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Effects of polymer degradation on drug release —a mechanistic study of morphology and transport properties in 50:50 poly(*dl*-lactide-co-glycolide)

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Abstract

50:50 Poly(*dl*-lactide-co-glycolide) (50:50 PLGA) was used to investigate the effects of polymer degradation on drug release from bulk degradable polymers. 5-Fluorouracil (5-FU) and Cyclosporin A (CyA) were used as model drugs. Using scanning electron microscopy, it was observed that initially non-porous 50:50 PLGA underwent significant morphological changes, becoming increasingly porous, as degradation proceeded. Concomitant increases in the transport parameters permeability and diffusivity of the model drugs through degrading 50:50 PLGA membranes were observed. Sharp transitions were observed in the relationship between the transport parameters and the residual polymer molecular weight and porosity —at values of molecular weight and porosity of about 5000–6000, and 70–80%, respectively. These transitions suggest that a shift in transport mechanism occurs with polymer degradation: the initial dominant transport pathway through degrading PLGA is the dense polymer phase, but as degradation progresses, the increase in porosity results in an increasingly connected pore structure such that, at some point in time, the pore network becomes the dominant pathway. By comparing experimentally measured 5-FU release profiles from PLGA matrices with release profiles calculated from experimentally measured permeability through degrading PLGA membranes containing no drug, it was shown that the shift in transport mechanism is the likely cause for the onset of the rapid final release stage of typical tri-modal release profiles from bulk-degradable polymer matrices.

Keywords: Degradable (erodible) polymers; Morphology; Transport mechanisms; Polylactide-co-glycolide (PLGA)

1. Introduction

Degradable polymers have been the focus of extensive research because of the potential for long-term unattended therapy and site-specific drug administration without the need for device retrieval (Pitt et al., 1979; Leong et al., 1985; Lewis, 1990; Maa and Heller, 1990). Among the degradable polymers currently under investigation, poly(lactide-co-glycolide) (PLGA) copolymers are the most widely studied because of their long history of safe clinical use as resorbable sutures (Laurencin and Elgendy, 1994; Lewis, 1990).

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Degradable polymers are commonly used in the form of matrices that contain dispersed drug particles. Drug release kinetics from such matrices typically exhibit tri-modal behavior (Sanders et al., 1982, Sanders et al., 1985; Beck and Tiu, 1983; Hutchinson and Furr, 1985; Juni and Nakano, 1986) starting with a high release rate stage attributed to the release of surface-connected drug particles, followed by a slow release stage attributed to molecular diffusion through the polymer phase, and a final rapid release stage attributed to dumping of residual drug during the later stage of degradation.

Drug release kinetics from bulk degradable polymer matrices are complex because matrix morphology and polymer properties change continuously during degradation (Nakamura et al., 1989; Li et al., 1990a,b; Shah et al., 1992), resulting in everchanging drug diffusivities and permeabilities. PLGAs have been shown to become porous upon degradation. Vert and colleagues (Li et al., 1990a,b) and Nakamura et al. (1989) showed that *l*-, *d*-, and *dl*-isomers of polylactic acid (PLA), PLGA with 10% or 25% glycolic acid (90:10 PLGA or 75:25 PLGA, respectively) became porous upon degradation. The interior regions of the polymers were observed to degrade faster than the surface regions, resulting in significant differences between bulk and surface morphologies. Recently, Shah et al. (1992) reported that 50:50 PLGA also became porous upon immersion in an aqueous medium; however, no differences were observed between bulk and surface morphologies.

The observation of pore formation during polymer degradation suggests that pores may represent an alternative transport pathway in addition to diffusion through the dense polymer phase, and may become the dominant drug release pathway as degradation progresses. The possible effects of degradation-induced morphology changes on drug release have not been addressed in previous experimental studies (Nakamura et al., 1989; Li et al., 1990a,b; Shah et al., 1992), and have not been considered in theoretical models of drug release from degrading polymers (Heller and Baker, 1980; Thombre and Himmelstein, 1985).

