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ARTICLE *in* COLLOID AND POLYMER SCIENCE · JULY 2014

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ORIGINAL CONTRIBUTION

Transport properties of ephedrine hydrochloride through poly(vinyl alcohol) matrices—a simple method for enantiomeric differentiation

Artur J. M. Valente · Cesar M. C. Filho · Adley Rubira · Edvani C. Muniz · Hugh D. Burrows

Received: 24 March 2014 / Accepted: 6 April 2014 / Published online: 29 April 2014

Abstract Equilibrium and transport properties have been investigated of ephedrines, a class of sympathomimetic amines, through cryogel membranes of poly(vinyl alcohol) (PVA). The effect of the PVA (10 to 18 % (*w*/*v*)) on the release properties of (1*S*,2*R*)-(+)-ephedrine hydrochloride has been discussed on the basis of partition–diffusion and power-law models. The effect of PVA concentration on the swelling degree of PVA–ephedrine matrices have been measured, allowing the estimation of the volume fraction of polymer in the gel. Ephedrine release rate constants, computed by using a first-order kinetics approach, have been modeled by using free-volume and hydrodynamic-scaling models. Differences in the release properties of the ephedrine isomers, (1*S*,2*R*)-(+)- and (1*R*,2*S*)-(−)-ephedrine as their hydrochlorides, have also been studied at different temperatures. The release kinetic constants and the corresponding activation energies show a marked discrimination between the two ephedrine isomers. This suggests that PVA cryogel membranes possess high potential for enantiomeric differentiation.

Keywords Ephedrine · Poly(vinyl alcohol) · Enantiodifferentiation · Transport properties · Cryogel membranes

Electronic supplementary material The online version of this article (doi:10.1007/s00396-014-3227-7) contains supplementary material, which is available to authorized users.

A. J. M. Valente (✉) · C. M. C. Filho · H. D. Burrows
Department of Chemistry, University of Coimbra,
3004-535 Coimbra, Portugal
e-mail: avalente@ci.uc.pt

A. Rubira · E. C. Muniz
Grupo de Materiais Poliméricos e Compósitos, GMPC - Departamento de Química, Universidade Estadual de Maringá, UEM, 87020-900 Maringá, Paraná, Brazil

Introduction

Ephedrine is an alkaloid extract from *Ephedra* or Ma Huang (*Ephedra sinica*) species. Until banned from use as a dietary supplement ingredient by the US Foods and Drugs Administration (FDA) in 2004 [1], ephedrine and ephedrine derivatives were widely used for weight loss [2] and for stimulating the central nervous system [3], producing excitement and euphoria, and increasing motor activity [4]; the latter had direct effects on the regulations of the World Anti-Doping Agency (WADA). However, ephedrines are also used as a major active component in medications for treatment of nasal congestion [5], asthma, and obesity [6].

Another important characteristic of ephedrines is the existence in their structure of two chiral centers, with the corresponding four isomers: (1*S*,2*R*)-(+)-ephedrine, (1*R*,2*S*)-(−)-ephedrine, (1*S*,2*S*)-(+)-pseudoephedrine, and (1*R*,2*R*)-(−)-pseudoephedrine [7]. These chiral properties make ephedrine an interesting model for the development of sensors [8–10] and molecular imprinted polymers for chiral recognition [11–14].

Hydrogels are polymeric materials with a three-dimensional network structure that can imbibe water under buffered or physiological solutions. They possess a high water content, soft and rubbery consistency, and low interfacial tension toward water or biological fluids [15]. Among their numerous applications, hydrogels have been used for chiral recognition [16–18]. Poly(vinyl alcohol) (PVA) hydrogels have demonstrated a great potential to act as a matrix for a wide variety of applications, such as sensors, biomedical, and separation processes [19, 20]. In the case of separation processes, PVA gels have been successfully used as matrices for isomer separation [21, 22].

In a previous paper [23], we have contributed toward the elucidation of the enantiodifferentiation mechanism involving (1*R*,2*S*)-(−)- and (1*S*,2*R*)-(+)-ephedrine

hydrochloride in aqueous solutions; this has been done on the basis of the analysis of mutual diffusion coefficients and complemented with electrical conductivity and molecular dynamics simulations studies. We extend these studies to hydrogel membranes. The ability of molecules of different sizes to diffuse into and out of hydrogels is well known and permits the use of such materials as, for example, delivery systems [24–26]. Release kinetics of (1*R*,2*S*)-(−)- and (1*S*,2*R*)-(+)-ephedrine hydrochloride from PVA cryogel membranes are reported in this work. The effect of various experimental conditions, such as PVA and ephedrine concentrations, on the release kinetics is discussed on the basis of the partition–diffusion [27] and power-law models [28]; the effect of PVA concentration leads to a non-negligible change in the volume fraction of the polymer in the gel, in agreement with the Cukier model. It is observed that the release kinetics at different temperatures lead to different activation energies for ephedrine release, clearly suggesting that PVA can be applied in the enantiomeric discrimination of (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*R*)-(+)-ephedrine isomers.

