Regulatory and Scientific Considerations on Characterizations of Complex Polymeric Excipients

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Biography and Contact Information

- Training background
  - Pharmaceutical Sciences
- Current role
  - Acting team lead for Complex Drug Substances & Formulation Team in the Division of Therapeutic Performance (DTP), Office of Research and Standards (ORS), Office of Generic Drugs (OGD), CDER, U.S. FDA.
- Research expertise
  - Characterization of complex polymeric excipients
  - Complex parenteral, ophthalmic, otic, intravaginal, and intrauterine formulations
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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Regulatory Requirements for Excipients in Parenteral Drug Products

- Demonstration of qualitative (Q1) and quantitative (Q2) sameness of excipients prior to conduct of bioequivalence (BE) studies of parenteral drug products

21 CFR 314.94 (a)(9)(iii) – *Inactive ingredient changes permitted in drug products intended for parenteral use.*

Generally, a drug product intended for parenteral use shall contain **the same inactive ingredients** (qualitatively the same – "Q1") and **in the same concentration** (quantitatively the same – "Q2") as the reference listed drug.

An applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

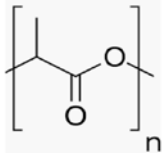
A formulation which contains an excipient not contained in the RLD and not considered to be an "exception excipient" cannot be submitted as an ANDA.

Challenges of Demonstrating Sameness Of Complex Excipients

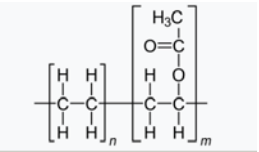
- Common Challenges:
  - Complexity in structure and composition
  - Non-compendial excipient
  - May be difficult to purify or analyze
  - Excipient in finished drug product may not be the same as starting raw material

Examples of Complex Polymeric Excipients

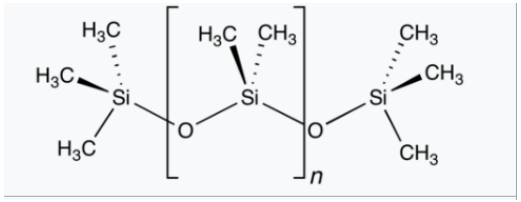
- Poly esters
  - Poly(D,L-lactic and glycolic acid) (PLGA) copolymers
  - Poly(D,L-lactic acid) (PLA) copolymers



- Poly (ethylene-vinyl acetate) (EVA)



- Polydimethylsiloxane (PDMS)

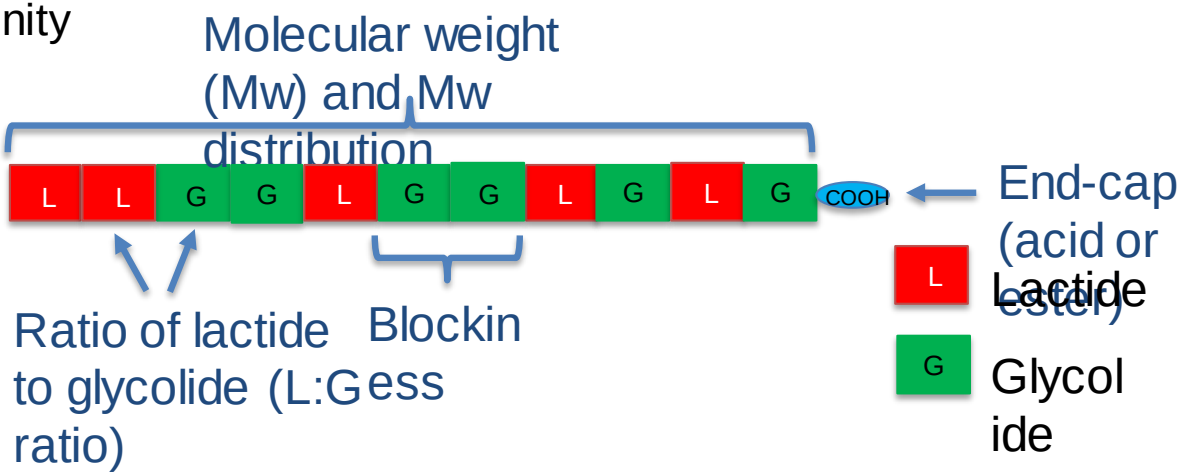


PLGA Copolymers

- 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 gels, solid implants
- Biodegradation depends on multiple factors:
  - e.g., Polymer properties, manufacture method, exposure to water

