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L-Ascorbic acid release from phema hydrogels

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ABSTRACT

Controlled release of L-ascorbic acid from poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels is reported. PHEMA hydrogels were synthesized from 2-hydroxyethyl methacrylate (HEMA) monomer in an oven. We studied the swelling of PHEMA discs in water as a fuction of temperature and thickness of xerogel discs. The fractional swelling was linear in $(time)^{1/2}$ at short times. Drug release has been examined as a fuction of temperature, initial drug load and thickness of the PHEMA discs. The fraction of avaible drug release was linear in $(time)^{1/2}$ during the initial stage too. The release experiments were carried out at 308 K. These studies allow to determinate a diffusion coefficient for transport of water into the hydrogels and a diffusion coefficient for L-ascorbic acid release from the hydrogel.

INTRODUCTION

Controlled release is a new field which has produced many studies (1). When a polymer is placed in contact with a compatible solvent, this solvent penetrates the polymer, forming a swollen gel phase in the wetted region. This fact may be used to release a bioactive agent to the enviroment by incorporating that agent into a suitable polymer matrix which swells in liquid medium, allowing the drug release from that system at a controlled rate (2-5). Hydrogels are polymers which represent an important group of biomaterials for the controlled release of a bioactive agent (6). Hydrogels are a cross-linked polymeric network that can imbibe large quantities of water without the dissolution of the polymeric network (7,8). The release of water soluble drugs from such hydrogels matrices generally involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism (9-11). PHEMA is a hydrogel widely used in this field (8,10,12,13).

In this study L-ascorbic acid release from PHEMA hydrogels was examined. L-ascorbic acid or vitamin C is a hydrosoluble vitamin which is stable in glassy state and in the absence of light. Ascorbic acid is well-known by its antiscorbutic properties although its physiological actions are a lot (14). This drug has been choosen because its aqueous solubility is very high and its aqueous solutions present an acid pH allowing to measure with a pHmeter. PHEMA polymers were synthesized from HEMA monomer in presence of 0.5% wt. EGDMA as cross-linker and 0.05% wt. AIBN as azoinitiator (15,16). Polymerizations were carried out in the absence of a solvent. The EGDMA concentration was choosen because allowing to put into the polymer a high amount of L-ascorbic acid. The kinetics of the hydrogel swelling and drug release from hydrogel matrices have been examined as a fuction of temperature, initial drug load and thickness of the PHEMA discs. Both, the swelling process and the drug release exhibit Fickian behaviour.

MATERIALS AND METHODS

Materials

2-hydroxyethyl methacrylate (HEMA) [Merck] was purified by vacuum distillation as described in the literature (2,16-18), our conditions were 315-318 K / 3.7 10^{-3} mmHg; ethylene glycol

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dimethacrylate (EGDMA) [Merck], α-α'-azoisobutyronitrile (AIBN) [BDH] and L(+)-ascorbic acid [Panreac] were used as received. Distilled water was used in both swelling and release studies.

Polymerization

Polymerization was initiated by placing the monomer, HEMA, together with EGDMA (0.5% wt.) and AIBN (0.05% wt.) in glass test tubes, which were siliconized previously (19). Mixture was outgassed by nitrogen for 30 minutes and was placed in an oven increasing the temperature to 353 K gradually. Temperature program was followed as had been reported by Korsmeyer et al. (2). Solid xerogel cylinders of PHEMA were obtained, which were immersed in distilled water for two weeks to remove any possible residual monomer and afterwards were cutting into discs with. They were dried at ambient temperature for two days and then in an oven at 318 K for one day. The diameter of the dry discs was 12.18-13.55 mm and their thickness between 1.16-1.95 mm.

