Morphological analysis of naltrexone-poly(lactide-co-glycolide) (NTX-PLGA) microparticles: Dynamic role of naltrexone on PLGA degradation

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Introduction

Drug release from poly (lactide-co-glycolide) (PLGA) microparticles is a dynamic process in which the drug, the polymer, and the surrounding solution interact to affect the drug release. Water plasticizes PLGA, affecting drug release properties [1]. Morphological analysis of naltrexone-loaded PLGA (NTX-PLGA) microparticles in the drug release medium and after semi-solvent vapor (SSV) exposures were conducted utilizing laser scanning confocal microscopy (LSCM).

Methods

PLGA (L:G=75:25) particles were manufactured by an emulsion method, including blank microparticles (PLGA only) and PLGA-NTX microparticles with varying times spent in different processing steps (e.g., times for washing and ethanol treatment). A sample of Vivitrol® (naltrexone for extended-release injectable suspension) for intramuscular use was also tested. The particles were incubated in triethylammonium acetate (TEAA) buffer, and samples were removed at 1-day and weekly time points, dried under reduced pressure, and imaged by LSCM. These were subsequently exposed to a sequence of SSV (ethyl isobutyrate (EI), toluene (TOL), 2-pentanone (2PE), and propyl acetate (PA)) dispersed in an argon carrier gas. After the final time point (4 weeks of drug release), the remaining material was tested by gel permeation chromatography (GPC) for PLGA molecular weight.

