the basis of the permeation mechanisms operating in each individual inner and outer layer. Thus, we have demonstrated that by judicious choice of the composition and relative thickness parameters the release rate can be adjusted to any desired level. Finally, the case of the NaCl excipient, released parallel to proxyphylline, serves as an example of a dual-drug releasing system.

1. Introduction

Monolithic or matrix-type controlled release (MCR) devices represent a category of controlled release systems where the loaded bioactive substance is uniformly distributed inside a polymeric matrix. One of the main benefits that these systems provide is their structural simplicity and thus low fabrication costs. However, release of the embedded solute in a surrounding aqueous medium from MCR systems is mainly diffusion-controlled, leading thus to continuously declining release rates which is more pronounced at the early stages of the process producing an initial "burst effect" (Abdul and Poddar, 2004; Huang et al., 1999; Papadokostaki et al., 2008). Many research reports aim on the optimization of MCR systems with respect to the uniformity of the release rate and the alleviation of the initial "burst effect".

One way of improving the uniformity of dose rate is by coating the systems with polymeric layers (Abdul and Poddar, 2004; Kajihara et al., 2003; Kaunisto et al., 2011; Siepmann et al., 2008) or by spatial distribution of the load or/and the properties of the matrix itself. Relevant examples, of the latter case, are the partial extraction of solute from poly(2-hydroxyethyl methacrylate) (PHEMA) spherical beads (Lee, 1984) and the surface crosslinking of cylindrical (Lee et al., 1980) or planar (Wu and Brazel, 2008) matrices based on PHEMA or poly(vinyl alcohol) (PVA), respectively. Another design strategy has been the use of multi-layer matrices, which have been studied both experimentally and theoretically as an alternative method for distributing the solute load and the permeation properties of the system independently of each other. Such composite matrices with uniform material properties which exhibited improved release performance in relation to their monolithic counterparts are presented in the works of Charalambopoulou et al. (2001) in cellulose acetate systems and of Lu and Anseth (1999) in PHEMA systems that were loaded to different concentrations of model dyes. A special case of multi-layer systems are loaded matrices coated with solute-free polymeric layers (Bodmeier and Paeratakul, 1990; Huang et al., 1999; Lei et al., 2011; Schulze Nahrup et al., 2004). Recent works, found in literature, refer to the preparation and characterization of multi-layered matrices composed from layers of different hydrogels [PHEMA and poly(ethylene glycol)] (Watkins et al., 2007) and on dual-drug delivery systems. In the latter case, the release rates of individual drugs are controlled independently and relevant reports include the works of Shah et al. (2011) on the release of dual growth factor from polyelectrolyte multi-layer films, the works of Huang et al. (2010) on a dual drug-eluting stent and Okuda et al. (2010) on the simultaneous release of two dyes used as model solutes.

In certain cases, pertaining to release performance under conditions of fast solvent penetration in relation to the rate of solute

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release, the specific experimental systems have also been simulated (Lu and Anseth, 1999; Charalambopoulou et al., 2001; Watkins et al., 2007; Soulas et al., 2011). The overall picture formed by the results on multi-layer MCR systems indicates that they offer many possibilities for reducing the intensity of, or even totally suppressing, the initial "burst effect", while they may also succeed in the stabilization of the overall rate of release, by judicious choice of the design parameters of the MCR device (such as the permeability properties of the polymeric materials employed, distribution of solute load and the relative thicknesses of the layers).

Finally, monolithic systems that tend to stabilise the declining dosage rate of pure diffusion-controlled release, are those involving other mechanisms of solute release. These are the cases of: (i) relaxation-controlled hydrogel matrices based on PHEMA and poly(vinyl alcohol) (Brazel and Peppas, 1999; Stavropoulou et al., 2005) and (ii) highly hydrophobic polymeric matrices incorporating excipients of high osmotic pressure, which allow the release of the drug through a network of microscopic cracks (Carelli et al., 1989; Di Colo, 1992; Di Colo et al., 1986; Soulas and Papadokostaki, 2011a). However in the latter case the release rates were kept constant for a limited period of time and the systems exhibited initially a "burst effect". In general, the incorporation of hydrophilic excipients in highly hydrophobic matrices, serves the purpose of increasing the water uptake of the matrix, making it suitable for the release of hydrophilic drugs. For this purpose, hydrophobic polymers, such as silicone rubber (SR), are blended with hydrophilic ones. Relevant examples are the works of Simmons et al. (2008), where a PDMS-polyurethane blend was used and the works of Schulze Nahrup et al. (2004) and Gao et al. (2005) where poly(ethylene glycol) 8000 at various loadings was used as channelling agent in PDMS.

In our previous reports we have studied in detail the mechanisms of release kinetics of a water-soluble drug (proxyphylline) from SR monolithic matrices in the absence (Soulas and Papadokostaki, 2011b) or the presence (Soulas and Papadokostaki, 2011a) of osmotically active excipients. Deviations from Fickian kinetics and thus a more uniform overall rate of release were observed either when proxyphylline load was near the drug particles' percolation threshold, or in the presence of inorganic salts. However, in the former case, a declining dose rate at the early stages of the process was still present. A preliminary effort (Soulas and Papadokostaki, 2011a) of coating the monolithic system with drug-free SR outer layers indicated that the overall uniformity of rate could be greatly improved by this method.

The main objective of the present work is to proceed in a detailed study of the release of proxyphylline from symmetrical three-layer ABA matrices made from SR with outer layers of varying permeability parameters and thickness. To this end, the studied ABA matrices were comprised of an inner drug-loaded layer B coated with two drug-free outer layers A containing excipients that enhance the capacity of the inherently hydrophobic SR to sorb water. The chosen excipients were: (a) poly(ethylene glycol) (PEG) of $M_w = 3000$, a hydrophilic compound which, due to its high molar volume is not leached out during the release experiments and (b) NaCl which has a high osmotic action and is released through polymer cracking (Amsden, 2003; Schirrer et al., 1992). Moreover, the latter case gave us the opportunity of studying an example of dual release of a drug and an excipient with a potential biological action and draw conclusions on the parallel release mechanisms. Finally, with respect to the effect of the outer layer's thickness on the release rates, we studied three-layer systems of various outer to inner thickness ratios so as to practically demonstrate the possibilities of adjusting the dosage rate through this design strategy.

