Kinetics and thermodynamics of swelling and dissolution of PVA gels obtained by freeze-thaw technique

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HIGHLIGHTS

- Freeze-thaw crosslinking of polyvinyl alcohol is a multiparametric process.
- Freeze-thaw parameters are crossdependent.
- A 4-D surface response of the swelling kinetics parameters is presented.
- A 4-D surface response of the swelling thermodynamics parameters is presented.
- A 4-D surface response of the dissolution kinetics parameters is presented.

ARTICLE INFO

ABSTRACT

PVA hydrogels obtained by freeze-thaw technique find important applications in regenerative medicine and controlled drug delivery technologies. The novelty of this contribution is the establishment of the cross-dependency of kinetics and thermodynamics parameters of swelling and dissolution of PVA hydrogels with the freeze-thaw process main variables. The work also establishes cross-correlations between the freeze-thaw process conditions, the gel microstructure and the properties of obtained hydrogel/hydrosoluble PVA materials. The conditions of the freeze-thaw process were selected by following an experimental design. The time evolution of the water up-take of PVA hydrogels was measured and used as main raw data generator. A 4-D surface response of the swelling and dissolution parameters in the space of freeze-thaw process variables was obtained and analyzed in terms of the resulting hydrogel and hydrosoluble polymeric structures. The 4-D surface response in the space of freeze-thaw process variables can predict very precisely the swelling and dissolution of PVA systems and their conditions for developing fully crosslinked hydrogel networks to fully hydrosoluble polymeric bodies.

1. Introduction

Freeze-thaw technique is an interesting approach to obtain polyvinyl alcohol (PVA) hydrogels for medical use. PVA hydrogels find extended applications in soft contact lens, soft tissue engineering, embolizing agents, patches, electrode contacts, artificial heart linings, artificial cartilages, catheters, skin, pancreas membranes among many others medical applications [1]. The excellent biocompatibility of PVA combined with the avoidance of toxic molecules required to promote crosslinking reactions explain the interest of the medical industry in the PVA freeze-thaw process. The freeze-thaw technique uses repetitive cycles of freezing and thawing of PVA aqueous solutions to obtain cryotropic elastic and robust hydrogels [2]. The properties of obtained

materials depend on the molecular characteristics of the PVA, its concentration in the solution and the conditions of the freeze-thaw process [3].

Briefly, the gelation mechanism starts with the preparation of a homogeneous solution of PVA and water. This solution is cooled down to temperatures below to the solidification temperature of water (0 °C). The former initial water crystals grow by incorporating water molecules from the liquid phase. The liquid phase cumulates PVA by supplying with water molecules the grow of water crystals. This process ultimately results in the formation of PVA-impoverished water crystals and PVA-enriched supercooled liquid microdomains [4]. The confinement and high concentration of PVA in the supercooled microdomains promote its crystallization. PVA crystallization is facilitated by increasing

its hydrolysis degree. The higher is the hydrolysis degree of PVA, the higher is its molecular regularity and the easier is its crystallization. The thawing process is carried out by increasing the temperature above 0 °C. The water crystals are melted forming a PVA-impoverished continuous liquid phase. The PVA crystals do not melt and remain stable linking together several polymer chains. Then, the PVA hydrogel is formed by a continuous liquid water phase retained in a physically crosslinked network. Multiple freeze-thaw cycles result in denser crosslinked networks and harder hydrogels [5].

Ritger and Peppas established a model to study the diffusion of small molecules such as drugs and water through hydrogel materials [6,7]. In general, hydrogels exhibit three behavioral water uptake (*WUT*) stages. In the first stage, the *WUT* of the gels increases progressively with time. In the second stage, the *WUT* progression slowdown and reaches a maximum. In the third stage, the *WUT* remains unchanged or decreases with time. The first and third stages are assumed to be governed by gel swelling and dissolution mechanisms, respectively. The second stage is considered a transitional stage. However, swelling and dissolution mechanisms may occur simultaneously [8,9].

Equations (1) and (2) were proposed by Ritger and Peppas to model the first and the third stages of hydrogels *WUT*.

$$WUT_s = kt^n \tag{1}$$

$$WUT_d = k_1 - k_2 t^m \tag{2}$$

Equation (1) describes the swelling of an initially dry hydrogel. Equation (2) describes the degrading dissolution of an initially swelled hydrogel. Here, k, n, k_1, k_2 and m are constants established by the hydrogel material and the immersion medium conditions (solvent, temperature, etc) and t is the immersion time.

Equation (1) is valid within the range where the influence of dissolution mechanisms is small. This condition is usually valid until 60% of the maximum WUT_s value. After this value, the dissolution effect became significant and the model deviates significantly from experimental data. The k and n values are related to the hydrogel material and process conditions. The k value is the swelling constant and the n value is the swelling exponent. The n value depends on the physical mechanism of the water uptake. Fickian diffusion mechanism is generally accepted when the n value takes values near to 0.5. Less Fickian mechanism is accepted when $n < 0.5$. Less Fickian mechanism happens when the water penetration rate is slower than the polymer chain relaxation rate. Anomalous transport mechanisms are accepted when $0.5 < n < 1$. And Case II transport associated with relaxation-controlled transport is accepted when $n = 1$. The k value also depends on the water uptake mechanism. And, to the best of our knowledge, its analysis has been mostly neglected by the literature [10,11].

