

# Effect of Solvent Isomeric Structures on the Dissolution of PLGAs with Different Lactide:Glycolide (L:G) Ratios

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## Abstract

**Background:** Poly(lactide-co-glycolide) (PLGA) is a biodegradable and biocompatible polymer widely used in medical applications. Previous studies have identified a series of semi-solvents which exhibit conditional PLGA solubility depending on the lactide:glycolide (L:G) ratio [1]. Certain patterns of solvents which exhibit this property have emerged including the tendency for esters and ketones to exhibit this property.

**Purpose:** The purpose of this study is to examine the effect of solvent isomeric structures on the PLGA solubility.

**Methodology:** PLGAs of varying L:G ratios were tested for dissolution in selected solvents and their isomers. The molecular weights of the PLGAs was characterized by gel permeation chromatography and ranged from approximately 60 kDa to 90 kDa. The L:G ratios of the PLGAs tested varied from 50:50 to 100:0 and were confirmed by nuclear magnetic resonance prior to use. A sample of each PLGA (100 mg) was incubated in 4 mL of each solvent with 100 RPM orbital agitation at 30°C overnight. The solvent was decanted and the remaining polymer was dried to a constant mass at 50-60°C under deep vacuum. Molar volumes were determined for each solvent using ACD/ChemSketch 2015 Pack 2 software.

**Results:** We observed that increasing length of the ketones or esters caused the solubility of PLGA to become more lactide-dependent for the solvents, requiring higher lactide content within the PLGA to dissolve. Analysis of isomers indicated that there was a general trend that relatively lower molar volumes (one indication of molecule size) improved the dissolution of PLGAs at lower glycolide content.

**Conclusion:** The molecular configuration of a solvent appears to be a factor affecting PLGA dissolution. These results suggest a relationship between the relative ability of a solvent to penetrate in between potentially glycolide-rich crystalline regions in its ability to dissolve PLGA. Solvent-dependent PLGA dissolution is useful in the manufacturing of PLGA-based formulations, as well as separation of PLGA mixtures for the evaluation of polymer composition sameness.

## Introduction

PLGA has been widely used in pharmaceutical applications. PLGA solubility in some semi-solvents depend on the PLGA lactide content (La%) [1]. The semi-solvent effects are affected by the chemical identity of the solvent as well as the isomeric molecular shape of the solvent. The purpose of this study was to examine the effect of solvent isomeric structures on the PLGA solubility. This may enable development of methods to predict solubility of solvents based on the solvent molecular shape.