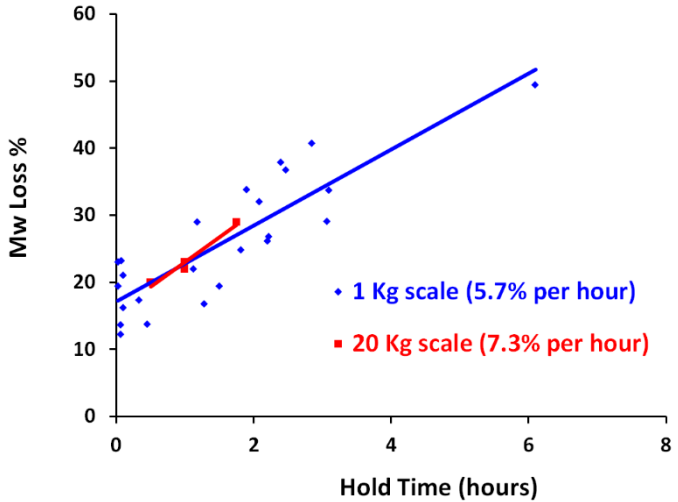
Characteristics of PLGA polymers

- Some key physicochemical properties of PLA/PLGA include:
  - **Polymer composition (L to G ratio)**
  - **Molecular weight and weight distribution**
  - **Polymer architecture (linear vs star-shaped)**
  - Intrinsic viscosity
  - Glass transition temperature
  - Polymer end-cap
  - Crystallinity



Characteristics of PLGA polymers

- The key physicochemical properties of PLA/PLGA could be altered during manufacturing process.



PLGA degradation during manufacturing of risperidone-PLGA microsphere

Alkermes, US 6,264,987 B1, 2001

Establishment of Q1/Q2 of PLGA Polymers

- The key physicochemical properties that are necessary for evaluation of Q1 sameness is on a **case-by-case basis**.

- The Q1/Q2 sameness of PLA/PLGA between the test and reference listed drug should be determined using the **FINISHED** formulation rather than the raw materials.

GDUFA Research Program on Long-Acting Drugs

- Improved understanding on characteristics of PLGA polymers
- Development of analytical tools for structural characterization for star-shaped polyesters used for drug delivery
- Advanced analytical techniques for separating PLGA polymers when used in the same formulation

Methods of Characterizations

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

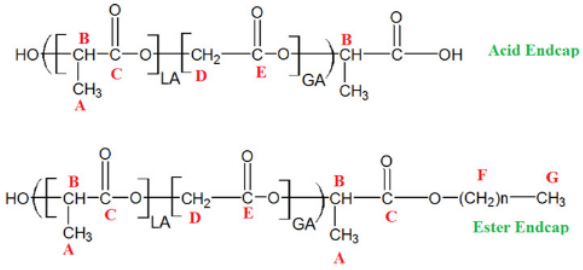
journal homepage: www.elsevier.com/locate/ijpharm

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]

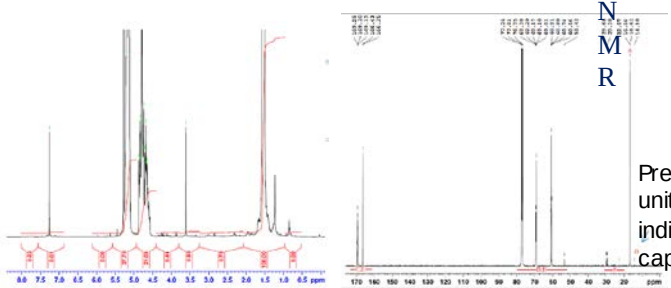
[a] Akina, Inc., 3495 Kent Avenue, Suite O-100, West Lafayette, IN 47906, USA
[b] Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product for all strengths (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial). Please provide characterization data on poly(lactide-co-glycolide) (PLGA) for both the test and reference product including polymer composition (ratio between glycolic acid and lactic acid), molecular weight and weight distribution, and PLGA architecture (e.g., linear or star-branched PLGA). Additional data on PLGA characterization may be requested during the review of the ANDA.



L:G Ratio: H-NMR

End Group: C-NMR



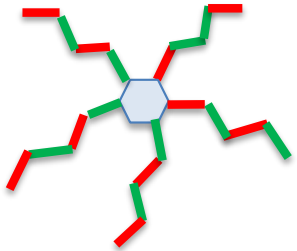
Present of methyl unit at 14 ppm indicates ester end-cap

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

A protocol for assay of poly(lactide-co-glycolide) in clinical products.
J. Garner, S. Skidmore, H. Park, K. Park. S. Choi, & Y. Wang
International Journal of Pharmaceutics 495 (2015) 87–92

More Complicated Scenarios

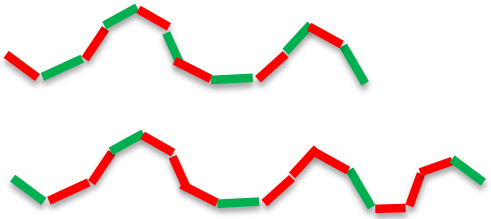
vs.



Linear polymer

glucose star polymer

vs.

