The distribution of water in degrading polyglycolide. Part II: Magnetic resonance imaging and drug release

GEORGINA E. MILROY, RUTH E. CAMERON*
Cambridge Centre for Medical Materials, University of Cambridge, Department of Materials Science and Metallurgy, Pembroke Street, Cambridge, CB2 3QZ, UK

MICHAEL D. MANTLE, LYNN F. GLADDEN
University of Cambridge, Department of Chemical Engineering, Pembroke Street, Cambridge, CB2 3RA, UK

HIEP HUATAN
Pfizer Ltd., Pharmaceutical R&D, Sandwich, Kent, CT13 9NJ, UK
E-mail: rec11@cam.ac.uk

This paper reports the use of magnetic resonance imaging (MRI) on polyglycolide disks to monitor the change in water ingress with degradation time. Very little response was measured before 13 days, but after this time, water began to penetrate the disks as fronts, starting from the sample surface and moving inwards towards the centre. These results provide more direct evidence in support of the four-stage degradation model for PGA outlined in previous literature, and in particular, that fairly sharp reaction-erosion fronts move in from the sample surface to the centre when the polymer is undergoing significant mass loss and water gain. A combination of MRI and drug release data suggest that fronts originate at the surface at about 7 ($\pm$ 2) days, and proceed at a rate of 0.033 ($\pm$ 0.002) mm/day. These results agree with results obtained from cumulative drug release profiles for different sample thicknesses presented in Part I. They support the hypothesis that drug releases quickly from the swollen regions behind the fronts where the polymer is open and porous, and that release finishes when the fronts meet in the centre of the sample.

1. Introduction

In Part I, we explored the effect of sample thickness on the degradation of polyglycolide disks and their drug release profiles [1]. The results supported the hypothesis of a four-stage degradation mechanism in monolithic samples of polyglycolide [1, 2]. In stage I, very small amounts of water (less than 1 wt %) are absorbed into the sample. In stage II, the molecular weight falls, but little water is absorbed and little drug is lost from the sample. Stage III begins at about 7 ($\pm$ 3) days and is characterized by the presence of highly hydrated reaction-erosion fronts that start at the surface of the disk and move through the sample at a linear rate of 0.032 ($\pm$ 0.002) mm/day. The drug diffuses quickly from the porous, hydrated regions behind the fronts and 100% release is achieved when the fronts meet in the centre of the sample at the beginning of stage IV. This model is similar to models for polylactide-co-glycolide [3–7], in which a porous surface layer is created on degradation, but differs in that in polyglycolide it is proposed the surface layers from each side move through the sample and meet in the middle.

However, these conclusions have been drawn from data from experimental techniques that monitor the mass transport effects of polyglycolide hydrolysis on the polymer and its degradation medium and not the behaviour of the chemical components directly involved in the degradation reaction. In this paper, magnetic resonance imaging (MRI) is used to monitor water ingress into the polymer during degradation and the results in the context of the degradation model proposed are discussed.

The MRI results may be correlated with the mass increase of the polymer due to water gain, and the start time and rate of movement through the polymer of the reaction-erosion fronts. Reaction-erosion fronts movement was deduced in Part I by assuming that fronts from each surface moved through half the thickness of the sample in the time taken for full drug release. In this paper, we compare the data obtained from MRI with these equivalent results.

* Author to whom all correspondence should be addressed.

MRI in various forms has proved a powerful tool for studying liquid transport in a wide range of polymers from epoxy resins to polylactide-co-glycolide [8–15]. It has the ability to give a wide range of information, both qualitative and quantitative, about the nature of liquid ingress and the consequential behaviour of the polymer system. It has many advantages over other imaging techniques; for example, it is non-invasive, chemically selective and suitable for *in situ* experiments.

1.1. Nuclear magnetic resonance and relaxation

The theory of nuclear magnetic resonance (NMR) is well documented, and the reader is referred to appropriate literature, as only a brief discussion of the theory behind NMR and MRI is presented here [16].

In modern NMR spectroscopy and imaging, the spin system (here proton nuclei) under study is placed in an external magnetic field, $\mathbf{B}_o$, and is subjected to electromagnetic radiation in the form of radio frequency (RF) pulses, which perturbs the distribution of nuclear spins between two energy levels. Irradiation of the sample by RF pulses may also be thought of as a rotation of longitudinal $\mathbf{M}_z$ magnetization into the x–y plane, thus producing transverse magnetization $\mathbf{M}_{xy}$. A NMR signal may then be detected as the equilibrium distribution between the two energy levels is restored via a process known as relaxation.

Two relaxation processes characterize the return of longitudinal and transverse magnetization to equilibrium. The first is called spin–lattice or T_1 relaxation, and is associated with the rate of energy transfer between the excited spin states and the surrounding lattice of the material. Spin–lattice relaxation is associated purely with the recovery of net magnetization in the z-direction. T_1 is the characteristic time constant for a particular system and is a measure of how long the nuclear spin system takes to recover back to equilibrium. The second relaxation constant, spin–spin or T_2 relaxation concerns how long the transverse magnetization remains in the x–y plane. T_2 gives a measure of the relaxation period before $\mathbf{M}_{xy}$ returns irreversibly to the equilibrium value of $\mathbf{M}_z$ $(t = 0)$ and thus $T_2 \leq T_1$. A knowledge of T_1 and T_2 allows us to study the physical and chemical properties of materials. This work involves investigating the transport of water into polyglycolide and a knowledge of T_1 and T_2 values are important in order to determine whether the spatial NMR signal recorded is a quantitative measure of the number of resonant spins present in the sample under study. In general, quantitative NMR measurements are only possible when the T_1 and T_2 relaxation behaviour of the system is known.

