Exploring the design and function of poly(lactic-co-glycolic) acid microspheres *in silico* and *in vitro*

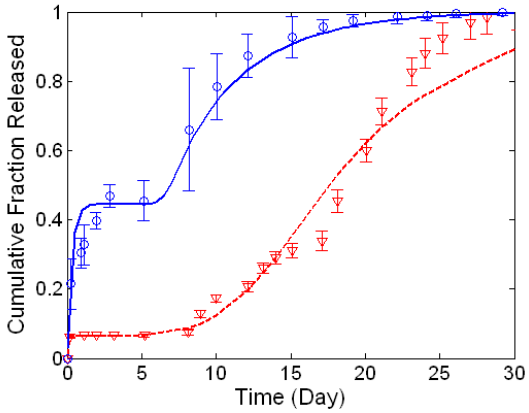
Sam N. Rothstein, Steven R. Little.
McGowan Institute of Regenerative Medicine, Department of Chemical Engineering, University of Pittsburgh

Statement of Purpose: Clear increases in efficacy would be apparent in 47 of the top 50 best selling drugs if they could be formulated into controlled release therapeutics that could prolong dosing in a rational manner (1). Yet, developing such a specific controlled release formulation traditionally requires months of tedious *in vitro* experiments to target the desired drug release profile. A new predictive model has been developed with the specific aim of enabling the rational design of controlled release vehicles.(2) Using this model, microparticle formulation parameters were computed for two different release schedules: 1) two precisely timed bursts (prime and boost), spaced one week apart, which could serve as a single injection vaccine platform, or 2) constant release for one month, which could serve as a sustained release medication by replacing tedious regular dosing schedules.

Methods: The desired dosing profile was translated into formulation parameters using our mathematical model. Specifically, the model computes the diffusive egress of encapsulated drug through pores that form during the degradation of the polymer matrix. The parameters defining these phenomena (average particle radius (R_p), radius of drug filled occlusions (R_{occ}), polydispersity index (PDI) and polymer initial molecular weight (Mw_o)) were optimized based on a minimized sum-squared error with the desired release profile. For each prediction, the system defined by these parameters was compared to those used to validate our original model. If the new system mandated dramatic extrapolation, median specifications were implemented to allow for additional confirmation of the model's predictive capabilities.

Standard single, or double, emulsion fabrication methods were used to processes the model-specified polymer(s) into peptide or protein-loaded microparticles that meet the set size requirements. Actual values for the formulation parameters were confirmed with common analytical techniques including size exclusion chromatography, confocal microscopy and scanning electron microscopy. Acceptable precision was defined based upon case-wise perturbation analysis. Having confirmed that the microparticle formulation conforms to the calculated specifications, its *in vitro* release behavior was determined using standard methods over a period of 1 to 2 months. The loading-normalized data from these release assays was compared to the model prediction based on relative sum of squared errors.

Results/Discussion: When using our model to design the prime-boost or constant release microparticles, unique design parameters were calculated for each formulation. For the prime-boost formulation, a particularly low Mw_o 50:50 PLGA was specified to set the duration of the lag phase at precisely one week. For the constant release system, an unprecedentedly high polydispersity (much higher than is found in most commercially available biodegradable polymers) was calculated. In fact, at least 6 commercially available polymers would need to be blended together to match this polydispersity with a r^2 of 0.968. To limit extrapolation, this PDI was approximated with just four polymers ($r^2 = 0.965$), which still maintains a broader initial molecular weight distribution (to the best of our knowledge) than any previously explored. Analyzing release data from this four polymer system with our model will help confirm the accuracy of predictions for more complex blends, which are under investigation for sustained linear release.



Experimental data and model predictions (*triangles*, *dashed line* respectively) for drug release from the four-polymer blend are shown in the figure above. Equivalent data for the prime-boost formulation appears as well (*circles*, *solid line*). As expected, the broader Mw_o distribution in the 4-polymer blend prolonged release more effectively than the formulation designed for priming and boosting. Ultimately, *in vitro* and *in silico* data sets follow similar trends, thus demonstrating how our model is useful as a rational design tool for targeting precise and novel release schedules with common, commercially available 50:50 PLGA copolymers.

Conclusions: A new predictive model efficiently targets design specifications for the controlled release formulations required to meet set dosing schedules. Such formulations have been designed, fabricated and tested for simple vehicles that provide precisely timed bursts and more complex polymer blends that may, with further modification, sustain linear release. These vehicles, designed to provide preset release profiles, suggest that PLGA might be a more viable option for replicating regular dosing schedules than novel, unapproved or less biocompatible polymers designed specifically for such behavior.

References

1. Humphreys, A. M. MedAdNews, 2007.
2. Rothstein, S.N. *J mat chem.* 2008; 18**:** 1873-1880.