Only a small number of models have been proposed to explain drug release kinetics from bulk degradable polymers. Heller and Baker (1980) proposed a simple model based on Higuchi's diffusional release model (Higuchi, 1963) and incorporated the assumption that drug permeability was inversely proportional to the number of remaining bonds between repeat units of a bulk degrading polymer. Thombre and Himmelstein (1985) reported a model that allowed for the position-dependence of polymer hydrolysis, and hence the position-dependence of polymer properties. Diffusivity was assumed to increase exponentially with the extent of hydrolysis. Neither of these studies explicitly included the effect of polymer morphology; the assumptions that diffusivity or permeability depend on the extent of hydrolysis or the number of remaining repeat units imply that release occurred predominantly through the dense polymer phase rather than through pores. The effect of changing pore morphology on drug release was considered by Chang and Himmelstein (1990) in a dissolution-diffusion model that described release kinetics from non-swellable and non-degradable drug loaded matrices. Changes in polymer morphology due to the dissolution of solid drug particles were accounted for by assuming time- and position-dependent drug diffusivities that increased linearly with decreasing local drug concentration.

The observation that pores are formed during degradation suggests that morphology changes may play an important role in determining drug release kinetics from degradable polymers. The objectives of this study are to establish the dependence of transport properties on polymer degradation and degradation-induced morphology changes. Specifically, 50:50 PLGA was used as a model degradable polymer in this study.

2. Materials and methods

2.1. Materials

PLGA ($M_w = 24000$, inherent viscosity 0.54 dl/g in hexafluoro-2-propanol at 30°C) was obtained from Birmingham Polymers (Birmingham, AL).

HPLC grade solvents methanol (Mallinckrodt, Louisville, KY), acetonitrile (Fisher, Fair Lawn, NJ), water (Millipore, Bedford, MA), tetrahydrofuran (THF) and methylene chloride ($MeCl_2$) (Baker, Phillipsburg, NJ) were used without further purification. Super-refined grade olive oil was purchased from Croda Canada (Toronto, ON), and used as supplied. 5-Fluorouracil (5-FU) was purchased from Sigma Chemicals (St. Louis, MO), while Cyclosporin A (CyA) was kindly supplied by Sandoz Canada, Inc. (Montreal, Quebec).

2.2. Disc preparation

PLGA discs containing 5-FU were prepared by dispersing 5-FU particles at 9% (w/w) loading into a solution of 1.5 g PLGA in 15 ml $MeCl_2$. The dispersion was rotated overnight to ensure thorough mixing, then poured into cooled methanol at 0°C to precipitate the polymer and entrap the dispersed drug particles. The drug/polymer mixture was then placed in a freezer overnight, degassed in a vacuum oven at 90°C until a constant weight was reached, then melt-pressed to the desired thickness (0.3–0.5 mm). Discs containing no drug were made via the same procedure, omitting the steps involving drug particles.

2.3. In vitro polymer degradation and drug release

Polymer discs of 1 cm by 1 cm were placed individually in polyethylene test tubes containing 30 ml of 1 mM pH 7.4 phosphate buffer solution (PBS) at 37°C. In polymer degradation studies, polymer discs were retrieved at specified times, and dried in a desiccator until a constant weight was reached; water uptake and polymer molecular weight were determined gravimetrically and by size exclusion chromatography (SEC), respectively. In drug release studies, drug-containing PLGA discs were used, and the drug contents in PBS were assayed by HPLC.

2.4. Water content

Water uptake, defined as the water weight divided by the total wet weight of the polymer, was determined gravimetrically from the wet weight of polymer samples retrieved from PBS and the final constant weight after drying.

2.5. Molecular weight characterization by size exclusion chromatography (SEC)

PLGA molecular weights were determined by SEC using two Supelco Progel-TSK columns in series (exclusion limits between 4×10^5 and 1×10^3 Da of polystyrene) maintained at 30°C, and a differential refractive index detector (Shimadzu RID-6A). Universal calibration with polystyrene standards (MW ranging from 760 to 2.07×10^5) and the Mark-Houwink equation with constants $K = 1.07 \times 10^{-4}$, and $a = 0.761$ for PLGA in THF (Kenley et al., 1987) were used to calculate PLGA molecular weights. The Mark-Houwink constants for polystyrene in THF are: $K = 1.10 \times 10^{-4}$ and $a = 0.725$ (Brandrup and Immergut, 1989).