Equation (2) starts with the initial WUT_d value: k_1. This value can be interpreted as the initial starting condition of an ideal fully swelled hydrogel. This fully swelled hydrogel starts to dissolve directly. The WUT_d decreases with time as a consequence of the dissolution of the polymer. The k_2 and m values are also related to the hydrogel material and process conditions. The k_2 value is the dissolution constant and the m value is the dissolution exponent. The m value depends on the diffusional mechanism that governs the mass loss from the gels. The m value is classified according to the above mentioned models. Eventually, the WUT_d may remain constant with time indicating a very slow dissolution or no-dissolution at all of the hydrogel. Equation (2) is valid within the range where the influence of the swelling mechanism is small. This condition is usually valid after the system has reached its maximum WUT value. Then, the modeled WUT_d values match the experimental WUT values [10,11].

The Flory-Rehner theory establishes the swelling behavior of a hydrogel to be governed by two opposing forces. The thermodynamic force of mixing of the pure solvent with the initially pure, amorphous and unstrained gel network (Δg_{mix}) against the retractive configurational forces of the polymer chains in the gel structure (ΔG_{gel}) [12]. Equation (3) describes this situation.

$$\Delta G_s = \Delta G_{mix} + \Delta G_{gel} \tag{3}$$

Equation (4) relates the free energy of a polymer with the osmotic pressure (π) of the swelled gel [13–15].

$$-\left(\frac{\partial \Delta G}{\partial V}\right)_{T,n_i} = \pi = \pi_1 + \pi_2 \tag{4}$$

Here, π_1 and π_2 are the osmotic pressures related to the polymeric solution and its configurational contribution. The π_1 and π_2 interactions can be calculated according to equations (5) and (6).

$$\pi_1 = -\frac{RT}{V_1}[\ln(1 - \upsilon) + \upsilon + \chi \upsilon^2] \tag{5}$$

In equation (5), υ, V_1 and χ are the polymer volume fraction, the molar volume of the solvent and the polymer-solvent interaction parameter, respectively. In equation (6), υ_0, υ_0 and n are the concentration of constituent chains in the gel formation, the polymer volume fraction at gel formation and the number of statistical segments per chain, respectively. The equilibrium condition of the swelling is reached when the osmotic pressure is set equal to zero [16–19].

$$\pi_2 = -\upsilon_0 RT\left[\left(\frac{\upsilon}{\upsilon_0}\right)^{\frac{1}{3}} - \frac{1}{2}\left(\frac{\upsilon}{\upsilon_0}\right)\right] - \upsilon_0 RT\left[\frac{3}{5}\left(\frac{\upsilon}{\upsilon_0}\right)^{\frac{1}{3}}\frac{1}{n} + \frac{99}{175}\left(\frac{\upsilon}{\upsilon_0}\right)\frac{1}{n^2}\right.$$
$$\left. + \frac{513}{875}\left(\frac{\upsilon}{\upsilon_0}\right)^{\frac{5}{3}}\frac{1}{n^3} + \ldots\right] \tag{6}$$

The swelling and dissolution of PVA hydrogels obtained by freeze-thaw technique have been previously studied by several authors [20]. However, the analysis of previous results is not the task of this contribution. For such purpose the authors suggest to consult the excellent works of Lozinsky et al. [21–23] Very important to note is that the knowledge cumulated in the literature is based on studies carried out varying one freeze-thaw process condition at a time while keeping the other conditions unchanged. This situation neglects the cross dependency of conditions and gives limited views of the process. These limitations are later propagated to the understanding of the properties of the resulting materials.

In the present contribution the simultaneous and cross dependence influences of the freeze-thaw process conditions (time of freeze, time of thaw, temperature of thaw and number of cycles) in the swelling and dissolution of PVA hydrogels were investigated. The molecular weight, the hydrolysis degree and the concentration of PVA in water were keep unchanged. PVA hydrogels were obtained by freeze-thaw technique under conditions defined according to a Taguchi type experimental design [24,25]. The resulting data were analyzed using response surface methods. The main out-come of this paper is a set of equations expressing the swelling and dissolution parameters of PVA hydrogels as functions of the freeze-thaw process conditions.

2. Experimental

2.1. Materials

High-viscosity PVA (Serquim S.A., Argentina) with a hydrolysis degree of $95 \pm 1\%$, Mw ≈ 146000, density: $\delta_p = 1.2\,\mathrm{g\,cm^{-3}}$ at 25 °C and specific volume: $\nu = 0.788\,\mathrm{cm^3\,g^{-1}}$ was used as raw material [26]. The water was of Millipore quality, molar volume: $V_1 = 18\,\mathrm{cm^3\,mol^{-1}}$ and density: $\delta_s = 1\,\mathrm{g\,cm^{-3}}$ at 25 °C. The PVA-water interaction parameter has been reported as: $\chi = 0{,}49$ [16,18]. The PVA gels were produced by repeatedly freezing and thawing of 5% PVA aqueous solutions. In those conditions the average number of segments per chain has been reported as: $n = 16.3$ [18].