1.2. Spatially resolved NMR

Spatial resolution is achieved by the application of additional smaller magnetic field gradients (usually in the x, y and z laboratory directions) to the main field $\mathbf{B}_o$ [16]. Magnetic field gradients and RF excitation pulses can then be combined to produce one, two or three-dimensional maps showing the spatial distribution of a molecular species.

2. Experimental

2.1. Sample preparation

Samples were made according to a method described in Part I, which gave them uniform and controlled thickness. A polyglycolide batch was obtained in powder form from Alkermes Medisorb Polymer, Ohio, USA, which had an intrinsic viscosity of 1.3 dl/g. Samples were processed into disks of diameter 15 and 2.3 mm thickness using a mould on a hot press. The mould consisted of a top and base made from PTFE coated aluminum, and an aluminum or steel spacer of chosen thickness with circular holes forming the mould cavity. The base and spacer of the mould was placed on the heated lower plate of a Magnus compressible hot press. The temperature varied across the face of the press and a thermocouple was used to calibrate the press before and after use. The mould was filled with polyglycolide powder or a 4.8 wt % theophylline-polymer powder mixture in stages to ensure that the mould fully filled. Between each stage, the lower and upper plates of the press were brought almost into contact for approximately 1 min to allow the polymer to melt before more polymer was added if required. Once the mould was filled, the second PTFE coated aluminum foil was placed over the polymer. A pressure of 10 bar at 236 °C was then applied for approximately 30 s. The mould and polymer were then removed immediately to iced water. Samples were removed from the mould once cooled and showed a slight rippling on the surface. The model drug theophylline was obtained from Sigma-Aldrich.

Samples were degraded, without agitation, at 37 °C in 100 ml of phosphate buffered saline, pH 7.4 and concentration 0.01 M, and were supported in perspex grooves to expose them to the buffer. The solutions and bottles were autoclaved at 120 °C and 1 bar for 30 min before use.

2.2. Magnetic resonance imaging (MRI)

In this study, two-dimensional (2D) spin density magnetic resonance imaging was used to record the water ingress into polyglycolide disks in the x–z plane (Fig. 1). A standard spin-echo pulse sequence was used [16], and is shown in Fig. 2. A 90° Gaussian-shaped selective RF excitation pulse is applied to the sample in the presence of the $\mathbf{G}_y$ (slice) magnetic field gradient. Classically, this causes the net magnetization, $\mathbf{M}_z$, within the selected slice to rotate by 90° from the z-direction into the x–y plane. This transverse magnetization is then further frequency and phase encoded by the application of two orthogonal magnetic field gradients in the x and z

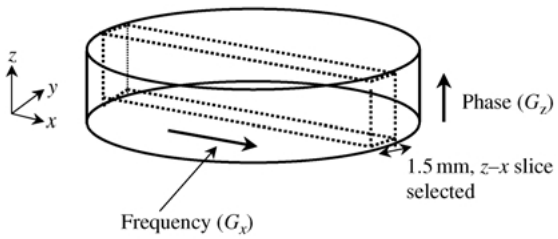

Figure 1 Schematic showing the location of the slice selected from the x–z plane in a PGA disk to record 2D MRI data.

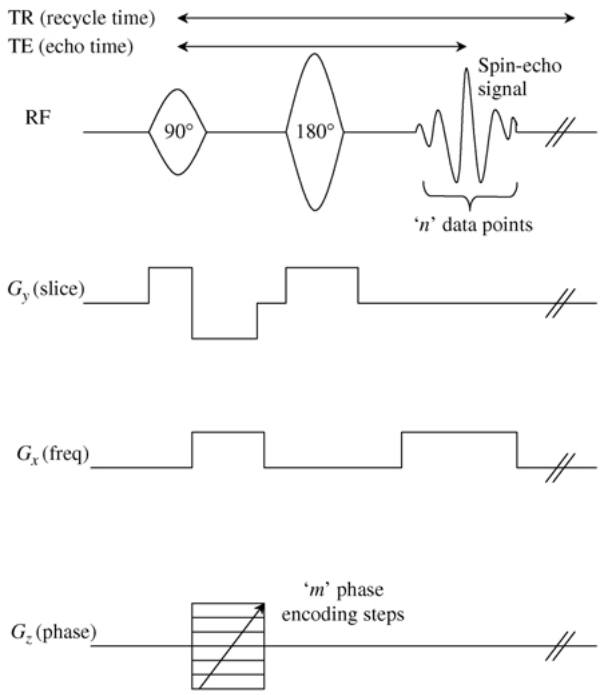

Figure 2 Schematic of spin-echo pulse sequence used to record MRI data for PGA disks.