Swelling of the polymer in water

Swelling experiments of PHEMA discs (without acid) were performed by placing the xerogel discs in a water bath and the degree of swelling (W_t) at different times (20,21) was obtained by withdrawing the discs, lightly drying with filter paper and weighing quickly in a tared sample bottle:

$$W_t = \frac{\text{(weight of swollen disc - weight of dry disc)}}{\text{(weight of swollen disc)}} \quad \text{(I)}$$

The equilibrium degree of swelling (W_∞) was obtained between 5 and 12 hours depending on the thickness of the discs and the temperature (285 K to 308 K).

Loading of gels

L-ascorbic acid (Vitamin C) is very soluble in water (333 mg/ml at 298 K) (14). Polymer discs were loaded with ascorbic acid by immersing them into aqueous solutions of the drug (concentrations between 0.3-1.9 M), in absence of light, until the equilibrium was obtained (1 week) and then dried at ambient temperature for two days and in an oven at 318 K for one day. The oxidated ascorbic acid solutions show yellow colour (22). The same way, the xerogel discs with oxidated acid exhibit that colour too. In our experiments both, the acid solutions and the xerogel discs with the acid were transparent, so no oxidation of L-ascorbic acid occured during the loading process and the release experiments. The loads (A) of the xerogel discs with salt were between 45-348 Kg m^{-3}.

Release of L-ascorbic acid from the discs

Release of ascorbic acid from PHEMA discs was followed with a pHmeter (Metrohm 654 pHmeter) which was able to measure 0.001 units of pH. Calibration with ascorbic acid solutions of known concentrations was made at each temperature (285 K to 308 K). The volume of water in the vessel was 100 ml and the stirring rate was constant. The release of the acid from PHEMA hydrogels mantained sink conditions (10), that is the amount of release ascorbic acid must not exceed 10% of its solubility in water which means 33.3 g taking into account the vessel volume. In our experiments, the maximun load was 348 Kg m^{-3} which correspond to 69 mg.

The release of L-ascorbic acid from PHEMA hydrogels was studied:

a) at four temperatures (285 K to 308 K).
b) at five different thickneses at 308 K.
c) at five different loads of L-ascorbic acid at 308 K.

These experiments were carried out in absence of light.

RESULTS AND DISCUSSION

Swelling of xerogel in water

Xerogel disc (thickness 1.16 - 1.95 mm and diameter 12.18 - 13.55 mm) were placing in a water bath and W_t was determined at different times using equation (I). The value of $W_\infty = 0.320 \pm 0.006$ was obtained for temperatures between 285 K and 308 K.

The fractional swelling due to water, F_w, for controlled diffusion process, may be expresed as (23):

$$F_w = W_t/W_\infty = 4(D_w\, t/\pi\, h^2)^{1/2} \qquad (II)$$

where D_w is the apparent diffusion coefficient for transport of water into the hydrogel, t the time and h the thickness of xerogel discs. Linearity between F_w and $t^{1/2}$ was found for values of F_w less than 0.5, at a constant temperature T and a fixed h, so D_w can be obtained from the sloped. Figure 1 shows a plot for h= 1.70 mm at 308 K which yields a $D_w = 4.01\ 10^{-11}\ m^2\ s^{-1}$. These studies were carried out at four temperatures (285 K, 298 K, 303 K and 308 K) and the results are shown in table 1.

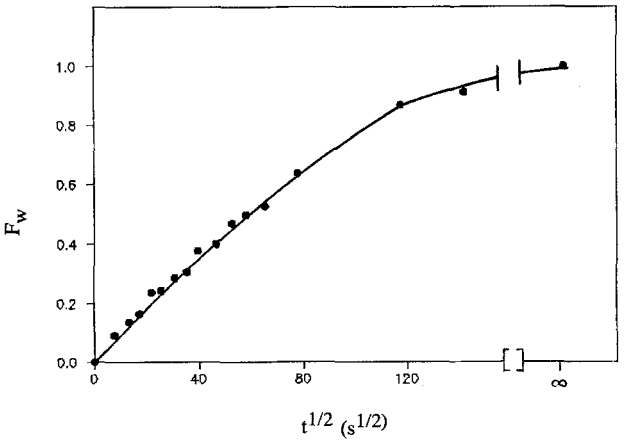

FIGURE 1: Fractional absorption of water by PHEMA as a fuction of $(time)^{1/2}$ (T= 308 K and h= 1.70 mm).