2.2. The experimental design

The Taguchi method is recommended for the study of processes with interdependent variables. The method proposes that a resulting response (Y) of the system can be expressed as a polynomial function of four process conditions (A, B, C, D) according to:

$$Y = \Sigma_{h,k,l,m} a_{h,k,l,m} A^h B^k C^l D^m \tag{7}$$

The indexes h, k, l and m are non-negative integers going from 0 to ∞. Each term of the sum is composed of an empirical coefficient ($a_{h,k,l,m}$) determined by a least squares fit multiplied by variables powered to non-negative integer exponents. The higher the complexity of the response to a given condition, the higher is the number of terms containing such condition and the higher are the exponents in these terms. The resulting polynomial function has infinite terms and can, eventually, describe any functionality $Y(A, B, C, D)$.

In the present contribution, the number of experiments was limited to nine. Therefore, nine experiments give the possibility to define a polynomial fit of nine terms. The selection of the nine terms with the best fitting combination was carried out using experimentally obtained raw data and iterating using Minitab 17 software.

The freeze-thaw variables: A, B, C and D correspond to the time of freeze, the temperature of thaw, the time of thaw and the number of freeze-thaw cycles, respectively. Each variable was set at three different levels. The temperature of freeze was kept constant at $-18\,°C$. The response, Y, corresponds to the WUT of the gels as a function of time.

The Y response resulted in a 4-D surface in the space of variables. Subsequently, 2-D plots were used to conclude tendencies and behaviors of the freeze-thaw process to the simultaneous variation of the process conditions.

2.3. Preparation of PVA gels

The experimental conditions are presented in Table 1. The solutions were dropped over glass slides to obtain 12 lenses-like specimens per each condition.

2.4. Swelling and dissolution of PVA hydrogels

The swelling and dissolution behavior of PVA gels were studied by monitoring their WUT. Gel specimens were retired from the glass slides after their freeze-thaw processes. Subsequently, the specimens were dehydrated, weighed and immediately immersed in vials filled with water. The vials were put in a chamber thermostatted at 37 °C. The specimens were withdrawn from the water periodically. The excess of water was wiped out carefully form the gel surface using absorbent paper. The specimens were weighted and immediately reintroduced in their corresponding thermostatted vials. The WUT was calculated using equation (8).

Table 1
Experimental conditions for the preparation of PVA hydrogels.

Nº	Time of freeze (hs)	Temp. of thaw (°C)	Time of thaw (hs)	cycles
1	0.5	22	0.5	2
2	0.5	40	1.0	3
3	0.5	4	1.5	4
4	1.0	22	1.0	4
5	1.0	40	1.5	2
6	1.0	4	0.5	3
7	1.5	22	1.5	3
8	1.5	40	0.5	4
9	1.5	4	1.0	2

5% of aqueous PVA solution. Temperature of freeze: $-18\,°C$.

$$WUT = \frac{m_t - m_0}{m_0} \tag{8}$$

Here, m_0 and m_t are the weight of the gel in the initial and swollen state at immersion time (t), respectively.

2.5. Calculation of thermodynamic parameters

The polymer volume fraction, υ, was calculated according to equation (9). The concentration of constituent chains in the gel formation, ν_0, was calculated according to equation (10). Here, M_c, is the average molecular weight between crosslinks. M_c was calculated according to equation (11), where M_n is generally approximated as the half of the average molecular weight of the polymer: $M_n = 0.5\,M_w$ and ν_p is the specific volume of the polymer. Finally, the polymer volume fraction at gel formation, υ_0, was calculated according to equation (12). Further details of the calculus can be found in references 16–19 [16–19].

$$\upsilon = \frac{\delta_p^{-1}}{\frac{m_t}{m_0}\delta_s^{-1} + \delta_p^{-1}} \tag{9}$$

$$\nu_0 = \frac{m_0}{M_c} \tag{10}$$

$$\frac{1}{M_c} = \frac{2}{M_n} - \frac{\frac{\nu_p}{V_1}(\ln(1-\upsilon) + \upsilon + \chi\upsilon^2)}{\left(\upsilon^{1/3} - \frac{\upsilon}{2}\right)} \tag{11}$$

$$\upsilon_0 = \frac{m_t}{m_0}\upsilon \tag{12}$$

3. Results and discussion

3.1. Swelling and dissolution parameters

Fig. 1 shows the experimental WUT behaviors of PVA hydrogels obtained by freeze-thaw technique according to the process conditions detailed in Table 1.

Samples 1, 2, 4, 5, 7 and 9 swelled to relatively low WUT reaching a maximum within 2 h. Afterwards, the WUT of samples 1, 4, 5 and 9 decreased slowly in time. Exceptionally, the WUT of sample 2 decreased very fast reaching almost zero at 3 h. And the WUT of sample 7 continued increasing with time. Samples 3, 6 and 8 swelled to relatively high WUT and stabilized within 2 h.

Stages 1 and 3 of the WUT were identified and fitted using equations (1) and (2). The resulting equation parameters are presented in Tables 2 and 3.