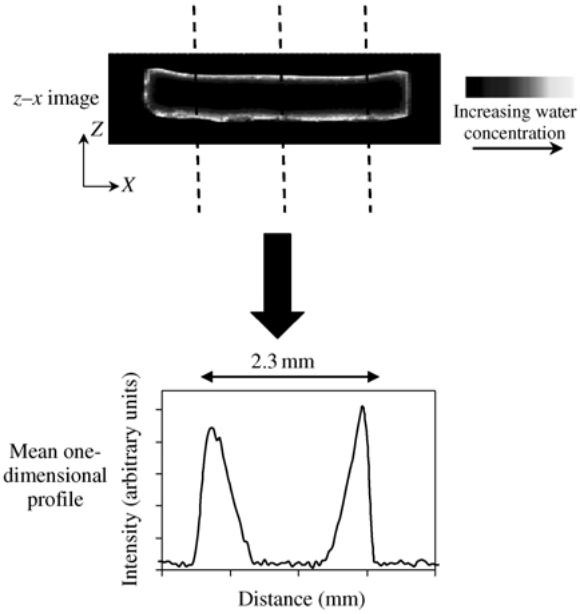

Figure 3 One-dimensional profiles are selected (dashed lines) in the *z*-direction from 2D MRI images at points along the *x*-direction where the sample outer surface is flat. A mean one-dimensional profile is determined from the three sets of data.

directions, respectively. After applying a refocusing 180° selective RF pulse, the signal is then acquired in the presence of a second frequency encoding gradient (Fig. 2) yielding typically *n* data points. The whole process is then repeated for *m* different value of the phase encoding gradient until enough data points are acquired to build up a spin density image, typically yielding an image of *n* by *m* data points. Two-dimensional (2D) Fourier transformation of the frequency-phase encoded data set then yields a 2D spin–density map or image in the *x*–*z* plane of the disk.

One-dimensional data were obtained by extracting individual profiles in the phase encoding direction (here in the *z*-direction). An average of three individual profiles were used to obtain a mean 1D profile (Fig. 3).

All experiments were conducted using a Bruker DMX 300 NMR spectrometer corresponding to a proton resonance frequency of 300.13 MHz. Polyglycolide samples were placed on a perspex support and then put in a glass tube and placed into the $\mathbf{B}_o$ external field and imaged individually (Fig. 4). The samples were covered with cling film to minimize water loss due to drying. A series of disks were tested, each degraded for a different time, and gave data corresponding to an individual time-point. A microimaging probe-head was used to obtain ^{1}H images of 128 by 64 pixels; was used. Spatial resolution was obtained with shielded magnetic field gradients of 15.98 G/cm in the $\mathbf{G}_z$ and $\mathbf{G}_x$ directions, and 10.79 G/cm for the $\mathbf{G}_y$ slice gradient. The field of view was approximately 20 mm × 6 mm in the *x*–*z* plane, and the pixel resolution was therefore approximately 156 µm × 94 µm. The *x*–*z* slice thickness was 1.5 mm. A data acquisition time of 25 min was used to achieve an acceptable signal-to-noise ratio. An echo time (TE) and recycle time (TR) of 2.9 ms and 3 s were used, respectively.

For the experimental conditions used here, MRI was not sensitive enough to measure the low levels of water at early times up to 13 days during the degradation process.

Several other smaller tests were performed on samples to determine extra information about PGA hydration behaviour. First, repeat samples degraded for 21 and 75 days were tested to determine the reproducibility of the MRI results. Second, MRI data were recorded for blank samples and samples containing theophylline (loaded to 4.8 wt %) to determine the effect of drug on water ingress into the polymer. Third, magnetization (signal) losses due to T_1 and T_2 relaxation were estimated for each time point tested, and a T_2 relaxation map was measured for a PGA sample tested after 27 days degradation to assess signal losses due to T_2 relaxation for the 2D image data. Fourth, samples were degraded in 100% D_2O 0.01 M PBS to determine if any signal was produced due to species other than H_2O, such as the mobilization of the polymer.

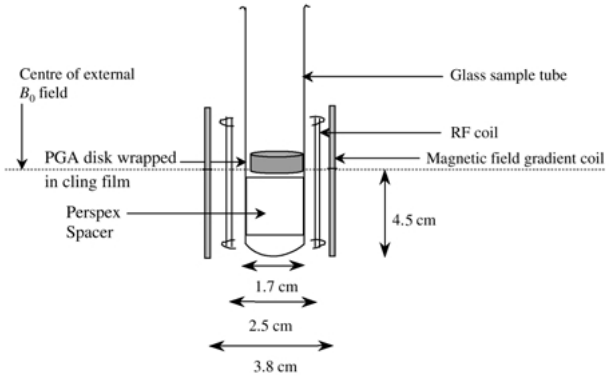

Figure 4 Sample holder and location of the RF and gradient coils used in the MRI experiments on PGA disks.

2.3. Drug release

After a known degradation time, the absorbance of the buffer solutions was measured at 271 nm (the absorbance wavelength of theophylline) using a UVIKON 860 double beam spectrophotometer. These readings were then entered into the Beer–Lambert equation to calculate the amount of theophylline release [17]. The buffer was diluted by mass, and not returned to the sample bottles after testing.

2.4. Water uptake

The initial masses of the samples were weighed using a microbalance to an accuracy of 0.001 mg. After degradation, the samples were removed from the buffer, dabbed dry with a tissue and weighed immediately by a different balance with an accuracy of 0.01 mg. The samples were then placed in a vacuum oven for 3 days (to reach constant weight) and reweighed again to an accuracy of 0.001 mg.

The mass loss (M_{loss}) is calculated by subtracting the original mass (M_o) from the dry mass (giving negative numbers once the mass is lost). The water gain (M_{gain}) is calculated by subtracting the dry mass (M_d) from the wet mass (M_w). Both are expressed in mg. Given the slight variation between original sample masses, M_{loss} and M_{gain} are divided by the original mass of the sample and converted to percentages. These steps are shown in Equations 1 and 2.

$$M_{loss} = \left(\frac{M_d - M_o}{M_o}\right) 100 \quad (1)$$

$$M_{gain} = \left(\frac{M_w - M_d}{M_o}\right) 100 \quad (2)$$

The mass change calculated using MRI data involves, first, calculating the area under the 1D MRI profiles for all time points using Simpson's rule [18]. The values are then normalized with respect to the water gain value determined gravimetrically for 35 days degradation time. This is valid because the size of the magnetization losses due to T_1 and T_2 relaxation at this time represents a mean average of the loss in signal for all time points tested, and hence provides a measure of these losses during PGA degradation.

