

Scanning Analysis of Semi-solvent Vapor Impact (SAVI): Microstructural and compositional analysis of leuprolide-loaded poly(lactide-co-glycolide) microparticles

J. Garner¹, Justin Hadar¹, S. Skidmore¹, F. Jessmon¹, H. Park¹, K. Park¹, A. Otte², X. Xu³, Y. K. Jhon⁴, B. Qin⁴, Y. Wang⁵

¹ Akina, Inc. West Lafayette, IN 47906, USA, ² Purdue University, West Lafayette, IN 47907, USA, ³ Office of Testing and Research, Office of Pharmaceutical Quality,

⁴ Office of Lifecycle Drug Products, Office of Pharmaceutical Quality, and ⁵ Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, the U.S. Food and Drug Administration, Silver Spring, MD 20993, USA
jg@akinainc.com

Introduction

Poly(lactide-co-glycolide) (PLGA) is utilized for long-acting injectable formulations of various drugs, including leuprolide, a peptide GnRH agonist. SAVI is the process of exposing PLGA microparticles to sequential semi-solvent vapors and assaying the resultant morphological changes. It can elucidate particle composition and microstructure that changes depending on the manufacturing process. Our previous work on the SAVI analysis of naltrexone-loaded microparticles [1] was used in the current study to analyze leuprolide-loaded PLGA microparticles (PLGA-Leup).

Methods

PLGA-Leup microparticles were manufactured in-house by a gelatin-stabilized double emulsion method [2] using similar PLGA to Lupron Depot (1 month) (in-house PLGA-Leup). Additionally, Lupron Depot (leuprolide acetate for depot suspension) 7.5 mg (1 month) and 11.25 mg (3 months) were also analyzed for comparison after washing away anticaking agents. SAVI was conducted as previously described. Each sample was applied to a glass microscope slide and exposed to vapors of ethyl isobutyrate (EI), toluene (TOL), 2-pentanone (2PE), and propyl acetate (PA) in sequence (**Fig 1**). The samples were imaged using laser-scanning confocal microscopy (LSCM) as previously described [1]. Profilometry was performed using LEXT (Olympus) software. Additionally, samples were assayed for PLGA polymer properties by ¹H NMR and gel permeation chromatography (GPC), as well as for in vitro release, as previously described [3].

