Challenges in Modeling Delayed Erosion due to Degradation of Novel Polyanhydride Biomaterials

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***Abstract* — The long induction period of degradation proceeding without a noticeable mass loss was found in the recent experiments on highly cross-linked photopolymerized polyanhydrides. In order to model the observed phenomenon, we describe the kinetics of several processes such as the intake of water followed by the hydrolytic degradation of the cross-linked polyanhydride matrix. We survey the model and experimental data fitting, which suggest that the long induction interval is caused by the nonlinear dependence of the degradation rates on the local water concentration in the material, suggesting a breakdown of the standard rate-equation approach.**

Keywords* — *Biomaterials; cross-linked polyanhydrides; erosion; hydrolysis; rate equations.

I. INTRODUCTION

A better understanding of the mechanisms and processes of degradation and erosion of various polymeric biomaterials [1]-[16] can be achieved by means of modeling. Here we review recent work on numerical modelling of cross-linked polyanhydrides [1], a specific biodegradable polymer material that has beneficial chemical and physical properties utilized in applications, because of its undergoing degradation and erosion in aqueous environments [2]-[5]. In a recently developed modeling approach [1], we aimed at explaining an important property found in the experiments [17][18]: a long induction interval of water intake prior to the noticeable erosion (mass loss) in highly cross-linked polyanhydrides produced via thiol-ene photopolymerization. This property might allow additional control in medical applications, such as drug release [19][20]. Utilizing a new theoretical model, we conclude that the observed long induction interval can be explained by a kinetic effect of the breakdown of the rate-equation approach, typically used for reaction-diffusion systems.

Specifically for medical applications [5][21]-[24], predictable degradation of biodegradable polymer materials is crucial for drug delivery capsules. Furthermore, biocompatibility is important for orthopedic applications. Some polyanhydrides actually have compressive strengths similar to the human cortical bone [24][25]. In addition to predictable degradation and biocompatibility, polymer implants can help avoid multiple surgeries and incorporate healing drugs [22] for long-term delivery during the implant degradation and erosion. Other benefits include making stress shielding unnecessary and absence of corrosion processes [22]. Furthermore, such materials could facilitate in tissue engineering [5] and development of new bio-adhesives [23].

In the experiments [17] that preceded the modeling work reported here, the authors investigated several aspects of the degradation kinetics of polyanhydrides synthetized by thiol-ene photopolymerization. They experimentally measured and reported several quantities including the time-dependent mass of the surviving eroding cross-linked polyanhydride sample, release rate of a chosen drug-mimicking substance (a hydrophilic dye) in an aqueous environment, and rate of anhydride bond breakage by hydrolysis. Other quantities that might have affected the process kinetics included the pH-dependent degradation product solubility, and the average pK_a of that product. The hydrolysis-involving experiment leading to the polymer matrix swelling and connectivity reduction was carried out at 37° C in phosphate buffered saline (PBS) solution at pH 7.4. A substantial induction period of water intake, about 10 h, before the onset of the noticeable erosion was observed in these experiments, unlike the earlier degradation experiments [4][9][13][22][26]-[29] done for linear polymers only, where typically no indications of such a property were reported, for which phenomenological modeling was reported [12].

In the experiments of interest [17], as the sample takes up the water and the anhydride bonds are subjected to hydrolysis, the connectivity of the polymer network is reduced. Consequently, low molecular weight degradation products and possibly small pieces are released into the solution. We focused on explaining the cause of the experimentally observed [17] induction interval preceding substantial mass loss of the degrading sample [1]. The aforementioned effect is illustrated on Figure 1, top panel, where the experimental data [17] and the model fit curves [1] are combined. The details of the system and of the modeling approach can be found in [1]; they are surveyed here.