2. Experimental methods

2.1. Materials

Poly(dimethylsiloxane) (PDMS) (RTV 615 type) was kindly supplied by Momentive (OH, USA). 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 PDMS occurs via Pt-catalysed hydrosilylation reaction leading to a densely crosslinked polymer network (SR).

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 size was below 1 μm as evaluated by means of optical and SEM microscopy of the loaded matrices.

The PEG used, of $M_w = 3000$ g/mol, was purchased by Merck (Germany) and the salt used was NaCl (Riedel-de Haën Fine Chemicals) of analytical grade, with particles in the range of 7–8 μm, obtained as described in the work of Soulas et al. (2009).

2.2. Preparation of three-layer ABA matrices

Two types of three-layer symmetrical ABA matrices (a schematic representation is given in Fig. 1) were prepared, consisting of an inner layer B, made exclusively by SR, uniformly loaded with proxyphylline at volume fraction $\upsilon_D = 0.22$ (38.2%, w/w) and two drug-free outer layers A made also from SR and loaded either with PEG at volume fraction $\upsilon_P = 0.085$ (10%, w/w) (type I three-layer system) or NaCl at volume fraction $\upsilon_N = 0.04$ (7.35%, w/w) (type II three-layer system). In all cases the three-layer matrices were prepared by casting the polymeric fluid of the first drug-free outer layer on a poly(propylene)-coated glass plate by means of a doctor's knife, followed by curing at 100 °C for 1 h according to the supplier's instructions to accelerate the crosslinking reaction. Then, on top of the already cured drug-free layer, the polymeric fluid containing the drug was cast, followed by new curing and finally a drug-free fluid, corresponding to the second drug-free outer layer, was cast and a final curing was performed.

Layer B was prepared by mixing simultaneously the prepolymers a and b (10:1, w/w) with the drug particles by means of a mechanical stirrer at 400 rpm and degassed in vacuum before casting.

For three-layer matrices of type I, the outer layers were prepared by mixing initially the prepolymers a and b for 1 h. Then a 60% (w/v) solution of PEG in dichloromethane was added in the mixture so as to achieve a 10% (w/w) PEG content in the composite matrix, followed by a second stirring for 30 min. In this case the step of degassing was omitted in order to avoid evaporation of the solvent. Finally, for the preparation of the type II outer layers, NaCl was also added along with the two prepolymers, in the form of particles. Then the whole mixture was stirred for 1 h and degassed prior to casting.

Three matrices of type I and two of type II, with different layer thicknesses were prepared and their properties are summarized in Table 1. In the same table, for reasons of comparison, we also included the characteristics of the corresponding single-layer proxyphylline-loaded SR matrix with $\upsilon_D = 0.22$ from the work of Soulas and Papadokostaki (2011b) and the multi-layer matrix with outer layers consisting by pure SR from the work of Soulas and Papadokostaki (2011a) (designated henceforth as mono-SR/Prx and multi-SR/Prx respectively).

Finally, a single-layer matrix of the same composition with the PEG-containing outer layers of type I matrices, was prepared and will be designated henceforth as PEG-doped SR.

Table 1
Properties of three-layer ABA matrices (results from 3 samples in each case).

Matrix	Composition of layer A	Range of total thickness $2L$ (μm)	Layer B average thickness $2L_B$ (μm)	% $L_A/2L$ ratio
Mono-SR/Prx[a]	–	390–410	–	–
Multi-SR/Prx[b]	SR	600–610	400 ± 5	16.9 ± 0.1
I_{240}	SR/PEG	393–396	238 ± 3	19.8 ± 0.1
Ia	SR/PEG	501–539	425 ± 3	9.1 ± 0.3
Ib	SR/PEG	907–923	408 ± 4	27.7 ± 0.2
IIa	SR/NaCl	569–575	389 ± 4	16.0 ± 0.2
IIb	SR/NaCl	946–954	380 ± 2	30.0 ± 0.1

[a] Data from the work of Soulas and Papadokostaki (2011b).
[b] Data from the work of Soulas and Papadokostaki (2011a).

2.3. Morphology of three-layer matrices

The morphology of the three-layer matrices was evaluated in cross-sections of the films, both in loaded and in depleted matrices by scanning electron microscopy (Leo 440 SEM, Leo, Germany).

The total thickness $2L$ of the matrices was measured by means of a micrometer, reading to 1 μm and was further verified in the photographs obtained by SEM. Moreover, from the SEM micrographs of the cross-section of the loaded matrices we were able to measure separately the thicknesses L_A and $2L_B$ of each layer and calculate thus the relative ratios $L_A/2L$.

