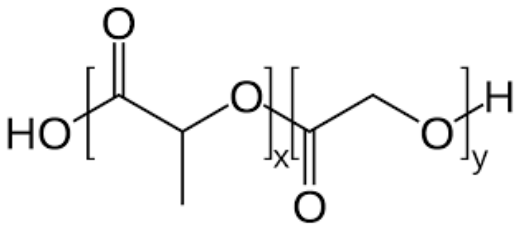
Biodegradable Polymers

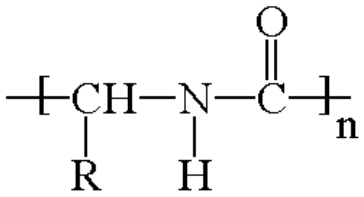
Biodegradable Polyesters

Biodegradable

Poly(lactide-co-glycolide) [PLGA]



Polypeptides

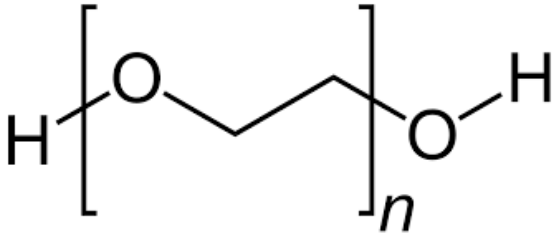


Characteristics of materials

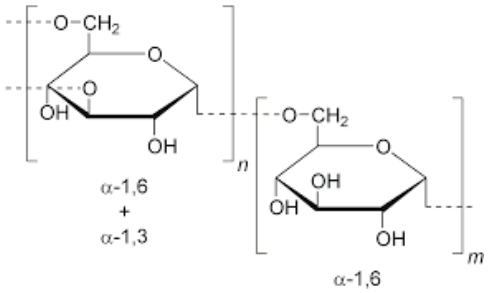
Hydrophilic or hydrophobic
Chemically unstable in Water

Bioeliminable

Poly(ethylene glycol) <10 kDa



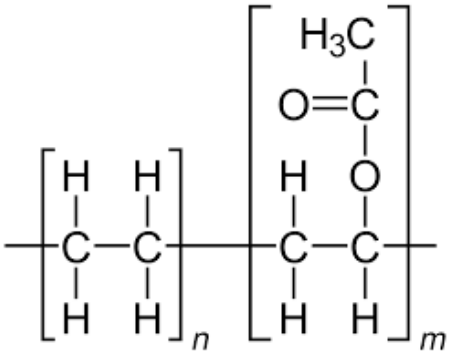
Dextran



Hydrophilic (water soluble)
Chemically stable in water

Removable

Poly(ethylene-co-vinyl acetate)



Hydrophobic/insoluble
Chemically stable in water

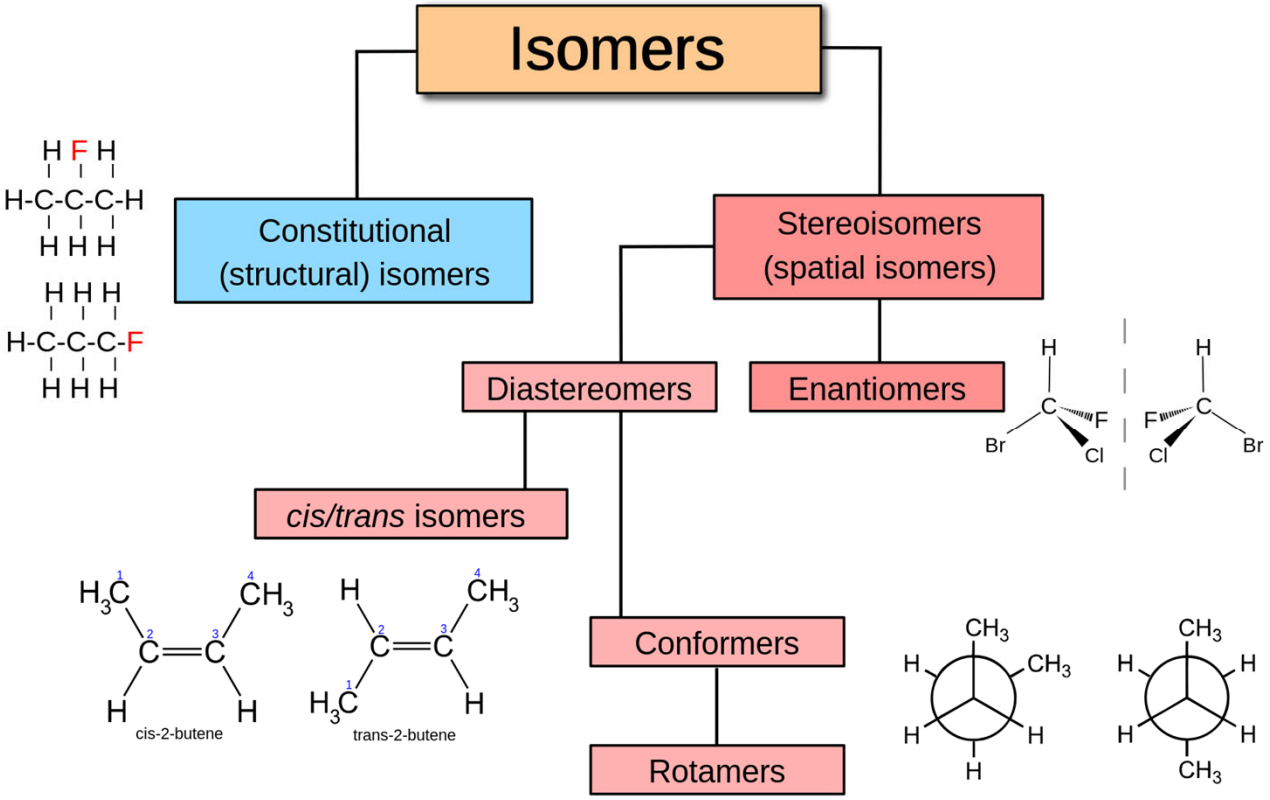
Biodegradable Polyesters

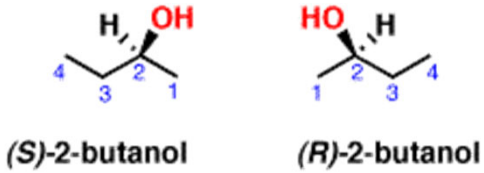
There are numerous aliphatic biodegradable polyesters. However, only a small number of them are commercially available. Some biobased polyesters that have gained commercial use or that are currently investigated for commercial use are polylactic acid (PLA), polyglycolic acid (PGA), poly-ε-caprolactone (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.

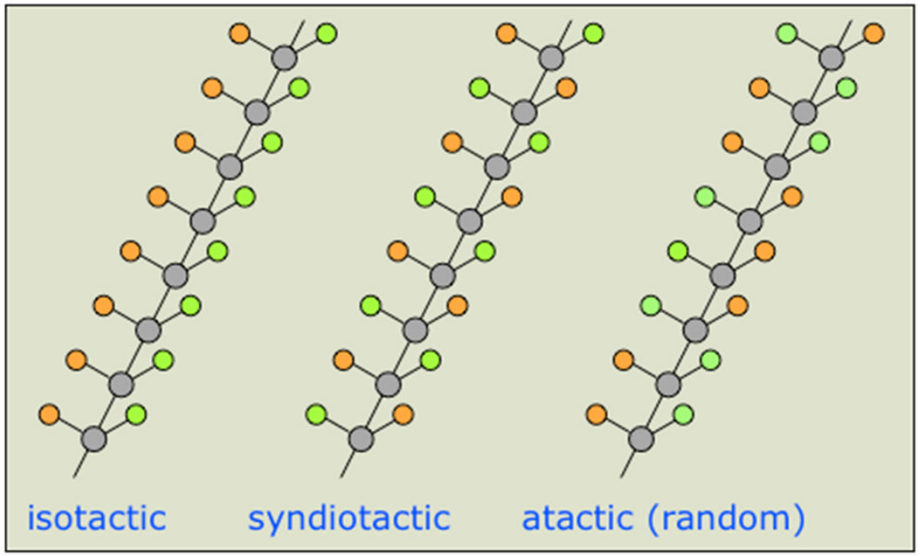
A racemic mixture: A solution containing equal amounts of (R)-2-butanol and (S)-2-butanol.

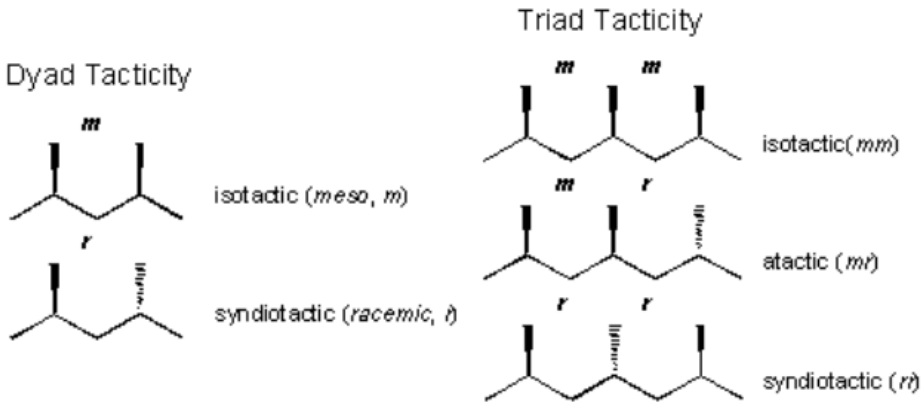
Enantioenriched: A solution containing an excess of either the (R)-enantiomer or the (S)-enantiomer.

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.



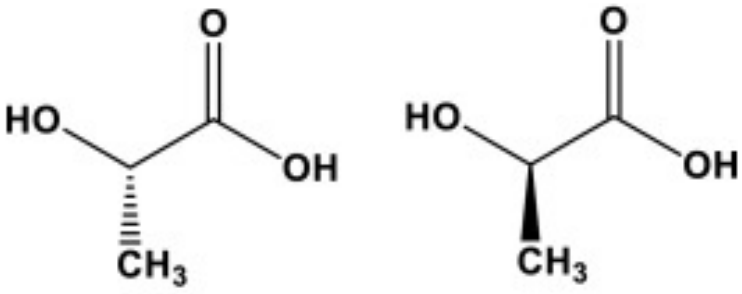


Polymer tacticity is another property of plastics, but one you usually don't hear about. Tacticity relates to the organization of monomer units within polymer strands. There are three categories of polymer tacticity: isotactic, syndiotactic and atactic polymers in order of increasing variability. Isotactic 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.

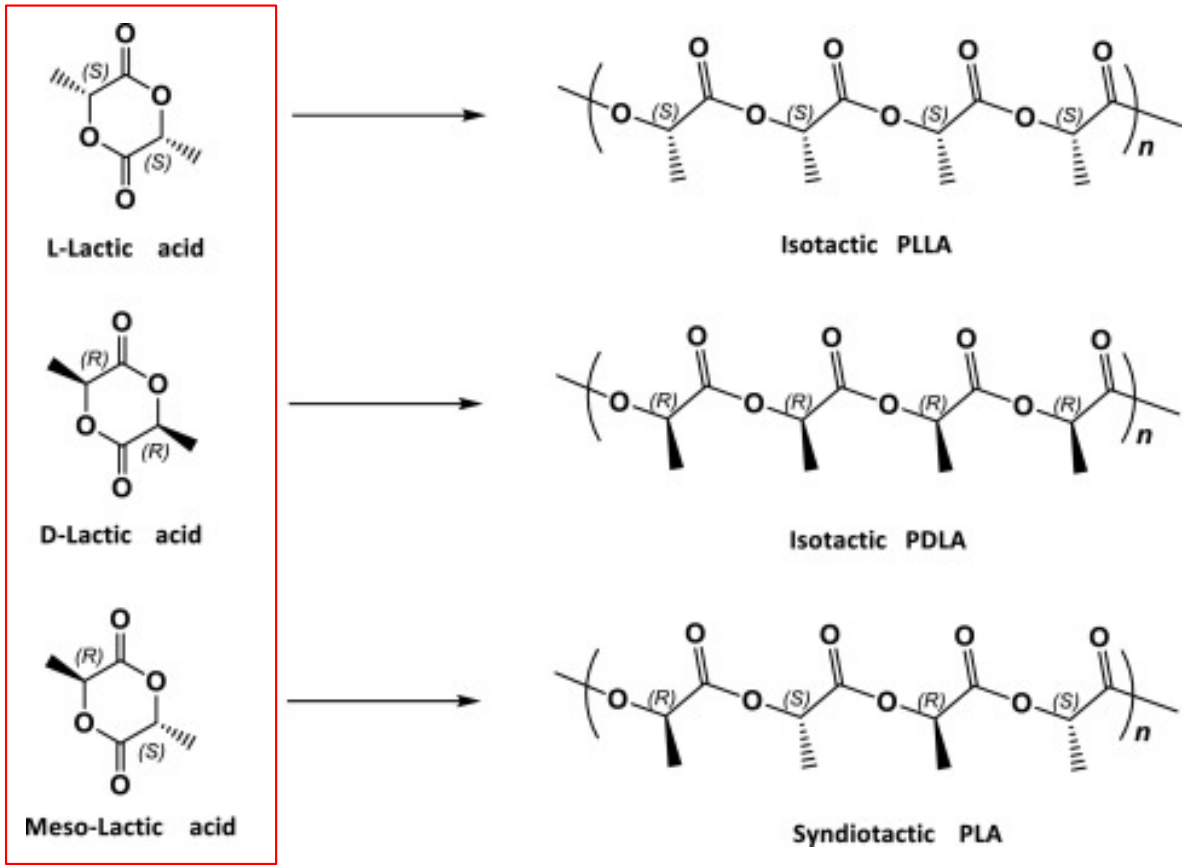
http://everydaythinkers.blogspot.com/2015/08/its-just-plastic-but-what-is-just.html

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.