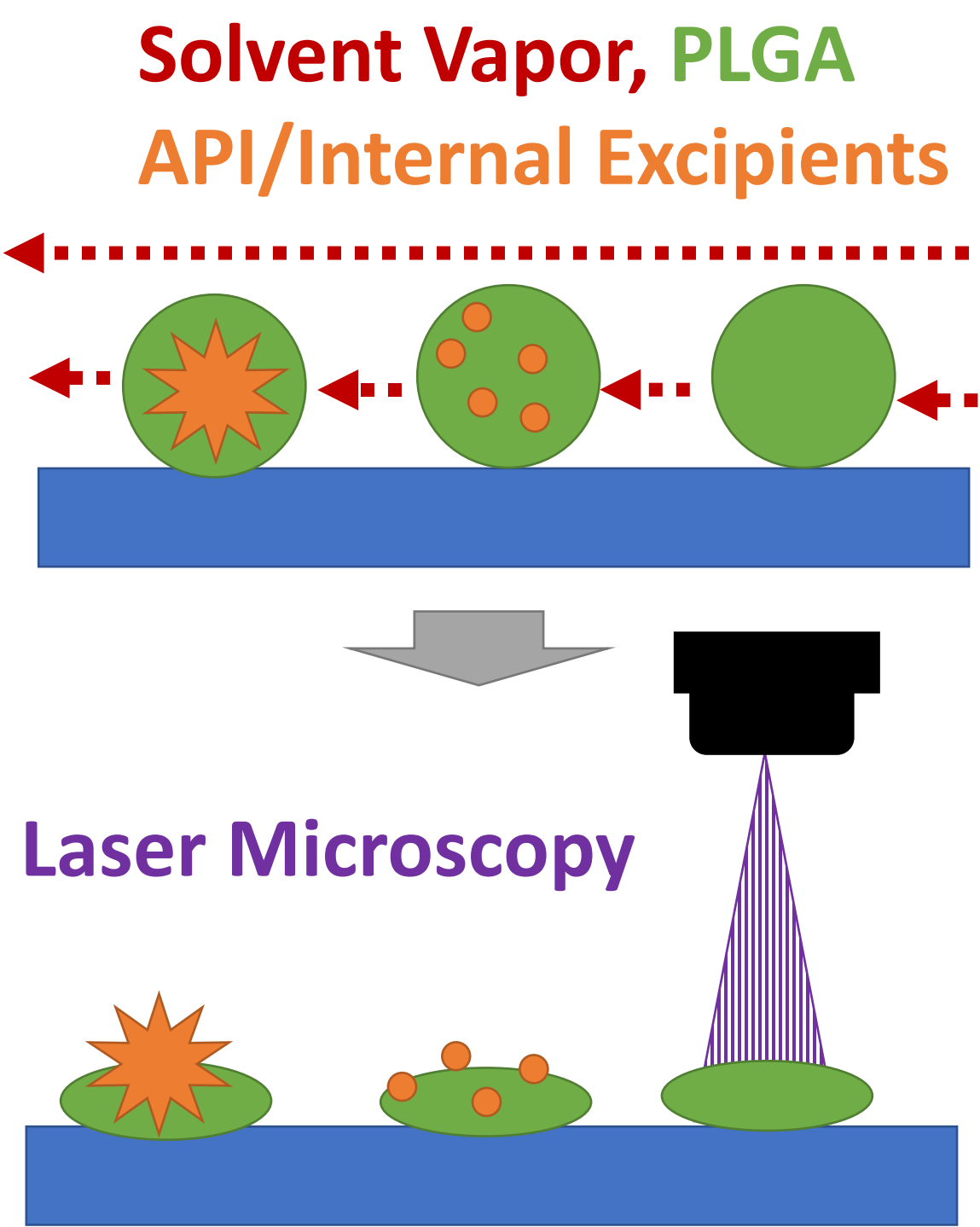


Figure 1. Schematic presentation of SAVI microparticle testing.

Sample (L%, M _n)	Dry	EI	TOL	2PE	PA
PLGA-Leup MFG 220726SMS 76% Lactide Mn: 8795					
Lupron 1-month RLD 73% Lactide Mn: 7691					
Lupron 3-month RLD 100% Lactide Mn: 11,391					

Figure 2. Example images in laser-intensity mode of selected leuprolide microparticles. (Lactide% by ¹H NMR and M_n by gel permeation chromatography quaternary detection, Red scale bar = 50 μm).

Results

Figure 2 displays the images from SAVI analysis of the Lupron 1-month, 3-month, and in-house PLGA-Leup. Comparing in-house PLGA-Leup to Lupron 1-month regarding arithmetic height (Sa) indicates a smoother/less featured form for the in-house PLGA-Leup than for the commercial Lupron 1-month (**Figure 3A**). These products have similar PLGAs, indicating microstructural differences between the reference listed drug (RLD, Lupron 1-month) and in-house prototype, especially as these apply to the gelatin particles inside the double-emulsion. Comparing Lupron 3-month to Lupron 1-month indicates the very rapid collapse of Lupron 3-month with exposure to semi-solvents as these preferentially dissolve the PLA of the Lupron 3-month relative to the PLGA (73% lactide content) of the Lupron 1-month formulation (**Figure 3B**).

