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European Polymer Journal 37 (2001) 1527–1532

EUROPEAN POLYMER JOURNAL

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Release kinetics of low molecular weight solutes from mixed cellulose ethers hydrogels: a critical experimental study

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Received 8 December 2000; accepted 5 February 2001

Abstract

Release kinetics in water of five low molecular weight model solutes (urea, cyclohexanone, acetaminophen, phenacetin, cafein) from mixed cellulose ether hydrogels have been investigated between 20°C and 60°C. Three different divinylsulfone crosslinked networks, showing acceptable mechanical resistance and variable temperature sensitivity (in terms of water swelling) have been studied. The solute molecular weight (ranging between 60 and 200×10^{-3} $kg\,mol^{-1}$) does not seem to play a crucial role for the diffusion coefficient variation. Network shrinking induced by a temperature increase results in a slight temperature dependency for diffusion coefficients. Data interpretation has not been attempted through mechanistic diffusion models, given the complex structure of mixed cellulose esters gels. The only approach which leads to an approximate description is based on the free volume model developed by Yasuda et al. According to this model, network density is shown to be the main explicating factor of the effective diffusion coefficient variation.

Keywords: Gels; Diffusion; Cellulose; Network

1. Introduction

The release of solutes (drugs, biological molecules, fragrances, deodorants...) from gels is a subject of considerable interest and has received increased attention the last years [1]. To that respect, hydrogels obtained from cellulosic materials are very attractive given their natural origin, low cost and biocompatibility [2,3]. Furthermore, their resemblance to human tissues is of value in order to study or mimic solute transport through biological media [4]. Recently, the possibility to synthesise temperature sensitive hydrogels from cellulose esters mixtures has opened a new field of interest [2,3]. Potential applications based on these novel materials call however for a sound understanding of the mass transfer phenomena in these matrices. The influence of swelling degree (below and above the critical expansion temperature) on solute diffusion is of particular interest and has not been investigated in these types of hydrogels so far. In fact, a competition between gel shrinking (hindering effect), and thermal motion enhancement (accelerating effect), both obtained by a temperature increase, can be anticipated [5].

The release of an active agent from hydrogels is classically assumed to take place by diffusion [6]. Diffusion coefficient thus appears as a key parameter if a device has to be designed to release a solute at a predetermined rate. An abundant literature deals with the diffusion of low molecular weight solutes in gels. Nevertheless, predicting the diffusion coefficient of any solute in a gel remains a challenge and is roughly approached by two major strategies [7]:

(i) geometrical and hydrodynamical considerations give rise to *structural* based models. A detailed knowledge of gel network structure is then necessary in order to adopt porous media transport analogy.

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0014-3057/01/$ - see front matter
PII: S0014-3057(01)00024-6

Numerous expressions making use of porosity, solute to pore size ratio, as well as some adjustable parameters have been already proposed. These models have unambiguously a large success for high molecular weight solutes. Discrepancies are observed however among solutes of similar molecular weight, for which diffusion coefficient variations, unpredictable by these models, are commonly observed.
(ii) *Molecular* approaches are often more successful for small solute transport. Among several mechanisms, free volume theory offers probably the best results, as soon as highly swollen polymers (such as hydrogels) are concerned. The fact that free volume theory application needs essentially two easily accessible parameters (i.e. gel swelling, expressed through water volume fraction for instance, and solute molar volume) makes it very attractive.

The objectives of this work are the following:

(i) experimentally determine diffusion coefficients of several model solutes in hydrogels obtained from cellulosic esters mixtures based on previously reported experimental procedures,
(ii) investigate how gel type, solute characteristics and temperature affect the diffusional process,
(iii) tentatively interpret the experimental data according to theories taking into account gel media properties. Models based on gel in water swelling, a characteristics which is easily accessible from experiment, have been selected in order to achieve that purpose.

This study has been voluntarily limited to low molecular weight solutes. For that reason, molecular models only have been considered. In any case, the application of structural models to complex media such as crosslinked polymer mixtures is largely questionable.