Experimental

Reagents and solutions

(1*R*,2*S*)-(−)-Ephedrine hydrochloride (99 %) and (1*S*,2*R*)-(+)-ephedrine hydrochloride (99 %) were purchased from Sigma-Aldrich and were used without further purification. PVA (molecular weight 72,000; degree of polymerization 1,600; degree of hydrolysis 97.5–99.5 mol%) was supplied by Fluka. Solutes were weighed using a Scaltec SBC22 balance with a resolution of ±0.01 mg.

Cryogel PVA membranes

PVA solutions of 10, 12, 14, 16, and 18 % (*w*/*v*) concentration were prepared by dissolving a known amount of PVA into distilled water at 80 °C under continuous stirring for 3 h. The encapsulation of ephedrine (Eph) into PVA has been achieved before the freeze-thawing process by dissolving a certain mass of the drug in 1 ml of PVA solution under continuous stirring for 5 h, leading to concentrations ranging from 1 to 5 % (*w*/*v*).

After mixing, solutions were cast in *Petri* boxes and submitted to freezing for 12 h at −20 °C and, after that, thawed for 12 h at 25 °C. The cycles of freezing and thawing were repeated three times. After that, the blended gel membranes show a good mechanical resistance and a white and opaque appearance caused by their heterogeneous structure [29].

Ephedrine release and sorption isotherms

Ephedrine desorption kinetics were performed by immersing a PVA cryogel membrane sample in a known volume (normally 60 mL) of solution. The samples were stirred at ca. 120 rpm by using a F20 FALC magnetic stirrer, with samples in a thermostatic bath (Velp Scientifica). Constant temperature (±0.01 °C) was maintained throughout the experiments by using a HAAKE Phoenix II P2 thermostat bath. Aliquots of the supernatant were collected at defined time intervals. The amount of Eph released from the polymeric matrices, C_{dt}, to the supernatant was quantified by using UV–vis spectrophotometry, measuring the absorbance at 557 nm with a Shimadzu UV-2450 spectrophotometer, and using an extinction coefficient of 185 M^{-1} cm^{-1}. The thickness of cryogels was measured using a *Mitutoyo* digimatic micrometer (±0.001 mm). All experiments have been performed in triplicate, and the imprecision is less than 5 %.

Sorption isotherm experiments were performed by using the following procedure: different samples of the same PVA cryogel membrane were cut and immersed in water at 25 °C until equilibrium was reached. Following this, they were transferred to (+)-ephedrine solution with a volume of 5 mL and left to reach equilibrium (ca. 1 week). The concentration of Eph sorbed by the PVA, *C*, was calculated by measuring the concentration of the Eph in solution prior to (c_i) and after (c_f) the sorption experiments, using the method described above. The reported experimental data are an average of three independent experiments.

Swelling degree

Membranes of PVA, previously loaded with ephedrine, were weighed and immersed in water/electrolyte aqueous solutions, under different experimental conditions. After attaining equilibrium (ca. 1 week is enough to guarantee that the equilibrium state is reached), they were removed from the solution and weighed by using an analytical balance (Scaltec SBC22, ±0.01 mg).

The swelling degree, *Q*, of the gel membranes in the aqueous solutions can be calculated from the weight of the membrane after the equilibrium has been achieved in a particular solution (swollen gel, M_s) and the weight of the dried samples (xerogel, M_x) [30] from $Q=M_s/M_x$. Each swelling degree reported is an average of at least three independent measurements, and the uncertainty of the average swelling degree is less than 8 %.

Release models

The quantification of the release kinetics of ephedrine has been performed by using two different models. The initial

and border conditions that best describe the release of Eph from PVA–Eph cryogels are those characterized by a non-steady state diffusion transport occurring in a stirred solution of limited volume. Taking this into account, the release kinetics have been treated as a partition phenomenon between the gel and aqueous phases [27]. This is because there will always be a difference between the loaded drug and released drug amounts, owing to a partitioning effect. This partition is the result of physical chemical affinities between the gel and the surrounding liquid. In other words, the interactions between the polymeric matrix and the drug hinder the total release of the loaded drug. This model, which considers the effects of both diffusion and partition, is characterized by the involvement of an activity coefficient, α. Such a parameter provides important information from a strategic point of view that will allow for better evaluation of the polymer matrix as a potential medium for drug delivery.

$$\alpha = \frac{F_{R,\max}}{1-F_{R,\max}} \tag{1}$$

where $F_{R,\max}$ is the maximum fraction of the released solute, and F_R is given by

$$F_R = \frac{C_{R,t}}{C_0} \tag{2}$$

where $C_{R,t}$ is the concentration of the solute released, at time t, and C_0 is the initial concentration of solute inside the gel matrix.

