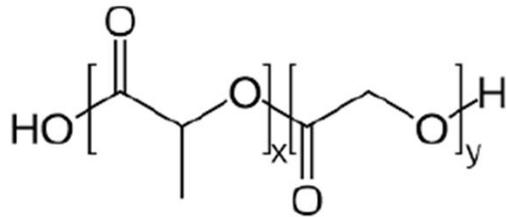


Biodegradable Polymers

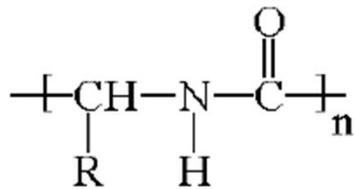
Biodegradable Polyesters

Biodegradable

Poly(lactide-co-glycolide) [PLGA]



Polypeptides

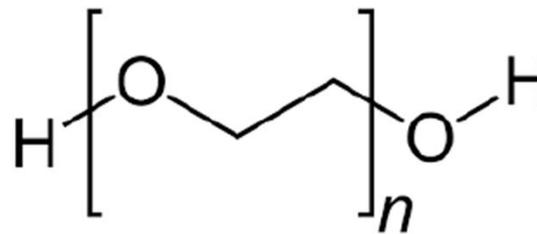


Characteristics of materials

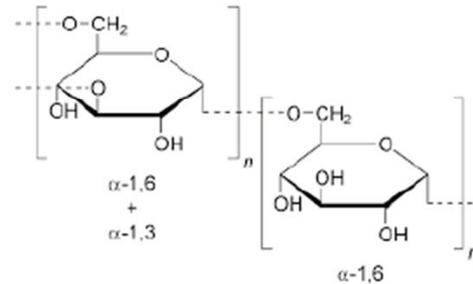
Hydrophilic or hydrophobic
Chemically unstable in Water

Bioeliminable

Poly(ethylene glycol) <10 kDa



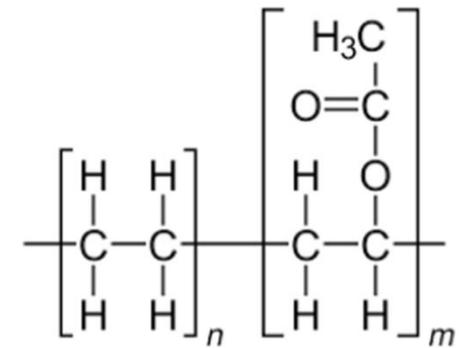
Dextran



Hydrophilic (water soluble)
Chemically stable in water

Removable

Poly(ethylene-co-vinyl acetate)



Hydrophobic/insoluble
Chemically stable in water

Biodegradable Polyesters

Table 1. Biodegradable Polyesters Commonly Used in Biomedical Applications

Polymer	Polymer structure	Synthetic Or natural	Metabolized in the body	Degradation by-products	Approx. biodegradation rate <i>in vivo</i>
PCL		Synthetic	Renal system	6-hydroxy caproic acid	24 – 48 months
PLA PLLA PDLA		Synthetic	Glycolytic energy cycle	Lactic acid	3 – 36 months (depending on stereoisomer)
PLGA		Synthetic	Glycolytic energy cycle	Lactic acid Glycolic acid	1 – 6 months (varying mol %)
PGA		Synthetic	Tricarboxylic acid cycle	Glycolic acid	1 – 12 months
PPF		Synthetic	Krebs cycle	Fumaric acid Propylene glycol	Varies, 10% weight loss @ 12 weeks
PGS		Natural	Krebs cycle	Glycerol Sebacic acid	1 – 2 months
PDO		Synthetic	Respiratory and gastrointestinal tract	2-Hydroxy-ethoxy acetic acid (degrades to CO ₂ and H ₂ O)	6 – 8 months
PBS		Synthetic	Krebs cycle	Succinic acid (degrades to CO ₂ and H ₂ O)	3 months
PHA PHB		Natural	Krebs cycle	Hydroxy-butyric acid	Varies, 58% weight loss @ 7 weeks

PCL: Polycaprolactone; PLA: Poly(lactic acid); PLLA: Poly(L-lactic acid); PDLA: Poly(D,L-lactic acid); PLGA: Poly(lactide-co-glycolide); PGA: Polyglycolide; PPF: Poly(propylene fumarate); PDO: Polydioxanone; PBS: Poly(butylene succinate); PHA: Polyhydroxyalkanoate; PHB: Polyhydroxybutyrate

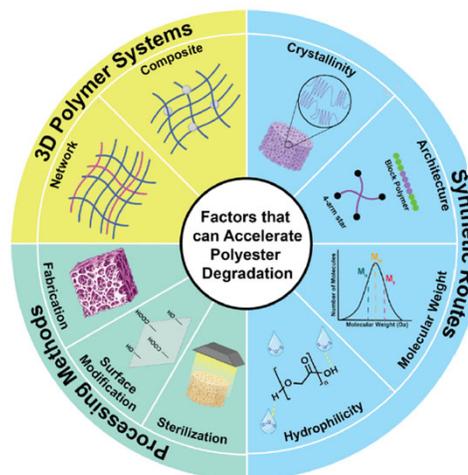
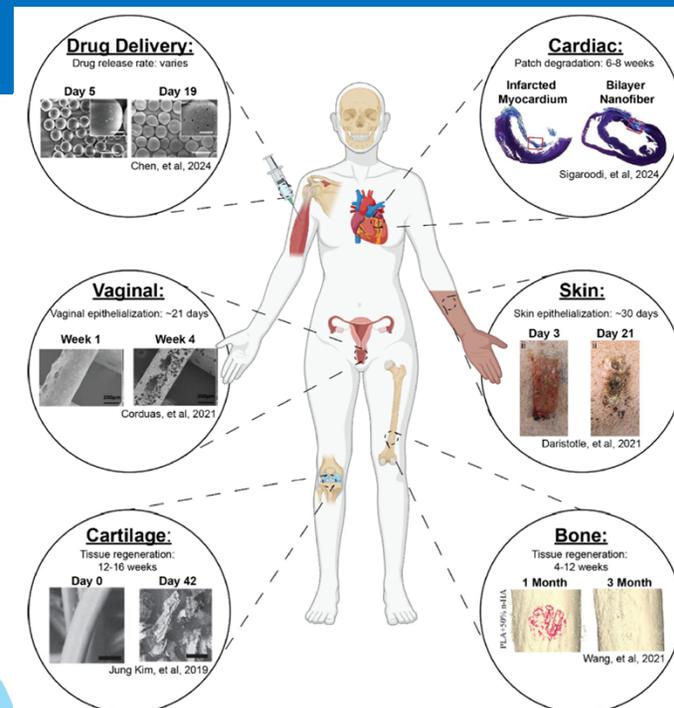


Figure 2. Various approaches alter the rate of polyester degradation



Roberts 2025, Biodegradable polyesters: Approaches to increase degradation rates for biomedical applications

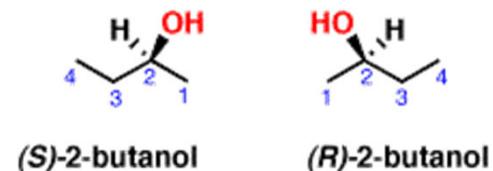
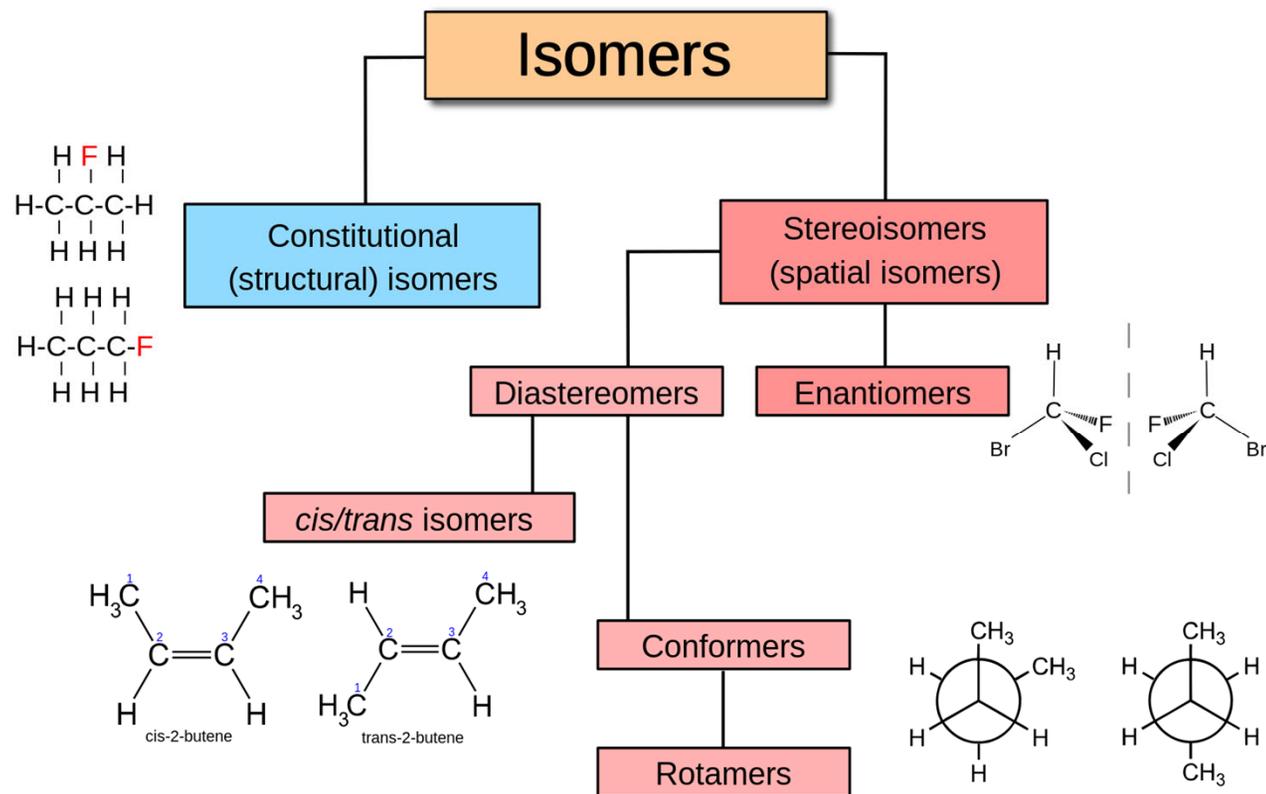
Biodegradable Polyesters

There are numerous aliphatic biodegradable polyesters. However, only a small number of them are commercially available. Some biobased polyesters that have gained commercial use or that are currently investigated for commercial use are **polylactic acid (PLA)**, **polyglycolic acid (PGA)**, **poly- ϵ -caprolactone (PCL)**, **polyhydroxybutyrate (PHB)**, and **poly(3-hydroxy valerate)**. Among these, PHB and PLA are probably the most extensively studied biodegradable thermoplastic polyesters. Both are a truly biodegradable and biocompatible and both have a relatively high melting point (160 to 180 °C). However, practical applications have often been limited by their brittleness and narrow processing window. Therefore, blending with other polymers has been often reported in the literature.

Tensile properties are usually best for those with the smallest molar volume (highest packing density). Especially strong are PGA and PLA, whereas PCL, on the other hand, is the softest polymer with an extraordinary high strain at failure. A very important factor is the molecular weight (MW). **Varying the MW will yield polyesters with very different mechanical properties**. For example, the tensile strength of PLA can vary between 1 and 150 MPa. **Another important factor is tacticity**. Many aliphatic polyesters have **an asymmetrical carbon atom** in the repeat unit which enables it to become optically active. For example, it is possible to obtain **isotactic L-PLA** or **D-PLA** and **syndiotactic DL-PLA** consisting of alternating L- and D-units. These polymers have very different mechanical properties. For example, L-PLA has two to three times higher tensile strength and Young's modulus than DL-PLA.

For the full story, please read the article available on <https://polymerdatabase.com/polymer%20classes/Biodegradable%20Polyester%20type.html>

Chemistry Review



Enantiomers: a pair of non-superimposable mirror images.

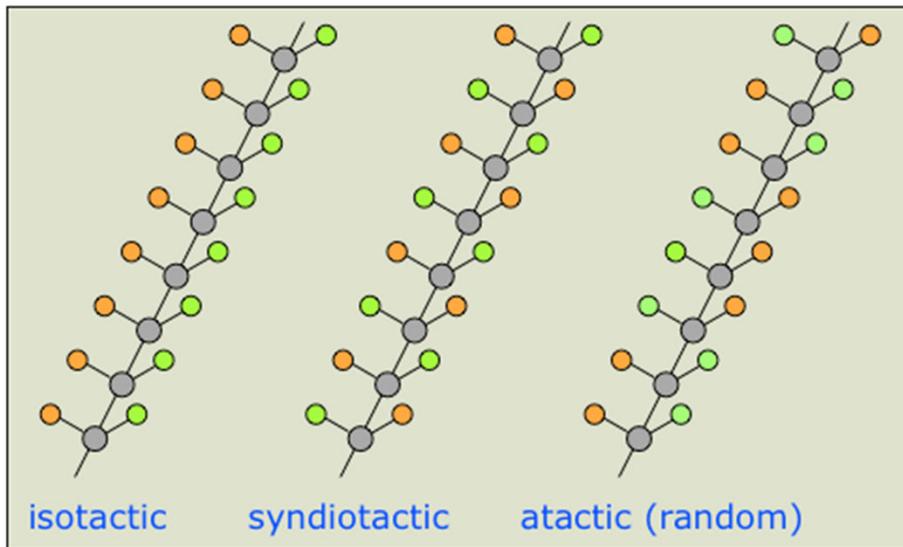
A **racemic** mixture: A solution containing **equal** amounts of (R)-2-butanol and (S)-2-butanol.

Enantioenriched: A solution containing an excess of either the (R)-enantiomer or the (S)-enantiomer.

Enantiomerically pure: A solution containing only the (R)-enantiomer or the (S)-enantiomer.

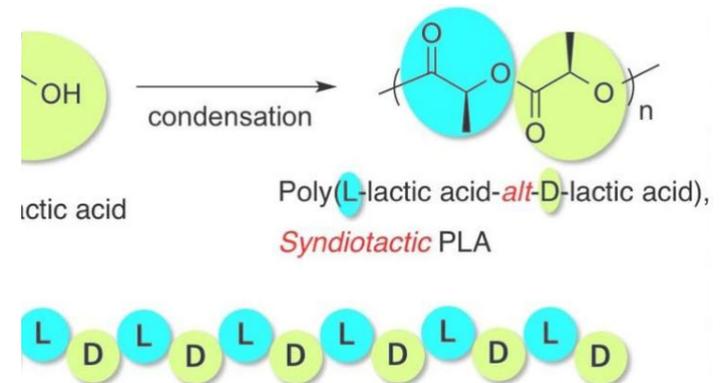
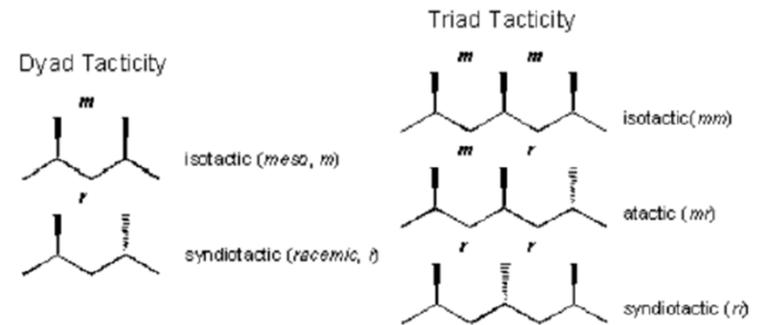
Isotactic, Syndiotactic and Atactic Polymer Models

A polymer can have very different properties depending on their tacticity, i.e., steric arrangement of monomers.



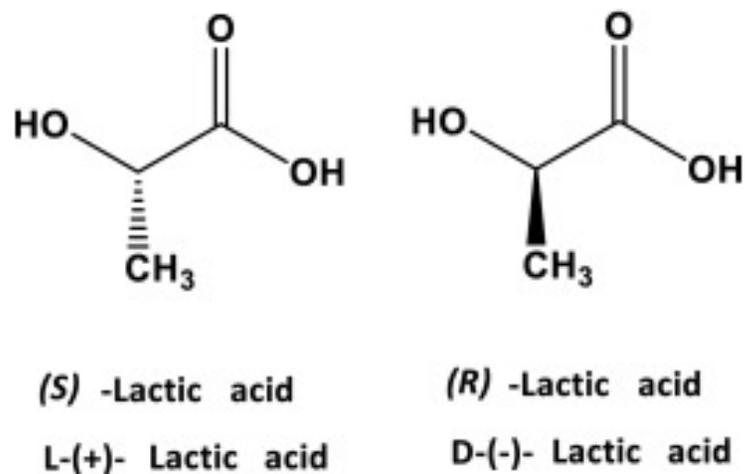
Polymer tacticity is another property of plastics, but one you usually don't hear about. Tacticity relates to the organization of monomer units within polymer strands. There are three categories of polymer tacticity: isotactic, syndiotactic and atactic polymers in order of increasing variability. Isotactic polymers are comprised of monomer units all connected in the same way to each other. Syndiotactic polymers have every other monomer unit in the same orientation and atactic polymers are oriented any which way.

<http://everydaythinkers.blogspot.com/2015/08/its-just-plastic-but-what-is-just.html>

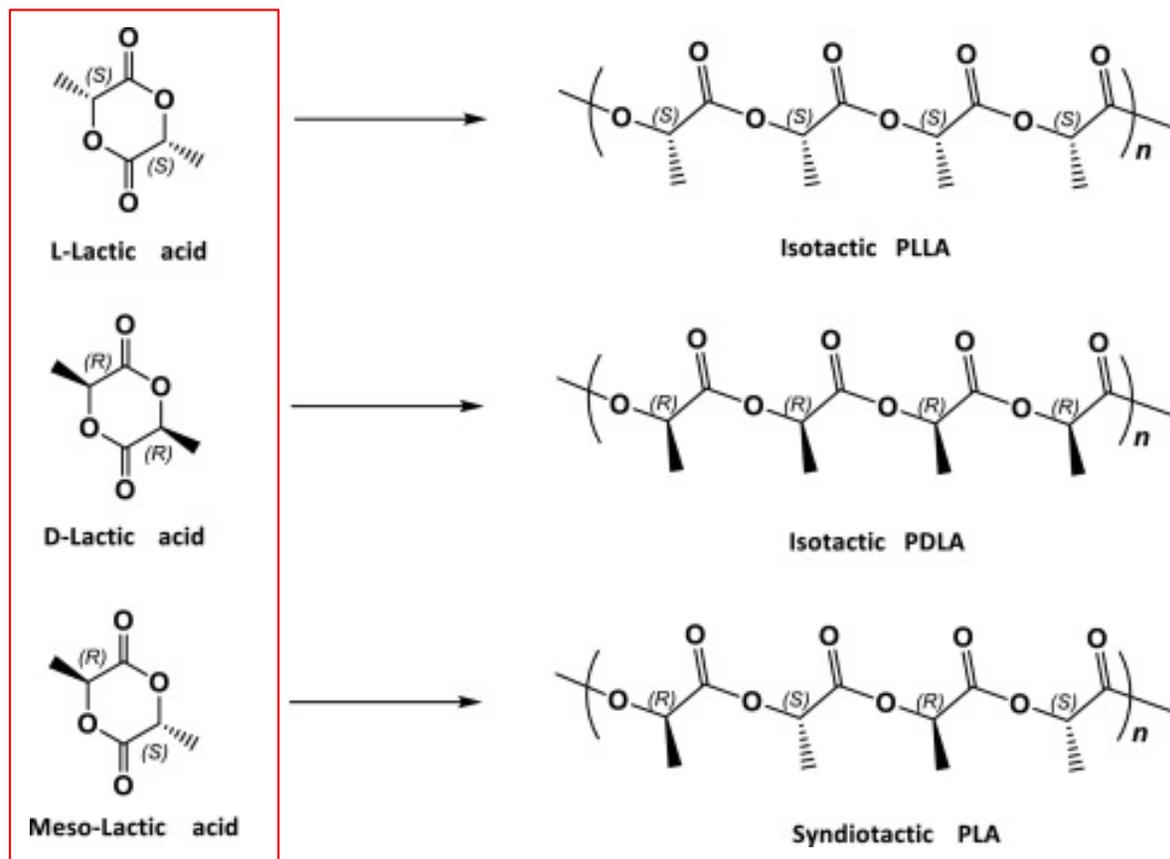


<https://phys.org/news/2018-05-method-polyester-alternating.html>

Poly(lactide)s: Stereoisomers and Enantiomers



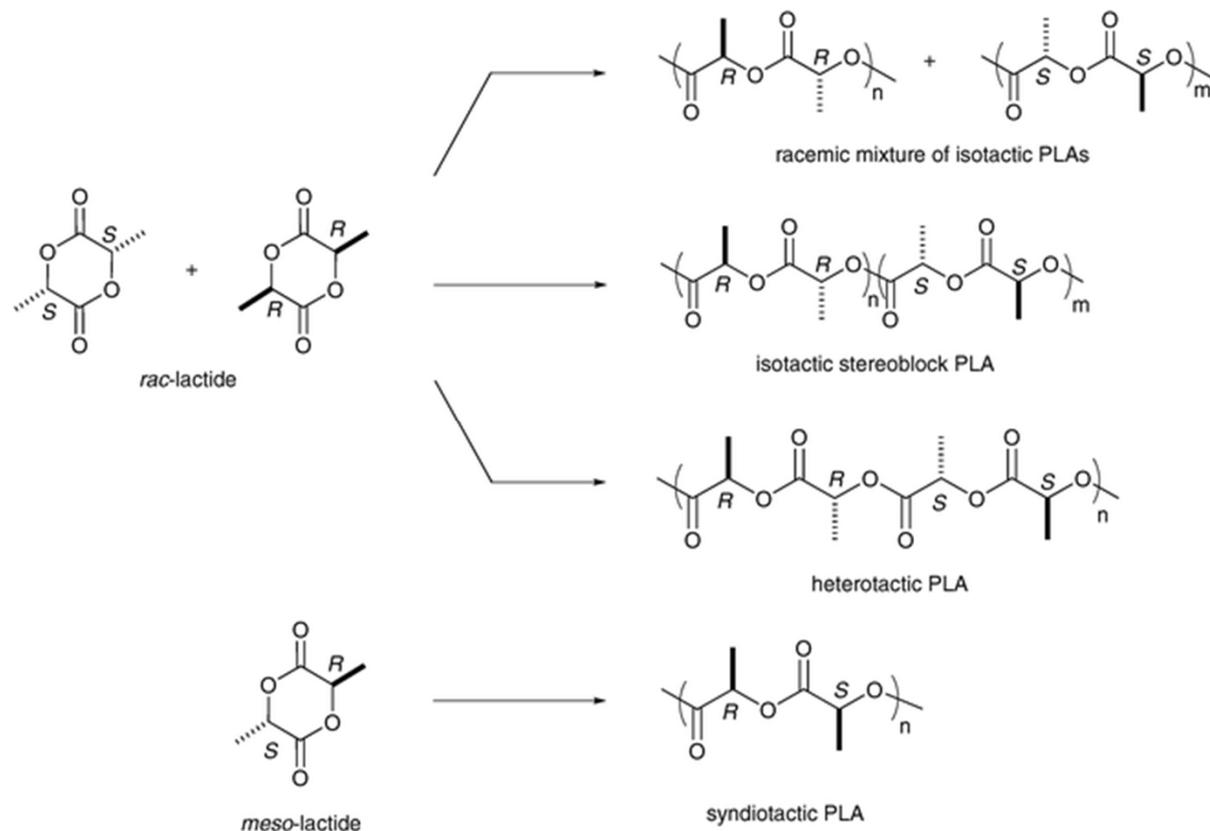
Scheme 1. Two enantiomeric forms of lactic acid: (S)- and (R)- 2-hydroxypropionic acid.



