

The Effect of Lactide:Glycolide Ratio on PLGA Solubility in Selective Solvents

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Introduction

- Poly(lactide-co-glycolide) (PLGA) is a biodegradable polymer used in a wide variety of clinical products. It degrades by hydrolysis into non-toxic components, lactic and glycolic acids.
- There are many different types of PLGAs resulting from different lactide:glycolide (LA:GA) ratio, endcap, and molecular weight.
- Thorough characterization of PLGA is necessary for ensuring qualitative and quantitative (Q1/Q2) sameness between a reference listed drug and a proposed generic formulation.
- The **purpose** of this study is to investigate the effect of the lactide content (i.e., LA:GA ratio) on the PLGA solubility in various solvents at three different temperatures.

Methods

- PLGA with similar molecular weights, but varying LA:GA ratios were purchased commercially or manufactured by Akina, Inc. (**Table 1**).
- The LA:GA ratios of PLGAs were verified by H-NMR at Purdue University. PLGA molecular weight was verified by GPC analysis at Akina, Inc.
- Each PLGA (~100 mg) was weighed in a tared glass vial and solvent was added to make the final concentration of 2.5% w/v.
- Each PLGA/solvent vial was then placed in 30 °C, 40 °C and 50 °C incubators with orbital agitation set to 100 rpm.
- After overnight mixing, decanted liquid and dried the remaining undissolved PLGA under deep vacuum.
- Dried PLGA was measured and the mass change was quantified.
- Test was performed in triplicate.
- Solvents which had boiling points too high for drying were checked visually for a qualitative determination of solubility and scored "0" – "2" to indicate no dissolution (0), partial dissolution (1), and full dissolution (2).

Table 1. PLGA used for testing.

Lactide %	Manufacturer: Catalog #	LA:GA HNMR (molar)	Weight average Mol. Wt. (Da)
50LA	Evonik RG504H	50:50	77,954
75LA	Evonik RG755S	75:25	72,176
88LA	Akina, Inc. AP085	88:12	80,885

Qualitative Observations

- PLGA solubility in some organic solvents depends on the LA:GA ratio, as shown in Table 2.

Table 2. Qualitative scores select solvents.

Solvent	50% LA	75% LA	88% LA
Butyl acetate	0	1-2*	2
Triacetin	2	2	2
PEG 400	2	2	0
Tetraethylene glycol	0	0	0

*Score of 1 at 30 °C and 40 °C, but score of 2 at 50 °C.

Quantitative Results

- Tables 3 below shows select quantitative results for given solvents (average ± st. dev.).

Table 3. Quantitative test of solubility

Solvent	Lactide (%)	Temp (°C)	Mass dissolved (%)
Xylene	88	30	15 ± 2
		40	33 ± 2
		50	49 ± 3
	75	30	0
		40	0
		50	0
	50	30	1 ± 0
		40	0
		50	0
Trichloroethylene (TCE)	88	30	99 ± 0
		40	98 ± 0
		50	97 ± 0
	75	30	98 ± 1
		40	99 ± 0
		50	99 ± 0
	50	30	0
		40	0
		50	0
Methyl ethyl ketone (MEK)	88	30	98 ± 0
		40	98 ± 0
		50	98 ± 0
	75	30	97 ± 3
		40	98 ± 1
		50	98 ± 0
	50	30	34 ± 1
		40	47 ± 1
		50	67 ± 2

- Table 4 outlines solvent results for each PLGA indicating good (o), poor (x), or solvents which had improved solubility at higher temperatures (Δ).

Table 4. Select semi-solvent synopsis

Solvent	LA:GA		
	88:12	75:25	50:50
Xylene	Δ	x	x
Toluene	o	Δ	x
TCE	o	o	x
Benzyl alcohol	o	o	Δ
MEK	o	o	Δ
PEG (400)	x	o	o

Figure 1. PLGA solvents grouped by type.

Full Solvents

Acetone, acetonitrile, anisole, chloroform, dichloromethane, dimethylformamide, dimethylsulfoxide, dioxane, ethyl acetate, formic acid, triacetin

Lactide-Selective Solvents

Chlorobenzene, benzyl alcohol, butyl acetate, ethyl lactate, methyl ethyl ketone, 2-pentanone, toluene, trichloroethylene, xylene,

Glycolide-Selective Solvents

Poly(ethylene glycol) (PEG) 400

Non-Solvents

Castor oil, ethanol, decanol, diethyl ether, hexane, lactic acid, methanol, water

Conclusions

- Solvent-selective solubility of PLGA with different LA:GA ratio holds promise to separate PLGAs with varying LA:GA ratios.
- Lactide-selective solvents tend to include phenyl derivatives and high alkyl content esters and ketones. Further testing will be conducted to elucidate trends and mechanisms.
- The selective solvent effect may be utilized both in de-formulation assays as well as in generating formulations with controlled microstructure.

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