The Kinetics of Swelling of Hydrogel Polymers studied using NMR Imaging

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This paper presents a detailed discussion of the use of NMR imaging to study the swelling of hydrogel polymers and the range of methods available for determination of the kinetic parameters. NMR imaging provides the most detailed description of the concentration of water through swelling hydrogel devices. The analysis of the kinetics of diffusion is greatly facilitated by such information.

NMR imaging has been extensively applied by us to the problem of swelling of polymers in contact with a solvent [1-5]. Some care must be exercised to ensure that the profiles obtained using this method reflects accurately the solvent concentration in the swelling polymer. The most robust imaging sequence is based on the spin-echo method; images should be collected with a range of echo times to ensure that differences in \( T_2 \) relaxation times of water molecules in different environments are taken account of. In addition the experiment should be repeated sufficiently slowly to allow full relaxation of the \(^1\)H spins.

This last condition necessitates in some cases long experiment times. The spin-lattice relaxation times of the protons of water molecules (which are imaged in these experiments) increase in proportion to the water content, so that water in hydrogels which absorb large concentrations of water tend to have long relaxation times, approaching the relaxation time of pure water. Thus the imaging experiment time for this class of hydrogel may be quite long. This point is significant as the rate of swelling of these hydrogels is often very rapid, and thus it may be difficult to obtain more than one image before equilibrium has been reached.

Two approaches to circumvent this problem can be envisaged. Firstly a small concentration of paramagnetic relaxation agent, usually a transition metal ion, can be added to the solvent. This has the effect of reducing the spin-lattice relaxation time of the water protons and hence decreases experiment time, however, care must be taken to ensure that the kinetics of swelling are not perturbed by the presence of the dissolved ions. A second method is to use a rapid imaging method which measures a parameter which can be related to solvent concentration, for example the spin-spin relaxation time. Examples of the use of such methodology will be given in this talk.

The materials we have investigated [1-11] span the full range of behaviour reported in the literature. As is well known, when the extent of swelling is relatively small, or the matrix has the ability to relax during the swelling process, the rate of diffusion of the solvent is proportional to the concentration gradient of that solvent in the hydrogel. This is the case in general for materials which absorb less than approximately 30-40% of their initial mass in solvent. In our case we have investigated the swelling of copolymers of HEMA with hydrophilic monomers where the equilibrium water content range from zero to 1 wt. %. All of these systems display Fickian diffusion kinetics.

Materials which absorb higher concentrations of water, for example copolymers of HEMA with the hydrophilic monomer MOEP, tend on the other hand, to show anomalous diffusion profiles. During free radical copolymerization with HEMA, MOEP initiates crosslinking, possibly through chain transfer to the monomer. Thus at high MOEP contents the materials are very brittle, and shatter.
through swelling stresses on exposure to water. At low MOEP contents the water profiles obtained by NMR imaging are strongly non-Fickian (see Figure 1). This behaviour can be described using a number of different models, and we have found that having the diffusion coefficient dependent on the exponential water concentration results in good fits to the profiles.

Figure 1. Profile of water concentration in a copolymer containing 3 wt.% MOEP after 24 hours immersion in distilled water. The upper curve was calculated assuming a concentration-dependent diffusion coefficient. There is some evidence of loss of water at the surface of the hydrogels.

An attempt will be made in this talk to present a unified approach to the analysis of such data based on the finite-difference methods described some years ago by Crank [12] and others. Systems discussed included copolymers of HEMA, blends of PVP and PVA and copolymers of NIPAM.

References

Diffusion in Polymeric Hydrogels studied using NMR Imaging

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Members of the
Department of Chemistry
and the Centre for High
Performance Polymers
Outline of this talk

- The problem defined
- Measurement of swelling of polymers
- NMR imaging methodology
- Experimental examples
  - PHEMA hydrogels
  - PVP/PNVP hydrogels
  - PHEMA-MOEP hydrogels
  - PNIPAM-DMA hydrogels
- Do we have a unified approach?
The problem defined

- Say an equilibrium is perturbed by addition of a solvent or a change in concentration
The end result?