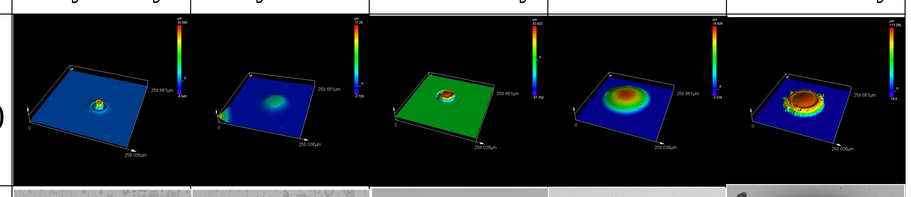
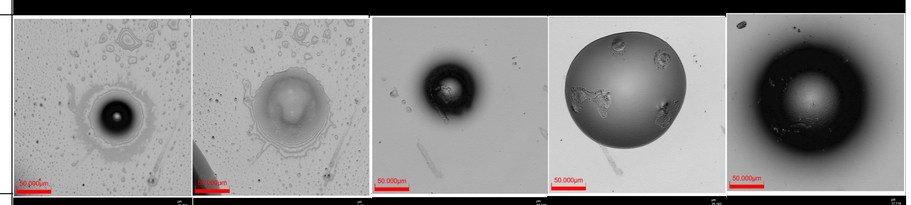
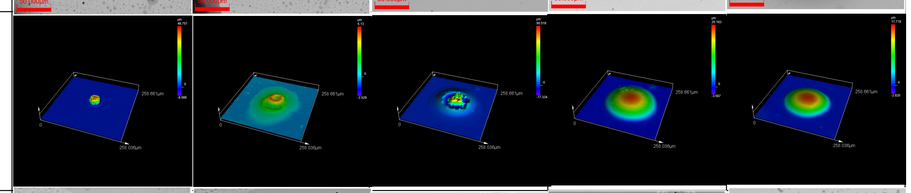
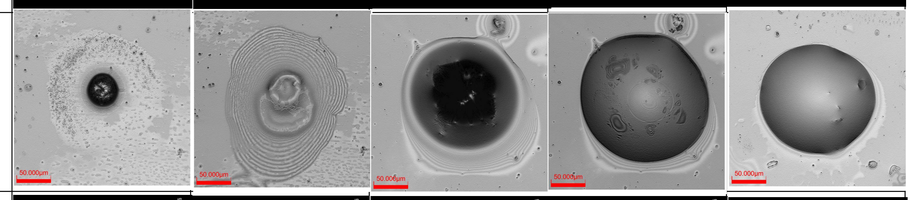
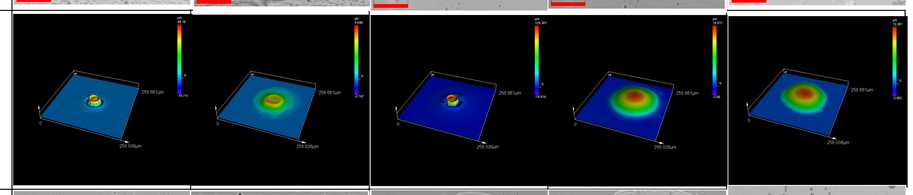
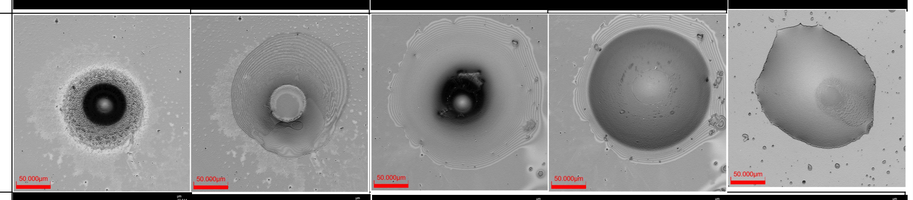
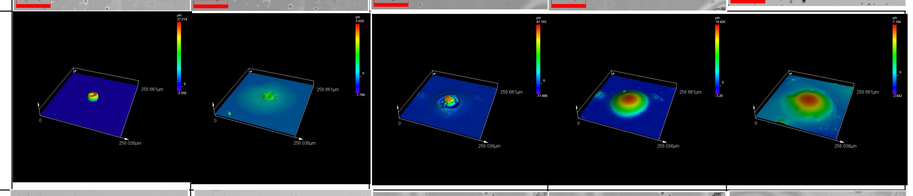
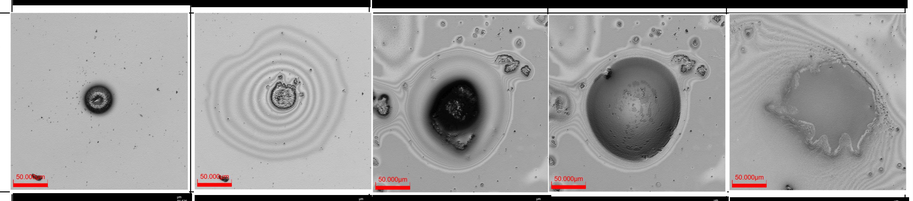
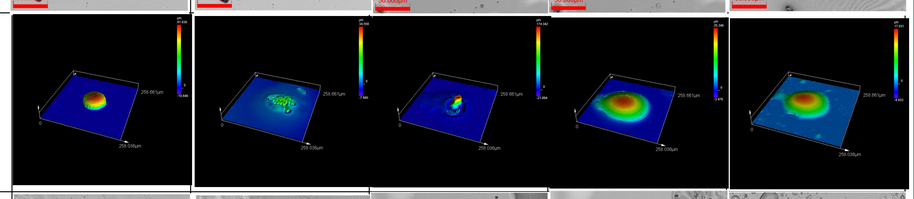
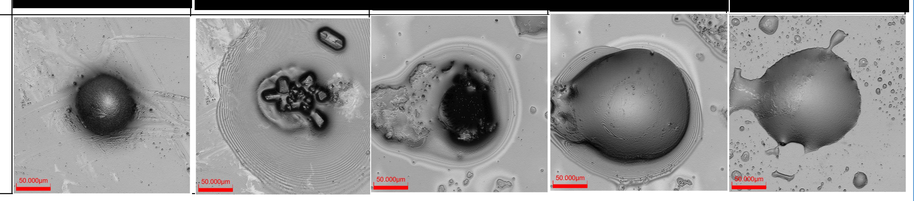
Results

Table 1 GPC-4D measured number average (M_n) molecular weight of indicated samples both initial and at 4 weeks.

Sample (NTX % w/w)	Initial (M_n, Da)	4-weeks incubated (M_n, Da)
PLGA Blank (0%)	33,941	30,089
Emulsion 4h PVA/8h ET (29.9%)	26,516	2299
Emulsion 24h PVA/8h ET (26.1%)	21,846	2341
Emulsion 4h PVA/24h ET (30.7%)	21,825	2539
Vivitrol® (RLD) (33.7%)	36,560	2995

Results

Figure 1. Example images from selected microparticles at indicated time points after exposure to PA vapor. (Red scale bar=50 μm).