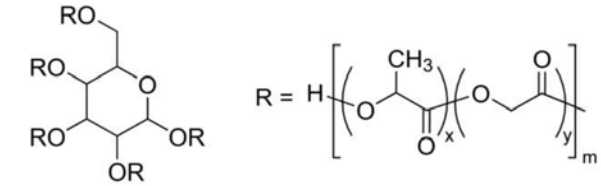


Single polymer

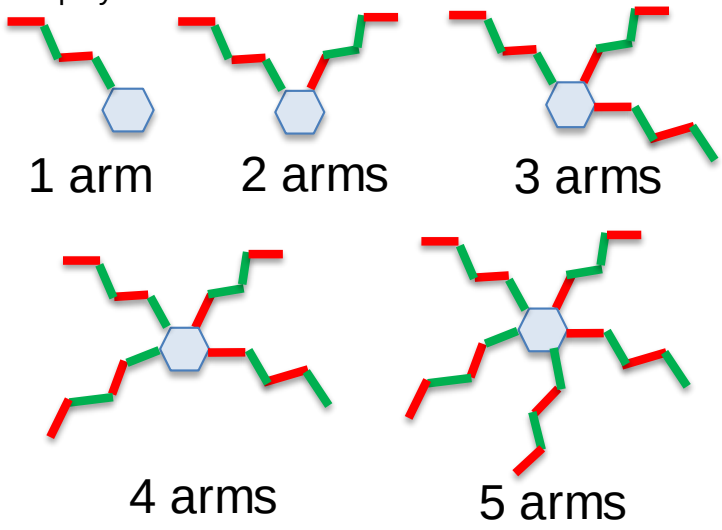
mixed polymers (e.g., different Mw, L:G ratio)

Glucose Star PLGA Polymer

- 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



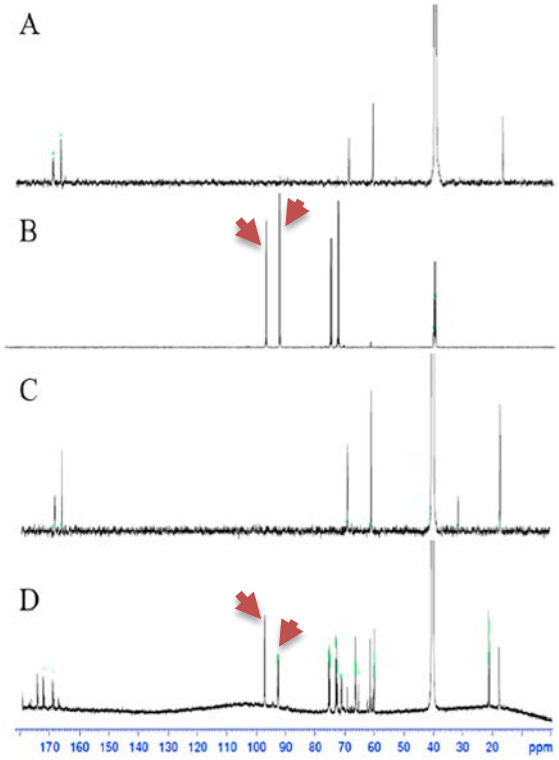
Confirmation of Presence of Glucose Core

Linear PLGA

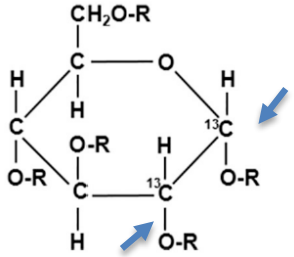
^{13}C labeled (C1,2) glucose

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

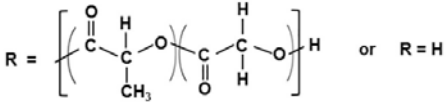
^{13}C labeled (C1,2) glucose PLGA after hydrolysis



^{13}C-NMR



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

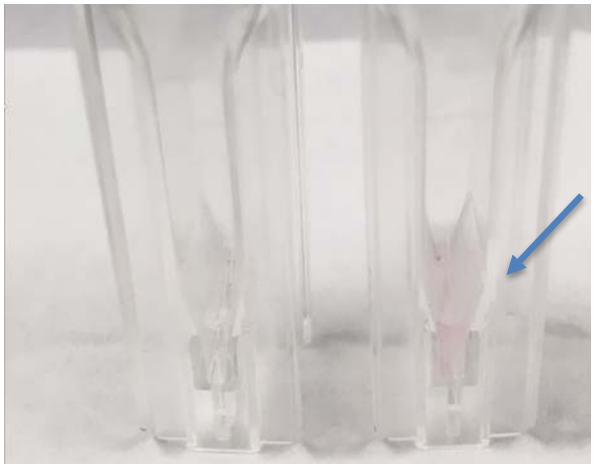


- Glucose peaks were not observed in the 13C NMR Spectra of ^{13}C labeled Glu-PLGA
- Glucose peaks (97 and 92 ppm) reappeared after hydrolysis of Glu-PLGA