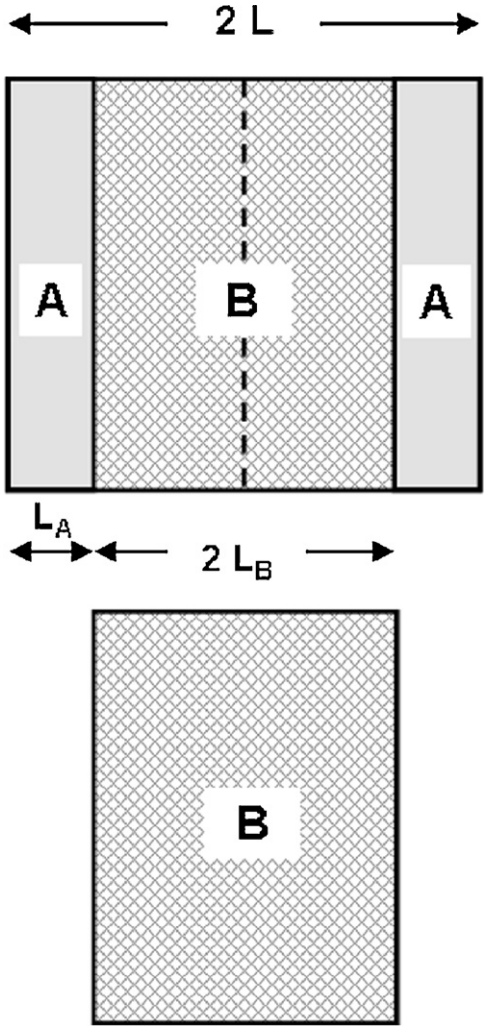

Fig. 1. Schematic representation of the ABA three-layer matrix and a single-layer matrix corresponding to the inner layer of its three-layer counterpart. In all cases layer B is made from SR loaded with proxyphylline at volume fraction 0.22. The outer, drug-free, layers A, are either SR-PEG blend or SR doped with NaCl. The total of the three-layer matrix is $2L$, L_A is the thickness of each outer layer and $2L_B$ is the thickness of the inner layer.

2.4. Release experiments

Three samples of 2 cm × 2 cm lateral dimensions were cut from each of the three-layer films and mounted on stirring rods, rotating at 50 rpm in frequently renewed, known volumes of distilled water, thermostatted at 25 ± 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. Each sample's perimeter was covered with silicone (Sista Silicone 5, Henkel, Düsseldorf, Germany) in order to avoid any leakage of the drug from the rims of the samples.

In the case of type II matrices, parallel to the drug's release, the release of NaCl (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 determination of $Q_{N,t}$ and $Q_{N,\infty}$.

2.5. Properties of individual layers

The permeability coefficient P_D, of proxyphylline from single-layer matrices of the same composition as those of the outer layers of type I and II three-layer matrices, was measured by means of a permeability apparatus consisting of two cells which 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. The methodology is described in detail in the work of Soulas and Papadokostaki (2011b) and the concentration of proxyphylline in the receptor cell was measured by means of the UV/Vis spectrophotometer as above. It should be noted that in the case of the NaCl-loaded single-layer matrices, the salt was depleted beforehand and that these matrices, along with the PEG-doped ones, were pre-equilibrated with water so as to measure the permeability of the drug through hydrated films bearing close analogy to the state of the outer layers during the release experiments. All experiments were performed in triplicate.

The kinetics of water uptake by mono-SR/PEG films was measured at 25 °C in triplicate. The water content of the films ($Q_{w,t}$ at time t and $Q_{w,\infty}$ at $t \to \infty$) was monitored by weighing of the blotted films at suitable time intervals.

Finally in order to characterise the hydrophilicity of the outer layers of each type of three-layer matrices we performed static contact angles measurements on the surface of all single-layer matrices. The measurements were performed at ambient temperature with a drop of ca. 1 μL deionized water on at least five points on each surface of the matrix. The angles were determined by means of a Cam 100 Optical Contact Angle Meter array (KSV Instruments Ltd., Finland).

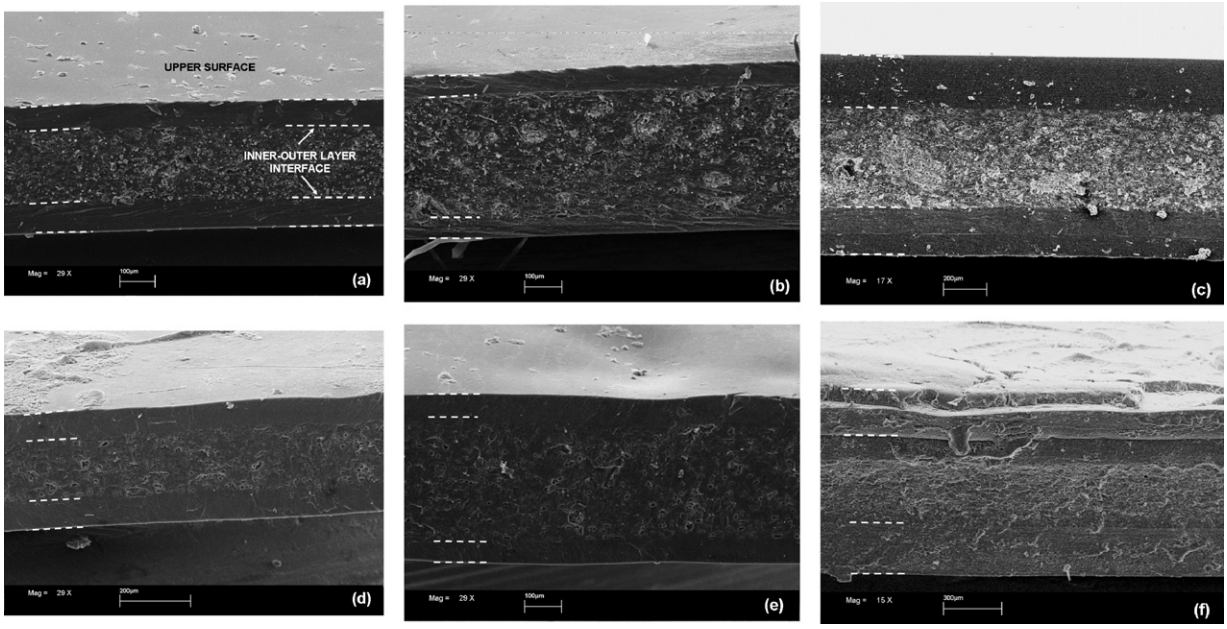

Fig. 2. SEM micrographs taken on the cross-section of three-layer matrices with PEG-loaded outer layers. ((a)–(c)): I_{240}, Ia, and Ib three-layer matrices respectively, before the drug's release. ((d)–(f)): corresponding depleted I_{240}, Ia and Ib matrices. The white dashed lines denote the interface between the inner and the outer layers.