The processes of release and absorption of ephedrine occur simultaneously at $t>0$, and mass transport between the hydrogel and the solution phase will occur. Assuming a first-order kinetic process, changes of the ephedrine concentration in solution at a given time t can be expressed as

$$\frac{dC_{R,t}}{dt} = k_R\left(C_0 - 0C_{R,t}\right) - k_A\left(C_{R,0} - C_{A,t}\right) \tag{3}$$

where $C_{R,0}$ and $C_{R,t}$ are the concentration of the released ephedrine at $t=0$ and at time t, respectively, C_0 is the initial concentration of Eph in the gel, $C_{A,t}$ is the concentration of absorbed Eph at a specific time t, and k_R and k_A are the rate constants of release and absorption, respectively.

From the above kinetic law equation (Eq. 3), taking into account various considerations of the present model [27], the release kinetics of Eph can be treated by using the following equation:

$$F_R = F_{R,\max}\left(1 - e^{-\left(k_R/F_{R,\max}\right)t}\right) \tag{4}$$

where $F_{R,\max}=C_{R,\max}/C_0$ and $C_{R,\max}$ is the maximum concentration of solute in solution released from the gel.

In a similar fashion, if the solute release follows second-order kinetics, the rate constant can be obtained from equation [27]

$$F_R = \frac{F_{R,\max}\left(e^{2(k_R/\alpha)t} - 1\right)}{1 - 2F_{R,\max} + e^{2(k_R/\alpha)t}}. \tag{5}$$

The experimental release kinetics data of Eph, from PVA–Eph gels to different aqueous solutions, were fitted to Eqs. (4) and (5) by using a nonlinear least-squares fitting procedure (Origin® 8.0, using a 95 % confidence level). Figure 1a shows a representative release profile of (+)-ephedrine, at a concentration of 2 % (*w*/*v*), from a 14 % (*w*/*v*) PVA matrix. The correlation coefficient found by fitting experimental data to Eq. (4) (R^2=0.9785, solid line in Fig. 1a) is better than that obtained by using Eq. (5) (R^2=0.9694, dashed line in Fig. 1a). However, a more detailed analysis shows that Eq. (5) seems to be more accurate for very short release range times. In order to provide an insight into this application and since the fraction of released Eph is, for all systems, greater than 0.95 (which implies that the volume is big enough to induce the release of the majority of Eph-loaded cryogels), the Eph release mechanism was evaluated by using the power-law equation

$$C_t/C_\infty = kt^n \tag{6}$$

where C_t and C_∞ are cumulative concentrations of the material released at time t and at infinite time, respectively, and k and n are fitting parameters, with the latter giving useful information on the release mechanism; from Eq. (6), the mean dissolution time (MDT), which characterizes the drug-release rate from a dosage form and indicates the drug-release-retarding efficiency of the polymer [31], can be calculated through the following equation [32]:

$$MDT = \left(\frac{n}{n+1}\right)k^{-n^{-1}}. \tag{7}$$

The application of Eq. (6) is restricted to cumulative release less than 60 % (the so-called short-range times).

Results and discussion

Effect of PVA concentration

The effect has been studied of the amount of PVA (from 10 to 18 %*w*/*v*) on the release kinetics of (+)-ephedrine (1 % *w*/*v*) loaded into PVA matrices. Table 1 shows the release parameters for desorption of (+)-ephedrine from PVA–Eph gel membranes. The parameters obtained from the fitting of Eqs. (4) and (6) to experimental data as a function of PVA concentration are summarized in Table 1, and those allowing the computation of values in more detail for a 14 % PVA gel are given in Table S1.