3. Results

The mean 1 and 2D MRI data in Fig. 5 show the progress of water into 2.3 mm thick polyglycolide disks with degradation time. All samples measured were in either

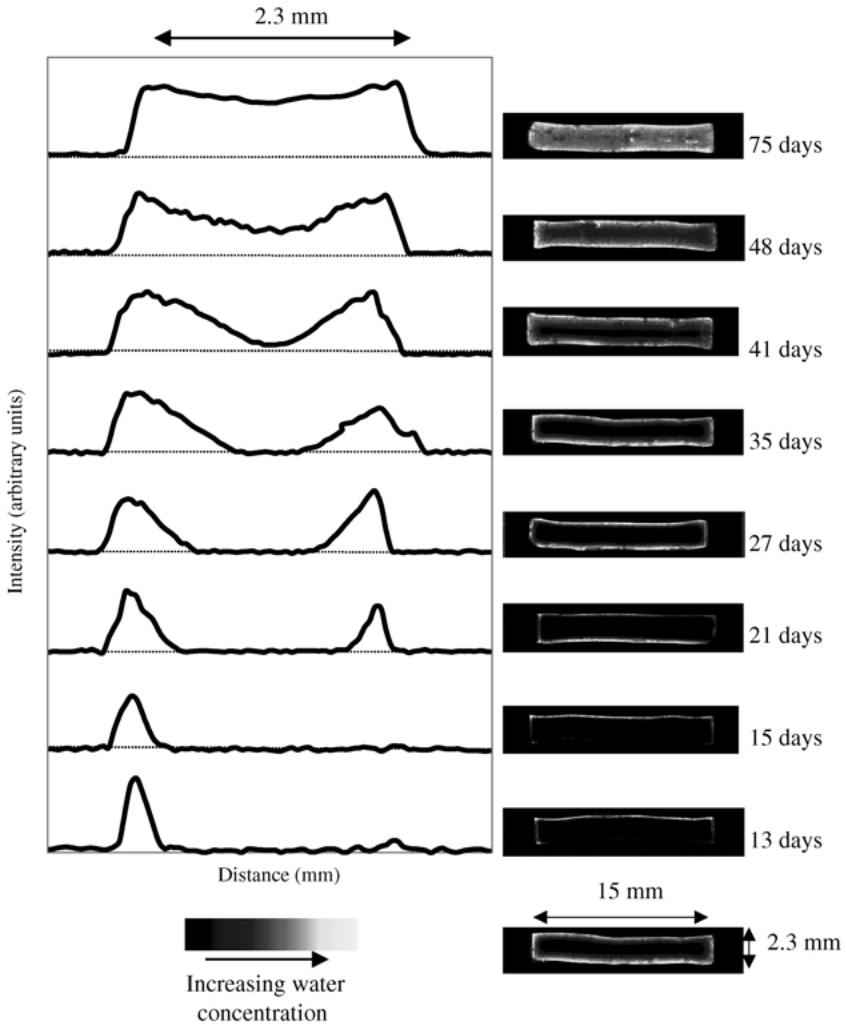

Figure 5 The mean 1 and 2D MRI data show the progress of water into 2.3 mm thick PGA disks with degradation time. All data are plotted on the same scale and lighter areas refer to a greater concentration of water. The experimental error estimated in the area under the mean 1D profile for each time point is $\pm$ 5%.

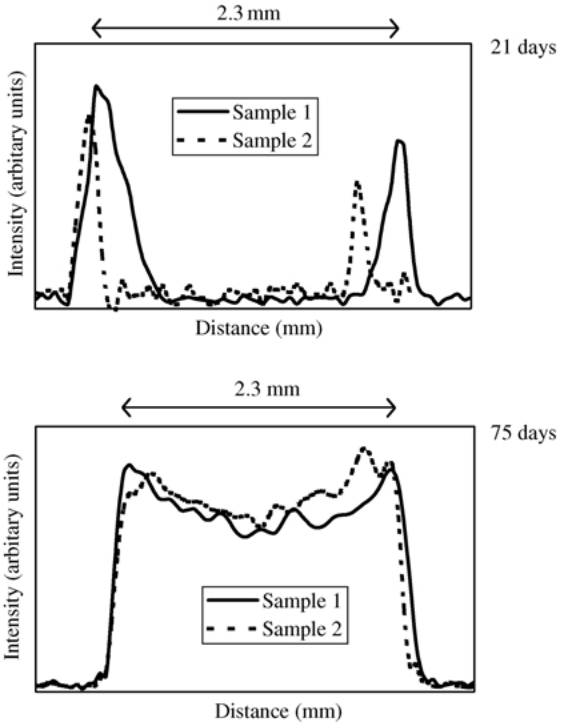

Figure 6 compares the 1D MRI profiles for two PGA disks, 2.3 mm thick, tested after 21 and 75 days degradation to assess the reproducibility of the MRI data.

stage III or stage IV of degradation because the levels of water at earlier degradation times were too low to be detected using MRI using the experimental parameters used here. One-dimensional profiles for 13 and 15 days degradation only show one distinct peak, and all the other profiles show asymmetry with respect to direction.