2.6. Scanning electron microscopy (SEM)

A Hitachi model S-520 scanning electron microscope (20 KV, 5000X) was used to examine degrading polymer discs. Samples were vacuum dried and sputter-coated with Au-Pd.

2.7. Permeation experiments

5-FU and CyA permeability and diffusivity through PLGA membranes that had been exposed to PBS for specified times were measured using standard side-by-side diffusion cells. Permeant concentrations in the receptor compartment were assayed by HPLC, and the time-lag method (Crank, 1975) was used to calculate drug permeability and diffusivity.

PBS was used as the donor and receptor medium for 5-FU permeation experiments, while olive oil was used for CyA experiments due to the extreme lipophilic nature of CyA. The reduction in PLGA molecular weight during permeation

experiments was less than 15% in all cases; the longest permeation experiments for 5-FU and CyA were 6 h and 72 h, respectively.

2.8. HPLC assays

5-FU was assayed by HPLC at room temperature using a Waters column (resolve C18, 5 μm particles, 100 × 8 mm^2 i.d.), 1 ml/min flow rate of 10 mM potassium phosphate buffer/2% methanol mobile phase, and a UV detector (Shimadzu SPD-M6A) set to 254 nm.

CyA was assayed by HPLC at 70°C using a Supelco LC-18 column (5 μm particles, 250 × 4.6 mm^2 i.d.), 1.5 ml/min flow rate of a 70% acetonitrile/30% water mixture mobile phase, and a UV detector (Shimadzu SPD-M6A) set to 204 nm.

3. Results

3.1. In vitro degradation kinetics of PLGA

The time-varying mass, weight-average and number-average molecular weights (M_w and M_n, respectively) of residual polymer in in vitro degradation experiments are shown in Fig. 1 as percentages of the respective original values. Decreases in M_w and M_n were seen immediately upon immersion in PBS while significant mass loss did not begin until 2 weeks later. This observation agrees with previous studies of PLGA degradation, and is consistent with the interpretation that PLGA is bulk-degradable (Wise et al., 1979; Reed and Gilding, 1981; Kenley et al., 1987; Lewis, 1990). M_w and M_n decay exponentially with time (Fig. 2), in agreement with first-order polymer hydrolysis. First-order rate constants of M_w and M_n decay were calculated and summarized in Table 1 along with previously reported in vitro and in vivo values. The rate constant of M_n decay from this study is within the range of literature in vitro values, while the rate constant of M_w decay is lower than literature values.

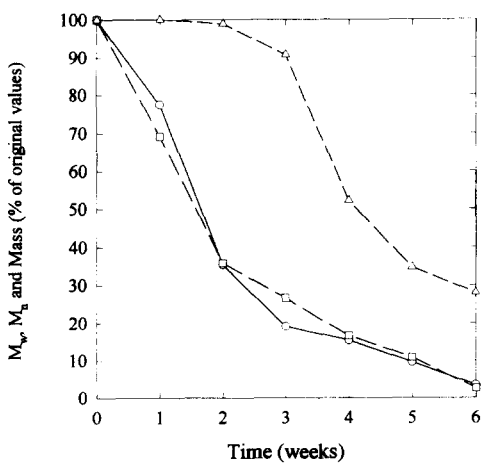

Fig. 1. In vitro degradation of 50:50 PLGA. ○, M_w; □, M_n; △, residual mass.