Scheme 2. Three stereoisomers of lactide which lead to distinct PLA structures upon polymerization.

Poly(lactide)s: Stereochemistry and Microstructure

In terms of stereochemistry, many types of lactide feedstocks are accessible. Diastereomers (S,S)-lactide, (R,R)-lactide, and meso-lactide are available in pure form, as well as the racemic mixture rac-lactide (50:50 (S,S)-LA and (R,R)-LA) (Scheme 2). Many polymer microstructures (i.e. atactic, isotactic, heterotactic and syndiotactic) can be constructed from this basic set of monomers. For example, polymerization of (R,R)-lactide with a typical (homoleptic or heteroleptic) catalyst gives isotactic poly((R)-lactide), a crystalline polymer with a high melting transition ($T_m = 170\text{--}180\text{ }^\circ\text{C}$). Atactic PLA, an amorphous polymer with a random distribution of stereocenters along the polymer backbone, can be prepared using a non-stereoselective metal-based catalyst and rac-lactide. Despite the recent development of achiral and chiral complexes for the ring-opening polymerization (ROP) of lactide, relatively few well-defined metal catalysts are capable of achieving high stereochemical control in the ROP of meso- or rac-lactide.



<https://pubs.rsc.org/en/content/articlehtml/2010/cs/b810065a>

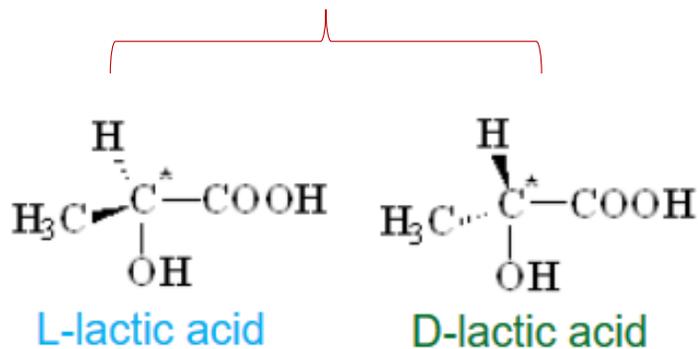
C.M. Thomas, Stereocontrolled ring-opening polymerization of cyclic esters: synthesis of new polyester microstructures, *Chem. Soc. Rev.*, 2010, 39, 165-173.

Lactide-Based Polymers: Tacticity & Isomerism

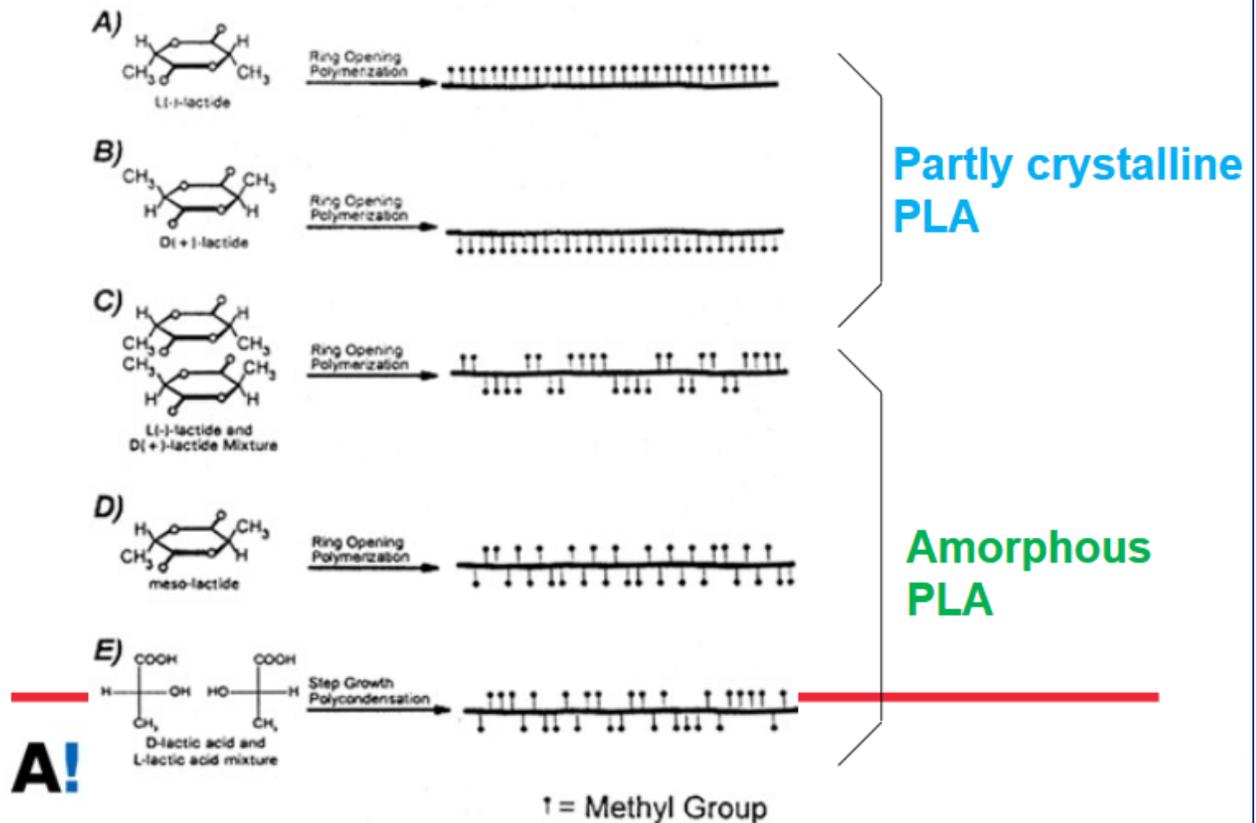
Note: Go to <https://slideplayer.com/slide/8939858/> and go through all slides, in particular Slides #15-26.

Crystalline polymer or a crystalline portion of a polymer does not dissolve in solvent or take a long time to dissolve, while amorphous polymer or an amorphous portion dissolves in the same solvent.

D,L-lactic acid is a mixture of the two



Poly lactides



<https://slideplayer.com/slide/8939858/>

KE-100.3410 Polymer Properties Steve Spoljaric, PhD.

Examples of Biodegradable Polyesters

Polyester	Structure of Repeat Unit
Poly(lactic acid) or Polylactide (PLA) $T_g \approx 45 - 60 \text{ }^\circ\text{C}$ $T_m \approx 150 - 160 \text{ }^\circ\text{C}$	$\text{H} \left[\text{O} - \underset{\text{CH}_3}{\text{CH}} - \underset{\text{O}}{\underset{\parallel}{\text{C}}} \right]_n \text{OH}$
Poly(L-lactic acid) or Poly(L-lactide) (L-PLA) $T_g \approx 55 - 65 \text{ }^\circ\text{C}$ $T_m \approx 170 - 200 \text{ }^\circ\text{C}$	$\text{H} \left[\text{O} - \underset{\text{CH}_3}{\text{CH}} - \underset{\text{O}}{\underset{\parallel}{\text{C}}} \right]_n \text{OH}$
Poly(DL-lactic acid) or Poly(DL-lactide) (DL-PLA) $T_g \approx 50 - 60 \text{ }^\circ\text{C}$ $T_m \approx \text{N/A (am.)}$	$\text{H} \left[\text{O} - \underset{\text{CH}_3}{\text{CH}} - \underset{\text{O}}{\underset{\parallel}{\text{C}}} \right]_n \text{OH}$

Polyester	Structure of Repeat Unit
Poly(glycolic acid) or Polyglycolide (PGA) $T_g \approx 35 - 45 \text{ }^\circ\text{C}$ $T_m \approx 220 - 235 \text{ }^\circ\text{C}$	$\text{H} \left[\text{O} - \text{CH}_2 - \underset{\text{O}}{\underset{\parallel}{\text{C}}} \right]_n \text{OH}$
Poly(ϵ -caprolactone) (PCL) $T_g \approx -60 - (-65) \text{ }^\circ\text{C}$ $T_m \approx 58 - 65 \text{ }^\circ\text{C}$	$\text{H} \left[\text{O} - \left(\text{CH}_2 \right)_5 - \underset{\text{O}}{\underset{\parallel}{\text{C}}} \right]_n \text{OH}$
Poly(hydroxybutyrate) (PHB) $T_g \approx 5 - 15 \text{ }^\circ\text{C}$ $T_m \approx 165 - 180 \text{ }^\circ\text{C}$	$\text{H} \left[\text{O} - \underset{\text{CH}_3}{\text{CH}} - \text{CH}_2 - \underset{\text{O}}{\underset{\parallel}{\text{C}}} \right]_n \text{OH}$

Poly(glycolide-co- ϵ -caprolactone) (PGCL)

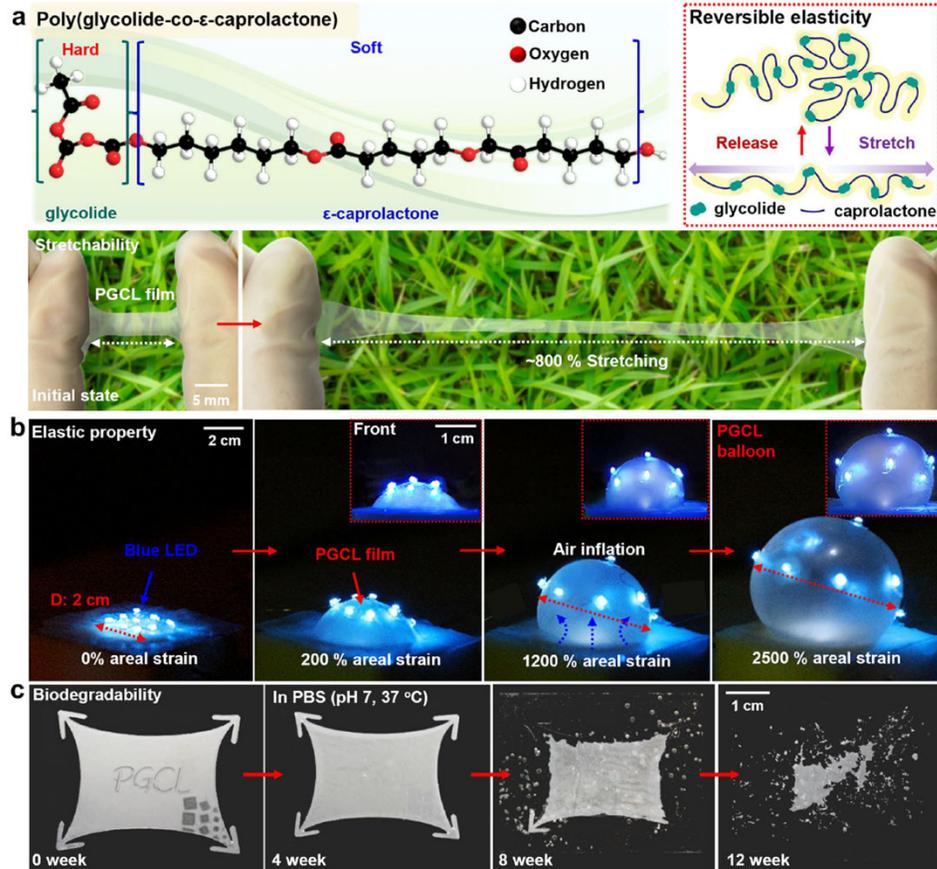


Fig. 1 Stretchable, biodegradable elastomeric polymer. **a** Chemical structure of stretchable and biodegradable elastomer, poly (glycolide-co- ϵ - caprolactone) (PGCL). The copolymer consists of glycolide as a hard, cross-linker segment and ϵ -caprolactone as a soft, elastic domain (top). Extreme stretchability up to $\sim 800\%$ of a PGCL film (150 μm thick), with an image at the initial state (bottom). **b** A set of images showing superior elasticity through a wide range of areal strains ($\sim 2500\%$) using inflation of PGCL balloons combined with light-emitting diodes (LEDs). **c** Time-sequential degradation images of a PGCL substrate (thickness: 250 μm) in phosphate buffer saline (PBS, pH 7) solution at body temperature (37 $^{\circ}\text{C}$) during 12 weeks

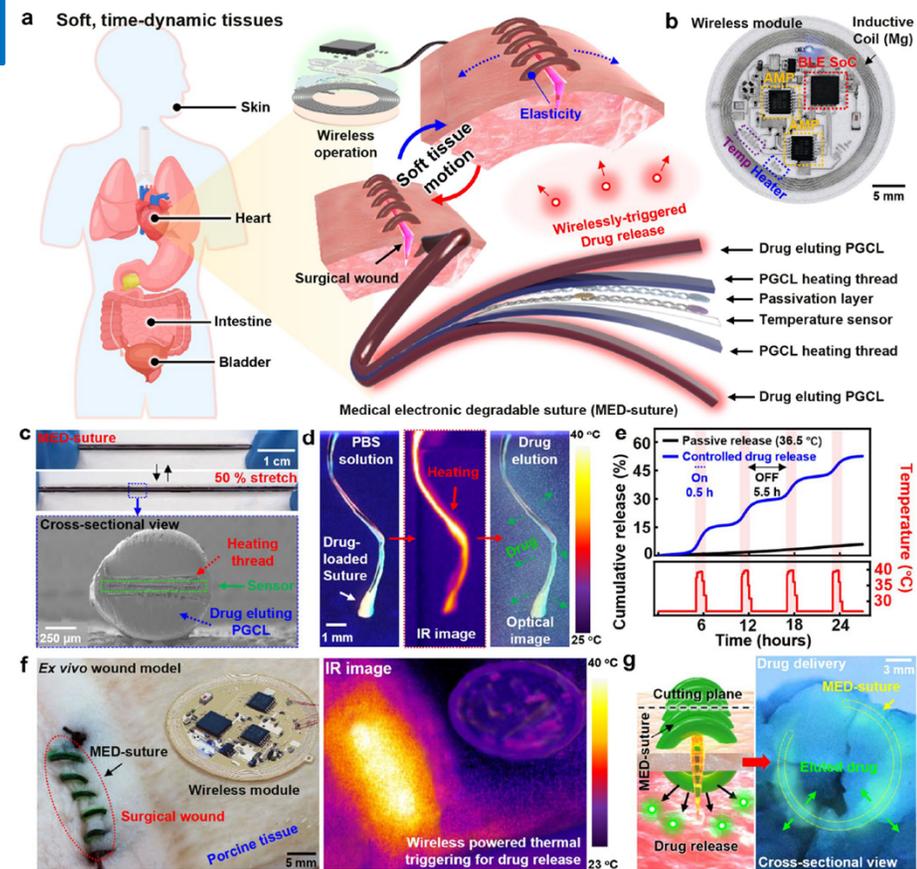
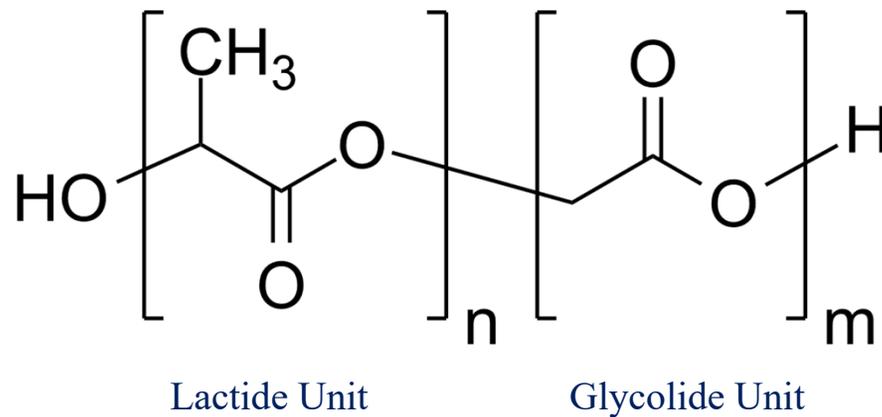


Fig. 4 Transient electronic suture system. **a** Illustration of a medical, electronic, and degradable suture (MED-suture) system with a wireless circuit for surgical wound healing of post-operation sites on soft, time-dynamic tissues in the body. The electronic suture includes layers of on-demand drug vehicle (PGCL 15:85), conductive composite-based resistive heater (PGCL 55:45 composite), passivation layer (SiO_2 , 300 nm), electrical interconnects (W/Mg, 100-nm/1- μm thick), and temperature meter (W/Mg, 10-nm/100-nm thick). The wireless circuit includes micro-controller and bluetooth modules, amplifier, diodes, capacitors, and inductive coil (Mg, 20- μm thick). **b** Photograph of fabricated wireless system for MED-suture with multiple functions of temperature measurements and heating actuation. **c** Elastic performance of MED-suture with 50% of uniaxial tensile strain and cross-sectional view of its overall structure observed with scanning electron microscope (SEM). **d** In vitro drug delivery demonstration of MED-suture immersed in PBS solution at room temperature: (1) initial state (left), (2) thermal actuation (middle), and (3) drug elution (right). **e** On-demand drug release behaviors with ON/OFF cyclic thermal actuations and temperature monitoring profile for 24 h. **f** Ex vivo experiment setup for MED-suture using porcine skin with surgical incisions and IR images of heat-induced drug release via thermal actuation. **g** Experimental result after drug release on porcine tissues with four cyclic actuations

Poly(Lactide-co-Glycolide) (PLGA)

A PLGA polymer is a random copolymer of lactide and glycolide monomers.

The properties of PLGA polymers depends on the molecular weight, molecular structure, and lactide:glycolide (L:G) ratio.

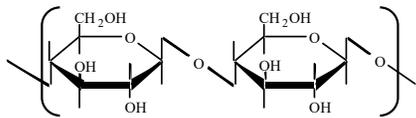


Polymers: Chemical Structure & Molecular Weight

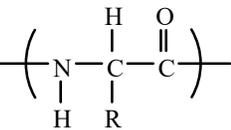
Note: Most polymers are usually described by their chemical structures and molecular weight.
But PLGA polymers require more information to fully characterize their properties, such as molecular structure and L:G ratio.

Natural Polymers

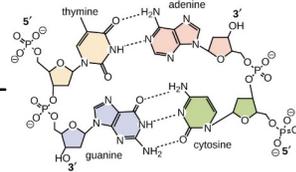
Cellulose



Protein

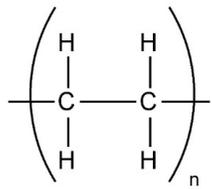


DNA

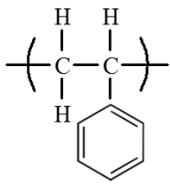


Synthetic Polymers

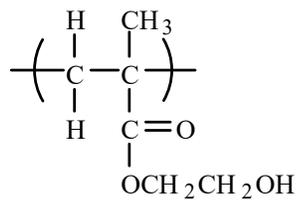
Polyethylene



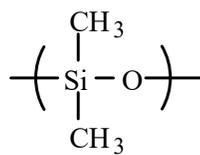
Polystyrene



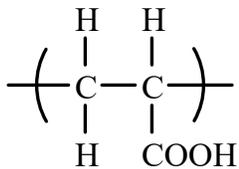
Poly(HEMA)



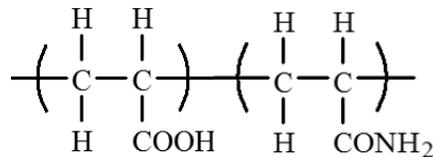
Silicone Rubber



Poly(acrylic acid)



Poly(acrylic acid-co-acrylamide)



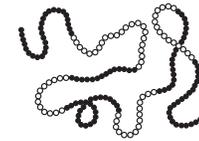
Types of Synthetic Polymers

Linear Polymers

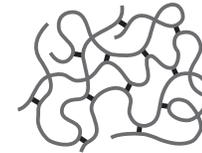
Homopolymer



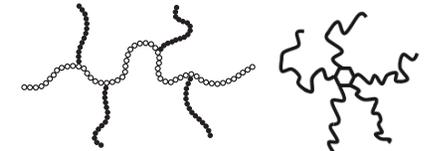
Block copolymer



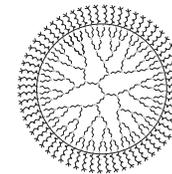
Crosslinked Gel



Branched Polymers



Dendrimers



How Do We Characterize PLGA?

PLGA Characterization Methods

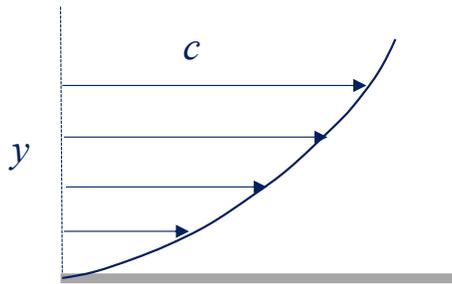
Molecular Weight
Lactide:Glycolide Ratio (L:G Ratio)
Endgroup

Viscosity of Polymer Solutions

Let's understand various viscosities of polymer solutions

Dynamic Viscosity (Absolute or Shear Viscosity)

Dynamic viscosity is a measure of the resistance of a fluid to gradual deformation by shear stress. The resistance is a result of friction caused by sliding layers of fluid.



Newton's Law of Friction

$$\tau = \eta \dot{\gamma}$$

τ : Shear stress in fluid in Pascal (N/m^2)

η : Dynamic viscosity of fluid ($\text{N}\cdot\text{s}/\text{m}^2$)

$\dot{\gamma}$: Shear rate (s^{-1}) = $\Delta c / \Delta y$

Δc : Unit velocity (m/s)

Δy : Unit distance between layers (m)

$$\eta = \frac{\tau}{\dot{\gamma}} = \left(\frac{\text{N}}{\text{m}^2} \right) / \left(\frac{\text{m}}{\text{s}} \right) / \text{m} = \frac{\text{Ns}}{\text{m}^2}$$

$$1 \frac{\text{Ns}}{\text{m}^2} = 1 \left(\frac{\text{Kg} \cdot \text{m}}{\text{s}^2} \right) \left(\frac{\text{s}}{\text{m}^2} \right) = 1 \text{Pa} \cdot \text{s} = 10 \text{P} = 10 \frac{\text{g}}{\text{cm} \cdot \text{s}}$$

1 Pa·s (Pascal second) P: Poise

1 Pa·s: Two plates are separated by 1 m with a fluid in between, and one plate is moving parallel to the other plate with a shear stress of 1 pascal to move 1 m/s. If 2 m/s, then the viscosity is ½ Pa·s.

The viscosity of water = 1 cP (= 0.01 g/cm·sec = 1 mPa·sec = 0.001 Pa·sec = 0.001 N·s/m²).

Viscosity of Polymer Solutions

Viscosity of a polymer solution can be measured by various methods. **Viscosity of a polymer solution is a function of temperature, solvent, polymer concentration, and polymer molecular weight.** When a polymer molecular weight is determined

Viscosity of a polymer solution provides insightful **information on the configuration of the polymer molecules in solution.** **At high polymer concentrations, polymer molecules tend to entangle each other, and this affect the measurement of viscosity.** Thus, it is necessary to estimate the effect of solvent viscosity and polymer concentration on the overall viscosity. Since the viscosity measurement procedures do not remove the effects of polymer-solvent interactions, **the viscosity average molecular weight (\overline{M}_v)** depends on some extent on the solvent used

In a dilute solution, the disturbance of the flow pattern of the suspending medium by one particle (i.e., a polymer molecule) does not overlap with that caused by another. Solvent trapped inside a polymer molecule has lower viscosity than the bulk solution. Thus, the polymer coil behaves as an impenetrable sphere.