3. Results and discussion

3.1. Morphology of three-layer matrices

Representative SEM micrographs (photographed at a 70 ° angle) in the cross-section of the studied three-layer films before and after the release experiments are shown in Figs. 2a–f and 3a–d for type I and type II three-layer matrices, respectively.

In all cases, the outer layers appear to be firmly attached to the inner layer both before as well as after the drug release. This optical verification of the good adhesion of the layers points to the formation of covalent bonds between groups located in the inner and outer layers formed during the consecutive curing processes at the stage of preparation.

In Figs. 2a–c, 3a and b, drug particles are discernible in the inner layer as compared to the micrographs coming from the

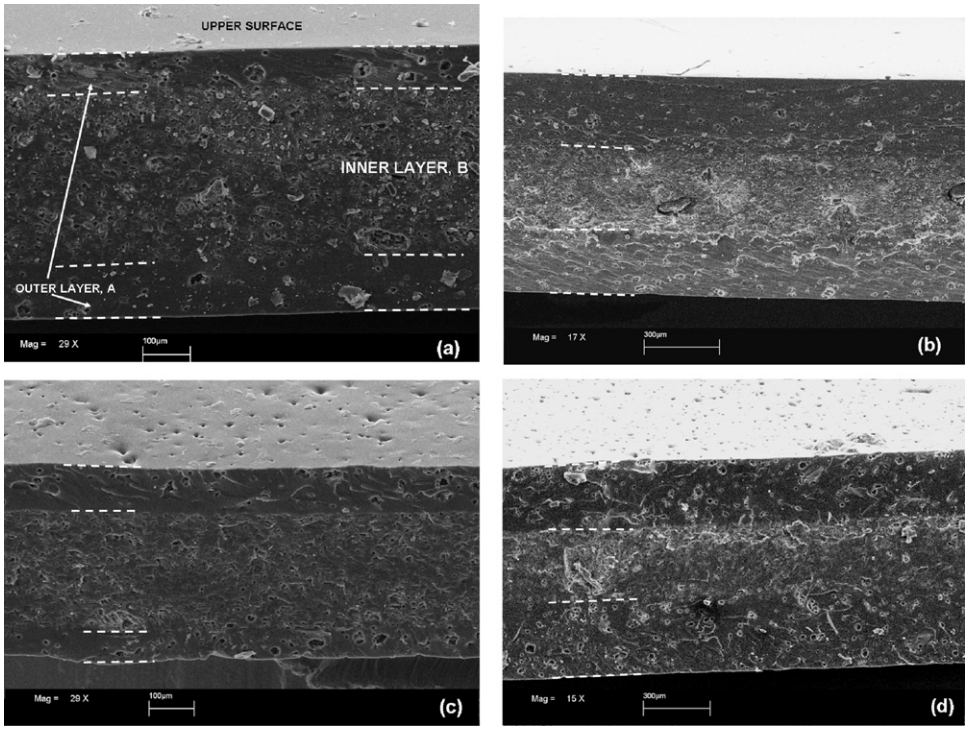

Fig. 3. SEM micrographs taken on the cross-section of three-layer matrices with NaCl-loaded outer layers. (a and b): IIa, and IIb matrices respectively, before the drug's release. (c and d): corresponding depleted IIa and IIb matrices. The white dashed lines denote the interface between the inner and the outer layers.

corresponding depleted matrices (Figs. 2d–f, 3c and d). White spots appearing in the drug-free PDMS/PEG outer layers in Fig. 2c are probably drug particles that have been detached from the inner layer upon scissoring the samples. Furthermore, as shown in Fig. 3a and b, NaCl particles are also discernible in the outer layers of type II matrices prior to release. In contrast, the particles are no longer present in Fig. 3c and d, where permanently formed pores are now present. The total thickness $2L$ of the three-layer matrices is shown in Table 1 and its variation for each sample was found to range between 0.3 and 2.3%. As mentioned above, the SEM micrographs were also used for measuring the thickness of the individual layers. In all cases (with the exception of I_{240} matrix) the inner thickness $2L_B$ ranged approximately between 380 and 425 μm (Table 1) and is comparable to the thickness of the mono-SR/Prx matrices and the inner layer of the multi-SR/Prx matrix of the works of Soulas and Papadokostaki (2011b,a) respectively.

Additionally, from the SEM micrographs we estimated the thickness ratios $L_A/2L$ (thickness of layer A towards the total matrix thickness) and the results are shown in Table 1.

3.2. Properties of individual layers

In order to interpret the behavior of the three-layer systems, each type of outer A layers and of the inner B layer were characterised separately, as single-layer systems, with respect to their water sorption capacity and permeability to proxyphylline.

The water sorption kinetics by each single-layer matrix is shown in Fig. 4, plotted on a $t^{1/2}/2L$ scale ($2L$: total film thickness). Neat SR adsorbs less than 1% water. However, the presence of osmotically active substances in the SR matrix, leads to imbibition of water. The extent of matrix hydration depends on various factors, the most important of which are the osmotic pressure and the concentration of the embedded substance. Thus, NaCl, characterised by a high osmotic pressure, leads to high levels of hydration even at low NaCl loads, as that of Fig. 4 ($\upsilon_N = 0.04$). The excess water uptake in the NaCl particle cavities, leads to rupture of the surrounding polymeric walls, and eventually a network of microscopic cracks is formed, through which the salt can be released. (Amsden, 2003; Schirrer et al., 1992; Soulas et al., 2009). The water sorption kinetic curve reaches a maximum and eventually drops to a final value as the salt is progressively released in the external water