Hadar et al, JCR 2019

Conformation Of Presence Of Glucose Core

Enzymatic Glucose assay



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Glu-PLGA from Sandostatin LAR

Hadar et al, 2019 CRS meeting, Poster

GPC with Quadruple Detectors

1. Refractive index	This establishes the exact concentration of the polymer.
2. Multiangle static light scattering (MASLS)	The component measures the absolute weight average molecular weight (M_w) without any calibration using standard molecules, as well as the radius of gyration (R_g).
3. Dynamic light scattering	This yields hydrodynamic volume (V_h), and thus hydrodynamic radius (R_h).
4. Viscometer	The viscometer provides intrinsic viscosity ($[\eta]$) values

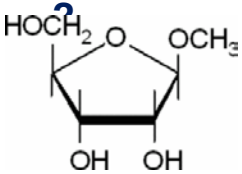
In addition to GPD-4D

5. Osmometer	This measures the absolute number average molecular weight (M_w).

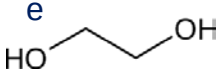
Hadar *et al.*, JCR, 2019

In-house Branched PLGA Polymers

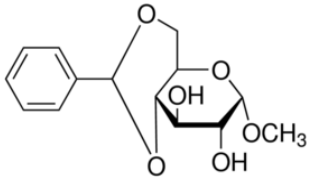
***f* = 2**



Methyl β-D-ribofuranoside

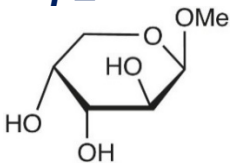


Ethylene glycol

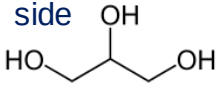


Methyl 4,6-O-benzylidene-α-D-glucopyranoside

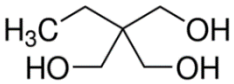
***f* = 3**



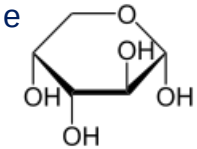
Methyl-β-D-arabinopyranoside



Glycerol

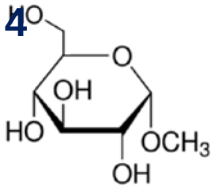


Trimethylolpropane

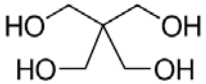


α-D-Arabinopyranose

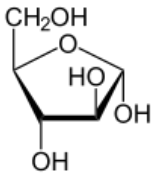
***f* = 4**



Methyl α-D-glucopyranoside

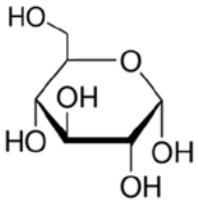


Pentaerythritol



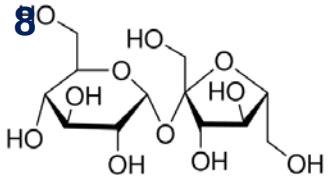
α-D-Arabinofuranose

***f* = 4**

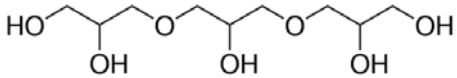


α-D-glucose

***f* = 8**



Sucrose



Triglycerol

Characterization of Branched PLGA Polymers

Journal of Controlled Release 304 (2019) 75–89

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Characterization of branched poly(lactide-*co*-glycolide) polymers used in injectable, long-acting formulations

Justin Hadar[a], Sarah Skidmore[a], John Garner[a], Haesun Park[a], Kinam Park[a,b,*], Yan Wang[c], Bin Qin[c], Xiaohui Jiang[c]

[a] *Akina, Inc., 3495 Kent Avenue, Suite A200, West Lafayette, IN 47906, USA*
[b] *Biomedical Engineering and Pharmaceutics, Purdue University, 206 S. Martin Jischke Drive, West Lafayette, IN 47907, USA*
[c] *Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA*

Characteristics of In-house Standards

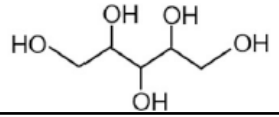
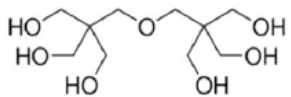
Initiator used for branch standards	Expected # of arms per molecule
Trimethylolpropane 	3
Pentaerythritol 	4
Adonitol 	5
Dipentaerythritol 	6

Table 3
Comparison Osmometer data to GPC-4D for indicated polymers.