Viscosity Measurement



Ubbelohde Viscometer

- Measuring viscosity of dilute solution

Upper and lower level

Measure the flow time t , of solution

$$\eta = k\rho t$$

k = viscometer constant
 ρ = density of solution
 t = flow time

t = time for solution

t_0 = time for solvent

$\rho \approx \rho_0$

Relative Viscosity

$$\eta_{rel} = \frac{\eta_{solution}}{\eta_{solvent}} = \frac{\eta}{\eta_0}$$

$$= \frac{k\rho t}{k\rho_0 t_0} = \frac{t}{t_0}$$

Specific Viscosity

$$\eta_{sp} = \eta_{rel} - 1$$

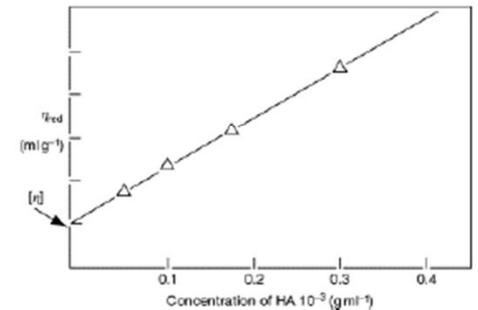
$$= \frac{\eta}{\eta_0} - \frac{\eta_0}{\eta_0}$$

Intrinsic Viscosity

$$[\eta] = \lim_{c \rightarrow 0} \left(\frac{\eta_{sp}}{c} \right)$$

Inherent Viscosity

$$\eta_{inh} = \frac{\ln \eta_{sp}}{c}$$



Viscosity of Polymer Solutions

Viscosity of spheres and random coil molecules.

$$\eta = \eta_o \left(1 + \frac{5}{2} \phi \right) = \eta_o \left(1 + \frac{5}{2} \frac{N_A c V_h}{M} \right)$$

where N_A is the Avogadro's number, c is the polymer concentration (g/ml), M is the polymer molecular weight, and V_h is the volume of a solvated molecule.

Relative viscosity (η_{rel}):
$$\eta_{rel} = \frac{\eta}{\eta_o} = 1 + \frac{5}{2} \phi$$

Inherent viscosity (η_{inh}):
$$\eta_{inh} = \frac{\ln(\eta_{rel})}{c}$$

Specific viscosity (η_{sp}):
$$\eta_{sp} = \frac{\Delta\eta}{\eta_o} = \frac{\eta - \eta_o}{\eta_o} = \eta_{rel} - 1 = \frac{5}{2} \phi$$

The specific viscosity accounts for the effect of solvent viscosity. The specific viscosity (η_{sp}) is a suitable indicator for the changes in shape.

Spherical polymer has low resistance to flow, and so, small η_{sp} .

Stretched, rod-like shape has higher resistance to flow, leading to high η_{sp} .

This is why the polymer solution viscosity depends on which solvent is used, as each polymer may swell differently in different solvents.

Viscosity of Polymer Solutions

Reduced viscosity (η_{red}):
$$\eta_{red} = \frac{\eta_{sp}}{c} = \left(\frac{1}{c}\right) \frac{\eta - \eta_o}{\eta_o}$$

The concentration effect is adjusted and it is valid only for dilute solution.

Intrinsic viscosity ($[\eta]$)
$$[\eta] = \frac{\Delta\eta}{c\eta_o} \Big|_{c \rightarrow 0} = \lim_{c \rightarrow 0} \frac{\eta_{sp}}{c} = \frac{5 N_A V_h}{2 M} = \frac{5 N_A}{2 M} \frac{4\pi \langle R_g^2 \rangle^{\frac{3}{2}}}{3} = \frac{\Phi \langle R_g^2 \rangle^{\frac{3}{2}}}{M} = K M^\alpha$$

The contribution of the individual macromolecules to the viscosity increase will be independent and additive only when the polymer molecules are infinitely far from each other. N_A and M are constants, so V_h can be calculated from the viscosity measurement.

The intrinsic viscosity is useful because it simple correlation to the Mark-Houwink equation (KM^α), which important to understanding the PLGA molecular structure and solution behavior.

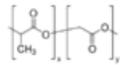
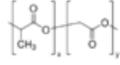
Huggins Equation:
$$\eta_{red} = \frac{\eta_{sp}}{c} = [\eta] + k_H [\eta]^2 c$$

In the Huggins equation, the reduced viscosity is related to $[\eta]$ by a power series of the form. It is useful, as it provides a way to calculate intrinsic viscosity from specific viscosity or reduced viscosity, which is relatively easier to measure. The constant k_H is termed the Huggins constant and has values ranging from 0.3 in good solvents to 0.5 in poor solvents. It contains information about hydrodynamic and thermodynamic interactions between coils in solution.

Poly(lactide-co-glycolide) (PLGA) Molecular Weights

65:35 (Lactide:Glycolide)

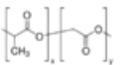
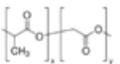
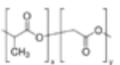
Sigma-Aldrich

Product #	Image	Description
P2066		Poly(D,L-lactide-co-glycolide) lactide:glycolide 65:35, M_w 40,000-75,000
900316		Poly(L-lactide-co-glycolide) lactide:glycolide 65:35, viscosity 0.6 dL/g
719862		Resomer [®] RG 653 H, Poly(D,L-lactide-co-glycolide) acid terminated, M_w 24,000-38,000

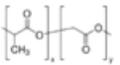
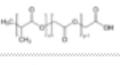
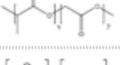
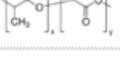
Each polymer has a range of molecular weights. The wide range in the molecular weight is common for polymers

Sometimes the molecular weight information is absent, and instead the inherent viscosity is shown. See the next slide.

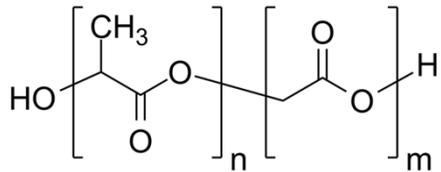
75:25 (Lactide:Glycolide)

Product #	Image	Description
P1941		Poly(D,L-lactide-co-glycolide) lactide:glycolide (75:25), mol wt 66,000-107,000
719919		Resomer [®] RG 752 H, Poly(D,L-lactide-co-glycolide) acid terminated, lactide:glycolide 75:25, M_w 4,000-15,000
719927		Resomer [®] RG 756 S, Poly(D,L-lactide-co-glycolide) ester terminated, lactide:glycolide 75:25, M_w 76,000-115,000

85:15 (Lactide:Glycolide)

Product #	Image	Description
430471		Poly(D,L-lactide-co-glycolide) ester terminated, M_w 50,000-75,000
798487		Poly(D,L-lactide-co-glycolide)-COOH M_w 17,000, lactide:glycolide 85:15
900571		Poly(D,L-lactide-co-glycolide) ester terminated lactide:glycolide 80:20, M_w 200,000
739979		Resomer [®] RG 858 S, Poly(D,L-lactide-co-glycolide) ester terminated, lactide:glycolide 85:15, M_w 190,000-240,000

Poly(lactide-co-glycolide) (PLGA)



The molecular weights of some commercial PLGA products are listed by their **inherent viscosity (IV)**, instead of actual molecular weight.

Question 1: Why IV is used instead of actual molecular weight of a polymer in many commercial products?

Is the molecular weight based on measuring IV accurate?

Commercial Products

Product No.	Chemical Name	End Group	Abbrev.	Inherent Viscosity (IV) dL/g
Ester Terminated Polymers				
B6017-1	50:50 Poly(DL-lactide-co-glycolide)	E	50:50 DL-PLG	0.15 - 0.25
B6010-1	50:50 Poly(DL-lactide-co-glycolide)	E	50:50 DL-PLG	0.26 - 0.54
B6010-2	50:50 Poly(DL-lactide-co-glycolide)	E	50:50 DL-PLG	0.55 - 0.75
B6029-2	50:50 Poly(DL-lactide-co-glycolide)	E	50:50 DL-PLG	0.62 - 0.65
B6029-1*	50:50 Poly(DL-lactide-co-glycolide)	E	50:50 DL-PLG	0.65 - 0.85
B6010-3	50:50 Poly(DL-lactide-co-glycolide)	E	50:50 DL-PLG	0.76 - 0.94
B6010-4	50:50 Poly(DL-lactide-co-glycolide)	E	50:50 DL-PLG	0.95 - 1.20
B6001-1	65:35 Poly(DL-lactide-co-glycolide)	E	65:35 DL-PLG	0.55 - 0.75
B6001-2*	65:35 Poly(DL-lactide-co-glycolide)	E	65:35 DL-PLG	0.83 - 0.93
B6007-1	75:25 Poly(DL-lactide-co-glycolide)	E	75:25 DL-PLG	0.55 - 0.75
B6007-2	75:25 Poly(DL-lactide-co-glycolide)	E	75:25 DL-PLG	0.80 - 1.20
B6006-1	85:15 Poly(DL-lactide-co-glycolide)	E	85:15 DL-PLG	0.55 - 0.75
B6006-2	85:15 Poly(DL-lactide-co-glycolide)	E	85:15 DL-PLG	0.76 - 0.85
Acid Terminated Polymers				

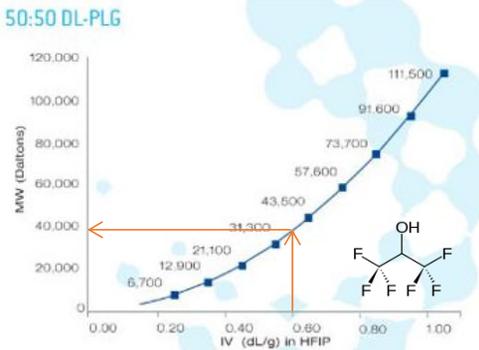
Inherent viscosity average molecular weight (Lactel)

There are relationships between polymer molecular weight and IV. Once you know the IV, you can find the corresponding molecular weight. See the arrows on the top left figure. But the measured IV of a polymer solution depends on organic solvent used. Thus, if a different solvent is used, the calibration curve has to be made again. For example, the calibration curve established using chloroform (bottom left) cannot be used, if another solvent is used.

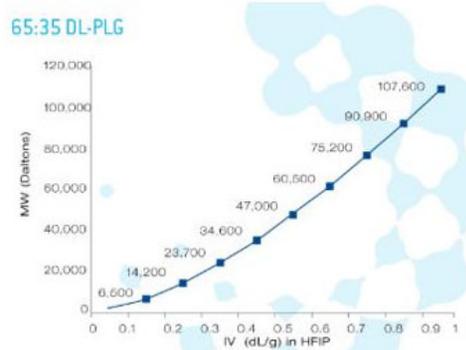
50:50 DL-PLG = PLGA with the L:G ratio of 50:50 = PLGA 50:50 or 50:50 PLGA

Question 2: In the examples on the right, why 50:50 PLGA used hexafluoro-2-isopropanol, while 85:15 PLGA used chloroform to dissolve PLGAs?

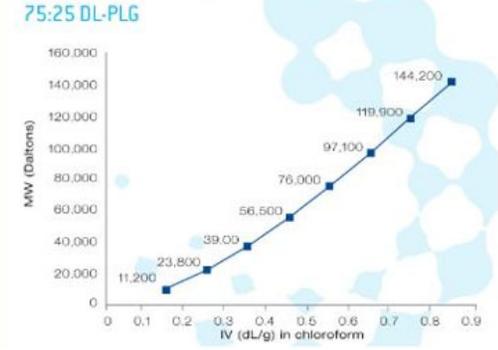
50:50 DL-PLG



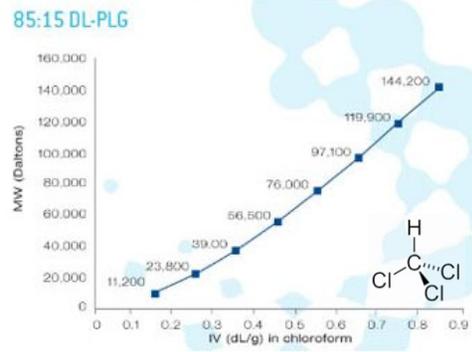
65:35 DL-PLG



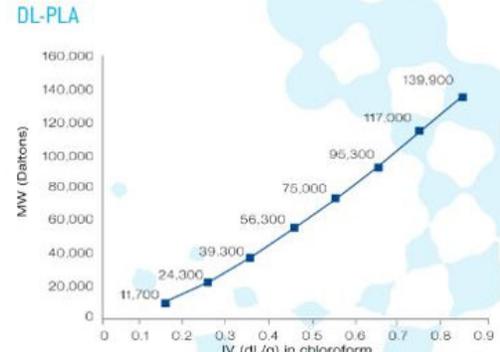
75:25 DL-PLG



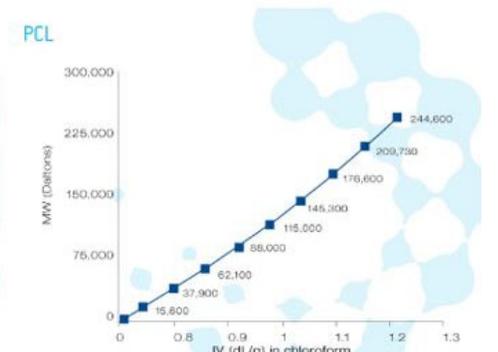
85:15 DL-PLG



DL-PLA

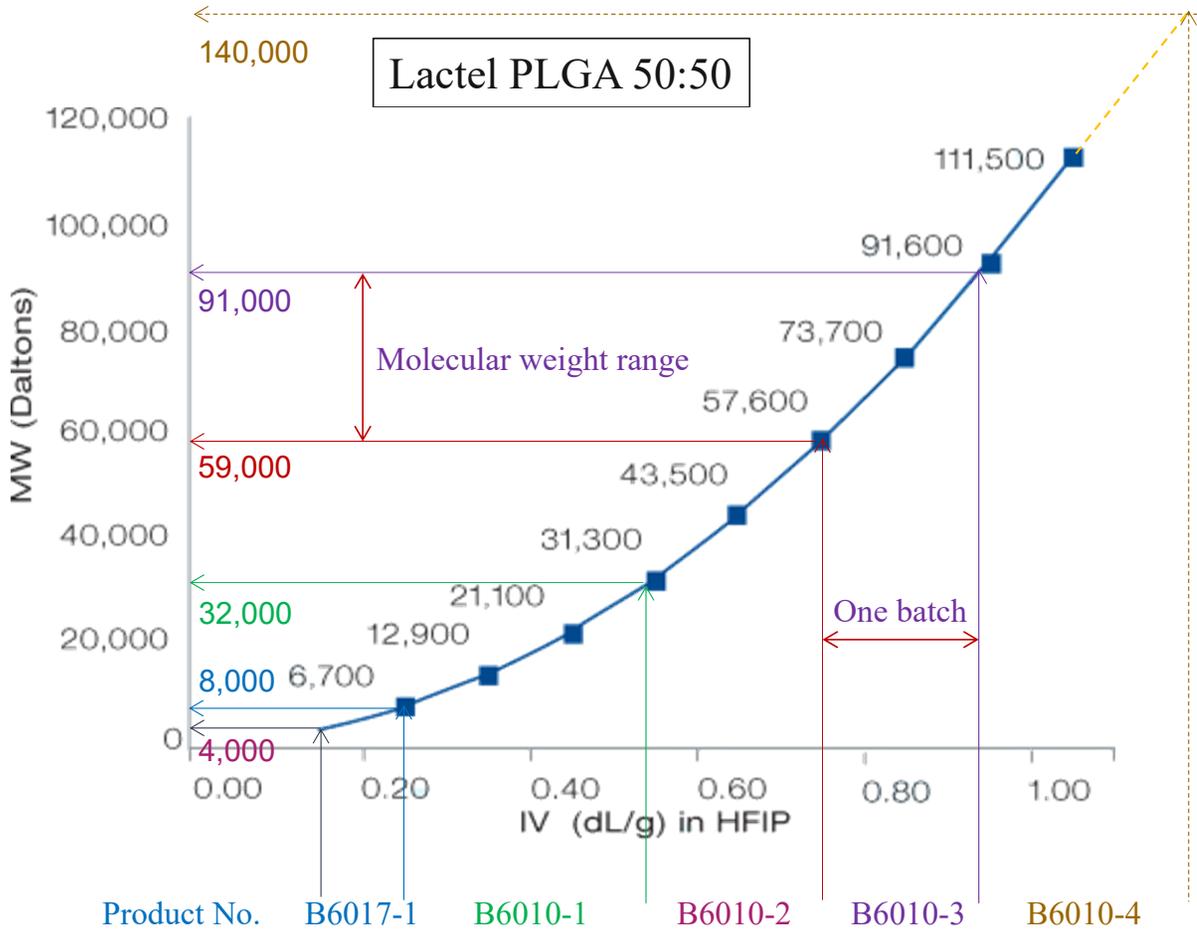


PCL

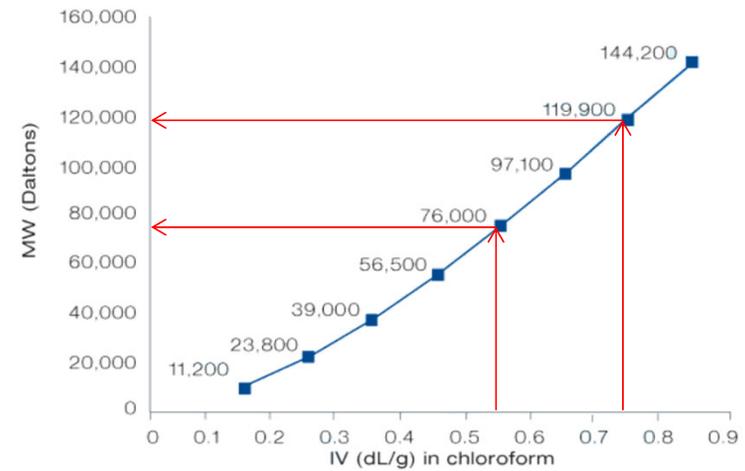


Inherent Viscosity Average Molecular Weight (Lactel)

Correlation of molecular weight (MW) and inherent viscosity (IV) of PLGA 50:50 and 75:25 from Lactel.



75:25 DL-PLG

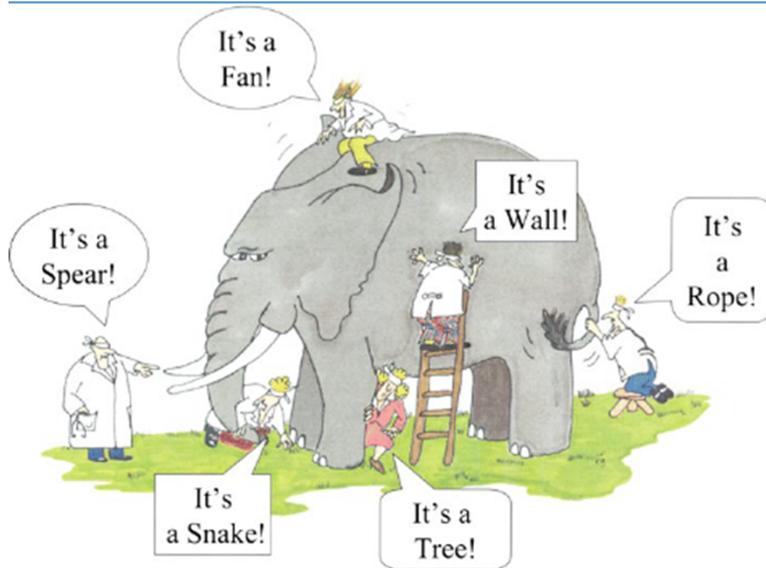


Determination of the Molecular Weight

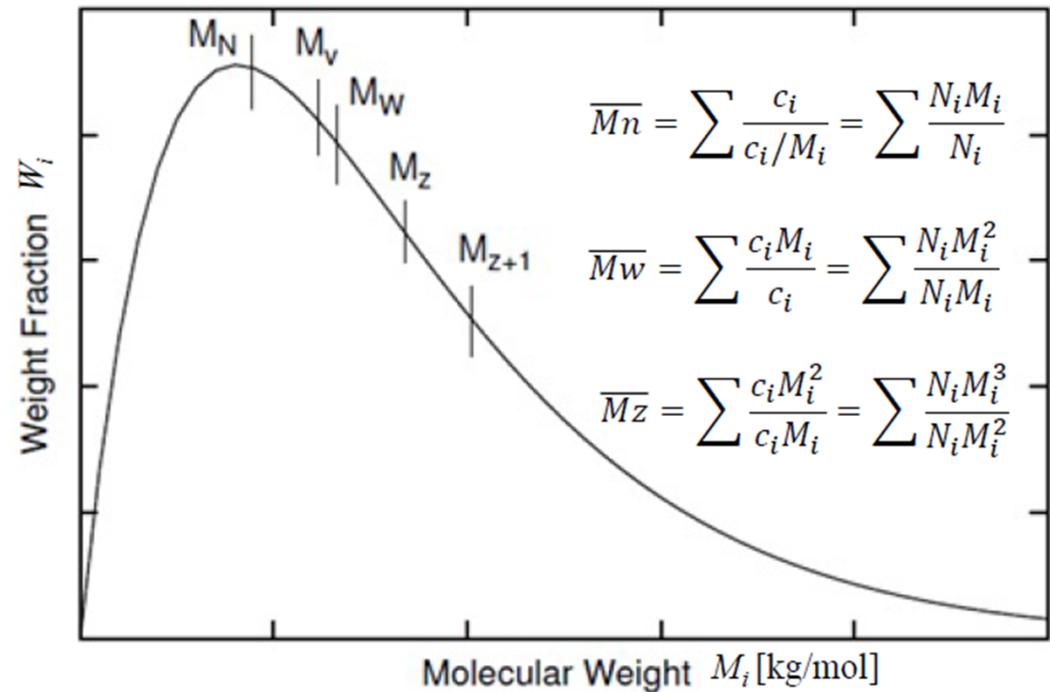
The polymer molecular weights are usually measured using gel-permeation chromatography (GPC) using an external standard. This approach does not provide accurate molecular weights of PLGAs, because the method uses polystyrene as the external standards. Multiangle laser light scattering (MALLS) method provides accurate molecular weight, because it measures the absolute molecular weight without using external standards.