2. Materials and methods

2.1. Hydrogel preparation

Three different hydrogel networks (Table 1) were prepared according to the following protocol:

(i) in a first step, a defined quantity of each polymer, summarised on Table 1, is dissolved in 20 mL NaOH (001 M) at room temperature and continuously stirred for 24 h in order to complete hydration,
(ii) in a second step, 5–15 μL of divinylsulfone (Sigma Aldrich) dissolved in 5 mL of NaOH (0.01 M) are gradually added and mixed thoroughly to the polymer mixture. This operation is carried out at ambient temperature, in order to promote a slow enough crosslinking process. Should this condition be neglected, a rapid viscosity increase occurs, leading to inhomogeneous crosslinking and mechanically deficient gels. The resulting solutions are poured in a Petri dish and let at 25°C in an oven for 3 days,
(iii) polymer films, showing a good mechanical consistency, are removed from the dishes and rinsed three times in distilled water bathes (rinsing time 24 h for each step). In a last step, the films are dried until a constant weight is obtained at ambient temperature in an oven operating under moderate vacuum.

Table 1
Composition of the three different hydrogels investigated[a]

Reference	MC (g)	HPC (g)	CMC (g)	DVS (μL)
1	0.9	–	0.1	5
2	0.5	0.5	–	5
3	0.45	0.45	0.1	15

[a] All products are purchased from Sigma Aldrich. MC: Methylcellulose (MW 385 000, % NaCl 1.11), HPC: hydroxypropylcellulose (MW: 370 000), CMC: carboxymethylcellulose (MW 250 000).

Flat polymer samples of circular shape (average thickness 1 mm) are cut into the dry films. Swelling in water is further determined based on the weight increase obtained after at least 24 h immersion in water at constant temperature. Gel sample is quickly removed from water, wiped by paper and put on a precision balance. This operation is repeated three times for each temperature (average error 2%). Swelling ratio (S) is then calculated from the relative weight increase compared to dry weight value.

2.2. Diffusion

Flat gel samples are further used for diffusion experiments, according to a procedure already developed by other authors [8–10]. Five model solutes have been selected for that purpose and are summarised in Table 2. At a given temperature, hydrated gel samples are put into contact to a 100 mL solution containing 1 g l^{-1} of solute for at least 10 h. For each release kinetics exper-

Table 2
Model low molecular weight solutes used for the study and corresponding wavelength used for their detection

Solute	MW (g)	λ (nm)
Urea	60.1	195
Cyclohexanone	98.0	275
Acetaminophen	151.2	245
Phenacetin	179.2	245
Cafein	194.2	245

iment, the gel sample is removed from the solution, quickly wiped by paper and put into an empty vessel. One face of the gel is partly in contact to air, the other is kept into contact with the bottom of the vessel. Thus, a single plane surface of the gel is exposed to the release liquid and a one dimensional diffusional situation can be postulated. Temperature is maintained at a constant value thanks to a thermostated bath. An optical fibre, connected to a UV spectrophotometer (Cary 50, Varian), is installed in the vicinity of the gel sample. At the beginning of the experiment, 100 mL of distilled water is added to the vessel and a light agitation by a magnetic stirrer is imposed. The absorbance of the solution at a specific wavelength for each solute (shown in Table 2) is then simultaneously monitored as a function of time. The determination of the specific extinction coefficient of the solutes (performed on a series of aqueous solution samples) enables the solute concentration in water to be computed. Typical release kinetics patterns can thus be obtained for each set of experiment. A series of experimental results for urea at 25°C is shown for illustrative purposes on Fig. 1. It can be seen that a good reproducibility can be achieved, providing no artefact occurs (air bubbles, gel movement...).

