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Polyester-Based Microdisc Systems for Sustained Release of Neuroprotective Phosphine-Borane Complexes

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Abstract

Phosphine-borane complexes are recently developed redox-active drugs that are neuroprotective in models of optic nerve injury and radioprotective in endothelial cells. However, a single dose of these compounds is short-lived, necessitating development of sustained-release formulations of these novel molecules. We screened a library of biodegradable co- and non-block polyester polymer systems for release of incorporated phosphine-borane complexes to evaluate them as drug delivery systems for use in chronic disease. Bis(3-propionic acid methyl ester)phenylphosphine borane complex (PB1) was combined with biodegradable polymers based on poly(D,L-lactide) (PDLLA), poly(L-lactide) (PLLA), poly(caprolactone) (PCL), poly(lactide-co-glycidide) (PLGA), or poly(dioxanone-co-caprolactone) (PDOCL) to make polymer microdiscs, and release over time quantified. Of 22 polymer-PB1 formulations tested, 17 formed rigid polymers. Rates of release differed significantly based on the chemical structure of the polymer. PB1 released from PLGA microdiscs released most slowly, with the most linear release in polymers of 60:40 LA:GA, acid endcap, Mn 15,000–25,000 and 75:25 LA:GA, acid endcap, Mn 45,000–55,000. Biodegradable polymer systems can therefore be used to produce sustained-release formulations for redox-active phosphine-borane complexes, with PLGA-based systems most suitable for very slow release. Sustained release could enable translation to a clinical neuroprotective strategy for chronic diseases such as glaucoma.

Keywords

Phosphine-Borane; Sustained Release; Polymer; Polyester; Neuroprotection

Introduction

Reactive oxygen species (ROS) play a prominent role in cell death, both via activation of cell death pathways and oxidation of macromolecules (Simon et al. 2000). This is true for

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Disclosure Statement

The following are declared as possible conflicts of interest: LAL is a consultant on neuroprotection to Aerie, Inotek, Quark, and Regenera. He is an inventor on patents for phosphine-borane complexes that have been assigned to the Wisconsin Alumni Research Foundation. DAJ, CJL, and MEC declare no conflicts of interest.

retinal ganglion cells (RGCs), a central nervous system neuron which is irreversibly lost in optic neuropathies such as glaucoma. We have previously observed elevated levels of superoxide in RGCs following axonal injury (Kanamori, Catrinescu, Kanamori, et al. 2010, Kanamori, Catrinescu, Mohammed, et al. 2010, Lieven et al. 2006), and scavenging of superoxide is neuroprotective in models of optic nerve injury (Kanamori, Catrinescu, Kanamori, Mears, Beaubien and Levin 2010, Thaler et al. 2010). A potential target for superoxide is cysteine thiols. We discovered that a reducing environment improves RGC survival *in vitro* after axotomy (Geiger et al. 2002) and that the disulfide reducing agent tris(2-carboxyethyl)phosphine (TCEP) protected RGCs both *in vitro* (Geiger, Kortuem, Alexejun and Levin 2002) and *in vivo* when administered through an intravitreal injection (Almasieh et al. 2011, Swanson et al. 2005).

Based on these findings, we developed disulfide reducing agents based on TCEP, but designed to have improved drug-like properties (Niemuth et al. 2016, Schlieve et al. 2006). These phosphine-borane complexes, bis(3-propionic acid methyl ester) phenylphosphine-borane complex (PB1) and (3-propionic acid methyl ester) diphenylphosphine-borane complex (PB2), proved to be more effective RGC neuroprotectants *in vitro* compared to TCEP (Schlieve, Tam, Nilsson, Lieven, Raines and Levin 2006), presumably due to their increased membrane permeability and enhanced stability. Compared to TCEP, PB1 and PB2 were more effective than TCEP at preventing RGC death in primary culture, even when administered at concentrations 4–6 orders of magnitude lower. PB1 delivered intravitreally also conferred significant *in vivo* neuroprotection in two rat models of axonal injury – optic nerve transection and experimental glaucoma (Almasieh, Lieven, Levin and Di Polo 2011).