## Materials and Methods

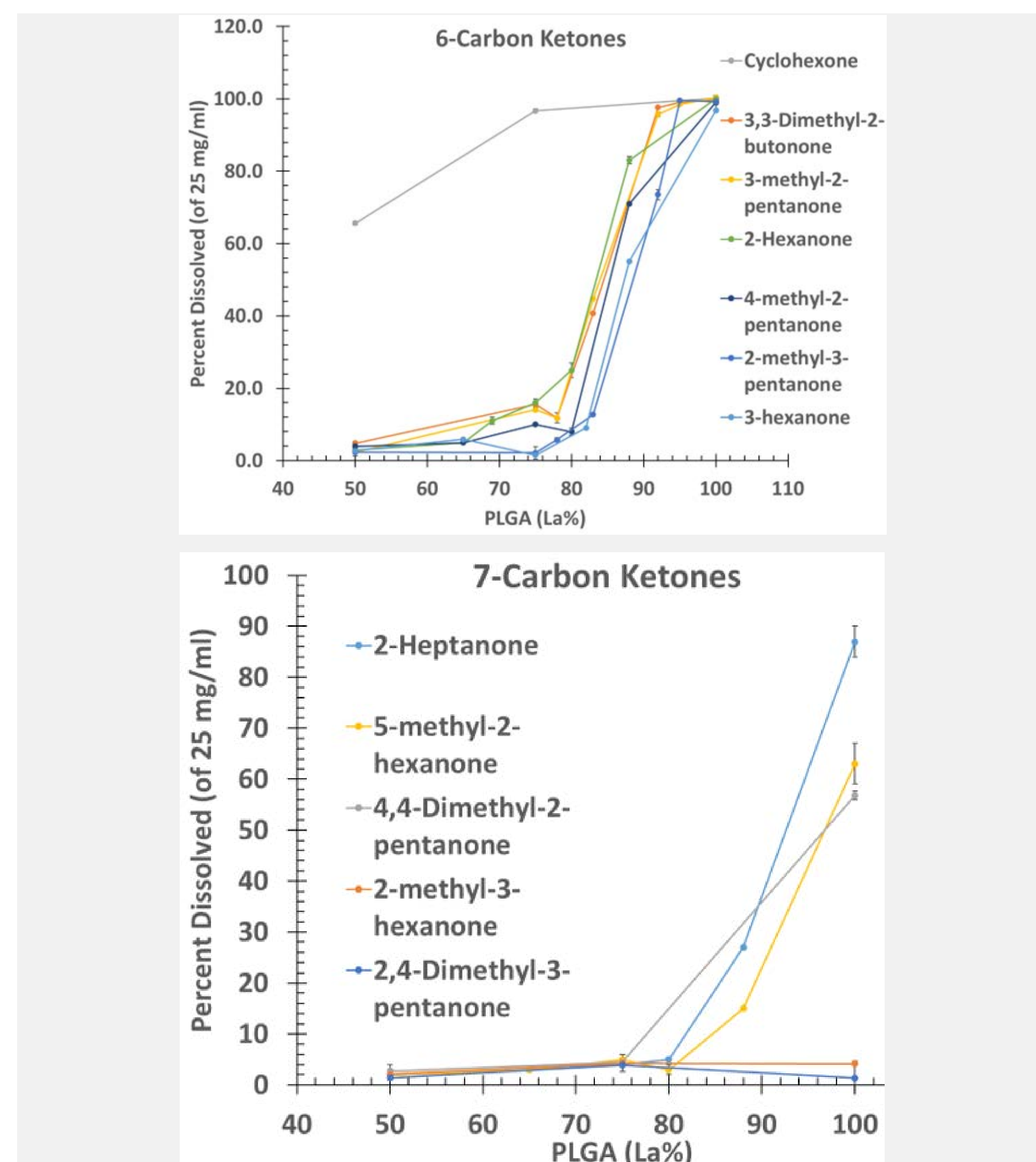
PLGAs of varying lactide content (La%) were tested for dissolution in selected solvents as previously described [1]. Briefly, PLGAs (Mw ~ 80 ± 20 kDa as determined by gel permeation chromatography (GPC)) were tested by H-NMR to confirm their lactide content (La%). Each PLGA (100 mg) was incubated in 4 mL of solvent at 30°C/100 RPM overnight (16-24 hrs). The solvent was then decanted away from undissolved polymer and the remaining polymer was dried to a constant mass at 60°C under vacuum. Solubility was determined as % of mass removed by solvent.