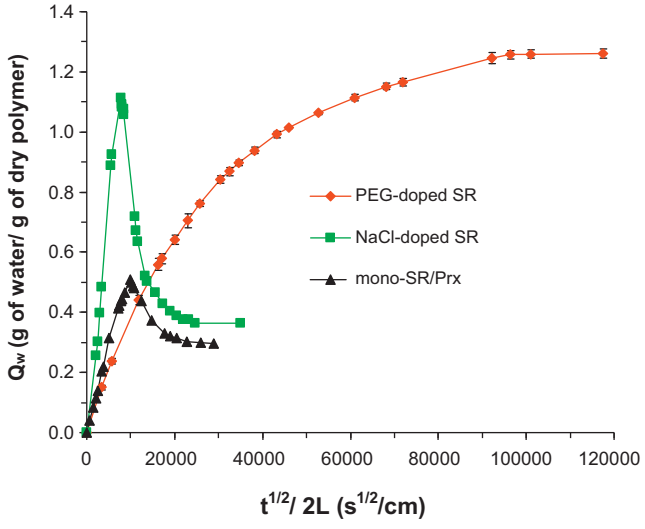

Fig. 4. Water sorption kinetics at 25°C, of single-layer matrices containing 10% (w/w) PEG (♦), 4% (v/v) NaCl (■) and 22% (v/v) proxyphylline (▲). Declining of water uptake is due to release of proxyphylline or NaCl. Sample thickness: 250 μm (♦), 380 μm (■) and 410 μm (▲).

Table 2
Permeability coefficients of single-layer films corresponding to the outer layers A (measured after equilibration in water).

Single-layer matrix	Average total thickness $2L$ (μm)	P_D ($\times 10^{-10}$ cm^2/s)
SR	400 ± 1[a]	0.34 ± 0.00[a]
PEG-doped SR	256 ± 10	0.73 ± 0.10
NaCl-doped SR[b]	380 ± 5	2.49 ± 0.25

[a] Data from the work of Soulas and Papadokostaki (2011b).
[b] NaCl has been leached out before measurement.

phase. The equilibrium hydration level of the matrix (Fig. 4) is due to water occupying the cavities left behind in the salt-depleted matrix. A similar water uptake kinetic curve is observed in the case of SR matrices loaded with the drug. Proxyphylline, having a two orders of magnitude lower osmotic pressure than NaCl (Soulas and Papadokostaki, 2011a), induces lower hydration levels in the SR matrix, even at a much higher initial load ($\upsilon_D = 0.22$) as compared to that of NaCl (Fig. 4). Note that the maximum water uptake attained in each of these two cases of Fig. 4 is not representative of the full osmotic capacity of each embedded substance, since both NaCl and proxyphylline are released parallel to water sorption, and thus the osmotic action inside the respective matrices is progressively diminished. In contrast, the osmotic action of PEG inside the polymer remains intact since PEG is permanently embedded in the polymeric matrix, and the matrix attains hydration levels comparable to those of NaCl-doped films, although its osmotic action is expected to be of the same order of magnitude as that of proxyphylline. Thus, on the basis of Fig. 4, NaCl-doped and PEG-doped films (corresponding to the outer A layers of ABA matrices) sorb at maximum 1.3 g/g and ~1.1 g/g, to be compared with 0.5 g/g for the proxyphylline-loaded layer (corresponding to the inner B layer of ABA matrices). This difference in swellability may be a crucial factor in the design of the ABA three-layer systems, since high differences may result into dissociation of the inner and outer layers upon their immersion in water, leading to sharp increase of the drug's release. No evidence of such dissociation is shown in the SEM photos of the depleted ABA matrices in Figs. 2 and 3. This may be partly due to the fact that in the ABA system, the depletion of the inner B layer from proxyphylline is delayed by the outer A layers. As a result, the drug's osmotic action is prolonged in the ABA system, and thus the B layer attains higher hydration levels than those of the corresponding single layer of Fig. 4.

The results of permeability measurements in water-equilibrated matrices are shown in Table 2. Previous work has shown (Soulas and Papadokostaki, 2011b) that at loads υ_D below the percolation threshold, proxyphylline may diffuse through both the SR matrix, as well as through the hydrated areas formed by its osmotic action (Fig. 4), without any evidence of a crack formation release mechanism. On the other hand, in the presence of NaCl, its permeability increases due to the NaCl-induced network of the microscopic cracks (Soulas and Papadokostaki, 2011a). Hence, as shown in Table 2, proxyphylline possesses a measurable permeability coefficient through neat SR, which on the other hand, is significantly lower than that through NaCl-depleted SR matrices. Finally proxyphylline's P_D through PEG-loaded SR is approximately twice that of the corresponding value in neat SR, due to the formation of hydrated sites in the matrix (Gao et al., 2005; Hron, 2003; Schulze Nahrup et al., 2004).

In relation to the ABA matrices under study here, the data of Fig. 4 and Table 2 indicate that the outer drug-free A layers doped with NaCl are expected to be more permeable to proxyphylline than those doped with PEG while the less permeable of all would be those of neat SR. On the other hand, the permeability of the inner B layer of ABA matrices, loaded in all cases at a proxyphylline concentration $\upsilon_D = 0.22$, has been found to be 4.52×10^{-10} cm^2/s (Soulas and Papadokostaki, 2011b). The said high value is attributed to the

