Characterization and Comparative Evaluation Strategies to Demonstrate Complex Excipient Sameness
Complex Generic Drug product Development Workshop
Session 3: Complex Formulations/Dosage Forms
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Outline

- Introduction: challenge of demonstrating sameness of complex excipient
- Research update-1: characterization of glucose star poly (D,L lactide-co-glycolide) (PLGA) polymer
- Research update-2: analytical techniques for mixed PLGA polymers

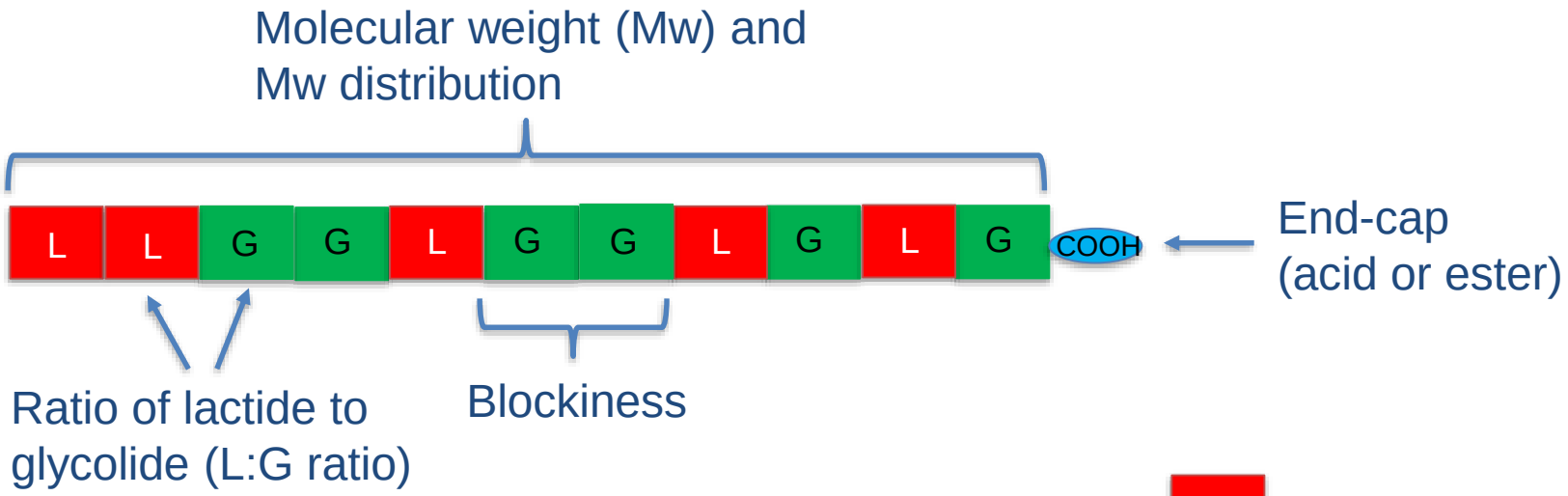
Challenges of demonstrating sameness of complex excipients

- Generic parenteral products generally need to establish Q1 and Q2 sameness per regulations (21 CFR 314.94(a)(9)(iii))
- Challenges:
  - Complexity in structure and composition
  - Non-compendial excipient
  - May be difficult to purify or analyze
  - Excipient in finished drug product may not be the same as starting raw material

PLGA copolymers

- PLGAs are biodegradable random copolymers
- PLGA polymers have been used in ~20 long acting injectable products as the rate controlling excipient
  - Dosage form: microspheres, in situ forming gel, solid implant
- Biodegradation depends on multiple factors:
  - e.g., Polymer properties, manufacture method, exposure to water