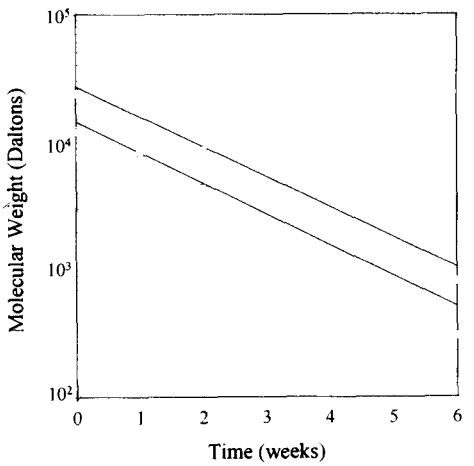

Fig. 2. In vitro degradation of 50:50 PLGA. ○, M_w; □, M_n.

Table 1
First order degradation rate constants (week^{-1})

	This study*	In-vivo[a,b,c]	In-vitro[a,b,c,d]
M_w	0.517 ± 0.136	0.53 – 0.737	0.582–0.729
M_n	0.541 ± 0.090	0.58 – 0.752	0.522–0.649

* ± represents 95% confidence level.
[a]Lewis, 1990.
[b]Kenley et al., 1987.
[c]Wise et al., 1979.
[d]Reed and Gilding, 1981.

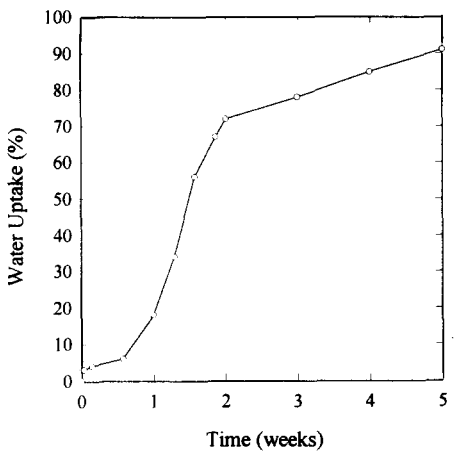

Fig. 3. Time profile of water uptake.

3.2. Water uptake into degrading PLGA discs

Fig. 3 shows that upon immersion in PBS, an initial period of slow water uptake lasting about 4 days was observed during which water content reached 6%. During this period, PLGA discs changed from clear to opaque, and no significant swelling was observed. During the period of Day 4 until about the end of Week 2, water content increased rapidly from 6% to 72%, PLGA discs swelled visibly, softened and became completely opaque. These observations suggest that the discs underwent significant structural changes during this period. Rate of water uptake slowed for the remainder of the experiment which terminated after 6 weeks.

3.3. Morphology of degrading PLGA

Fig. 4 (a and b) shows SEM photographs of PLGA before and after 4 days of PBS exposure, respectively. PLGA discs were sliced to expose the bulk structure. These figures show that PLGA was initially smooth and non-porous, and became porous after 4 days with pores approximately 2–6 μm in diameter. Fig. 4 (c and d) shows the surface and bulk morphologies, respectively, of PLGA after 2 weeks of PBS exposure. The figures show increases in pore volume fractions as well as pore diameters (6–40 μm) compared with earlier SEMs. At 3 weeks of degradation, Fig. 4(e) shows continued growth in pore size as well as pore volume fraction; this trend continues up through 5 weeks of PBS exposure. No differences were seen between surface and bulk morphologies at any of the time points examined. These observations are qualitatively similar to those of Shah et al. (1992) who reported porosities of 45% and 65% in 50:50 PLGA after 15 and 25 days of exposure to PBS, respectively. However, Shah et al. (1992) reported larger pores than those observed in this study —a difference that may be attributed to the different sources of 50:50 PLGA used in the two studies.

The observed pores can be attributed to either absorbed water, or to voids left behind by the release of polymer degradation products. Fig. 1 and Fig. 3 show that, at 2 weeks, the values of polymer mass loss and water uptake are 1.5% and 72%, respectively, suggesting that most of the pores seen in Fig. 4(b) through Fig. 4(d) should be attributed to absorbed water. It is therefore reasonable to approximately equate the volume fraction of absorbed water to the volume fraction of pores during the first 2 weeks of degradation, and conclude that the porosity increased to 72% during this time interval. Based on percolation theory (Broadbent and Hammersley, 1957), at 6% porosity (4 days), the pore space should be largely unconnected; permeation through pores should therefore be insignificant. At 2 weeks, however, the large volume fraction of pores, 72%, should result in a highly connected pore structure that represents a significant transport pathway. The SEM pictures therefore, suggest that a shift in transport mechanism may occur due to the changes in morphology as PLGA degrades.

