Effect of solvent molar volume on its ability to solubilize PLGAs and potential implications for understanding polymer structure

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Introduction

Poly(lactide-co-glycolide) (PLGA) polymers have been widely used in pharmaceutical and biomedical applications. PLGAs, like other polymers, can dissolve better in some solvents than others. Recently, PLGA solubilities in various solvents were examined to find a wide range of semi-solvents which have the ability to dissolve only certain PLGAs having their lactide content (L%), or L:G ratio, above the critical value unique for each semi-solvent [1]. The exact mechanisms for the semi-solvent effect have not been elucidated. It is suspected that the tendency of glycolide-rich regions to form semi-crystalline domains attributes to the limited solubilities of glycolide-rich, i.e., low L% or low L:G ratio, PLGAs.

Methods

PLGAs with weight average molecular weights of 80 ± 20 kDa were used to evaluate solvents for their ability to dissolve PLGA [2]. Briefly, each sample of 100 mg PLGA was combined with 4 mL of solvent, incubated overnight at 30°C, decanted, and the remaining undissolved polymer was dried under a vacuum before weighing to determine the mass dissolved. Comparison to our previous data [1] indicates that the method used is reproducible (Table 1). The minimal lactide content required to dissolve PLGA (≥10 mg/mL) (L_{min}) for solvents exhibiting a solubility transition between 50-100% L:G was determined by linear extrapolation. Some solvents exhibited ≥10 mg/ml solubility for PLGAs with all lactide contents of 50-100%, and they are designated as $L_{min,50}$. For solvents that have PLGA solubility of <10 mg/mL irrespective of L%, they are designated as $L_{min,100}$. ChemSketch (ACDLabs, 2015) was used to predict the molar volume of each solvent.

Table 1. Comparison of PLGA solubilities (% of 25 mg/ml) in ethyl lactate between previous and current data (mean ± Standard deviation, n = 3).

L%	Previous [1]	Current [2]
50	17 ± 7.0	18 ± 2.1
54		55 ± 0.8
57		92 ± 5.1
64		100 ± 0.1
65	97 ± 3.0	
68		100 ± 0.1
71		100 ± 0.2
75	99 ± 0.1	100 ± 1.1
80	100 ± 0.0	
88	98 ± 0.4	
100		101 ± 0.6

Results

The semi-solvent properties of various solvents were examined using a simple metric. Semi-solvents were compared by using the molar percent of the lactide content (L%) of PLGA that is required to dissolve ≥10 mg/mL of the PLGA in a given solvent. **Table 2** shows a list of the indicated solvents, organized by the type (ester or ketone), the number of carbons, their experimentally determined L_{min}, and the predicted molar volume. In addition, aromatic solvents were classified into ketones, esters, and simple aromatics.

Figure 1 shows that the PLGA solubilization by aliphatic solvents is related to each solvent's molar volume. **Figure 2** displays the same trends for aromatic solvents. The data indicate that a semi-solvent that dissolves PLGAs with lower L%, or lower L:G ratios, has a lower molar volume. Solvents with smaller molar volumes can diffuse into semi-crystalline glycolide-rich domains more effectively to dissolve the polymers.

Table 2. Solvent isomers with the lactide % (L%) and molar volume that dissolve ≥10 mg/ml PLGA.

Solvent Type	Solvent Name	L% with ≥10 mg/mL Solubility	Molar Vol (cm^3)
Ester (6 carbon)	Caprolactone	50	111.7
	Propyl propionate	80	131
	Ethylcyclopropane carboxylate	52.6	107.3
	Butyl acetate	71	131
	Methyl cyclobutane-carboxylate	50	108.5
Ester (7 carbon)	Isobutyl propionate	93	147.9
	Pentyl acetate	84	147.5
	Tert-butyl propanoate	100	147.6
	Methyl cyclopropanecarboxylate	64	126.3
	Isopentyl acetate	84	147.9
Ketone (6 carbon)	2-Methyl-3-pentanone	87	125
	3,3-Dimethyl-2-butonone	82.9	124.7
	Cyclohexanone	50	102.9
	3-Methyl-2-pentanone	82.3	125
	3-Hexanone	86	124.6
	2-Hexanone	82.1	124.6
	4-Methyl-2-pentanone	84.1	125
Ketone (7 carbon)	2,4-Dimethyl-3-pentanone	100	141.9
	2-Methyl-3-hexanone	100	141.5
	4,4-Dimethyl-2-pentanone	92	141.2
	Cycloheptanone	59.07	120.6
	5-Methyl-2-hexanone	94.3	141.5
	2-Heptanone	91	141.2

