## SUPPLEMENTARY MATERIAL

# *In-situ* nanomechanical characterization of the early stages of swelling and degradation of a biodegradable polymer

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## The model

When a dry polymer is placed in contact with a thermodynamically good solvent, the solvent enters the polymer and may induce major structural changes in its morphology. The polymer responds to the stimulus provided by the permeation of the solvent, with a mechanical action, this is, a volume change. Mathematical models of swellable polymers involve at least two aspects, the diffusion of the penetrant in the polymer and the volume changes due to penetrant adsorption. As far as the transport is concerned, diffusion in polymers is not always best described by Fick's law. In 1966 Alfrey, Gurnee, and Lloyd distinguished three types of diffusion according to the relative rates of diffusion and polymer relaxation [1]. They were (i) Case I or Fickian diffusion, (ii) Case II or diffusion and (iii) Case III or non-Fickian or anomalous diffusion<sup>1</sup>.

To distinguish between these regimes the Deborah number, De, is introduced

$$De=\frac{\lambda}{\theta}$$
 (1)

where  $\lambda$  is the characteristic stress-relaxation time of the polymer-penetrant system and  $\theta$  is the time for diffusion of the solvent in the polymer<sup>2</sup>. Depending on the magnitude of *De*, the process may be Fickian or Non-Fickian. For *De* >> 1 the Fickian regime dominates as the solvent diffuses through the unswollen polymer. For *De* << 1 Case II transport occurs, the solvent penetrates mainly through the swollen polymer. If the rates of the solvent diffusion and polymer relaxation are comparable, *De* ~ 1, the transport mechanism is often called anomalous or Non-Fickian. From a microscopic point of view, diffusion is influenced by the polymer uncoiling which occurs at about the same rate of the penetrant transport. The relaxation of the macromolecules is strongly coupled to the diffusion of the solvent. Among the anomalous behaviors observed, oscillation-with-decay and overshoot sorption have been reported. <sup>3, 4</sup>.

In order to model closely experimental and practical situations we chose a numerical approach. The backbone of the model is based on Peppas et al.'s work<sup>5</sup>. The model explicitly describes swelling. It

is able to portray a range of diffusional behaviours, from Fickian to Case II. Non-ideal concentration effects on the diffusion coefficient can be included. The model is solved numerically using finite element methodology<sup>6</sup>.

At the basis of the model is Fick's law

$$\frac{\delta C}{\delta \tau} = \frac{\delta}{\delta \xi} \left( D \frac{\delta C}{\delta \xi} \right) (2)$$

where

$$C = \frac{C_w}{C_{w,e}} \quad (3)$$

with Cw,e the equilibrium concentration of the solvent, C becomes a normalized concentration. The spatial coordinate is normalized with respect to the polymer dry thickness (4) and the penetrant diffusion coefficient normalizes the time scale (5)

$$\xi = \frac{x}{L_0}$$
 (4)  $\tau = \frac{Dt}{L_0^2}$  (5)

Boundary and initial conditions of the system are expressed by equations (6) and (7). The concentration at the two interfaces is set at 1 to mimic a polymer film placed in an infinite bath of penetrant. Initially, the concentration of the solvent inside the polymer is set to zero.

$$C(0, \tau) = C(\xi, \tau) = 1$$
 (6)  
 $C(\xi, 0) = 0$  (7)

Diffusion coefficients in polymer systems are often concentration dependent. The normalized diffusivity is taken as an exponential function of the concentration according to the free-volume theory<sup>7</sup>. The diffusion coefficient is described by a Fujita-type exponential

$$D = e^{-\beta(l-C)}$$
 (8)

where  $\beta$  is a parameter defining concentration dependence of *D*. Fig. 1 illustrates the relationship between the diffusion coefficient *D* and the normalized concentration *C* with varying  $\beta$ . An increase of  $\beta$  decreases the diffusion coefficient.

The polymer response to the diffusant is explicitly modeled. The space has been divided into 20 layers each of width 0.05 (in dimensionless units). The layers are further subdivided by multiple meshes. Each layer is allowed to expand according to the amount of diffusant it contains. A high solvent concentration results in more swelling. The material response is controlled by

$$\Delta \xi_{I,i} = \frac{\Delta \xi_0}{\left(1 - v_e C_i\right)} \quad (9)$$

$$\Delta \xi_{3,i} = \left[ \frac{\Delta \xi_0^3}{\left( 1 - v_e C_i \right)} \right]^{1/3} (10)$$

Initially the polymer slab is glassy in nature, which prevents isotropic diffusion. The diffusion of the solvent molecules is restricted to one-dimension with the elongation of the polymer layer governed by (9). As a solvent concentration sufficient to plasticize the polymer is reached, the mechanism of transport changes. The movement of the solvent molecules is less hindered by the material. The process of diffusion becomes three-dimensional and the polymer swells following eq. (10). Both the one and three-dimensional processes are governed by the material constant  $v_e$ , but the one-dimensional process elongates the system to a greater extent than the isotropic process.