The desorption of (+)-Eph follows first-order kinetics, independent of the amount of PVA in the matrix; this is in agreement with what is observed for the release of other

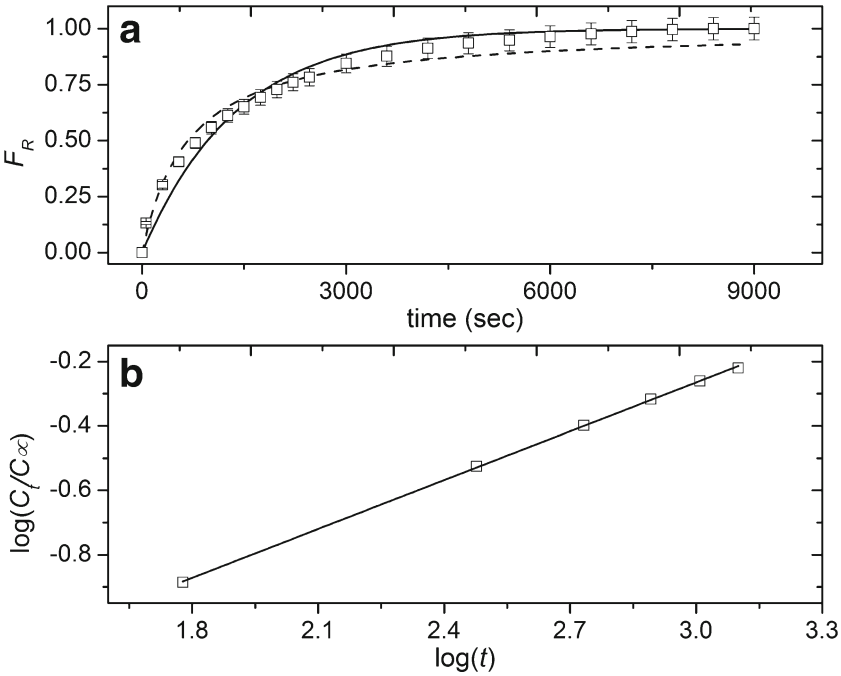

Fig. 1 Representative (+)-ephedrine release from PVA (2 % *w*/*v*)-Eph cryogels to water and the best fittings of Eqs. (4)—*solid line*—and (5)—*dashed line*—**a**—and the linear version of Eq. (6)—**b**—to the experimental data

molecules from PVA cryogels [25]. It is also possible to conclude that almost all the encapsulated Eph is released into the water (F_{MAX}>0.95), which clearly suggests that, in the limit, the border and initial conditions for Eq. (4) approach these conditions allowing the assumption of a drug concentration in the aqueous phase much lower than that in the gel matrix.

The release kinetics of (+)-ephedrine from the PVA–Eph cryogels shows a Fickian mechanism (n=0.5). This arises in polymer/drug systems where the diffusion of drug is much less than the polymer segment mobility and the rate at which the desorption equilibrium is approached is independent on the swelling kinetics. From the fitting parameters of Eq. (6), shown in Table 1, it is possible to calculate the MDT (Eq. 7). MDT values increase upon increasing the concentration of PVA. Such a dependence is in agreement with release constants computed by using Eq. (4); in fact, there is a good correlation between these two parameters (R^2=0.9831) showing the validity and consistency of the first-order kinetic equation for modeling the release kinetics in this drug/hydrogel system. The dependence of both MDT and k_R on the PVA concentration suggests that the Eph desorption can be controlled by the cryogel free volume (*latus sensus*). To obtain stronger support of this, the effect of the PVA concentration on the swelling degree has been evaluated. It was found that Q values (Table 2) are similar to those obtained elsewhere [33–35] and show that by increasing the PVA concentration, the network becomes more rigid. In fact, since the formation of a gel network by physical crosslinks can be mainly explained by the formation of hydrogen bonds and crystallites, an increase of available hydroxyl groups will contribute to an increase in the cross-linking [36]. From the Q values, the polymer volume fraction, φ, can be calculated (Table 2) by using [37]

$$\varphi = \{1 + [(Q–1)r/d]\}^{-1} \tag{8}$$

where ρ is the polymer density, (=1.17 g.cm^{-3} [34]) and d is the density of water (=0.9971 g.cm^{-3}, at 25 °C [38]).

The release of solutes from hydrogels composed of flexible polymer chains, such as PVA, can be estimated by two different models [39]: the Cukier hydrodynamic-scaling model [40]

$$\ln D/D_0 = -k_c r_s \varphi^{0.75} \tag{9}$$

where D and D_0 are the diffusion coefficient of the solute in gel and in aqueous solution, respectively, r_s is the solute radius, and k_c is an undefined constant for a given polymer–solvent system, and the free-volume model of Lusting and Peppas [41] without the sieving term [39]

$$\ln\ D/D_0 = -k_2 r_s{}^2[\varphi/(1-\varphi)] \tag{10}$$

where k_2 is an undefined constant.

