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

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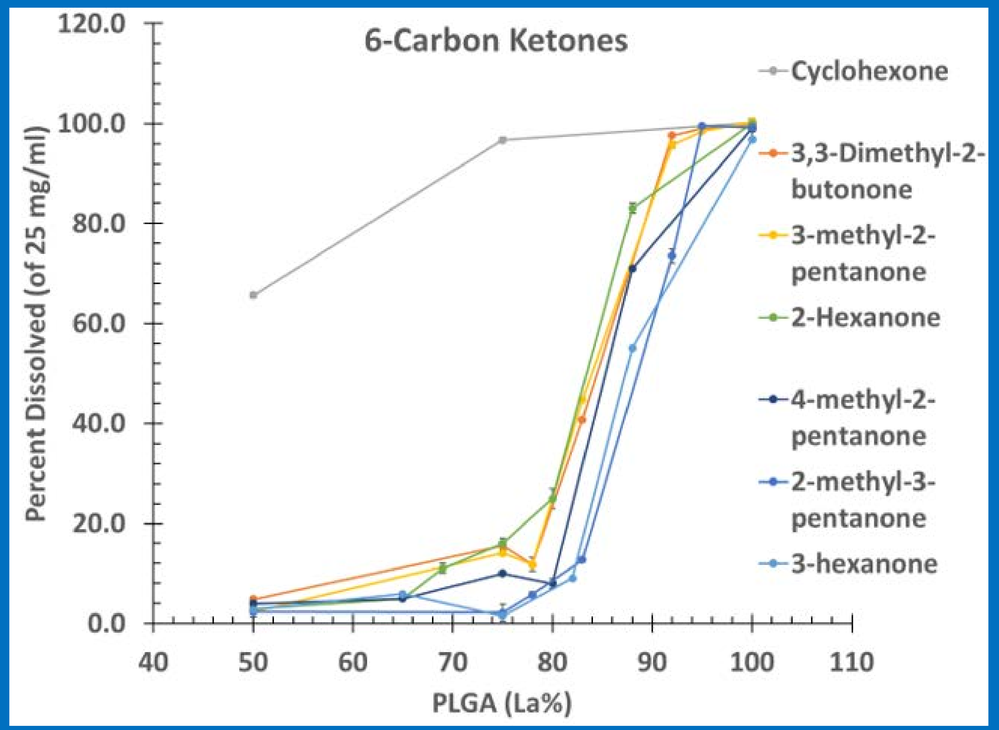
Introduction: Poly(lactide-co-glycolide) (PLGA) has been widely used in pharmaceutical applications. A series of semi-solvents which exhibit conditional PLGA solubility depending on the lactide content (La%) [1]. The semi-solvent effects are affected by not only the chemical identity but also the isomeric 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.

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 HNMR to confirm their lactide content (La%). Each PLGA (100 mg) was orbitally 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. Dissolution was determined as % of mass removed by solvent.