Characteristics of PLGA polymers



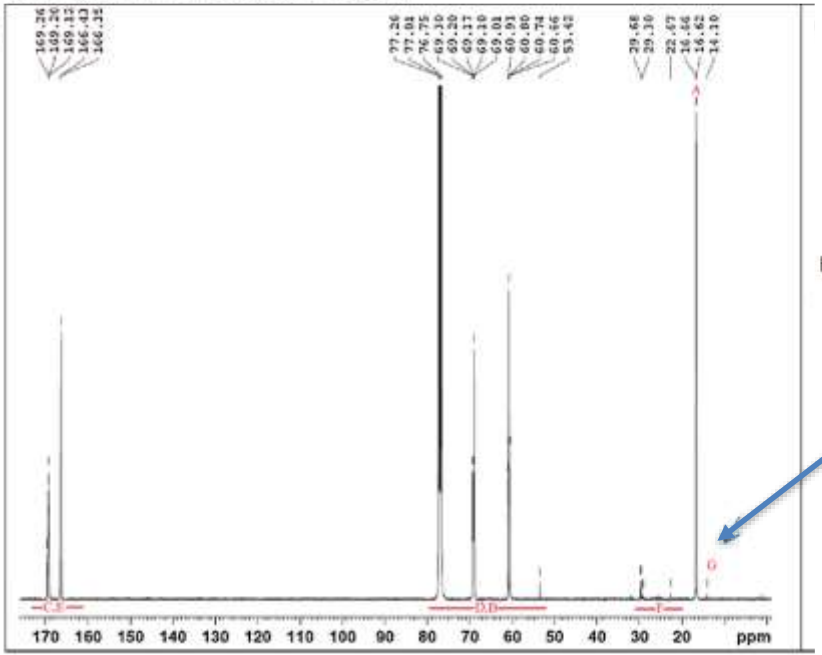
Other characteristics include inherent viscosity, glass transition temperature, crystallinity, polymer structure/shape

Contents lists available at ScienceDirect
International Journal of Pharmaceutics
journal homepage: www.elsevier.com/locate/ijpharm

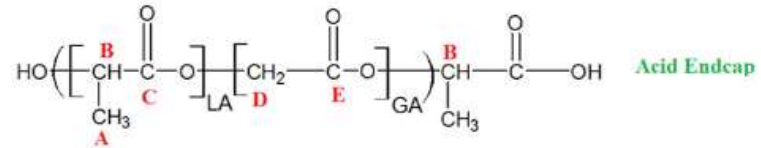
A protocol for assay of poly(lactide-*co*-glycolide) in clinical products

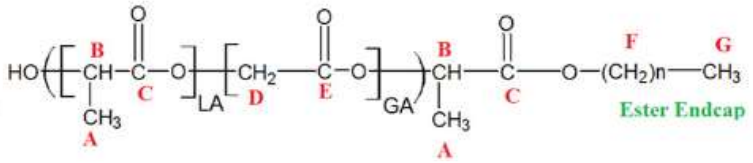
John Garner[a], Sarah Skidmore[a], Haesun Park[a], Kinam Park[a,*], Stephanie Choi[b], Yan Wang[b]

GDUFA research
Grant U01FD05168



^{13}C NMR of purified PLGA from Trelstar formulation

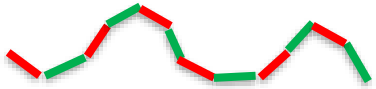




Presence of methyl unit at 14 ppm indicates ester end-cap

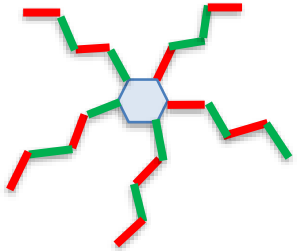
Int J Pharm (2015) 495(1): 87-92

More complicated scenarios

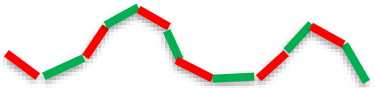


Linear polymer

vs.

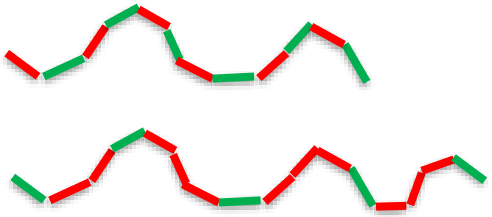


Glucose star polymer



Single polymer

vs.



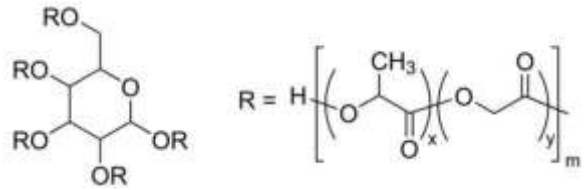
Mixed polymers (e.g., different Mw, L:G ratio)