The values of D_w decrease with the temperature. Equivalently, when the slopes, $F_w\, t^{-1/2}$, are plotted versus h^{-1},afford a straight line whose slope yields an average D_w for the thicknes used. Such values are indicated in table 2.

Three different diffusion mechanisms from water absorption studies have been described (24): 1) a dissolution mechanisms for higher crosslinker content (above 4 mole-%), 2) a pore flow mechanism for low crosslinker content (from 0 to 2.5 mole-%), and 3) an intermediate mechanism at intermediate crosslinker concentrations (between 2.5 and 4 mole-%). The crosslinker concentration used in our experiments was 0.33 mole-% so the diffusion mechanism from water absorption is involved in the second group.

TABLE 1.- Values of the apparent diffusion coefficient for uptake of water in PHEMA at different temperatures and discs with different thickness.

T (K)	h (mm)	$D_w\ 10^{11}$ ($m^2\ s^{-1}$)
308	1.22	3.60
	1.47	3.87
303	1.22	2.60
	1.39	2.73
	1.95	3.44
298	1.22	2.08
	1.41	2.57
	1.75	2.78
285	1.22	1.81
	1.47	1.82
	1.70	2.39

TABLE 2.- Values of the average diffusion coefficient for uptake of water in PHEMA at different temperatures.

T (K)	h (mm)			$D_w\ 10^{11}$ ($m^2\ s^{-1}$)
	disc n°			
	1	2	3	
308	1.22	1.47	1.70	3.79
303	1.22	1.39	1.95	2.59
298	1.22	1.41	1.75	2.28
285	1.22	1.47	1.70	1.77

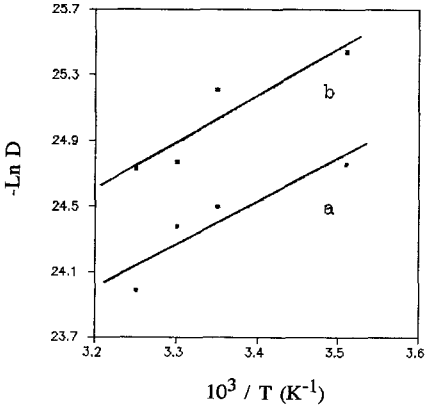

FIGURE 2: Arrhenius activation energy plots in terms of (a) apparent diffusion coefficient for absorption of water into PHEMA matrix and (b) apparent diffusion coefficient for release of L-ascorbic acid from the same matrix into water.

An Arrhenius dependence of D_w on temperature was examined (Figure 2a). The activation energy for diffusion of water calculated from the slope is 22 KJ mol^{-1} within the temperature range between 285 K and 308 K.

Release of L-ascorbic acid from PHEMA hydrogels

Diffusion from a gel phase can be considered one-dimensional when the thickness of the discs is not very large. It has been taking into account in chloramphenicol diffusion from PHEMA discs with swollen thickness between 1.1 and 2.0 mm (16) where the drug desorption was linear versus $t^{1/2}$. The same assumption was considered in the theophyline release from poly(HEMA-co-NVP) discs with dry thickness between 1 and 3 mm (2) and in the sodium salicylate release from a copolymeric hydrogel discs of HEMA with a sulphobetaine (19) with dry thickness within the range 0.9-2.5 mm. In the same way, this approach has been followed here in the determination of diffusion coefficients for uptake of water and acid release since the thickness of dry discs was between 1.05 and 1.95 mm.