The first model (Eq. 9) describes the diffusion in gels based in the concept that solute molecules are hard spheres which are larger than the solvent molecules in which they move, and that the Brownian motion of these species can serve as a probe of the nature of hydrodynamic screening in the solution. In contrast, the free volume (Eq. 10) can be qualitatively visualized as the volume that is not occupied by the polymer molecules but which constitutes a part of the bulk volume of either the overall polymer–solvent or the solution system. The free volume may be closely related to the void volume in

Table 1 Effect of the PVA concentration on the release kinetics of (+)-ephedrine from PVA cryogel matrices to water, at 25 °C

PVA % (*w*/*v*)	10	12	14	16	18
F_{MAX}	0.95 (±0.01)	0.97 (±0.01)	0.98 (±0.01)	0.95 (±0.01)	0.96 (±0.01)
$k_R/(10^{-4}\ s^{-1})$	8.32 (±0.16)	7.84 (±0.15)	7.24 (±0.16)	6.59 (±0.15)	5.37 (±0.12)
R^2	0.9792	0.9980	0.9901	0.9920	0.9930
n	0.50 (±0.01)	0.51 (±0.01)	0.50 (±0.01)	0.51 (±0.01)	0.53 (±0.01)
$k/(10^{-2}\ s^{-n})$	1.95 (±0.03)	1.74 (±0.05)	1.71 (±0.06)	1.53 (±0.04)	1.18 (±0.03)
R^2	0.9994	0.9984	0.9970	0.9979	0.9984
MDT/s	837	960	1,168	1,242	1,560

R^2 correlation coefficient

semicrystalline polymers and may be more generally visualized as a "hole," either opened up by thermal fluctuation of molecules or present because of geometrical requirements of random chain packing [42, 43].

In the absence of experimental diffusion coefficients, these can be replaced by the corresponding rate constants, i.e., $D/D_0 \propto k/k_0$. Consequently, the dependence of the polymer free volume on the rate constants (Table 1) for the release of Eph can be evaluated by Eqs. (9) and (10): the regression parameters of these equations for the experimental data are shown in Table 3.

The examination of R^2 and χ^2 values in Table 3 suggests that although the lowest values are found for the free-volume model, both equations provide a reasonable fit to the data. Furthermore, k_0 values obtained by both models are similar, proving their self-consistency. However, as has been discussed in detail by Amsden [39], the Cukier model has been developed based on more solid and consistent grounds compared with the free-volume model. Thus, the hydrodynamic model cannot be discarded, despite its lower statistical consistency. In fact, taking advantage of the fact that the release of Eph follows a Fickian process, and assuming that the gel matrix thickness, l, is constant and equal to 1.95 mm, the values of apparent diffusion coefficient (D) of Eph can be computed by using the equation

$$D = \pi(kl/4)^2 \tag{11}$$

and are equal to 7.08×10^{-10} $m^2\ s^{-1}$ (PVA 10 %) and 2.61×10^{-10} $m^2\ s^{-1}$ (PVA 18 %). These values are an order of magnitude lower than the corresponding values for Eph in aqueous solutions [23]. Consequently, and not surprisingly, it can be stated that the frictional drag acting on Eph movement inside PVA is higher than that occurring in the liquid water.

Effect of (+)-ephedrine concentration

In contrast to the effect of PVA concentration, the release kinetic parameters of Eph are only slightly dependent on the concentration of Eph loaded into PVA matrices. From Fig. 2 and Table 2, it can be seen that the release rate constant decreases from 7.24×10^{-4} to 6.98×10^{-4} s^{-1} when the (+)-Eph concentration increases from 1 to 5 % (*w*/*v*). This trend is in agreement with a first-order kinetic process and indicates that the release of (+)-Eph follows a dependence somewhat similar to that occurring in aqueous solution. A simple possible explanation for this comes from the increase of Eph–Eph interactions. Such an effect was also observed for other drug-gel systems, such as curcumin loaded into starch-based hydrogels [44]. To obtain a deeper insight into the way solute–solute or solute–polymer interactions are affecting transport properties, the sorption isotherm has been studied of (+)-Eph, in the concentration range of 10 mM (0.2 % (*w*/*v*)) to 0.3 M (6 % (*w*/*v*)), in PVA gels. From the analysis of Fig. 3, it can be concluded that a type-I sorption is occurring with a partition coefficient (C(Eph)/c(Eph)) equal to 5.95 (±0.08) mmol/(M.g-PVA) and an amount of Eph sorbed by PVA gels equal to 0.87 times the initial amount (see inset in the Fig. 3), demonstrating the high affinity of ephedrine for the PVA hydrogel. This confirms that Eph–Eph and Eph–water interactions are stronger relative to Eph–PVA interactions. Such an increase of Eph–Eph interactions will lead to an increase of the resistance coefficient, which is a measure of the friction acting on a solute as it moves through a solvent [45]. The