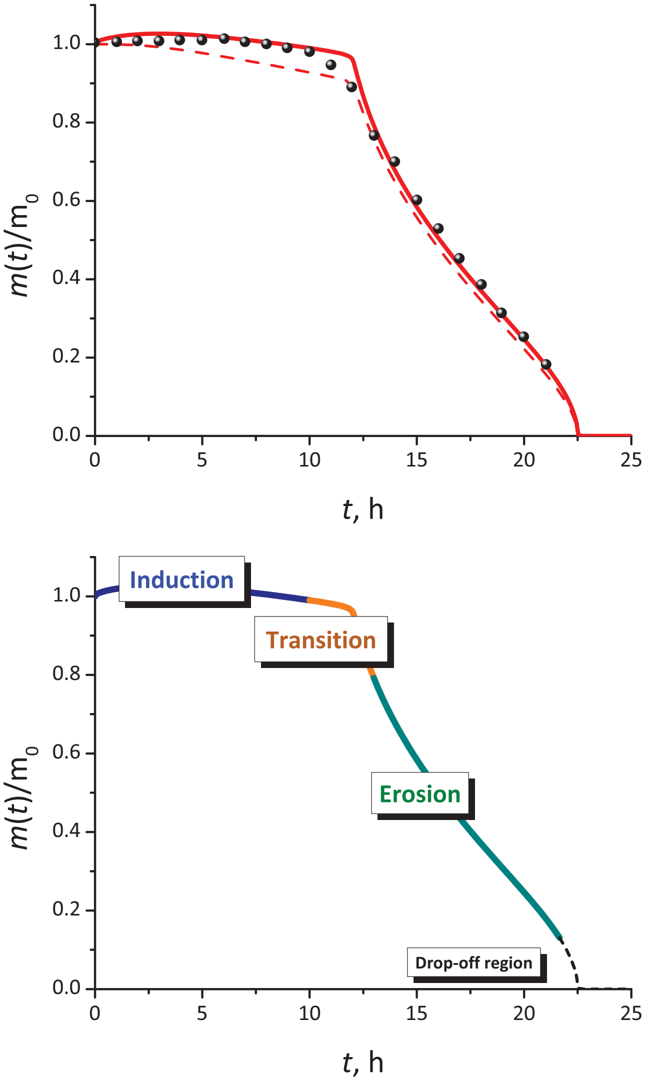

Fig. 1. The relative mass of the remaining undissolved sample as a function of time. Top panel: Black spheres represent the experimental data points [17], measured in hourly intervals. The solid line is the model fit [1] for the sample's relative mass, whereas the dashed line is the polymer-fraction mass in the remaining sample. Bottom panel: Stages of the model-predicted erosion [1].

For the recently developed and studied highly cross-linked amorphous polyanhydrides [17][18][31][32], the existing modeling work [6]-[16][30] on bulk and surface eroding polymers is not applicable as it does not provide an explanation of the long induction interval, comparable to the overall erosion timescale. Figure 1 illustrates the primary modeling results of our new modeling approach [1], reviewed here. The objectives of the modeling were to explore the kinetic mechanisms of the relevant processes and influence of various system parameters. We concluded that the long induction interval of water intake without measurable erosion can be attributed to an effect of the rate-equation description breakdown due to altered water reactivity.

We note that the polymer materials examined in [17] are amorphous. Most of the previous modeling and experimental work was done on semi-crystalline polyanhydrides. For the latter, the presence of two phases adds complexity to the erosion, as the amorphous and crystalline phases can exhibit different degradation behaviors [8].