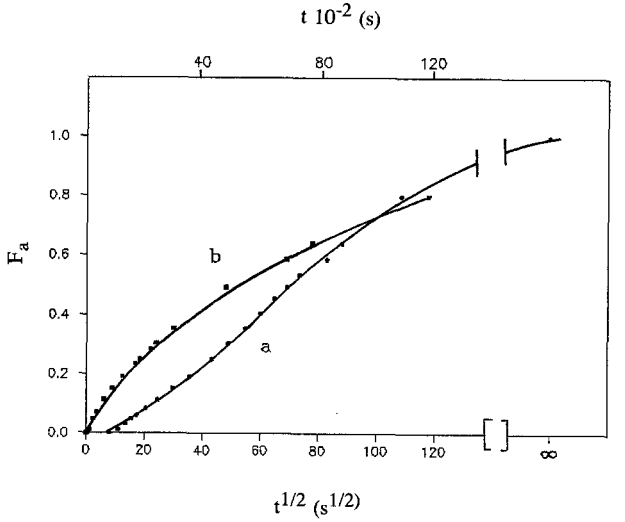

FIGURE 3: Fractional release of L-accorbic acid from PHEMA disc as a fuction of (a) $(time)^{1/2}$ and (b) time (T= 308 K, A= 370 Kg m^{-3} and h= 1.32mm).

Figure 3 demostrates that fractional release of drug, F_a, is not linear in time, t, but is linear in the squared root of time, $t^{1/2}$, for values of F_a less than 0.4. So the expression used for acid release from PHEMA discs is similar to the one used for swelling process (equation II):

$$F_a = M_t/M_\infty = 4\,(D_a\, t/\pi\, h^2)^{1/2} \qquad \text{(III)}$$

where M_t is the amount of acid releases at time t, M_∞ is the maximun amount of acid releases, D_a is the apparent diffusion coefficient for L-ascorbic acid release from the hydrogel and h the thickness of the xerogel disc with salt.This linear dependence yields D_a from the slope. The equation (III) has been used

in similar systems with high loading range too (19,20).

The experiments of L-ascorbic acid release as a fuction of temperature (between 285 K - 308 K) were carried out using disc with thickness 1.4±0.1 mm and acid load 335 ± 15 Kg m^{-3}. The diffusion coefficient for release of ascorbic acid from PHEMA discs are shown in table 3 where can be appreciated D_a increases with temperature.

TABLE 3.- Diffusion coefficients for L-ascorbic acid release from PHEMA discs at four temperatures.

T (K)	h (mm)	A (Kg m^{-3})	D_a 10^{11} (m^2 s^{-1})
308	1.23	3.28	1.82
303	1.58	3.21	1.73
298	1.31	3.21	1.13
285	1.50	3.54	0.89

The activation energy for release, which is obtained from Arrhenius plot (Figure 2b) is 24 $KJmol^{-1}$. This value is greater than activation energy for uptake of water. It sugests drug release is a more difficult process, from an energetic viewpoint, than the uptake of water. That kind of differences have been reported previously for both theophyline (20) and sodium salicylate release (19).

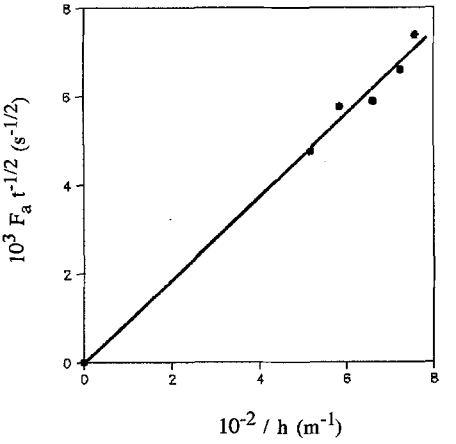

FIGURE 4: Dependence of rate of fractional release of L-ascorbic acid on reciprocal thickness of PHEMA with drug discs (T= 308 K and A about 352 Kg m^{-3}).

