Effect of solvents and their isomers on dissolution of PLGAs with different lactide:glycolide (L:G) ratios

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Introduction

Poly(lactide-co-glycolide) (PLGA) is a polymeric excipient used in injectable, long-acting formulations. Previous studies of PLGA have shown that the PLGA solubility in various solvents depends on the lactide:glycolide (L:G) ratio [1-3]. The driving force behind the PLGA dissolution in various solvents is not well understood. The purpose of this study is to examine the effect of solvent chemical structure on the PLGA solubility.

Methods

PLGAs of varying L:G ratios were tested for dissolution in selected esters, ketones and their isomers. The weight-average molecular weights of the PLGAs were approximately 80 ± 20 kDa as determined by gel permeation chromatography (GPC). The L:G ratios of the PLGAs tested ranged from 50:50 to 100:0 (P(DL)La). Each PLGA (100 mg) was incubated in 4 mL of each solvent at 30°C overnight (~16-24 hrs) with orbital agitation set at 100 rpm. The solvent was then decanted away from any undissolved polymer. The remaining polymer was dried to a constant mass at 60°C under deep vacuum. Dissolution (% w/w) was determined gravimetrically in triplicate.

Results

The percent dissolution of each PLGA in the ketone and ester solvents and their respective isomers are displayed in **Figures 1** and **2**. Higher lactide PLGA dissolves more readily in these semi-solvents which allows them to separate high lactide PLGA from low lactide PLGA [2]. For ketones and esters increasing the chain-length of the solvent (i.e., hexanone versus pentanone) decreases its solubility for PLGA (i.e., requires higher lactide content to solubilize). However, the effect of isomers of same overall composition is more complex.

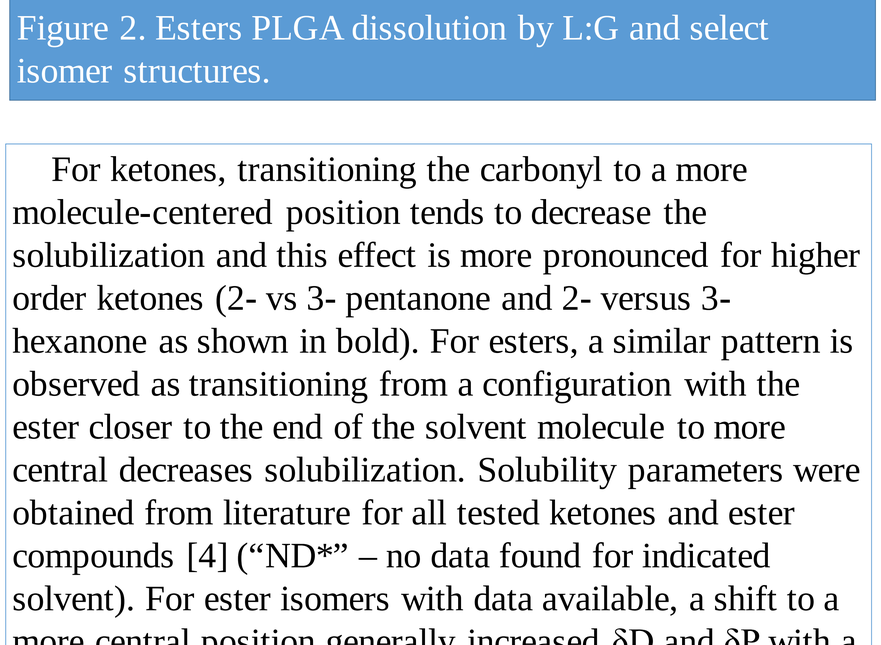

Figure 2. Esters PLGA dissolution by L:G and select isomer structures.

For ketones, transitioning the carbonyl to a more molecule-centered position tends to decrease the solubilization and this effect is more pronounced for higher order ketones (2- vs 3- pentanone and 2- versus 3-hexanone as shown in bold). For esters, a similar pattern is observed as transitioning from a configuration with the ester closer to the end of the solvent molecule to more central decreases solubilization. Solubility parameters were obtained from literature for all tested ketones and ester compounds [4] ("ND*" – no data found for indicated solvent). For ester isomers with data available, a shift to a more central position generally increased δD and δP with a decrease in δH for esters. For ketone isomers, only a general decrease in δD was observed. Further testing of isomers will establish if these trends are universal or only applicable to these particular solvent sets.