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



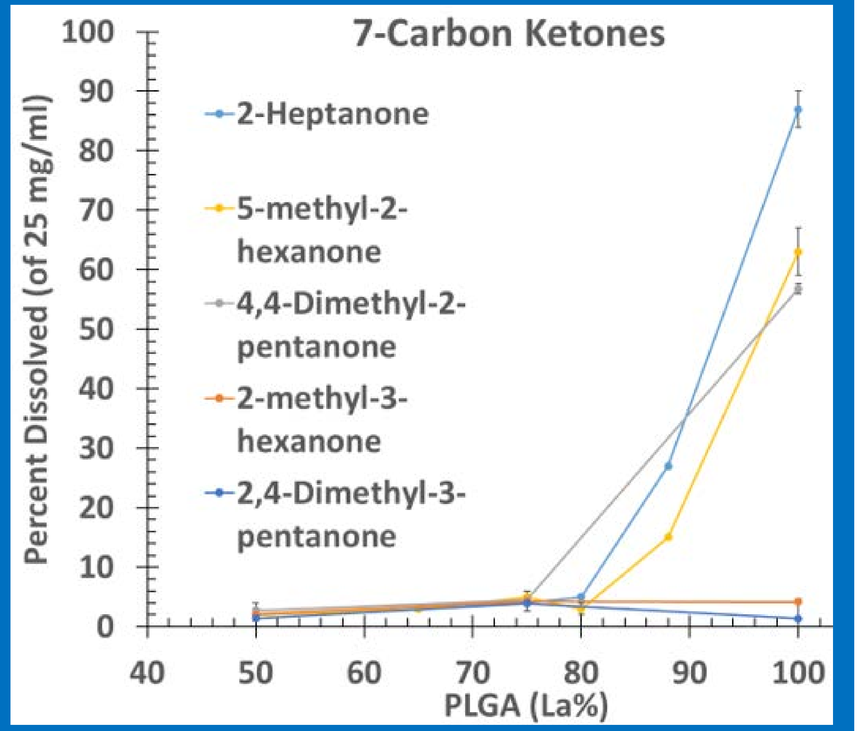
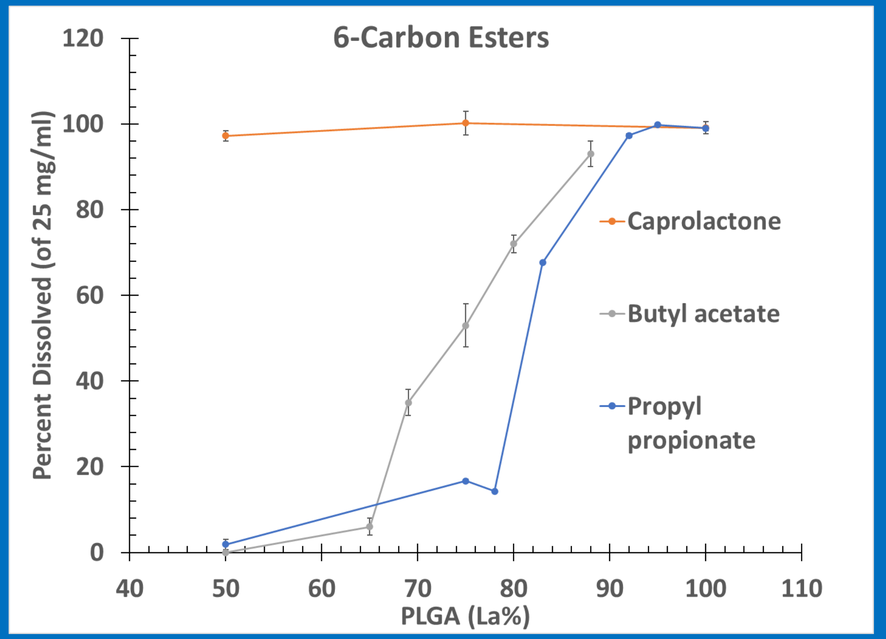


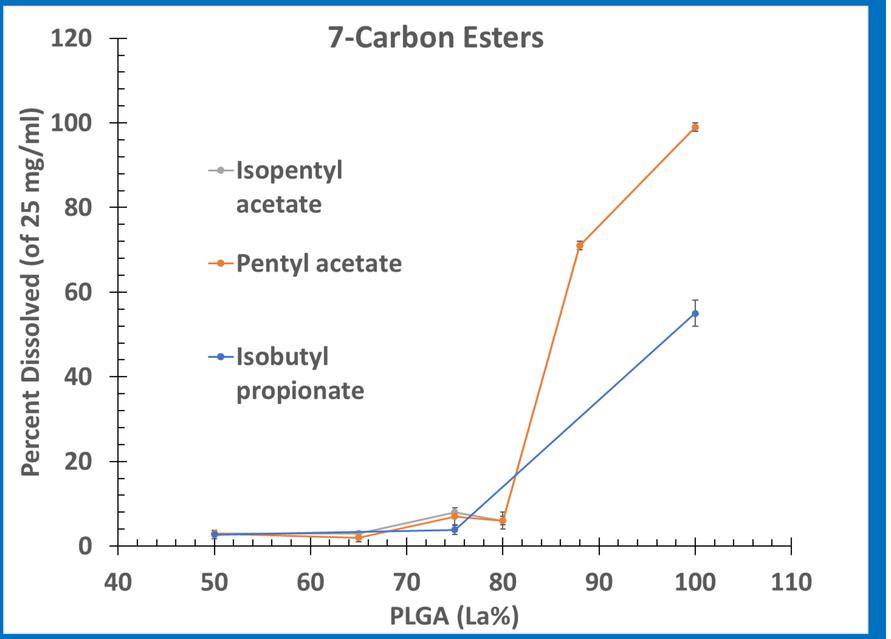
Figure 1. PLGA solubility in ketone solvents of indicated carbon number.