3.4. Transport through degrading PLGA membranes

The permeability (P) and diffusivity (D) of 5-FU and CyA through degrading PLGA membranes, obtained from the time lag method as described in Section 2.7, are shown in Fig. 5(a) through Fig. 5(c) as a function of time, molecular weight of residual polymer, and porosity, respectively. P is defined as the diffusion coefficient

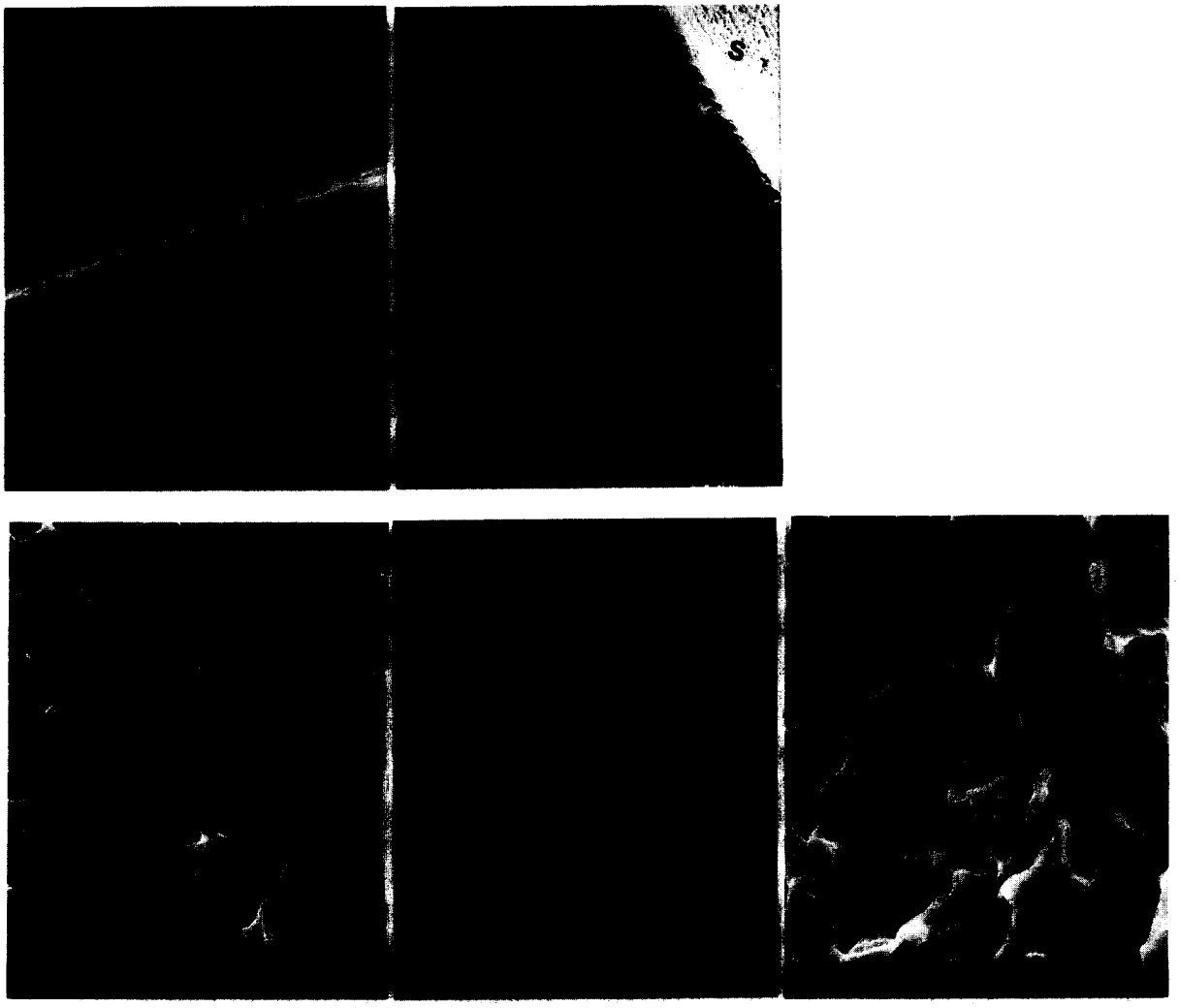

Fig. 4. SEM photographs of degrading 50:50 PLGA discs. (a) Freshly prepared PLGA; s, surface; b, bulk; (b) 4 days; (c) PLGA surface at 2 weeks; (d) PLGA bulk at 2 weeks; (e) 3 weeks.

times the partition coefficient of the solute between the membrane and the surrounding medium. The effect of degradation on P and D, are qualitatively similar, both P and D increase with degradation time, reduction in molecular weight, and increasing porosity. P and D show an exponential increase with time, in qualitative agreement with a previous model (Heller and Baker, 1980) based on the assumptions that permeability is inversely proportional to the number of remaining