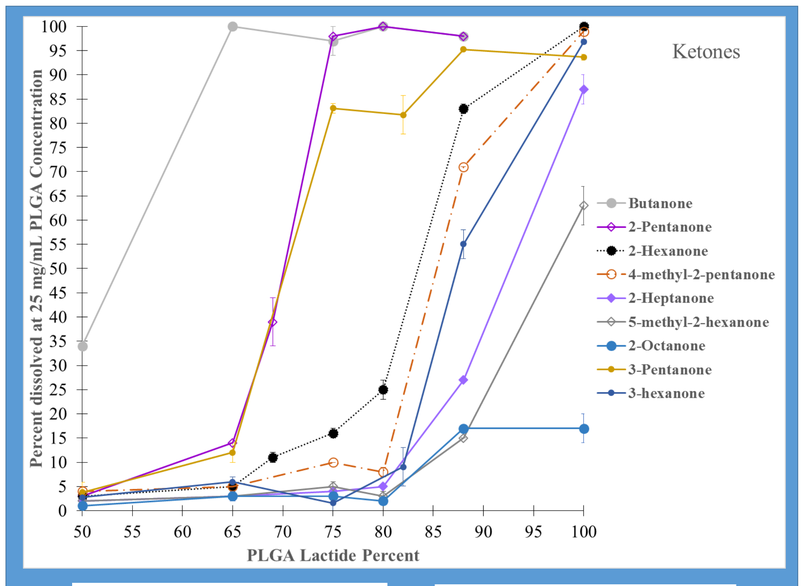

Figure 1. Ketones PLGA dissolution by L:G and select isomer structures.

Table 1. Ester semi-solvents solubility parameters

Solvent (most solubilizing to least solubilizing)		Hansen Solubility Parameters			
Common name	Chemical name	δD	δP	δH	Molar volume
Ethyl Lactate	Ethyl 2-hydroxypropanoate	16	7.6	12.5	115
Ethyl Benzoate	**Benzoic acid ethyl ester**	**17.9**	**6.2**	**6**	**144.1**
Propyl Acetate	**Acetic acid, propyl ester**	**15.3**	**4.3**	**7.6**	**115.8**
Ethyl Propionate	Propanoic acid, ethyl ester	15.5	6.1	4.9	115.6
Butyl Acetate	1-Butyl Acetate	15.8	3.7	6.3	132.6
Isobutyl Acetate	2-methylpropyl ethanoate	15.1	3.7	6.3	133.8
Amyl Acetate	Pentyl acetate	15.8	3.3	6.1	148
Isoamyl Acetate	isopentyl acetate	15.3	3.1	7	150.2
Ethyl isobutyrate	Ethyl 2,2-dimethylacetate	ND*	ND*	ND*	ND*

Table 2. Ketone semi-solvents solubility parameters

Solvent (ordered by decreasing PLGA solubility)		Hansen Solubility Parameters			
Common name	Chemical name	δD	δP	δH	Molar Volume
Methyl Ethyl Ketone (MEK)	2-Butanone	16	9	5.1	90.2
Methyl n-Propyl Ketone	**2-Pentanone**	**16**	**7.6**	**4.7**	**107.3**
Diethyl Ketone	**3-Pentanone**	**15.8**	**7.6**	**4.7**	**106.4**
Methyl Butyl Ketone	2-Hexanone	15.3	6.1	4.1	124.1
Methyl Isobutyl Ketone (MIBK)	4-Methyl-2-pentanone	15.3	6.1	4.1	125.8
Ethyl propyl ketone	3-Hexanone	ND*	ND*	ND*	ND*
Methyl n-Amyl Ketone	2-Heptanone	16.2	5.7	4.1	140.8
Methyl Isoamyl Ketone	5-Methyl-2-hexanone	16	5.7	4.1	141.3

Conclusion

PLGAs show different solubility in isomers of select solvents which exhibit semi-solvent properties and molecular configuration of a solvent is a factor in dissolving PLGA with a general preference of higher solubility for solvents that have carbonyl units closer to endcap. More details remain to be discovered regarding the semi-solvent effect which may find applicability in both analytical and formulatory applications.

References

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[3] J. Hadar, J. Garner, S. Skidmore, K. Park, H. Park, S. Choi, Y. Wang. "The Effect of Lactide:Glycolide Ratio on PLGA Solubility in Selective Solvents". Poster Presentation at FDA public workshop "Demonstrating Equivalence of Generic Complex Drug Substances and Formulations" October 6, 2017.

[4] HSPiP Software 5th Edition build 5.0.04.

Acknowledgements

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