Effect of reaction temperature on PLGA properties and semi-solvent interactions

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Introduction

Poly(lactide-co-glycolide) (PLGA) has been used in an array of biomedical applications. Ring-opening polymerization of PLGA is a process involving various reactions. Due to its higher reactivity and lower melting point, glycolide tends to react rapidly forming glycolide-rich regions which are subsequently randomized with lactide by reactions [1]. The impact of the reaction temperature on the resultant polymer properties and on semi-solvent interactions were investigated.

Methods

A series of PLGAs having a nominal lactide:glycolide (L:G) of 75:25 were reacted in a glass flask reactor according to a standard recipe (21 g glycolide, 79 g D,L-lactide, 80 µL lactic acid (LA), and 0.5 g stannous octanoate) with magnetic stirring at temperatures ranging from 145 to 175 ℃ (418 – 448 K). To study the molecular weight effect, an extra set of PLGAs at each of the extreme temperatures (145 ℃ and 175 ℃) were reacted with 10-fold excess of the initiator. After the reaction, the polymers were filtered and purified by solvent precipitation and characterized using gel-permeation chromatography (quaternary detection) (GPC-4D) and nuclear magnetic resonance (NMR) as previously described [2]. PLGA solubilities in different solvents were measured by adding 100 mg PLGA to 4 mL of toluene, 2-pentanone, or butanone with shaking at 30 ℃ overnight followed by decantation, vacuum drying, and weighing the remaining polymers.

Results

The PLGAs reacted at specific temperatures for 8 hours yielded materials which ranged widely in molecular weight and in sequencing with roughly comparable L:G ratios between them (within 2.8% L) (Table 1). PLGAs synthesized at varying temperatures with the same initiator content showed that both Rcms (representing the randomness of glycolide-rich regions) and molecular weight were dependent on the reaction temperatures used (Fig. 1). Use of higher amount of the initiator led to a significant decrease in molecular weight with little notable impact on Rcms.

Table 1. PLGA properties from varying reaction temperatures and initiator conditions.

Reaction Temp (Initiator)	NMR		GPC-ES		GPC-4D		Solubility (% of 25 mg/ml) (AVG ± STDEV, N = 3)		
	L%*	**Rcms^**	**M_n**	**M_w**	**M_n**	**M_w**	**2-BE**	**2-PE**	**Toluene**
418 K	75.3%	1.10	78,066	115,297	174,973	211,114	97.8 ± 0.4	36.6 ± 1.1	6.1 ± 1.7
423 K	72.5%	1.17	117,284	169,932	133,309	152,455	99.7 ± 0.1	26.1 ± 1.2	7.1 ± 0.7
428 K	73.7%	1.19	108,950	186,936	116,587	130,519	99.6 ± 0.1	29.1 ± 1.3	8.3 ± 0.2
433 K	73.9%	1.31	87,559	133,103	79,545	92,217	99.6 ± 0.3	52.8 ± 0.2	9.0 ± 3.2
438 K	73.3%	1.44	56,697	113,741	65,506	77,192	99.5 ± 0.2	48.4 ± 8.6	8.4 ± 0.4
443 K	74.1%	1.45	93,098	151,291	77,516	97,801	100.4 ± 1.2	38.0 ± 0.6	10.7 ± 2.0
448 K	74.3%	1.72	53,952	86,653	68,802	85,094	97.1 ± 0.7	68.4 ± 3.6	11.5 ± 1.3
418 K (0.8 ml LA)	73.6%	1.10	15,469	29,394	32,590	38,779	98.9 ± 2.0	96.0 ± 1.9	17.7 ± 1.0
448 K (0.8 ml LA)	74.4	2.13	18,710	29,162	24,986	31,006	98.5 ± 0.9	99.0 ± 0.3	18.3 ± 0.7

***Molar % by HNMR.** **^(166.4 ppm/166.3 ppm) in ^{13}CNMR**
2-BE: 2-Butanone. 2-PE:2-Pentanone

Results (Cont.)

The resultant solubilities in indicated semi-solvents were plotted against the reaction temperature **(Fig. 2)**. Toluene exhibited the strongest relationship between temperature and solubility and was used to compare impacts on the molecular weight and Rcms. The molecular weight showed a strong correlation to the toluene solubility, and Rcms has a weaker correlation (**Fig. 3**).

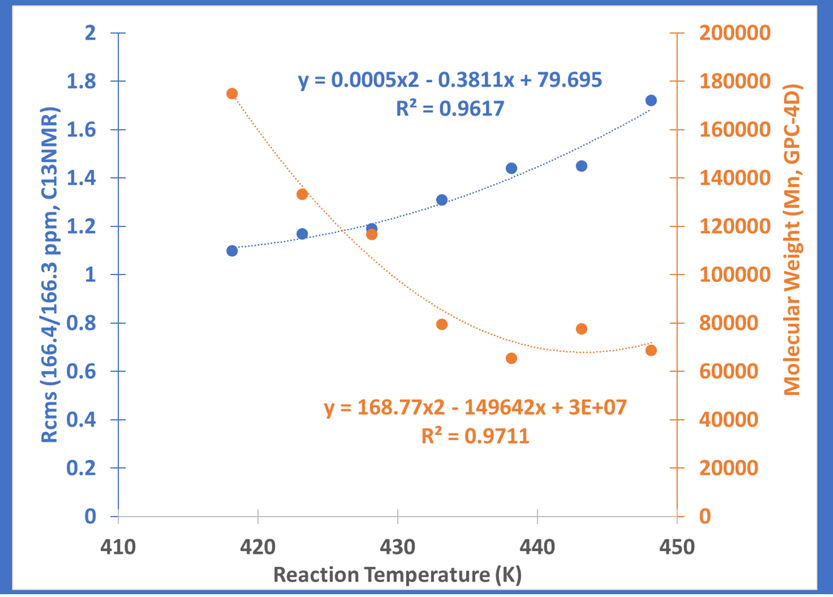

Figure 1. Rcms and molecular weight as a function of the reaction temperature.