Fig. 6 compares the 1D MRI profiles for duplicated samples degraded for 21 and 75 days.

Fig. 7 compares the 1D MRI profiles for blank samples and samples containing theophylline with a loading of 4.8 wt %, both degraded for 21 days.

Fig. 8 shows (a) the fitted I_0 intensity map; (b) the chi-squared fitted 2D T_2 relaxation time map; (c) the T_2 error map and (d) a correlation plot of T_2 value against fitted I_0 intensity for a sample degraded for 27 days.

Fig. 9 shows the correlation between integrated one-dimensional MRI profile data and gravimetric mass

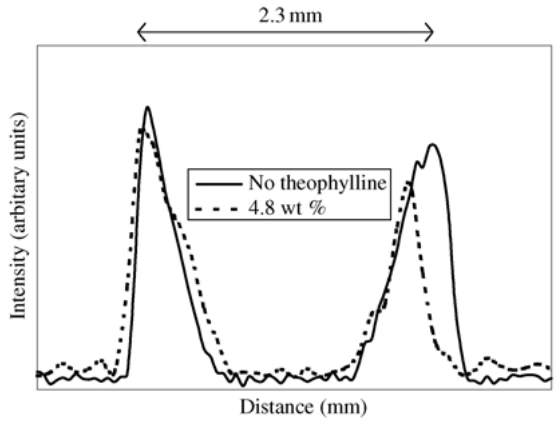

Figure 7 Comparison of the 1D MRI profiles for two PGA disks, 2.3 mm thick, one blank and the other containing 4.8 wt % theophylline. Both samples are tested after 21 days degradation to assess the effect of theophylline on the hydration of PGA.

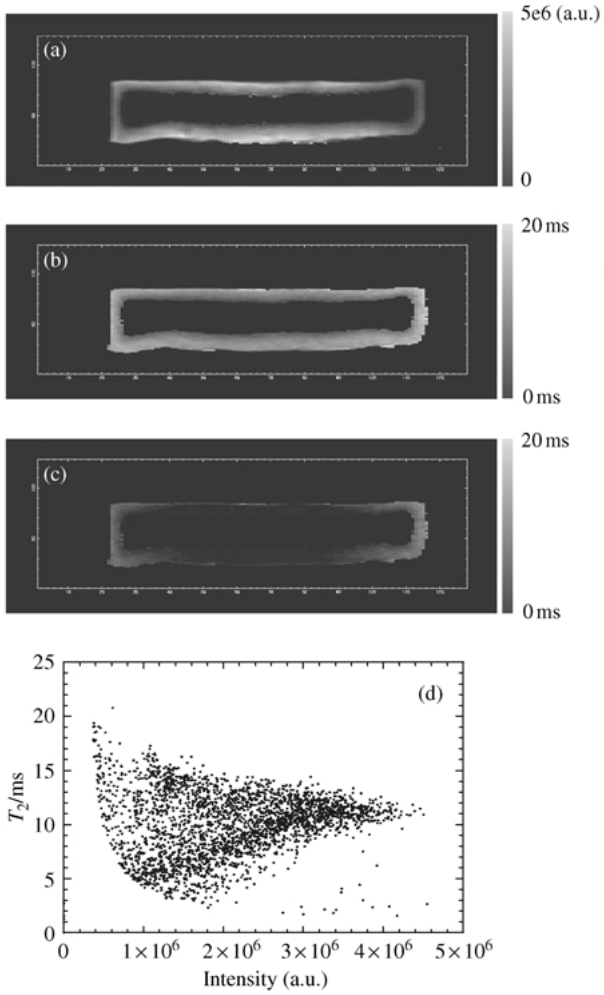

Figure 8 This shows for the sample degraded for 27 days: (a) the fitted I_0 intensity map; (b) the fitted relaxation time, T_2, map; (c) the error in T_2 relaxation time map and (d) a correlation plot of T_2 versus I_0 intensity. The figure shows there is considerable spatial variation in the values of T_2.

change caused by water gain for polyglycolide samples. The MRI data were normalized to the gravimetric data at 35 days degradation time.

Fig. 10 shows the cumulative drug release profile per unit surface area for 2.3 mm thick polyglycolide disks. Drug release starts at about 7 days, and proceeds at a constant rate until it finishes at about 40 days. Fig. 8 also

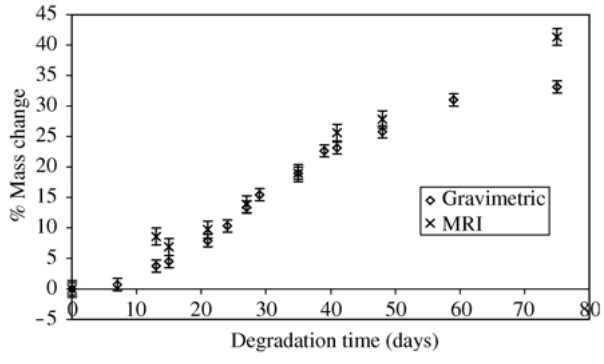

Figure 9 The percentage mass change of 2.3 mm PGA disks due to water gain determined from gravimetric analysis and MRI one-dimensional profiles. Both data sets agree with each other within experimental error, and both show little water gain during the first 7 days degradation, after which it occurs more significantly.