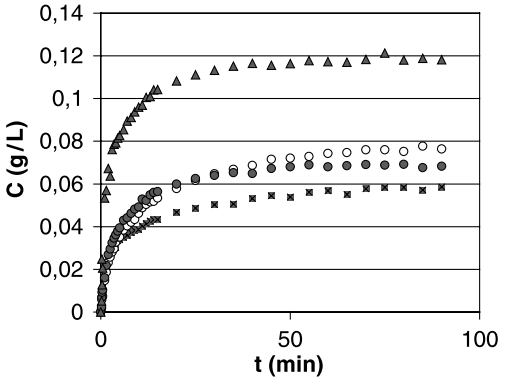

Fig. 1. Example of urea release kinetics (concentration in release medium vs time) at 20°C from different hydrogels (see Table 1) obtained thanks to the experimental set-up. (1) ■, (2) ● and ○, and (3) ▲.

3. Results and discussion

3.1. Gel swelling properties

The swelling ratio of a gel (S) is defined as the ratio of the weight of the gel swollen to equilibrium in water to that of the dry gel. The variation of the swelling ratio with temperature for the three different gels prepared in this work is shown on Fig. 2. A gradual decrease with increasing temperature, similar to that classically reported with pure cellulose ethers hydrogels, is obtained for formulations 1 and 2. Gel 3 shows a very different pattern with a sharp decrease around 40°C, typical of a temperature sensitive media. This characteristic can be very attractive for medical application where a critical shrinking temperature close to human body temperature is needed. Furthermore, gel 3 shows a higher swelling ratio compared to the two others. This is striking since it contains all three cellulose ethers and a higher divinylsulfone content. Based on this, a restricted swelling capability should be a priori anticipated. The increased hydrophilic behaviour and higher temperature sensitivity of gel number 3 confirms the complex synergistic phenomena which can occur in temperature sensitive hydrogel preparation [2,3].

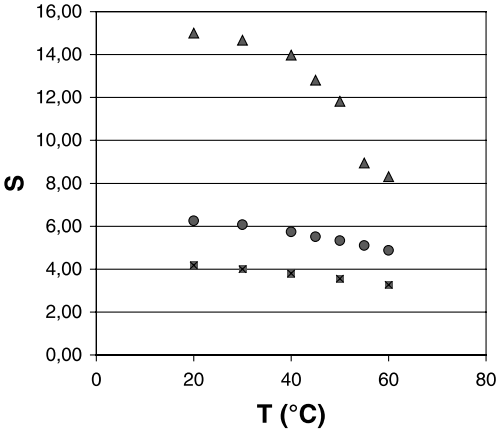

Fig. 2. Influence of temperature on swelling ratio (S%) for the three different hydrogels: (1) ■, (2) ●, and (3) ▲.

3.2. Influence of solute on diffusion coefficient

In a second step, a series of diffusion coefficient determination has been achieved based on the release kinetics curve fitting. The strategy is similar to that classically proposed for transitory diffusional mass transfer treatment [8]. The starting point is Fick's law, which gives the solute concentration variation in the gel flat sample (c) as a function of time (t) and distance (z):

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial z^2} \tag{1}$$

If D is assumed to be constant, Eq. (1) can be integrated. A simplified determination of the diffusion coefficient value can be proposed under this hypothesis, which consists at plotting the relative solute mass released at time t, versus the square root of time:

$$\frac{M}{M_\infty} = f\left(\sqrt{t}\right) \tag{2}$$

Under the assumptions detailed above (constant diffusion coefficient D and sample thickness, L), a linear relationship is obtained for the first part of the curve (typically for $(M/M_\infty) \leqslant 0.5$). The solute diffusion coefficient can be computed through:

$$\frac{M}{M_\infty} = \frac{4}{L}\left(\frac{Dt}{\pi}\right)^{0.5} \quad (3)$$

A precision around 5% is reported to be achievable based on this strategy.

