Microstructural and compositional analysis of dexamethasone-loaded poly(lactide-co-glycolide) rods

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Introduction

Poly(lactide-co-glycolide) (PLGA) has been used widely for developing long-acting injectable formulations, including Ozurdex®, a miniature-size implant for ocular delivery of dexamethasone for up to 3 months. Previously, the sequential exposure of semi-solvents and subsequent morphological evaluations by Surface Analysis of Sequential Semi-Solvent Vapor Impact (SAVI) were developed to elucidate the internal microstructural characteristics of PLGA microparticles [1]. The current work applied the SAVI method to study dexamethasone-loaded mini-rods.

Methods

Dexamethasone-loaded PLGA mini-rods were provided by Professor Feng Zhang at the University of Texas at Austin [2]. Each sample was mounted onto a glass microscope slide and exposed to vapors of sequential semi-solvents (each having a unique lactide % (La%) solublization limit): ethyl isobutyrate (EI, 85% La), toluene (TOL, 78% La), 2-pentanone (2PE, 69% La), propyl acetate (PA, 63% La), methyl ethyl ketone (MEK or butanone. 51% La), and acetone (ACE, full solvent) under laser-scanning confocal microscopy (LSCM) similar to that previously described [1]. Images of Dry (no semi-solvent) through MEK were collected at 10X magnification, while acetone imaging was obtained with 5X magnification to accommodate the high degree of spread. Profilometry was performed using LEXT (Olympus) software to characterize morphological changes. PLGA in the samples were extracted and analyzed by ^{1}H NMR and GPC to determine the polymer properties.

Results

Figure 1 displays the resultant images, while Table 1 lists the measured values of selected parameters. Relatively little change occurred in the mini-rod samples, with only minor hydration observed starting from 2-pentanone. Significant changes occurred only after exposure to acetone vapor, resulting in substantial melting and dissolution of the PLGA mini-rods. Such melting/ dissolution resulted in the appearance of insoluble dexamethasone crystals collected in an area around the PLGA mini-rods as the PLGA layers were removed by acetone vapor (Figure 1).