Multiangle laser light scattering (MALLS) = Multiangle light scattering (MALS)

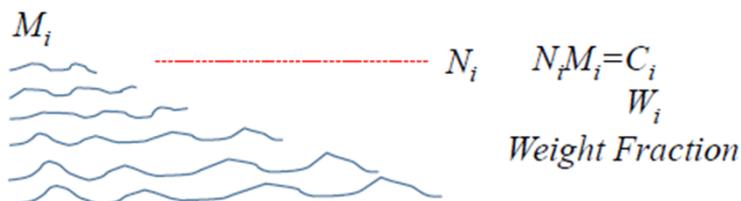
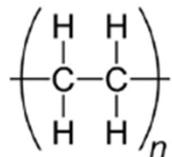
Polymer Molecular Weight ... Distribution



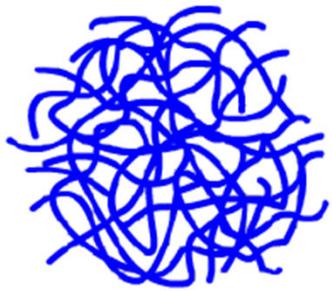
$$M_N \leq M_W \leq M_Z$$



$$M_w = 18 \text{ g/mol}$$



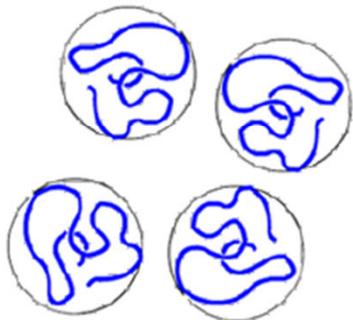
Gel Permeation Chromatography



Polymer molecules in the solid state
Just after added to solvent



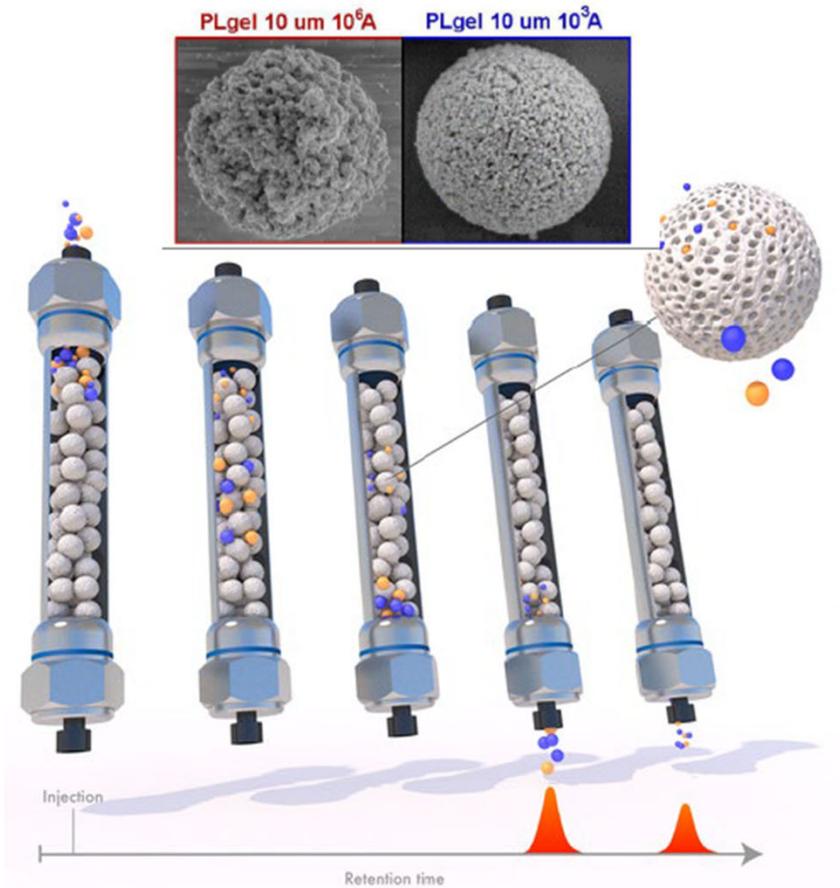
Step 1. A swollen gel in solvent



Step 2. solvated polymer molecules
dispersed into a solution

Solubility depends on

- Crystallinity
- Molecular weight
- Branching
- Polarity
- Crosslinking degree

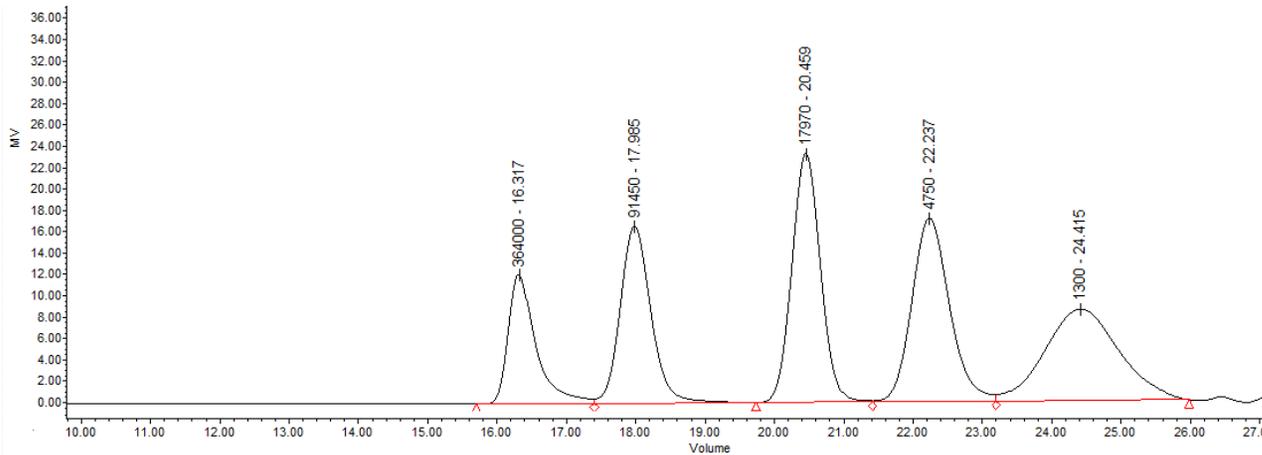


M. Striegel, W. W. Yau, J. J. Kirkland, and D. D. Bly. Modern Size-Exclusion Liquid Chromatography-Practice of Gel Permeation and Gel Filtration Chromatography, 2nd Edition. Hoboken. N.J. (2009) Anilent.com

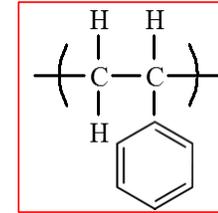
PLGA Molecular Weight by GPC with Polystyrene External Standard

Polystyrene Standards with indicated molecular weights.

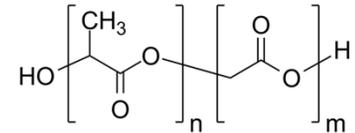
Polystyrene and PLGAs are dissolved in tetrahydrofuran (THF).



Retention Volume (or Retention Time)



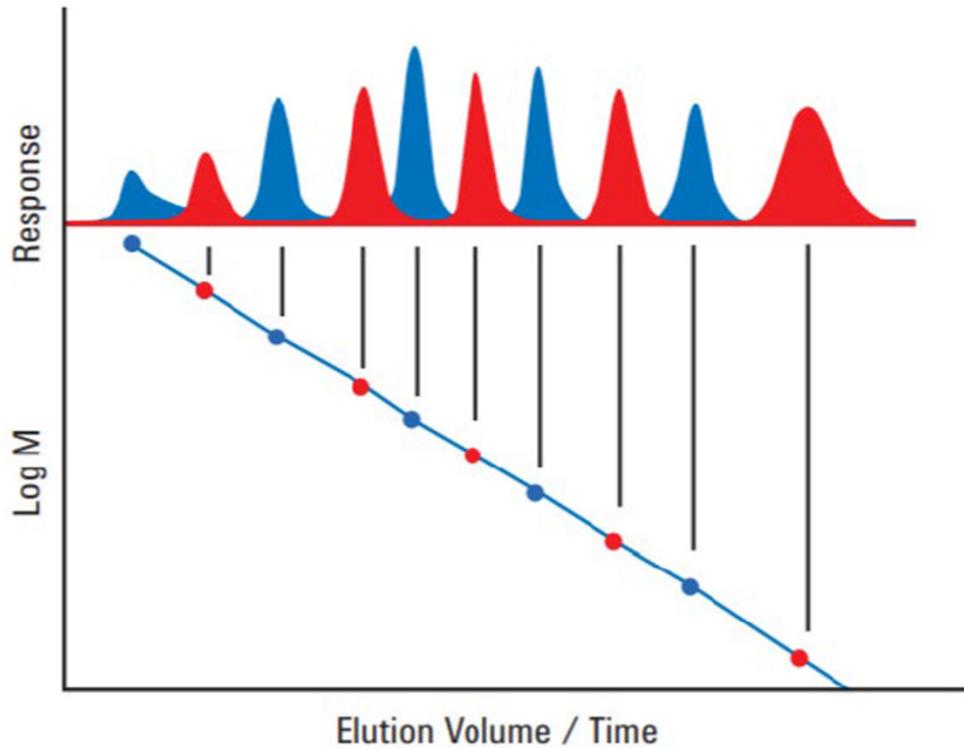
≠



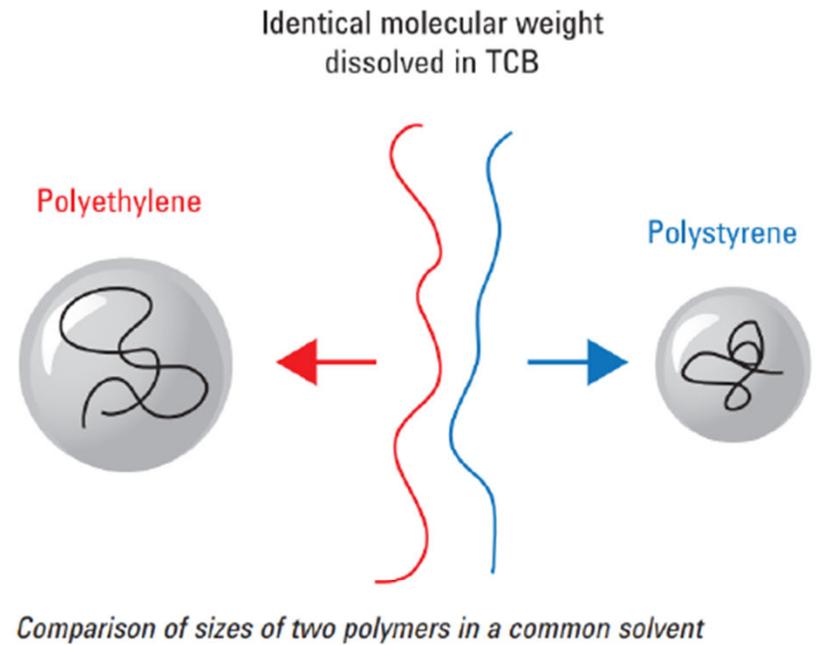
Polystyrene and PLGAs swell to different degrees (i.e., different hydrodynamic volume) even at the same molecular weight, and thus, the retention volume will be different. This results in inaccurate PLGA molecular weight.

- Size-exclusion chromatography/Gel-permeation chromatography separate polymer molecules based on the hydrodynamic volume
- Solvation between polymer/solvent, interaction with column also controls the retention time.
- Non-representative standard (typically polystyrene) and the lack of standardized methods mean lab-to-lab differences in GPC measured molecular weights.

GPC Limitations

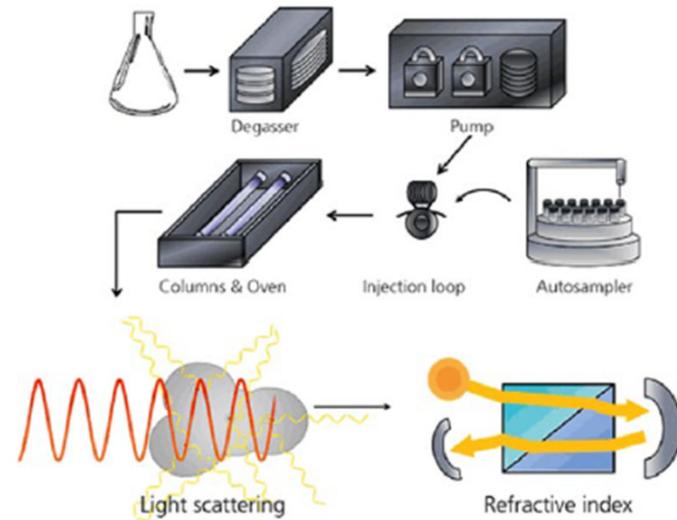
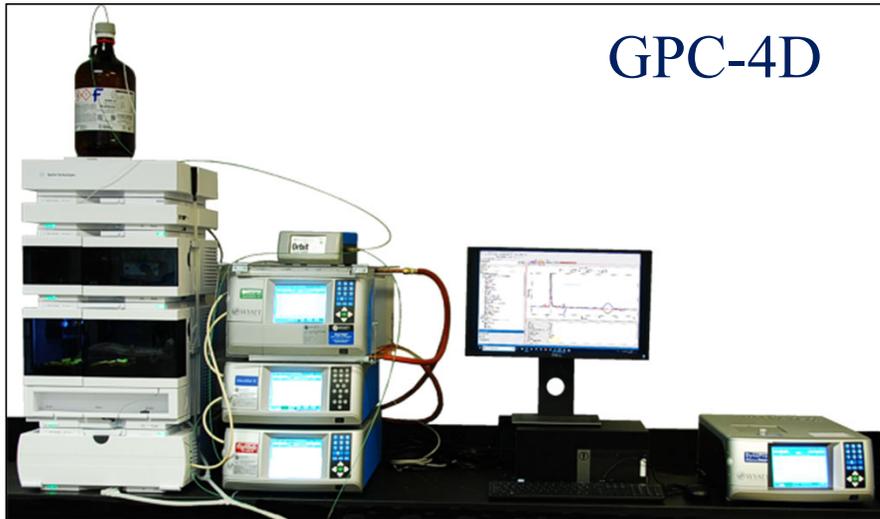


Typical chromatograms for two mixtures of standards and resulting calibration curve



M. Striegel, W. W. Yau, J. J. Kirkland, and D. D. Bly. *Modern Size-Exclusion Liquid Chromatography-Practice of Gel Permeation and Gel Filtration Chromatography, 2nd Edition*. Hoboken, N.J. (2009) Agilent.com

PLGA Molecular Weight by Multiangle Laser Light Scattering (MALLS)



- GPC is used to separate polymer molecules based on the molecular weight. The separated polymers are measured by 4 different detectors, such as MALLS (measuring molecular weight and radius of gyration, R_g), Viscometry (for intrinsic viscosity), in-line dynamic light scattering (for hydrodynamic radius, R_h), and refractive index (for concentration).
- MALLS does not require calibration, and thus, **no external standards, no solvation-artifacts**.
- The light-scattering signal is better with low-RI solvents (**acetone**) than high-RI solvents (**THF**).
- The MALLS data provides an in-depth information for determination of molecular shape & branching of PLGA. This is through using the Markk-Houwink equation: $[\eta] = KM^\alpha$. Examples are shown below using Sandostatin.

Differences in Molecular Weights measured by MALLS and PS External Standards (PES)

The following example shows the magnitude of differences of molecular weights measured by MALLS and PES (polystyrene external standard) methods. The degree of the difference in measured molecular weight ranges from 13% to 62% for the weight average molecular weight (M_w) and from 1% to 69% for the number average molecular weight (M_n).

Sample	L:G ratio	M_w (Da)			M_n (Da)		
		MALLS	PES	Difference	MALLS	PES	Difference
PLGA 50L-S	51:49	8,303	12,523	51%	5,834	8,415	44%
PLGA 50L-M	50:50	23,790	34,975	47%	16,280	24,121	48%
PLGA 75L-S	78:22	17,830	28,889	62%	12,180	20,557	69%
PLGA 75L-M	72:28	25,370	37,973	50%	16,290	24,595	51%
PLGA 75L-H	71:29	96,330	141,117	46%	76,170	97,812	29%
PLA 100L-S	100:0	15,890	13,829	-13%	8,142	9,350	15%
PLA 100L-M	100:0	33,900	53,429	58%	24,900	34,998	41%
PLA 100L-H	100:0	132,700	176,477	33%	103,200	104,474	1%

The mobile phase for the DAWN HELEOS II MALS measurement was acetone.

On the other hand, the mobile phase for the polystyrene external standard was tetrahydrofuran (THF). THF was not suitable for MALS measurement due to its low refractive index.

Comparison of Molecular Weights of PLGAs from Two Commercial Sources

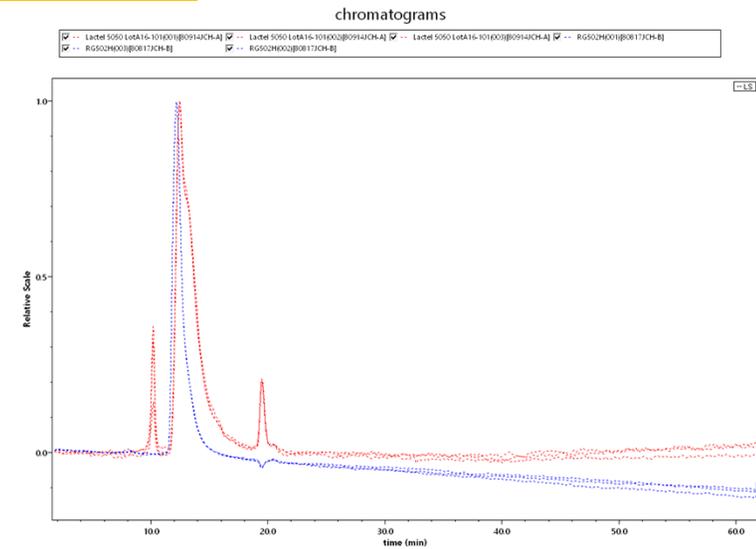
When PLGAs of the same molecular weight, as determined by IV, were obtained from two different companies and analyzed, the two PLGAs have very different molecular weights as measured by MALLS.

Product	Inherent Viscosity (IV)	M_n (n=3)	M_w (n=3)	M_z (n=3)
RG502H (Evonik, Lot# D170300516)	0.16 ~ 0.24 dL/g	11,647 ± 131	13,370 ± 131	15,739 ± 166
B6013-1 (Lactel, Lot# A16-101)	0.15 ~ 0.25 dL/g	5,386 ± 208	6,501 ± 156	8,393 ± 222

Question 3: Different companies produce PLGAs with the same L:G ratio and the same molecular weight measured by inherent viscosity. Scientist A may buy a PLGA from Evonik, while Scientist B may purchase the PLGA from Lactel. If two scientists make the same formulation using each PLGA, will the formulations have the same properties?

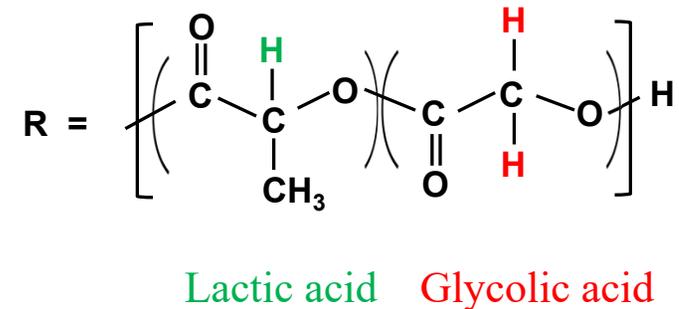
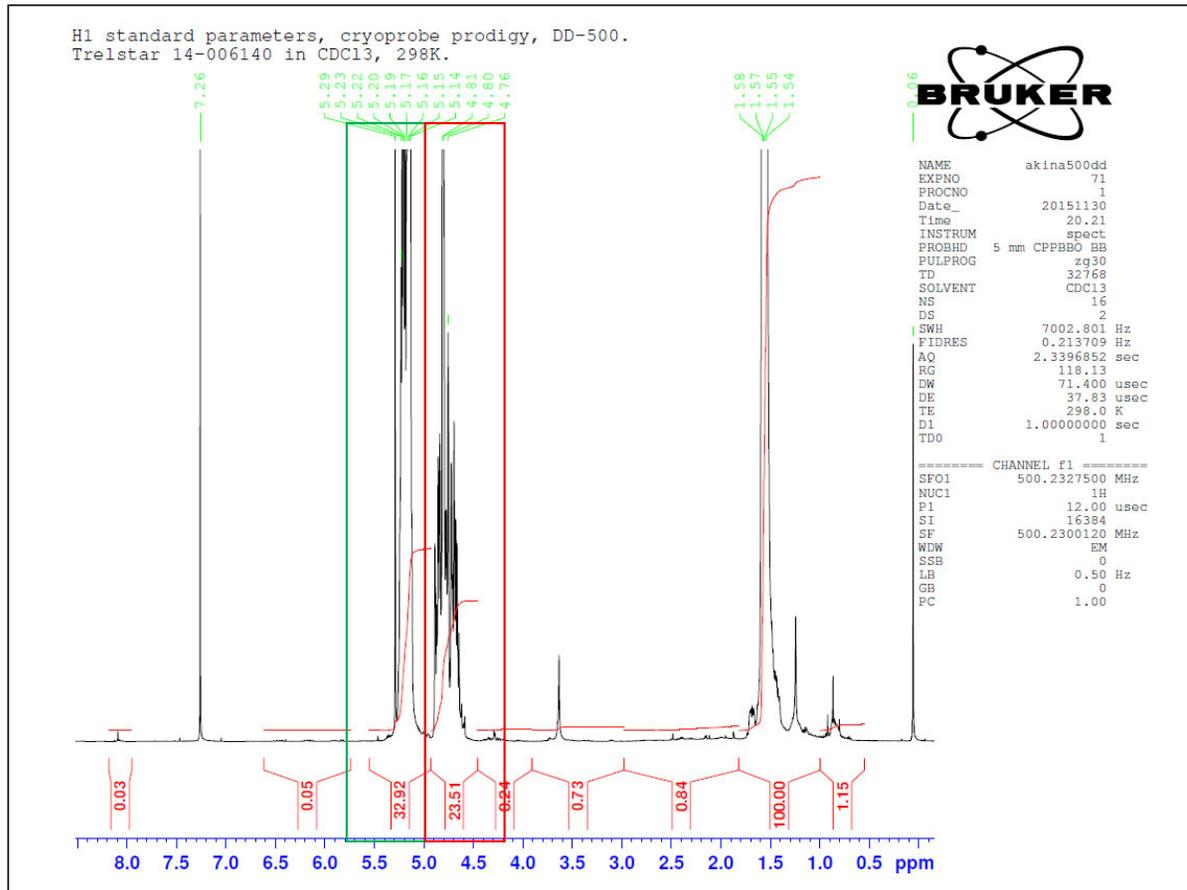
Comparison of GPC-4D results across two commercially manufactured PLGAs of comparable inherent viscosity specifications. (Molecular weights were measured by GPC-4D).

Chromatographic overlay of RG502H from Evonik (blue) and B6013-1 from Lactel (red). Both have almost the same IV ranges, but the molecular weight distribution is quite wider for B6013-1, resulting in much smaller average molecular weight.



PLGA: L:G ratio by ¹H-NMR

The L:G ratio of PLGAs is determined from the ¹H-NMR spectrum by comparing the peak intensities of glycolic acid (4.5-5.0 ppm) and lactic acid (5.0-5.5 ppm). The glycolic acid peak is divided by 2, because each glycolic acid has two hydrogen atoms.