In Peppas' model the polymer relaxation process is not directly portrayed. Relaxation is assumed to be faster than the sorption process and virtually instantaneous. It can be thought as a vertical drop in volume, as the system moves from the 1D to the 3D regime. Experimentally the structural changes in the polymer are slow and the relaxation time is not zero. A better description of the relaxation is provided by Ishida et al<sup>8</sup>. A time-dependent formulation of the polymer relaxation is given as  $A_{i}^{B} = A_{i}^{B}$ 

 $\Delta \xi_R = c\tau^B \quad (11)$ 

where c and B are parameters linked to the polymer relaxation time.

#### Results

Initially, we consider a simple Fickian diffusion. The D coefficient is assumed independent of the concentration,  $\beta$  equal 0. The swelling is considered negligible and v is set to 0. The concentration profile in Fig. 2 shows a progressive smooth penetration of the solvent into the material from the external interfaces. The profile is half of a Gaussian function whose width increases with time. The response is symmetric with respect to L<sub>0</sub>/2. Similar results can be obtained analytically<sup>9</sup>.

Then, we take into account a diffusion coefficient that depends on the concentration of the penetrant. The concentration profile in Fig. 3 shows sharp advancing concentration fronts that meet at the centre of the sample. The solvent uptake is slow in the unsolvated polymer domain, while it becomes faster in the region where the polymer has already been solvated. The solvation of the macromolecules favors chain rearrangement, which leads to an increment of the free volume. The solvent diffusion path is less hindered. This is a Case II diffusion.

In the third system, we introduce the swelling factor (Fig. 4). The swelling process is assumed monodimensional and the material constant v is set to 0.5. The parameter  $\beta$  is set to 2. Both swelling and diffusion coefficient depend on the concentration. As expected the concentration profile is modified and the system expands to the right and to the left.

In order to accommodate the solvent molecules the polymer chains rearrange. With respect to the diffusion of the solvent, part of the movement may be almost instantaneous and part relatively slow<sup>10</sup>. The instantaneous change consists of the movement of individual functional groups and/or small segments of chains. The instantaneous volume change takes place in the first part of Fig. 5. The diffusion coefficient is concentration-dependent ( $\beta$ =1). Since the swelling process appears to be coupled with solvent penetration we set *v* to 0.76.

The slow response is triggered by internal stresses experienced by the polymer due to the presence of the diffusant. It involves the uncoiling/rearrangement of large segments of the polymer chains. The slow volume change appears in the second part of the Fig. 5. A similar behavior occurs to polymers under other circumstances, for instance polymers subject to a sudden increase in temperature<sup>11</sup>. When the temperature is suddenly increased the polymer undergoes an instantaneous expansion, followed by a slow shrinking. The description of the relaxation process is considered as proposed by Ishida. The experimental results are fitted as c=1.12, B=0.21.

As soon as the stresses are removed further uptake is possible. The polymer is solvated and the diffusion coefficient is no longer concentration dependent ( $\beta$ =0). The value of v is kept at 0.76. The process is slow and the volume changes. This feature is depicted in the third part of Fig. 5.

We assumed PLGA degradation to be negligible in the early stages of the process. The time scales of diffusion and degradation process are not the same. The polymer film has to be solvated before it can undergo hydrolysis. It has been reported that PLGA follows a first order degradation process, which starts after the first week<sup>12</sup>.

In summary, a model to gain understanding of the coupled diffusion-swelling process in PLGA is proposed. It describes the three regimes that have been experimentally observed (Fig. 5) 1D diffusion dominates in the first region. The initial swelling is followed by the polymer relaxation. As the stresses are dissipated by the viscous flow of the polymer, a second swelling is observed.



Fig. 1. Diffusion coefficient-concentration relationships. The dependence of the diffusion coefficient on the concentration is controlled by equation (8) through  $\beta$ .



Fig. 2. Time evolution of concentration profile with constant diffusion coefficient ( $\beta$ =0) and no swelling (v=0). Lines refer to dimensionless time increments  $\Delta \tau$ =0.02.



Fig. 3. Time evolution of concentration profile with concentration-dependent diffusion coefficient ( $\beta$ =5) and no swelling (v=0). Lines refer to dimensionless time increments  $\Delta \tau$ =0.02.



Fig. 4. Time evolution of concentration profile for nonconstant volume and nonconstant penetrant diffusion coefficient ( $\beta$ =2). The process is assumed monodimensional and the material constant v is set to 0.5. Lines refer to dimensionless time increments  $\Delta \tau$ =0.02.



Fig. 5. Normalized width expansion of the PLGA as a function of time. Experimental results are in agreement with the solution of the model, which is plotted as a dashed line.

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