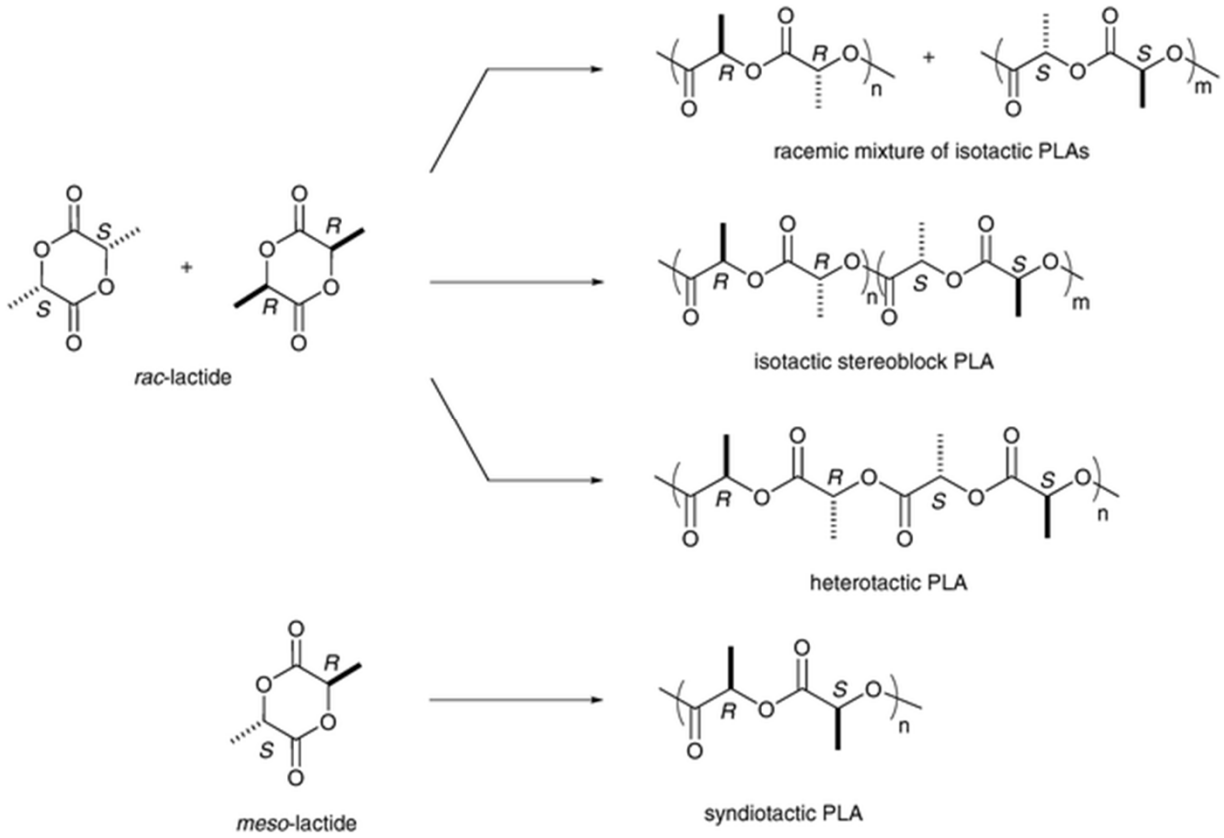


Scheme 2. Three stereoisomers of lactide which lead to distinct PLA structures upon polymerization.

https://www.sciencedirect.com/science/article/pii/S0079670016300235
Li et al., Recent advances in stereocomplexation of enantiomeric PLA-based copolymers and applications, Progress in Polymer Science, 62: 22-72, 2016.

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 = 170–180 °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.



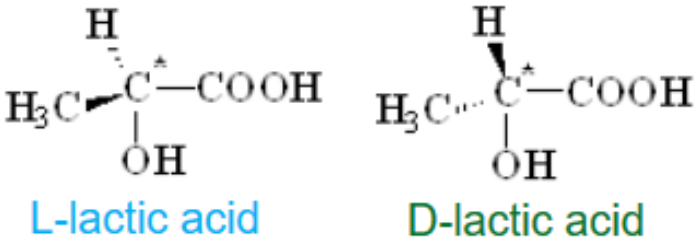
https://pubs.rsc.org/en/content/articlehtml/2010/cs/b810065a

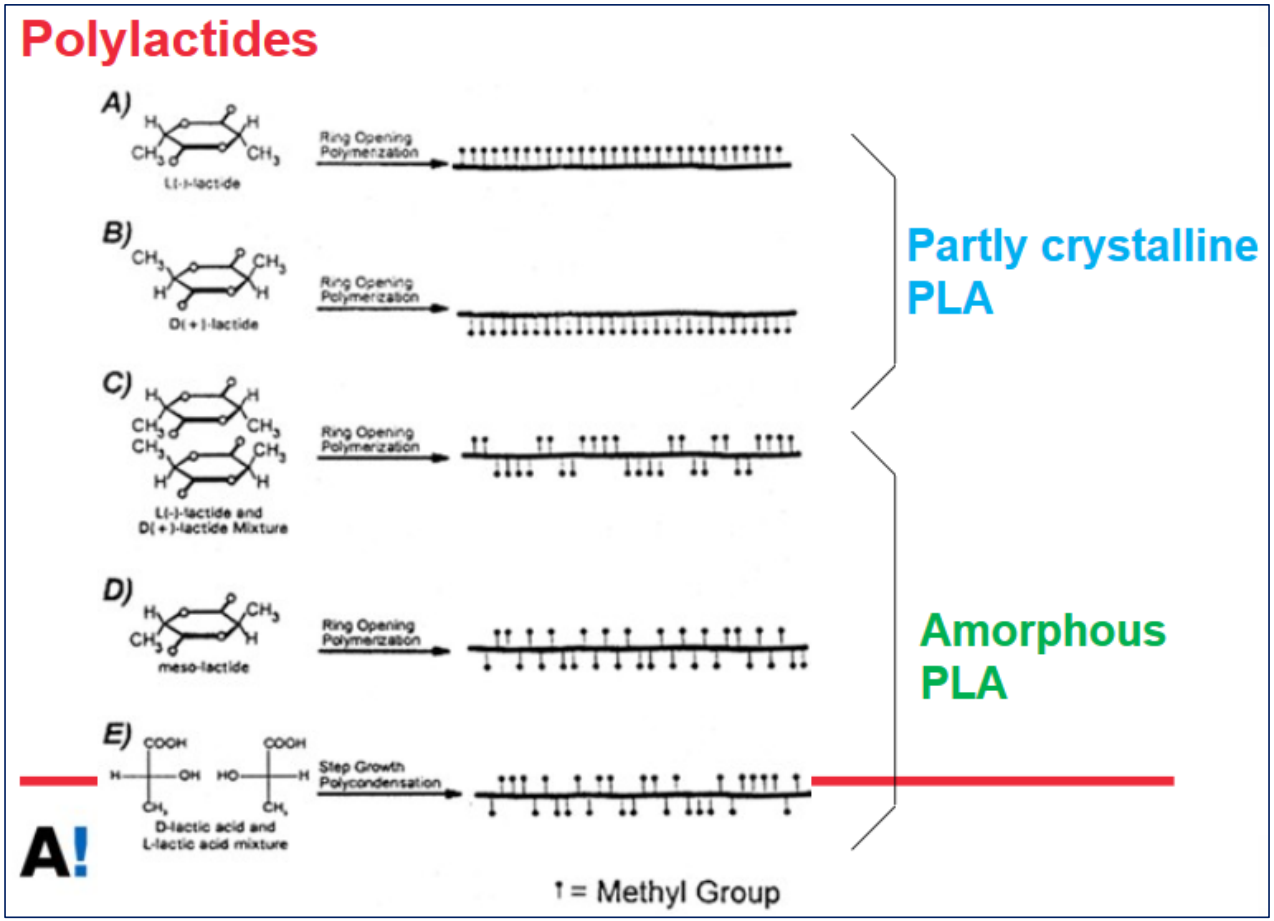
C.M. Thomas, Stereocontrolled ring-opening polymerization of cyclic esters: synthesis of new polyester microstructures, Chem. Soc. Rev., 2010, 39, 165-173.

Lactide-Based Polymers: Tacticity & Isomerism

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

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





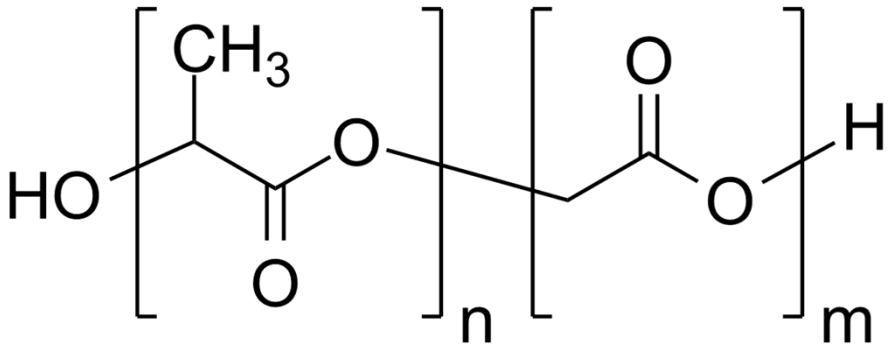
https://slideplayer.com/slide/8939858/

KE-100.3410 Polymer Properties Steve Spoljaric, PhD.

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.



Lactide Unit Glycolide Unit

How Do We Characterize PLGA?

PLGA Characterization Methods

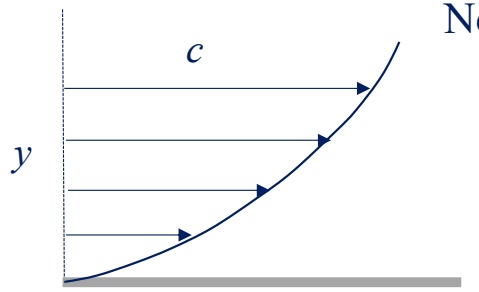
Molecular Weight
Lactide:Glycolide Ratio (L:G Ratio)
Endgroup

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.

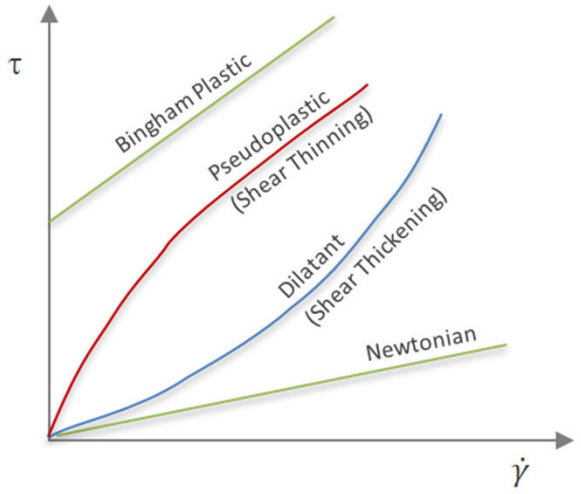


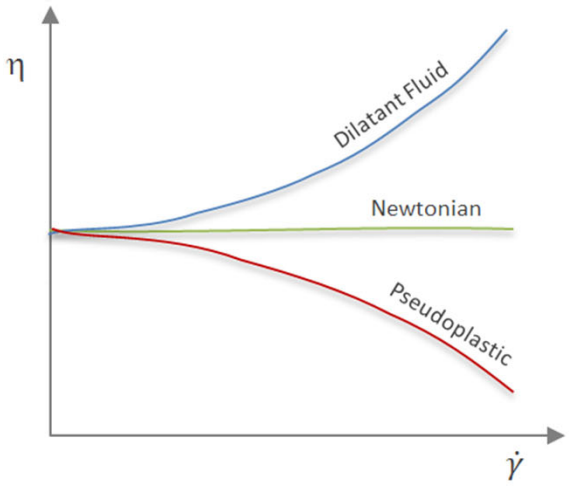
Newton's Law of Friction

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

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

τ: Shear stress in fluid in Pascal (N/m^2)
η: Dynamic viscosity of fluid ($N{\cdot}s/m^2$)
$\dot{\gamma}$: Shear rate (s^{-1}) = $\Delta c/\Delta y$
Δc: Unit velocity (m/s)
Δy: Unit distance between layers (m)





The viscosity of water = 1 cP (= 0.01 g/cm·sec = 1 mPa·sec = 0.001 Pa·sec = 0.001 $N{\cdot}s/m^2$).

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 soluition
t_0 = time for solvent
$\rho \approx \rho_0$

Relative Viscosity

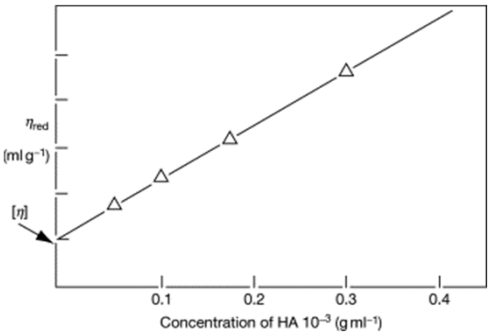
$$\eta_{rel} = \frac{\eta_{solution}}{\eta_{solvent}} = \frac{\eta}{\eta_o} = \frac{k\rho t}{k\rho_o t_o} = \frac{t}{t_o}$$

Specific Viscosity

$$\eta_{sp} = \eta_{rel}\text{-}1 = \frac{\eta}{\eta_o} - \frac{\eta_o}{\eta_o}$$

Intrinsic Viscosity

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



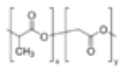
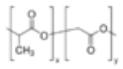
Inherent Viscosity

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

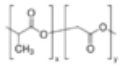
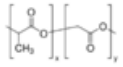
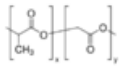
Poly(lactide-co-glycolide) (PLGA) Molecular Weights

Sigma-Aldrich

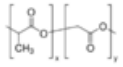
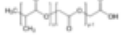
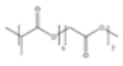
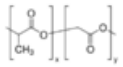
65:35 (Lactide:Glycolide)

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

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

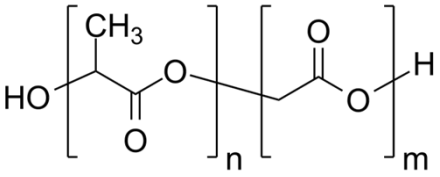
85:15 (Lactide:Glycolide)

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

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.

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.