The influence of the molecular weight of the model solutes on their diffusion coefficient for each of the three hydrogels at 30°C is shown on Fig. 3. Comparison with Fig. 2 shows that the diffusion coefficient of a given solute decreases in a gel showing a decreased swelling coefficient. This observation confirms the crucial role of gel network density on the diffusion process, expressed in free volume models for instance, and experimentally confirmed in hydrogels [4]. The role of solute molecular weight on diffusion coefficient variation in a given gel appears however to be less evident. A trend towards lower figures is obtained for gel 3 when the solute molecular weight increases. Generally speaking the very high diffusion coefficients observed in all three hydrogels is surprising and can by no means be attributed to a pure diffusional mechanism. In fact, solute "true" diffusion coefficients in water at 25°C are around 10^{-9} $m^2\,s^{-1}$. The obstruction effect exerted by the polymeric network, even minimal, can only shift towards lower diffusion coefficient values [11]. The fact that high and reproducible values are experimentally determined can only be accounted for if a supplementary phenomenon such as convection simultaneously occurs. Two major explanations could possibly be proposed in that sense:

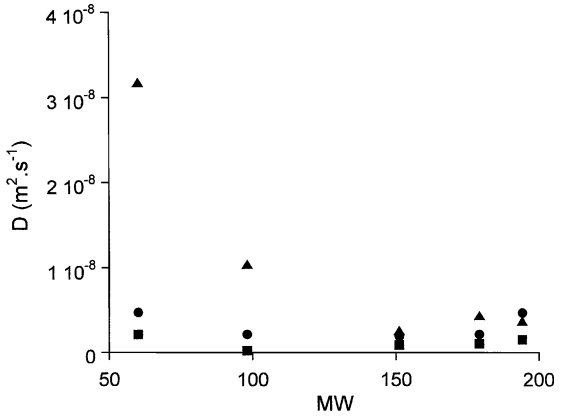

Fig. 3. Influence of solute molecular weight (MW) on diffusion coefficients (D) in three different hydrogels at 30°C: (1) ■, (2) ●, and (3) ▲.

(i) the agitation exerted by the magnetic impeller leads to a rapid but intense solute release in the early events of the test from the interfacial gel layer in contact to water. Some observations of similar effects (5–10% release during the first minute of the release experiment) have been already reported but have not been clearly explained. The best proof would consist to change the agitation rate and see how it affects the release kinetics. Nevertheless this cannot be easily achieved since the homogeneity criterion within the release vessel has to be respected. In any case, a great sensitivity of hydrogels towards fluid shear forces should be advanced in order to validate this first hypothesis.

(ii) The solute content of the hydrogels used for this study being rather high compared to other release kinetics experiments (typically 1 $g\,l^{-1}$ in this work compared to 1–30 $mg\,l^{-1}$ for other studies), a significant water exchange could possibly occur simultaneously to the solute release and significantly increases the overall kinetics. This phenomenon is occasionally mentioned in release studies [12] or gel use under transitory conditions [13] but remains rarely taken into account.

In any case, the high experimental values obtained in this work through a classical procedure call for a detailed analysis of the mass transfer phenomena which occur during the release test. Furthermore, they unambiguously show that the coefficient computed from the experimental data has to be considered as an effective diffusion coefficient, but by no means as a strict diffusion coefficient such as those reported in diffusion mass transfer processes.

3.3. Influence of temperature on urea diffusion coefficient

A systematic study of the influence of temperature on urea diffusion coefficient has been undertaken in the following step. The results are summarised on Fig. 4. A slight variation is observed within the temperature range used for experiments. A quasi constancy is obtained for gel 2. The tendency to decreasing diffusion coefficients when temperature increases, more apparent for gel 1, is striking. The interplay between network shrinking and temperature activation could possibly explain this atypical situation. The same argument obviously does not hold for gel 3, for which diffusion coefficient increases with temperature, similarly to the situation classically observed in liquid phases. This can be related to the fact that gel 3 shows much higher swelling values compared to the two others. This is likely to result from a much lower importance of the network obstruction effect when the gel collapses. These results suggest that the activation effect of temperature occurs only when a loose enough network exists. As a consequence, it