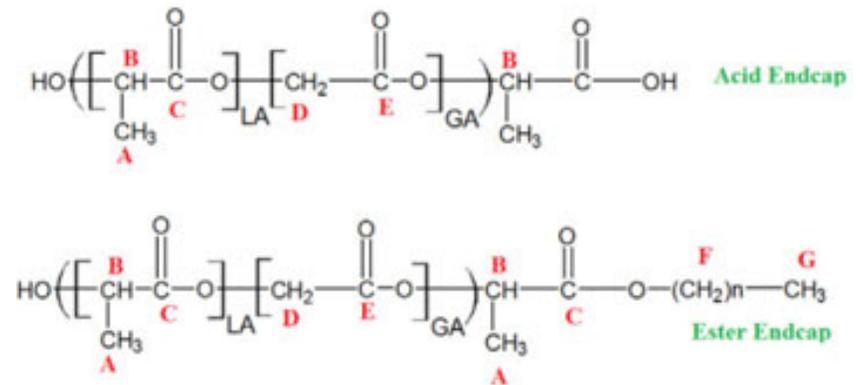
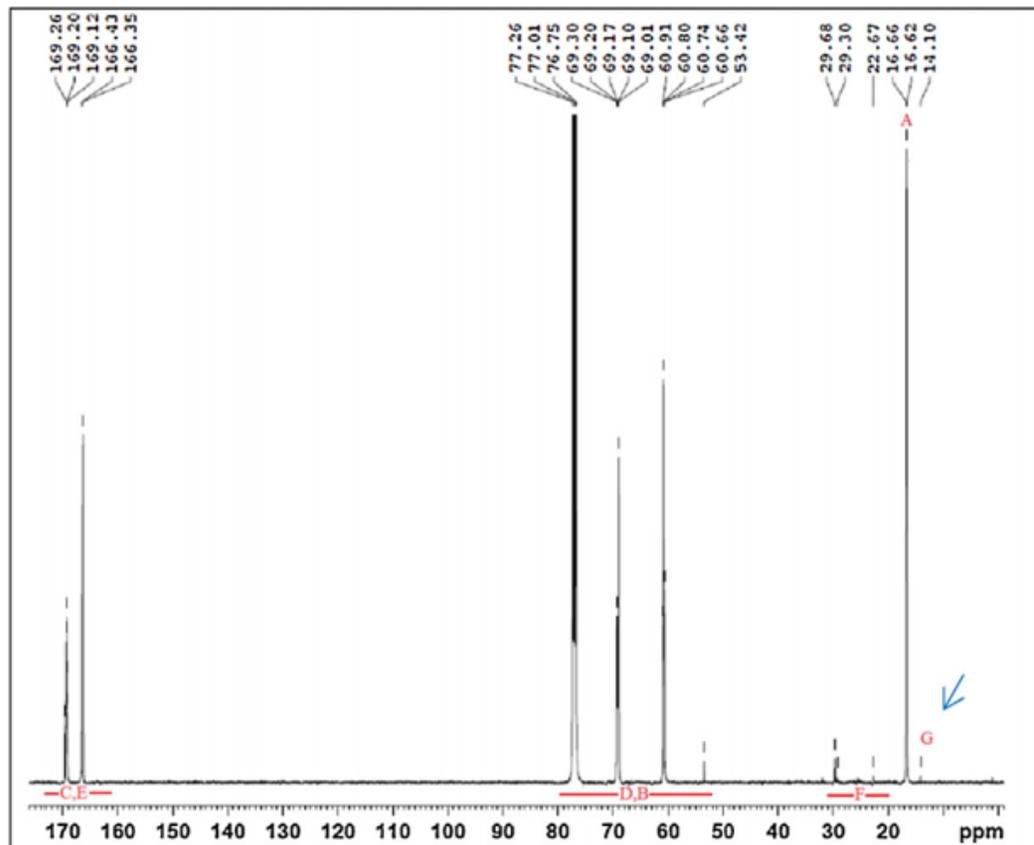
$$M_L = P_L / (P_L + (P_G/2))$$

$$M_G = (P_G/2) / (P_L + (P_G/2))$$

- L:G ratio is critical to the degradation kinetics.
- Higher L:G ratio (i.e., higher lactide content) degrades more slowly.

PLGA: Endcap by ^{13}C -NMR

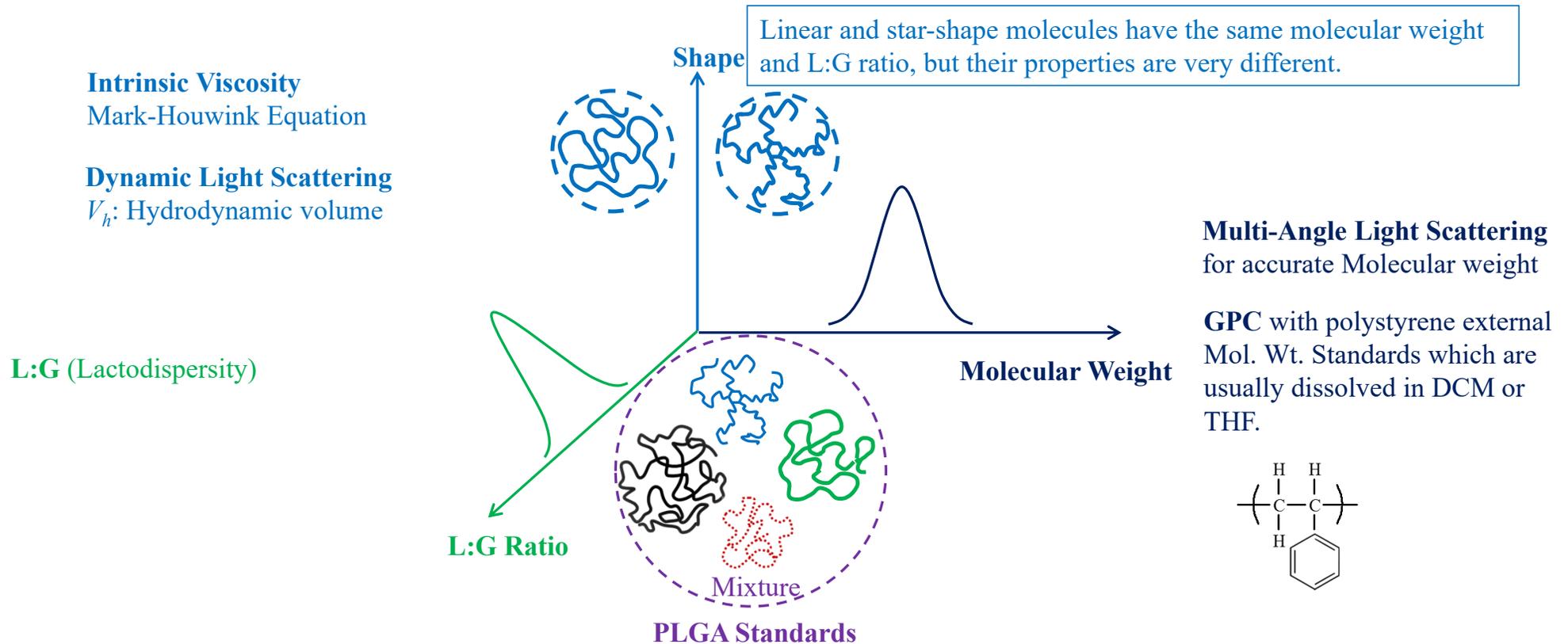
The nature of the end group of PLGA, i.e., acid or ester, is determined by ^{13}C -NMR. The presence of ester endcap is determined from the peak at 14 ppm.



- Requires extremely clean sample (alkanes can give false positive).
- High number of scans required for high Signal/Noise.

Characterization of Poly(lactide-co-glycolide) (PLGA)

Characterization of PLGA polymers requires more than just measuring the molecular weight. As shown below, the molecular weight of PLGAs is usually measured using a GPC with polystyrene external standards and/or inherent viscosity, providing inaccurate molecular weights. Also, PLGAs having the same molecular weight may have different L:G ratios, affecting the polymer properties. Furthermore, PLGAs with the same molecular weight and the same L:G ratio may have different molecular structures, e.g., linear or star-shape branched structure.



Solvent Solubility of PLGAs with Different L:G Ratios

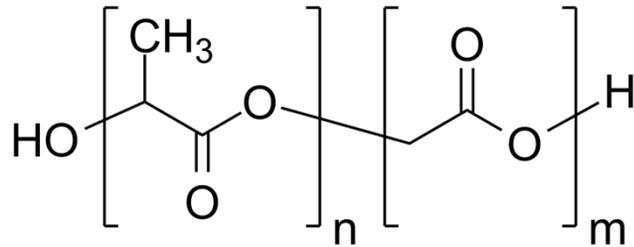
As shown below, PLGA dissolves in different solvents depending on its L:G ratio. As the L:G ratio increases, i.e., higher lactide content, PLGA dissolves in a variety of solvents. The reason PLGAs with low L:G ratio dissolve in only a limited number of solvents is due to the formation of crystalline structure of the glycolide segments. As the L:G ratio decreases, the glycolide segments increase to form the crystalline glycolide segments.

Solvent	PLGA L:G Ratio										
	50:50	55:45	60:40	65:35	70:30	75:25	80:20	85:15	90:10	95:5	100:0
Dichloromethane											
Dimethyl sulfoxide											
Dimethyl formamide											
Ethyl acetate											
Methyl ethyl ketone											
Tetrahydrofuran											
Ethyl benzoate											
Chlorobenzene											
Benzyl alcohol											
Methyl n-propyl ketone											
n-Butyl acetate											
Trichloroethylene											
Ethyl-L-lactate											
2-Methyl tetrahydrofuran											
1,2-Dichlorobenzene											
Toluene											
Methyl isobutyl ketone											
Butyl lactate											
p-Xylene											

The solubility chart on the left can vary depending on the PLGA concentration, its molecular weight, and the temperature for measuring solubility.

PLGA Solubility in Solvents

When the L:G ratio decreases below 50:50, PLGA polymers do not dissolve in most solvent. The only solvent that dissolves PLGAs with low L:G ratios is hexafluoro-2-propanol, which is a very difficult solvent to handle.



Lactide

Glycolide

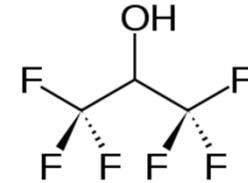
L:G Ratio



Insoluble in most solvents

Solvent-dependent solubility

Hexafluoro-2-propanol



Question 4: If Scientist A uses PLGA 75:25 to make a drug-containing PLGA microparticles using dichloromethane and Scientist B using ethyl acetate, will the final PLGA microparticles have the same drug release profiles or not?

PLGA: Blockiness

When we say PLGA 75:25, it means that the PLGA polymer has the L:G ratio of 75:25. But please note that the 75:25 ratio is the average of all PLGA molecules. Some may have lower L:G ratio (e.g., 70:30) or higher (80:20). The extent of the heterogeneity of the lactide content (or L:G ratio) is currently not known. Some glycolide monomers may exist as neighbors, and in this case, they form crystalline structure. The segments consisting of lactide monomers do not form crystalline structures because of the presence of a bulky methyl group. Thus, PLGAs with the same molecular weight and the same L:G ratio may behave differently depending on the distribution of glycolide monomers, forming crystalline blocks.

- **Blockiness** refers to the distribution of L:G in a given PLGA batch, in particular to the glycolide segments.
- Glycolide-rich regions tend to self-crystallize making difficult to dissolve domains.



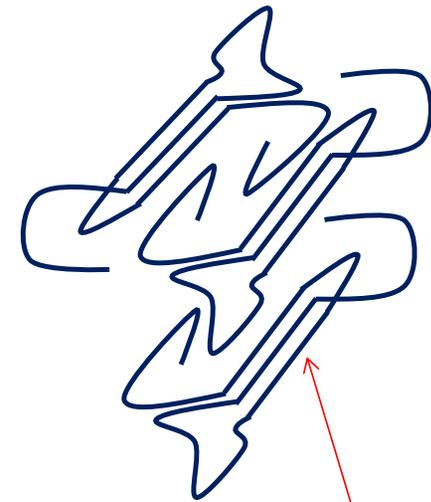
Uniform



Partial Block



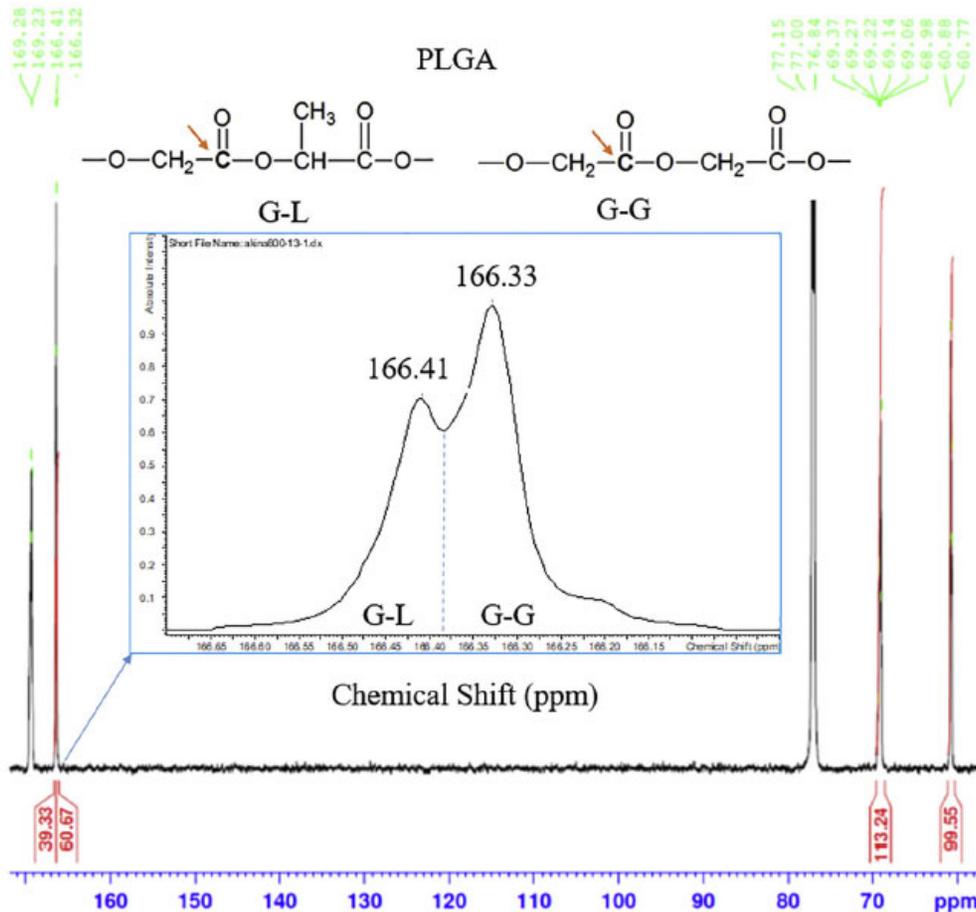
Block polymer



Glycolide-rich regions form crystalline domains

PLGA: Blockiness

The blockiness of the glycolide segment can be measured by ^{13}C -NMR.



When the molecular weight and the polymer concentration were in the similar range, the factors that may affect PLGA solubility in different solvents include the L:G ratio and the glycolide sequence distribution, commonly known as the glycolide blockiness. As the blockiness of the glycolide increases, the PLGA solubility in solvents decreases. The blockiness was determined using the glycolide carbonyl group located at 166–167 ppm. It was calculated by dividing the peak intensity of the glycolide carbonyl adjacent to another glycolide unit ($I_{\text{G-G}}$, upfield G-G peak at 166.33 ppm) by the peak intensity of the glycolide carbonyl adjacent to a lactide unit ($I_{\text{G-L}}$, downfield G-L peak at 166.41 ppm). This ratio of the two carbonyl peaks is described as the R_c value:

$$R_c = \frac{I_{\text{G-G}}}{I_{\text{G-L}}}$$

The higher R_c value indicates the higher the degree of blockiness of PLGA. As the blockiness increases, more glycolide monomers are aggregated by themselves and less interfaced with lactides, leading to higher heterogeneity. The R_c value can be a useful parameter for comparing glycolide sequence distribution of PLGAs, as the PLGA microstructure can affect its physicochemical properties, such as solubility and degradability [9]. In fact, the blockiness value provides an additional piece of information that is critical in determining the composition of PLGAs based on the L:G ratios.

Injectable, Long-acting Formulations

Oral Peptide Delivery System

Table 2. Examples of various types of long-acting injectables (LAIs).

Product	LAI type	Drug	Mol. wt. (g/mol)	LogP	Water solubility (mg/ml)	Dose	
1	Faslolex	Oily solution	Fulvestrant	293.4	2.10	0.5000	500 mg/month
2	Androcur Depot	Oily solution	Cyproterone acetate	416.9	3.81	0.0001	300 mg/2 weeks
3	Haldol Depot	Oily solution	Haloperidol decanoate	530.1	4.30	0.0001	140, 400 mg/month
4	Testoviron Depot	Oily solution	Testosterone propionate	344.5	4.40	0.0001	50 mg/month
5	Cisordinol-Acutard	Oily solution	Zaclofenixol acetate	443.0	4.79	0.0006	200, 500 mg/month
6	Proluton Depot	Oily solution	Hydroxyprogesterone caproate	428.6	4.81	0.0009	250 mg/week
7	Naldebin ER	Oily solution	Dinalbuphine sebacate	881.1	5.34	0.0003	20 mg/week
8	Makena	Oily solution	Hydroxyprogesterone caproate	428.6	5.88	0.0065	250 mg/week
9	Delastrogen	Oily solution	Estradiol valerate	356.5	6.00	0.0001	10-20 mg/month
10	Noristerat	Oily solution	Norethisterone enantate	410.6	6.00	0.0010	100, 200 mg/2 months
11	Gynodian Depot	Oily solution	Estradiol valerate	356.5	6.00	0.0001	4 mg/month
12	Depo-Testosterone	Oily solution	Testosterone cypionate	412.6	6.11	0.0001	400 mg/month
13	Gynodian Depot	Oily solution	Prasterone enanthate	400.6	6.28	0.0001	200 mg/month
14	Testoviron Depot	Oily solution	Testosterone enanthate	400.6	6.30	0.0001	200 mg/month
15	Primobolan Depot	Oily solution	Methenolone enanthate	414.6	6.90	0.0001	200, 400 mg/week
16	Deca-Durabolin	Oily solution	Nandrolone decanoate	428.6	7.30	0.0561	50 mg/3 weeks
17	Fluanxol Depot	Oily solution	Fluphenazine decanoate	591.8	8.22	0.0002	5 mg/2 weeks
18	Lyogen Depot	Oily solution	Fluphenazine decanoate	591.8	8.22	0.0002	45 mg/6 months
19	Prolixin Decanoate	Oily solution	Fluphenazine decanoate	591.8	8.22	0.0002	12.5-100 mg/month
20	Nebido	Oily solution	Testosterone Undecanoate	456.7	8.50	0.0001	1000 mg/3 months
21	Depixol	Oily solution	Flupentixol decanoate	588.8	8.80	0.0001	50 mg/month
22	Clopixol Depot	Oily solution	Zaclofenixol decanoate	555.2	9.00	0.0001	200, 500 mg/month
23	Piporil	Oily solution	Pipozazine palmitate	714.1	10.50	0.0001	50-100 mg/month
24	Apritide	Suspension	Cabotegravir	405.4	1.04	0.0001	600 mg/2 months
25	Bicillin L-A	Suspension	Penicillin G benzathine	981.2	1.92	0.2850	917 mg/month
26	Kenalog (IM)	Suspension	Triamcinolone acetonide	434.5	1.94	0.0210	60 mg/1.5 months
27	Xipere (eye)	Suspension	Triamcinolone acetonide	434.5	1.94	0.0210	4 mg/3 months
28	Depo-Medrol	Suspension	Methylprednisolone acetate	416.5	2.58	0.0193	40 mg/2 weeks
29	Depo-Provera	Suspension	Medroxyprogesterone acetate	386.5	4.10	0.0001	150, 400 mg/3 months
30	Depo-SubQ Provera	Suspension	Medroxyprogesterone acetate	386.5	4.10	0.0001	104 mg/3 months
31	Zyprexa Relprevv	Suspension	Olanzapine pamoate	718.8	4.58	0.0042	300-405 mg/month
32	Abilify Maintena	Suspension	Aripiprazole	448.4	4.60	0.0078	300-400 mg/month
33	Abilify Asintufufi	Suspension	Aripiprazole	448.4	4.60	0.0078	720, 960 mg/2 months
34	Aristada	Suspension	Aripiprazole lauroxil	660.7	4.70	0.0002	880 mg/2 months
35	Aristada Initio	Suspension	Aripiprazole lauroxil	660.7	4.70	0.0002	880 mg/1.5 months
36	Cabenuva	Suspension	(Cabotegravir &) rilpivirine	366.4	4.86	0.0185	600, 900 mg/month
37	Sunlenca	Suspension	Lenacapavir	968.3	6.47	0.0036	927 mg/6 months
38	Invega Sustenna	Suspension	Paliperidone palmitate	664.9	10.10	0.0070	234 mg/month
39	Invega Trinza	Suspension	Paliperidone palmitate	664.9	10.10	0.0070	819 mg/3 months
40	Invega Hafyera	Suspension	Paliperidone palmitate	664.9	10.10	0.0070	1092, 1560 mg/6 months
41	Bydureon	Microparticle	Exenatide	4187.0	-21.00	25.0000	2 mg/week
42	Triptodur	Microparticle	Triptorelin	1311.5	-0.41	0.3050	22.5 mg/6 months
43	Arestin	Microparticle	Minocycline HCl	493.9	-0.03	3.0700	1 mg/2 weeks
44	Sandostatim LAR	Microparticle	Octreotide acetate	1139.3	0.42	0.0122	20 mg/month
45	Lupron Depot	Microparticle	Leuprolide acetate	1209.4	1.07	0.0354	45 mg/6 months
46	Lutrate Depot	Microparticle	Leuprolide acetate	1209.4	1.07	0.0354	67.5 mg/3 months
47	Trelstar	Microparticle	Triptorelin pamoate	1699.8	1.73	0.0337	22.5 mg/6 months
48	Vivitrol	Microparticle	Naltrexone	341.4	1.92	3.0700	380 mg/month
49	Zilretta	Microparticle	Triamcinolone acetonide	434.5	1.94	0.0210	32 mg/3 months
50	Somatuline Depot	Microparticle	Lanreotide acetate	1156.4	0.91	0.0050	60, 120 mg/month
51	Signifor LAR	Microparticle	Pasireotide	1313.4	3.03	0.0020	20-60 mg/month
52	Risperdal Consta	Microparticle	Risperidone	410.5	3.27	0.1700	50 mg/2 weeks
53	Rykindo	Microparticle	Risperidone	410.5	3.27	0.1700	25, 50 mg/2 weeks
54	Nutropin Depot	Microparticle	Somatropin	22125.0		10.0000	13.5 mg/month
55	Atridox	ISF implant	Doxycycline hyclate	460.4	-0.06	0.0641	50 mg/month
56	Camcevi	ISF implant	Leuprorelin mesilate	1305.5	1.04	0.0338	42 mg/6 months
57	Eligard	ISF implant	Leuprolide acetate	1209.4	1.07	0.0354	45 mg/6 months
58	Fensolvi	ISF implant	Leuprolide acetate	1209.4	1.07	0.0354	45 mg/6 months
59	Perseris	ISF implant	Risperidone	410.5	3.27	0.1700	90, 120 mg/month
60	Uzedy	ISF implant	Risperidone	410.5	3.27	0.1700	250 mg/2 months
61	Sublocade	ISF implant	Buprenorphine	467.6	3.55	0.0168	100, 300 mg/month
62	Scenesse	Solid implant	Alamclanotide	1646.8	-1.40	0.0230	16 mg/2 months
63	Zoladex	Solid implant	Goserelin acetate	1329.5	1.55	0.0493	10.8 mg/3 months
64	Ozurdex	Solid Implant	Dexamethasone	392.5	1.90	0.1000	0.7 mg/3 months
65	Durysta	Solid Implant	Bimatoprost	415.6	3.41	0.0187	10 µg/6 months
66	Propel	Solid implant	Mometasone furoate	539.5	4.27	0.0108	0.37 mg/month

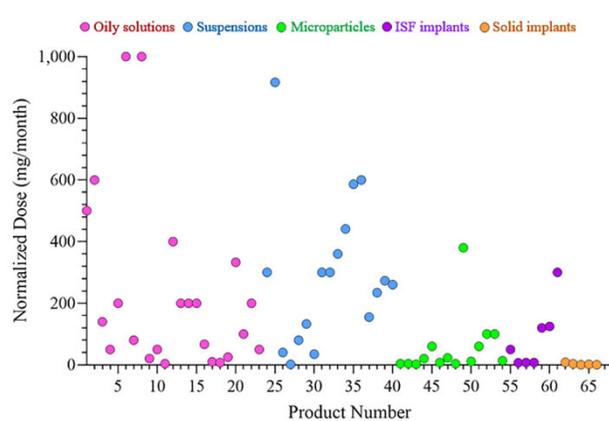


Figure 1. Normalized doses of LAI products categorized into five LAI types: oily solution, suspension, microparticle, ISF implant, and solid implant.