GDUFA research program on PLGA characterization

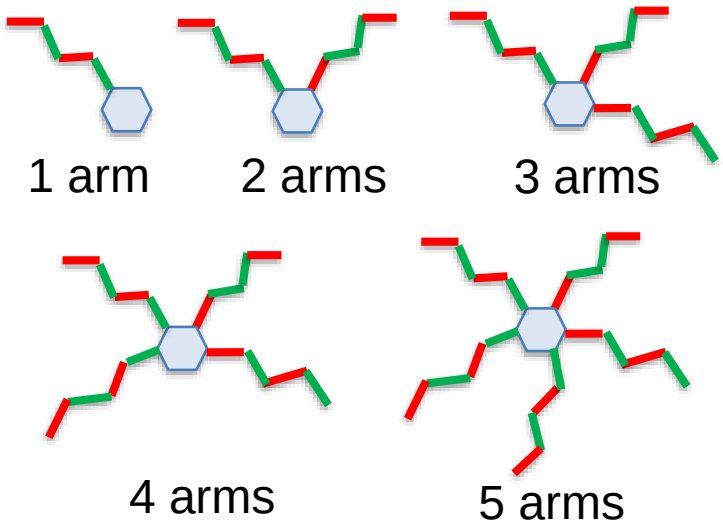
- Development of analysis technique for structural characterization for star-shaped polyesters used for drug delivery
  - Awarded to Akina, Inc. (HHSF223201710123C)
- Advanced analytical techniques for mixed polymer drug-delivery systems
  - Awarded to Akina, Inc. (HHSF223201610091C)

Glucose star PLGA polymer

- Glucose star polymer has been used in FDA approved product(s)
- Five sites for esterification in glucose can lead to variations in branch formation
- Molecular weight measured by GPC does not provide information on branch frequency (# of arm per molecule)



Glucose star polymer, D, L lactic and glycolic acid copolymer



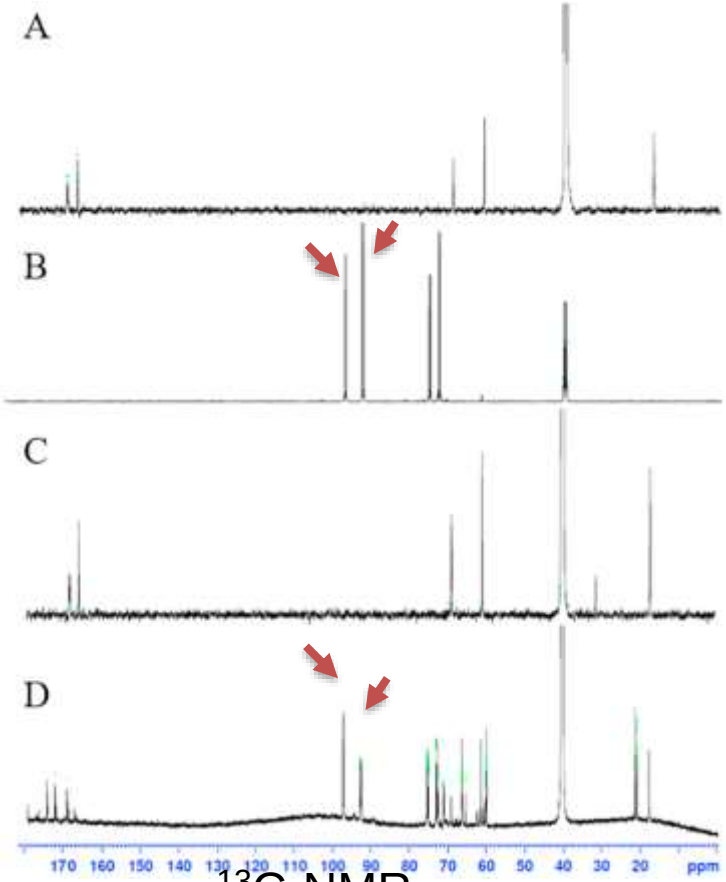
Confirmation of presence of glucose core

Linear PLGA

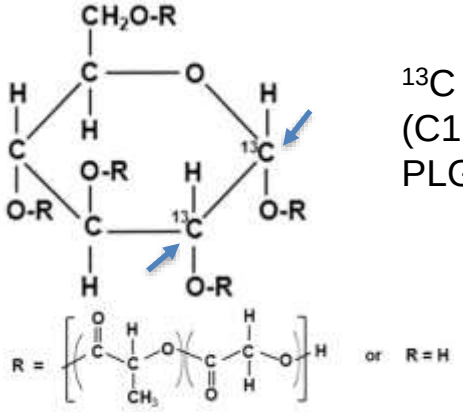
^{13}C labeled (C1,2) glucose

^{13}C labeled (C1,2) Glucose PLGA

^{13}C labeled (C1,2) glucose PLGA after hydrolysis



^{13}C-NMR



^{13}C labeled (C1,2) glucose PLGA

- ^{13}C labeled Glu-PLGA showed not glucose peaks
- Glucose peaks (97 and 92 ppm) reappeared after hydrolysis of Glu-PLGA