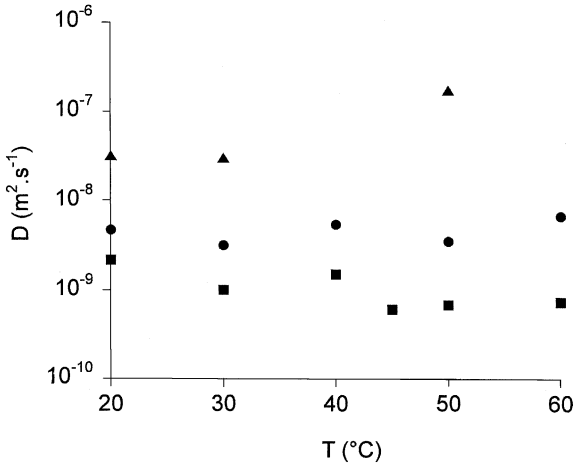

Fig. 4. Influence of temperature on urea diffusion coefficient in three different hydrogels: (1) ■, (2) ●, and (3) ▲.

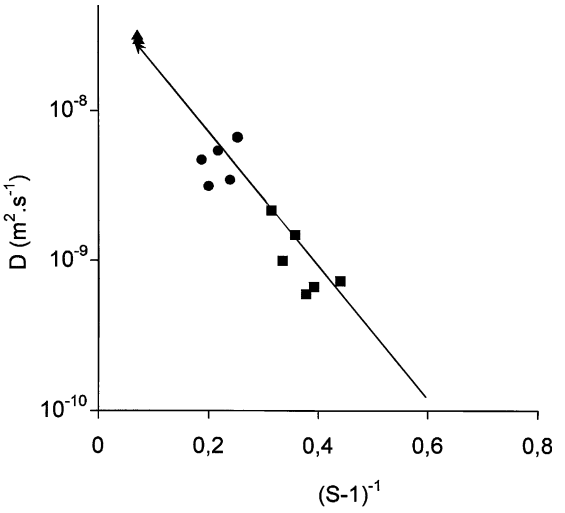

Fig. 5. Data treatment according to Yasuda model: diffusion coefficient of urea in gels (1) ■, (2) ● and (3) ▲ vs inverse gel relative swelling $(S-1)^{-1}$.

appears that for cellulose ethers hydrogels, temperature increase does not compensate the increased obstruction effect which results from network shrinking below a given swelling value.

3.4. Data interpretation

In a last step, an overall data treatment according to various free volume theory derived expressions has been attempted. The best result has been clearly obtained based on a curve fit proposed earlier by Yasuda et al. [14], leading to an exponential variation of diffusion coefficient vs an overall inverse swelling degree expressed as $(S-1)^{-1}$. Fig. 5 shows an example of curve fit for urea under different temperature conditions, in the three different hydrogels. An approximate linear relationship, predicted by the theory, is obtained. According to this theory, the slope reflects the ratio of the molar volume of the solute to the water free volume in the gel. Given the small variation range of the molar volume of a liquid with temperature, a roughly constant slope value results. Similarly, the intercept value should correspond to the solute diffusion coefficient in water.

4. Conclusion

In this work, three different mixed cellulose ether hydrogels, showing various temperature sensitivity in terms of water swelling, have been prepared and studied for controlled release studies. The opposite influence of higher kinetic energy and network shrinking, both resulting from a temperature increase, towards the release kinetics of model low molecular weight solutes under isothermal conditions was questioned. It has been shown that these two parameters could globally be taken through the overall gel swelling value. Thus, the key role of gel swelling for effective release kinetics estimation, already anticipated by theoretical developments, has been confirmed. A critical look at the absolute values computed from release kinetics clearly show these are hardly compatible to a strict diffusional process. The possible role of either agitation rate or water flux in the enhancement of the kinetics has been pointed out and will be analysed in detail in a forthcoming work.

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