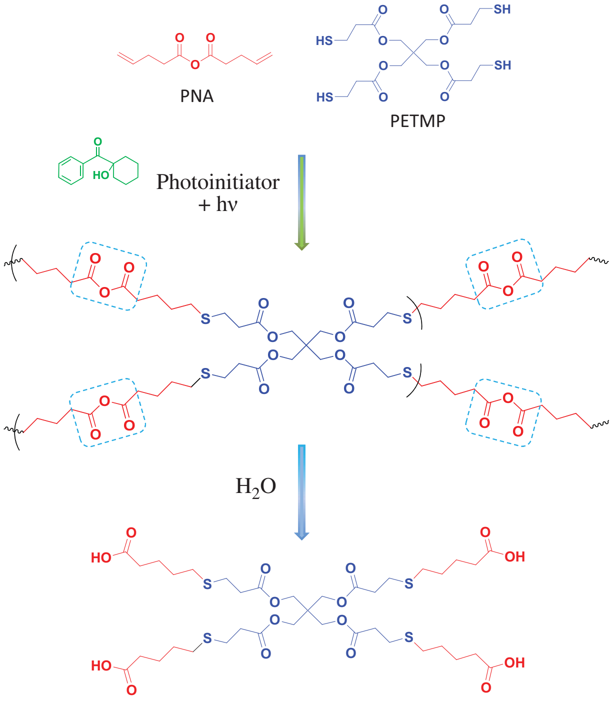

Fig. 2. The scheme shows PNA and PETMP molecules (top section) used in synthesizing polyanhydrides. In the cross-linked structure (middle section) the dashed-line boxes mark the anhydride functional groups, which degrade by hydrolysis, resulting in the polymer breakup into small units (bottom section).

For linear non-cross-linked polymers used in previous works, polymer molecular weight was a determining factor in the erosion process. Polyanhydrides explored here have highly cross-linked structure in addition to being amorphous. These polyanhydrides were synthesized [17] through the thiol-ene photopolymerization of pentaerythritol tetrakis(3-mercaptopropionate) (PETMP) and 4-pentenoic anhydride (PNA); see Figure 2. This type of polymerization, termed a radical-mediated thiol-ene reaction, is often referred to as "click" chemistry, meaning it is highly efficient and easy to perform [33]-[35]. For the system considered here, reaction of the PETMP (1 mole equivalent) and the PNA (2 mole equivalent), yields the highly cross-linked network structure shown in Figure 2. The PNA monomer contains the anhydride functionality that readily undergoes hydrolysis, thus these highly cross-linked polymers degrade in aqueous environments. The polymers were synthesized by combining 0.27 ml PETMP, 0.26 ml PNA, and 0.6 mg photoinitiator (1-hydroxycyclohexyl phenyl ketone) in a silicone mold (10 × 10 × 2 mm) and irradiating with UV light for 15 minutes.

The samples were subsequently degraded in 100 mL of phosphate buffered saline (PBS) solution at 37° C and pH 7.4. Mass of the sample was measured every hour after removing it from the solution and wiping off the excess of the solution and loose (not cross-linked) layer. After each measurement, the PBS solution was renewed to maintain pH 7.4. In the rest of this survey, in Section II we describe the modeling approach. Section III offers a concluding discussion.

II. THE MODELING APPROACH

The degradation and erosion processes are controlled by many parameters. The breakup of the polyanhydride bonds by hydrolysis is typically described using rate equations that introduce rate constants. For the process of erosion we considered diffusion of water into the structure and diffusion of the detached small degradation products within and out of the polymer matrix. Kinetic parameters might be pH-dependent, specifically, the rate of hydrolysis [9][11][26][28][36][37] and solubility of the degradation products [10][13][27].

The buffer diffusion into the sample may also need to be included into the model. We introduced additional parameters for the receding sample boundary, at which variation of buffer, degradation products and water concentration occurs as the sample degrades. The swelling of the outer layer of the polymer sample [17] was also considered [1], yielding more parameters for modeling.

The details of the model are described in [1]. Here, we survey the findings. Consider the standard rate equations, used in earlier modeling [6][7][12][30][38] for the degradation of the polymer matrix, here in a shape of a narrow slab as in the experiment [17], with *x* measured from the middle (and *t* representing time),

$$\begin{aligned} \frac{\partial u_4(x,t)}{\partial t} &= -k_4 u_4 u_\mathrm{w}; \\ \frac{\partial u_i(x,t)}{\partial t} &= k_{i+1} u_{i+1} u_\mathrm{w} - k_i u_i u_\mathrm{w},\ i = 1,2,3; \\ \frac{\partial u_0(x,t)}{\partial t} &= k_1 u_1 u_\mathrm{w} + D_0 \frac{\partial^2 u_0}{\partial x^2}; \\ \frac{\partial u_\mathrm{w}(x,t)}{\partial t} &= D_\mathrm{w} \frac{\partial^2 u_\mathrm{w}}{\partial x^2}. \end{aligned} \tag{1}$$

Here we have several adjustable parameters, including the rate constants $k_{i=1,2,3,4}$, molar concentrations $u_{i=0,1,2,3,4}$ of the 4-, 3-, 2-, 1-(cross-)linked (within the network) units, as well as 0-linked disconnected small diffusing units. These 0-linked units are assumed to diffuse with the average diffusion constant D_0. The water (with molar concentration u_w) diffuses into the matrix with diffusion constant D_w. The reaction terms $k_i u_i u_\mathrm{w}, i = 1,2,3,4$, in the rate equations quantify the hydrolytic break up of the network.