Durect.com

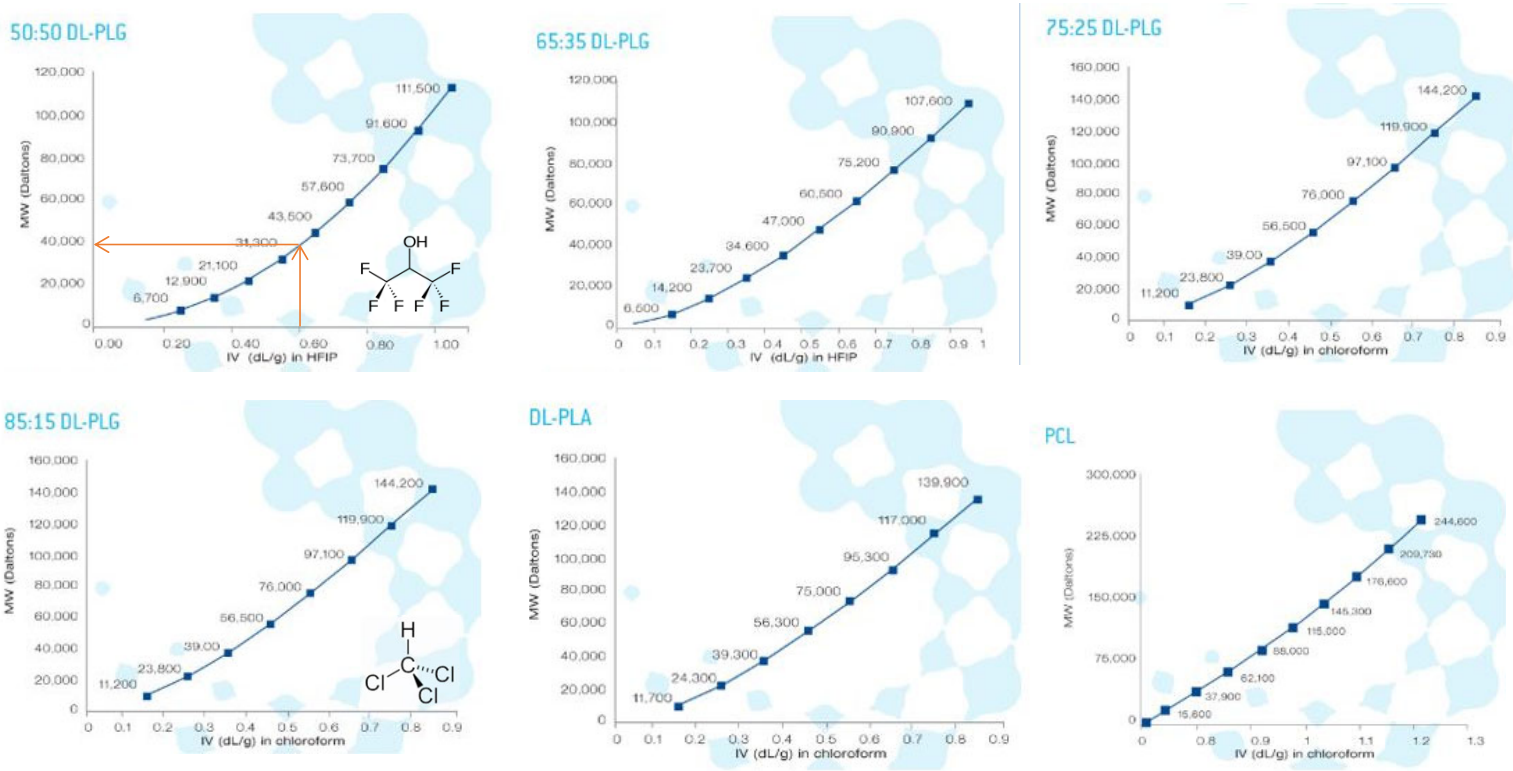
Commercial Products

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)

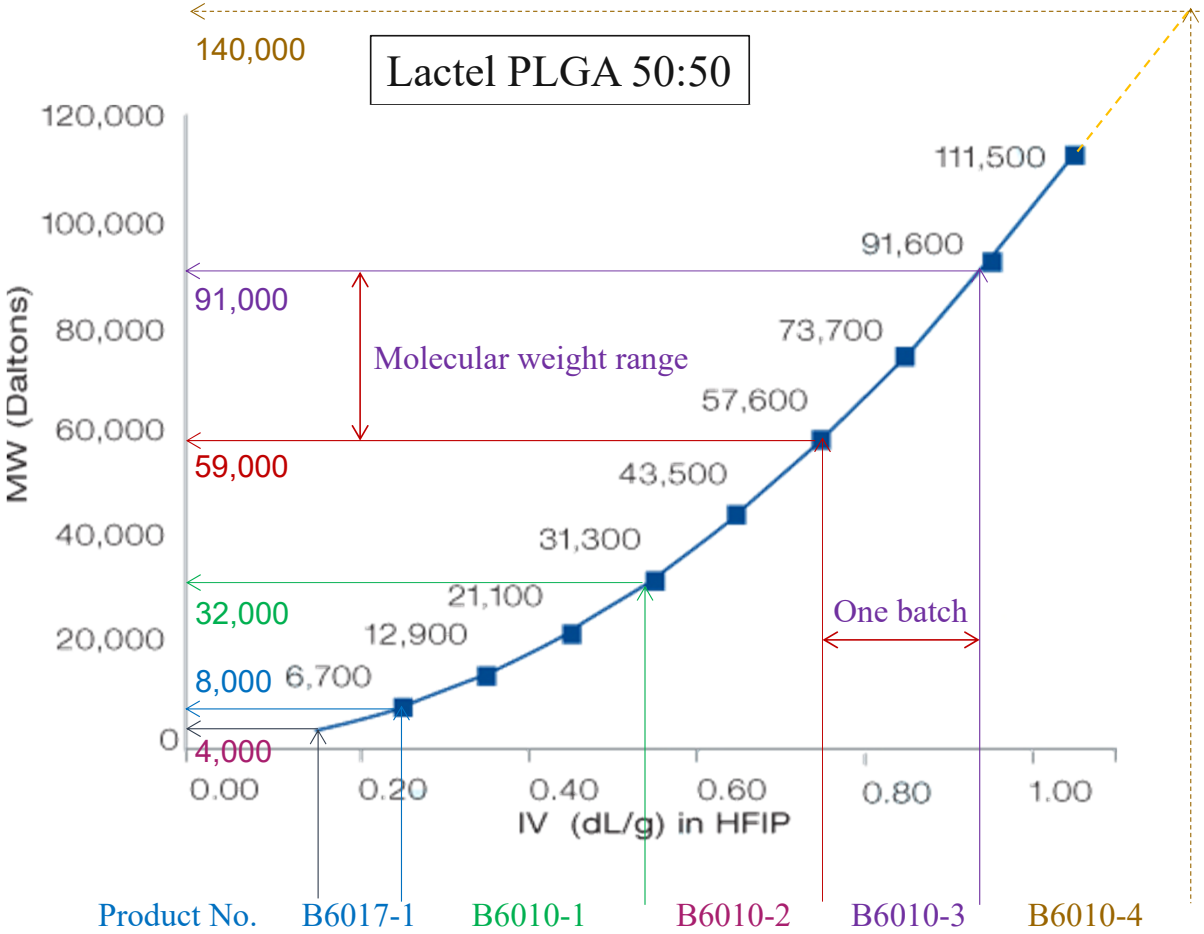
There are relationships between polymer molecular weight and IV. Once you know the IV, you can find the corresponding molecular weight. See the arrows on the top left figure. But the measured IV of a polymer solution depends on organic solvent used. Thus, if a different solvent is used, the calibration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

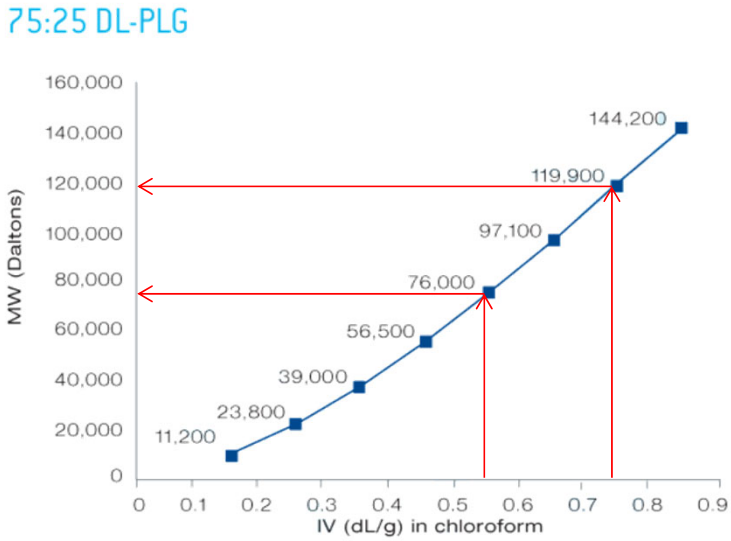
50:50 DL-PLG = PLGA with the L:G ratio of 50:50 = PLGA 50:50 or 50:50 PLGA



Inherent Viscosity Average Molecular Weight (Lactel)

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





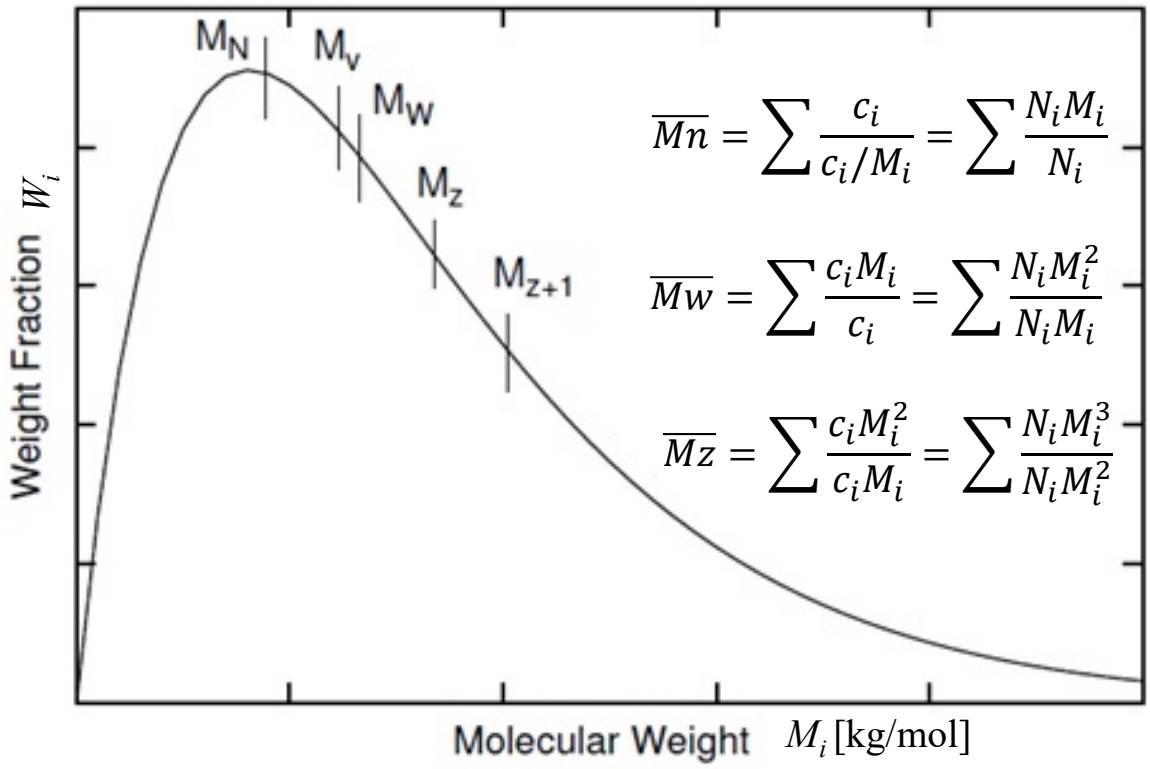
Determination of the Molecular Weight

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

$$M_N \leq M_W \leq M_Z$$

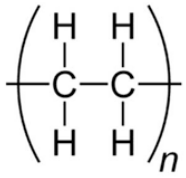


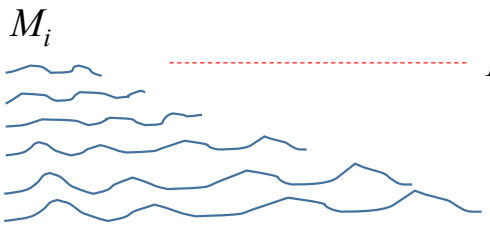
$$\overline{Mn} = \sum \frac{c_i}{c_i/M_i} = \sum \frac{N_i M_i}{N_i}$$

$$\overline{Mw} = \sum \frac{c_i M_i}{c_i} = \sum \frac{N_i M_i^2}{N_i M_i}$$

$$\overline{Mz} = \sum \frac{c_i M_i^2}{c_i M_i} = \sum \frac{N_i M_i^3}{N_i M_i^2}$$

M_w = 18 g/mol





$N_i M_i = C_i$

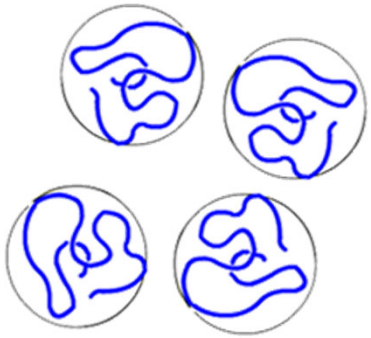
W_i

Weight Fraction

Gel Permeation Chromatography

Polymer molecules in the solid state
Just after added to solvent

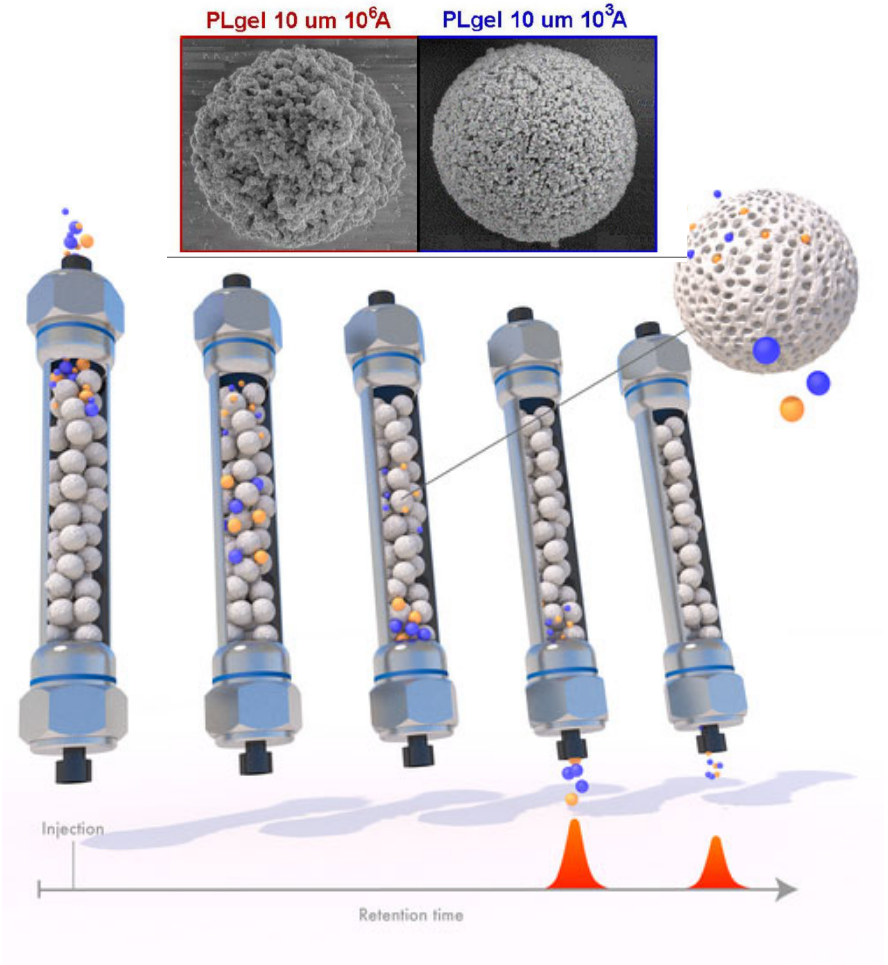
Step 1. A swollen gel in solvent



Step 2. solvated polymer molecules
dispersed into a solution

Solubility depends on

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

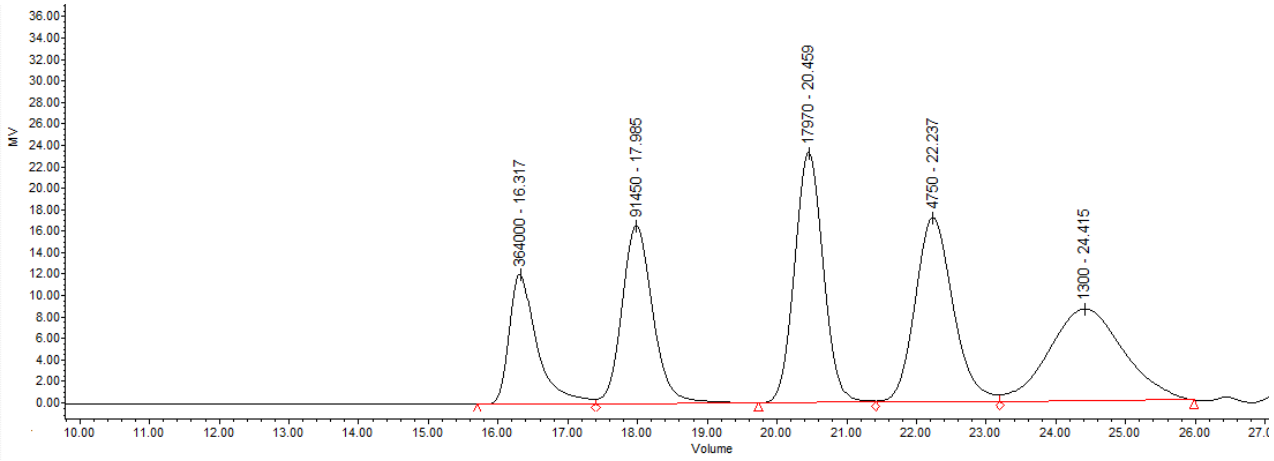


M. Striegel, W. W. Yau, J. J. Kirkland, and D. D. Bly. Modern Size-Exclusion Liquid Chromatography-Practice of Gel Permeation and Gel Filtration Chromatography, 2nd Edition. Hoboken. N.J. (2009)
Agilent.com

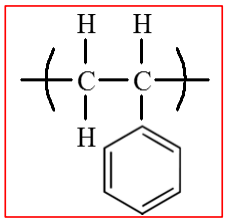
PLGA Molecular Weight by GPC with Polystyrene External Standard

Polystyrene Standards with indicated molecular weights.