Polymer	M_w (GPC-4D)	M_n (GPC-4D)	Osmometer M_n ($n = 4$)
3-Arm PLGA (AP229)	42,010 ± 177	36,714 ± 115	39,464 ± 3129
4-Arm PLGA (AP227)	44,869 ± 395	39,496 ± 438	43,513 ± 1174
6-Arm PLGA (AP228)	49,375 ± 269	46,715 ± 281	51,879 ± 5569
Glu-PLGA (Corbion)	52,148 ± 84	40,985 ± 48	42,440 ± 2093
Glu-PLGA (Evonik)	52,943 ± 306	40,061 ± 466	43,339 ± 2195
Glu-PLGA (Sandostatin LAR)	43,835 ± 1196	37,188 ± 950	39,306 ± 6071

Hadar *et al.*, JCR, 2019

Branch Analysis Of In-house Branch Standards Using GPC-4D

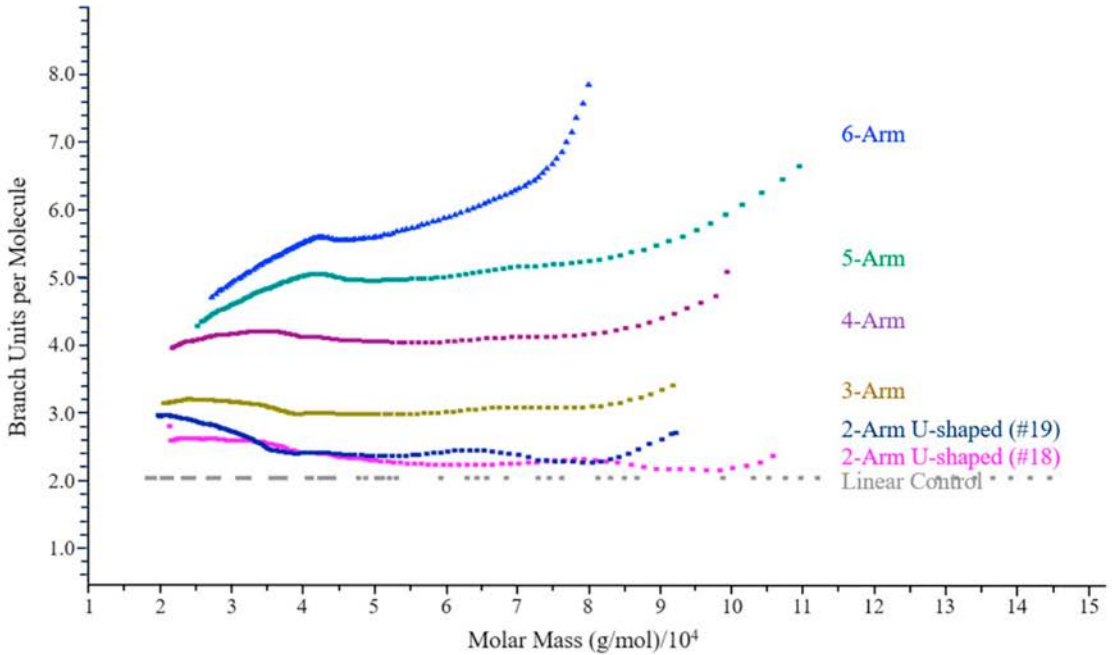
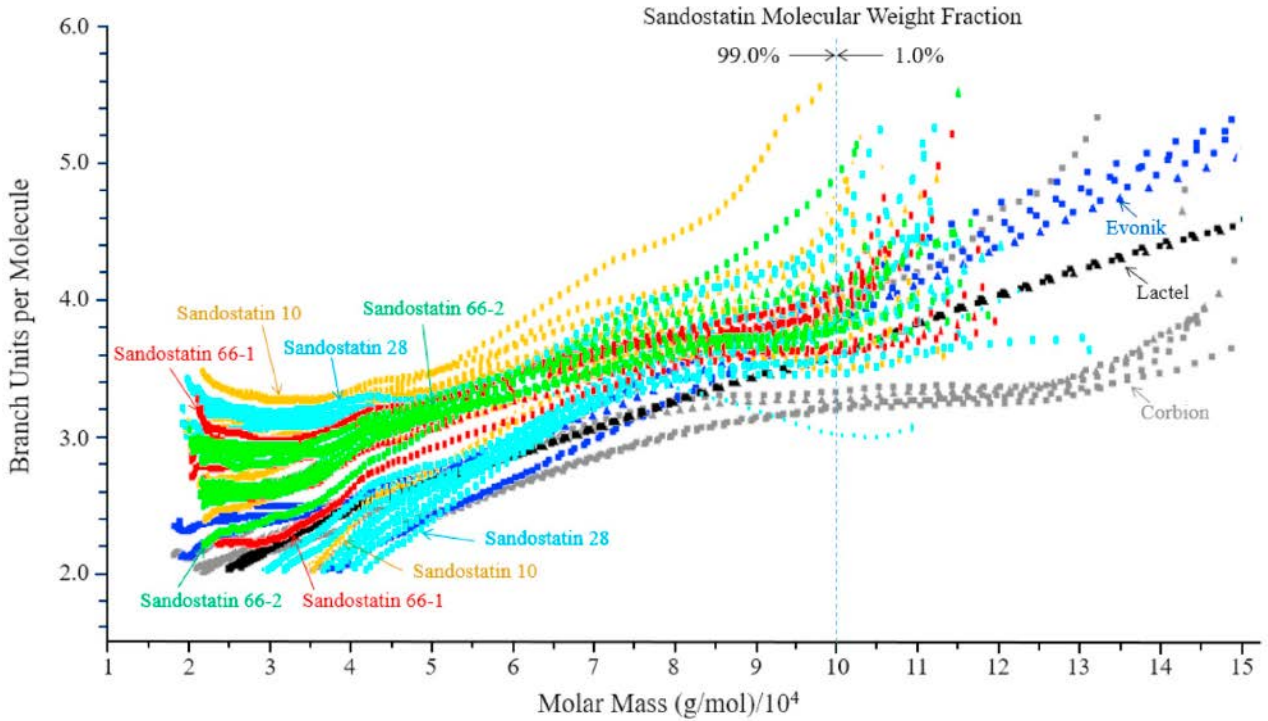