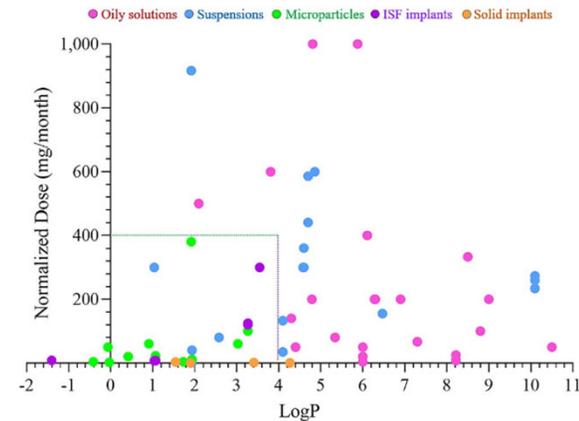


Figure 4. Normalized dose of LAI products in Table 2 as a function of logP of the drugs (in the figure, the logP value of -21.00 for exenatide with an 8 mg/month dose (#41 in Table 2) was omitted).

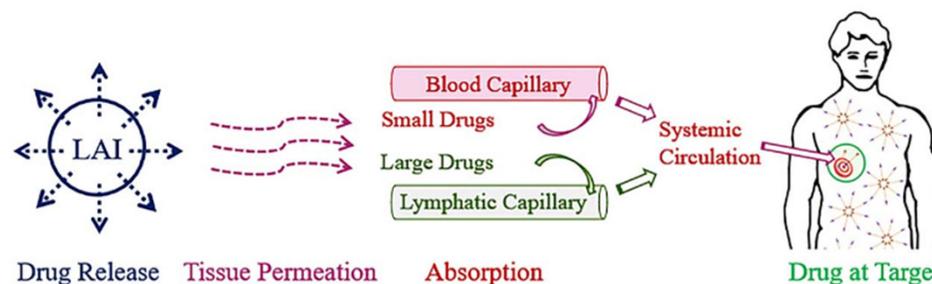


Figure 2. Simplified steps of drug release from an LAI formulation to reach the target site (Modified from [32]).

Injectable, Long-acting PLGA Formulations

Injectable Long-Acting Formulations Approved by the FDA

All injectable, long-acting formulations approved by the FDA are based on PLGA polymers.

Lupron Depot[®]
 leuprolide acetate for depot suspension
 1,3,4,6 months MP
 1989, 1996, 1997, 2011
 7.5 mg/month (IM)

Zoladex[®] 3-MONTH
 10.8 mg DEPOT
 GOSERELIN ACETATE IMPLANT
 1, 3 months SI 1989
 3.6 mg/month (IM)

Sandostatin LAR[®] Depot
 (octreotide acetate for injectable suspension)
 1 month MP 1998
 20 mg/month (IM)

ATRIDOX[®]
 (doxycycline hyclate) 10%
 Cost Effective
 1 week, IS 1998
 50 mg/week (PD)

Nutropin DEPOT[®]
 (somatropin (rDNA origin) for injectable suspension)
 1 month MP 1999
 13.5 mg/month
 (Discontinued)

TRELSTAR[®]
 (triptorelin pamoate for injectable suspension)
 1,3,6 months MP
 2000, 2001, 2010
 3.75 mg/month (IM)

Somatuline[®] Depot
 (lanreotide) Injection
 1 month MP 2000
 60 mg/month

Arestin[®]
 minocycline HCl 1mg
 MICROSPHERES
 2 weeks MP 2001
 1 mg/2 weeks (PD)

Eliard[®]
 (leuprolide acetate for injectable suspension)
 1,3,4,6 months IS 2002
 7.5 mg/month (SC)

Risperdal CONSTA[®]
 risperidone Long-Acting Injection
 2 weeks MP 2003
 25 mg/2 weeks (IM)

Vivitrol[®]
 (naltrexone for extended-release injectable suspension)
 1 month MP 2006
 380 mg/month (IM)

Ozurdex[®]
 (dexamethasone intravitreal
 implant) 0.7 mg
 3 months SI 2009
 0.7 mg/3 months (IV)

PROPEL[®]
 MOMETASONE FUROATE IMPLANT
 1 month SI 2011
 0.37 mg/month

Once-weekly 
BYDUREON[®]
 exenatide extended-release for
 injectable suspension
 1 week MP 2012
 2 mg/week (SC)

Lupaneta Pack[™]
 leuprolide acetate for depot suspension, 11.25 mg for intramuscular injection
 and norethindrone acetate tablets, 5 mg for oral administration
 3 month, MP 2012
 3.75 mg/month

Signifor[®] LAR
 (pasireotide) for injectable suspension
 1 month, MP 2014
 20, 40, or 60 mg/month (IM)

Zilretta[®]
 triamcinolone acetonide extended release
 injectable suspension 32 mg
 3 months MP 2017
 32 mg/3 months

Sublocade[™]
 (buprenorphine extended-release)
 injection for subcutaneous use ©
 100mg-300mg
 1 month, IS 2017
 100, 300 mg/month

once-monthly
PERSERIS[™]
 (risperidone)
 1 month, IS 2018
 90, 120 mg/month

Question 5: Why all FDA-approved injectable, long-acting depot formulations are based on PLGA polymers? Why not other biodegradable polymers?

MP: Microparticle (12)

IS: In Situ forming implant (4)

SI: Solid implant (3)

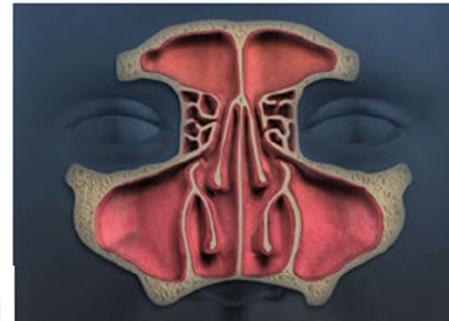
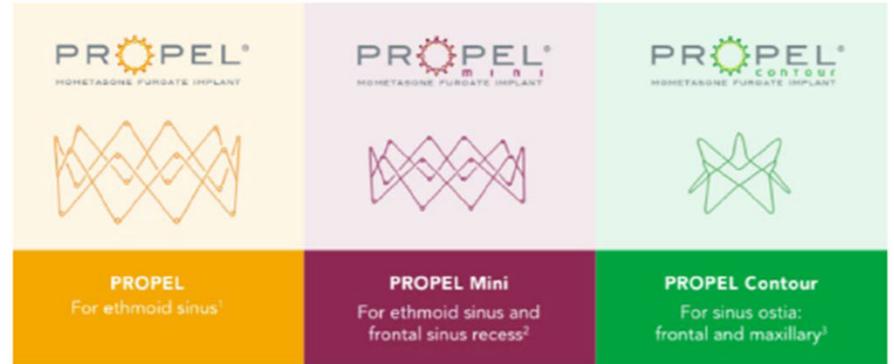
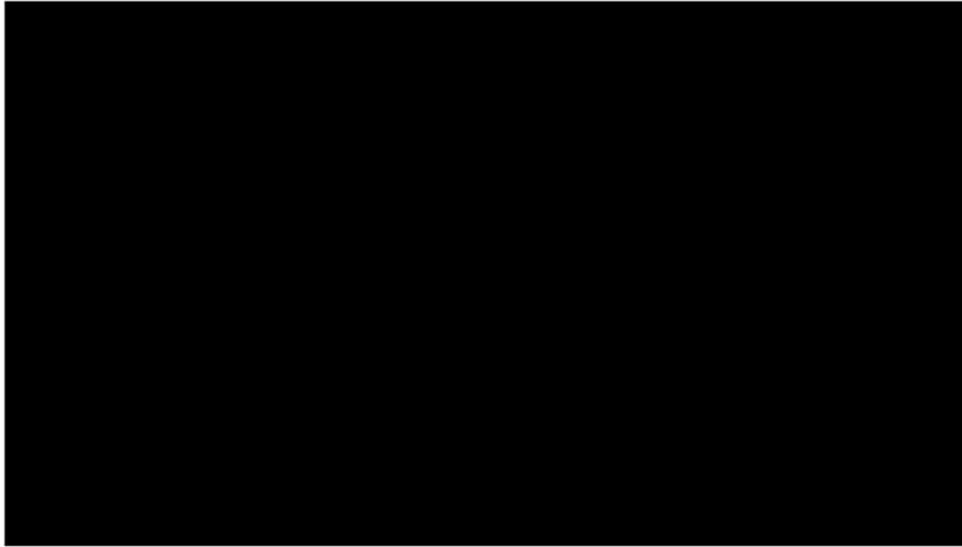
IM: Intramuscular

IV: Intravitreal

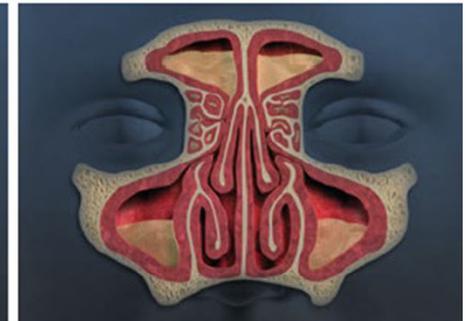
SC: Subcutaneous

PD: Periodontal

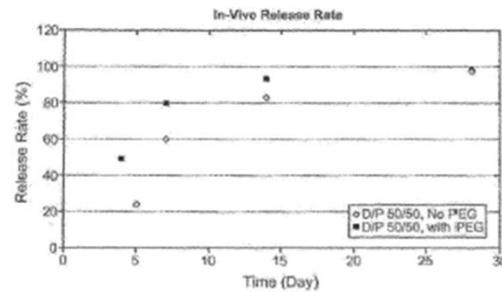
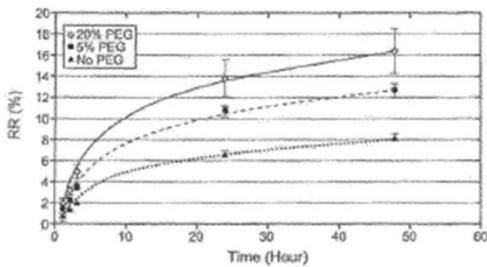
Novel Implant Designs - Propel



Normal Sinuses



Diseased Sinuses

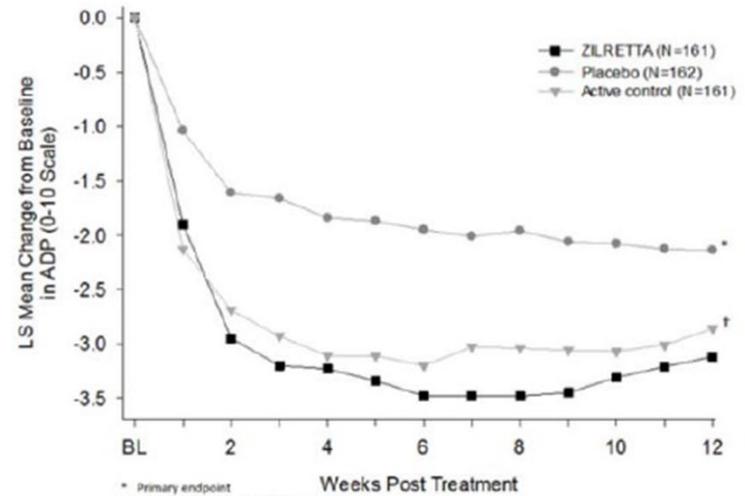


Localized Activity - Zilretta

Normal Knee



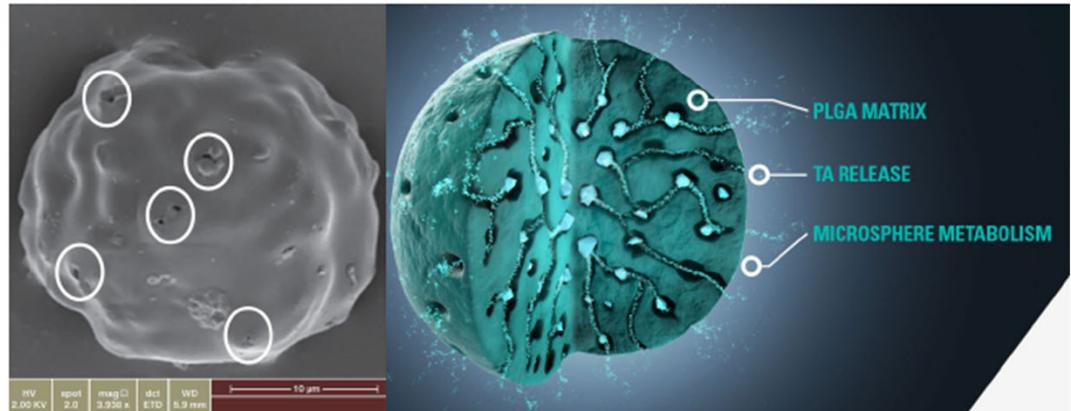
Osteoarthritis



* Primary endpoint
 † Secondary exploratory endpoint
 Active control = immediate-release triamcinolone acetonide; ADP = Average Daily Pain; LS = Least Square



Zilretta Package Insert



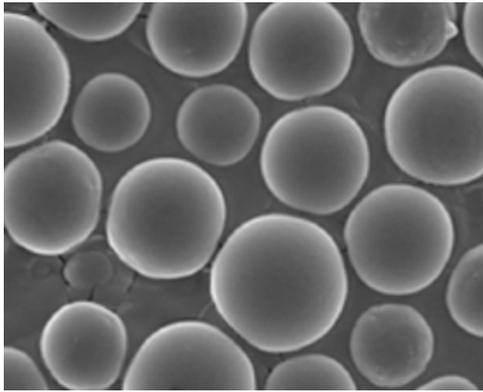
Understanding PLGA Microparticles

PLGA Microparticle Structures

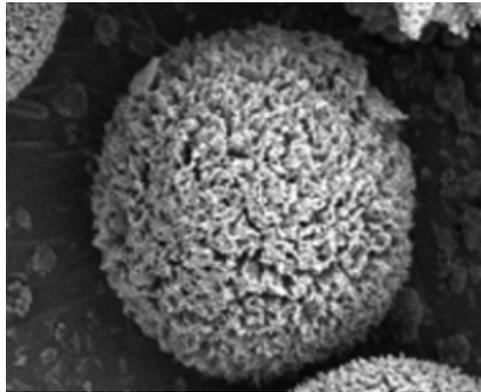
Forensic Analysis of PLGA Microparticles: Surface Morphology

PLGA microparticles have different surface profiles, which indicates different manufacturing processes. Their drug release properties are different, too. From the surface profiles of each microparticle, one can deduce how the microparticles were made.

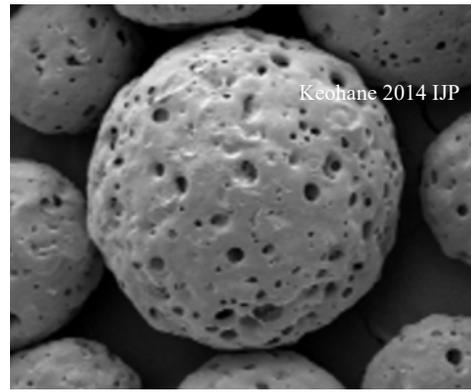
Smooth



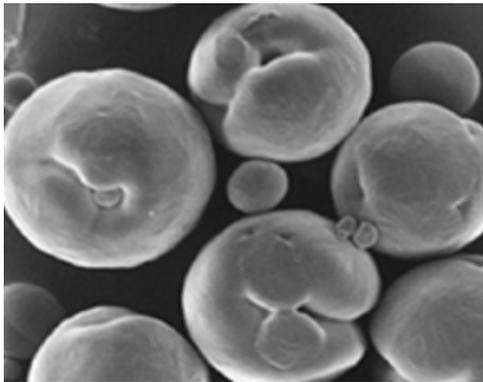
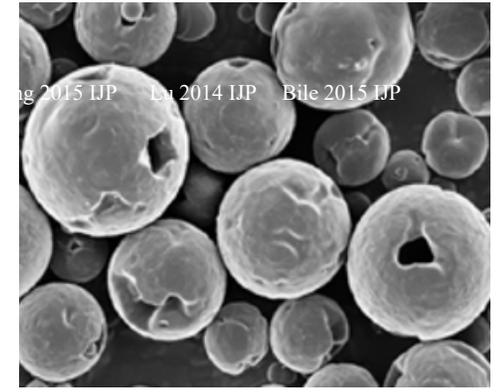
Spongy



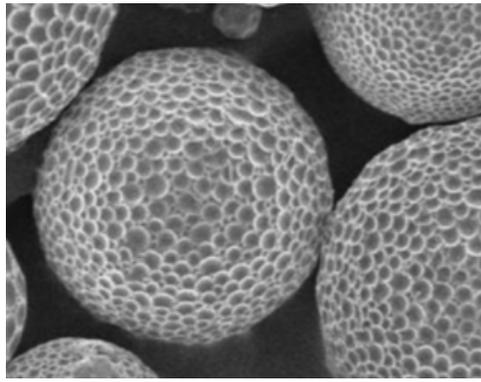
Porous



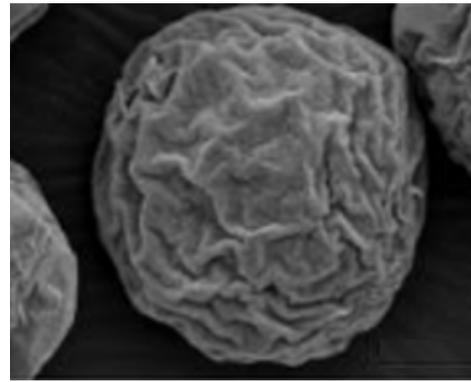
Holey



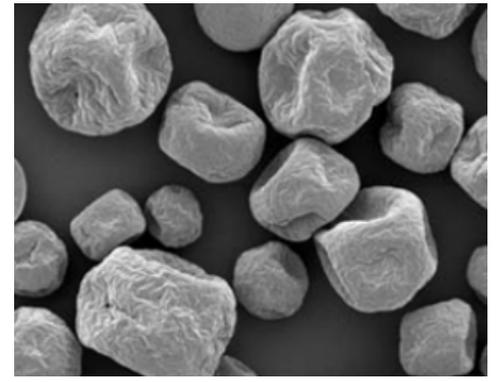
Scarred



Dimpled



Wrinkled

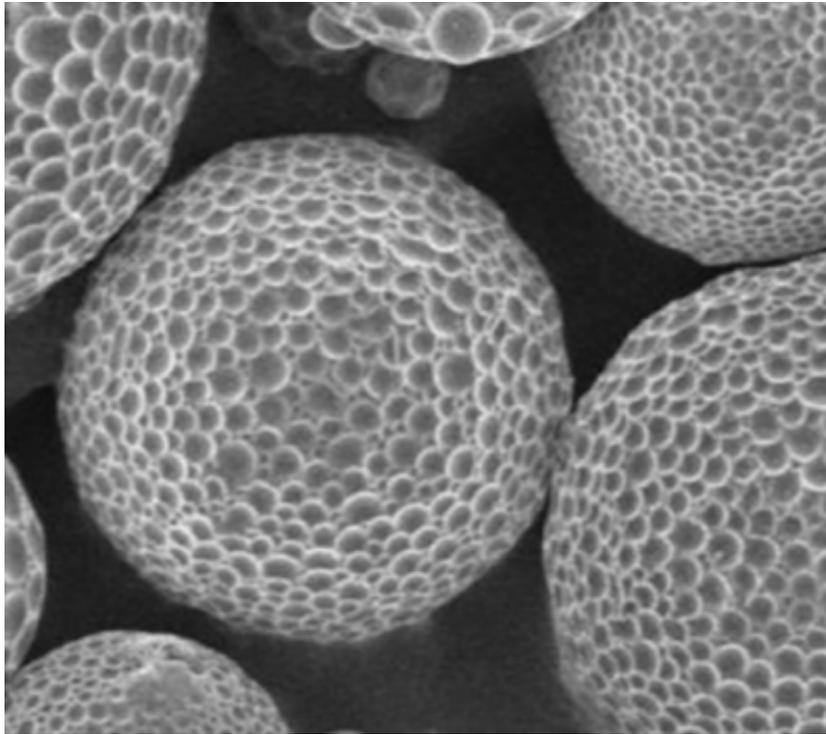


Irregular

Forensic Analysis of PLGA Microparticles: Surface Morphology

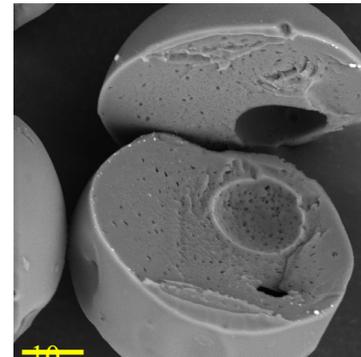
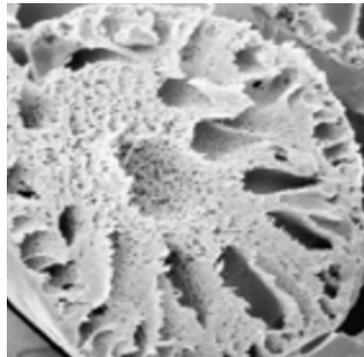
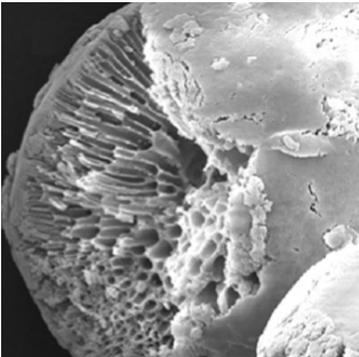
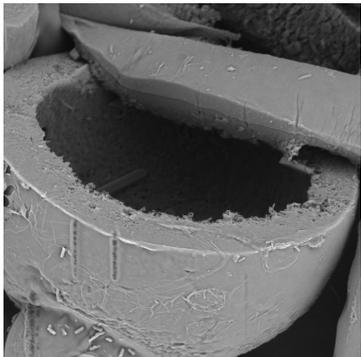
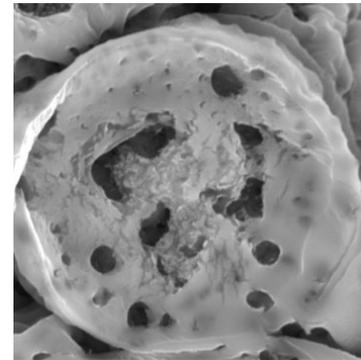
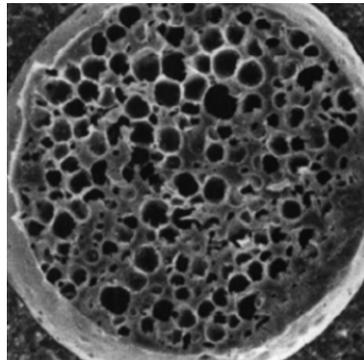
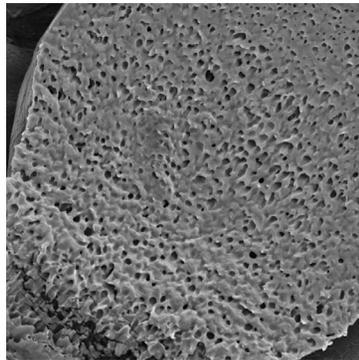
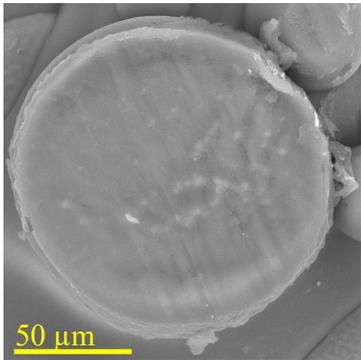
It is noted that each surface morphology is unique. The surface morphology indicates how each microparticles were made. The dimples in the image on the left below is due to the formation of pickering emulsion, while the image on the right is a result of an entirely different manufacturing process.