The sample boundary was defined at $x = X_\mathrm{B}(t)$, such that the total amount of the cross-linked material at this *x* value dropped to some reference fraction, *g* (the parameter introduced in [1]), of the initial concentration of the fully cross-linked network at time *t* = 0,

$$\textstyle\sum_{i=1}^{4} u_i(X_\mathrm{B}(t), t) = g u_4(0). \tag{2}$$

Several modifications of the above description are required for $x > X_\mathrm{B}(t)$ where some quantities undergo qualitative changes in properties at the boundary.

The set of equations (1) involves 7 parameters, and only some of them can be found in the literature at least approximately, e.g., D_w in such a polymeric material environment [6][39]-[42]. Other parameters can be only estimated, rather than obtained precisely from data fitting because of the noise in the experimental data, or possibly the model not fitting the considered data. Thus, we are left with several rate constants, etc., including some of the parameters defined at the boundary and outside the sample (described in [1]), and even more quantities that can be fitted in relation to the observed swelling, which we also modeled, see [1] where all the relevant parameter values are given. The available experimental data has only two well-defined time scales as the key measurable properties to fit (see Figure 1). One is the induction time, the other is the erosion time scale measured by the rate of erosion in the approximately linear decay regime.

These two time scales could not be reproduced, as discussed in [1], even when involving numerous adjustable parameters. The standard rate-equation model that included (1), with various boundary considerations and with the inclusion of swelling into the model, etc., was insufficient to fit the experiments data.

Figure 3, top panel, demonstrates how for different values of the rate constants, $k_{i=1,2,3,4}$, no substantial delay time (the induction region) can be produced, cf. Figure 1. By changing some of the parameters (rate constants), the time scale of the fast erosion region can be adjusted, but the duration of the delay remains small, see Figure 3, bottom panel. Furthermore, there is a “bottleneck” effect, also exemplified in Figure 3, in that only a single rate constant is the rate-limiting one. This generally leaves much less freedom in the parameter determination by data fitting than one would expect from the large number of the introduced model parameters, which is actually typical for models of such chemical kinetics.