J Control Release (2019), 304: 75-89

Conformation of presence of glucose core

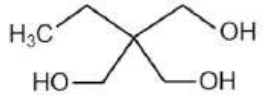
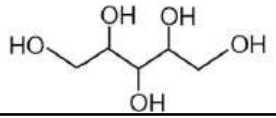
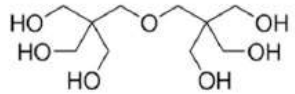
Enzymatic glucose assay

Blank

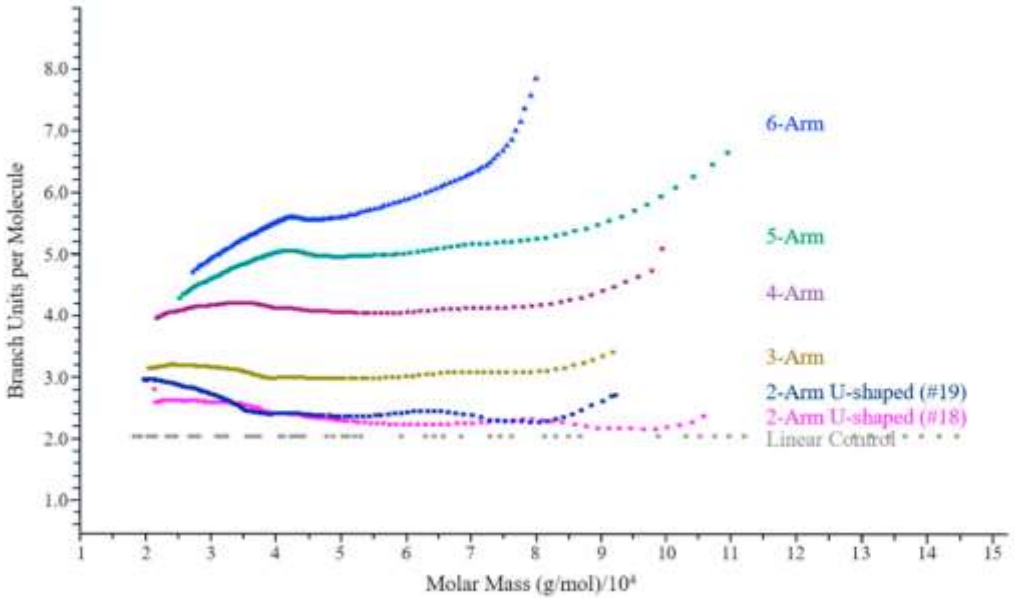
Glu-PLGA from Sandostatin LAR

Hadar *et al*, 2019 CRS Annual meeting poster

Branch analysis of in-house branch standards using GPC-4D

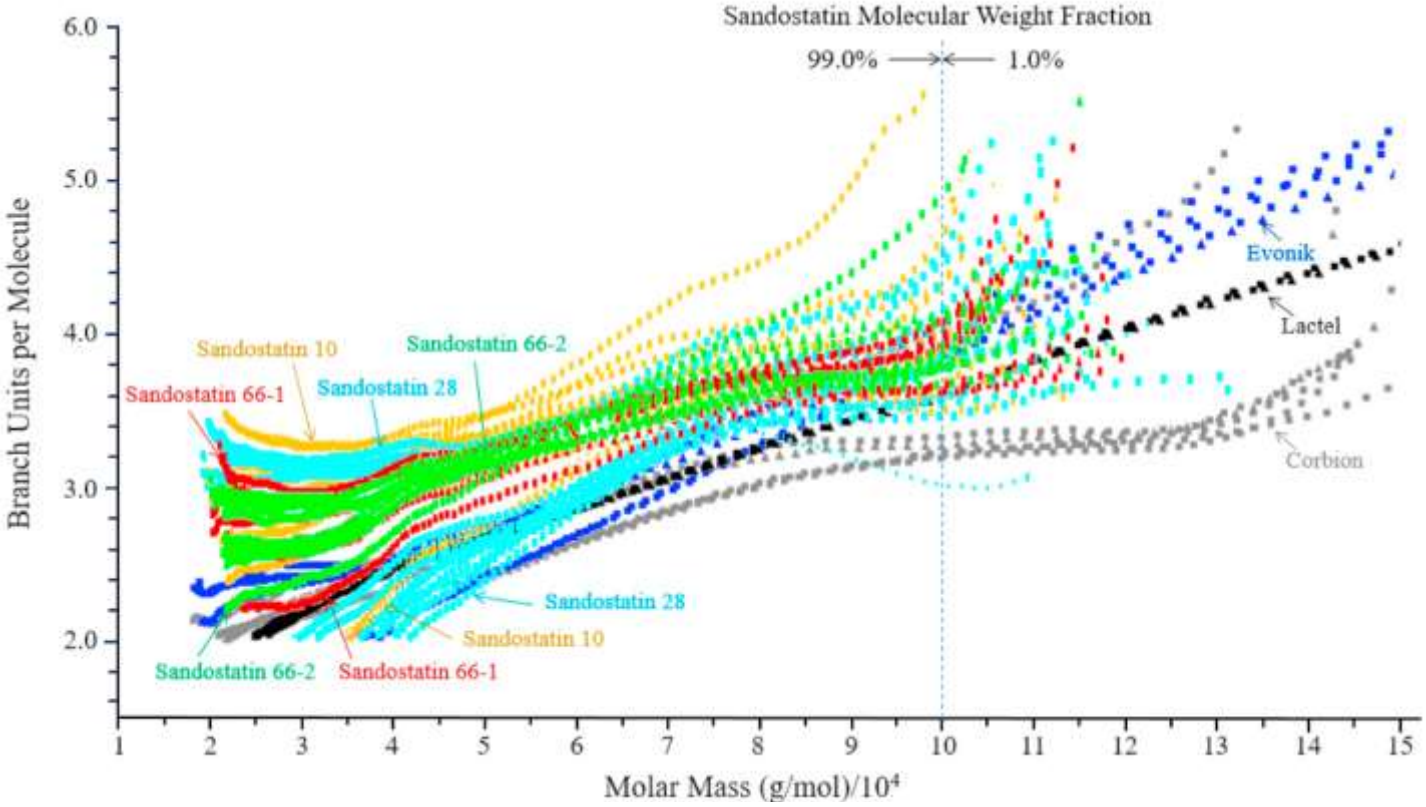
Initiator used for branch standards	Expected # of arms per molecule
Trimethylolpropane 	3
Pentaerythritol 	4
Adonitol 	5
Dipentaerythritol 	6