Table 2 Effect of PVA concentration on the swelling degree and polymer volume fraction of PVA cryogels, at 25 °C

PVA % (w/v)	10	12	14	16	18
Q_{MAX}	10.6 (±0.4)	9.5 (±0.5)	8.6 (±0.4)	8.0 (±0.5)	6.7 (±0.5)
φ	0.082	0.091	0.10	0.11	0.13

Table 3 Regression results of the application of the free-volume and hydrodynamic-scaling models to desorption of Eph through PVA cryogels

	$\ln k_0$	m	R^2	χ^2
Eq. (9)	−6.02 (±0.08)	−6.9 (±0.4)	0.98389	0.00142
Eq. (10)	−6.44 (±0.04)	−7.2 (±0.3)	0.99055	0.00084

R^2 correlation coefficient, χ^2 sum of squares of the residuals

Equation (9) $m=k_c r_s$; Eq.(10) $m=k_2 r_s^2$

decrease of k_R is accompanied by a concomitant increase of MDT as a function of PVA concentration (Fig. 2). However, in a similar fashion, an increase of PVA content to 5 % only leads to a 6 % variation of the MDT values, in close agreement with the k_R dependence.

It is worth noting that upon increasing the Eph concentration, the release mechanism remains, essentially, Fickian or pseudo-Fickian (i.e., $n<0.5$). This latter mechanism is characterized by an initial curvature of the amount of desorbed drug as a function of the square root of time from the concave origin to the time axis.

Effect of isomers and temperature

Following from the experimental data shown in the previous section, further experiments were carried out by loading the PVA cryogel membranes with 1 % (*w*/*v*) (+)-Eph and (−)-Eph. The effect of temperature (from 20 to 37 °C) on the release kinetics of both isomers shows Fickian (or pseudo-Fickian) release mechanisms (see Table 4). It can also be observed that the constant k increases, while MDT decreases, upon increasing the temperature, suggesting an Arrhenius-like dependence for both parameters. From the assessment of mean dissolution times, it is also noted that the release of (−)-Eph is less sensitive to temperature changes than the (+)-Eph isomer.

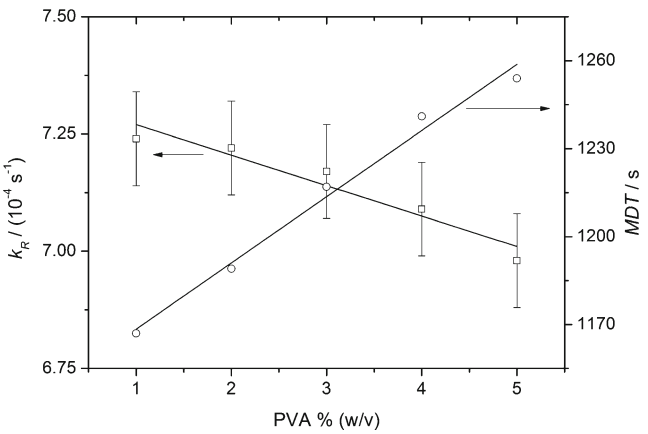

Fig. 2 Dependence of release rate constant (Eq. 6) and mean dissolution time (Eq. 7) on the content of PVA in the cryogel matrices. *Solid lines* are just to guide the eyes

Similar conclusions can be obtained from the analysis of the release rate constants (Table 4), computed by fitting Eq. (4) to the overall range of experimental ephedrine release data. An Arrhenius plot ($\ln k_R$ as a function of $1/T$) is given for both ephedrine isomers (Fig. 4). The release of ephedrines from PVA cryogels follows the activated rate theory, from which activation energies for the release process (E_a) can be calculated using the following equation:

$$E_a = -RT\frac{d\ln k_R}{d(1/T)} \tag{12}$$

where R is the gas constant and T is the absolute temperature; from slopes of $(\ln k_R)=f(1/T)$, the activation energies obtained were 20.4 and 15.2 kJ mol^{-1} for (+)- and (−)-Eph, respectively. These values have similar magnitudes to those found for related systems [46, 47]. These data are also comparable to activation enthalpies for ionic migration of these enantiomers (19.3 and 17.4 kJ mol^{-1} for (+)- and (−)-Eph, respectively), as studied by electrical conductivity [23]. The behavior of these enantiomers in aqueous solutions strongly suggests that (+)-Eph has a negative hydration compared to the (−)-Eph, i.e., the migration of water molecules from its hydration sphere to the