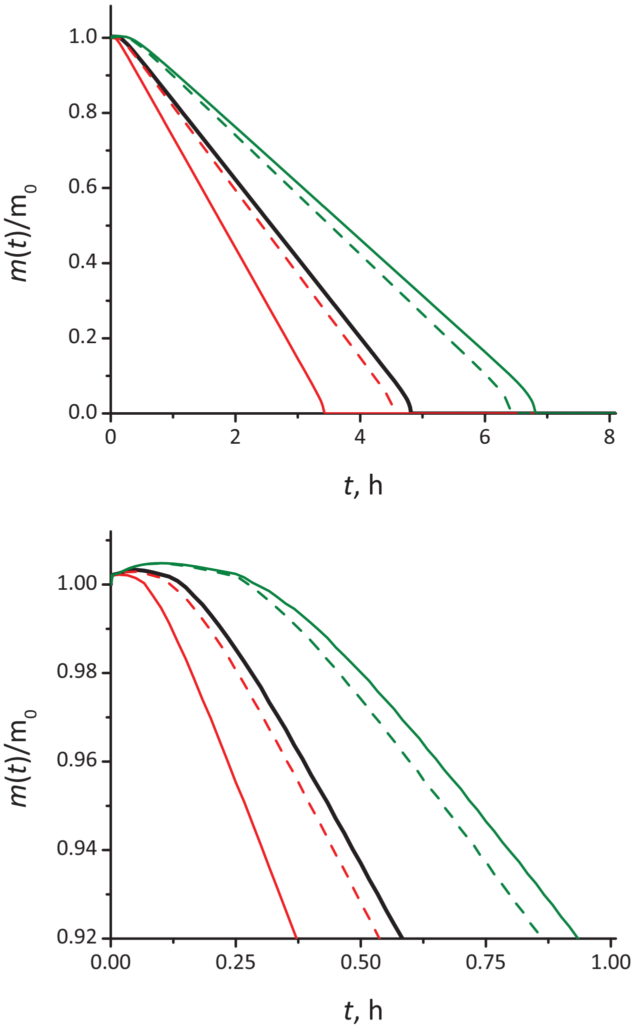

Fig. 3. Top panel: relative mass of the cross-linked polyanhydride sample as a function of time in the standard-rate-equation model. The solid red line was produced with all the rate constants, k_i, doubled as compared to the black line. The green line was obtained by instead halving all the rate constants together. The bottleneck effect is illustrated as follows: The dashed red line represents the case when only k_2 is doubled. The dashed green line is for the case when $k_{1,2}$ are halved. Bottom panel: the initial fast variation time scale is magnified. The parameter values are given in [1].

The overall finding is that the standard rate equation model is not suitable to explain the experimentally observed large induction period. We mention again that several other experiments, which involved less cross-linked networks did not report the long induction time preceding erosion [4][9][13][22][26][27][29][37], however in some of them the delay stage can be observed [7][9][17][18][43]-[45]. For different model modifications, the rate constants in (1) were found [1] to be the basic rate-determining parameters. These equations were common to the different model variations considered. Therefore, the validity of the rate equations (1) should be questioned, and we found that the concentration-of-water dependence is the reason. The model, even in its simplified variant provides a good fit of the data if each of the reaction terms in (1) is modified according to

$$k_i u_i u_\mathrm{w} \Rightarrow k_i u_i u_\mathrm{w} f(u_\mathrm{w}),\ i = 1,2,3,4, \tag{3}$$

with a single-parameter, u_∞, function

$$f(u_\mathrm{w}) = \frac{u_\infty}{u_\infty + u_\mathrm{w}}, \tag{4}$$

that phenomenologically describes the deviation of the original u_w-dependence of the reaction rates from linear, here saturating as a finite value, u_∞, for large $u_\mathrm{w} (\gg u_\infty)$.

Only such a model modification yielded the curves in Figure 1, where the new parameter, u_∞, controls the induction time. We also noted that the shape and sharpness of the transition region from induction to fast erosion, see Figure 1, bottom panel, are mostly controlled by the assumed initial degree of cross-linking near the sample boundary and the diffusion constant, D_0, for detached 0-connected units. However, the given data are too noisy for the precise fitting of this diffusion constant. Additionally, the model-predicted sharp drop-off region at the end of the erosion time, see Figure 1, bottom panel, is difficult to measure experimentally as the sample integrity is mostly compromised when its remaining mass is below ~20%.

III. CONCLUSION

We found evidence that the induction delay time correlates with the water reactivity in hydrolysis in the considered system. One possible explanation of this property is that the dense amorphous network prevents fast enough local water equilibration by diffusion as the water concentration increases. The local reaction rates are then effectively slowed down. However, assuming a standard water diffusion mechanism in the amorphous polymer matrix, statistical-mechanics considerations [46][47] make this explanation questionable.

An alternative explanation could be that a dense cross-linked polymer network prevents resupply of buffer by diffusion from outside the sample, and the reaction rates are lowered due to local pH changes. Another possible explanation of the observed decrease in water reactivity is due to a completely different effect: During the erosion and continuous water intake, some of it will be entrapped in small crevices and only part of that water will be surface-reacting with the surrounding network, causing further anhydride bonds breakup. Such explanation for surface-only reactivity has been noted in a different context [10][13].

These possibilities cannot be sorted out by modeling alone, and they pose a challenge for experimental studies to yield microscopic, rather than the presently available primarily macroscopic degradation/erosion data, providing information on local cross-linked polyanhydride material properties.

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