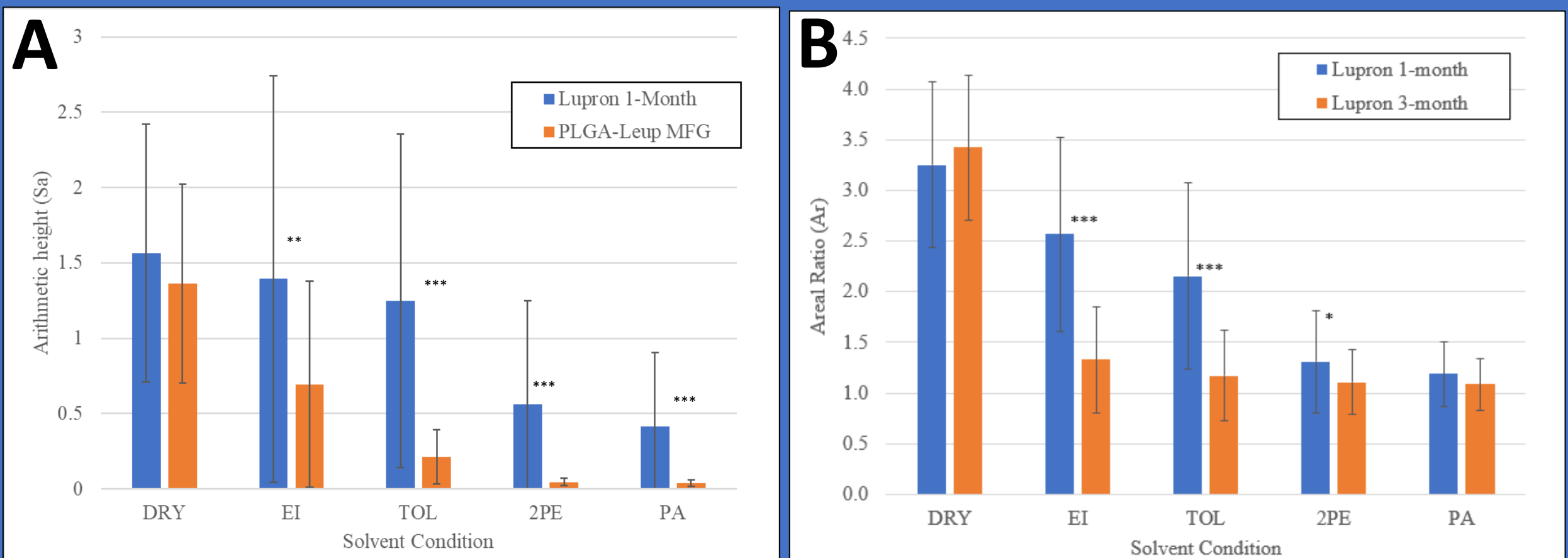


Figure 3. SAVI analysis results. (A) Arithmetic height (Sa) of Lupron 1-month and manufactured PLGA-Leup and (B) Areal ratio (Ar) of Lupron 1-month and Lupron 3-month (“**” p < 0.05, “***” p < 0.01 “****” p < 0.001, Average + STDEV, N = 40-45)