Evidently, the swelling and dissolution parameters varied according to different combinations of process conditions. These parameters were fitted and their responses were composed in the form of 4-D polynomial
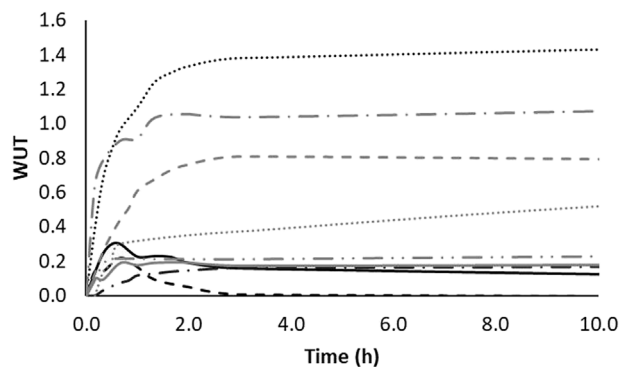
Fig. 1. WUT behavior of PVA gels produced by freeze-thaw technique. In black, samples: 1(-), 2(——), 3(·····) and 4(— · —). In gray, samples: 5(-), 6(——), 7(·····), 8(— · —) and 9(— · · —).

Table 2
WUT swelling parameters.

Nº	k	n
1	0.69	0.91
2	0.33	0.80
3	1.31	0.65
4	0.11	1.12
5	0.30	1.01
6	0.60	0.79
7	0.51	0.80
8	2.62	0.80
9	0.58	1.02

Table 3
WUT dissolution parameters.

Nº	k_1	k_2	m
1	3.92	3.66	0.02
2	3.02	2.85	0.06
3	2.69	0.97	0.06
4	0.18	0.00	2.04
5	0.21	0.01	0.52
6	0.88	0.05	0.28
7	0.89	0.09	0.22
8	1.08	0.00	0.84
9	0.25	0.03	0.36

surfaces in the space of process variables.

Equations (13)–(17) present the resulting surface responses of swelling and dissolution parameters to the freeze-thaw process variables.

$$k = 8.17 - 490A - 0.063B - 5.91C - 2.30D + 2.68A^2 + 0.0016B^2 + 2.66C^2 + 0.45D^2 \tag{13}$$

$$n = 0.89 + 1.34A + 0.016B + 1.30C - 0.85D - 0.63A^2 - 0.00033B^2 - 0.66C^2 + 0.13D^2 \tag{14}$$

$$k_1 = 9.50 - 14.88A + 0.047B - 4.42C + 1.15D + 6.21A^2 - 0.001B^2 + 1.86C^2 - 0.20D^2 \tag{15}$$

$$k_2 = -6.46 + 12.44A - 0.098B - 0.43C - 0.86D - 4.99A^2 + 0.002B^2 + 0.65C^2 + 0.22D^2 \tag{16}$$

$$m = -1.48 + 5.91A + 0.061B + 3.86C - 2.39D - 2.74A^2 - 0.0012B^2 - 1.99C^2 + 0.454D^2 \tag{17}$$

Here, *A* is the time of freeze in hours, *B* is the temperature of thaw in Celsius degrees, *C* is the time of thaw in hours and *D* is the number of freeze-thaw cycles.

Figs. 2–6 present the functionality of *k*, *n*, k_1, k_2 and *m* parameters with different process conditions.

The parameters needed for the thermodynamic studies were obtained according to the calculus procedure previously detailed and using materials data specified in the Materials section. The resulting values for the different parameters are presented in Table 4.