Solvent Type	Solvent Name	L% with ≥10 mg/mL Solubility	Molar Vol (cm^3)
Aromatic (Ketone)	2,2-Dimethyl-propiophenone	83	170.5
	Butyrophenone	79	153.9
	Isobutyrophenone	80	154.3
	Propiophenone	57	137.4
Aromatic (Ester)	Ethyl Benzoate	61	143.8
	Isobutyl Benzoate	86	177.2
	Propyl benzoate	74	160.3
	Butyl benzoate	87	176.8
Aromatic (simple)	Chlorobenzene	69	101.3
	Toluene	78	105.7
	Xylenes (m-xylene)	92	121.9
	Benzyl alcohol	56	103.2
	Benzene	50	89.4
	Mesitylene	100	138.2
Other	2-Methyl Tetrahydrofuran	70	99.7
	Trichloroethylene	67	89.1

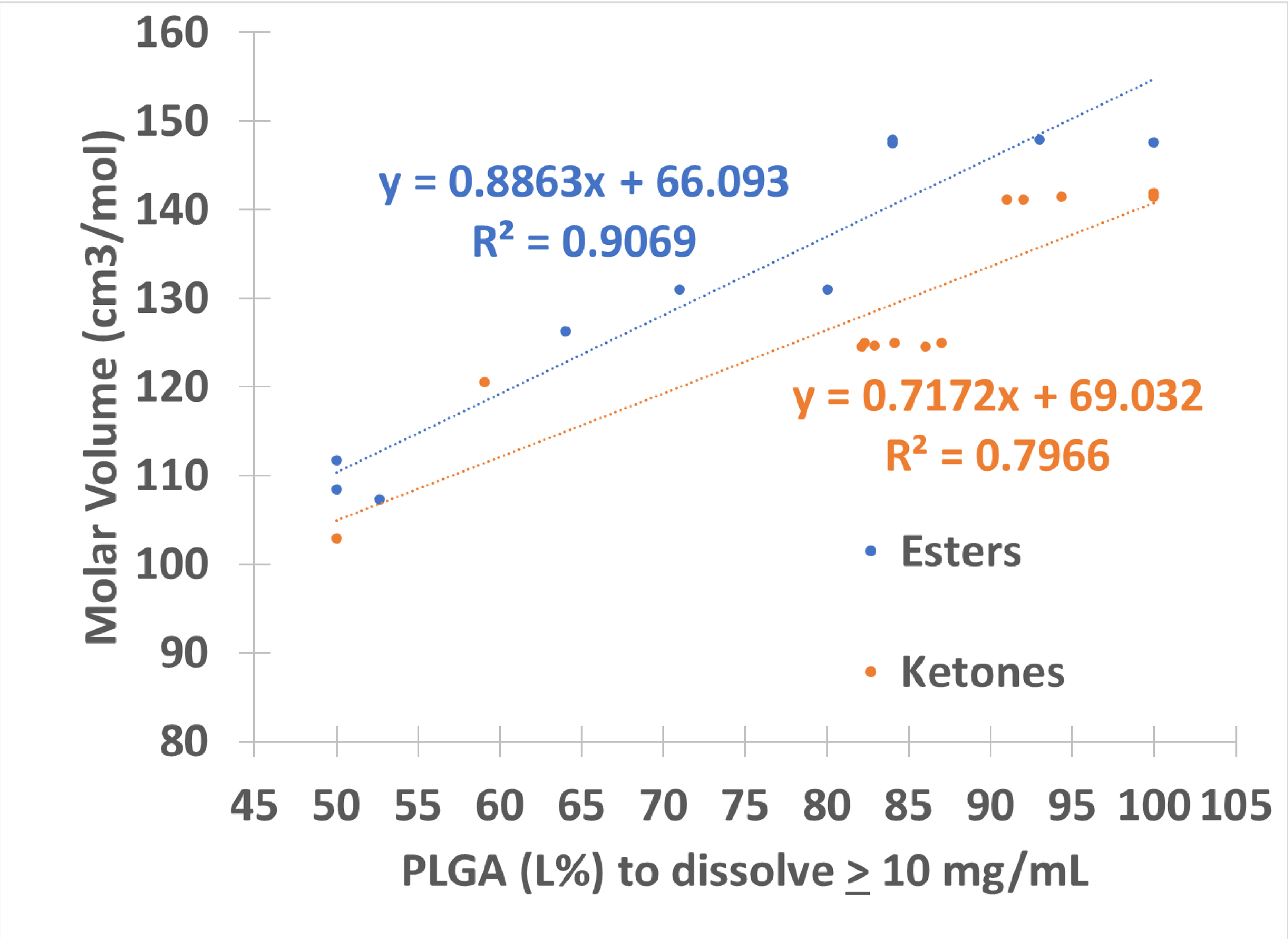

Figure 1. The molar volume of aliphatic semi-solvents as a function of the lactide percent (L%) in PLGA. Semi-solvents with smaller molar volumes can dissolve PLGAs with higher glycolide contents.