Fig. 5. The branch units per molecule as a function of the molar mass of branched PLGAs with branch units ranging from 2 to 6.

Hadar *et al.*, JCR, 2019

Branch Analysis of Sandostatin LAR Polymer and Commercial Available Star Polymers



Hadar *et al.*, JCR, 2019

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.

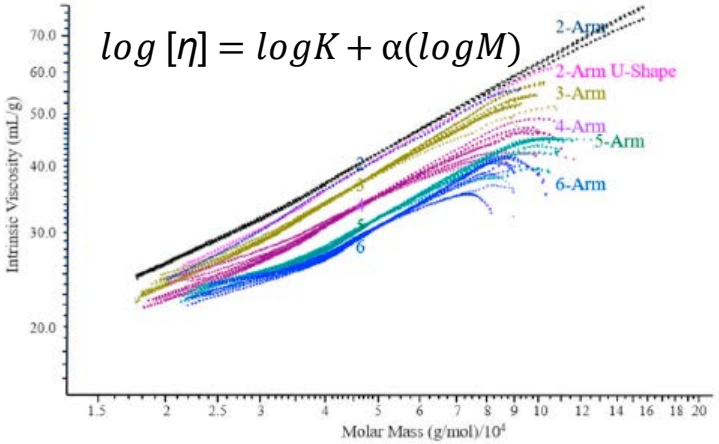
$$g' = g^e \quad (3)$$

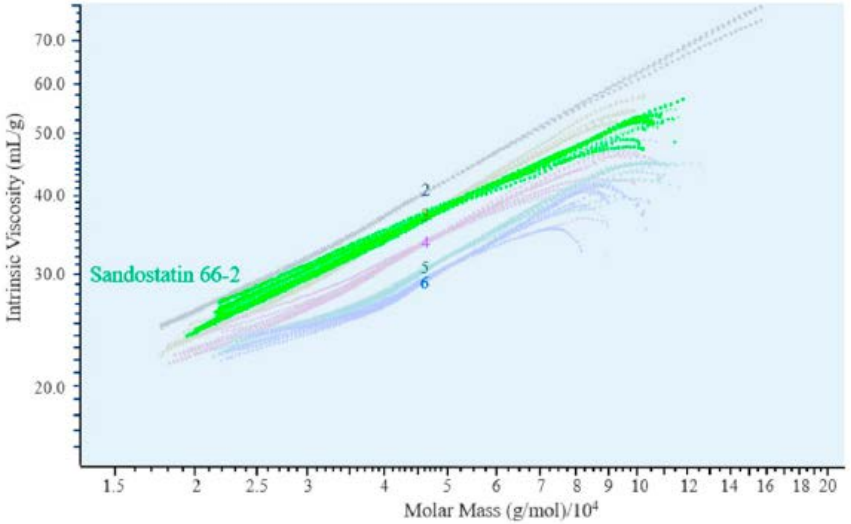
e: drainage factor

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

B: branch units per molecule

Mark-Houwink Plots of Branch Standards





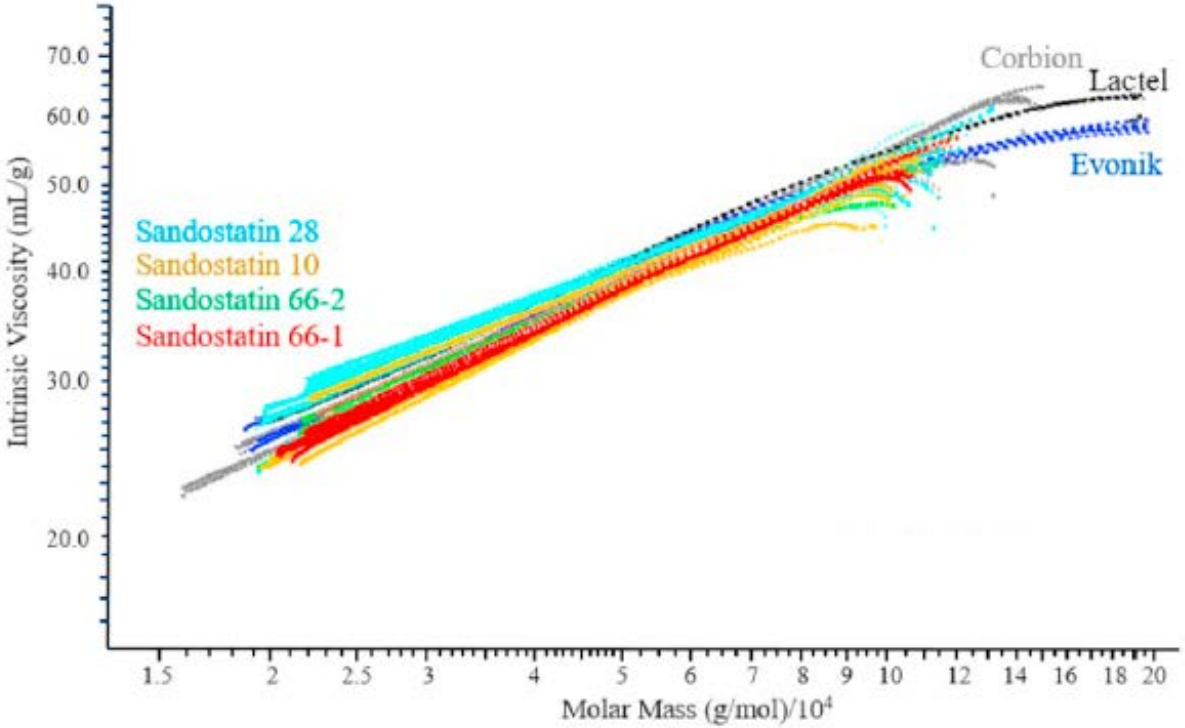
$[\eta]$ Intrinsic viscosity

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.

Hadar *et al.*, JCR, 2019

Mark-Houwink Plots of Glucose Star Polymers



Hadar *et al.*, JCR, 2019

Trelstar® (Triptorelin Pamoate Injectable Suspension)