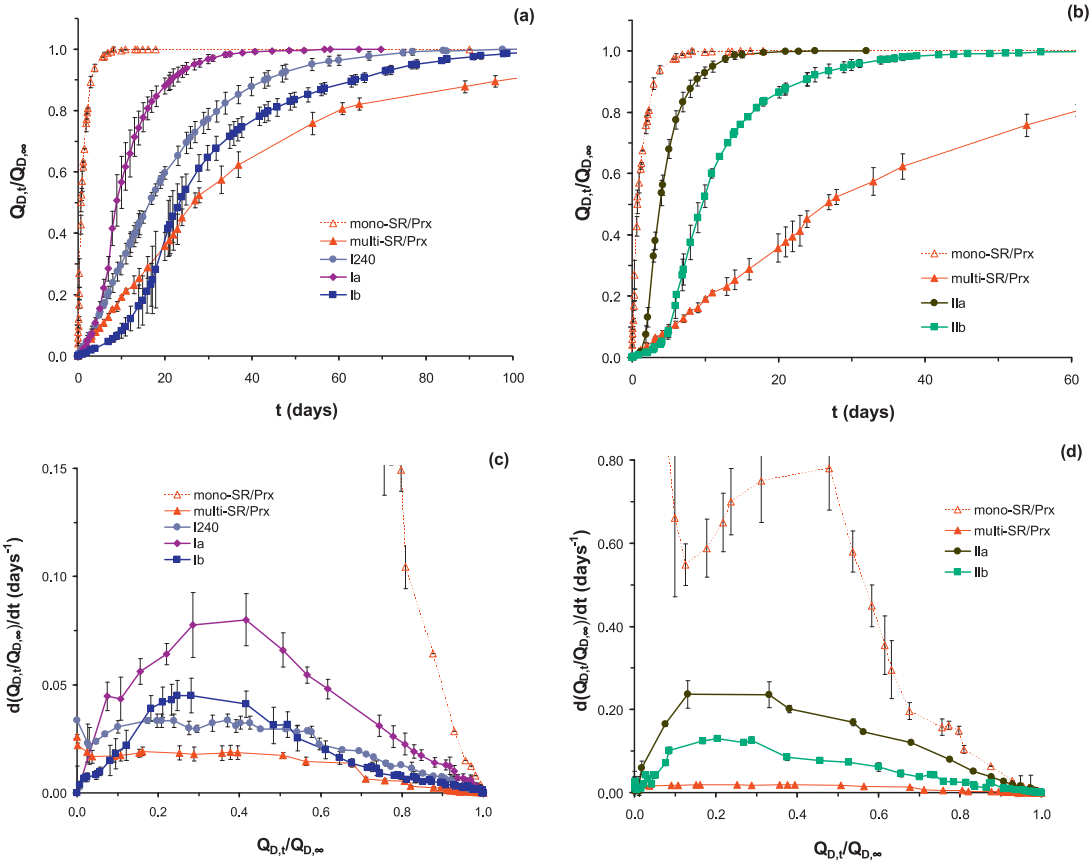

Fig. 5. Proxyphylline's release, at 25 °C, from: (a) three-layer systems with PEG-doped outer layers: I_{240} (●), Ia (♦) and Ib (■) and (b) three-layer systems, with NaCl-doped outer layers: IIa (●) and Ib (■), compared to the release of proxyphylline from mono-SR/Prx (△) and multi-SR/Prx (▲) systems on a *t* scale. (c and d): Corresponding release rates. Data for mono-SR/Prx and multi-SR/Prx systems taken from the works of Soulas and Papadokostaki, 2011b,a respectively.

high proxyphylline load in this case, leading to interconnection of the drug particles, rupturing of the surrounding thin polymeric walls and formation of a water-filled network of drug depleted cavities, facilitating the permeation of proxyphylline (Amsden and Cheng, 1994; Amsden, 2003; Soulas and Papadokostaki, 2011b). On this basis, the permeability of the inner B layer is expected to exceed that of both PEG-, as well as NaCl-doped outer A layers. According to this finding, together with the fact that A layers are here drug-free, the outer layers of the ABA systems are expected to be rate-controlling during the release process.

Finally, the hydrophilicity of silicone rubber surfaces was not materially affected by the presence of NaCl particles as shown by the measured contact angles: $114.64 \pm 1.50^{\circ}$ and $115.51 \pm 1.16^{\circ}$ for neat SR matrices and NaCl-doped matrices respectively. On the other hand, the presence of PEG results to a slight increase in hydrophilicity giving contact angles $106.21 \pm 1.70^{\circ}$. This finding gives a hint on how to exploit coating of mono-layer films not only for regulating the drug release rate but also for making the system more hydrophilic and hence more biocompatible (Alauzun et al., 2010; Hron, 2003; Lin et al., 2010).

3.3. Release experiments

3.3.1. Release of proxyphylline

The release of proxyphylline from type I and II three-layer matrices is shown in Fig. 5a and b in plots of fractional amount $Q_{D,t}/Q_{D,\infty}$ of the drug vs. time *t*. In all cases the initial volume fraction of the drug in layer B was $\upsilon_D = 0.22$ and the exposed surface was 8 cm^2. Each plot represents the average of three samples coming from the same initial film. For reasons of comparison the release of proxyphylline from the mono-SR/Prx and the three-SR/Prx matrices of the works of Soulas and Papadokostaki (2011b, a) are also presented in the same graph. The total amount of the embedded drug in all cases ranged from 49 to 62 mg depending on the inner layer thickness, except for the I_{240} matrix were it was ~31.5 mg. The variation in proxyphylline content between samples of the same category, ranged from 2.9 to 7.6%.

The common observation in Fig. 5a and b is that the drug's release from either type I or II three-layer systems is characterised, as expected, by the appearance of a time lag due to the drug-free outer layers. However, although PEG- and NaCl-doped outer layers act as barriers that prolong proxyphylline's release, at the same time they are more permeable, compared to neat SR outer layers of the multi-SR/Prx system, in accordance with the results of the previous section.

Furthermore, as expected for a certain type of ABA matrices (either type I or II), any increase in the $L_A/2L$ ratio leads to the retardation of the drug's release and to more pronounced time lags (compare for example curves Ia with Ib of Fig. 5a and curves IIa with IIb of Fig. 5b). On the other hand, for comparable $L_A/2L$ ratios (e.g. curves Ib and IIb of Fig. 5a and 5b), proxyphylline's release kinetics from type II matrices is faster compared to type I systems. This is in line with the higher permeability of the drug through NaCl-doped A layers as compared to the PEG-doped ones, shown in Section 3.2.

The drug release rates are shown in Fig. 5c and d on a fractional amount scale. As shown, the initial "burst effect" of the mono-SR/Prx system is effectively suppressed and a fairly uniform overall dosage rate was achieved in all cases.