## Results and Discussion

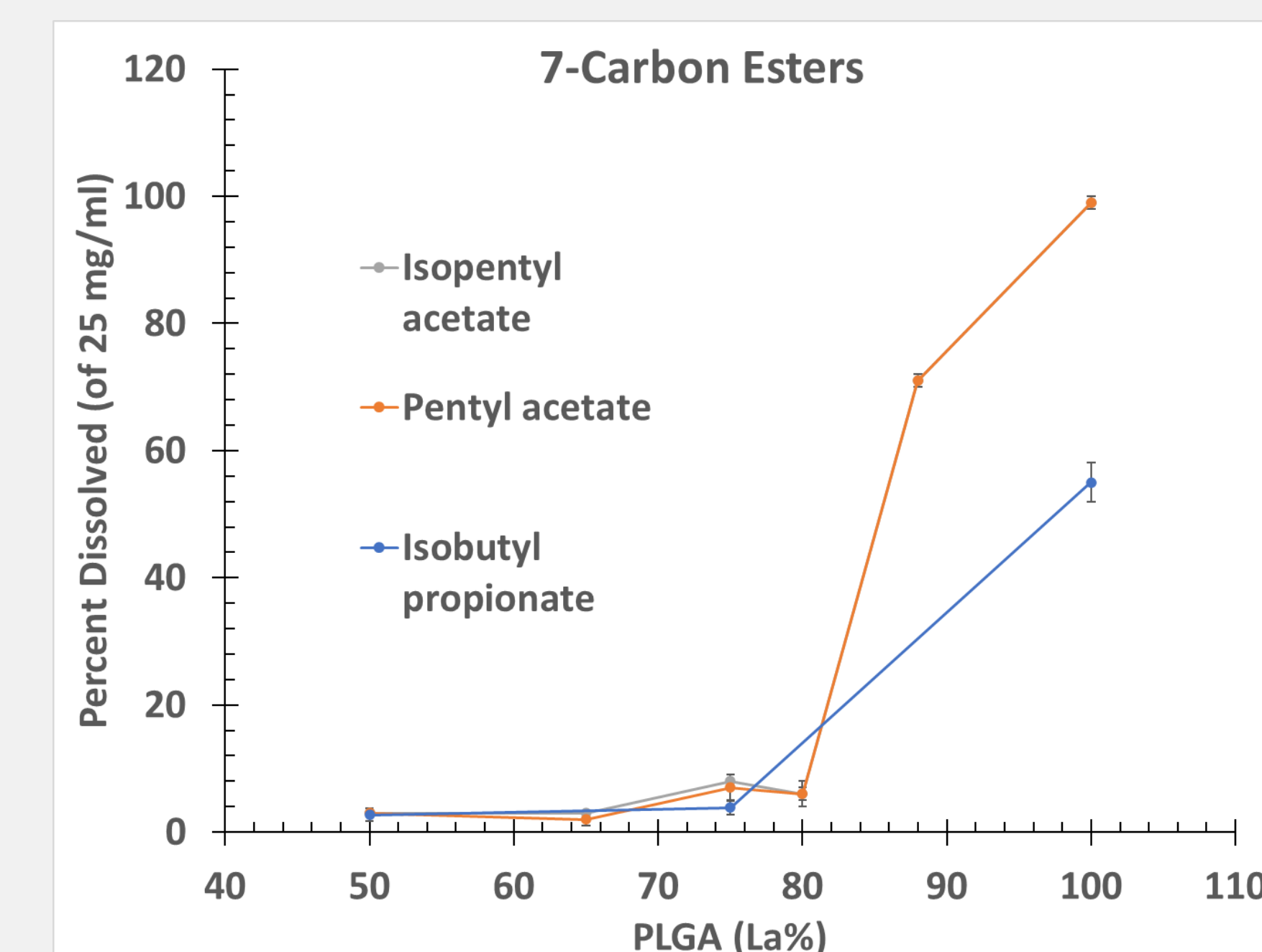
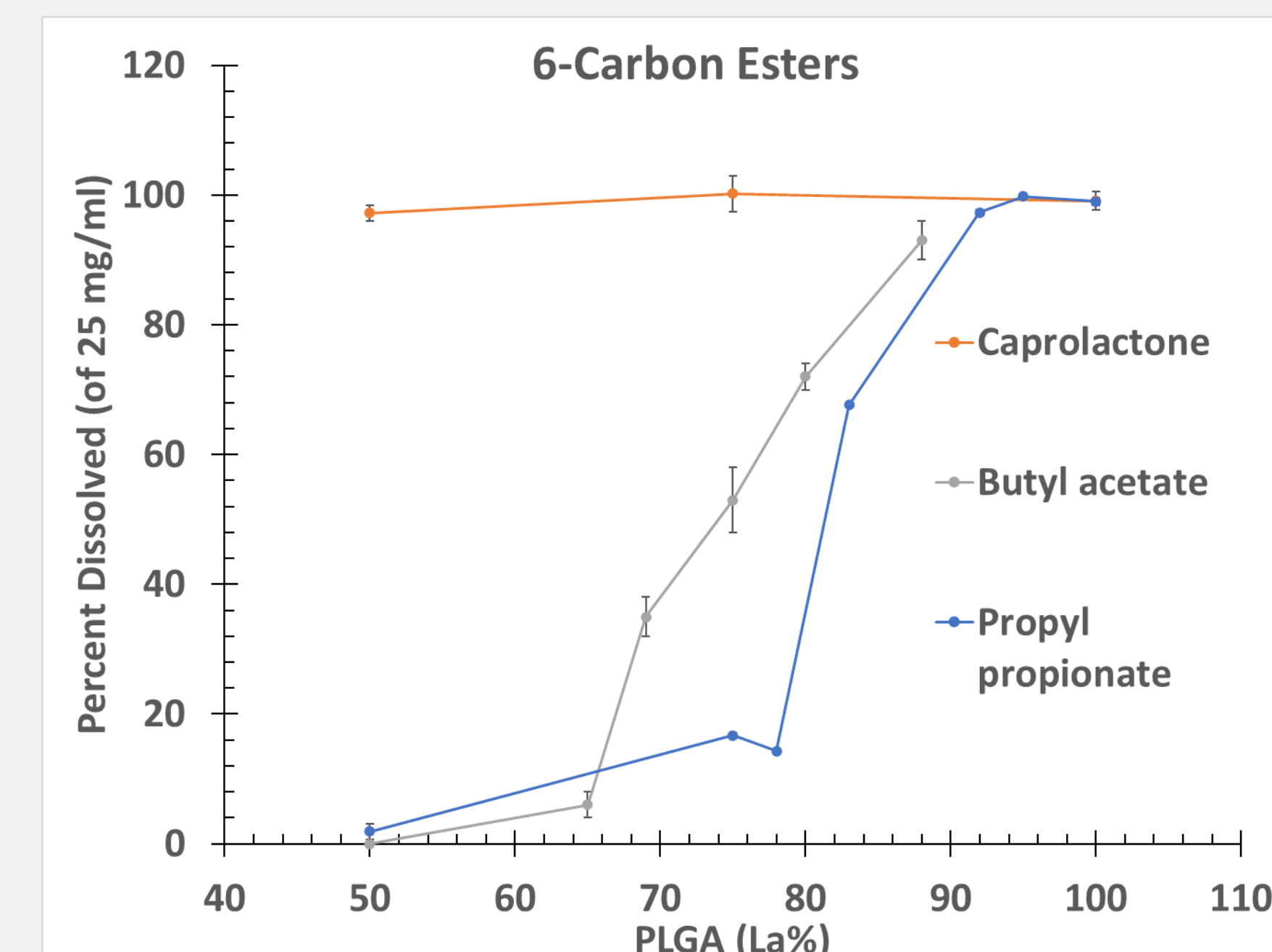
The tested solvents displayed a range of dissolution profiles. Figure 1 shows semi-solvent effects of ketone solvents grouped together based on the number of carbons in the ketone. The same data for esters are shown in Figure 2.