The TRELSTAR products are sterile, lyophilized biodegradable microgranule formulations supplied as single dose vials. Refer to Table 5 for the composition of each TRELSTAR product.

Table 5. TRELSTAR Composition

	1 Month	3 Months	6 Months
Ingredients	**TRELSTAR 3.75 mg**	**TRELSTAR 11.25 mg**	**TRELSTAR 22.5 mg**
triptorelin pamoate (base units)	3.75 mg 2.7%	11.25 mg 8.7%	22.5 mg 11.0%
poly-*d,l*-lactide-co-glycolide	136 mg	118 mg	182 mg
mannitol, USP	69 mg	76 mg	68 mg
carboxymethylcellulose sodium, USP	24 mg	27 mg	24 mg
polysorbate 80, NF	1.6 mg	1.8 mg	1.6 mg

Molecular Weight: GPC. (Polystyrene standards)

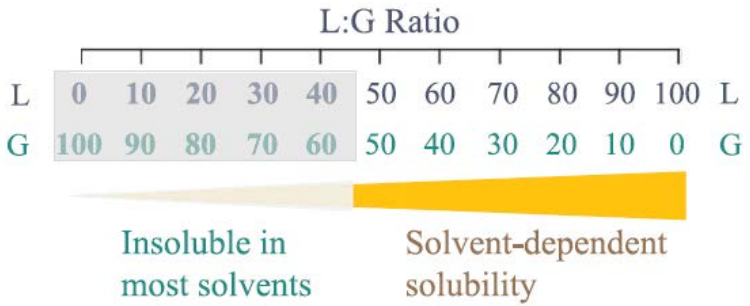
L:G Ratio: H-NMR

End Group: C-NMR

Sample	M_n (Da)	M_w (Da)	L:G (mol:mol)	Endcap
Trelstar® 3.75 mg	25,192	85,207	52:48	Ester
Trelstar® 11.25 mg	47,214	72,286	74:26	Acid
Trelstar® 22.50 mg	46,368	74,042	77:23	N/A

- Considering how PLGA properties generally control drug release, further investigation was needed to better understand the observation.