3.2. The swelling zone kinetics

The variation of *n* and *k* with the time of thaw can be explained in terms of crystallites formation and their function as physical cross-linking sites. If the time of thaw is too short the system does not thaw. The PVA molecular segments do not get enough mobility to relax and accommodate favorably to form new crystallites in the next freezing step. Therefore, the *k* value results very high and the *n* value results very low. This situation suggests low density of crystallites in the resulting hydrogel. The low density of crystallites can be associated to soft
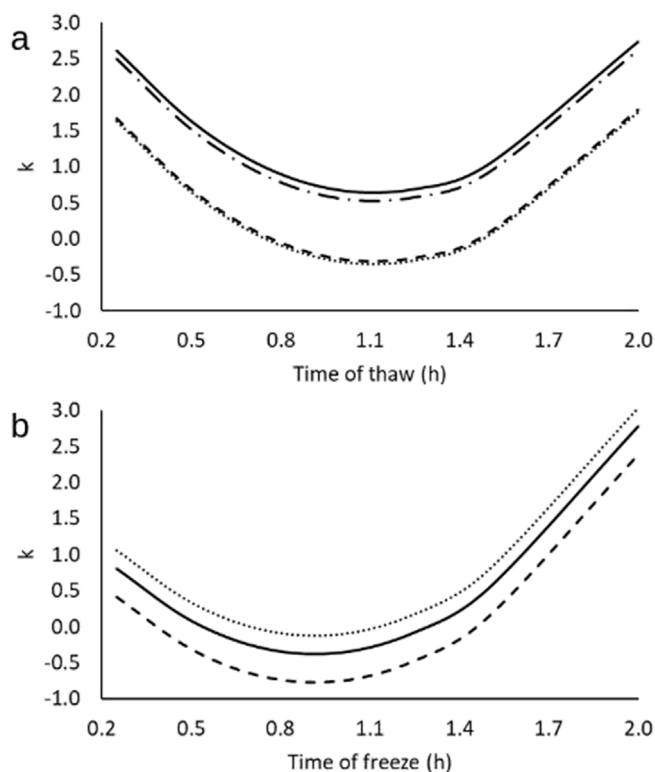
Fig. 2. a: freeze-thaw cycles: 1 (-), 2 (—), 3 (⋯), 4 (—·—). Time of freeze: 0.5 h, temp. of thaw: 22.0 °C. b: temp. of thaw: 4.0 °C (-), 22.0 °C (—), 44.0 °C (⋯). Time of thaw: 1.0 h, freeze-thaw cycles: 3.
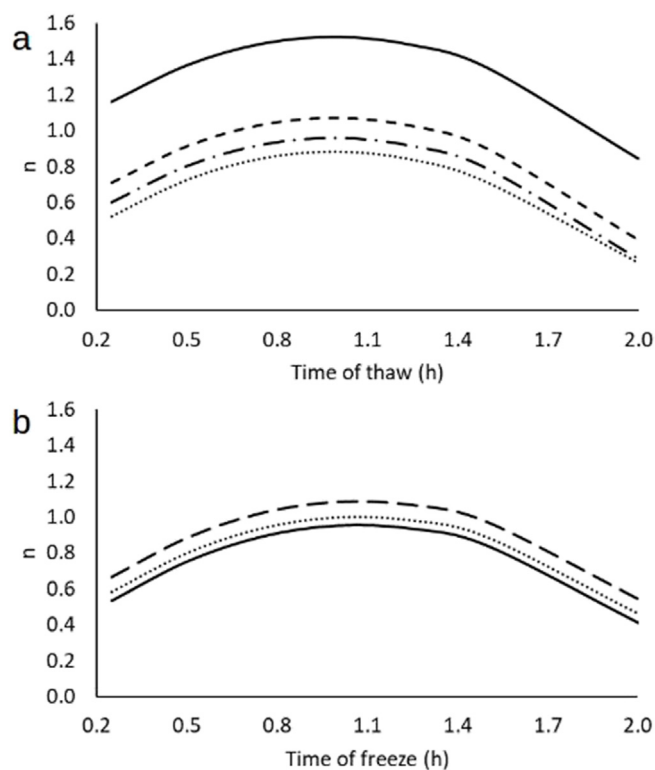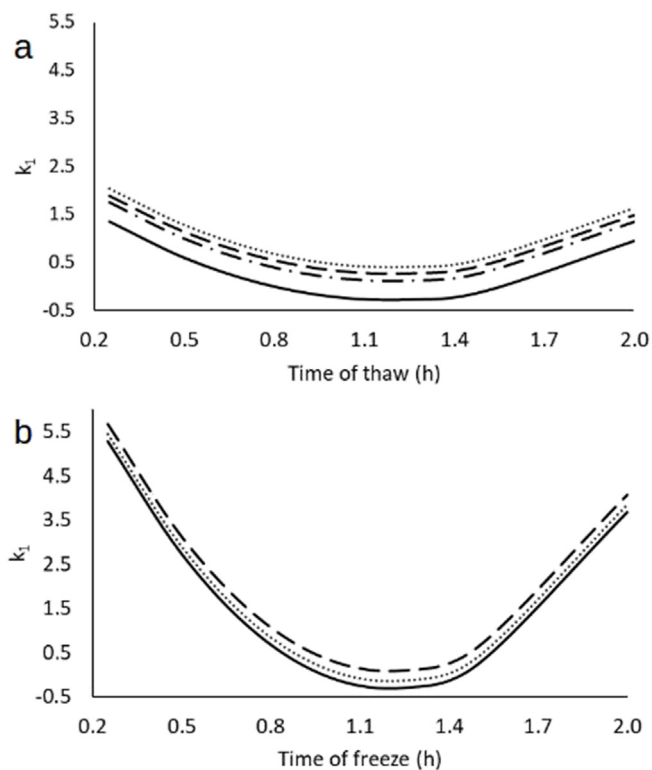

Fig. 3. a: freeze-thaw cycles: 1 (-), 2 (—), 3 (⋯), 4 (—·—). Time of freeze: 0.5 h, temp. of thaw: 22.0 °C. b: temp. of thaw: 4.0 °C (-), 22.0 °C (—), 44.0 °C (⋯). Time of thaw: 1.0 h, freeze-thaw cycles: 3.