Since many solvent properties are not consistently reported in the literature, the properties of each solvent were calculated according to its structure using a computer program (ACD) [2].

**Table 1** shows examples of structures and calculated molar volume for 6-carbon ketones of different isomer configurations. These predicted properties were compared to the semi-solvent solubility results quantified as PLGA (La%) necessary to obtain 10 mg/ml solubility (40% of 25 mg/mL) with linear extrapolation across the two closest data points that fall above and below 40% dissolution used to estimate the La% for 10 mg/mL solubility cross-over point. Solvents which dissolved all PLGAs were set as 50 La% and those which could not dissolve any PLGA were set as 100 La%. The correlation for each parameter to solubility was determined using Microsoft Excel. A positive correlation was noted for molar volume for all solvent types, but the correlation was weak 7-carbon solvents (Figure 3). These correlations are based on data available and inclusion of other isomers, notably cyclic 7-carbon semi-solvents.



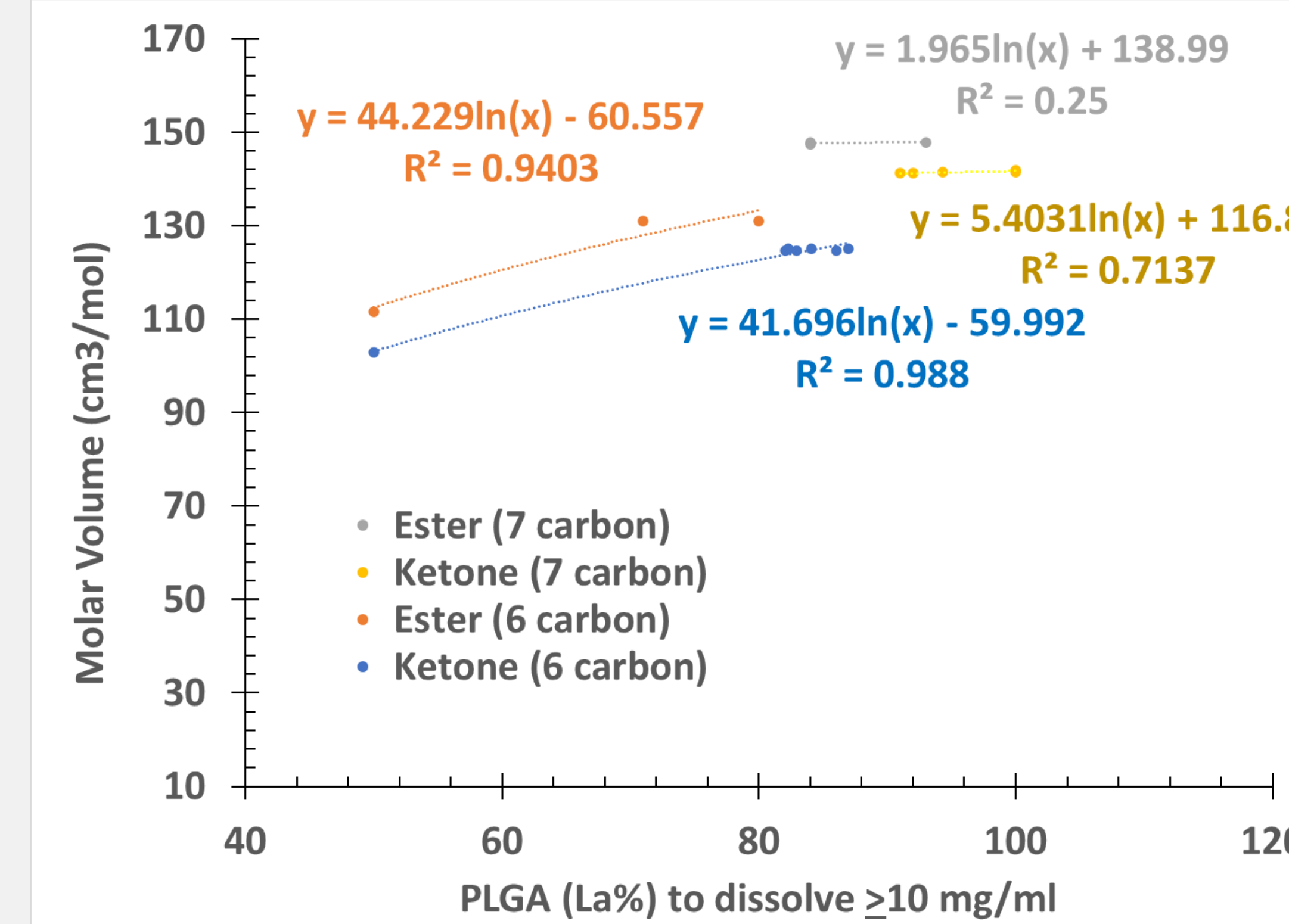
**Figure 1.** PLGA solubility in ketone solvents of indicated carbon number. La% = lactide % Average ± S.D. (N=3)



**Figure 2.** PLGA solubility in ester solvents of indicated carbon number. La% = lactide % Average ± S.D. (N=3)

**Table 1.** Isomers of ketone 6-carbon, solubilizing power and ACD software-calculated properties

Name	Structure	PLGA (La%) to dissolve >10 mg/ml	Molar Refractivity	Molar volume	Parachor	Surface tension	Density	Polarizability
2-hexanone	<chem>CCCC(=O)C</chem>	82	29.87	124.6	275.9	23.9	0.803	11.84
3-hexanone	<chem>CCC(=O)CC</chem>	86	29.87	124.6	275.9	23.9	0.803	11.84
4-methyl-2-pentanone	<chem>CC(C)C(=O)CC</chem>	84	29.83	125	273.3	22.8	0.8	11.82
3,3-dimethyl-2-butanone	<chem>CC(C)(C)C(=O)C</chem>	83	29.84	124.7	271	22.2	0.802	11.83
Cyclohexanone	<chem>C1CCCCC1=O</chem>	50	27.8	102.9	245.8	32.5	0.953	11.02



**Figure 3.** Relationship of the solvent molar volume to La%-dependent dissolution of PLGAs.

## Conclusion

The current understanding of the semi-solvent effects on various PLGAs allows separation of different PLGAs of complex formulations based on their lactide content (La%), but more thorough understanding is necessary to identify different PLGAs used in various formulations.

Determining trends for semi-solvent performance can provide elucidation as to the mechanisms of the semi-solvent effect. For all solvents, increasing molar volume increased the lactide content required to achieve solvation. The effect was stronger for 6-carbon solvents than the 7-carbon solvents likely due to relatively poor solvation of the tested 7-carbon solvents in general. These results support the hypothesis that the varying ability of a solvent to penetrate into semi-crystalline glycolide-rich region is a mechanism of semi-solvent. Confirming this hypothesis, however, requires more studies to obtain thorough semi-solvent effects using more solvents.

## References

- [1] S. Skidmore, H. Justin, J. Garner, H. Park, K. Park, Y. Wang, and X. Jiang. "Complex sameness: Separation of mixed poly (lactide-co-glycolide)s based on the lactide: glycolide ratio". Journal of Controlled Release 300 (2019) 174-184.
- [2] ACD/ChemSketch 2015 (Pack 2 Build 78694)

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