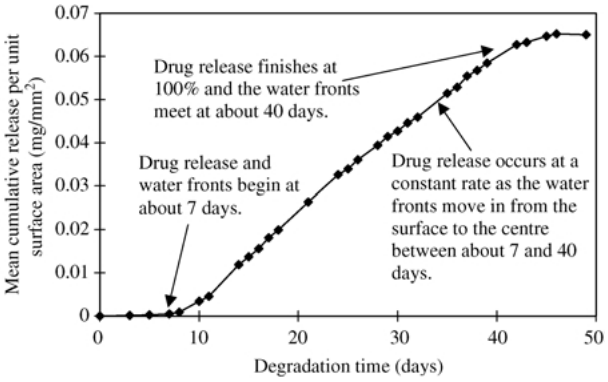

Figure 10 Profile showing the cumulative drug release per unit surface area for 2.3 mm thick PGA disks. Drug release starts at about 7 days, and the rate of release is constant (approximately zero order) until it finishes at about 40 days. This figure also shows how the MRI data for the same sample thickness correlates with the drug release behaviour. The experimental error is $\pm$ 8.5% of the value of each experimental point.

shows how the MRI data for 2.3 mm disks, presented in Fig. 5, correlate with the drug release data.

In Fig. 11, data from the MRI results in Fig. 5, shows the distance moved by water fronts against degradation time. This is plotted alongside data showing the relationship between the half-sample thickness and the time when the drug release finishes for different disk thicknesses determined from cumulative release data and presented in Part I. The 1D MRI profiles are used to produce this figure. The first step is to measure the mean width in pixels of the water fronts from profiles showing them before they meet. These values are converted to units of distance by equating the width across a profile to the thickness of the sample. The distance of front penetration against degradation time was also calculated in Part I by assuming that the drug release finishes when the reaction-erosion fronts from each surface meet in the centre of the sample. For a sample of a given thickness, the drug release finishes when each of the fronts have each moved half the thickness of the sample.

Table I lists the percentage loss in magnetization signal due to bulk T_1 and T_2 relaxation when acquiring MRI data for PGA disks.

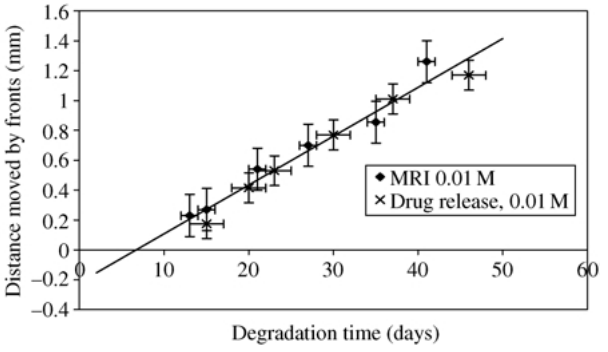

Figure 11 A plot of distance moved by reaction-erosion fronts against degradation time determined from MRI (closed diamonds) and drug release (crosses). Both show a linear relationship, and suggest that the reaction-erosion fronts start at about 7 ($\pm$ 2) days, and proceed at a rate of 0.033 ($\pm$ 0.002) mm/day into the sample until they meet in the centre.

TABLE I Losses of magnetization of NMR signal due to relaxation

Sample	T_1(s)	T_2(ms)	T_1 loss (%)	T_2 loss (%)	Total relaxation losses (%)
21 days	0.9	6.8	3.6	34.7	37.0
27 days	1.4	10.7	11.7	23.7	32.7
35 days	1.1	11.4	6.5	22.5	27.5
41 days	1.6	11.6	15.3	22.1	34.0
48 days	1.1	11.4	6.5	22.5	27.5

4. Discussion

Fig. 5 presents 1D profiles and 2D images showing the water distribution in polyglycolide at different degradation times. The MRI data show the penetration of moderately sharp water fronts during stage III. The earliest time point measured is 13 days (a few days after the start of stage III at 7 days), because the low levels of water that present at earlier times (less than 1 wt % according to previous work [1]) do not yield an MRI signal. The profiles for later time points show the fronts progress inwards from the sample surface until they meet after 35 and before 41 days. Afterwards, the water uptake continues, with levels increasing by more in the centre than at the edges. The water distribution is largely homogeneous by 75 days. Therefore, the data provides direct evidence supporting the hypothesis that, during stage III, reaction-erosion fronts start at the sample surface and penetrate inward towards the centre where they meet. It is assumed that the images show the water content of the reaction-erosion fronts and that there is not a contribution from mobile polymer and polymer fragments. This assumption is validated by the fact that samples degraded in 100% D_2O 0.01 M PBS for 46 days gave no MRI signal, indicating that the polymer is not mobilized sufficiently during degradation in PBS made with H_2O to produce a contribution to the MRI signal.

The 1D profiles in particular show that water seems to penetrate more from one side of the sample than the other before the fronts meet. This effect has caused the 1D profiles for 13 and 15 days to only show one peak. By marking the topside of the disks after sample preparation, before imaging, it was possible to conclude that this occurred to sides of disks that were in contact with the bottom of the press during processing. One possible explanation is that the polymer on this side of the sample is in contact with the press for longer, causing it to undergo more thermal degradation and making the molecular weight lower as a result. This would mean that the critical molecular weight was reached sooner. GPC results [19] show that after processing, the molecular weight has fallen by a factor of 1.7, which supports this hypothesis.

From the 2D MRI images in Fig. 5, it is clear that water fronts also ingress from the sides of the disk during stage III. The aspect ratio chosen for the samples meant that the water ingress from the sides of the disks made a small contribution to the bulk hydration of the polymer because the fronts have much further to travel before they meet in the centre than fronts penetrating from the top and bottom of the sample. The data extracted from the MRI images yielding 1D profiles were selected from regions close to the centre of the images to ensure they

corresponded to water ingress from the top and bottom of the disks alone.