Polystyrene and PLGAs are dissolved in tetrahydrofuran (THF).



Retention Volume (or Retention Time)



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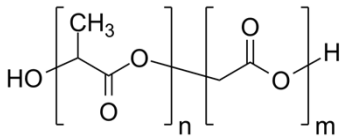
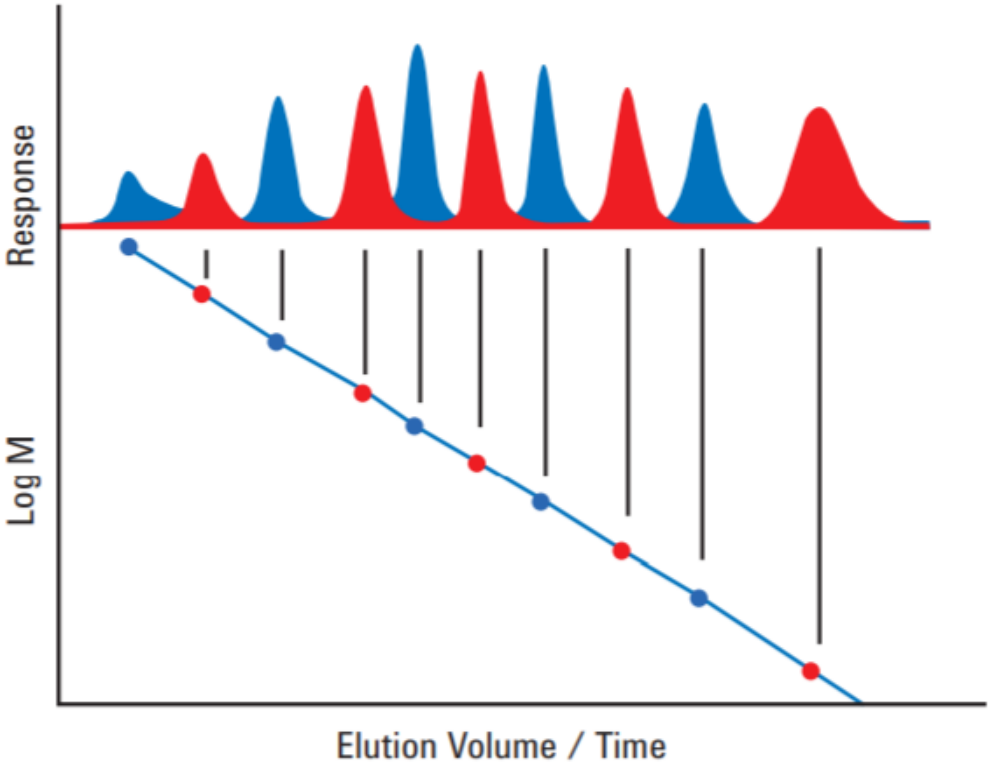


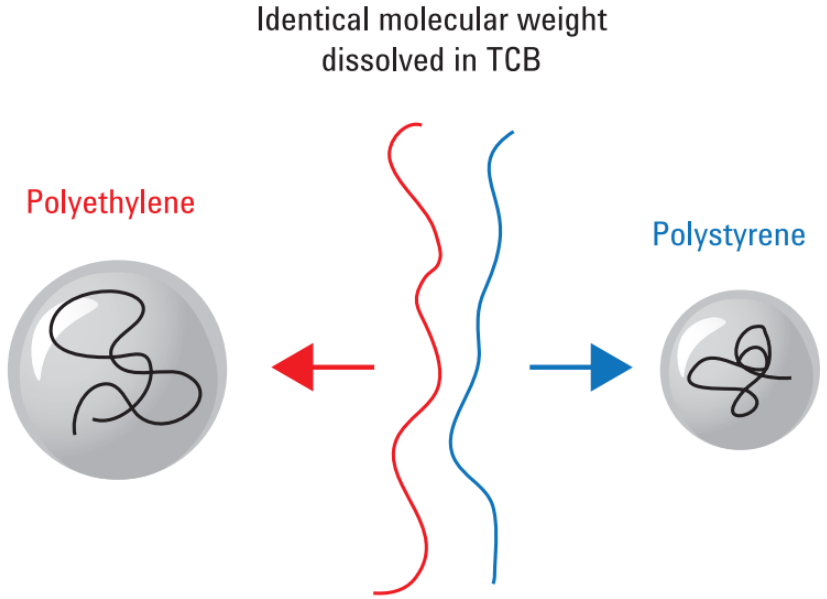
Polystyrene and PLGAs swell to different degrees (i.e., different hydrodynamic volume) even at the same molecular weight, and thus, the retention volume will be different. This results in inaccurate PLGA molecular weight.

- 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



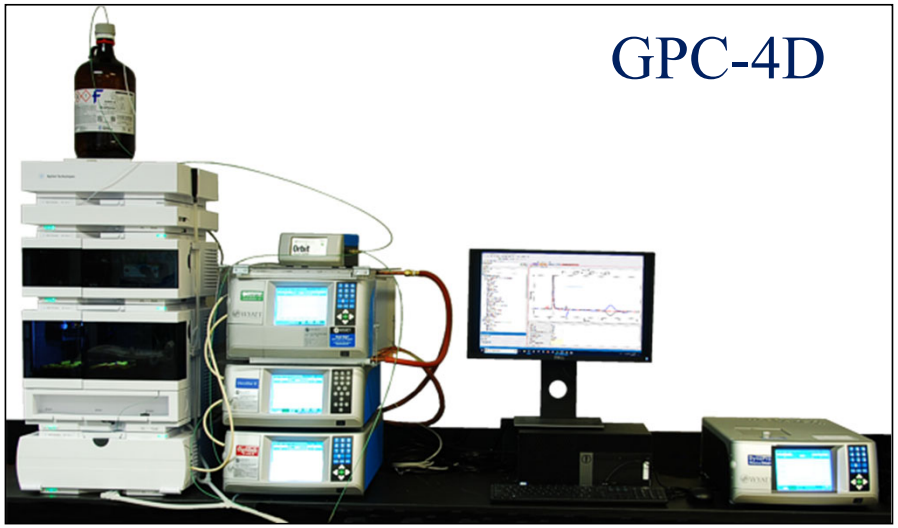
Typical chromatograms for two mixtures of standards and resulting calibration curve

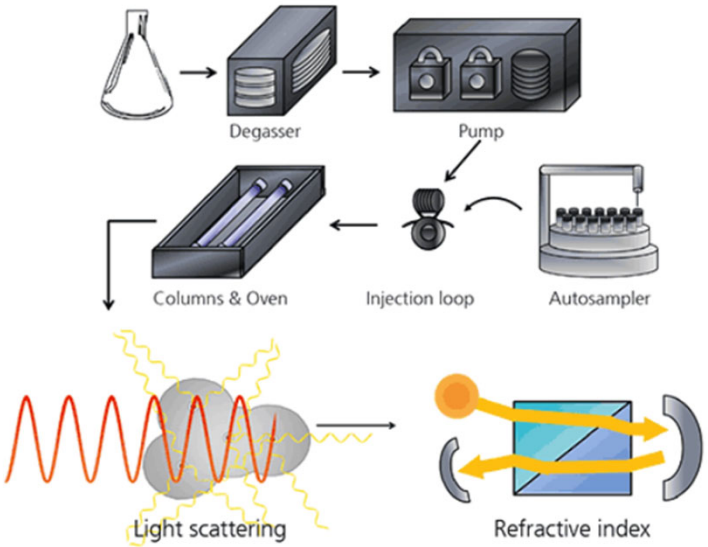


Comparison of sizes of two polymers in a common solvent

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)
- 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.

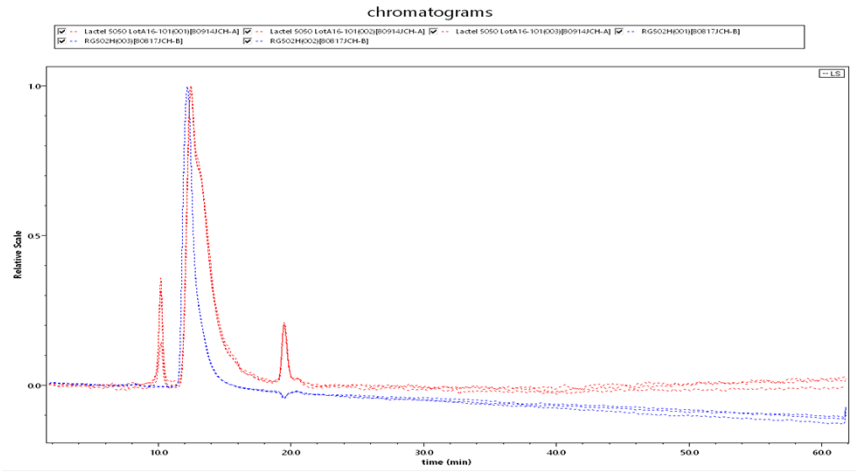
Comparison of Molecular Weights of PLGAs from Two Commercial Sources

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

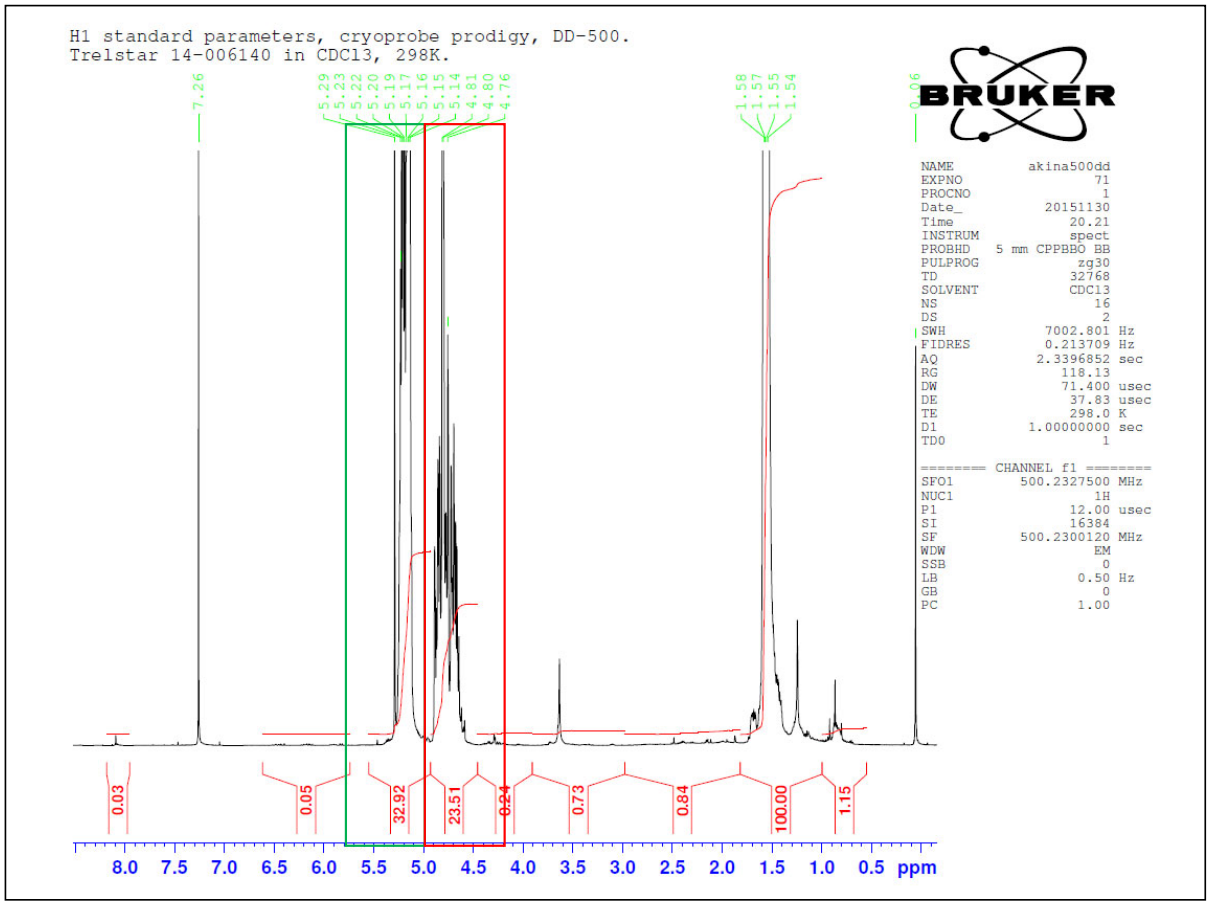
Comparison of GPC-4D results across two commercially manufactured PLGAs of comparable inherent viscosity specifications. (Molecular weights were measured by GPC-4D).

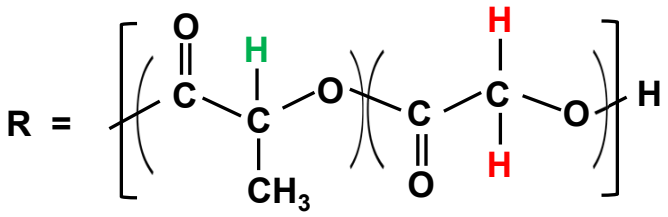
Chromatographic overlay of RG502H from Evonik (blue) and B6013-1 from Lactel (red). Both have almost the same IV ranges, but the molecular weight distribution is quite wider for B6013-1, resulting in much smaller average molecular weight.



PLGA: L:G ratio by ^{1}H-NMR

The L:G ratio of PLGAs is determined from the ^{1}H-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.