In prior studies, PB1 was delivered by multiple intravitreal injections over a short time course to protect RGCs during a rat model of glaucoma. From a clinical perspective, this approach is not feasible for the treatment of a chronic condition such as glaucoma, both in terms of demands on medical staffing and patient experience. Minimizing injection frequency would likely lead to higher adoption rates and adherence to therapy in patients with glaucoma. For example, glaucoma patients are willing to have subconjunctival injections every three months instead of receiving topical (eye drop) therapy (Chong et al. 2013).

The use of biodegradable polymers for sustained release of drugs is well-established. Early work using poly(dl-lactide-co-glycolide) demonstrated excellent physical characteristics and lack of toxicity (Visscher et al. 1985). Subsequent studies by several groups in *in vivo* models demonstrated that sustained release of drug had significant translational potential (Heya et al. 1994, Okada et al. 1994, Okada et al. 1988, Okada and Toguchi 1995, Redding et al. 1984).

Although sustained release using polyesters is well-established, phosphine-borane complexes are structurally different from all other pharmaceuticals. In development of drugs for long-term use, each compound has different physicochemical characteristics that affect their behavior with respect to various copolymers, particularly the kinetics of sustained release. Given that phosphine-borane complexes are novel chemical entities unlike all other drugs that have been used in sustained release formulations, we evaluated multiple different

polyester candidates in different classes. We produced 22 polymer-based sustained release formulations based on PB1 and poly(D,L-lactide) (PDLLA), poly(L-lactide) (PLLA), poly(caprolactone) (PCL), or poly(lactide-co-glycide) (PLGA), and screened them with respect to degradation and release kinetics suitable for the long-term release of PB1 into the vitreous following implantation. The molecular weights of our polymers ranged from 14 kDa to 85 kDa for PDLLA, 180 kDa to 500 kDa for PLLA, 55 kDa to 500 kDa for PCL, 10 kDa to 150 kDa for PLGA, and 75 kDa for PDOCL. These polymer and copolymer formulations were tested for their ability to form solid polymers and release rates determined in order to generate lead candidates for future clinical development.

Materials and Methods

Materials

PB1 (Figure 1) was synthesized according to previously published methods (Schlieve, Tam, Nilsson, Lieven, Raines and Levin 2006). It is an oil at room temperature, with a molecular mass of 296.1 g/mol. Dichloromethane (DCM; 99.8%, spectroscopy-grade) was obtained from Acros Organics (Geel, Belgium). Absolute ethanol was obtained from Decon Laboratories (King of Prussia, PA). Non-block polyester polymers based on PDLLA, PLLA, PCL, PLGA, and PDOCL (Figure 2) were from PolySciTech (West Lafayette, IN).

Generation of microdiscs

PB1 was added to glass vials under argon gas and weighed. Polymer was then added to achieve a drug loading content of 22%, based on the need to have as high a drug concentration as possible but at the same time maintain the mechanical properties and integrity of an implant that would be used clinically in the eye (Chou and Woodrow 2017). Dichloromethane was added in 70 μ l increments to dissolve the drug/polymer mixture. Solutions were also generated with each polymer in the absence of PB1.

Each solution was then drawn up into a syringe with a 25G needle and microdiscs made by expelling single drops onto a clean glass dish. Following a brief drying period, a second drop was added to each microdisc to increase thickness. The glass dishes were then covered loosely to prevent contamination and the microdiscs allowed to air dry at room temperature for 48 hours. Following drying, microdiscs were removed from the glass dish with a razor blade. Dimensions of each disc were approximately 4 mm in diameter and 1 mm thick, with a total volume of 12.6 mm³ and mass of 15 mg.

In vitro release of PB1 from microdiscs

15 mg PB1-polymer microdiscs (containing 3.3 mg PB1) were incubated with 1.2 mL phosphate-buffered saline (PBS; pH 7.2) in glass vials, a ratio of 1:80 (*mass/volume*), to simulate injection into the vitreous. Samples were continuously rotated at 18 rpm on a rotary mixer (Invitrogen, Carlsbad, CA) at room temperature. PBS samples containing the various microdisc formulations were sampled by withdrawal of 17% of the original volume, at 1 and 6 hrs, and 1, 2, 6, 10, 13, 22, 30, and 56 days. The withdrawn volume was immediately replaced with fresh PBS.