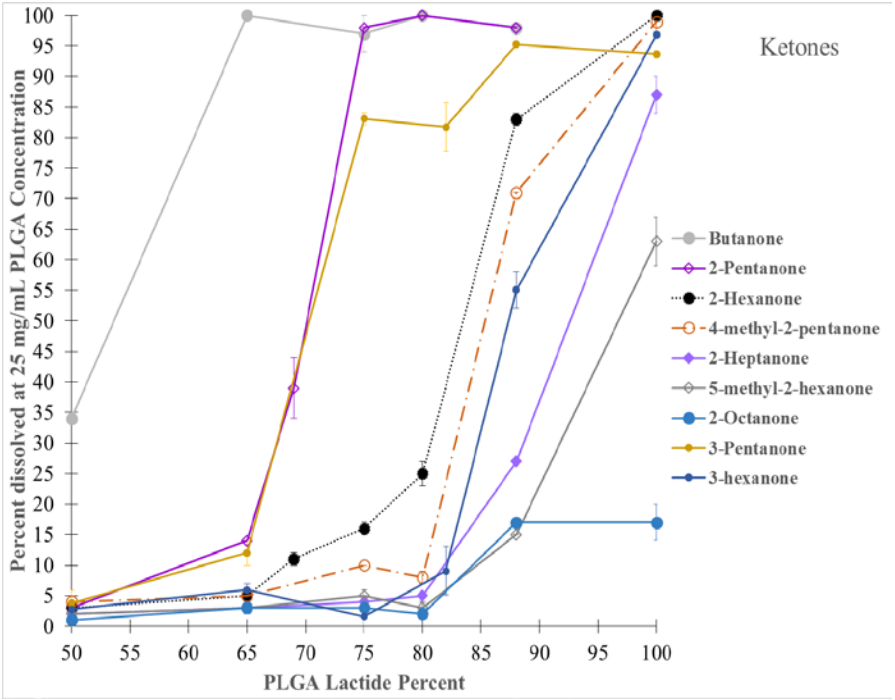
Mixtures of PLGA Polymers

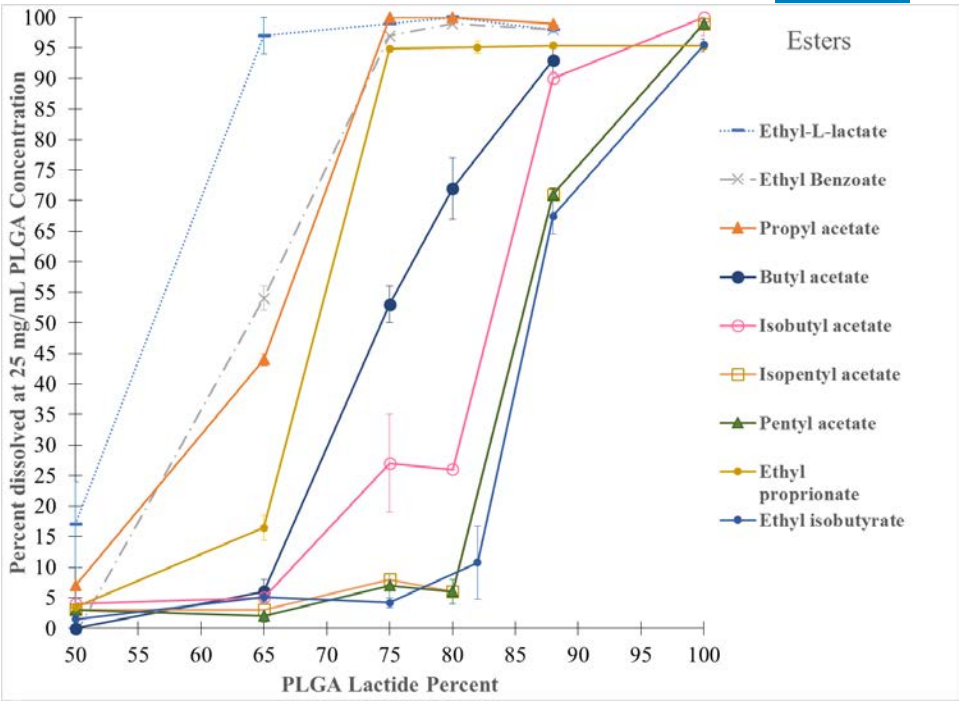


JCR, 2019, 304: 125-134

- A drug product may contain 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 is the same.

PLGA Dissolution by L:G Ratio





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Separation and Analysis of PLGA in Trelstar

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

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 (Average)	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	24,453 ± 1316	19,429 ± 811	0.48 ± 0.08
Toluene	25.5 ± 1.3	82.9 ± 0.1	47,790 ± 939	39,084 ± 2888	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.

- The data on the PLGA extracted from the formulation without any further treatment
- Fraction 1 with L:G above 80:20
- Fraction 2 with L:G in the range of 70:30 – 75:25
- Good mass recovery

➢ The results demonstrate that it is feasible to separate PLGA mixtures by dissolution of PLGA with different L:G ratio using various semi-solvents.

➢ More studies are needed to better understand the impact of MW/weight distribution on solubility of PLGA polymers

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Summary

- Generic parenteral products need to contain the same excipients in the same concentration as the reference listed drugs
- Understanding of characteristics of complex polymeric excipients is critical for successful new and generic drug product development
- Characteristics of PLGA polymers are complex
- GPC-4D is a promising tool for structural characterization of branched PLGA polymer
- It is possible to separate mixtures of PLGA polymers based on L:G ratio


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