The average dosage of proxyphylline from each system is given in Table 3. The degree of rate uniformity achieved for 50% of the

Table 3
Average dosage rate and duration for the release of 50% of the amount of drug.

Matrix	Average dosage rate ($days^{-1}$)	Fluctuation of average rate (%)	Duration (days)
Multi-SR[a]	0.0160	8.8	30
I_{240}	0.0285	19.3	16
Ia	0.0618	29.5	7
Ib	0.0287	23.8	15
IIa	0.1914	23.5	2
IIb	0.1009	28.7	6

[a] Data from the work of Soulas and Papadokostaki (2011a).

proxyphylline load by the type-I and II three-layer systems is comparable, and significantly lower than the corresponding one achieved by the multi-SR/Prx system. For the range of L_A/L ratios studied, we can make a rough estimate on each ABA type's rate sensitivity to thickness changes. The combination of L_A/L ratios from Table 1 and of the average dosage rates from Table 3 shows that an approximately 50% decrease on the dosage rate is produced by a 3-fold increase of L_A/L for type I systems, and by a 2-fold increase for type II systems. This gives a hint that type II systems are more susceptible to thickness changes.

Regarding I_{240} system, that was designed as an example of a three-layer system with thinner inner layer B (~240 μm), the observed release kinetics is related on the one hand to its relative L_A/L ratio and on the other hand to the lower initial amount of drug. As shown in Table 1, the L_A/L ratio of I_{240} system is an intermediate case compared to Ia and Ib systems and therefore, as expected, the release kinetics of I_{240} lays in between the curves of the other two type I systems (Fig. 5a). Secondly, since the amount of drug is lower in I_{240} system, the inner layer is depleted sooner which in turn reduces the diffusion driving force and as a result, the enhancement of release taking place in the middle portion of Ia and Ib release curves is not observed here, leading to better uniformity of the release rate (Fig. 5c and Table 3).

In Fig. 6 the release curves of the drug, from type I and II matrices, are re-plotted on a $t^{1/2}/2L$ scale for further theoretical interpretation and comparison of the release kinetics without the contribution of thickness. With respect to the release of the drug from the mono-SR/Prx system, we assume that it follows $t^{1/2}$ release kinetics which can be approached by Higuchi's release kinetics

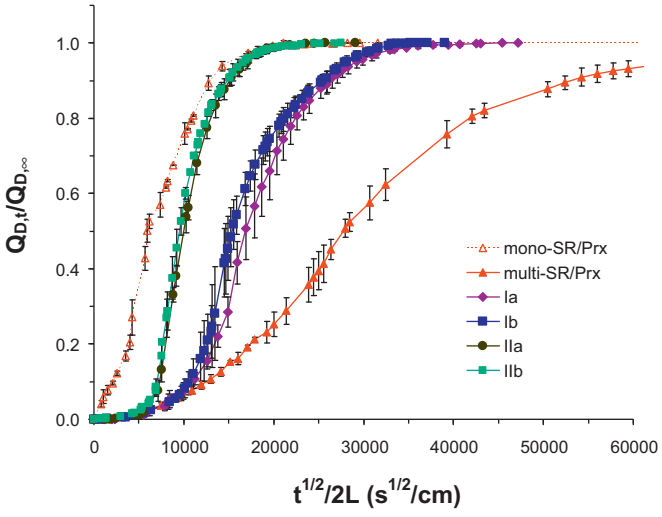

Fig. 6. Proxyphylline's release, at 25 °C, from type I (PEG-doped outer layers) and type II (NaCl-doped outer layers) three-layer systems compared to the release of proxyphylline from mono-SR/Prx (△) and multi-SR/Prx (▲) systems on a $t^{1/2}/2L$ scale.

although osmotically driven water is imbibed and therefore not all the criteria are met. Hence we may use Eq. (1) (Higuchi, 1961):

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

where C^o_{DS} is the drug's solubility in the polymer, C_{D0} is the initial drug's concentration and D_D is the diffusion coefficient of the drug through the polymer. However, since the drug's solubility in the polymer was unavailable, by replacing D_D in Eq. (1) with $P_D/K_D = [P_D \times (C^o_{DS}/C^o_{DS})]$, where K_D is the partition coefficient of the drug and c^o_{DS} is the drug's solubility in water (0.55 g/cm³ at 25 °C), the said equation transforms to Eq. (2) (Papadokostaki et al., 1998):

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

Through Eq. (2) we may calculate the apparent permeability coefficient of the drug from a mono-layer system loaded at a proxyphylline concentration $\upsilon_D = 0.22$ which corresponds to the inner B layer of the ABA matrices. The permeability was found to be 4.52×10^{-10} cm²/s. On the other hand as shown by the release curves corresponding to the three-layer systems in Fig. 6, it is obvious that the release kinetics deviate strongly from $t^{1/2}$ release kinetics due to the complexity of their design as predicted from relevant theoretical works (Lu and Anseth, 1999; Charalambopoulou et al., 2001; Watkins et al., 2007; Paul, 2011; Soulas et al., 2011).

With respect to the three-layer systems, faster release of the drug from type II matrices is clearly shown here, as discussed above. On the other hand, the presence of PEG in the outer layers of the type I systems, accelerates the release relatively to that from systems with pure SR A layers, in line with the results of the previous section. Another interesting observation is the coincidence of the drug's release kinetics on a $t^{1/2}/2L$ scale, from three-layer matrices of the same type. This coincidence points to that, taking out the relevant L_A/L ratio, the main rate determining factor is the composition of the outer layers. Non-significant dependence of the release on reduced L_A/L is also predicted for similar range of thicknesses as shown by the theoretical calculations corresponding to lines A1 and A1a of Fig. 4a, presented in the work of Papadokostaki et al. (2009).