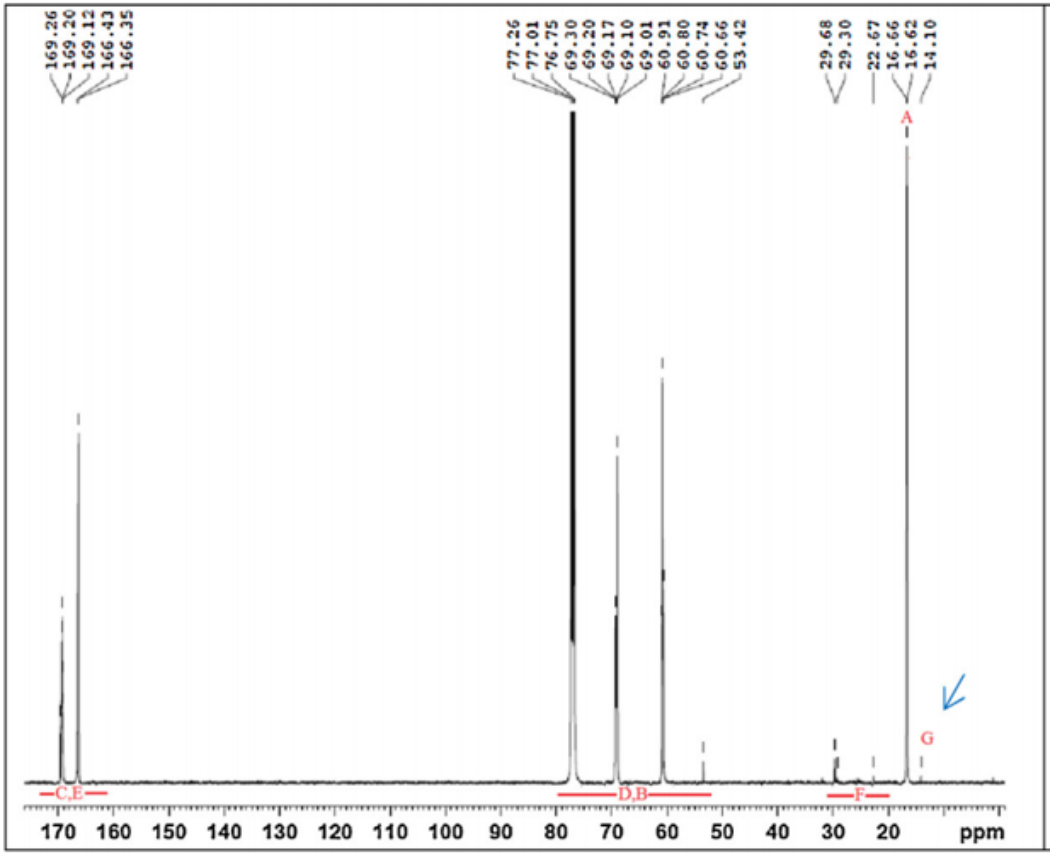
Lactic acid Glycolic acid

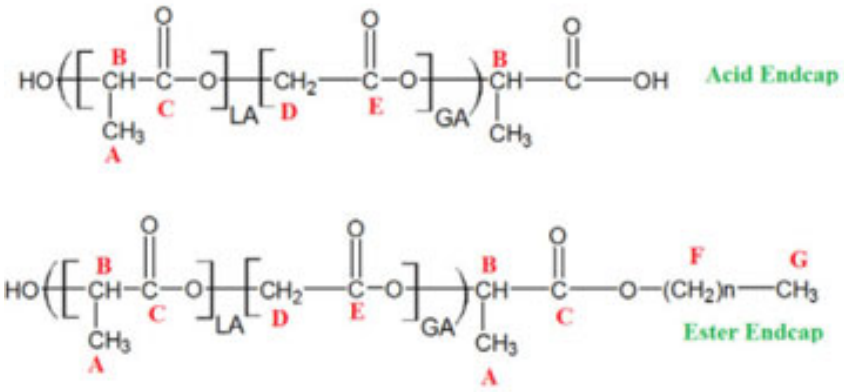
$$M_L = P_L/(P_L + (P_G/2))$$
$$M_G = (P_G/2))/(P_L + (P_G/2))$$

- 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.

John Garner, Skidmore, Sarah, Haesun Park, Kinam Park, Stephanie Choi, Yan Wang, A protocol for assay of poly(lactide-co-glycolide) in clinical products. Int. J. Pharm. 495 (2015) 87-92.

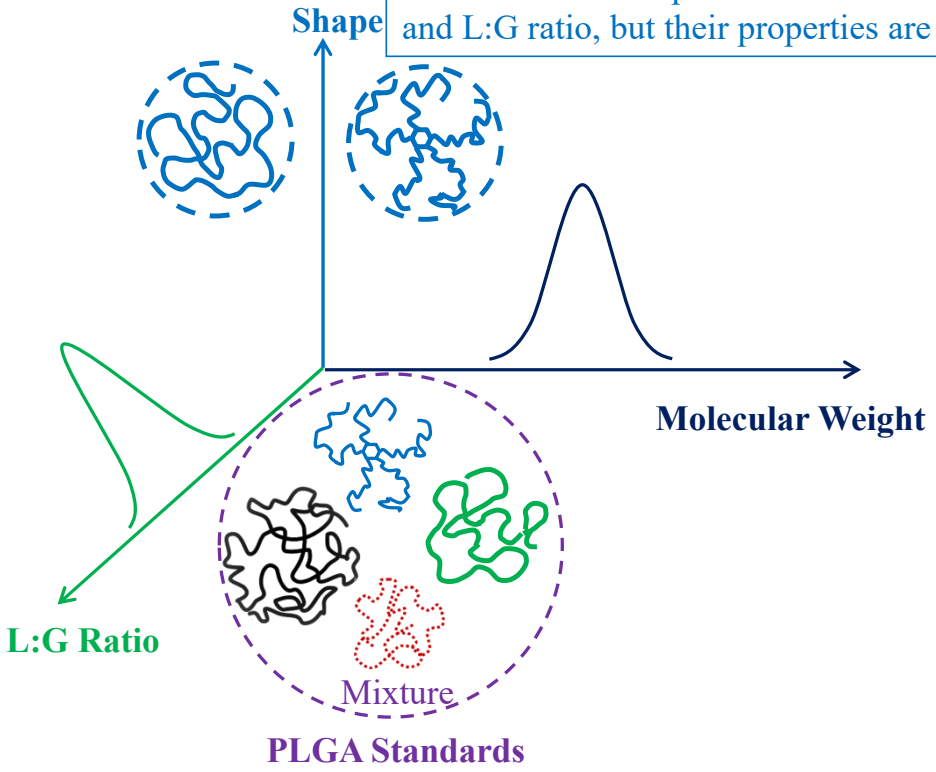
Characterization of Poly(lactide-co-glycolide) (PLGA)

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.

Linear and star-shape molecules have the same molecular weight and L:G ratio, but their properties are very different.

Intrinsic Viscosity
Mark-Houwink Equation

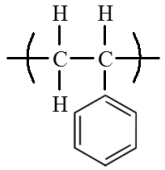
Dynamic Light Scattering
V_h: Hydrodynamic volume



L:G (Lactodispersity)

Multi-Angle Light Scattering
for accurate Molecular weight

GPC with polystyrene external Mol. Wt. Standards which are usually dissolved in DCM or THF.



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.

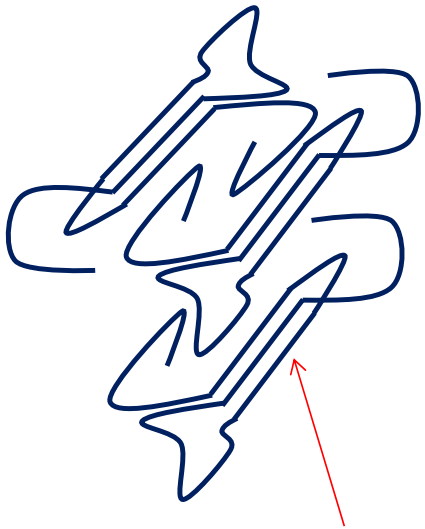
Solvent	PLGA L:G Ratio										
	50:50	55:45	60:40	65:35	70:30	75:25	80:20	85:15	90:10	95:5	100:0
Dichloromethane											
Dimethyl sulfoxide											
Dimethyl formamide											
Ethyl acetate											
Methyl ethyl ketone											
Tetrahydrofuran											
Ethyl benzoate											
Chlorobenzene											
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: 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.

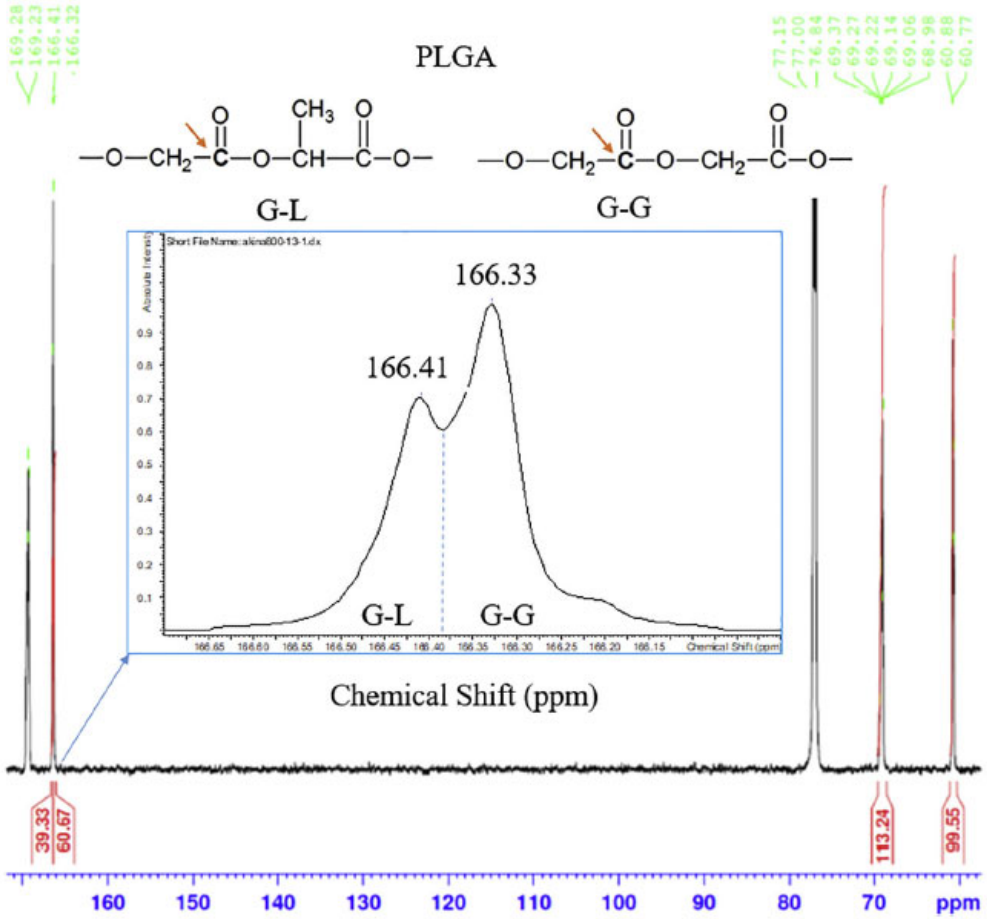
- **Blockiness** refers to the distribution of L:G in a given PLGA batch, in particular to the glycolide segments.
- Glycolide-rich regions tend to self-crystalize making difficult to dissolve domains.



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_{G-G}, upfield G-G peak at 166.33 ppm) by the peak intensity of the glycolide carbonyl adjacent to a lactide unit (I_{G-L}, downfield G-L peak at 166.41 ppm). This ratio of the two carbonyl peaks is described as the R_c value:

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

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 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)

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)

Eligard®
(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

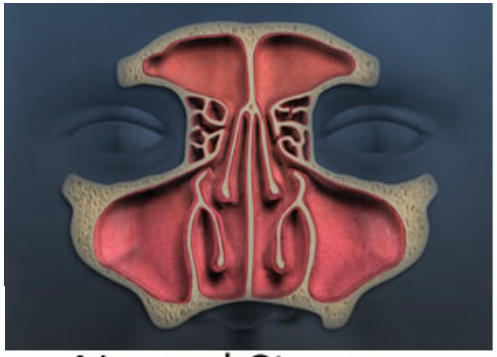
Sublocade™
(buprenorphine extended-release) injection for subcutaneous use ®
100mg·300mg
1 month, IS 2017
100, 300 mg/month

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

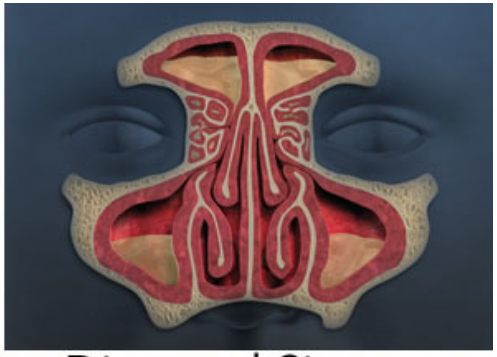
MP: Microparticle (12)
IS: In Situ forming implant (4)
SI: Solid implant (3)