Fig. 4. a: freeze-thaw cycles: 1 (-), 2 (—), 3 (···), 4 (—·—). Time of freeze: 0.5 h, temp. of thaw: 22.0 °C. b: temp. of thaw: 4.0 °C (-), 22.0 °C (—), 44.0 °C (···). Time of thaw: 1.0 h, freeze-thaw cycles: 3.
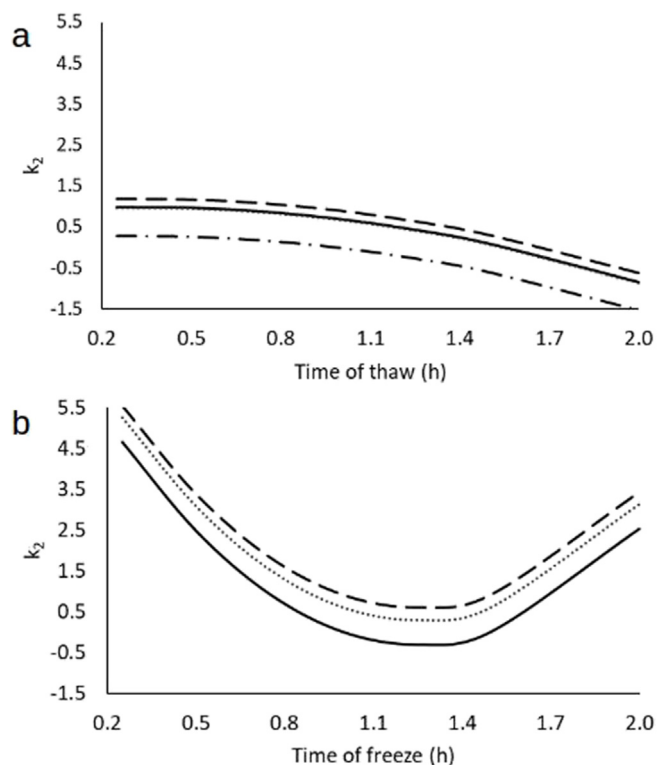

Fig. 5. a: freeze-thaw cycles: 1 (-), 2 (—), 3 (···), 4 (—·—). Time of freeze: 0.5 h, temp. of thaw: 22.0 °C. b: temp. of thaw: 4.0 °C (-), 22.0 °C (—), 44.0 °C (···). Time of thaw: 1.0 h, freeze-thaw cycles: 3.

Fig. 6. a: freeze-thaw cycles: 1 (-), 2 (—), 3 (···), 4 (—·—). Time of freeze: 0.5 h, temp. of thaw: 22.0 °C. b: temp. of thaw: 4.0 °C (-), 22.0 °C (—), 44.0 °C (···). Time of thaw: 1.0 h, freeze-thaw cycles: 3.
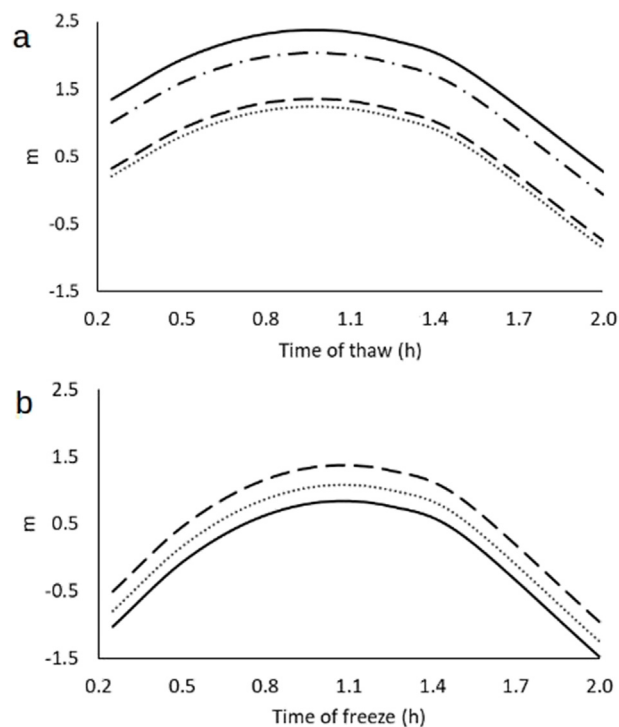
Table 4
Osmotic pressure parameter values.

Nº	v	v_0	ν_0
1	0.39	0.51	4.97E-04
2	0.40	0.49	2.18E-04
3	0.24	0.64	0.12E-04
4	0.41	0.49	7.00E-04
5	0.41	0.49	2.16E-04
6	0.31	0.57	1.64E-04
7	0.32	0.57	0.94E-04
8	0.29	0.59	0.28E-04
9	0.40	0.50	5.09E-04

and fast dissolving hydrogels. It also explains the low *WUT* of hydrogels obtained under these conditions. The increment of the time of thaw permits the system to thaw between the freezing cycles. The thaw state relaxes the molecular structure and permits PVA segments to accommodate favorably to form new and to grow bigger crystallites during the subsequent freezing steps. As result, the *k* value decreases and the *n* value increases suggesting higher density of crystallites in the resulting hydrogels. The higher density of crystallites promotes stronger and higher *WUT* of the hydrogel. However, if the time of thaw is too long the previously formed crystallites start to dissolve. This situation reduces the size and the amount of cristallites and ultimately the cross-linking density of the hydrogel. Thus, the decrease of its *WUT* is justified. The time of thaw that minimizes the *k* and maximizes the *n* is in intimate relationship with the mass of the system. The higher is the mass of the system, the higher would be its heat capacity and the longer will be its time of thaw to get the minimal *k* and maximum *n*.