GPC-4D combines light scattering, viscometer, and refractive index detectors to characterize polymer size and structure



J Control Release (2019), 304: 75-89

Branch analysis of Sandostatin LAR polymer and commercial available star polymers



J Control Release (2019), 304: 75-89

Theoretical model used for branch analysis

$$g = \left(\frac{R^2_{branched}}{R^2_{linear}} \right)_M \quad (1)$$

g: branch ratio

R^2 mean square radius of branched and linear polymers having the same molar mass (*M*)

$$g' = \left(\frac{[\eta]_{branched}}{[\eta]_{linear}} \right)_M \quad (2)$$

[*η*]: intrinsic viscosity of linear and branched polymers, having the same molar mass.

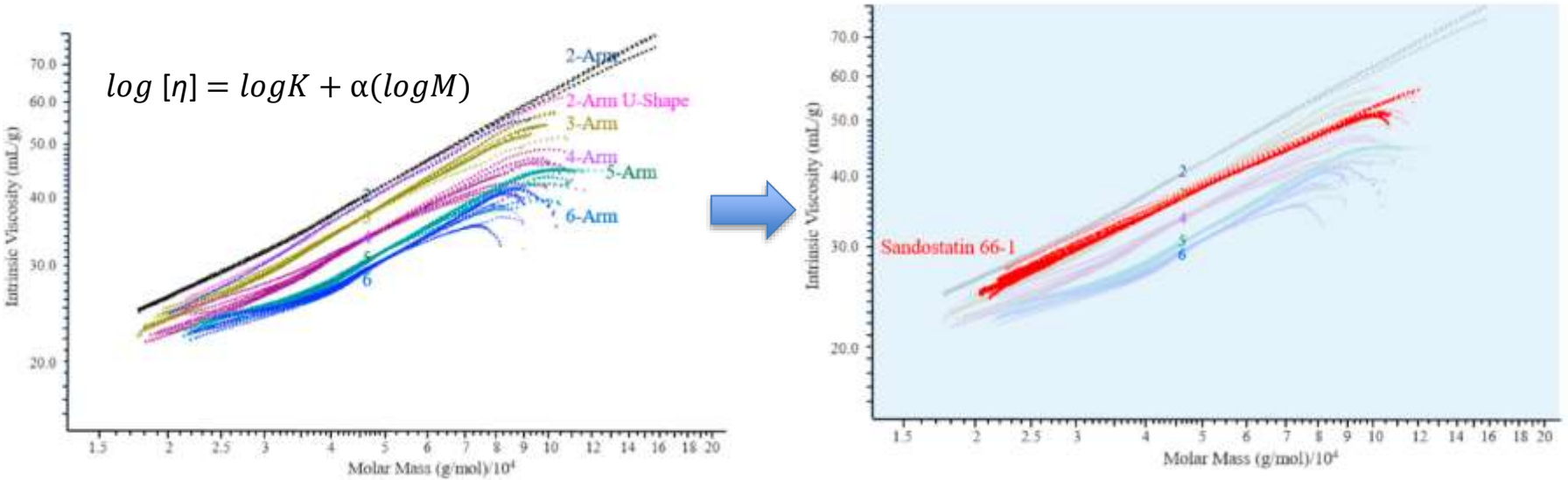
$$g' = g^e \quad (3)$$

e: drainage factor

$$g = \frac{6B}{B^2 + 3B + 2} \quad (4)$$

B: branch units per molecule

Mark-Houwink plots of branch standards



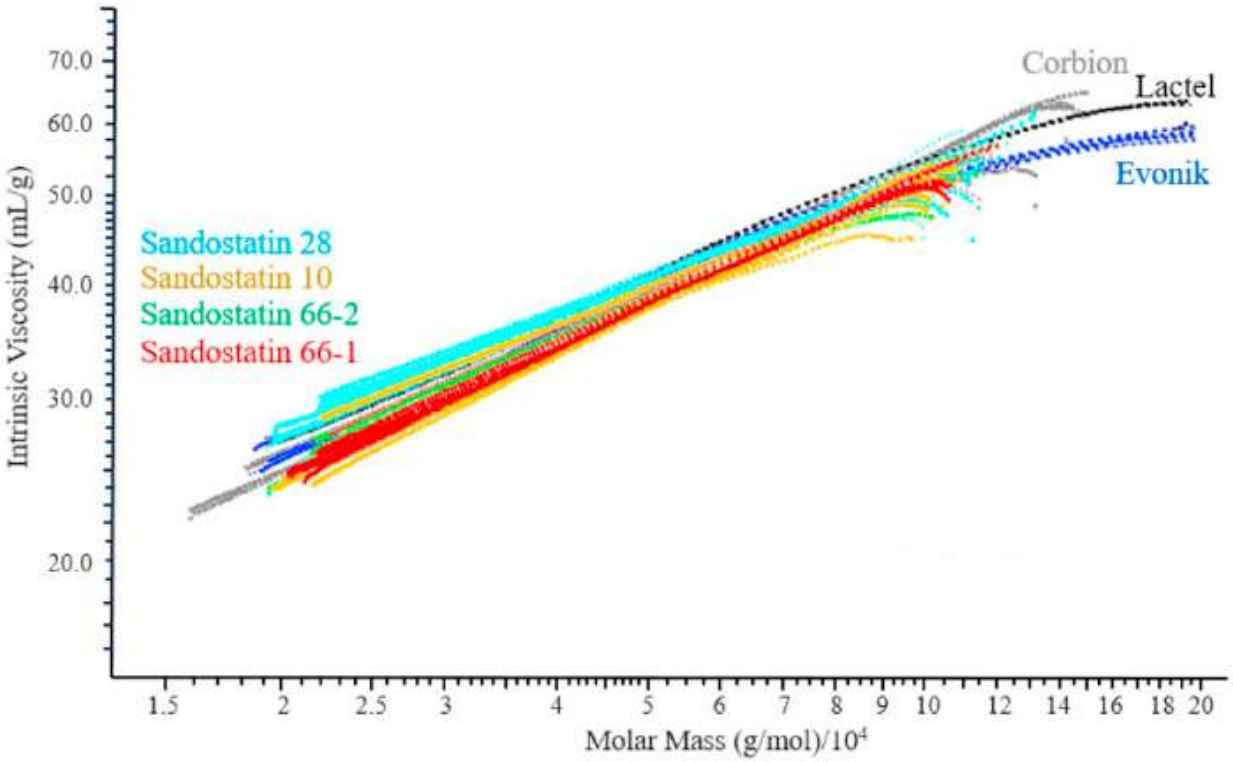
$[\eta]$ Intrinsic viscosity

M Molecular weight

- With results of branch standards, the branch units of Glucose star polymer can be determined without theoretical model from the Mark-Houwink plots