IM: Intramuscular
IV: Intravitreal
SC: Subcutaneous
PD: Periodontal

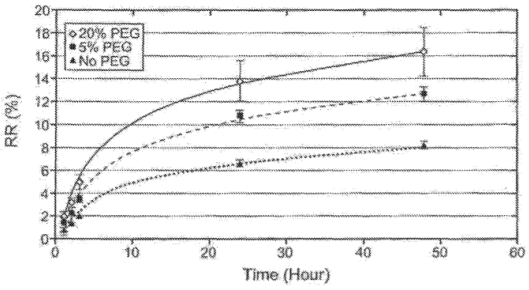
Novel Implant Designs - Propel

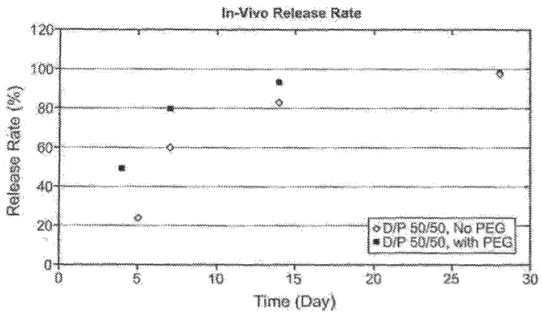


Normal Sinuses



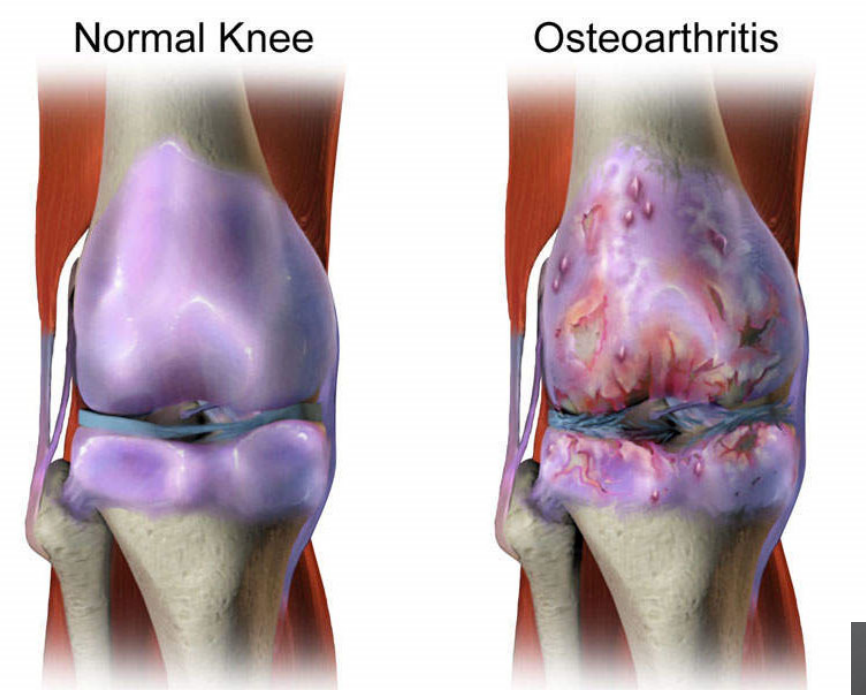
Diseased Sinuses



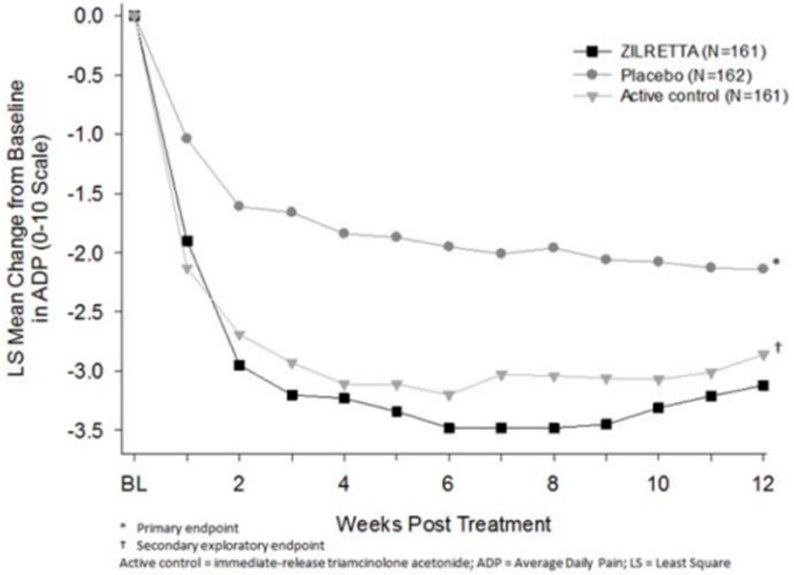


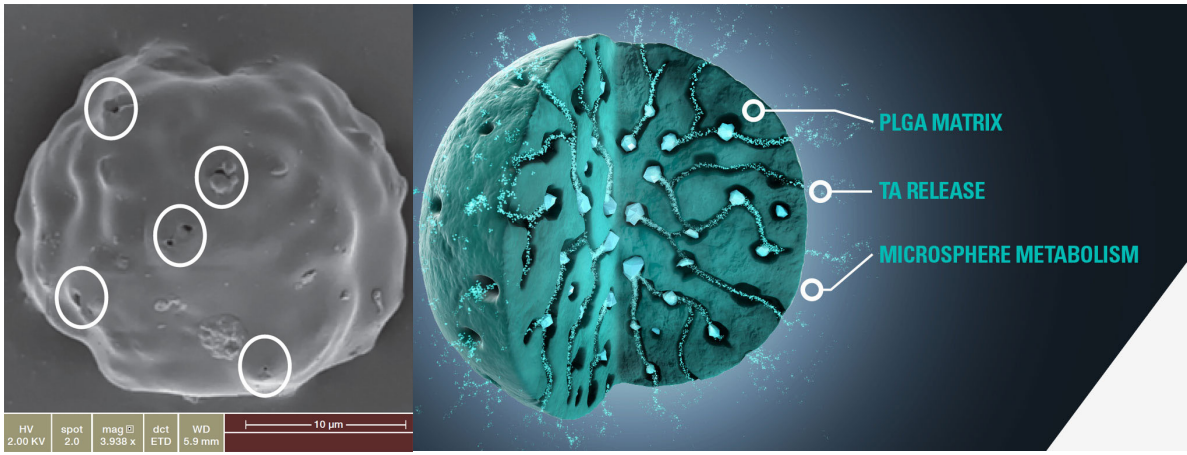
Intersectent.com
US10471185B2

Localized Activity - Zilretta



Zilretta Package Insert



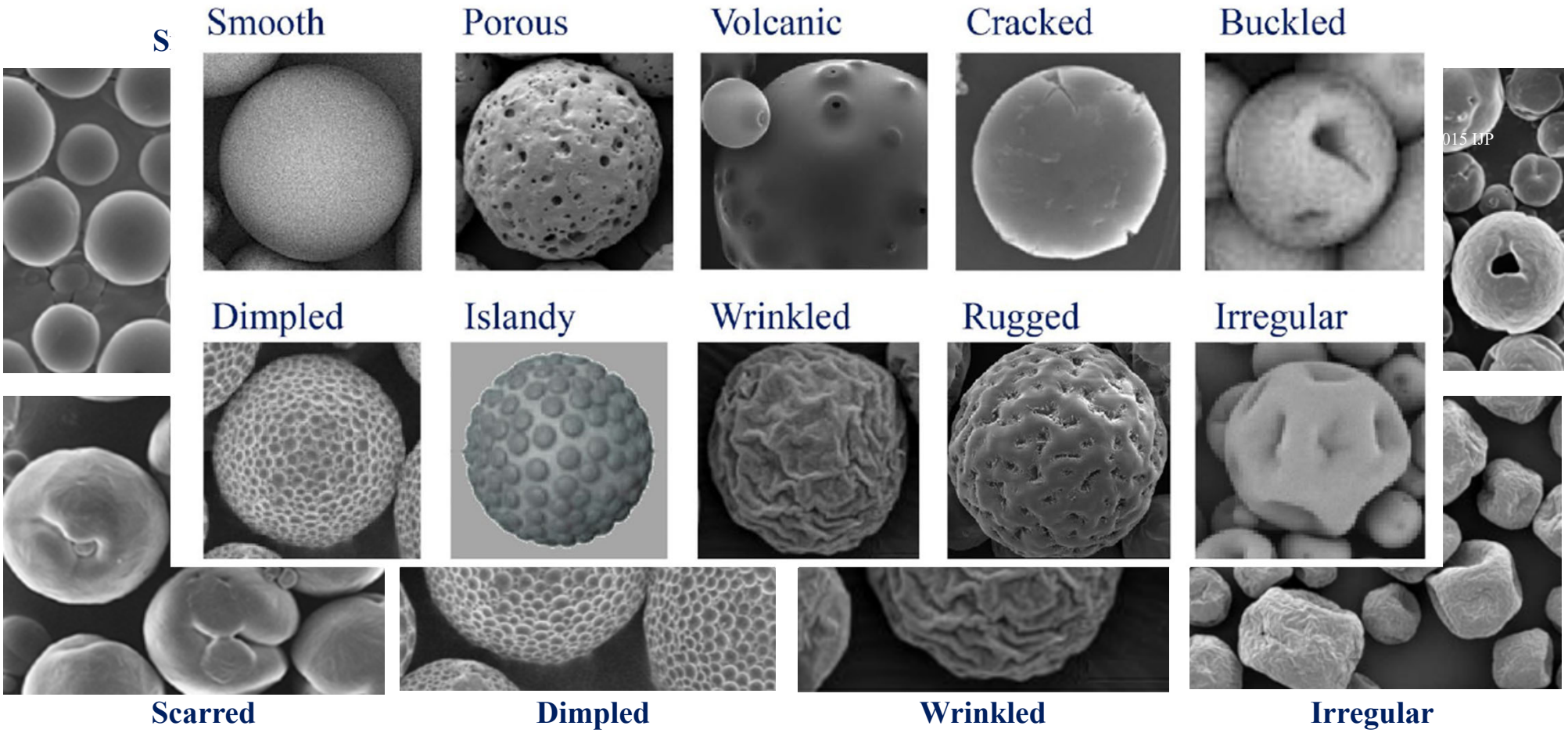


Understanding PLGA Microparticles

PLGA Microparticle Structures

Forensic Analysis of PLGA Microparticles: Surface Morphology

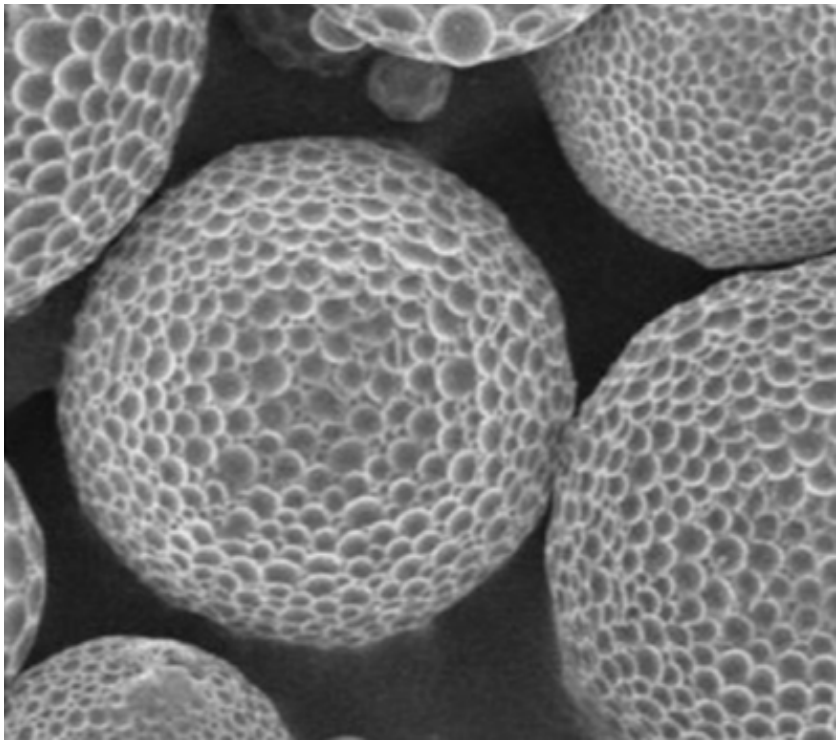
PLGA microparticles have different surface profiles, which indicates different manufacturing processes. Their drug release properties are different, too. From the surface profiles of each microparticle, one can deduct how the microparticles were made.

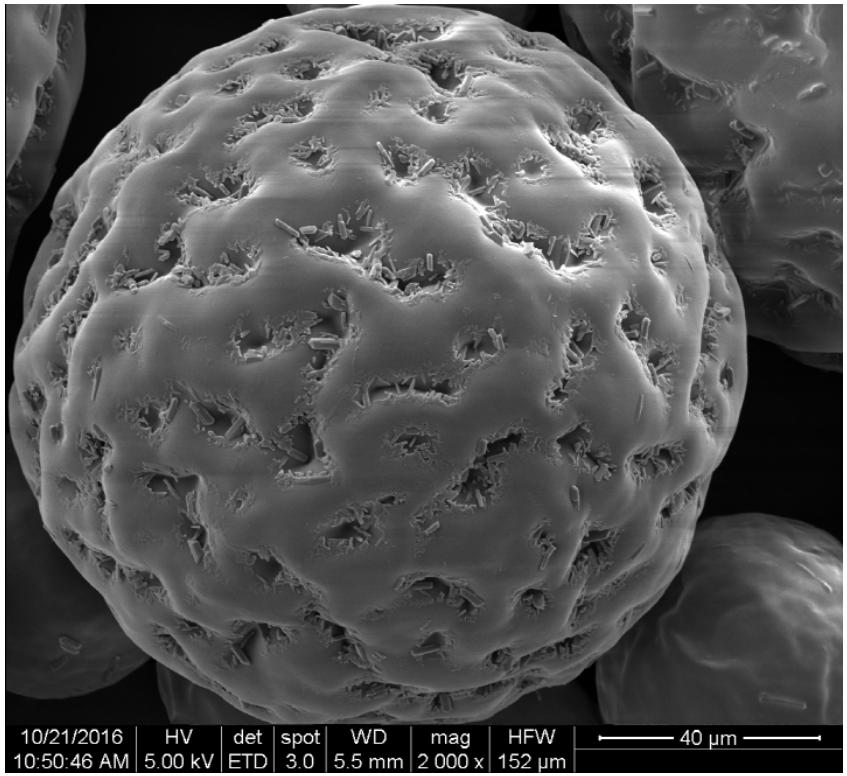


Forensic Analysis of PLGA Microparticles: Surface Morphology

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.

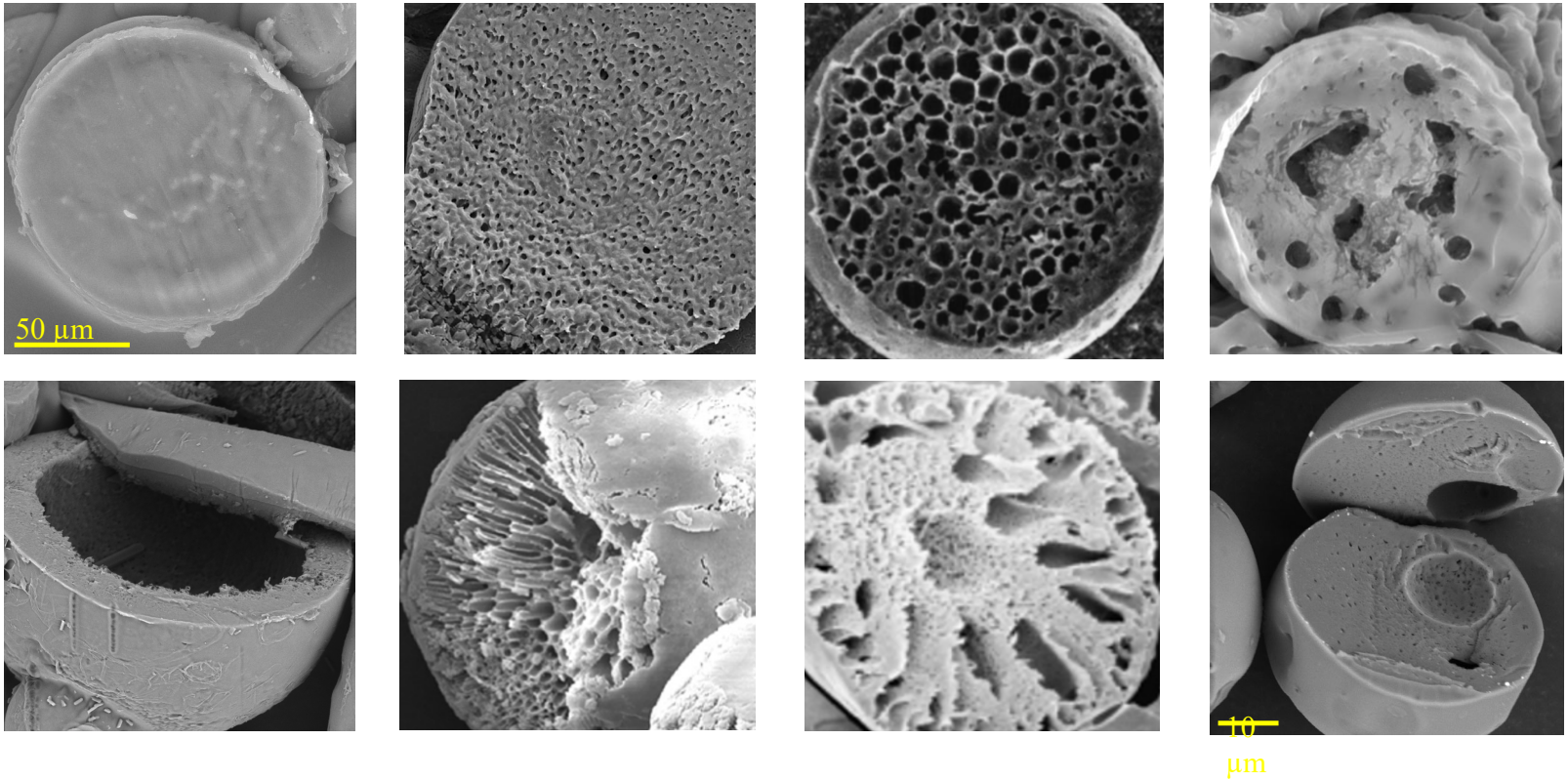
The message is that the information on the surface morphology tells a lot about how each set of microparticles are made.