The dependence of release rate F_a $t^{-1/2}$ on reciprocal disc thickness at 308 K is shown in figure 4 with discs having A = 352 ± 27 Kg m^{-3} and h between 1.32 - 1.99 mm. That plot demostrates F_a $t^{-1/2}$ is linear in 1/h, so the slope of this plot yields an average D_a = 1.73 ± 0.40 10^{-11} m^2 s^{-1} at 308 K.

The influence of drug load, A, was studied at 308 K with discs having h = 1.35 ± 0.04 mm and A between 45-348 Kg m^{-3}. Since M_∞ = A V = A S h, where V is the volume of the disc and S is its surface area, then equation (III) may be express as:

$$\frac{F_a}{t^{1/2}} A\,h = \frac{M_t}{t^{1/2}} \frac{1}{S} = 4\,(D_a/\pi)^{1/2} A \qquad (IV)$$

where $M_t t^{-1/2} S^{-1}$ is the release rate per unit disc area with drug load. The variation of this parameter with A is shown in figure 6 where linearity can be appreciated. From the slope a value of 2.11 ± 0.25 10^{-11} m^2 s^{-1} is derived for D_a at 308 K.

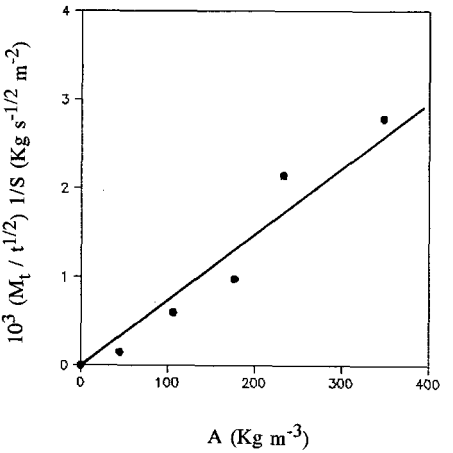

FIGURE 5: Variation of release rate per unit disc area with drug load (T= 308 K and h about 1.35 mm).

The difference between the value of D_a obtained as a fuction of h (Figure 4) and one obtained as a fuction of A (Figure 5) is not significative which is consistent with results reported previously (20). It is possible to obtain an average diffusion coefficient for L-ascorbic acid release of 1.91 10^{-11} m^2 s^{-1} at 308 K. Comparison of diffusion coefficient value for water uptake (3.79 10^{-11} m^2 s^{-1}) and diffusion coefficient for drug release (1.91 10^{-11} m^2 s^{-1}) at 308 K suggests drug release process is slower than hydrogel swelling which is in agreement with E_a values obtained from both swelling and drug release studies.

The influence of the nature of the medium on the values of the diffusion coefficient has been reported (20). It shows water diffusion into PHEMA is 25 times smaller than water diffusion into water. In our study the diffusion coefficient for water transport into PHEMA hydrogel is 66 times smaller than the coefficient for water diffusion into water. Finally, when the diffusion of a buffer 7 mM HCl into PHEMA gels was studied (20), the diffusion coefficient was found to be 93 times smaller than diffusion coefficient into pure water. Synthesis conditions have a large influence on the diffusional characteristics of PHEMA gels and so it is very difficult to compare results of differents authors.

Experiments carried out for the diffusion of pharmacologically active substances such as progesterone (10) and ergotamine (20) from PHEMA gels show the influence of penetrant solute size on the diffusion coefficient. Such coefficients decrease with increased molecular weights although PHEMA polymerization must be taken into account too. So the diffusion coefficient determinated for L-ascorbic acid, with a molecular weight of 176 Da, is bigger than those obtained for progesterone (M = 314 Da) (10) and ergotamine (M = 582 Da) (20).

This kind of formulation of biological active substances, which are incorporated into a PHEMA gel, can be very useful to release them "in situ" in an organism. This technique could improve dosage control and avoid secondary actions. L-ascorbic acid release from hydrogels can be measured easily, this is helpful to obtain its diffusion coefficient from new copolymeric hydrogels that can be compare with one obtained from PHEMA in our polymerization conditions.

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