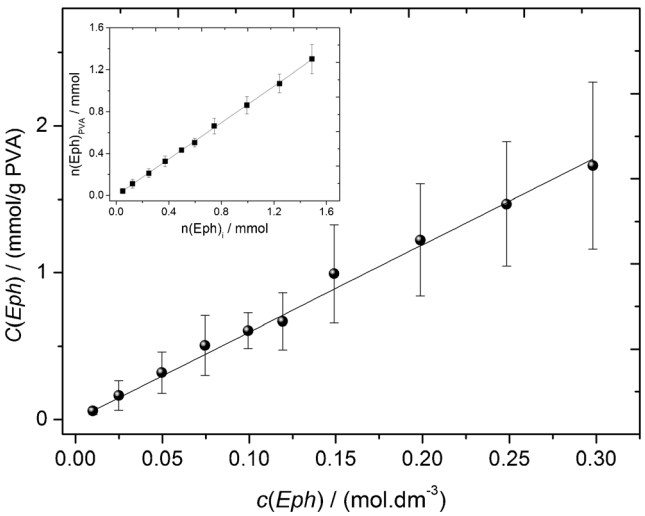

Fig. 3 Sorption isotherms of (+)-ephedrine on PVA cryogel membrane, at 25 °C. *Inset figure* sorption isotherms of (+)-ephedrine in terms of number of moles. *Solid lines* were obtained by fitting a straight line equation to the experimental data. Correlation coefficients are equal to 0.9980 and 0.9999 (*inset figure*)

Table 4 Effect of the temperature and ephedrine enantiomers (1 % (*w*/*v*)) on the fitting parameters of Eqs. (4) and (6) to experimental release data from PVA cryogel matrices to water

T/°C	20	25	30	37
(+)-Eph				
F_{MAX}	0.95 (±0.02)	0.98 (±0.01)	0.98 (±0.02)	0.99 (±0.01)
$k_R/(10^{-4}\ s^{-1})$	6.1 (±0.5)	7.2 (±0.4)	7.9 (±0.5)	9.8 (±0.6)
R^2	0.9994	0.9901	0.9809	0.9894
n	0.49 (±0.01)	0.50 (±0.01)	0.47 (±0.01)	0.48 (±0.01)
$k/(10^{-2}\ s^{-n})$	1.53 (±0.04)	1.71 (±0.06)	2.02 (±0.04)	2.43 (±0.03)
R^2	0.9980	0.9970	0.9987	0.9995
MDT/s	1,581	1,176	1,220	757
(−)-Eph				
F_{MAX}	0.97 (±0.02)	0.98 (±0.02)	0.97 (±0.02)	0.96 (±0.02)
$k_R/(10^{-4}\ s^{-1})$	5.9 (±0.4)	6.4 (±0.4)	7.2 (±0.5)	8.3 (±0.6)
R^2	0.9970	0.9921	0.9850	0.9820
n	0.50 (±0.01)	0.48 (±0.01)	0.47 (±0.01)	0.46 (±0.02)
$k/(10^{-2}\ s^{-n})$	1.79 (±0.03)	2.01 (±0.07)	2.20 (±0.04)	2.53 (±0.01)
R^2	0.9991	0.9965	0.9990	0.9999
MDT/s	1,090	1,046	1,002	980

R^2 correlation coefficient

bulk solution is more difficult in the former case [48]. It also seems that this behavior is due to the occurrence of stronger interactions between water molecules and the hydrophobic part (aromatic ring) of (+)-ephedrine, suggesting that the desolvation and rearrangement of ions in the vicinity of ephedrine hydrochloride are mainly controlled by the hydrophobic part of ephedrine structure, in agreement with other related systems [49].

Comparing the electrical conductivity data to those obtained through the release of ephedrine from PVA membranes, it should be stressed that the use of PVA leads to a well-defined ephedrine enatiodifferentiation, with an activation energy shift of ca. 5 kJ mol^{-1} (two times higher than that found in aqueous solution) between the two ephedrines.

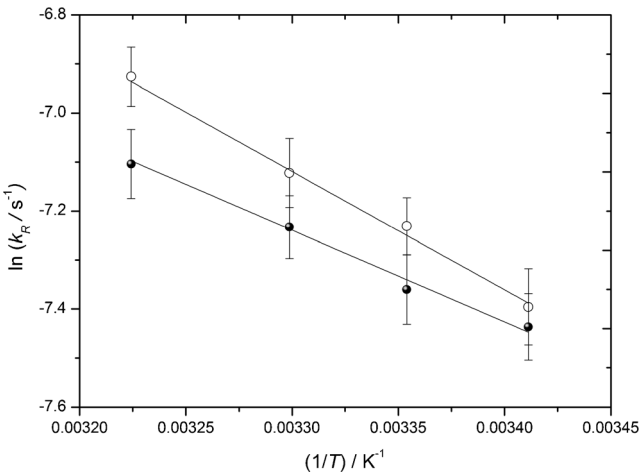

Fig. 4 Variation of the logarithm of the release rate constants (Eq. 4) for (+)-Eph (*white circle*) and (−)-Eph (*black circle*), from PVA cryogels, with the reciprocal temperature