The message is that the information on the surface morphology tells a lot about how each set of microparticles are made.



Forensic Analysis of PLGA Microparticles: Inner Morphology

As the surface morphology provides information how each set of PLGA microparticles were made, the morphology of inner structure of microparticles also provide information on the manufacturing process. The presence of one huge inner volume indicates that the viscosity was low enough for individual water droplets move to form one giant water block. The presence of distinct empty spaces indicates that the viscosity was high enough to prevent coalescence of water droplets.



PLGA Microparticles: The Presence of Pores

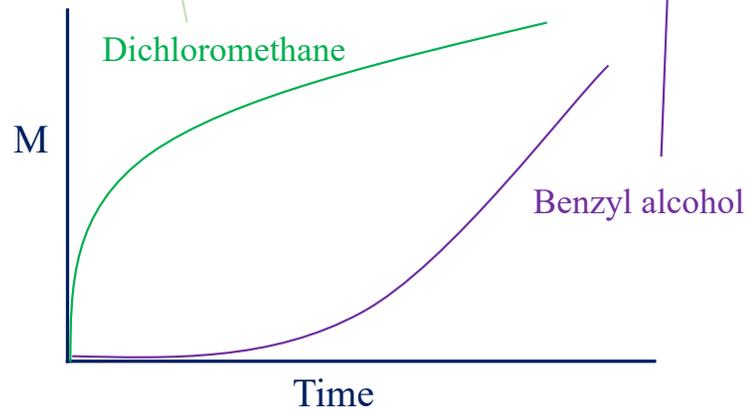
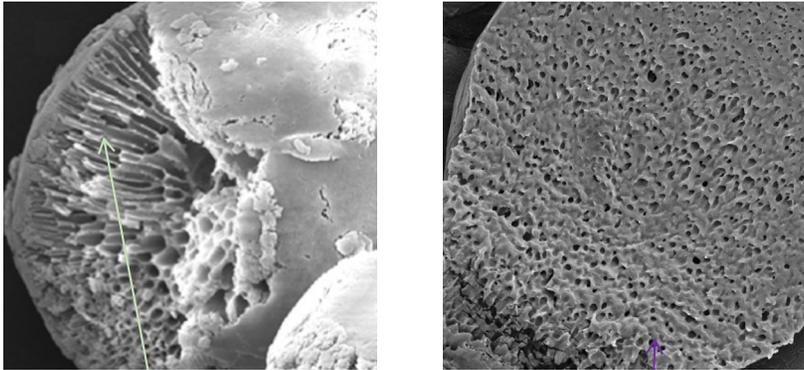
The pictures below are presentations of an artist in Berlin, Germany. The artist may not have intended to describe a polymeric network. But the images describe a polymeric network. The papers on the left picture can represent drug particles present in PLGA microparticles. It is important to visualize an object at the molecular level, and it helps to appreciate the properties of any polymeric system at the molecular level.



Bewegte Zeiten. Archäologie in Deutschland

Impact of PLGA Microstructure on Drug Release Kinetics

The inner structure of PLGA microparticles provide a clue how each microparticle may behave in its drug release properties. Depending on which solvent is used, the inner morphology become very different, resulting in different drug release properties.



Factors affecting drug release kinetics

PLGA Type

L:G ratio

End group

Mol. Wt.

Molecular shape

Solvent Type

Good solvent vs. Semi-Solvent

Solvent Removal Kinetics

Water solubility, T_b

Drug Type

Interaction with PLGA

Plasticizer effect

PLGA Microstructure

Imaging Analysis of PLGA Microparticles by Raman Spectroscopy

T

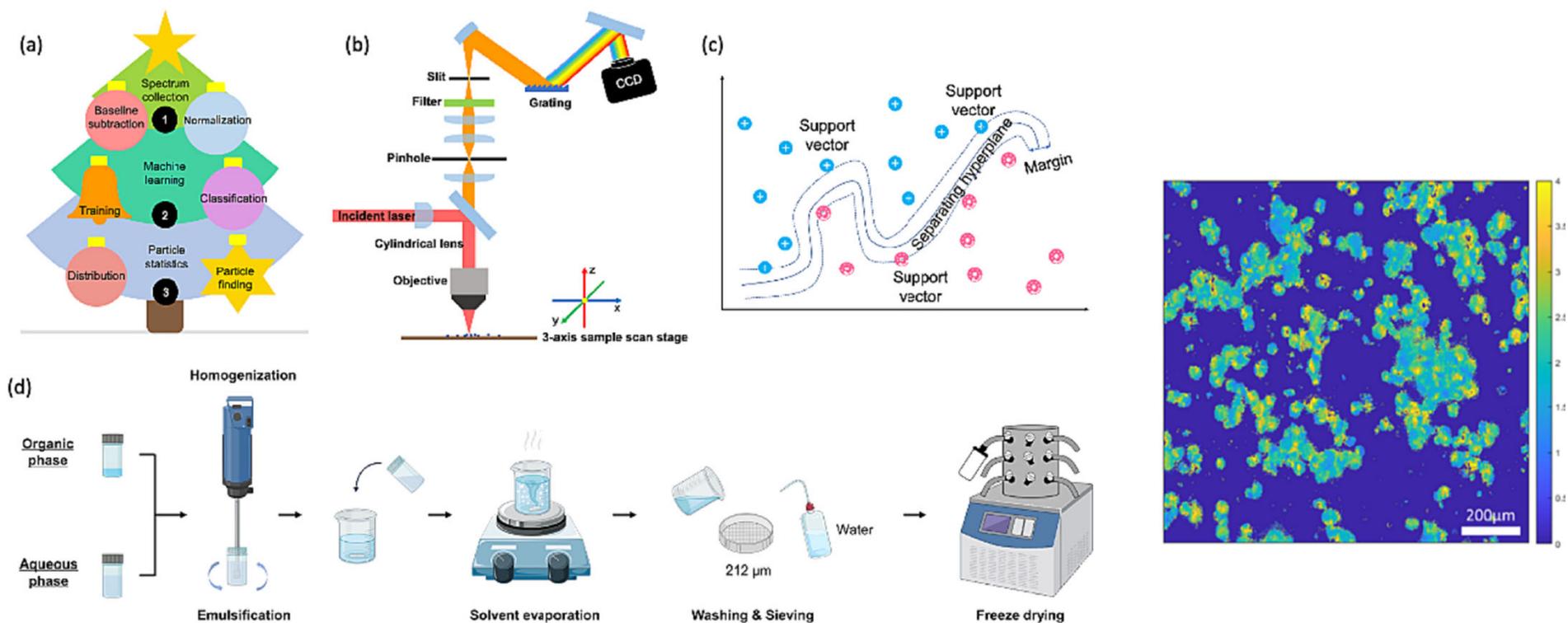


Fig. 1. (a) Workflow of the machine learning enhanced data acquisition and processing. (b) Line focus Raman imaging system. The cylindrical lens elongates the point focus into line focus to improve the throughput of the spectrum collection. (c) Nonlinear kernel support vector machine (SVM). (d) Schematic drawing of microsphere preparation process.

Li 2024, Hyper-spectra imaging analysis of PLGA microspheres via machine learning enhanced Raman spectroscopy

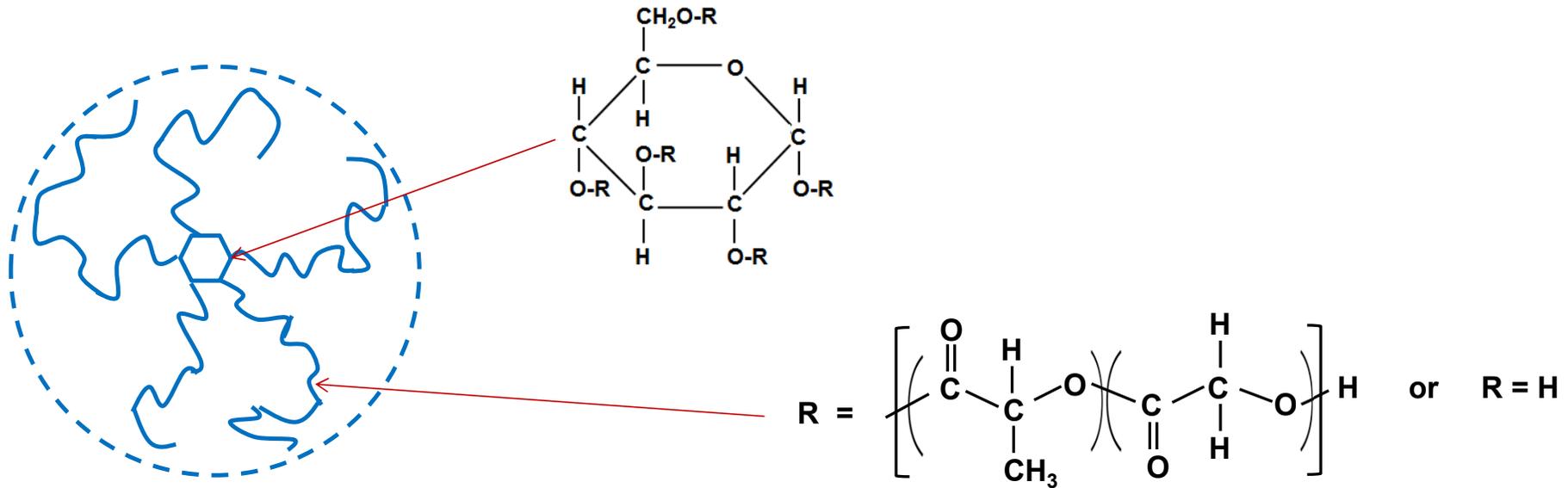
Formulations with Glucose-PLGA

Sandostatin LAR Depot[®] is made of glucose-PLGA, a star-polymer



PLGA: Branching Units/Molecule of Sandostatin®

Sandostatin is a clinical product approved by the FDA. It is the only PLGA product that used glucose-PLGA to make a formulation.



- Sandostatin lists Glucose-PLGA without any specific information on branching.
- GPC-4D branched-PLGA method was developed/validated using a series of standards.
- Tested Sandostatin extract: branching average typically ranges between ~ 2.5 -4 branching units/molecule.

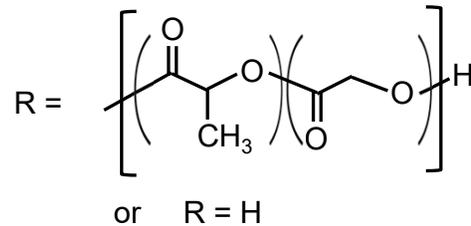
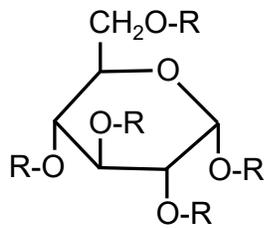
Hadar, Justin, Sarah Skidmore, John Garner, Haesun Park, Kinam Park, Yan Wang, Bin Qin, and Xiaohui Jiang.

[“Characterization of branched poly \(lactide-co-glycolide\) polymers used in injectable, long-acting formulations.”](#) *Journal of Controlled Release* (2019).

Star-Shaped PLGA (Glucose-PLGA)

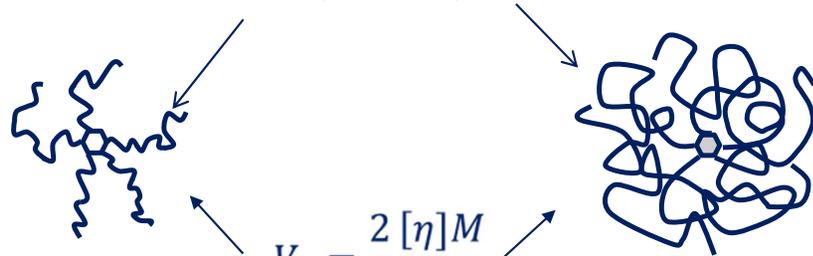
The difficulty in identifying the molecular structure of PLGAs is that when PLGAs have the same molecular weight, there is no experimental method that can distinguish linear PLGA from star-shape PLGA, e.g., glucose-PLGA.

Glu-PLGA



R represents either PLGA or hydrogen

Arm (= Branch)

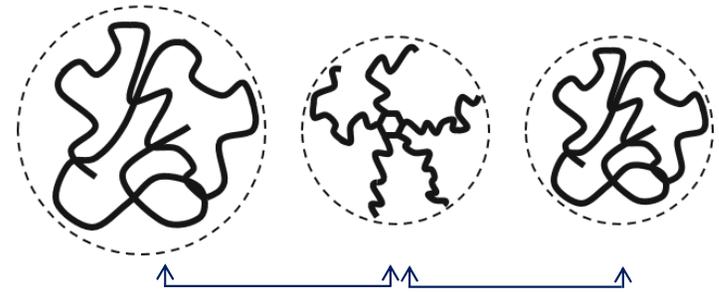


$$V_h = \frac{2 [\eta] M}{5 N_A}$$

(V_h : Hydrodynamic Volume)

Low Molecular Weight

High Molecular Weight

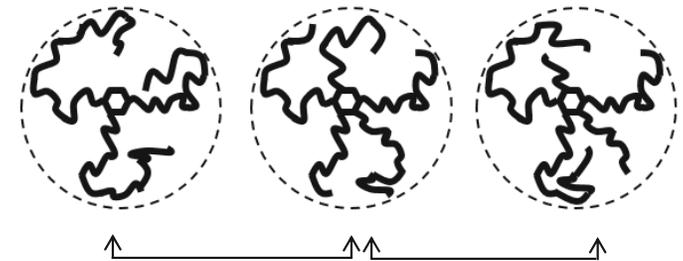


$$M_{lin} = M_{star}$$

$$M_{star} > M_{lin}$$

$$V_{h,lin} > V_{h,star}$$

$$V_{h,star} = V_{h,lin}$$



$$f = 3$$

$$f = 5$$

$$f = 5$$

$$PDI_{3arm} \approx PDI_{5arm}$$

$$PDI_{5arm} \leq PDI_{5arm}$$

Q1/Q2 assessment on generic PLGA products



- Provide comparative characterization data on PLGA polymer from the Generic and RLD
- Characterization should include, but is not limited to: composition (L/G ratio), molecular weight and molecular weight distribution, polymer structure (i.e., linear or star), inherent viscosity, glass transition temperature, and polymer end-cap
- Should characterize the branch frequency if it is a star polymer
- If there are differences, need to provide justification on why these differences would not impact the safety or efficacy of the generic drug as compared to the RLD

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

GPC with Quadruple Detectors (Wyatt)

GPC with 4 detectors help us understand the molecular structure using MALLS and intrinsic viscosity measurement.

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 which provide Mark-Houwink coefficients and distributive properties of long chain branching and hydrodynamic volume V_h of a polymer.

$$[\eta] = \lim_{c \rightarrow 0} \frac{\eta_{sp}}{c} = \frac{5 N_A V_h}{2 M} = \frac{5 N_A 4\pi \langle R_g^2 \rangle^{\frac{3}{2}}}{2 M 3} = \frac{\Phi \langle R_g^2 \rangle^{\frac{3}{2}}}{M} = KM^\alpha$$

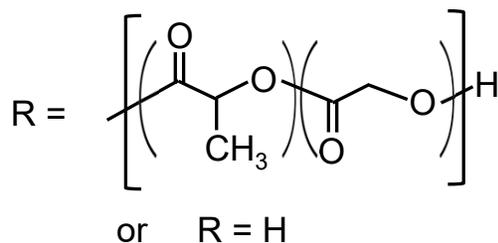
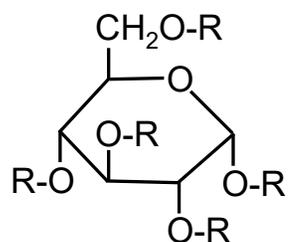
5. Osmometer This measures **the absolute number average molecular weight (M_w)**.



Standard Branched PLGA Molecules

To determine how many branches a Glucose-PLGA polymer may have, we need to have standards, i.e., molecules with known branches. Various molecules with different number of hydroxyl groups were used to prepare standard branch molecules.

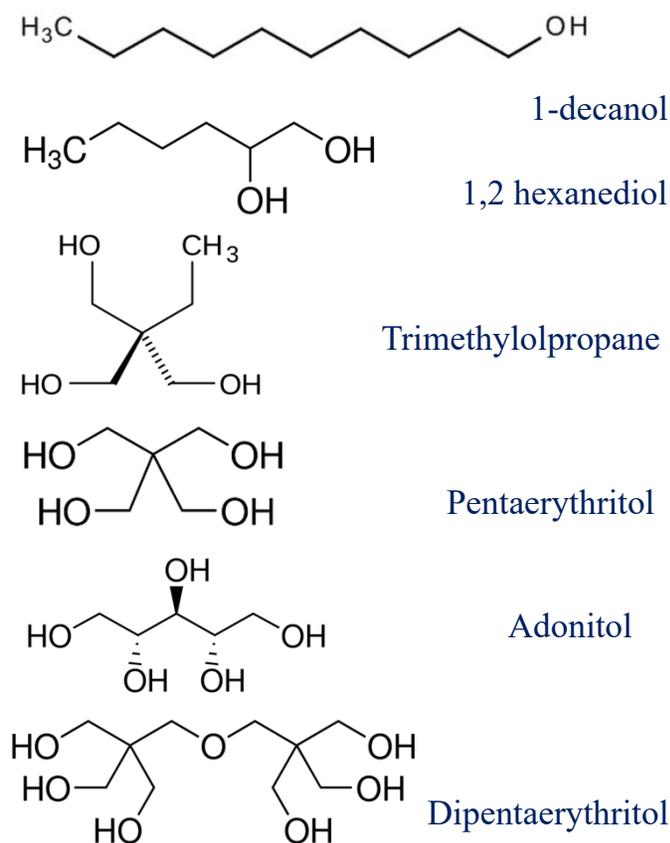
Glu-PLGA



R represents either PLGA or hydrogen

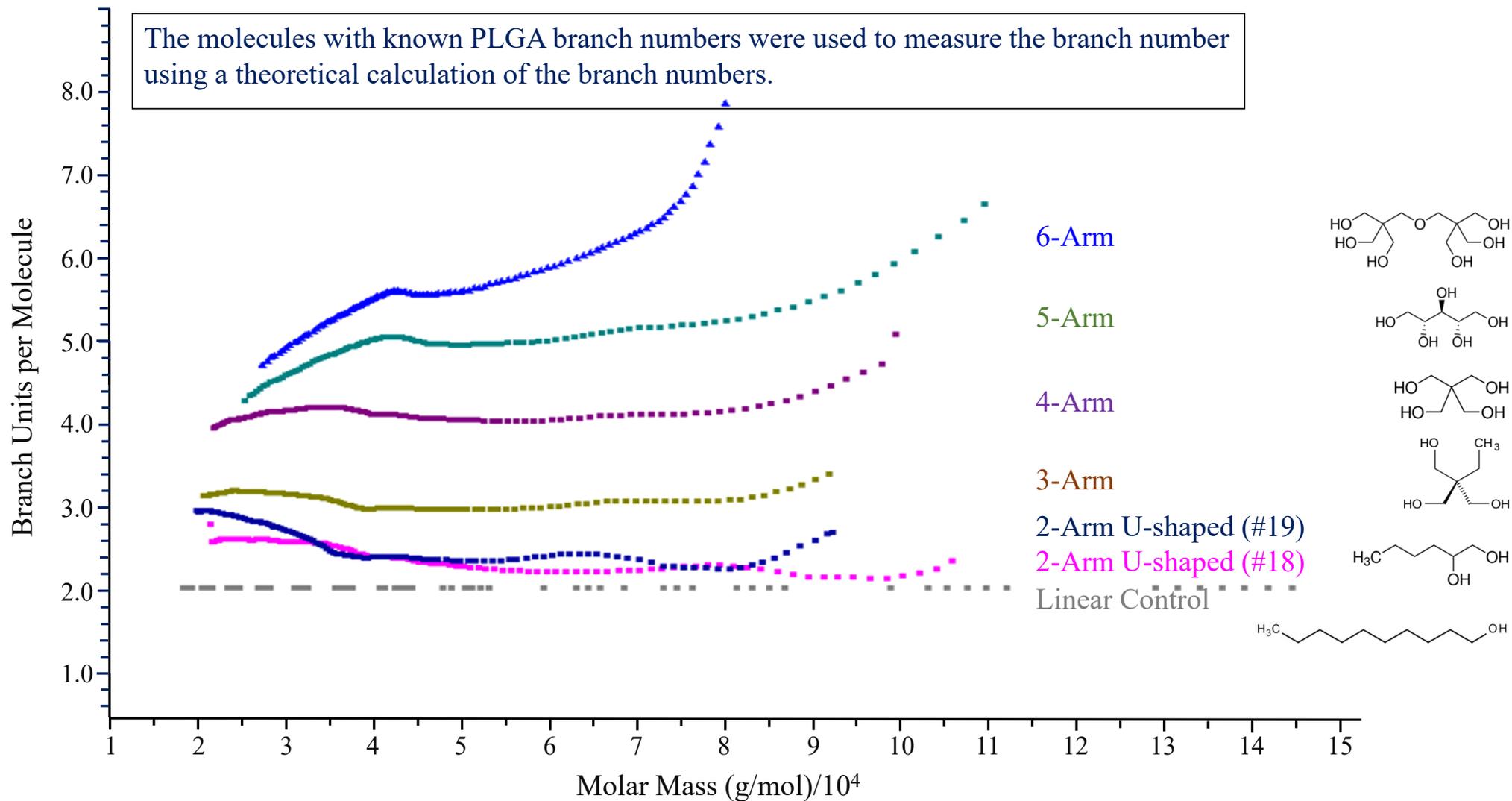
It is difficult to quantitate the number of PLGA branches by NMR. The carbons in glucose do not show any peaks. The carbon peaks from glucose is shielded by the carbon signals from PLGA. Thus, a new method is necessary to determine the number of branches, i.e., the number of PLGA chains on a glucose molecule.

Fortunately, the carbon molecules on molecules on the right shows distinctive peaks even with a PLGA branch.