Measurement of release

Removed PBS samples were dried in a vacuum concentrator (SpeedVac; Savant, Farmingdale, NY) at a low heat setting. Dried samples were reconstituted in absolute ethanol at one-tenth of the original volume for spectrophotometric analysis and quantitation at 4 different wavelengths (206, 216, 230, and 265 nm). The wavelengths used for quantitation for each polymer system were based on analysis of each polymer in the absence of PB1 and selection of wavelengths without interference from polymer. The wavelength (206 nm) corresponding to the combination of high absorbance and low coefficient of variation was used for subsequent calculation of release kinetics. Samples were compared to a standard curve prepared in the same manner (diluted in PBS, vacuum dried, and resuspended in one-tenth volume). All samples and standards were read in triplicate on a NanoDrop spectrometer (Thermo Scientific, Pittsburgh, PA). The total fraction of released PB1 was determined from known volumes and calculated concentrations, and considered the amount withdrawn and replaced by PBS at each measurement. Calculated concentrations above the aqueous solubility limit of PB1 (~230 μ M) were not used because of concerns about variability from insoluble PB1. PDLLA polymers 001 and 002; PLGA polymers AP006, AP007 and AP008; PCL polymers AP010 and AP011; and PLLA polymers AP021, AP024, AP030 appeared to reach these solubility limits.

Calculation of release kinetics

Release curves showing concentration in solution are useful for determining if clinical levels can be achieved and if drug levels are approaching solubility limits, which could indicate rapid and uncontrolled “dumping” of the drug by the microdisc. However, they do not consider the 17% dilution which occurs at each sampling point, which confound quantification of release rates. To take these factors into account, cumulative drug release was calculated from the change in concentration from the post-dilution concentration at the time of previous sampling and plotted as a fraction of total PB1 present in the initial microdiscs (Figures 3–5). Plots were terminated when the concentration exceeds 200 μ M, as release rates beyond that point may be affected by saturation.

Eight of the studied formulations achieved relatively linear release rates after initial solubilization of external PB1. The rate of PB1 release from 13 days through 8 weeks was calculated from a linear fit, with the rate calculated in terms of percent of loaded PB1 released per day (Table 2).

DDSolver (Zhang et al. 2010) was used to apply several models for release kinetics by dissociation, including various orders, zero order, first order, Higuchi, Korsmeyer-Peppas (Akash et al. 2012). Comparison of goodness of fit was based on the Akaike information criterion (AIC) (Akaike 1974), with lower values representing better fit. Nature of diffusion was evaluated using the value of “n” derived by the Korsmeyer-Peppas model. A value of $n = 0.45$ indicates Fickian diffusion for a cylinder, or case I, while $0.89 > n > 0.45$ is non-Fickian. Non-Fickian release suggests that drug is released through both erosion and diffusion of the polymer (Peppas 1985). Values of n lower than 0.43 are seen with dispersed particles (Ritger and Peppas 1987).

In the human eye, 110 nanograms per day would need to be released assuming a desired concentration of 100 nM, a molecular weight of 296 g/mol, an estimated half-life of 4 hours (Palakurthi et al. 2010, Pang et al. 1992), and a vitreous volume of 3.8 mL, based on exponential decay:

$$100 \text{ nM in } 3.8 \text{ mL} = 112 \text{ nanograms}$$

Using the equation for exponential decay,

$$N(t) = N_0(1/2)^{t/h}$$

$$N(t) = 112 * (1/2)^{24/4}$$

$$N(t) = 2 \text{ nanograms left after 24 hours}$$

Results

PB1 incorporates into polymer microdiscs

A library of PB1-containing polymer microdiscs were generated using commercially available polymers (Figure 2) with a goal of generating a solid, degradable implant. Of the 22 tested polymers (Figure 2), 17 formed rigid polymer microdiscs. The 10–15 kDa poly(lactide-co-glycolide) (AP023) and 4 of the caprolactone-containing copolymers (AP013, AP014, AP032, and AP034) failed to form rigid polymers and were not studied further.