3.3.2. *Concurrent NaCl and proxyphylline release from type II three-layer matrices*

As mentioned in the introduction, one of the features of type II systems is their capacity of releasing a second solute which also acts as an osmotic excipient that modifies the release of the drug.

In Fig. 7 we present the simultaneous release of proxyphylline and NaCl from type II three-layer matrices on a t scale. In every case the salt's release is faster compared to the drug's release and it is characterised by an initial steep rise up to ~10% of the initial salt load, in contrast to the initial time lag that is observed in the case of the drug. After this time-lag period, during which ~50% of the salt is released, the release rate of the drug builds up. Based on previous discussion, the release mechanism from the particular ABA system is further explained in the schematic representation of Fig. 8. As shown in Fig. 8a, before immersing the system in the aqueous medium the drug and salt particles are embedded in separate layers. As soon as the matrix is immersed in water (Fig. 8b) osmotically driven water, attracted by NaCl, is sorbed in layer A and a network of microscopic cracks starts to form. The observed initial delay in proxyphylline's release (Fig. 7), corresponds to the formation of this network in the drug-free layer. As the water front reaches the inner layer (Fig. 8c) the release of the drug starts to accelerate since diffusion is facilitated through the network of cracks of the outer layer. Meanwhile, a wall-rupture mechanism (Amsden and Cheng, 1994) occurs in parallel inside layer B due to the proximity of the drug particles.

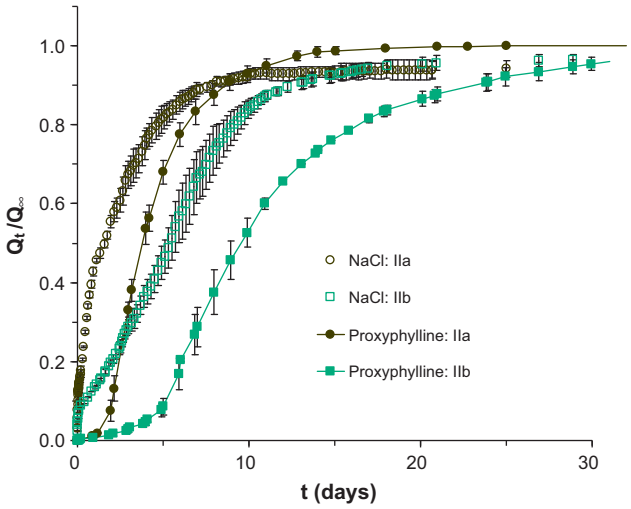

Fig. 7. Concurrent release of proxyphylline (full points) and NaCl (open points) from IIa (circles) and IIb (squares) three-layer matrices at 25 °C.

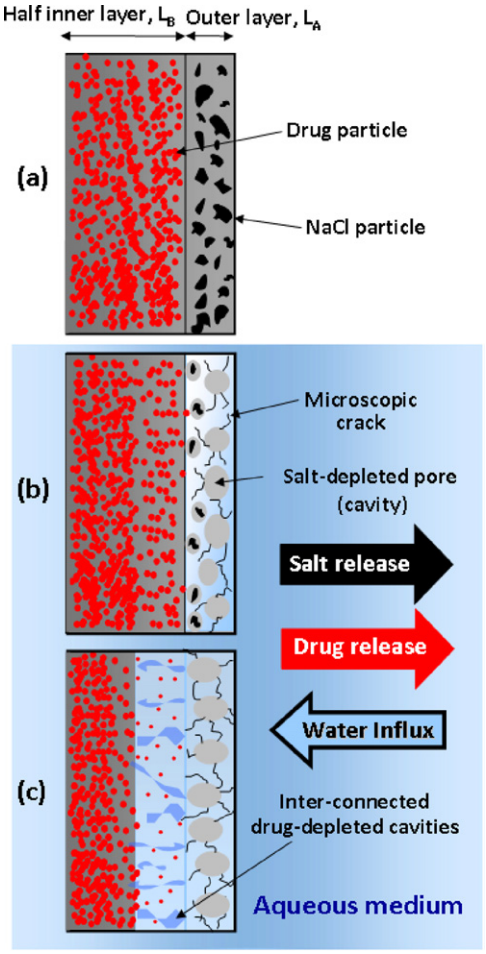

Fig. 8. A simplified schematic representation of proxyphylline's release from type II three-layer systems (half device). (a) Three-layer matrix before its immersion in the aqueous medium, (b) formation of the microscopic cracks network after its immersion in water and (c) hydration of the inner layer B, formation of inter-connected cavities and acceleration of the release through the cracks network of the outer layer A.

4. Conclusion

A comparative study on the release of a model hydrophilic drug (loaded at 22%, v/v) from symmetrical three-layer systems, with different permeability properties in their outer layers, has been made, in view of regulating the release rate of the drug. The study was also approached with respect to the effect of the relative thickness of the outer and inner layers and the results were compared to the release of the drug from a single-layer system and a three-layer system with neat SR outer layers.

The results showed that in all cases the addition of hydrophilic excipients in the outer layers enhances the drug's release compared to the previously studied multi-layer system with neat SR outer layers. In particular, the presence of PEG in the outer layers allows the imbibition of water which accelerates the drug's release, while the presence of NaCl creates a network of microscopic cracks through which the drug's release rate is significantly enhanced, compared to the three-layer system with neat SR outer layers. As expected, in both cases (ABA systems with PEG or NaCl-doped outer layers) the initial "burst effect", characterising the SR single-layer matrix, is eliminated by the outer drug-free layers, as was also the case for the ABA system with neat SR outer layers. However the degree of the overall uniformity of release achieved in each case is different. In particular, although PEG and NaCl-doped outer layers serve as barriers, the uniformity of release rate, corresponding to the release of approximately 50% of the initial drug load, is more effectively achieved by neat SR outer layers. Finally, NaCl and proxyphylline-loaded three-layer matrices serve as model dual-drug loaded systems in which one of the biologically active substances may also modify the release kinetics of the other.

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