- At equilibrium, the degree of swelling will depend on a number of factors:
  - Chemistry (hydrophilicity)
  - Crosslink density
  - Cracking
  - Geometry
  - Additives, for e.g. drugs
  - Activity of solution
Kinetics of swelling

- What affects rate of initial diffusion?
- What about subsequent molecules?
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Other methods

- Gravimetry
Analysis of gravimetric data

- In the case of relatively small weight gains we use classical solutions to Fick’s laws

\[
\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{4}{a^2 \alpha_n^2} \exp(-D\alpha_n^2 t)
\]
Need for imaging data

- Many solutions to the previous data
- Require more detailed information:
  - Optical density
  - Rutherford backscattering
  - Microinterferometry
  - Fluorescence techniques
  - ESR imaging
  - FT-IR imaging
  - NMR imaging
Analysis of swelling hydrogels

- Require numerical methods
- Finite difference methods

- Planar sheet divided into layers of thickness $h$
- Initial concentrations at interfaces = $C_0, C_1, C_2$...
- The flux of fluid passing through R is given by $q_R = -D \frac{\alpha (C_1 - C_0)}{h}$
- Simple extension to plane S
- More stable solutions available, e.g. Crank-Nicholson method
Swelling of a gel matrix

- Li and Tanaka, 1990
- Derive a collective diffusion constant

\[ D_0 = \frac{(K + 4\mu/3)}{f} \]

- Solutions provided for all geometries
- For cylinders define an apparent \( D_e \)
- \( D_e \) depends on time and position

\( K = \) compressional modulus
\( \mu = \) zero shear modulus
\( f = \) friction coefficient
Swelling of a glassy matrix

- Thomas and Windle have provided the most successful description of so-called Case-II diffusion.
- Couples viscoelastic response of glassy polymer to osmotic swelling stress, and Fickian diffusion.

\[
\frac{\partial \phi}{\partial t} = \frac{P}{\eta}
\]

Linear viscous response

\[
P = \left(\frac{k_B T}{\Omega}\right) \ln\left(\frac{\phi_e}{\phi}\right)
\]

Osmotic swelling pressure

\[
\eta = \eta_0 \exp(-m\phi)
\]

Viscosity
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Magnetic resonance imaging

**Conventional spin-echo sequence**

- Frequency-selective 90° RF pulse is applied in the presence of a gradient $G_{\text{slice}}$ to excite a slice within the sample.
- The MR signal is refocused with a 180° pulse.
- FID signal is collected after echo time $TE$ in the presence of the gradient $G_{\text{read}}$ to encode frequency as a function of a spatial position in the direction of $G_{\text{read}}$.
- The sequence is repeated and increasing $G_{\text{phase}}$ is applied perpendicular to slice and read gradients, thus providing spatial resolution in the direction of $G_{\text{phase}}$. 

Time resolution in MRI experiment

- In polymers with slower equilibration in water, imaging time brings small uncertainty into the water content measured.

- In polymers with faster equilibration the uncertainty becomes significant, so there is need to reduce imaging time.

- Imaging time depends on the rate of spin relaxation.
Relaxation of nuclear spins

- Two kinds of spin relaxation: spin-lattice \((T_1)\) and spin-spin \((T_2)\)
- Both depend on the “state of water”

**HEMA hydrogels** (equilibrium over 48 hours)
- Water content 5 40 %
- \(T_1\) (spin lattice relaxation time) \(ca. 600\)ms.
- \(T_{\text{repetition}}\) in imaging pulse sequence is \(ca. 2\) sec.
- Total imaging time 25 30min
Relaxation of nuclear spins

- Two kinds of spin relaxation: spin-lattice ($T_1$) and spin-spin ($T_2$)
- Both depend on the “state of water”

**PVA/PVP hydrogels** (equilibrium over 12 hours)
- Water content ~ 80\%.
- $T_1$ is ca. 1.2 sec
- $T_{\text{repetition}}$ ~ 5-10 sec
- Total imaging time ca. 2 hrs.
NMR contrast – gift or curse?

- Differences in $T_1$, $T_2$ are used in *medical imaging* to create contrast
- Examples of parameter-weighted images

Goal of medical imaging is *contrast*, not quantitative intensities
How to overcome this problem?

- Addition of paramagnetic relaxation agent
  - *But* these salts can affect diffusion kinetics
- Measure a property proportional to proton density
  - $T_1$ relaxation time – *but* experiment very long
  - $T_2$ relaxation time – need to cope with diffusion attenuation
Pulse sequences for $T_2$ map

RF

$90_x$ $180_y$ $90_x$ $90_x$ $180_y$

Increasing echo time, $TE^*$
Diffusion profiles

- $T_2$ depends on water content
- Calculated for each point according to:

  \[
  \frac{1}{T_2} = \frac{n_w}{T_{2w}} + \frac{n_p}{T_{2p}}
  \]

- Known values: before swelling 0.879 mol water, at equilibrium 0.983 mol.

