What do we know about PLGA polymers in FDA-approved drug products: A journey of characterizing PLGA polymers and formulations

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Introduction

Poly(lactide-co-glycolide) (PLGA) polymers have been used as a key inactive ingredient in over 20 FDA-approved drug products for sustained drug release. However, it is recognized that methods for characterizing PLGA polymers and their formulations present key challenges in developing new and generic PLGA-based drug products. This poster summarizes the journey of better understanding PLGA polymers by providing a comprehensive review of the developed characterization methods through FDA's Generic Drug User Fee Amendments (GDUFA)-funded research projects and the regulatory impact of these methods on supporting generic drug development and approval.

Methods

FDA launched the first GDUFA-funded research program for PLGA-based drug product in 2013. To date, 9 grants and 12 contracts have been awarded to investigate PLGA-based drug products. Data and information in this poster were collected from relevant research project outcomes.

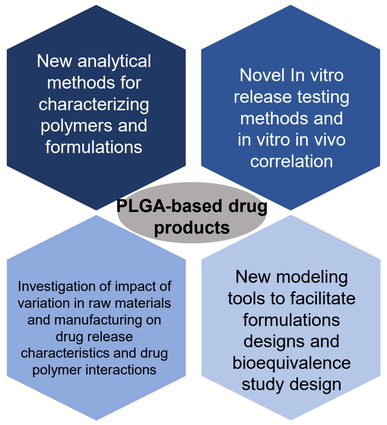


Figure 1. Research areas encompassed in the research program for PLGA-based drug products

Results

Table 1 New characterization methods for PLGA polymers and formulation developed by GDUFA-funded research projects

Grant or Contract#	New Characterization Methods	Relevant Publications
U01FD05168	An analytical protocol to separate PLGA from the drug product for characterizing molecular weight/weight distribution, monomer ratio, and end group	*Int. J. Pharm.* 495 (2015) 87–92
HHSF223201710123C	Analytical method for structural characterization of glucose-cored, star-shaped PLGA (Glu-PLGA)	*J. Control. Release* 204 (2019) 75-89 *J. Control. Release* 320 (2020) 484-494
HHSF223201610091C	A method to separate mixed PLGA based on lactide to glycolide (L:G) ratio differences	*J. Control. Release* 300 (2019) 174-184
75F40119C10096	Surface analysis of sequential semi-solvent vapor impact	*J. Control. Release* 350 (2022) 600-612 *Mol. Pharmaceutics* (2022), 19, 4286-4298
75F40119C10157	FIB-SEM (or XRM) combined with AI-based image analytics to characterize microstructural attributes of microspheres	*J. Control. Release* 349 (2022) 580-591 *J. Control. Release* 358 (2023) 626-635

FIB-SEM: Focused ion beam scanning electron microscopy; XRM: X-ray microscopy; AI: Artificial intelligence

Protocol to characterize PLGA in drug products:

Commercial or test PLGA-based microspheres → 1) Dissolved; 2) Filtered; 3) Dialysis; 4) Precipitation; 5) vacuum-dried → **Extracted PLGA** → **Physicochemical characterization**

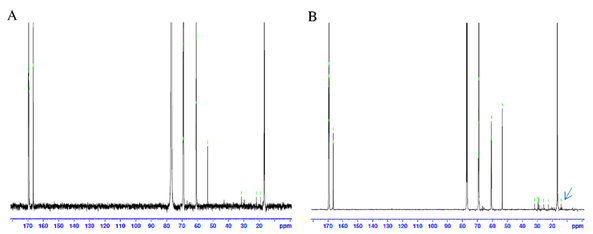


Figure 2. ^{13}C NMR of purified PLGA from microparticles made of acid end cap PLGA (A) and ester end capped PLGA (B). The presence or absence of methyl unit at 14 ppm can be used as a means to determine PLGA endcap. (*Int. J. Pharm.* 495 (2015) 87–92)

Structure analysis of branched PLGA:

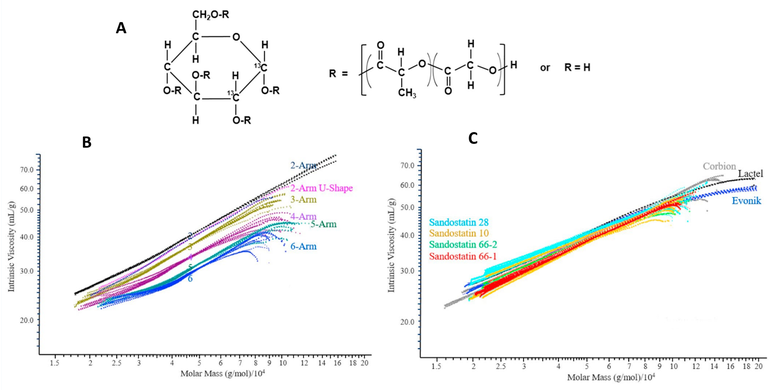
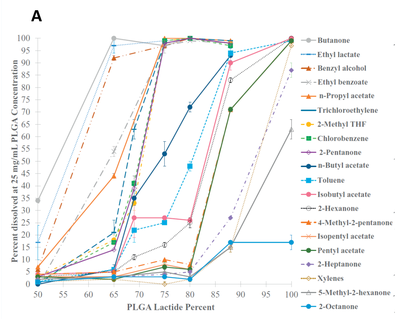


Figure 3. (A) Structure of Glu-PLGA. (B) Mark-Houwink plots of branch PLGA standards of 2-6 arms. (C) Mark-Houwink plots of Glu-PLGA of Sandostatin LAR and Glu-PLGA obtained from different vendors. (*J. Control. Release* 204 (2019) 75-89)

Method to separate mixed PLGAs based on L:G ratio:



B

Sample	M_w (Da)	M_n (Da)	End Group	L:G Ratio (Molar)
Trelstar® 3.75 mg	85,207	25,191	Ester	57:43
Trelstar® 11.25 mg	72,286	47,214	Acid	78:22
Trelstar® 22.50 mg	74,042	46,368	Acid	80:20

C

Sequence	Solvent	L:G Ratio of PLGA	Mass of PLGA (mg)	% of Total PLGA
1	Xylenes	84.0:16.0	9.3	6.3
2	Isopentyl acetate	82.9:17.1	24.8	16.4[b]
3	Toluene	82.9:17.1	37.3	24.6
4	n-Butyl acetate	74.3:25.7	19.3	12.7
5	2-Pentanone	72.6:27.4	22.0	14.5
6	Butanone[b]	70.9:29.1	38.2	25.2
	Butanone residual	70.9:29.1	0.5	0.3
			Total: 151.4[b]	Total:100.0

Figure 4. (A) Dissolution of PLGAs in solvents as a function of the lactide content at 30°C. (B) characterization of PLGAs obtained from Trelstar. (C) the L:G ratio and masses of solvent-separated PLGA fractions of Trelstar (*J. Control. Release* 300 (2019) 174-184)

Surface analysis of sequential semi-solvent vapor impact (SAVI):

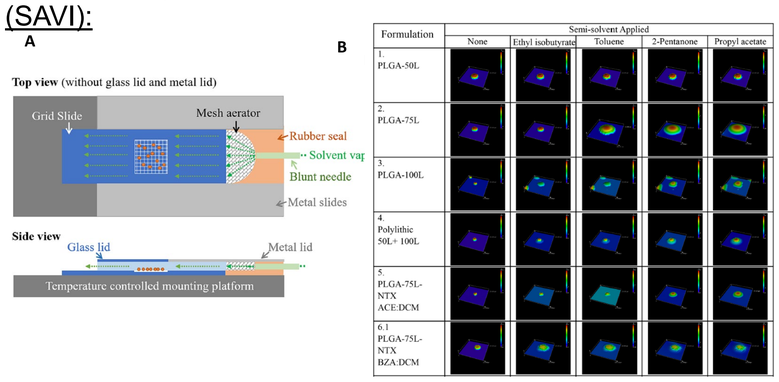


Figure 5. (A) a schematic overview of the semi-solvent vapor flow cell; (B) 3D scan image of different formulations in the dry state and after semi-solvent vapor exposure of each semi-solvent. The surface morphological changes of PLGA microparticles could be described using parameters, such as Sa (arithmetical mean height), Sz (maximum height), Ssk (Skewness), Sku (kurtosis), Sal (auto-correlation height), Vmc (core material volume), Sk (core roughness depth) and Hm (maximum height from glass threshold). (*J. Control. Release* 350 (2022) 600-612)