The increase of the number of freeze-thaw cycles decreases the *k* and *n* values consistently during the first three cycles. Further cycles do not modify the *k* and *n* values. The mechanism for crystallites formation may also explain this behavior. The first cycle results in the first PVA crystallites and PVA impoverished water domains of the initial hydrogel structure. The second cycle incorporates new crystallites to the

hydrogel structure and grows the crystallites formed during the first cycle. These crystallites are formed at the expenses of PVA molecular segments that remained in the water domains after the first freezing cycle. The second cycle increase the crosslinking density and decrease the *WUT* of resulting hydrogels. The PVA impoverishing of the water domains also increases with the number of cycles. Consequently, the availability of PVA segments for further cristallites formation and grow is significantly reduced. Ultimately, the hydrogel structure does not progress after the third freeze-thaw cycle.

The variation of the *k* and *n* values with the time of freeze can be also explained in terms of crystallite formation and their function as physical crosslinking sites. If the time of freeze is too short the system does not freeze completely. Then, the concentration of PVA in the PVA-enriched supercooled liquid microdomains do not reach its possible maximum. Therefore, the PVA crystallization conditions are not optimal and the density of crystallites in the hydrogel material results low. If the time of freeze is too long the PVA chain segments between the crystallites breaks due to ice expansion. As result, the crystallites loose connectivity in the gel network softening and degrading the gel and reducing its *WUT*. The temperature of thaw seems to have little influence on the *WUT* of the hydrogels. However, the *k* and *n* values slightly decrease if the temperature of thaw is too low or too high. If the temperature of thaw is too low the system does not thaw completely. In this case, the formation of crystallites is impaired from one cycle to another. If the temperature of thaw is too high the crystallites formed in the freezing step are melted in the next thawing step. In both cases, the result is a low density of crystallites in the hydrogels. These situations explain the decrease of *WUT* at too low or too high temperatures of thaw.

In general, the PVA hydrogels were found to swell according to the Fickian mechanism, $n \sim 0.5$. However, Less Fickian ($n < < 0.5$) and Anomalous transport ($0.5 < n < 1$) mechanisms were present at the extremes of the studied process conditions. Case II transport mechanism ($n > > 1$) was only observed in samples obtained under conditions set within mid ranges of the studied process conditions. This situation may generate a density of crystallites so that maximize the *WUT* rate of the PVA hydrogels.

3.3. The swelling zone thermodynamics

The free energy of the hydrogels was calculated by composing equations (5) and (6) into equation (4) and equation (3). Materials data and Table 4 values were also used. Fig. 7 shows the free energy of the hydrogels as a function of the freeze-thaw process variables.

The free energy can be interpreted as the degree of natural tendency of the evaluated process to go in the purposed direction. The free energy of the swelling process is more negative (more favorable process) when the time of thaw and the time of freeze were set within mid-range values, minimal number of cycles and maximal temperature of thaw. This situation can be associated to hydrogels with very low crystallite density. In such condition, the polymer chains are very relaxed. In the presence of water they behave more as dissolving polymers than a swelling polymer network. Any change in the process conditions driving an increase of the density of crystallites would constrain the polymer chains and increase the associated swelling free energy of the hydrogel.

3.4. The dissolution zone kinetics

The variation of k_1, k_2 and m with the freeze-thaw process conditions is explained in terms of the structure of the hydrogels. The higher the crystallite density in the hydrogels, the slower is its dissolution rate and the lower is its initial WUT_d. Fig. 8 shows the relationship between the initial WUT_d: k_1 and the dissolution rate: $k_2 t^m$, presented in Table 3.

Clearly, when $k_1 < 2$, the dissolution rate is zero or close to zero. Such condition suggests the crystallite density and stability are high
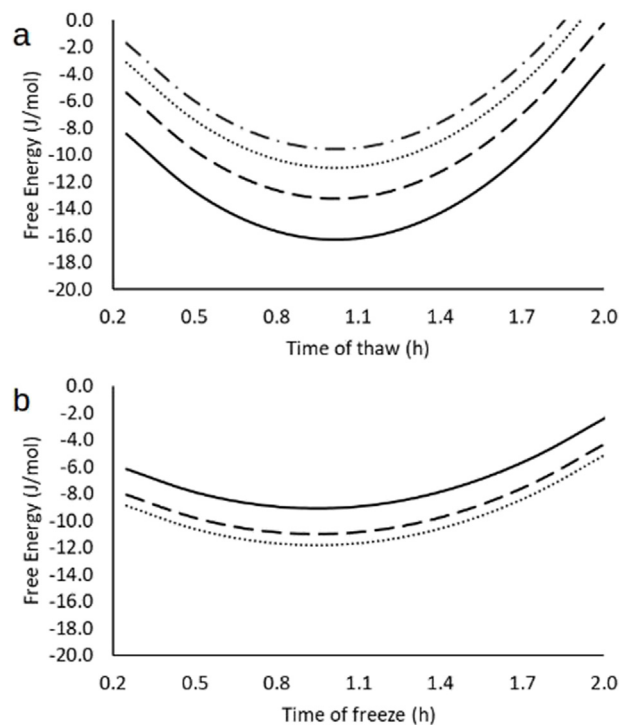