bonds in the polymer, and that polymer degradation follows first-order kinetics. However, this model should result in a slope of natural log P vs. time which is the same as the rate constant of polymer degradation, and independent of the permeating solute. The slopes of natural log P vs. time for CyA and 5-FU calculated from Fig. 5(a) are 1.11 $week^{-1}$ and 2.45 $week^{-1}$, respectively. That these slopes are different from each other, and neither corresponds to the first-order degradation rate constant of 0.54 $week^{-1}$ for M_n, suggests that degradation-induced changes in permeability are not simply correlated to bond breakage.

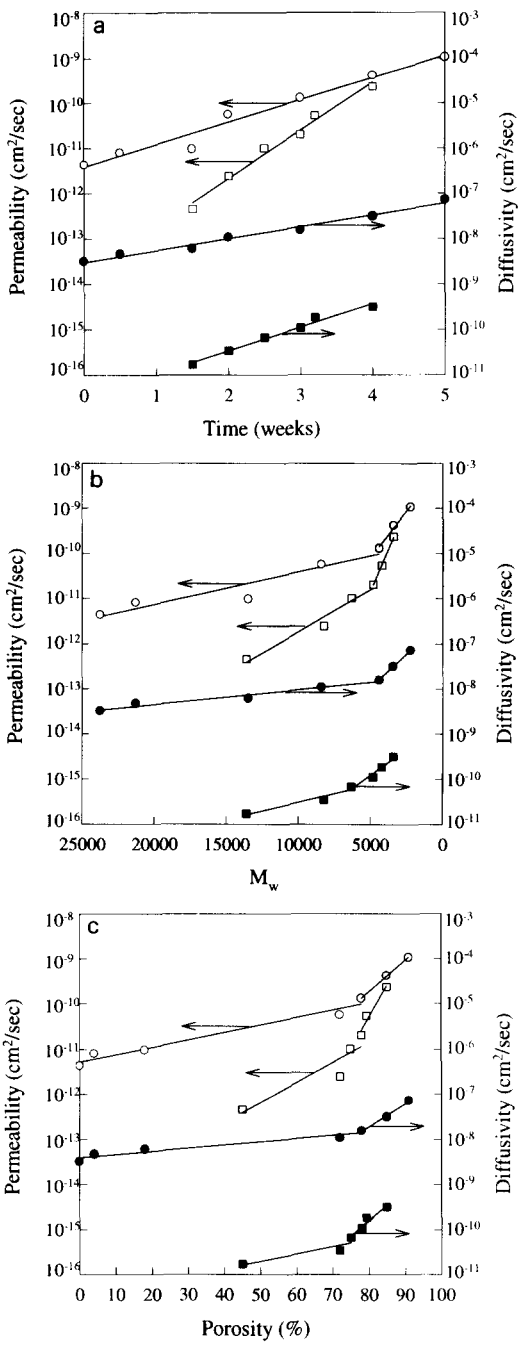

Fig. 5. (a) Permeability and diffusivity vs. time. ○, 5-FU permeability; □, CyA permeability; ●, 5-FU diffusivity; ■, CyA diffusivity. (b) Permeability and diffusivity vs. M_w. ○, 5-FU permeability; □, CyA permeability; ●, 5-FU diffusivity; ■, CyA diffusivity. (c) Permeability and diffusivity vs. porosity. ○, 5-FU permeability; □, CyA permeability; ●, 5-FU diffusivity; ■, CyA diffusivity.