Profile from $T_2$ map after 29 h

Calculated water content profiles
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HEMA copolymers

- Application is *drug delivery*
- We aim for a fundamental understanding
- Copolymerized to control diffusion kinetics

The copolymer structure shows a combination of hydrophilic and hydrophobic segments.
Mass uptake

High HEMA content

Slight overshoot at high HEMA content

D, EWC depend on composition

Water Uptake (g H2O / g dry polymer)

f HEMA

PHEMA
T10H90
T20H80
T30H70
T40H60
T50H50
Mass uptake

Low HEMA content

Slow second stage at low HEMA contents
NMR imaging

Contour plot of MRI image, central slice, of PHEMA-co-THFMA (90:10), 2 hrs diffusion time, 37 °C

Profile along this plane
Initial stages

Water concentration profiles

- $M_t / M_{\infty} = 0.18$
- $D = 1.5 \times 10^{-7} \text{ cm}^2\text{s}^{-1}$

Distance Across Diameter (mm)

$C / C_0$

Distance Across Diameter (mm)

$C / C_0$

$M_t / M_{\infty} = 0.33$
Prior to fronts meeting

![Graph showing Time vs. Mt / M_{\text{inf}} with two peaks representing C / C_{0} at Mt / M_{\text{inf}} = 0.43 and Mt / M_{\text{inf}} = 0.62.]

- A
- B
Diffusion fronts have met

Mt / Minf = 0.75
D = 1.5 \times 10^{-7} \text{ cm}^2\text{s}^{-1}

Mt / Minf = 0.72
Close to overshoot

\[ \frac{M_t}{M_{\infty}} = 0.79 \]
\[ D = 1.5 \times 10^{-7} \text{ cm}^2\text{s}^{-1} \]

\[ \frac{M_t}{M_{\infty}} = 0.83 \]
\[ D = 2.1 \times 10^{-7} \text{ cm}^2\text{s}^{-1} \]
Final stages

![Graphs showing final stages of a process](image)

- **A**: Graph with time on the x-axis and $M_t / M_{inf}$ on the y-axis. The value of $M_t / M_{inf}$ is 0.84.

- **B**: Graph with distance across diameter on the x-axis and $C/C_0$ on the y-axis. The value of $M_t / M_{inf}$ is 1.00.

The graphs illustrate the characteristics of the final stages of the process.
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PVP-PVA hydrogels

- Application is *wound dressing*
- Crosslinked in swollen state in water
- Initial WC = 85 %
- Final equilibrium swelling depends on crosslink density (90-97%)
Mass uptake

- At intermediate times obeys Fickian diffusion
- Kinetics over full range not fully understood
- Require higher order model
- Acquire $T_2$ maps as described earlier
Images

<table>
<thead>
<tr>
<th>Time, h</th>
<th>0</th>
<th>2.9</th>
<th>12.6</th>
<th>24.3</th>
<th>43.2</th>
<th>100.7</th>
<th>142.3</th>
<th>225.6</th>
</tr>
</thead>
</table>

Increase $T_2$
Numerical modelling of water concentration profiles

- Water content profiles were modelled using equations based on Fick’s second law

\[
\frac{C_t}{C_\infty} = 1 - 2 \sum_{n=1}^{\infty} \frac{J_0 (r \beta_n / R)}{\beta_n J_1 (\beta_n)} \exp \left( -D \frac{\beta_n^2}{R^2} t \right)
\]

- Diffusion coefficients were determined numerically

\[
D = \begin{cases} 
0.86 & \text{at } 1 \text{ h}, \\
0.88 & \text{at } 5.7 \text{ h}, \\
0.9 & \text{at } 72.1 \text{ h}, \\
0.92 & \text{at } 100.7 \text{ h}, \\
0.94 & \text{at } 227.5 \text{ h}
\end{cases}
\]
Diffusion coefficients

- Diffusion coefficient is time dependent due to:
  - Increased resistance to deformation as the polymer approaches equilibrium swelling ratio
  - Result broadly consistent with Li and Tanaka
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Copolymers of HEMA and MOEP