FIB-SEM (or XRM) combined with AI-based image analytics:

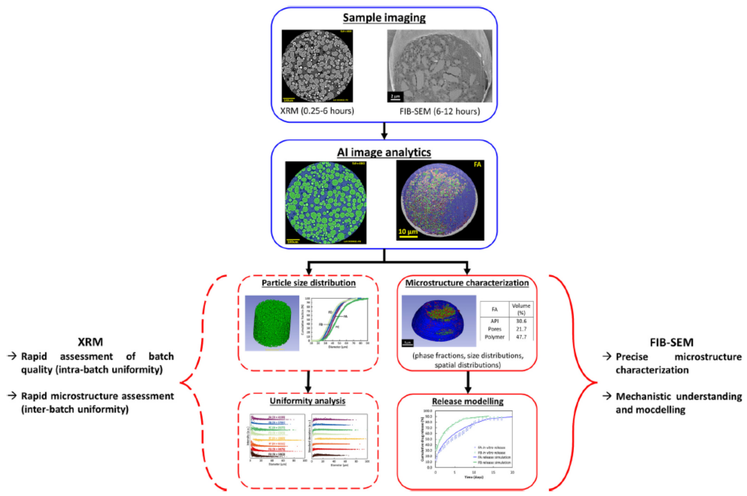


Figure 6. Full corrective XRM and FIB-SEM workflow (*J. Control. Release* 358 (2023) 626-635).

Regulatory impact of these methods

- Improved understanding on characterizing PLGA polymers has been utilized to support various regulative activities, including product-specific guidance development (Table 2), controlled correspondence and pre-ANDA meeting review and ANDA assessment. The published articles have been widely cited by generic applicants in regulatory submissions.
- SAVI and FIB-SEM (or XRM) combined with AI-based image analytics are relatively new tools to characterize PLGA-based product. it has been observed that FIB-SEM with AI-based image analytics are used as a characterization method to support proposed alternative bioequivalence (BE) approach, suggesting that the industry start to consider these new characterization methods in the product development.

Table 2. Example product-specific guidances (PSGs) that contain recommendation of PLGA characterization

Drug product	PSG recommendation	Post time	Note
Risperidone injectable; intramuscular	In vitro drug release studies and in vivo steady state BE study	Recommended Feb 2010; Revised Aug 2013, May 2015, Aug 2016	This is the first PSG that provides guidance on specific PLGA characterization data needed for a Q1 sameness assessment (Rev May 2015). The additional recommendations on PLGA characterization have provided greater clarity to generic companies seeking to develop generic PLGA-based products.
Doxycycline hyclate system, extended release; periodontal	Two options: One in vitro drug release study with supportive characterization studies or one in vivo BE study with clinical end points	Recommended Aug 2022	This is the first PSG that recommends an in vitro only BE approach for a PLGA-based drug product (i.e., consider polylactic acid as a PLGA with L:G ratio of 100:0). The PSG includes detailed characterization on polylactic acid as part of supportive characterization data
Triamcinolone acetonide for suspension, extended release; intra-articular	One in vitro BE study on drug release testing, one in vivo BE study with pharmacokinetic endpoints, and supportive comparative characterization studies	Recommended Nov 2022	PSG recommends use comparative characterization of PLGA extracted from test and reference products as part of supportive characterization data.

Conclusion

GDUFA research projects have helped develop new analytical methods to characterize PLGA polymers and PLGA polymer-based drug products. These tools are helping industry and FDA to better understand the critical quality attributes of these products that are important for generic drug development, regulatory assessment, and approval.

Acknowledgement

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This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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