Fig. 5(b) shows the correlation between P and D and vs. residual polymer M_w, further illustrating that P and D are not simply related to bond breakage. P and D of both permeants show a sharp transition at M_w of about 5000 to 6000, corresponding to 2 weeks of PBS exposure. Beyond the transition point, P and D increase much more rapidly with further decreases in M_w. A similar trend in the correlation between P and D vs. porosity is seen in Fig. 5(c). P and D increase with increasing porosity, with a sharp transition seen at a porosity of about 70–80%, corresponding to approximately 2 weeks of degradation, beyond which further increases in porosity produced more rapid increases in P and D.

These results are consistent with the hypothesis that a shift in transport mechanism occurs as polymer degradation progresses. Soon after PLGA is exposed to PBS, very few pores are present (Fig. 4 (a and b)), transport should occur primarily through the dense polymer phase. As polymer degradation proceeds, the size as well as the volume fraction of pores increase (Fig. 4, c through e), so that transport through pores should increase in importance. At some point during the degradation process, the pores may become the dominant transport pathway, resulting in a shift in transport mechanism. The observation that the transition occurs at approximately 2 weeks, M_w of about 5000–6000, and porosity of about 70–80%, corresponding to a point during degradation when rapid changes in morphology and water uptake was observed, adds further credence to the hypothesis.

When transport through the polymer phase is dominant (before the transition), P and D are expect to depend exponentially on M_w since polymer viscosity is exponentially dependent on M_w, and solute diffusivity is inversely proportional to the viscosity of the medium in which diffusion takes place. When pore transport is dominant (after the transition), transport properties should be dependent on porosity, and should be influenced by the extent of connectivity within the pore space. Percolation theory predicts that the effective transport properties should increase rapidly, and should be proportional to the porosity raised to a fixed power as porosity increases

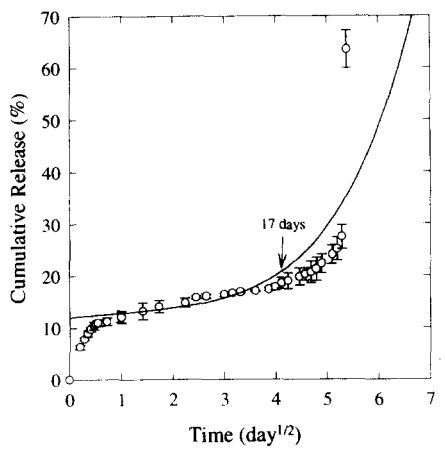

Fig. 6. Release of 5-FU from PLGA matrices. - - -, Higuchi model with time-varying permeability; ○, in vitro release rates, bars represent 95% confidence level ($n = 3$).

beyond the percolation threshold (Broadbent and Hammersley, 1957; Mohanty et al., 1982). Our results of P and D vs. porosity after the transition are consistent with this expected trend.

It should be noted that transport parameters should not be directly correlated to porosity before the transition when porosity is low, nor to M_w after the transition since the polymer phase would act only as a largely inert support for the pore structure when pore transport is dominant. The existence of a log-linear correlation between P and D vs. M_w after the transition, and vs. porosity before the transition (Fig. 5, b and c), can be explained by the fact that, as polymer degrades, M_w decreases and porosity increases, and an apparent, perhaps coincidental linear relationship exists between M_w and porosity.