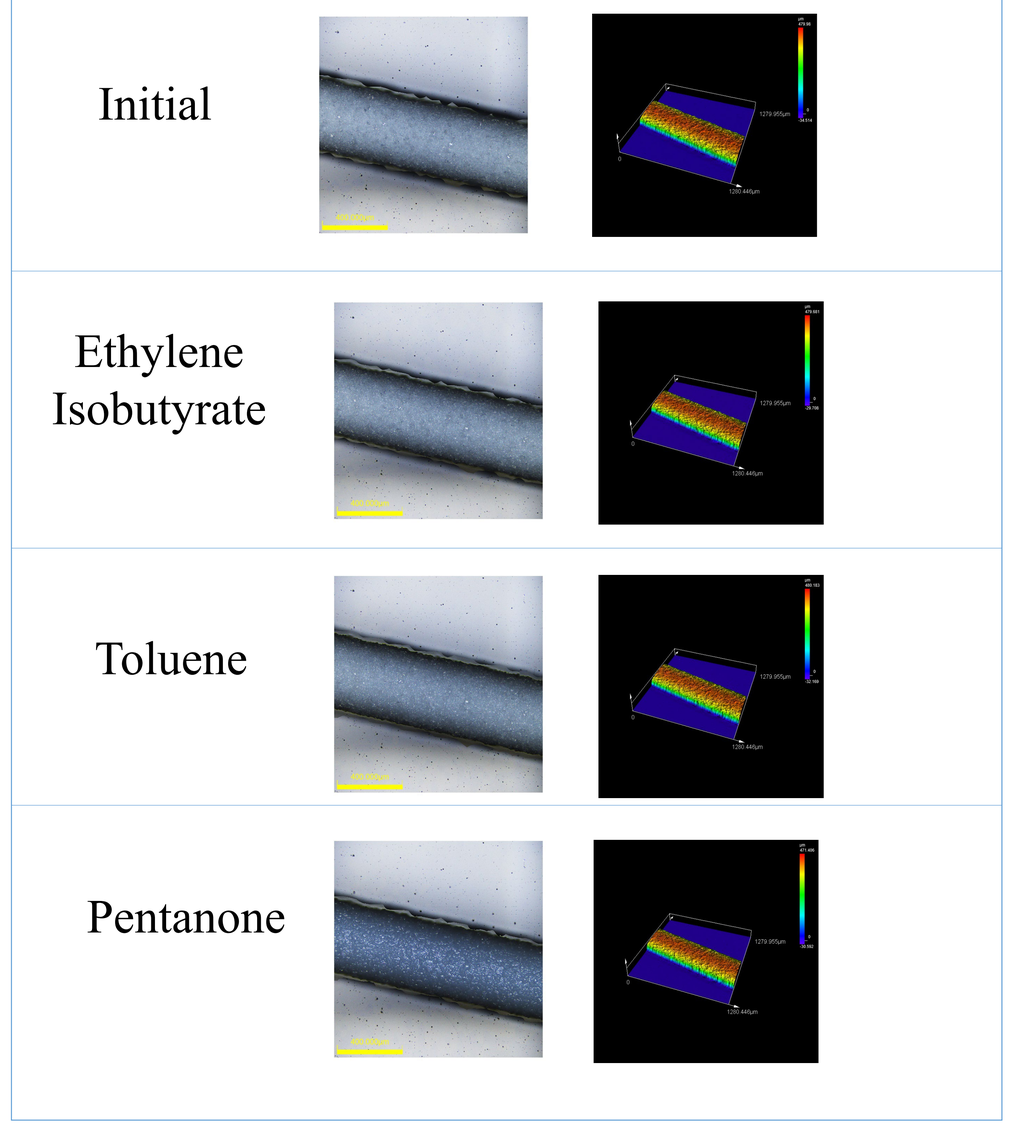

Figure 1. Confocal images collected at indicated solvent vapor conditions. All solvents collected at 10X magnification except for acetone which was collected at 5X. Display shows both color image (left) and color-coded height image (right).

Table 1. Calculated surface/dimensional parameter for indicated solvent condition. (Average ± standard deviation, N = 10).

Solvent	Sq[µm] (root mean square height)	Ssk (skewness)	Sxp[µm] (peak extreme height)	Smc(mr)[µm] (inverse areal material ratio)	Surface area ratio (surface area /contact area)
Dry	29.1 + 9.6	1.8 + 0.5	49.3 + 15.6	7.6 + 9.5	3.7 + 0.6
EI	31.3 + 9.5	1.7 + 0.4	53.6 + 14.0	7.2 + 8.8	3.8 + 0.5
TOL	29.9 + 8.5	1.7 + 0.5	51.5 + 17.7	7.3 + 8.6	3.8 + 0.5
2PE	30.7 + 8.8	1.7 + 0.5	51.6 + 18.1	7.9 + 8.9	3.6 + 0.4
PA	30.8 + 9.0	1.7 + 0.5	52.4 + 18.4	7.8 + 8.7	3.5 + 0.4
MEK	30.7 + 9.1	1.7 + 0.4	54.1 + 18.8	7.1 + 8.0	3.4 + 0.3
ACE	51.3 + 21.5	0.2 + 0.5*	112.5 + 38.5	-27.0 + 20.9	2.5 + 0.3

Results

In **Table 1**, little parameter changes were observed until the samples were treated with acetone. At this point, the parameters shifted dramatically as the rods were partially dissolved. Separate testing by ^{1}H NMR and GPC confirmed that the samples contain PLGA with 51% lactide and the number average molecular weight of 8,394 Da. Although butanone vapor should be able to melt/dissolve microparticles made of PLGA 51% La, only a full solvent, acetone, was able to dissolve the rods made of similar PLGA. This observed behavior difference indicates that the polymer in the rod samples was tightly packed and became resilient to semi-solvent vapor exposure. This is indicative of the extrusion process by which these rods are manufactured.

Conclusion

SAVI can be applied to the compositional and microstructural analysis of dexamethasone-loaded PLGA mini rods. In situations where the sample is substantially limited, it may prove valuable in elucidating the polymer lactide ratio via interactions of the polymer implant with semi-solvents.

References

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