Polymer microdiscs release PB1 during degradation

In prior *in vivo* work (Almasieh, Lieven, Levin and Di Polo 2011), PB1 has been effective at preventing the superoxide-mediated apoptosis of RGCs in a rat model of glaucoma with a single intravitreal dose of 10 μM , though the protective effect does not extend more than a few weeks after administration. In short term *in vitro* studies, PB1 confers protection to cultured RGCs at nanomolar levels or below (Schlieve, Tam, Nilsson, Lieven, Raines and Levin 2006). We therefore screened our library of polymer discs for release of low levels of PB1. PB1-containing microdiscs were placed in PBS at a ratio of 1:80 (*m/vol*) and rotated continuously at room temperature to simulate presence in the vitreous of a moving eye. Samples drawn off at various time points were used to establish the PB1 concentrations in solution and release rates via degradation.

Poly(D,L-lactide)-based microdiscs (PDLLA; AP001-AP004) released at a moderate rate, reaching 40–90 μM within the first 24 hours. Release from three of these polymers (AP001, AP003 and AP004) reached levels greater than 150 μM within 6 days and 200 μM at 22 days. Microdiscs of polymer AP002 released at a lower rate, and levels did not reach 150 μM until 13 days (Figure 4). PB1 release continued for 8-weeks, with levels eventually approaching the aqueous solubility limit of PB1 (~230 μM) in PDLLA polymers 001 and 002; PLGA polymers AP006, AP007 and AP008; PCL polymers AP010 and AP011; and PLLA polymers AP021, AP024, AP030. Most of these polymers also exhibited a

Korsmeyer-Peppas n value lower than 0.43 (Table 1). Values of n lower than 0.43 are seen with dispersed particles, which could explain the sharp rise in PB1 concentration over time (Ritger and Peppas 1987).

Of the tested polymer formations, five reached concentrations greater than 150 μM within 24 hrs: polymers based on poly-L-lactide (PLLA; AP006–008) and those based on poly(ϵ -caprolactone) (PCL; AP010–011) (Figure 5). While an initial spike in concentration is expected as PB1 is released from the microdisc surface (Lee et al. 2010), levels of PB1 quickly approached the aqueous solubility limits of PB1. In the eye, regular turnover of the vitreous fluid would prevent saturation and release may proceed at a greater rate, so observed release rates following initial solubilization and diffusion may not reflect *in vivo* release.

Of the polymer compositions tested, poly(lactide-co-glycolide acid)-based polymers (PLGA) had the most variation in release patterns with respect to polymer molecular weight (M_n) and composition. Of the two polymers with a 60:40 ratio of lactide to glycolide (L:G), the species with the higher M_n (AP017: 75–85 kDa) released PB1 with a curve very similar to polymer AP002 (PDLLA, 25–35 kDa). The species with lower M_n (AP016: 15–25 kDa) exhibited dramatically slower release. Initial concentrations were approximately 50 μM after 6 days, and remained at those levels for three additional weeks. Levels approached 100 μM when sampled at 8 weeks (Figure 6A). Microdiscs of polymer AP018 (PLGA; 75:25 LA:GA, 45–55 kDa) released with kinetics very similar to polymer AP016, with a peak concentration of 76 μM after 8 weeks in solution.

PLGA formulations with an 85:15 lactide-glycolide ratio (AP020, AP021, AP024, AP030, and AP031) showed different release characteristics compared to the PLGA polymers with different ratios (Figure 6B). Microdiscs of polymers AP021, AP024, and AP030 approached solubility limits within 1–3 weeks, followed by slow release and an eventual decline in observed concentrations. Release from microdiscs of polymers AP020 and AP031 were similar to polymer AP002, reaching 150 μM at 2–3 weeks (Figure 6B).

Release kinetics

Release curves showing concentration in solution are useful for determining whether clinically-relevant levels could be achieved and if drug levels approach solubility limits, which could indicate rapid and uncontrolled release of the drug by the microdisc.

Release kinetics were studied using four release models with DDSolver, zero order, first order, Higuchi, and Korsmeyer-Peppas. Results are presented in Table 1. The Akaike information criterion overall goodness of fit indicator demonstrated that AP016 and AP018 fit all models better than any of the other molecules.