Fig. 7. a: freeze-thaw cycles: 1 (-), 2 (—), 3 (⋯), 4 (—·—). Time of freeze: 1.0 h, temp. of thaw: 22.0 °C. b: temp. of thaw: 4.0 °C (-), 22.0 °C (—), 44.0 °C (⋯). Time of thaw: 1.0 h, freeze-thaw cycles: 3.
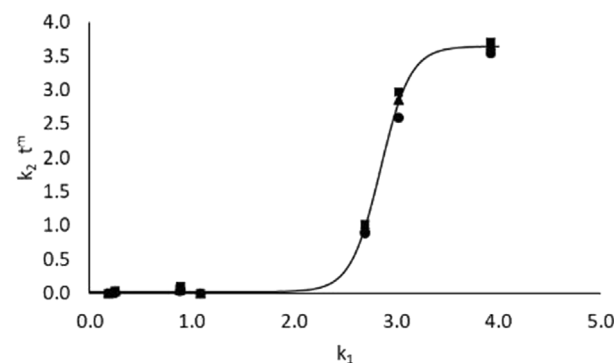

Fig. 8. Dissolution rate: $k_2 t^m$ vs. initial WUT_d: k_1 at different water immersion times: 0.2 h (●); 1.0 h (▲); 2.0 h (■).

enough to retain the entire hydrogel network in swelled state. All PVA polymer chains are linked together by stable crystallites. When $2 < k_1 < 3$, the dissolution rate increases sharply, indicating a growing amount of free hydrosoluble polymer chains and suggesting a substantial decrease of the crystallite density in the hydrogel. However, the dissolution rate seems to reach a limit at $k_1 > 4$. In this condition the mechanism of dissolution seems to switch from crystallite density conditioning hydrogel to diffusional conditioning hydrosoluble polymer.

The dissolution rate: $k_2 t^m$, and the initial WUT_d: k_1 were found to fit a Boltzmann type functionality according to:a

$$k_2 t^m = \frac{A_1 - A_2}{1 + e^{\frac{(k_1 - k_0)}{dk}}} + A_2 \tag{18}$$

The resulting Boltzmann factors are listed in Table 5.

A_1 and A_2 are interpreted as the dissolution rates of a fully crosslinked PVA hydrogel network and a fully hydrosoluble PVA body, respectively. k_0 is interpreted as the *WUT* of a system where the hydrogel and hydrosoluble contributions are equal. And dk is interpreted as the

Table 5

Parameters of the Boltzmann type relationship between the dissolution rate: $k_2\,t^m$ and the initial WUT_d: k_1 of PVA gels.

Boltzmann parameters	
A_1	0.0
A_2	3.64
k_0	2.85
dk	0.15
R^2	0.9994

Table 6

Comparison between experimental and calculated dissolution times of PVA hydrogels.

Nº	Dissolution time (days)	
	Experimental	Calculated
1	2.2	2.5
2	0.4	0.1
3	N.D.	1.0E6 ($\sim$2700 years)
4	7.6	7.6
5	17.3	16.4
6	N.D.	1286 ($\sim$3.5 years)
7	N.D.	1783 ($\sim$5 years)
8	N.D.	116 ($\sim$4 months)
9	19.1	22

width of range where the system turns from pure hydrogel to pure hydrosoluble behaviors.

The combined effect of the freeze-thaw process conditions on the dissolution kinetics of PVA hydrogels is defined according to their resulting structures: fully crosslinked hydrogel, transitional hydrogel-hydrosoluble polymeric body and fully hydrosoluble polymeric body. In general, the system turns to the hydrogel side by increasing the number of cycles of freeze-thaw and setting optimal times of thaw and freeze. The temperature of thaw does not have an important effect if it is higher than the melting temperature of water.

3.5. Experimental verification of the dissolution kinetic model

The dissolution time of PVA hydrogels was calculated by composing equations (15)–(17) into equation (2). The calculated dissolution times were compared against experimental dissolution times. The experimental dissolution times were obtained by following the *WUT* of the hydrogels during 30 days. The experimental dissolution time was defined as the time needed by the hydrogel to reach *WUT* = 0. Table 6 presents the comparison between calculated and experimental dissolution times.

The experimental and calculated dissolution times present an excellent correlation. This result suggests that the set of equations (13)–(17) may find important applications to define the freeze-thaw process conditions to obtain PVA hydrophilic materials with tailored swelling degree and dissolution times. For example, hydrogel samples 3, 6 and 7 have the properties typically required for permanent embolic agents. Sample 8 may be useful as temporary embolic agents, patches, skin and membranes. And, samples 5 and 9, 4 and 1 may find applications as slow, medium and fast controlled drug release devices.

4. Conclusions

The cross-dependency of swelling and dissolution parameters of PVA hydrogels obtained through freeze-thaw process were investigated. A set of equations in the form of a 4-D surface was developed. The surfaces relate the swelling and dissolution kinetics parameters with the time of thaw, time of freeze, temperature of thaw and number of freeze-

thaw cycles. The results were discussed in terms of the conformation of a hydrogel - hydrosoluble structured polymers. The correlation of the free energy of swelling with the freeze-thaw process variables was also discussed. The system responded developing structures from fully crosslinked hydrogel networks to fully hydrosoluble polymeric bodies. The 4-D surface of the PVA hydrogel-hydrosoluble system permits to predict precisely their swelling and dissolution behaviors.

Acknowledgements

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