- Application is *controlled calcification*
- Random copolymers grafted onto surfaces
- MOEP enhances rate of calcification
Effect of crosslinking on EWC

Increasing EWC due to hydrophilicity of MOEP

Decreasing EWC due to crosslinking through MOEP
MRI of 3% MOEP copolymer

PHEMA-co-MOEP (97:3),
12 hrs diffusion time, 37 ºC
Water concentration profiles

- 6% MOEP
- 20% MOEP
- Fickian Profile
Full time course

$$D = D_0 e^{\frac{A}{C/C_0}}$$

3% MOEP

$$D_0 = 3.0 \times 10^{-8} \text{ cm}^2/\text{s}$$
$$A = 3$$
$$\text{Time} = 1 \text{ hr}$$
Full time course

\[ D = D_0 e^{\frac{A C}{C_0}} \]

3% MOEP

\[ D_0 = 3.0 \times 10^{-8} \text{ cm}^2/\text{s} \]
\[ A = 3 \]
\[ Time = 3.5 \text{ hr} \]
Full time course

$$D = D_0 e^{\frac{AC}{C_0}}$$

$3\%$ MOEP

$D_0 = 3.0 \times 10^{-8} \text{ cm}^2/\text{s}$

$A = 1.6$

$Time = 7 \text{ hr}$
Full time course

\[ D = D_0 e^{\frac{A C}{C_0}} \]

3% MOEP

\( D_0 = 2.5 \times 10^{-8} \text{ cm}^2/\text{s} \)

\( A = 2 \)

Time = 8.7 hr
Full time course

$$D = D_0 e^{\frac{A}{C_0}}$$

3% MOEP

$$D_0 = 2.6 \times 10^{-8} \text{ cm}^2/\text{s}$$

$$A = 2$$

$$\text{Time} = 12 \text{ hr}$$
Full time course

\[ D = D_0 e^{\frac{A}{C_0}} \]

3% MOEP

- **Distance across diameter**
- **Relative concentration**

**Experimental Profile**

**Calculated Profile**

\[ D_0 = 3.0 \times 10^{-8} \text{ cm}^2/\text{s} \]

\[ A = 1.6 \]

**Time = 18 hr**
Full time course

\[ D = D_0 e^{\frac{A C}{C_0}} \]

3% MOEP

Experimental Profile
Calculated Profile

\[ D_0 = 4.5 \times 10^{-8} \text{ cm}^2/\text{s} \]
\[ A = 2 \]

Time = 24 hr
Full time course

\[ D = D_0 e^{\frac{A}{C_0}} \]

3% MOEP

\[ D_0 = 4.0 \times 10^{-8} \text{ cm}^2/\text{s} \]

\[ A = 3.8 \]

\[ \text{Time} = 24 \text{ hr} \]
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Copolymers of DMA and NIPAM

- Application is *thermally-responsive gels*
- Absorb up to 900 % water
Mass uptake

![Mass uptake graph]

- PDMA
- 75:25 DMA:NIPAM
- 50:50 DMA:NIPAM
- 25:75 DMA:NIPAM
- PNIPAM
MRI of swelling hydrogels

- Images of swelling cylinder in water

PNIPAM, 30 mins diffusion time, 37 oC

Image intensity ~ water content
Images during swelling

- Imaged every nine minutes
- $T_{\text{echo}} = 14 \text{ ms}$
- Quantitative images
Profiles of water concentration
Poly(DMA)
D scales with concentration

\[ D = D_0 (1 + 8[H_2O]) \]
Diffusion into PNIPAM

Poor fit to diffusion profiles for PNIPAM
Thomas and Windle model

Systematic changes seen in TW parameters seen across copolymer composition range
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Model development

- Approach depends on whether rate of diffusion varies with:
  - Concentration gradient
  - Chemistry
  - Rate of deformation of matrix
Low water contents

- Classical Fickian diffusion confirmed
- Additional features such as cracking confirmed
Intermediate water contents

- Chemistry determines the form of kinetics
- Concentration-dependent diffusion coefficients

Experimental Profile

Calculated Profile

$D_0 = 3 \times 10^{-8} \text{ cm}^2/\text{s}$

$A = 1.6$
High water contents

- Swelling from dry polymer results in Case-II diffusion
- Deformation of matrix determines kinetics
Elastic networks

- Fickian diffusion again confirmed
- Diffusion coefficient decreases and so evidence for swelling stress
- Care need with measurement techniques
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