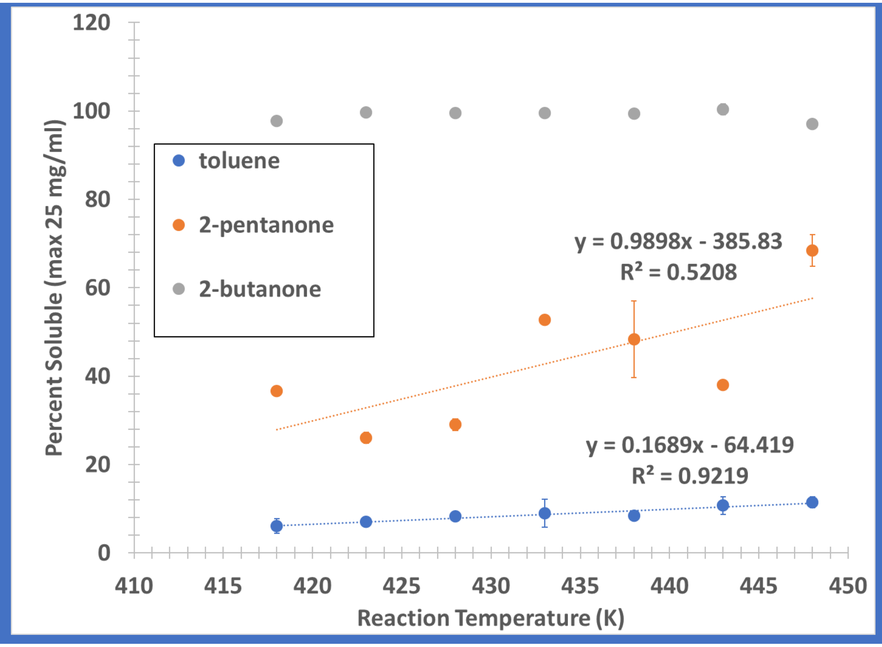

Figure 2. Solubility of PLGAs reacted at varying temperatures in indicated semi-solvents (Average ± Standard deviation, N = 3).

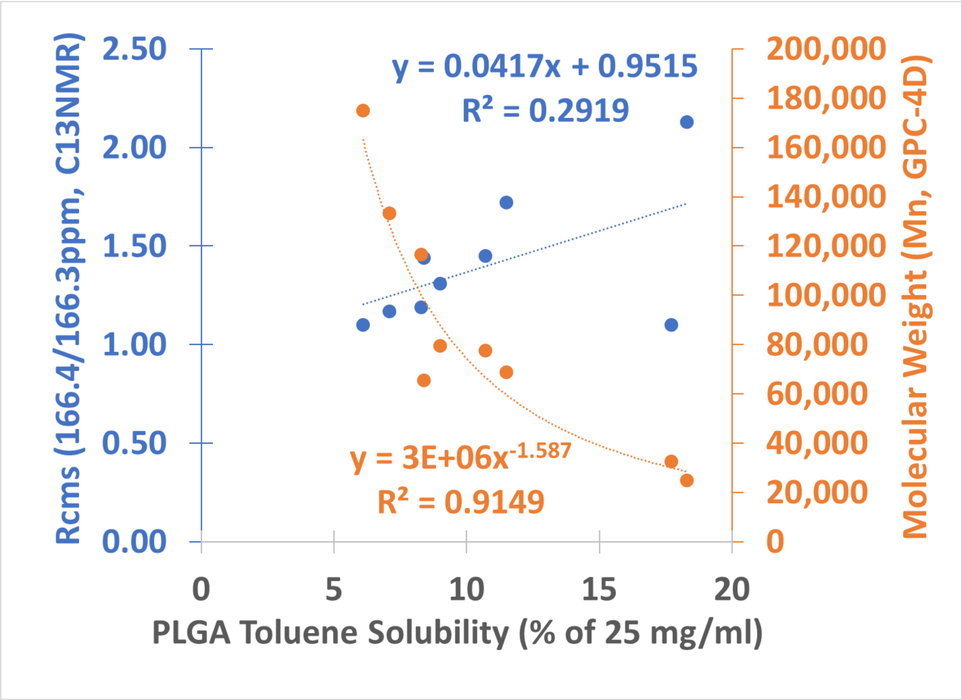

Figure 3. The PLGA molecular weight as a function of the solubility in toluene.

Conclusion

Transesterification is a process in which PLGA chains react with one another to form different molecular weights. This process decreases both the blockiness and molecular weight of formed polymers, and reactions at lower temperatures reduce the transesterification extent. This impact on the semi-solvent behavior is correlated to the ability of the solvent to dissolve the polymer at a given L%. The solubility cut-off (i.e., the lactide content required for the 10 mg/ml solubility) for 2-butanone, 2-pentanone, and toluene are 51, 69, and 78 %, respectively [3]. In this case, 2-butanone and 2-pentanone are good solvents for PLGA-75L, so that the trends regarding molecular weight and Rcms were not observed. However, toluene displays a strong relationship, as shown in Figure 3. These data indicate that PLGAs having the same L:G ratio can be potentially separated by using certain semi-solvents based on their Rcms and molecular weights.

References

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