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)

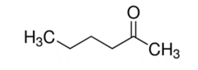
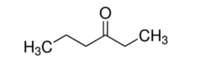
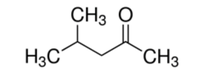
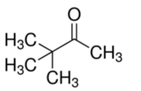
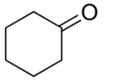




Since many solvent properties are not consistently reported in the literature, the properties of each solvent were calculated according to its structure using a computer program (ACD) [2].

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, can clarify these initial results.

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		82	29.87	124.6	275.9	23.9	0.803	11.84
3-hexanone		86	29.87	124.6	275.9	23.9	0.803	11.84
4-methyl-2-pentanone		84	29.83	125	273.3	22.8	0.8	11.82
3,3-dimethyl-2-butanone		83	29.84	124.7	271	22.2	0.802	11.83
Cyclohexanone		50	27.8	102.9	245.8	32.5	0.953	11.02

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-solvation. Confirming this hypothesis, however, requires more studies to obtain thorough semi-solvent effects using more solvents.

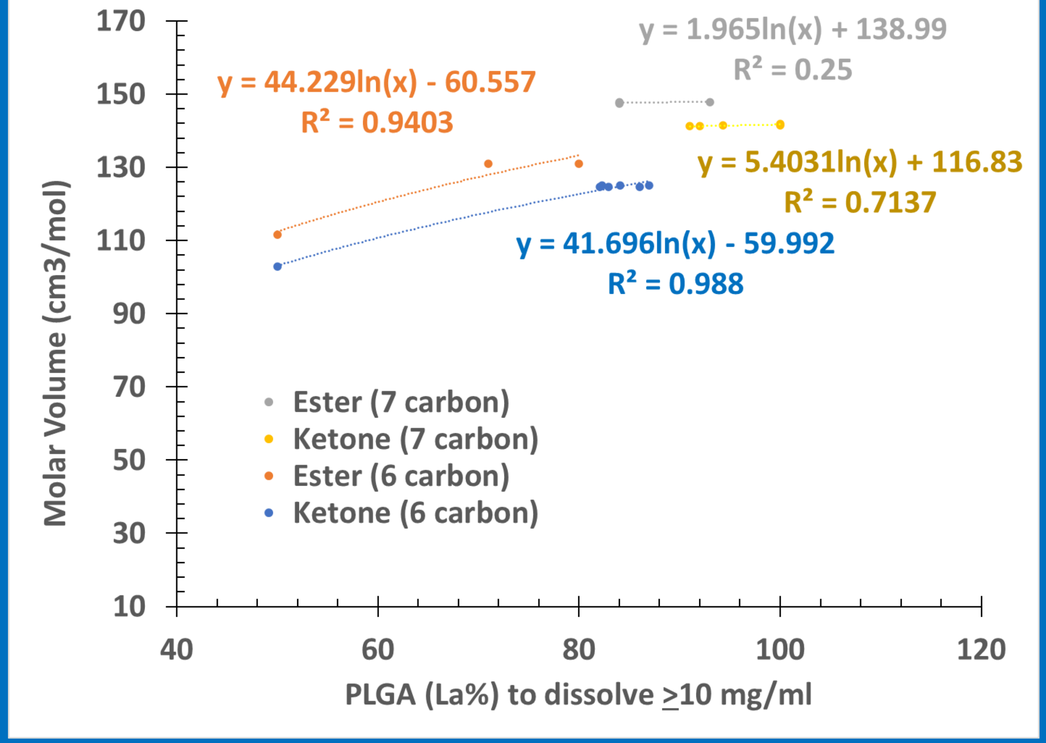


Figure 3. Relationship of the solvent molar volume to La%-dependent dissolution of PLGAs.

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)

Acknowledgements

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