J Control Release (2019), 304: 75-89

Mark-Houwink plots of glucose star polymers



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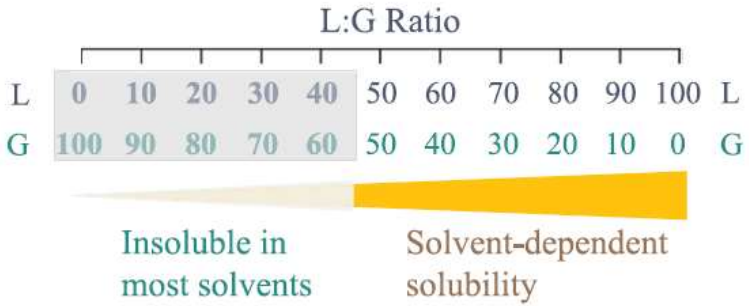
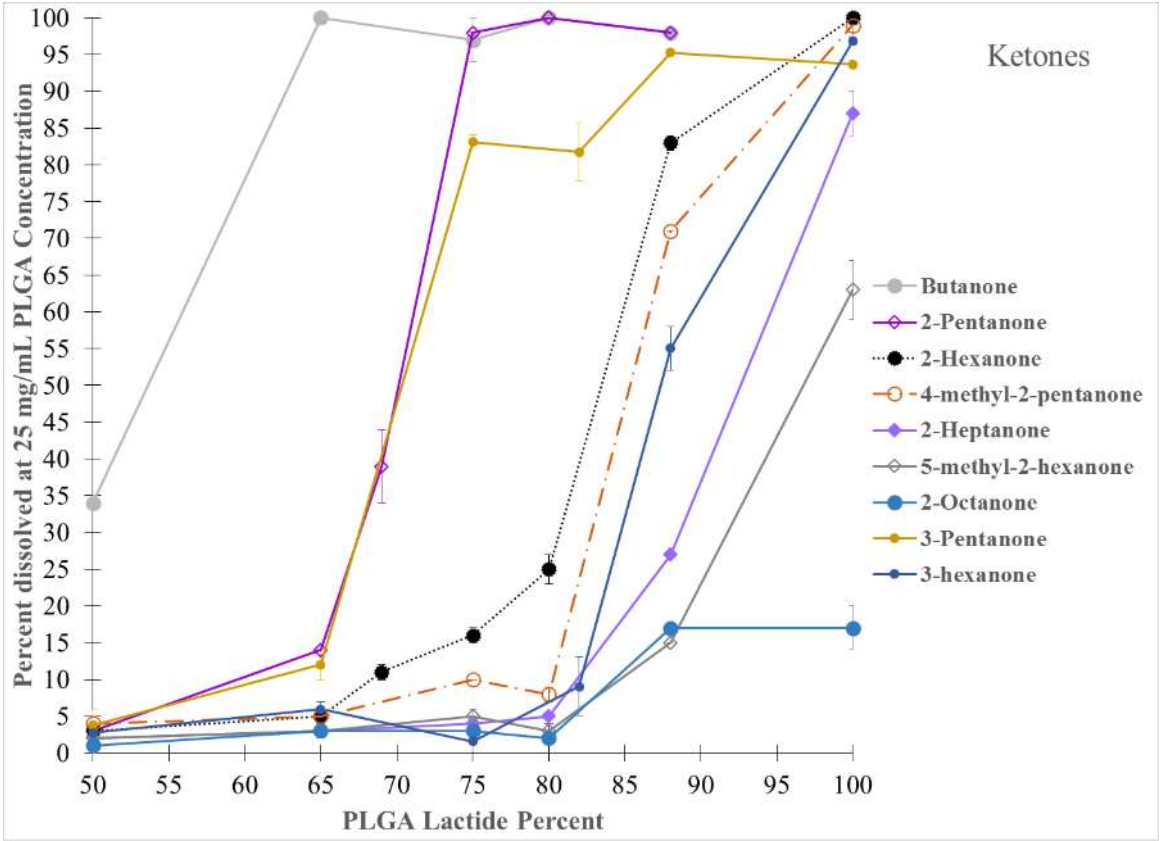
Mixed polymers of different L:G ratio