The effect of isomers and temperature on the average molecular mass between crosslinks, or the network parameter, M_c, of the hydrogel matrix has also been evaluated. M_c should change as the solute is released to the surrounding liquid. The movement of solutes toward the outside of the hydrogel, through the release process, can be related to the swelling rate and, consequently, the volume fraction. The interactions between the polymeric matrix and the drug hinder both the total release of the loaded drug and the absorption of water molecules. In other words, when the solute is released, the chemical groups on polymer chains are free to interact with water, increasing solvent penetration during the release process.

M_c was calculated by Flory–Rehner theory [50] adapted to release at equilibrium (F_{MAX}), using the following equation:

$$M_c = -\delta_p V_s \phi^{1/3} \left[\ln(1-\phi) + \phi + \chi\phi^2\right]^{-1} \quad (13)$$

where δ_p and V_s are the polymer density and the solvent molar volume, respectively, and χ is the Flory polymer–solvent interaction parameter [51]. For PVA, χ=0.494. The volume fraction of polymer at the equilibrium swollen state, ϕ, is given by

$$\phi = -\delta_p V_s \phi^{1/3} \left[1 + \delta_p \delta_s^{-1}(Q-1) - \delta_p \delta_s^{-1}\right]^{-1} \quad (14)$$

where δ_s is the solvent density.

Table S2 shows the effect of the temperature and ephedrine enantiomers on M_c to experimental release data from PVA cryogel matrices with 0, 1, 2, 3, 4, and 5 % Eph to water.

In general, M_c significantly decreases when the ephedrine concentration in the gel increases from 0 to 1 %, owing to an increase in the density of polymer chains. By varying the concentration from 1 to 5 %, there is no additional reduction in the M_c, because the tighter structure prevents the expansion/contraction of the polymer-gel network. However, taking into account the effect of ephedrine enantiomers, M_c values of (−)-Eph are lower than those of the isomer (+)-Eph in the temperature range studied. This effect could be related with stronger (−)-Eph-polymer affinity that inhibits the absorption of water and, consequently, the solute release. In such a case, possible interactions between chemical groups on polymer chains and ephedrine seem to be favored for the case of the (−)-Eph isomer.

Conclusions

Activation enthalpies of the transport process in aqueous solutions for ephedrine cations, (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*R*)-(+)-ephedrine of 17 and 19 kJ mol^{-1}, respectively, show a slight discrimination between the two enantiomers [23]. The desorption release of these two ephedrine isomers, previously encapsulated into PVA cryogel matrices, leads to a slightly better enantiomeric discrimination, with activation energies equal to 15 and 20 kJ mol^{-1}, respectively. This is also in agreement with M_c analysis. This selectivity enhancement seems to be due to a better affinity of ephedrine for the PVA gel phase. However, it is worth noticing that such an affinity does not imply interactions with PVA but is due instead to an enhancement of Eph–Eph or Eph–water interactions. This justifies the observed type-I sorption isotherms as well as the Fickian (or pseudo-Fickian) desorption mechanism of Eph from PVA matrices. The release rate constants, computed by using a first-order kinetics law of a partition-diffusion model, show a dependence on the polymer volume fraction according to the free-volume and hydrodynamic model. Although both models seems to be robust for interpreting the experimental results, the latter is more consistent in its development and, consequently, more suitable for the transport interpretation. This is in agreement with diffusion coefficients of Eph from PVA cryogels which are one order of magnitude lower than the corresponding values in aqueous solution, suggesting that the transport is occurring with stronger Eph–Eph or Eph–water interactions. In conclusion, the PVA cryogels are promising matrices for enantiomeric differentiation, especially when such differentiation arises as due to competition between drug–drug and drug–solvent interactions.

Acknowledgments The authors are grateful to the financial support from the Fundação para a Ciência e a Tecnologia (FCT, Portugal) and Coordenação para Aperfeiçoamento de Pessoal de Nível Superior (Brazil), for FCT/CAPES application (Proc. no. 329/13), allowing scientific cooperation between Brazilian and Portuguese researches groups. The Coimbra group are also grateful for the financial support from FEDER through COMPETE program and the FCT (PEst-C/QUI/UI0313/2011 and PEst-OE/QUI/UI0313/2014).

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