Of the formulations tested, AP016 and AP018 achieved relatively linear release rates after initial solubilization and diffusion of PB1. Both had negative AIC values for the zero-order model, indicating linear release. The rate of PB1 release from 13 days through 8 weeks is calculated from a linear fit, in terms of percent of loaded PB1 released per day (Table 1).

Discussion

The phosphine-borane complex PB1 is a novel redox-active molecule that is neuroprotective (Schlieve, Tam, Nilsson, Lieven, Raines and Levin 2006, Seidler et al. 2010) and radioprotective (Crowe et al. 2015). PB1 has clinical relevance because it is able to protect retinal ganglion cells in a rodent model of glaucoma (Almasieh, Lieven, Almasieh, Lieven, Levin and Di Polo 2011). However, the effects of a single administration are not maintained over a long period of time, necessitating frequent intravitreal injection for drug delivery. The latter is not feasible for translation to clinical practice.

The use of polyesters for sustained release is well-established, but the determination of an optimal sustained release formulation for the novel chemical entity, PB1, a new class of neuroprotective drugs that are structurally unlike other pharmaceuticals, is not. We therefore generated a library of rigid biodegradable polymer formulations incorporating PB1 with the goal of sustained release of sufficient drug to be neuroprotective in the vitreous. Of the 22 candidate polymers, 17 formed rigid discs which were then tested for degradation and release of PB1 in PBS. The library displayed a wide range of release rates, with some saturating the solution with PB1 within hours while others releasing less than 2% of the incorporated PB1 over the course of 8 weeks. Interestingly, release from PLGA 60:40 with a low Mn was much slower compared to that from PLGA 60:40 with a higher Mn, contrary to what is usually observed with PLGA-based implants. This could be due to the nature of interactions with phosphine-borane complexes.

The candidate polymer systems screened here achieved linear release rates, as low as 0.01% of theoretical drug load per day. Others released far more quickly, with the maximum aqueous solubility of PB1 preventing release calculations beyond that point. Predicting vitreous levels of a drug from “tube-based” release studies is challenging. The vitreous is not a static fluid, and drugs delivered there are cleared across the retina via choroid or through the aqueous humor via Schlemm’s canal or the uveoscleral outflow pathway. For these reasons, small drug molecules often have half-lives in the vitreous of several hours (Palakurthi, Krishnamoorthy, Augsburger, Correa and Banerjee 2010, Pang, Branchflower, Chang, Peyman, Blatt and Minatoya 1992), implying that achieving a steady state concentration of 100 nM in a human eye would require release of 112 ng of PB1 each day, based on a vitreous half-life of 4 hrs. Based on these absolute release rates, and the drug loading content used in these studies, we can calculate the amount of a polymer implant needed to deliver a steady-state dose of 100 nM PB1 (Table 2). The smallest of these (AP002) would weigh 4.4 mg including polymer, which is approximately 0.12% of the human vitreous volume (3.8 ml), and would be acceptable for translation to clinical use assuming similar kinetics in the human.

It is also possible that a chronic dose lower than 100 nM would be effective for ganglion cell neuroprotection. PB1 was highly effective against acute axotomy in short-term primary RGC cultures at concentrations down to 1 nM, so it is possible that with continuous dosing the required drug levels, and consequent implant size, could be significantly scaled back. Full release of the drug reservoir at the calculated rate for AP002:PB1 copolymer would be 370 to 1370 weeks, or 7 to 26 years. While such long windows for treatment are attractive,

studies will be needed to test the linearity of the release rate, polymer toxicity, and the chemical stability of the drug within the polymer complex in vitreous fluid over long periods of time, all features relevant to the design of intravitreal implants (Kuno and Fujii 2010). Although our own data demonstrates excellent stability of PB1, even at elevated temperatures (Niemuth, Thompson, Crowe, Lieven and Levin 2016), there is no benefit to a formulation which remains intact for years if the drug it delivers has degraded.