J control Release (2019) 304:125-134

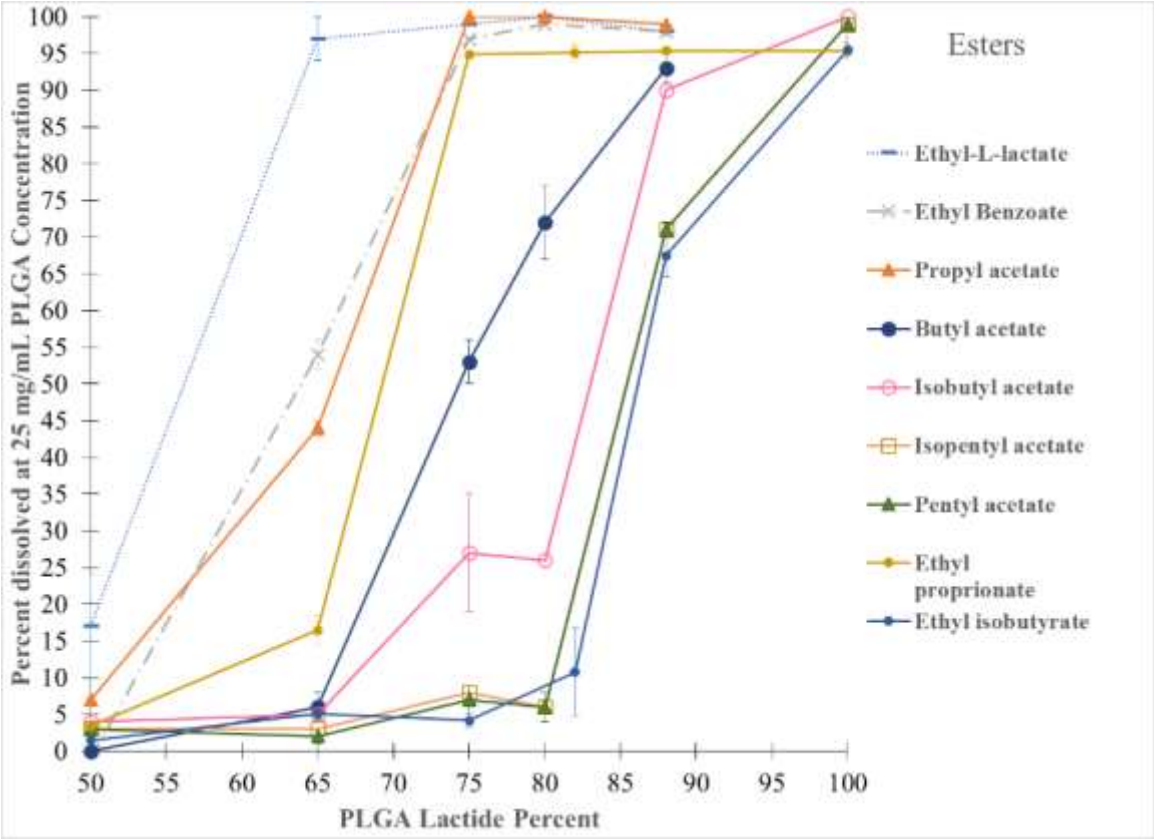
- A drug product may contains more than one PLGA polymers for sustained release of drug
- PLGAs of different L:G ratio have different solubility in solvents
  - It is possible to separate PLGAs based on this property even if their molecular weight are the same

PLGA dissolution by L:G ratio in ketones



Garner et al. CRS Annual meeting poster, 2019

PLGA dissolution by L:G ratio in esters



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Separation and analysis of PLGA in Trelstar

Table 1. Trelstar® Fraction Separation Analysis (Average ± STDEV, N=2 lots)

Solvent (fraction)	Percent polymer (w/w%)	Lactide content (%L, NMR)	Mw (GPC-4D)	Mn (GPC-4D)	Rc (NMR)
Original Mixture	100%	76.9 ± 0.1	41,377 ± 135	31,475 ± 81	0.78 ± 0.01
Xylenes	6.0 ± 0.1	84.0 ± 0.1	13,063 ± 2695	8755 ± 4799	0.46 ± 0.16
Isopentyl acetate	15.8 ± 0.8	82.8 ± 0.1	24,653 ± 1316	19,429 ± 811	0.48 ± 0.08
Toluene	25.5 ± 1.3	82.9 ± 0.1	47,790 ± 939	39,084± 2588	0.55 ± 0.12
Butyl acetate	12.6 ± 0.2	74.2 ± 0.2	26,592 ± 665	22,760 ± 99	0.81 ± 0.02
2-Pentanone	14.7 ± 0.2	72.5 ± 0.2	35,483 ± 264	29,658 ± 88	0.88 ± 0.001
Butanone	24.7 ± 0.7	70.8 ± 0.2	52,930 ± 640	45,267 ± 1467	0.89 ± 0.01
Butanone residual	0.6 ± 0.4	70.5 ± 0.6	NT*	NT*	NT*

* NT = Not Tested, too little quantity extracted to test.

- Trelstar® 22.5 mg formulation was successfully separated into fractions based on lactide content of PLGA

Garner et al. CRS Annual meeting poster, 2019

Summary

- Comprehensive polymer characterization on test product and RLD products is recommended for establishing Q1/Q2 sameness of PLGA
- GDUFA research projects provided key knowledge addressing scientific gaps in PLGA polymer characterization


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