3.5. Drug release kinetics

The release kinetics of 5-FU from PLGA matrices containing 9% (w/w) drug, well above 5-FU solubility in PLGA, are presented in Fig. 6. Trimodal release kinetics were observed. During the initial stage of approximately 1 day, release was rapid, and approximately 12% of the drug was released. Release during this stage is usually attributed to the dissolution and diffusional release of surface-connected drug particles. A period of slow release followed from approximately Day 2 to Day 17 during which release rate increased gradually. Release during this stage is typically attributed to drug permeation through the polymer phase; the observed gradual increase in release rate is consistent with the correlation between permeability and residual polymer molecular weight before the transition shown in Fig. 5(a). At approximately Day 17, the release rate accelerates dramatically, marking the transition to the final stage of release. The onset of the final release stage corresponds approximately to the point when a sharp transition in transport properties was observed in degrading PLGA membranes (Fig. 5, b and c), suggesting that pore transport is the dominant transport mechanism in the final stage of release.

Higuchi's well-known model for drug release from a dispersed matrix is based on the assumptions that at any instant in time, the matrix consists of two regions: a central core with uniform drug loading equalling the initial drug loading A, and a diffusional region of thickness α between the central core and the membrane surface that contains only dissolved drug. The diffusion front moves inwards with time so that α increases with time. At the diffusional front, the central core side contains drug loading A, while the drug concentration on the diffusional region side is the saturated concentration. It was further assumed that at all times, a steady-state concentration profile exists in the diffusional region such that

$$\frac{dQ_t}{dt} = \frac{DC_s}{\alpha} \tag{1}$$

where Q_t is the cumulative mass of drug released per unit release area at time t, and D and C_s are the drug diffusivity and solubility, respectively, in the matrix. A total mass balance further gives

$$Q_t = \left(A - \frac{C_s}{2}\right)\alpha \tag{2}$$

With drug permeability in the matrix P defined as the diffusion coefficient times the partition coefficient of the solute between the membrane and the surrounding medium, then DC_s can be equated to PC_w^* where C_w^* is the drug solubility in the release medium. Then assuming $A \gg C_s$ combining Eqs. (1) and (2), and allowing for the time-dependence of P gives:

$$\frac{Q(t)}{Q_\infty} = \frac{1}{L}\sqrt{\frac{2C_w^*}{A}\int_o^t P(t)\mathrm{d}t} \quad (3)$$

where L is the half-thickness of the matrix, and $Q_\infty = AL$ is the drug loading per unit release area. Using the experimentally observed $P(t)$ as shown in Fig. 5(a), which incorporates all the effects of changes in polymer molecular weight and matrix porosity, a release profile is calculated using Eq. (3) and shown in Fig. 6. Since the initial stage in which surface-connected drug particles are released cannot be predicted, the calculated release profile was shifted upwards by 12%, corresponding to the fraction of drug released during the initial stage. The actual release profiles showed a later onset of accelerated release than the calculated profiles. Two possible factors contribute to this discrepancy: the presence of drug particles in the release systems may contribute to an increased porosity relative to the membranes used for permeability and diffusivity measurements which contained no drug particles, and the presence of 5-FU drug particles may influence the polymer degradation kinetics. Nevertheless, a qualitative agreement was seen between the calculated and experimentally measured release profiles, supporting the hypothesis of a shift in transport mechanism from polymer to pore permeation, and suggesting that the shift in mechanism is responsible for the transition from Stage 2 to Stage 3 of the tri-modal release profile.

4. Conclusions

The morphology of 50:50 PLGA membranes was shown to undergo a significant change due to polymer degradation. Porosity increases upon polymer degradation, and was correlated to water uptake before significant polymer mass loss occurred, indicating that the pores were formed predominantly due to absorbed water rather than due to release of polymer degradation products. The morphological changes result in a shift in transport mechanism: diffusion in the polymer phase is the initial dominant mode of transport, and as porosity increases beyond a certain point, diffusion in the pore network becomes the dominant transport mechanism. Sharp transitions were observed in the relationships between permeability and diffusivity with respect to polymer molecular weight and porosity, corresponding to the shift in transport mechanism. It was also shown that the shift in transport mechanism is the likely factor for the onset of the rapid third stage of release in commonly observed tri-modal release profiles from bulk degrading polymers.

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