Future studies could attempt to imitate physiological conditions to address the issue of PB1's limited solubility. Once optimal release dynamics are determined *in vitro*, the next step is *in vivo* animal models. If higher steady-state intravitreal concentrations (e.g. 1 μ M) are necessary for RGC neuroprotection, it is possible that one of the other candidates with higher release rates may be acceptable *in vivo*. While those polymers released PB1 too quickly for meaningful analysis in our experimental paradigm, the rate may be appropriate for delivery over a moderately-extended duration. For example, polymers AP021, AP024, and AP030 reached 2.5% cumulative release prior to saturation in roughly 5, 7 and 15 days respectively. If these initial release rates continued, the polymers would release for roughly 20, 30, and 60 weeks respectively, which may be acceptable timelines for administration of an intravitreal implant.

Conclusions

Phosphine-borane complexes are novel cytoprotective chemical entities that have neuroprotective effects *in vitro* and *in vivo*, but for which translation to chronic disease is limited by their duration of availability. The development of a PLGA-based sustained release formulation could be applicable for chronic disorders such as glaucoma or dry macular degeneration, with dosing intervals theoretically ranging from every 4 months to potentially every year or more.

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Predicted size of human vitreous implant based on the following assumptions:

- Release rates calculated from release data over weeks 2–8
- Volume of human vitreous fluid: 3.8 cm³
- Target intravitreal concentration: 100 nM (112 ng)
- t_{1/2} of PB1 in vitreous: 4 hrs
- Drug loading content: 22% of total microdisc mass

Figure 1.
Structure of bis(3-propionic acid methyl ester)phenylphosphine borane complex (PB1).

A. Poly(D,L-lactide) (PDLLA)

Polymer	Ratio (A:B)	M _n (approximate)	Endcap	PDI	M _w (approximate)	Tg (°C)
AP001	—	10-15 kDa	ester	2.46	35 kDa	45.28
AP002	—	25-35 kDa	ester	2.32	80 kDa	N/A*
AP003	—	45-55 kDa	ester	2.83	145 kDa	38.04
AP004	—	65-75 kDa	ester	1.95	140 kDa	48.17

B. Poly(L-lactide) (PLLA)

Polymer	Ratio (A:B)	M _n (approximate)	Endcap	PDI	M _w (approximate)	Tg (°C)
AP006	—	100-125 kDa	acid	1.58	180 kDa	27.59
AP007	—	125-150 kDa	acid	1.69	210 kDa	34.63
AP008	—	400-500 kDa	acid	1.46	590 kDa	35.90

C. Poly(caprolactone) (PCL)

Polymer	Ratio (A:B)	M _n (approximate)	Endcap	PDI	M _w (approximate)	Tg (°C)
AP010	—	500+ kDa	acid	1.12	630 kDa	42.05
AP011	—	65-75 kDa	acid	2.25	165 kDa	55.72

D. Poly((D,L)Lactic-co-caprolactone) (PLCL)

Polymer	Ratio (A:B)	M _n (approximate)	Endcap	PDI	M _w (approximate)	Tg (°C)
AP013*	80:20	100-200 kDa	acid	1.44	145 kDa	N/A*
AP014*	30:70	35-45 kDa	acid	1.87	85 kDa	29.10

E. Poly(lactide-co-glycolide) (PLGA)

Polymer	Ratio (A:B)	M _n (approximate)	Endcap	PDI	M _w (approximate)	T _g (°C)
AP016	60:40	15-25 kDa	acid	2.01	32 kDa	40.60
AP017	60:40	75-85 kDa	acid	1.35	105 kDa	51.80
AP018	75:25	45-55 kDa	acid	1.61	75 kDa	41.02
AP020	85:15	100-200 kDa	acid	1.05	165 kDa	64.25
AP021	85:15	35-45 kDa	acid	2.83	100 kDa	N/A*
AP023*	50:50	10-15 kDa	ester	1.88	22 kDa	31.65
AP024	85:15	35-45 kDa	ester	1.66	65 kDa	40.88
AP030	85:15	10-15 kDa	ester	1.91	30 kDa	40.05
AP031	85:15	25-35 kDa	ester	1.35	45 kDa	47.75

F. Poly(dioxanone-co-caprolactone) (PDOCL)

Polymer	Ratio (A:B)	M _n (approximate)	Endcap	PDI	M _w (approximate)	T _g (°C)
AP032*	50:50	50 kDa	ester	1.80	90 kDa	33.72

G. Poly(D,L-lactide-co-caprolactone) (PDLLCL)

Polymer	Ratio (A:B)	M _n (approximate)	Endcap	PDI	M _w (approximate)	T _g (°C)
AP034*	1:99	60 kDa	ester	1.53	90 kDa	57.39

Figure 2.

