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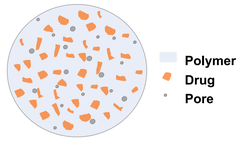
Investigating the Relationship Between Microstructural Properties and *In Vitro* Release Characteristics of PLGA Microspheres

Ruifeng Wang[1], Andrew G. Clark[2], Quanying Bao[1], Yan Wang[3], Bin Qin[3], Shawn Zhang[2], Diane J. Burgess[1]

[1]University of Connecticut, School of Pharmacy, Storrs, CT 06269, USA
[2]DigiM Solution LLC, 500 West Cummings Park, Suite 3650, Woburn, MA 01801, USA
[3]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993, USA
Contact Information: ruifeng.2.wang@uconn.edu; d.burgess@uconn.edu

Purpose

- In the development of complex generic products such as poly (lactic-co-glycolic acid) (PLGA)-based microspheres, qualitative (Q1) and quantitative (Q2) sameness may not be sufficient to achieve comparable product performance as formulation characteristics are manufacturing dependent. This warrants special attention on similarity in microstructure (Q3).
- The Q3 properties can affect drug release and consequently, the efficacy and safety. The objective of this work was to investigate the relationship between microstructure and the release characteristics of microspheres using focused ion beam scanning electron microscopy (FIB-SEM) and quantitative artificial intelligence (AI)-based image analytics.

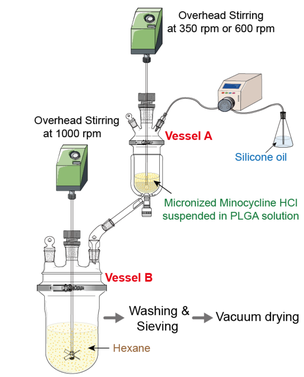


Microstructure properties of material phases (polymer, drug, and pore) :

- volume fraction
- size distribution
- spatial distribution

Methods

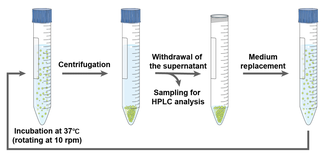
Formulation process of minocycline hydrochloride microspheres



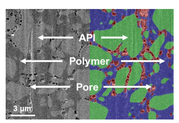
Formulation characterization

- Drug loading
- Particle size
- Morphology

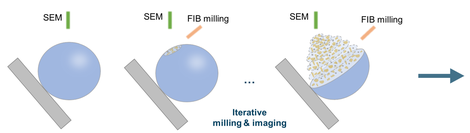
In vitro release testing and degradation study



AI-based image analysis



Repeated FIB milling and subsequent SEM imaging



3D reconstruction and microstructure quantification

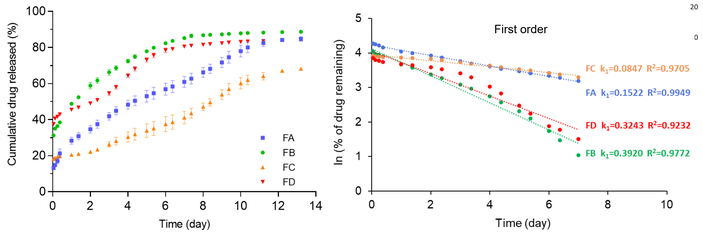
Results

Physicochemical properties of the prepared microspheres

Table 1. Drug loadings and size of minocycline hydrochloride microspheres prepared with different coacervation processing parameters. All data are presented as mean ± SD (n=3).

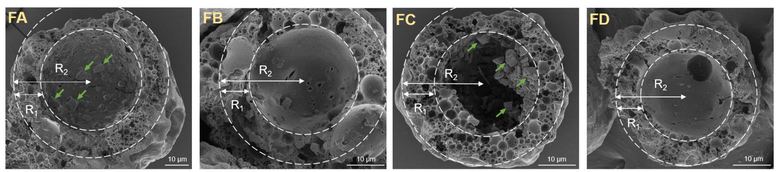
	Stirring rate (rpm)	Silicone oil viscosity (cSt)	Drug Loading (%, w/w)	Particle Size (D_{50}, Volume, µm)	Particle Size (D_{50}, Number, µm)
FA	350	350	26.18 ± 0.31	74.01±1.81	56.10±0.43
FB	350	1000	26.17 ± 0.14	62.34±0.39	48.03±0.18
FC	600	350	26.37 ± 0.27	72.47±0.81	54.12±0.16
FD	600	1000	26.41 ± 0.47	57.56±0.40	41.43±0.36