Fig. 6 compares 1D MRI profiles from two separate samples degraded for 21 days. There is a high level of scatter in these data because they are recorded early on during stage III when the low levels of water give a small response from the MRI. The profiles also show an asymmetrical distribution of water and a variation in intensity and width. Despite these complications, which are attributed to experimental error, the profiles show similar distances moved inwards by the water fronts. Therefore, it would seem that MRI gives reasonably reproducible information about water ingress into polyglycolide during degradation.

Fig. 7 compares 1D MRI profiles from a blank PGA sample with a sample containing theophylline drug loaded to 4.8 wt %. Both samples were degraded for 27 days. It appears that the water fronts move the same average distance inwards from the disk surface for both blank and drug loaded samples, and that the presence of theophylline for loadings upto 4.8 wt % does not alter the hydration of PGA. This finding fits with work by Hurrell and Cameron, who observed the same water uptake and mass loss for unloaded PGA samples, and samples containing 4.8 wt % theophylline [2]. This result is perhaps surprising because theophylline is a hydrophilic drug, which might be expected to increase the rate of hydration into the sample. The drug loading used in this work is quite low and it is possible that higher loadings of theophylline would increase the rate of water ingress into PGA.

Table I lists the values of bulk T_1 and T_2 measurements made on some samples along with the calculated losses in water signal due to relaxation. It should be noted that the T_2 relaxation losses are far more severe than T_1. In order to gain a better understanding of how the T_2 relaxation losses affect quantitation, a T_2 relaxation map was calculated from a series of 2D magnetic resonance (MR) images taken at different echo times, TE. Each pixel within the image is then fitted to the standard exponential decay model for T_2 relaxation [16]:

$$I_0 = \frac{I}{\exp\left(\frac{-\mathrm{TE}}{T_2}\right)} \tag{3}$$

where I is the measured signal intensity, I_0 is the fitted intensity at a hypothetical time of $t = 0$, TE is the experimental variable (the echo time), and T_2 is the fitted relaxation time for that pixel.

Fig. 8 shows for the sample degraded for 27 days: (a) the fitted I_0 intensity map; (b) the fitted relaxation time, T_2, map; (c) the error in T_2 relaxation time map and (d) a correlation plot of T_2 versus I_0 intensity. Fig. 8(b) shows that there is considerable spatial variation in the values of T_2. At first sight it would appear that the T_2 value decreases with water concentration. That is to say that the T_2 appears to decrease as the front progresses from the outer surface toward the middle of the sample. However, Fig. 8(d) shows that whilst there is an interesting ''shape'' to the correlation plot, no simple correlation is evident. This then precludes any simple, that is, linear, correction of the signal intensity for the other spin-density images/profiles to give quantitative results. The general decrease in T_2 relaxation time toward the leading edge of the reaction-erosion fronts is likely to be a result of the fact that the water is less mobile at the water–polymer interface due to the decrease in mobility of the polymer with degradation time. Any correction due to T_1 is ignored but it is recognized that any quantitative comparison between MRI signal intensity and gravimetric mass uptake of water in PGA would still have an error of approximately 10% even if a signal intensity correction for T_2 relaxation were possible.

Whilst it is not possible to correct the MRI intensity data for relaxation losses (due to practical time constraints), the integrated MRI profile data can be overlayed with the gravimetric data. Fig. 9 indicates there is a good correlation between integrated MRI profile signal intensity and the actual water gain measured gravimetrically. Both show very little water gain occurring in polyglycolide during about the first 7 days of degradation (less than 1 wt %,), followed by more significant amounts taking place subsequently. This finding agrees with the degradation model, which predicts little degradation during the first few days of hydration (stages I and II), followed by more significant microstructural deterioration by the polymer (stages III and IV). The agreement between the two sets of data also verifies that spatially resolved MRI data can give semi-quantitative information about the water content levels in polyglycolide in this study.

The bulk self-diffusion coefficient, D, of water in polyglycolide was determined for a sample degraded for 27 days using a standard pulsed field gradient (PFG) simulated-echo nuclear magnetic resonance technique [3]. The value recorded was $1.2 \times 10^{-10}\,\mathrm{m^2/s}$ and is associated with the water behind the hydrated fronts in stage III because MRI was not sensitive enough to measure a signal due to water at earlier stages of degradation. This value is associated with the diffusional movement of individual water molecules and not the bulk diffusion of water through the polymer. It was not possible to find a comparative value for PGA in the literature. If it is assumed this is also the self-diffusion coefficient for the drug in the polymer, this approach predicts that release of the drug from the centre of the disks (a distance of 1.15 mm) once the fronts have penetrated fully, takes about 1.5 h. This calculation uses the following equation for 1D diffusion [16]

$$\mathrm{rms} = \sqrt{2Dt} \tag{4}$$

where rms is the root mean squared distance, D the diffusion coefficient, and t the time.

This result means that when drug release finishes, the period of 1 day before the next reading is taken on the UV spectrometer is long enough for the last of the drug to diffuse out of the sample. This confirms that the end of drug release is determined to within an accuracy of 1 day.

The self-diffusion of theophylline through a water/PGA matrix could behave according to the Stokes–Einstein relation [20], which relates the frictional coefficient of the movement of molecules through a liquid with the diffusion coefficient of the molecular transport. It is interesting to check whether, according to this model, the time taken for drug to diffuse from the

centre to the surface of the sample is less than one day. The form of the relation used here is given below.

$$D = \frac{kT}{T6\pi a\eta} \quad (5)$$

where D is the diffusion coefficient, k the Boltzmann constant, T the temperature, a the molecular radius, and η the viscosity.