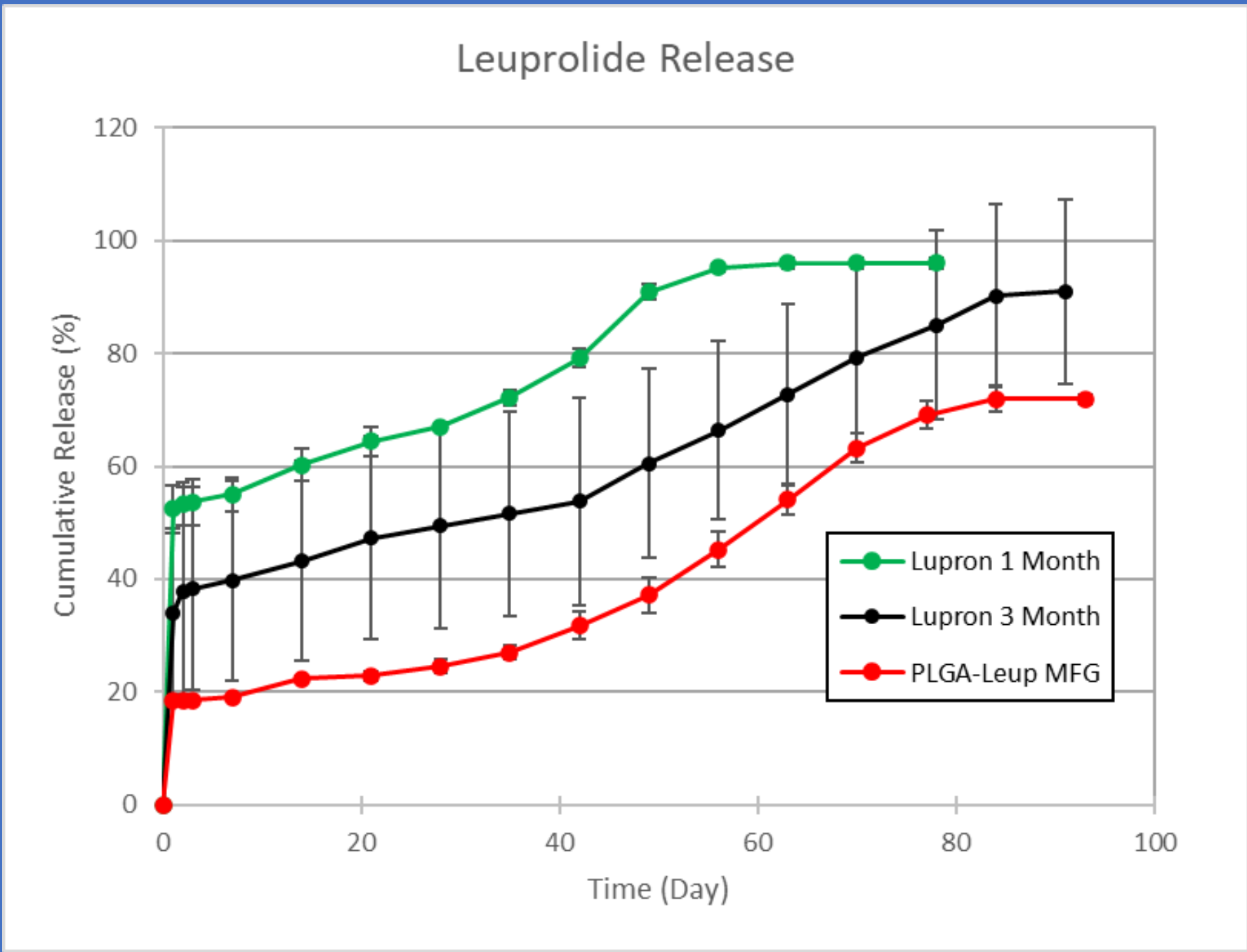


Figure 4. In-vitro release of Lupron 3- month, Lupron 1-month, and manufactured PLGA-Leup microparticles. (Average ± STDEV, N = 3).

Figure 4 displays the *in vitro* release rate of all formulations. Lupron 3-month exhibits more extended control of release relative to Lupron 1-month due to slower degradation of PLA versus PLGA, while in-house PLGA-Leup indicates Incomplete release due to microstructural differences.

Conclusion

SAVI can be applied to microstructural analysis of leuprolide-loaded PLGA formulations. It can demonstrate differences in the microstructural arrangement between qualitatively similar batches based on their morphological reactions to semi-solvent exposure.

References

- [1] Garner, J., et al. Surface analysis of sequential semi-solvent vapor impact (SAVI) for studying microstructural arrangements of poly (lactide-co-glycolide) microparticles. J. Control. Release. 350: 600-612, 2022.
- [2] Zhou, Jia, et al. "Effect of manufacturing variables and raw materials on the composition-equivalent PLGA microspheres for 1-month controlled release of leuprolide." Mol. Pharm. 17 (5): 1502-1515, 2020.
- [3] Garner, J., et al. Scanning Analysis of sequential semisolvent vapor impact to study naltrexone release from poly(lactide-co-glycolide) microparticles." Mol. Pharm.19: 4286-4298, 2022.

Acknowledgements

This work was supported by the Broad Agency Announcement (BAA) Contract # 75F40119C10096 from the U.S. Food and Drug Administration (FDA). The content is solely the responsibility of the authors and does not necessarily represent the official views or policies of the U.S. FDA.