Structures of polymers in the study. An asterisk indicates that the copolymer did not form solid disc and was not studied further. N/A indicates transitions >100°C that were sharp peaks and typically indicate a melting endotherm rather than glass transition.

Figure 3. PB1 release from PDLLA polymer microdiscs. PDLLA-based microdiscs release PB1 into solution at a moderate rate, with concentrations approaching solubility limits after 3–8 weeks.

Figure 4. PB1 release from PLLA and PCL polymer microdiscs. (A) PLLA-based microdiscs (AP006–008) quickly release PB1 to levels close to the aqueous solubility limit. (B) PCL-based microdiscs (AP010–011) released high levels of PB1 within a few hours. Note the different scale on the x-axis compared to Figures 3 and 5.

Figure 5.

PB1 release from PLGA polymer microdiscs. Release from PLGA-based microdiscs varied based on polymer composition. (A) PLGA with a 60:40 (AP016–017) or 75:25 (AP018) ratio of lactide:glycolide monomer units released PB1 at low rates. (B) PLGA with a 85:15 (AP020, AP021, AP024, AP030, AP031) ratio of lactide:glycolide monomer units release at varying rates which do not correlate with polymer mass (M_n).

Table 1.

Akaike information criterion for each polymer. More negative numbers indicate a better fit. The two best-fitting values are in bold italics. PLGA-based polymers AP016 and AP018 fit most models the best and display the most linear release.

Polymer	Type	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	Korsmeyer-Peppas n
AP001	PDLLA	15.4776	15.1446	-22.3719	-23.2847	0.472
AP002	PDLLA	18.9385	18.5832	-15.6014	-15.1969	0.470
AP003	PDLLA	15.6014	15.2721	-13.7175	-12.3255	0.481
AP004	PDLLA	15.9446	15.6584	-11.5918	-11.9004	0.455
AP006	PLLA	37.9203	37.7285	24.8723	2.6098	0.217
AP007	PLLA	17.8572	17.7275	4.8090	-4.4857	0.327
AP008	PLLA	23.6735	23.5848	15.3898	-3.6589	0.204
AP010	PCL	38.1583	38.0007	28.5280	13.8379	0.149
AP011	PCL	29.2857	29.1909	23.3400	14.2731	0.127
AP016	PLGA	-3.6232	-3.7338	-29.9768	-28.9897	0.465
AP017	PLGA	21.5132	21.2116	-7.4766	-12.2678	0.422
AP018	PLGA	-0.3253	-0.4280	-29.6094	-42.1680	0.399
AP020	PLGA	16.6253	16.3323	-12.1391	-11.7238	0.460
AP021	PLGA	38.6334	38.4207	25.4809	14.6281	0.249
AP024	PLGA	35.1851	34.9348	20.3413	14.5457	0.308
AP030	PLGA	23.1305	22.7946	4.8717	6.4104	0.464
AP031	PLGA	17.2773	16.9628	-20.9169	-24.1340	0.455

Table 2.

Release rates of polymer microdiscs in the linear phase of degradation and predicted size of clinical release system

Polymer number	Polymer formula	Fraction of Drug Released Over 8 Weeks	Linear release rate (% of drug load/day)	Size of human implant (mg)
AP002	25–35 kDa PDLLA ester	3.8%	0.037	4.4
AP004	65–75 kDa PDLLA ester	4.2%	0.034	4.7
AP006	100–125 kDa PLLA acid	3.8%	0.010	16.2
AP016	15–25 kDa 60:40 PLGA acid	32.8%	0.180	9.0
AP017	75–85 kDa 60:40 PLGA acid	3.6%	0.030	5.4
AP018	45–55 kDa 75:25 PLGA acid	1.3%	0.013	12.6
AP020	100–200 kDa 85:15 PLGA acid	3.1%	0.026	6.3
AP031	25–35 kDa 85:15 PLGA ester	3.5%	0.036	6.0