The result, for theophylline taking a molecular radius of about 0.5 nm and approximating its viscosity to that of water, at 37 °C, is approximately $7.1 \times 10^{-10}\,m^2\,s^{-1}$. The self-diffusion coefficient of water at 37 °C is approximately $3.1 \times 10^{-9}\,m^2/s^{-1}$, indicating that theophylline is about 4.4 times slower than pure water [20]. Given this result, it is reasonable to assume that the self-diffusion coefficient of theophylline in the hydrated polymer matrix is therefore at least 4.4 times smaller than the coefficient value for water in PGA measured using MRI, which would give a maximum value for theophylline of $2.7 \times 10^{-11}\,m^2/s$. If this value is entered into Equation 4, it predicts that theophylline takes about 7 h for the drug to travel from the centre of a fully porous disk to the surface. This result gives more confidence that the end of drug release is determined to within an accuracy of 1 day.

The shape and linear movement of the water fronts in Fig. 5 demonstrates that Fickian diffusion is not obeyed when water penetrates the sample in stage III. Part I commented that the reaction-erosion model shares some similarities with Case II diffusion. However, further evidence indicated that the model is not an example of this type of diffusion. The kinetics might be determined by the effect of autocatalysis mentioned in the four-stage model. This process results from the build up of acidic oligomers in the sample centre, which catalyzes the ester-hydrolysis. Future work could use confocal microscopy to investigate the variation in internal pH for PGA samples, which would be affected by the presence of acidic oligomers, to obtain evidence for the autocatalytic effect. This technique has already successfully been used to measure internal pH for pharmaceutical formulations for aliphatic polyesters [21]. It would also be interesting to use computer modeling in the future to investigate the kinetic behaviour of the system, given that although the ester hydrolysis is heterogeneous, the front movement is linear.

Fig. 10 presents cumulative drug release data for 2.3 mm thick polyglycolide disks and shows that the release behaviour correlates with the movement of water fronts recorded by MRI. Initially, there is a lag of about 7 days, which according to the four-stage model, occurs because the polymer morphology still consists of densely packed chains which prevent any significant water ingress into and hence diffusion of drug out of the sample, despite chain scission and a lowering in molecular weight during stages I and II. At the start of stage III, drug release starts because the polymer has now obtained sufficient porosity to cause substantial water ingress to occur and allow the drug molecules to diffuse out of the system. During stage III, release occurs at a constant (approximately zero order) rate until it achieves 100% after about 40 days. It is over this time that MRI records water fronts progressing into the sample and meeting in the centre between 35 and 41 days, the same time period that, within experimental error, the drug release finishes. It appears that the drug release occurs as the reaction-erosion fronts penetrate the sample during stage III.

The correlation between the MRI data and drug release can be presented quantitatively by plotting the distance moved by the water fronts at different degradation times from the MRI data alongside the same result obtained from cumulative drug release data for different sample thicknesses presented in Part I. Fig. 11 shows clearly that both sets of data fall on the same straight line giving excellent correlation within experimental error. The linear variation shown in this figure is much more conclusive than the plot presented in Part I, using just drug release data. In the latter, the arrangement of data points suggested that the movement by the fronts might not be linear and could show other types of kinetics.

The x-intercept and gradient, obtained from the best fit line of the data determined from MRI and drug release, indicate that the reaction-erosion fronts begin at about 7 ($\pm$ 2) days, and move inwards from the surface to the centre of the sample at a rate of 0.033 ($\pm$ 0.002) mm/day. These values agree within experimental error with those determined using just the drug release data in Part I (7 days and 0.032 mm/day, respectively).

In other words, the correlation between the MRI data and the drug release data provides strong evidence in favour of the hypothesis that drug releases quickly from the regions behind the water fronts where significant hydration has left the polymer open and porous, and has consequently made diffusion of the drug out of the polymer much easier. The model offers information about how to alter the degradation rate of polyglycolide and hence tailor the drug release from the polymer. Using MRI and drug release data together provides a powerful, quantitative way of assessing the potential of polyglycolide for different controled drug delivery applications used currently and in the future. In addition, MRI could be used to perform *in situ* experiments on PGA, giving it potential to image water ingress into the polymer during *in vivo* tests. This means that a detailed assessment can now be performed easily on polyglycolide drug delivery implants, which improves the commercial potential of the polymer very significantly.

5. Conclusions

MRI was successfully used to monitor water ingress into polyglycolide disks during degradation, and provide strong, direct evidence to support the four-stage degradation model for polyglycolide. The results suggest that reaction-erosion fronts start at the sample surface at about 7 ($\pm$ 2) days, and advance inwards by 0.033 ($\pm$ 0.002) mm/day until they meet in the centre between 35 and 41 days. Water continues to ingress until it achieves a largely homogenous water distribution after about 75 days. The data also correlates drug release behaviour with degradation. It suggests, in agreement with previous work, that after an initial lag, drug releases during stage III as the reaction-erosion fronts move from the surface toward the centre of the polymer. The drug

molecules are thought to release from the regions behind the fronts where the polymer is highly open and porous, and release finishes when the fronts meet in the centre of the sample.

Acknowledgments

The authors are grateful to Pfizer Ltd. and the EPSRC for financial support, and to Dr Susan Hurrell for help and advice.

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Received 1 November 2001
and accepted 20 August 2002