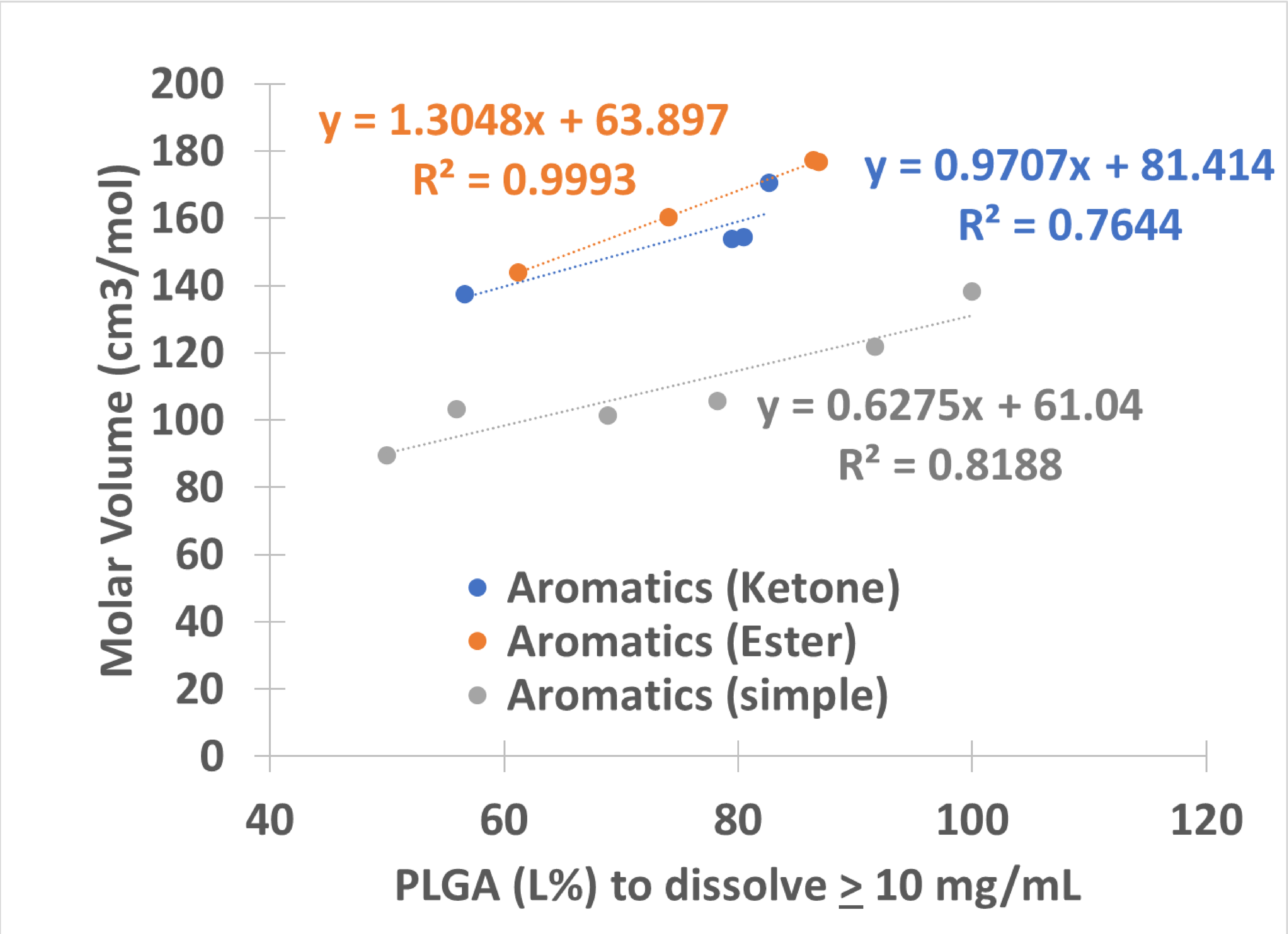

Figure 2. The molar volume of aromatic semi-solvents as a function of the lactide percent (L%) in PLGA.

Conclusion

Semi-solvents with smaller molar volumes tend to dissolve the same PLGAs better than their isomers with higher molar volumes, when other factors are held constant. This trend holds for both saturated and aromatic solvents. These results suggest that molar volume is one of the factors playing a role in PLGA solubilization. This indicates that the ability of a solvent to penetrate into semi-crystalline glycolide-rich domains is a critical factor for the semi-solvent effect.

References

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