In vitro enzymatic degradation of PLGA microparticles

USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences

Dalila Miele, Jennica Zaro
dmiele@usc.edu
[1] USC Mann School of Pharmacy and Pharmaceutical Sciences, Zaro Lab – PSC 404B, 1985 Zonal Ave, 90089, Los Angeles, CA, USA

INTRODUCTION

Poly(lactic-co-glycolic acid) (PLGA) is a leading synthetic polymer employed in the development of drug delivery platforms due to its favorable properties. While PLGA is frequently employed in the preparation of microparticles (MPs), its degradation profile and matrix lifetime in biological tissues are often underexplored despite their critical importance for applications involving repeated administration [1]. In an aqueous environment, the abiotic degradation of a solid PLGA matrix occurs primarily through bulk erosion. This process involves the hydration of amorphous regions of the polymer, leading to passive hydrolysis of ester bonds. As a result, substantial mass loss occurs alongside the solubilization of oligomers. Moreover, studies indicate that the final 10% of the polymer mass can persist in tissue for extended periods, highlighting the need to understand the full degradation timeline [2-3] (Scheme 1). Enzymatic degradation adds another layer of complexity, driven by depolymerizing enzymes such as proteases, lipases, and esterases that are secreted by cells [4]. The concentration of these enzymes varies by organ and tissue, which can affect both the degradation rate and mechanisms of the PLGA matrix depending on its location within the body. The extent of the enzymatic activity is essential for the breakdown of PLGA, making it a valuable mechanism for controlled degradation in therapeutic applications (Scheme 2.). A thorough understanding of both abiotic and enzymatic degradation pathways is crucial for optimizing PLGA-based MPs and improving their safety and efficacy in drug delivery.

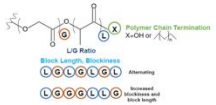
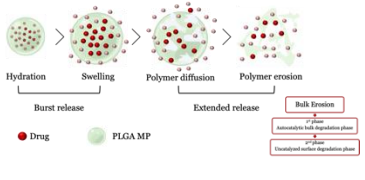
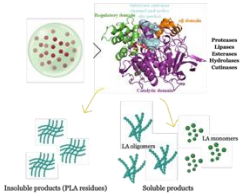


Figure 1. PLGA structure – hydrophobic polyester allows for a tunable degradation rate, which is influenced by factors such as molecular weight, end groups, and segment ratios within the polymer matrix.

OBJECTIVES



Scheme 1. Abiotic degradation mechanism of PLGA MPs.

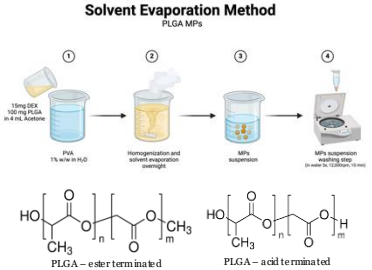


Scheme 2. Enzymatic activity on PLGA MPs.

This study aims to investigate the *in vitro* degradation mechanism of PLGA MPs mediated by enzymes typically present within the vitreous humor.

MATERIALS AND METHODS

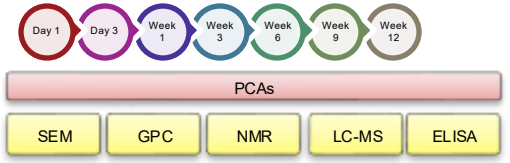
This study investigates the *in vitro* enzymatic degradation of PLGA MPs in a simulated biological environment. PLGA MPs with varying end-group chemistries (acid or ester terminated) were fabricated using PLGA an oil-in-water (o/w) emulsion/solvent evaporation technique [5], encapsulating a model drug. The degradation profiles were monitored in artificial vitreous humor at physiological conditions (pH 7.4, 35°C), focusing on bulk hydrolysis and enzymatic activity from hydrolases, esterases, and proteases. The experimental design and the physicochemical analyses (PCAs) in progress for this study are summarized below.



Working parameters
- **PBS pH 7.4**;
- *Volume*: **1 mL**
- *Temperature:* **35 °C**
- Replicates: 3

Enzymes
- Carboxylesterases (CES1 and CES2)
- Paraoxonases (PON 1)
- Lysosomal glycoside hydrolase (HEXA)
- Combination of the 4 Enzymes

Timepoints - Polymer degradation kinetic



In an abiotic environment, PLGA microparticles exhibited a degradation profile primarily governed by bulk erosion, with significant mass loss occurring over time. Enzymatic conditions are anticipated to accelerate mass loss compared to purely hydrolytic settings. Additionally, formulation parameters, such as polymer molecular weight and end-group chemistry, are expected to modulate degradation kinetics. Further studies are ongoing to evaluate the impact of enzymatic activity on degradation kinetics and drug release profiles.

CONCLUSION

Elucidating the interactions between enzymes and the PLGA matrix provides valuable insights on the polymer matrix remains in tissue and whether the presence of enzymes affects its degradation rate. A deeper understanding of these interactions may enable better control over drug release profiles, leading to improved treatment outcomes and reduced patient side effects.

REFERENCES

1. Cao, Y., Samy, K. E., Bernards, D. A., & Desai, T. A. (2019). Recent advances in intraocular sustained-release drug delivery devices. Drug discovery today, 24(8), 1694-1700.
2. Boimvaser, S., Mariano, R. N., Turino, L. N., & Vega, J. R. (2016). In vitro bulk/surface erosion pattern of PLGA implant in physiological conditions: a study based on auxiliary microsphere systems. Polymer Bulletin, 73, 209-227.
3. Darestani, F. T., Abtahi, M., Entezami, A. A., & Mobedi, H. (2005). Degradation of Poly (D, L-Lactide-CO-Glycolide) 50: 50 Implant in Aqueous Medium. 753-763
4. Shalem, A., Yehezkeli, O., & Fishman, A. (2024). Enzymatic degradation of polylactic acid (PLA). Applied Microbiology and Biotechnology, 108(1), 413.
5. Wan, F., Bohr, A., Maltesen, M. J., Bjerregaard, S., Foged, C., Rantanen, J., & Yang, M. (2013). Critical solvent properties affecting the particle formation process and characteristics of celecoxib-loaded PLGA microparticles via spray-drying. Pharmaceutical research, 30, 1065-1076.

ACKNOWLEDGMENT

- Dr. Black C., Senior Scientist, II (AbbVie, Department of Drug Delivery and Biomaterials – 2525 Dupont Dr, 92612, Irvine, CA, USA).
- Dr. Rajagopal, K., Senior Research Fellow (AbbVie, Department of Drug Delivery and Biomaterials – 2525 Dupont Dr, 92612, Irvine, CA, USA).
- Dr. Wang C.C., Full Professor, Chair & Professor of the Department of Pharmacology and Pharmaceutical Sciences (USC Mann School of Pharmacy and Pharmaceutical Sciences, Los Angeles, CA, USA).
- Cunningham J., Executive Director, Drug Delivery and Biomaterials Department (AbbVie, Irvine, CA, USA).
- Dr. Gong W. and Dr. Lim M., coordinators of the USC Postdoctoral Fellowship Industrial Program (USC Mann School of Pharmacy and Pharmaceutical Sciences, Los Angeles, CA, USA).