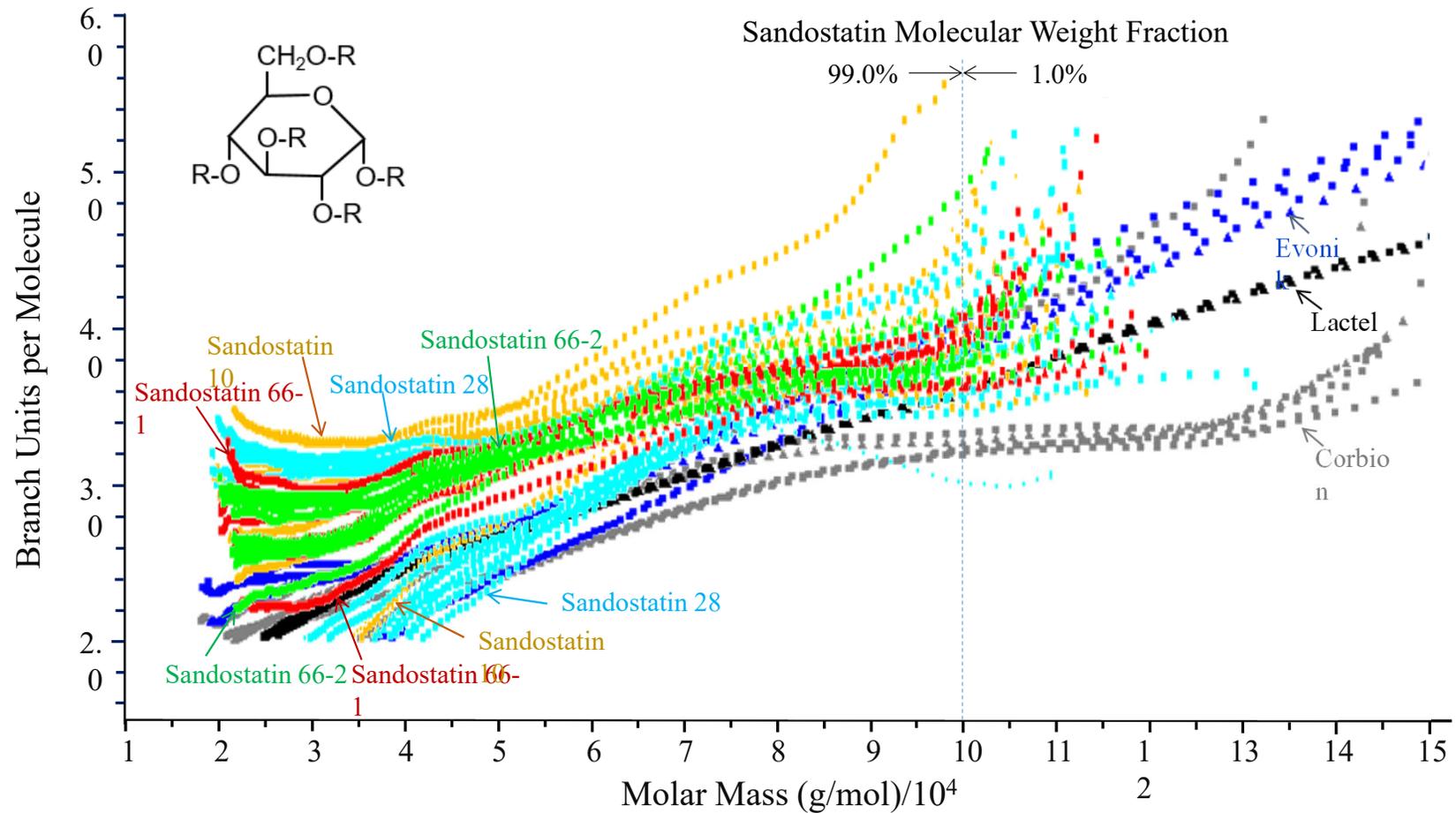
Branch Units per Molecule of Branched PLGAs

The molecules with known PLGA branch numbers were used to measure the branch number using a theoretical calculation of the branch numbers.



Branch Units per Molecule of Branched PLGAs

As shown below, the branch number of glucose-PLGA does not appear to be described by just one number. As the molecular weight increases, the number of PLGA branches seems to increase.



Theoretical Model of Branching

$$g = \left(\frac{R_{branched}^2}{R_{linear}^2} \right)_M$$

g: branch ratio

R²: mean square radius of branched and linear polymers having the same molar mass (M)

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

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

$$g' = g^e$$

e: drainage factor

$$g = \frac{6B}{B^2 + 3B + 2}$$

B: branch units per molecule

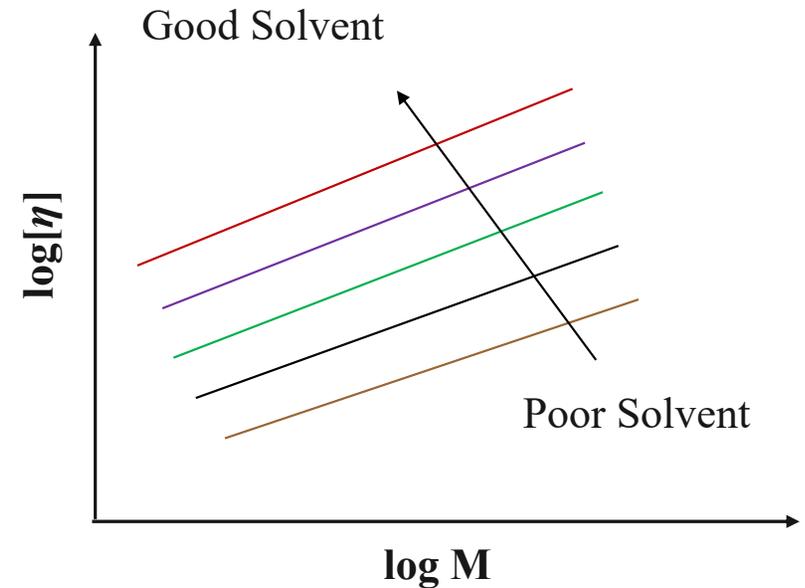
The Mark-Houwink Plot

The dependence of intrinsic viscosity $[\eta]$ of a polymer on its molecular weight M is given by the Mark-Houwink(-Sakurada) equation:

$$[\eta] = KM^\alpha \quad \text{or} \quad \log[\eta] = \log K + \alpha \log M$$

where K and α are two parameters that depend on the solvent, polymer, and temperature.

It is common to plot the Mark-Houwink equation in a log-log graph to calculate the K and α values from the intercept and the slope. The slope is related to the shape of the polymer molecules and the polymer-solvent interactions. $\alpha = 0.5$ for a polymer under θ conditions (i.e., an unperturbed random coil). $\alpha = 0.8$ for a polymer in a good solvent, while $\alpha = 2$ for rod-like polymers. The slope α is related to the solubility parameters of the polymer and the solvent.



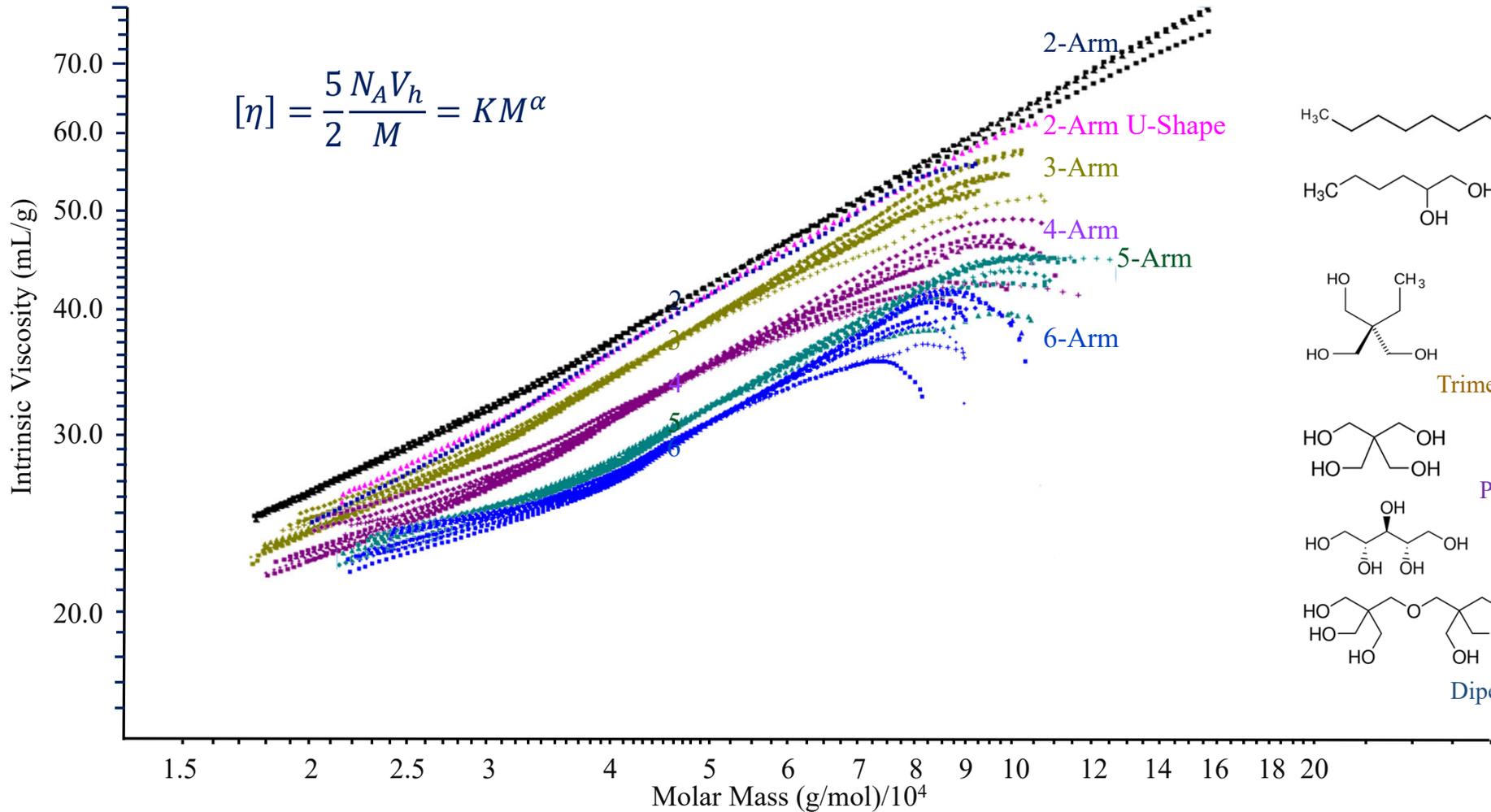
Mark-Houwink plots of a polymer in different solvents.

The molecular weight (M) remains the same but the V_h of the polymer changes in different solvents. The intrinsic viscosity $[\eta]$ increases as the V_h increases in good solvents. Thus, the solvent quality for each PLGA can be characterized by using the K and α values.

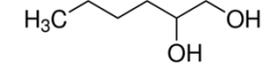
Branch Units per Molecule of Branched PLGAs

Another way of calculating the PLGA branch number is to use Mark-Houwink equation: $[\eta] = KM^\alpha$

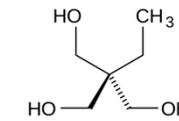
$$[\eta] = \frac{5 N_A V_h}{2 M} = KM^\alpha$$



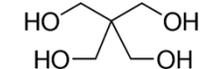
1-decanol



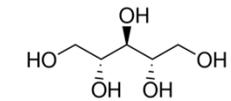
1,2 hexanediol



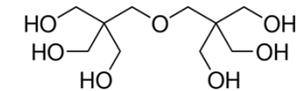
Trimethylolpropane



Pentaerythritol



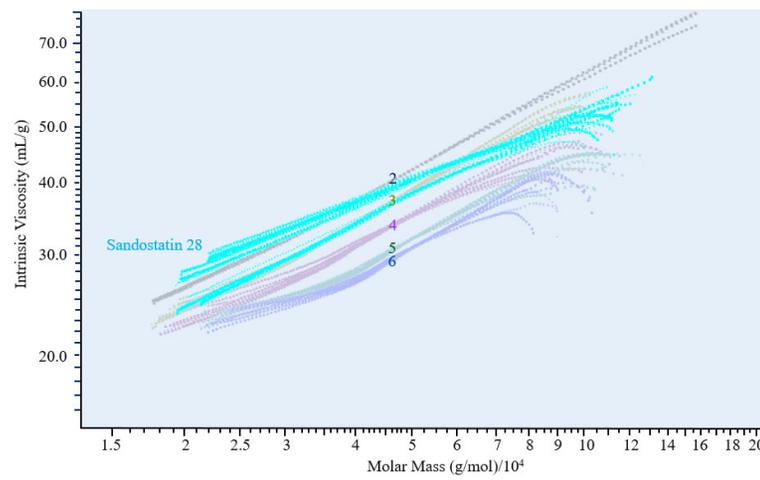
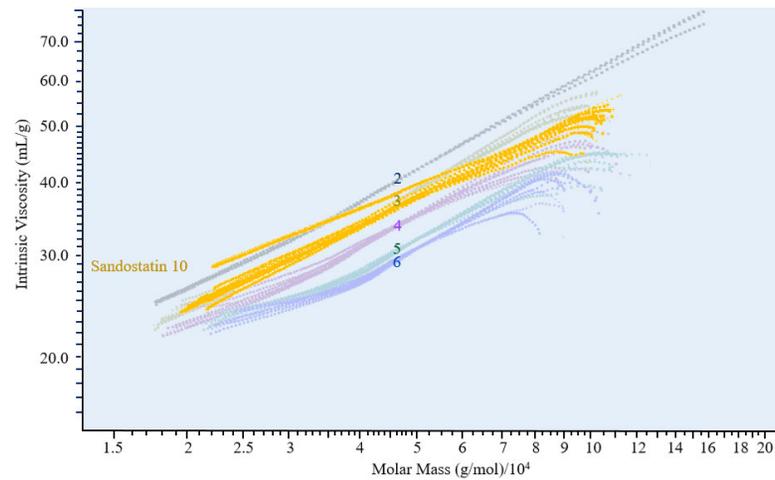
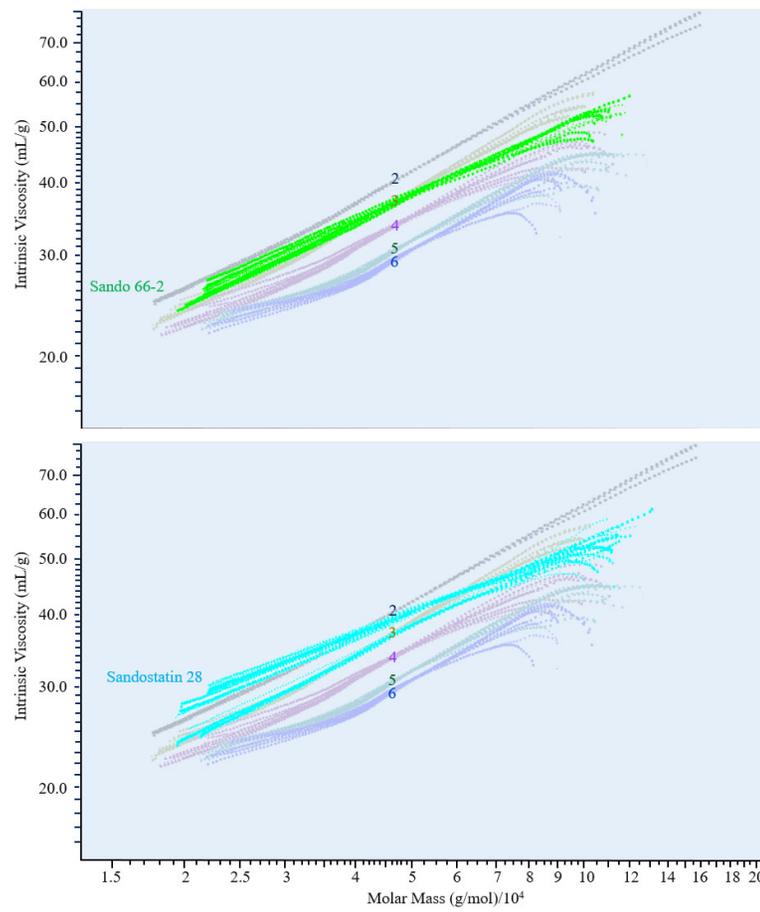
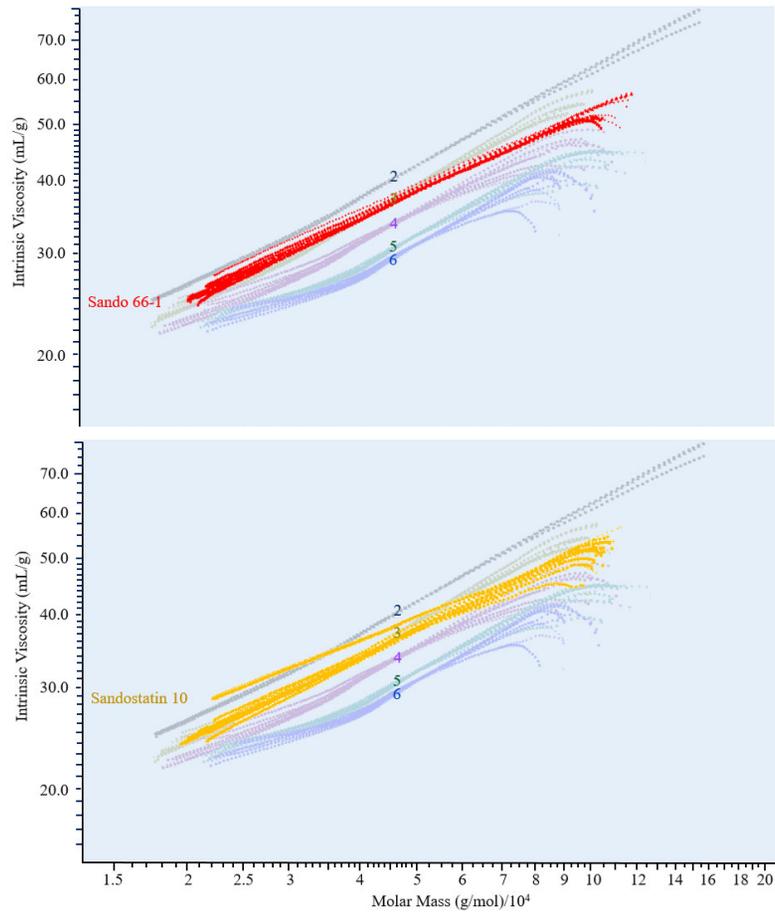
Adonitol



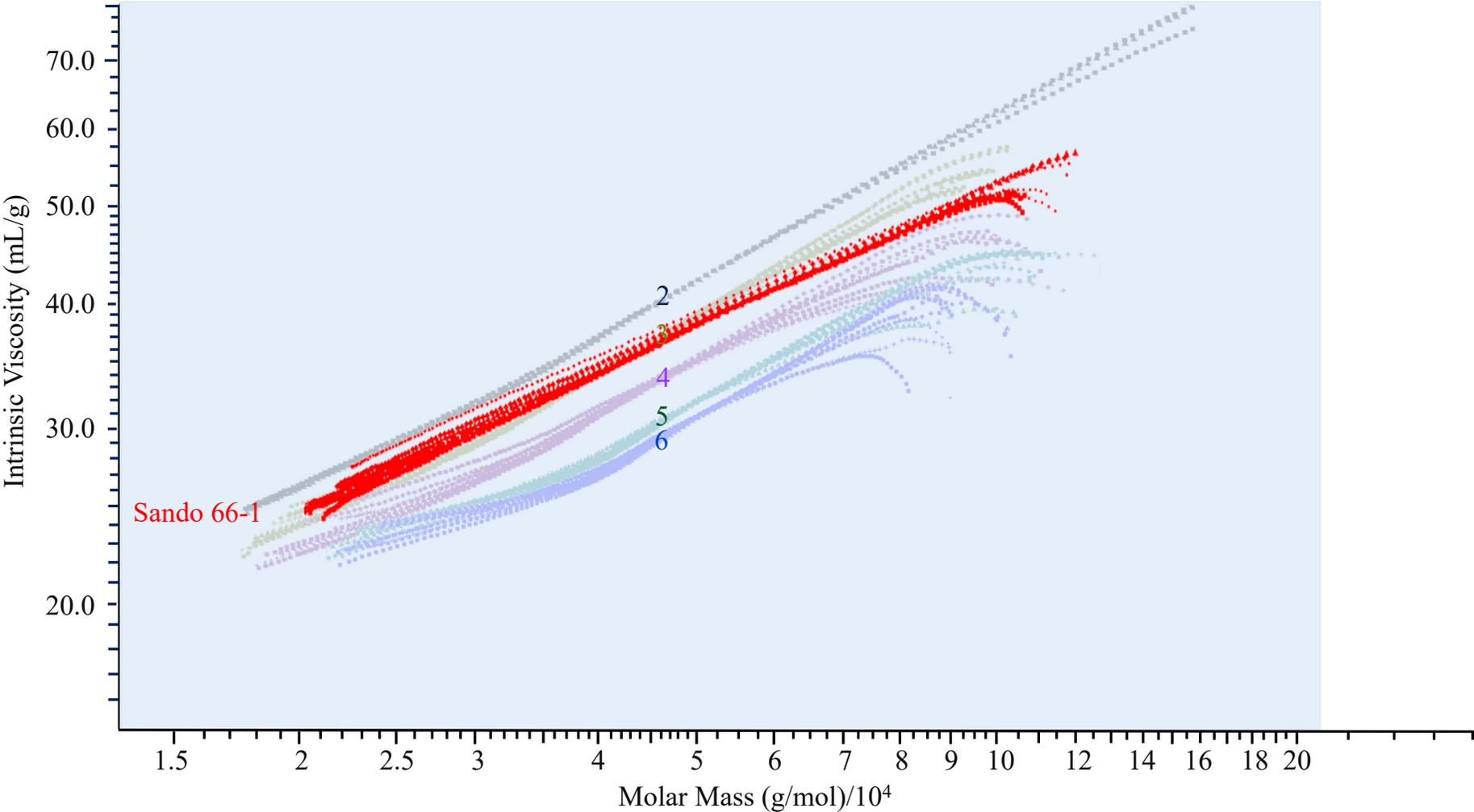
Dipentaerythritol

Mark-Houwink Plots of Glu-PLGAs of Sandostatin

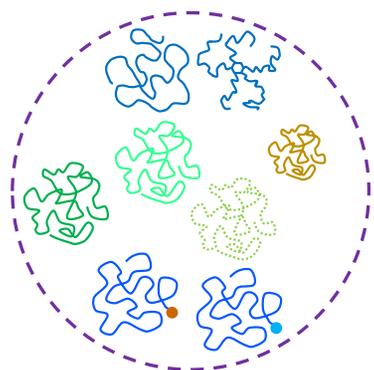
The figures below show that the branch number of glucose-PLGA varies from 2 at low molecular weights to 4 at high molecular weights. Also it shows that Sandostatin in different batches may have slightly different branch numbers.



Mark-Houwink Plots of Glu-PLGAs of Sandostatin



Analysis of **Complex Mini-size (≤ 1 mg)** Formulations



Formulation made of different

- Molecular structures
- Molecular weight
- Molecular Composition
 - L:G ratios
 - End-groups
 - Blockiness



Different PLGAs with

Similar Molecular Weights & Similar L:G Ratios



Amounts necessary for conventional assays

$^1\text{H-NMR}$: ≥ 5 mg
 $^{13}\text{C-NMR}$: ≥ 25 mg
 GPC: ≥ 2 mg



Product	Drug	Polymers	Size
Durysta [®] (Allegan)	Bimatoprost, 10 μg , 15 μg for 6 months	PLGA, PLA-Ester PLA-Acid PEG 3350	~ 0.2 mm in diameter x ~ 1.1 mm and 1.7 mm in length (Total weight < 100 μg)
Ozurdex [®] (Allegan)	Dexamethasone, 700 μg for 3 months	PLGA-Ester PLGA-Acid (both 50:50) (Resomer RG 502 & RG 502H, M_w 7,000-17,000)	116 μg (Ester) 350 μg (Acid) 0.46 mm x 6 mm in length
Signifor [®] LAR (Novartis)	Pasireotide, 10, 20, 30, 40, and 60 mg for 1 month	PLGA 50:50 ~ 60:40 PLGA 50:50	13~79 mg (Star PLGA), 13~79 mg (Linear PLGA)

Understanding **scientific rationale** for making complex formulations

PLGA-based LAIs by QbD