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.



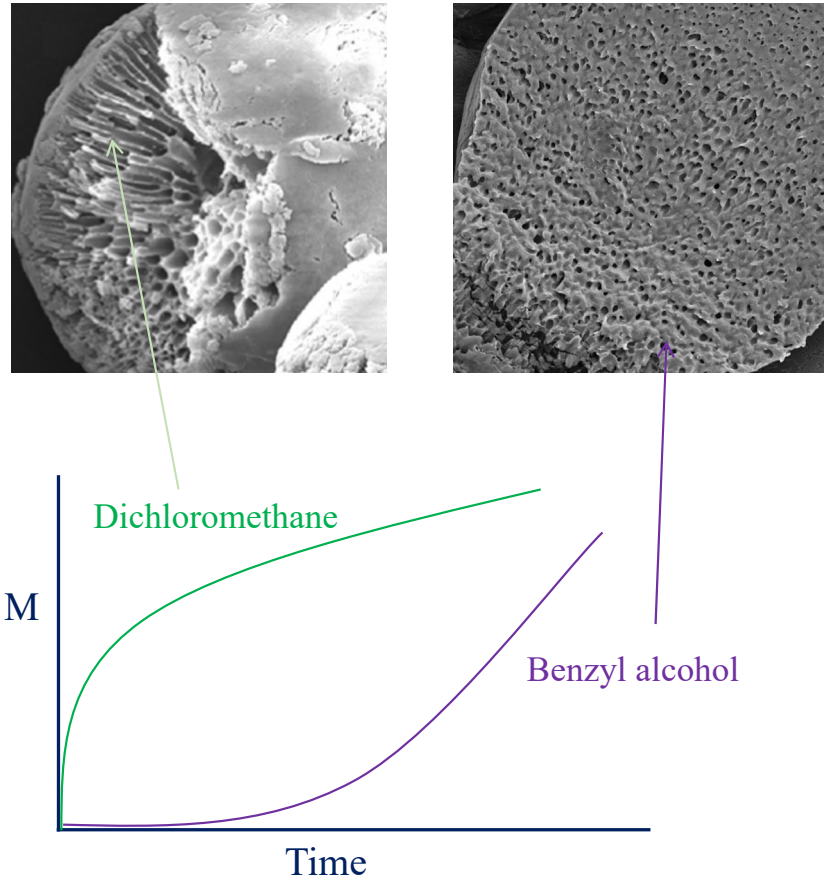
PLGA Microparticles: The Presence of Pores

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 Deutshcland

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

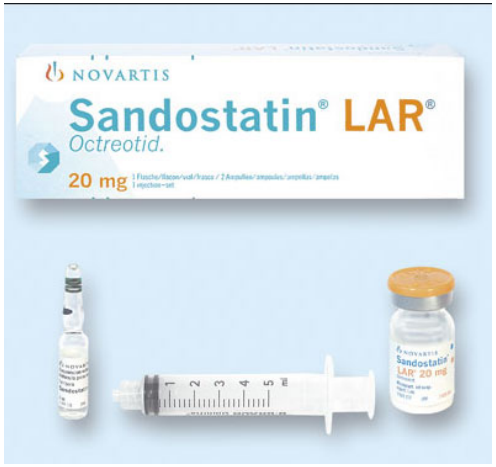
Solvent Removal Kinetics
- Water solubility, T_b

Drug Type
- Interaction with PLGA
- Plasticizer effect

PLGA Microstructure

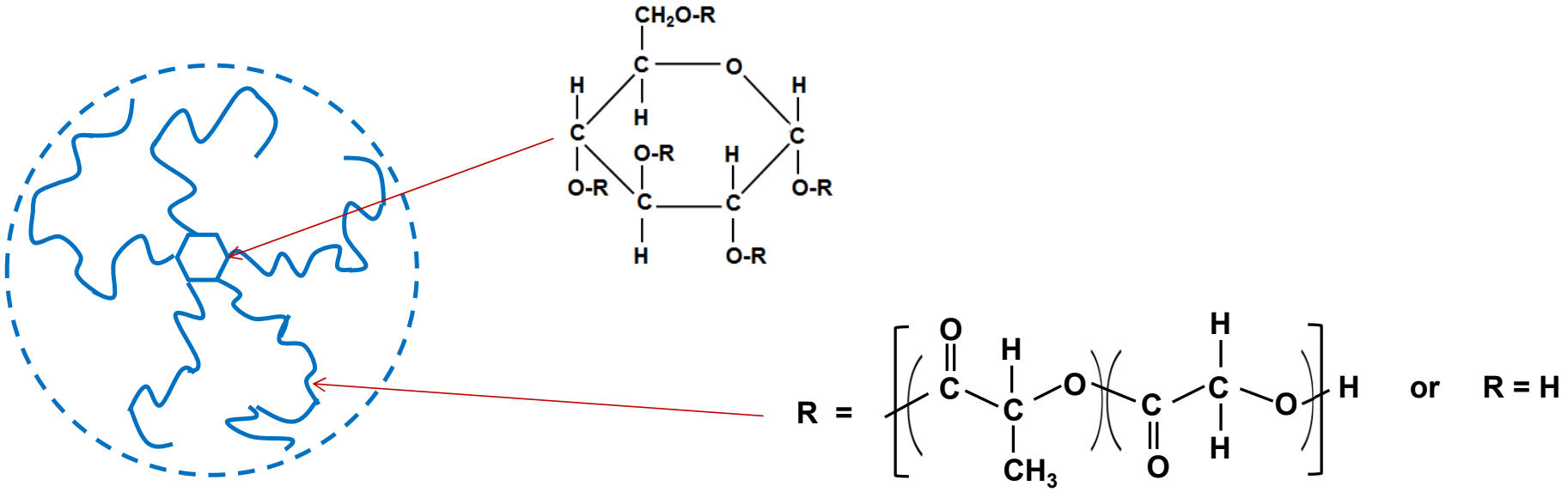
Formulations with Glucose-PLGA

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.



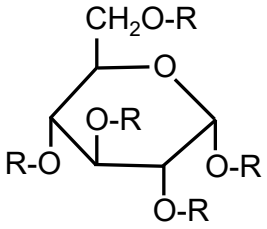
- Sandostatin lists Glucose-PLGA without any specific information on branching.
- GPC-4D branched-PLGA method was developed/validated using a series of standards.
- Tested Sandostatin extract: branching average typically ranges between ~ 2.5-4 branching units/molecule.

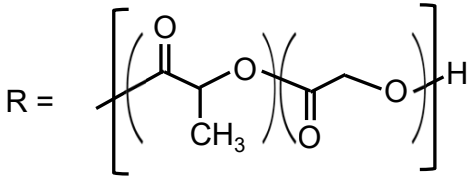
Hadar, Justin, Sarah Skidmore, John Garner, Haesun Park, Kinam Park, Yan Wang, Bin Qin, and Xiaohui Jiang.
"Characterization of branched poly (lactide-co-glycolide) polymers used in injectable, long-acting formulations." *Journal of Controlled Release* (2019).

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.

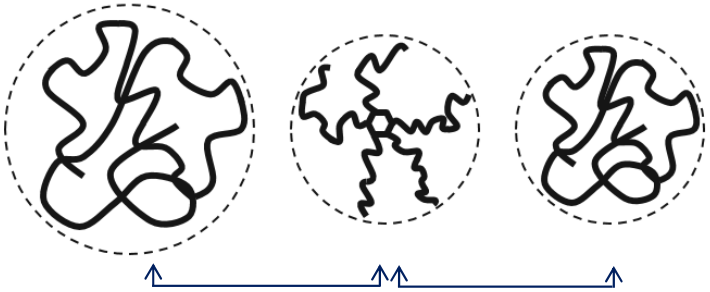
Glu-PLGA





or R = H

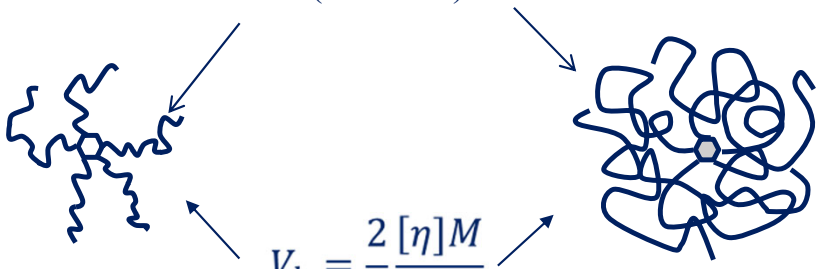
R represents either PLGA or hydrogen



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

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

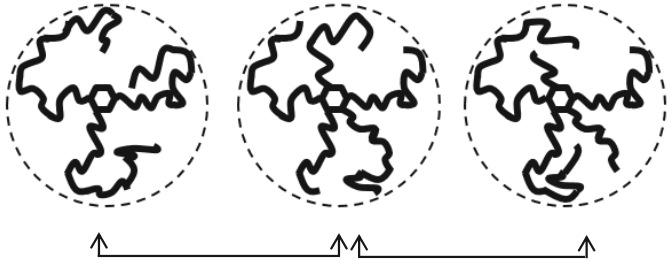
Arm (= Branch)



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

(V_h: Hydrodynamic Volume)

Low Molecular Weight High Molecular Weight



$f = 3$ $f = 5$ $f = 5$

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

Complex Formulations in PLGA Microparticles

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

Presentation from Bin Qin, PhD., Complex Generic Drug product Development Workshop, September 12, 2018

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

Presentation from Bin Qin, PhD., Complex Generic Drug product Development Workshop, September 12, 2018

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.

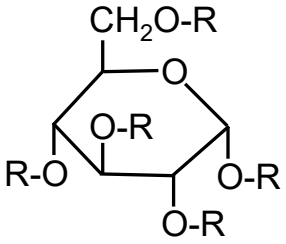
$$[\eta] = \lim_{c\to 0} \frac{\eta_{sp}}{c} = \frac{5}{2}\frac{N_A V_h}{M} = \frac{5}{2}\frac{N_A}{M}\frac{4\pi < R_g^2 >^{\frac{3}{2}}}{3} = \frac{\Phi < R_g^2 >^{\frac{3}{2}}}{M} = KM^{\alpha}$$

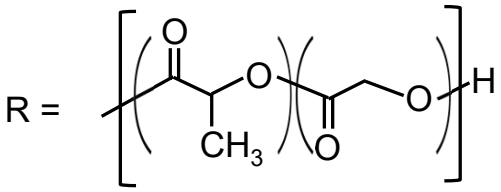
5. Osmometer	This measures the absolute number average molecular weight (M_w).

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





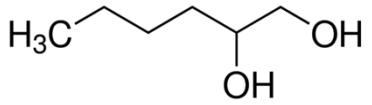
or R = H

R represents either PLGA or hydrogen

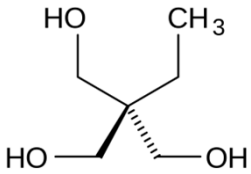
It is difficult to quantitate the number of PLGA branches by NMR. The carbons in glucose do not show any peaks. The carbon peaks from glucose is shielded by the carbon signals from PLGA. Thus, a new method is necessary to determine the number of branches, i.e., the number of PLGA chains on a glucose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