In vitro release characteristics



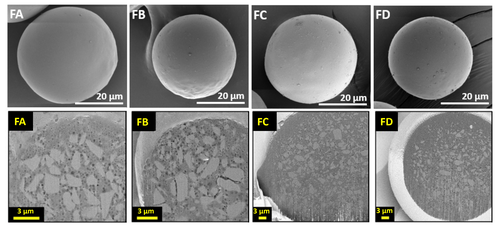
In vitro release profiles of the prepared microspheres using the sample-and-separate method. All data are presented as mean ± SD (n=3).The release profiles were analyzed using the first order model.

In vitro degradation

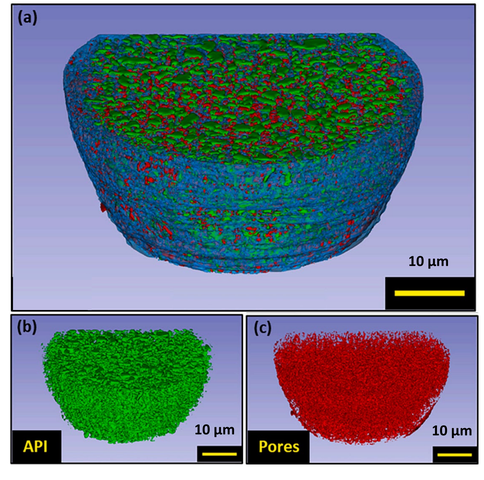


SEM cross-sectional images of the prepared microsphere formulations incubated in release medium at day 6. The green arrows point to the remaining drug particles inside the microspheres. The ratio of R_1/R_2 is 35%.

Morphology and representative FIB-SEM images

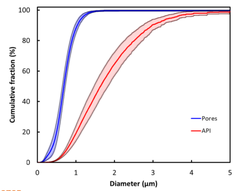


Representative 3D reconstruction

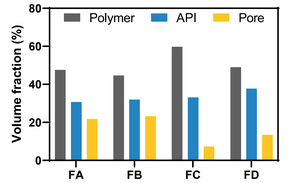


Microstructural properties

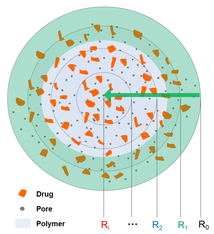
➢ Size distribution of API and pores



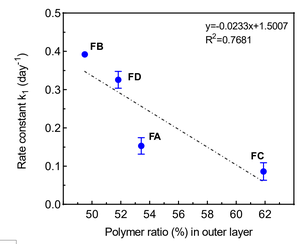
➢ 3D volume fractions of different phases

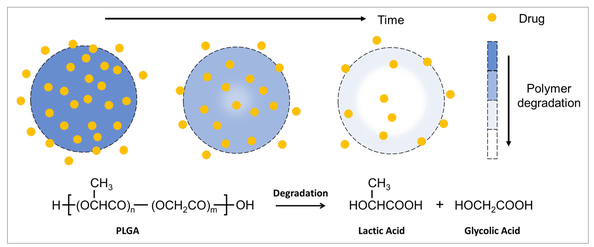


Correlation



	Polymer ratio (%) in 35% outer layer	k_1
FA	53.42	0.1522
FB	49.49	0.392
FC	61.90	0.0847
FD	51.82	0.3243





- Upon contact with the release medium. PLGA is degraded into shorter chain acids. An accumulation of the degradation product can lead to local pH decrease and the autocatalytic effect, resulting an accelerated heterogenous degradation of PLGA.

Conclusions

- Microstructural properties (e.g., volume fraction and spatial distribution of polymer, drug, and pores) of four in-house microsphere formulations were determined using FIB-SEM.
- Internal phase fractions and phase spatial distributions were identified that related to the release performance. The release rate was correlated to the polymer content in outer layer.
- The established correlation between microstructural properties and release characteristics can potentially support a more robust understanding of the impact of the microstructure properties underlying the release mechanisms of microspheres and facilitate the establishment of Q3 equivalence of two products.

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References

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2. Andrew G., C., Ruifeng, W., Yuri, Q., et al. *J. Control. Release.* 349, 580-591.
3. Jie, S., & Diane J., B. *J. Pharm. Pharmacol.* 64(7), 986–996.