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

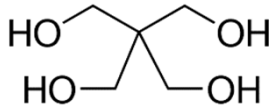
1-decanol



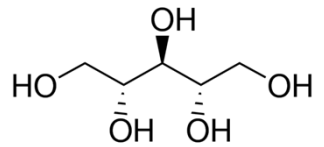
1,2 hexanediol



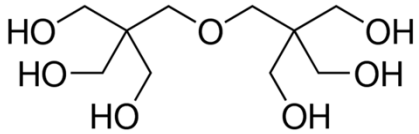
Trimethylolpropane



Pentaerythritol



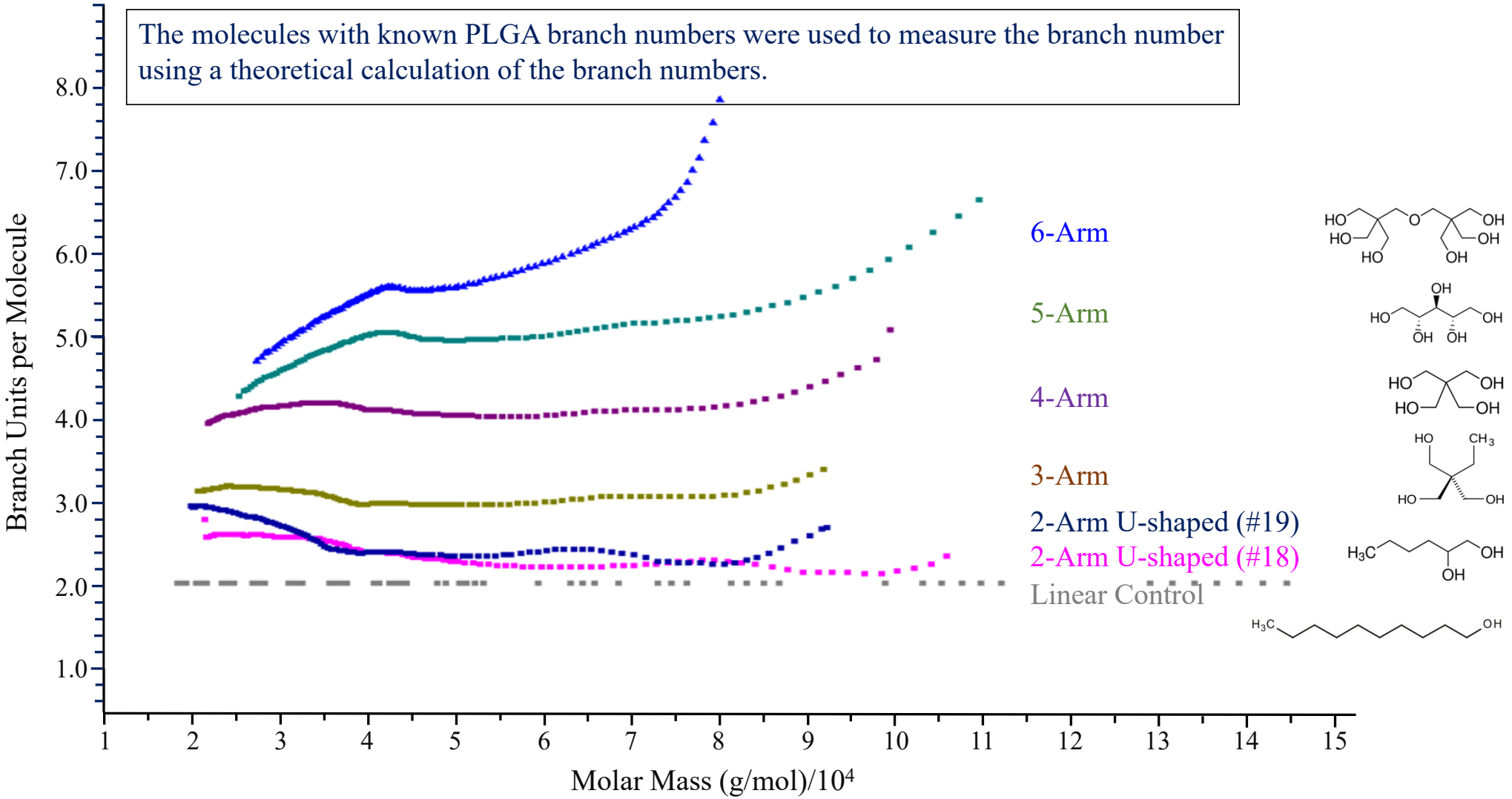
Adonitol



Dipentaerythritol

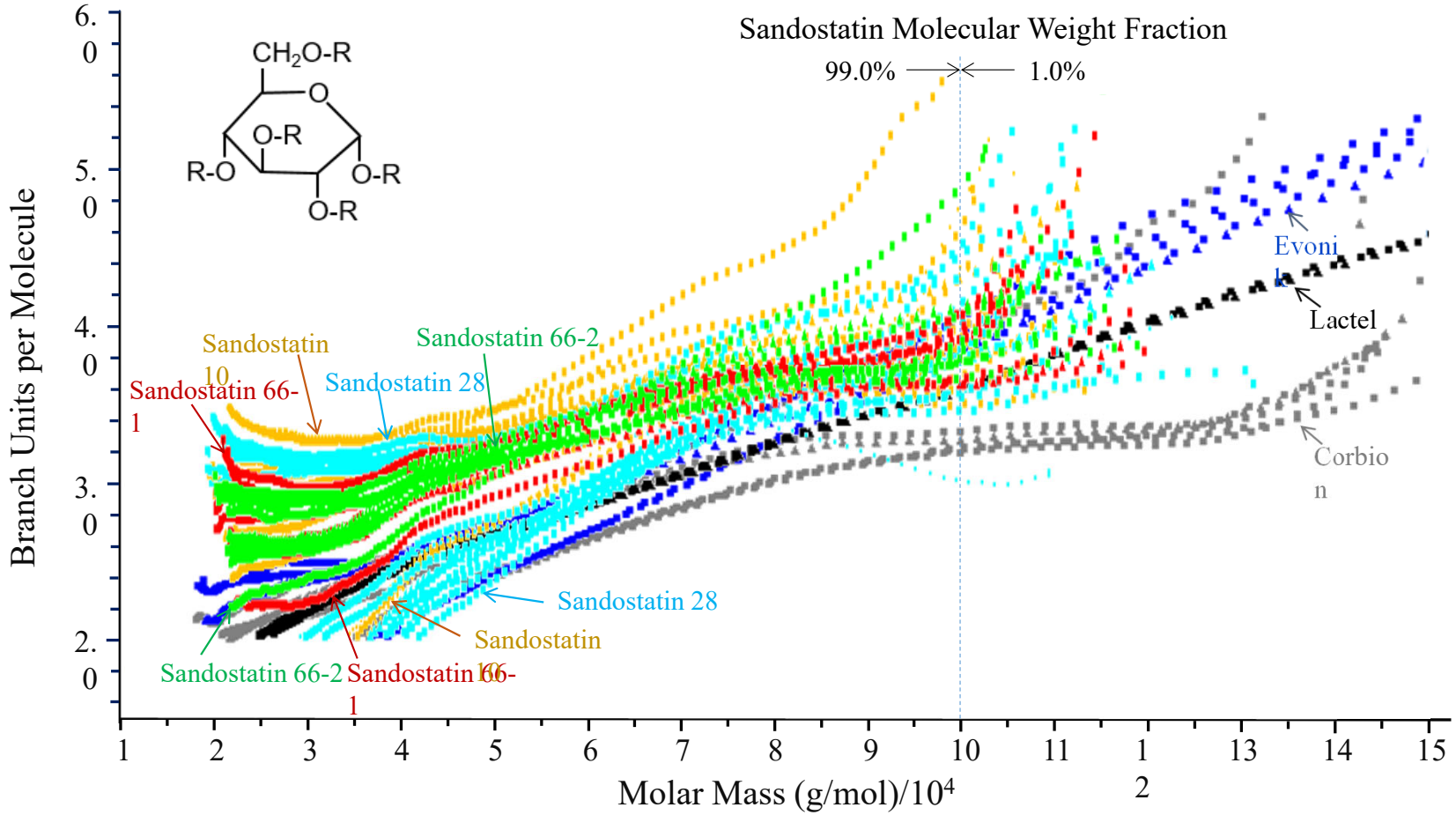
Branch Units per Molecule of Branched PLGAs

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

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

g: branch ratio

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

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

$[\eta]$: 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

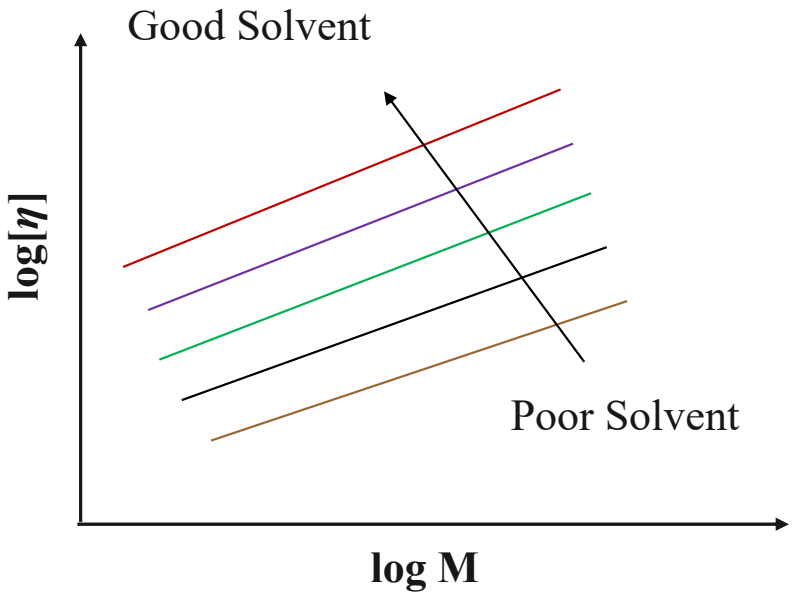
The Mark-Houwink Plot

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

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

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. α = 0.5 for a polymer under θ conditions (i.e., an unperturbed random coil). α = 0.8 for a polymer in a good solvent, while α = 2 for rod-like polymers. The slope α is related to the solubility parameters of the polymer and the solvent.

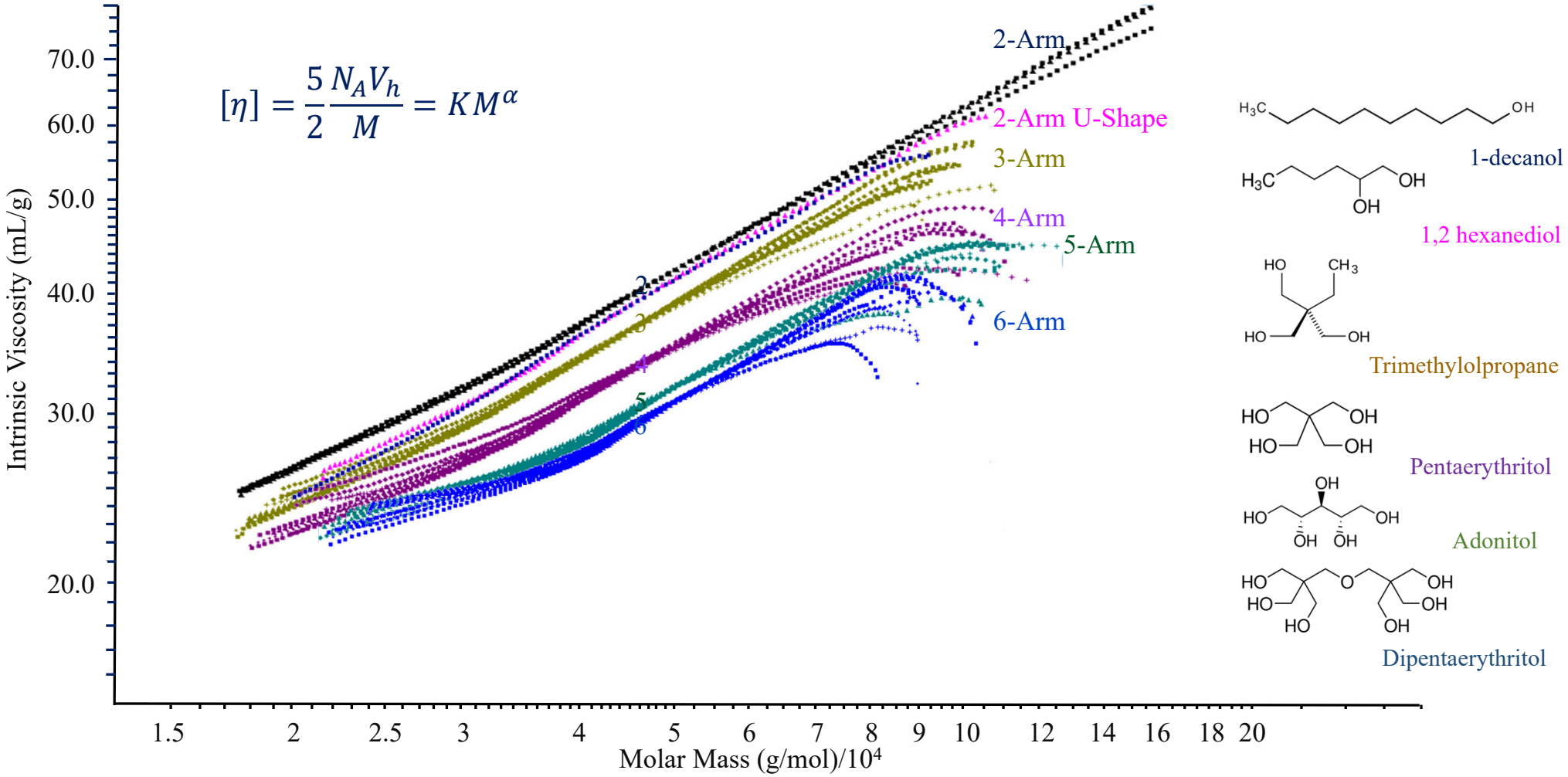


Mark-Houwink plots of a polymer in different solvents.

The molecular weight (M) remains the same but the V_h of the polymer changes in different solvents. The intrinsic viscosity [η] 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.

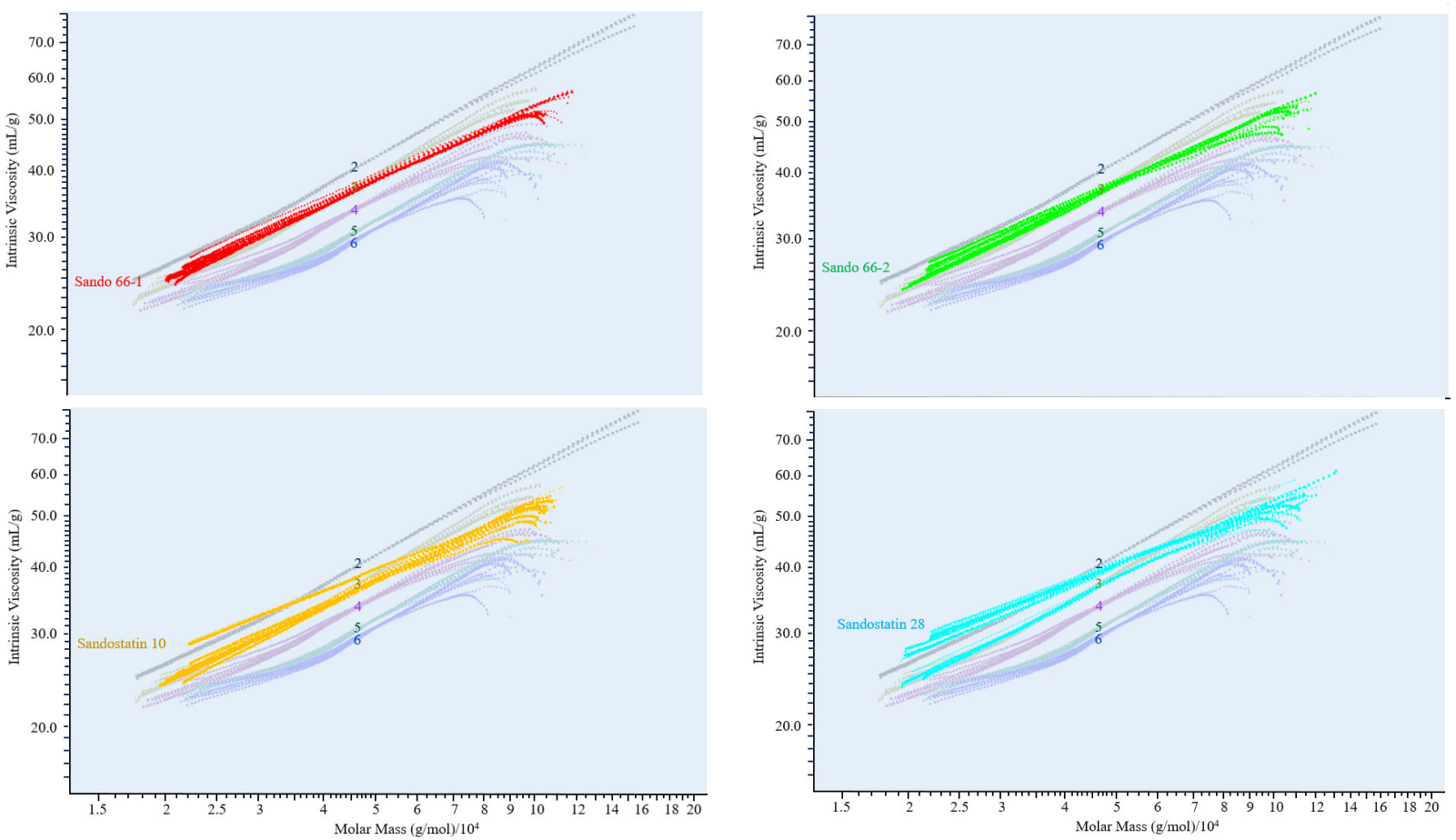
Branch Units per Molecule of Branched PLGAs

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



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