Sample	Day 1 Dry	Day 1 PA	Week 2 Dry	Week 2 PA	Week 4 Dry
Emulsion Blank no drug (Height)					
Emulsion Blank no drug (Intensity)					
Emulsion 4h PVA/8h ETOH (Height)					
Emulsion 4h PVA/8h ETOH (Intensity)					
Emulsion 24h PVA/8h ETOH (Height)					
Emulsion 24h PVA/8h ETOH (Intensity)					
Emulsion 4h PVA/24h ETOH (Height)					
Emulsion 4h PVA/24h ETOH (Intensity)					
Vivitrol® (RLD) (Height)					
Vivitrol® (RLD) (Intensity)					

The PLGA blank particles exhibited relatively minor hydrolysis during the study. They behaved mostly in a consistent manner of general melting and plasticization upon exposure to SSV across all 4 weeks of *in vitro* release. After about 2-3 weeks of incubation, The NTX-loaded particles exhibited a drastic reduction in initial height, and the roughness (root mean square height, Sq) even before addition of any solvent vapor. At day 1, Vivitrol® exhibited cubic NTX crystals after melting the PLGA with PA vapor while the manufactured particles did not, indicating the method's ability to detect differences between these formulations. GPC analysis confirms the catalyzed degradation of the PLGA by NTX presence which has been reported to occur via nucleophilic attack [2].

Table 1. Particle height and root mean square height (Sq) from samples (average ± standard deviation, N = 10).

Time	Day 1		Week 2		Week 4	
Condition	Sq	Height	Sq	Height	Sq	Height
PLGA blank						
Dry	10.6 ± 8.6	40 ± 36	19.4±10.1	115 ± 34	15.3 ± 2.9	131 ± 36
EI	9.2 ± 8.9	34 ± 34	21.5 ± 8.1	110 ± 22	12.8 ± 2.1	134 ± 29
TOL	6.6 ± 8.0	37 ± 41	16.9 ± 4.3	111 ± 21	2.8 ± 1.7	58 ± 28
2PE	0.3 ± 0.1	20 ± 17	1.3 ± 1.1	37 ± 12	0.3 ± 0.1	33 ± 8
PA	0.3 ± 0.1	19 ± 16	1.1 ± 0.9	34 ± 11	0.1 ± 0.0	19 ± 3
Emulsion-wash (4h PVA/8h ETOH)						
Dry	14.3 ± 5.7	58 ± 19	5.0 ± 2.5	60 ± 26	0.3 ± 0.1	14 ± 2
EI	1.5 ± 2.4	15 ± 7	1.1 ± 0.9	27 ± 14	0.3 ± 0.1	14 ± 3
TOL	1.4 ± 3.0	12 ± 8	0.8 ± 0.5	20 ± 6	0.3 ± 0.1	13 ± 3
2PE	0.7 ± 1.3	12 ± 8	0.8 ± 0.4	19 ± 6	0.2 ± 0.1	9 ± 2
PA	0.6 ± 0.9	16 ± 12	0.6 ± 0.4	17 ± 6	0.2 ± 0.1	9 ± 2
Emulsion-wash (24h PVA/8h ETOH)						
Dry	9.6 ± 4.7	37 ± 33	6.6 ± 3.1	82 ± 18	0.4 ± 0.2	7 ± 3
EI	0.5 ± 0.6	11 ± 6	1.4 ± 1.3	24 ± 12	0.3 ± 0.1	6 ± 3
TOL	0.6 ± 0.8	10 ± 7	1.0 ± 0.6	19 ± 4	0.3 ± 0.1	6 ± 3
2PE	0.3 ± 0.1	8 ± 4	0.4 ± 0.3	14 ± 4	0.2 ± 0.1	5 ± 3
PA	0.2 ± 0.1	7 ± 2	0.4 ± 0.1	12 ± 4	0.2 ± 0.1	5 ± 3
Emulsion-wash (4h PVA/24h ETOH)						
Dry	5.3 ± 2.0	23 ± 11	6.1 ± 3.3	58 ± 25	0.4 ± 0.1	6 ± 3
EI	1.1 ± 2.5	7 ± 10	2.0 ± 2.1	30 ± 17	0.2 ± 0.1	4 ± 3
TOL	0.3 ± 0.2	4 ± 2	1.8 ± 1.7	25 ± 12	0.2 ± 0.1	4 ± 3
2PE	0.1 ± 0.1	2 ± 1	1.3 ± 1.0	19 ± 6	0.1 ± 0.1	3 ± 2
PA	0.1 ± 0.1	3 ± 2	1.0 ± 0.9	19 ± 6	0.1 ± 0.0	3 ± 2
Vivitrol (RLD)						
Dry	9.8 ± 3.2	61 ± 23	7.3 ± 6.4	85 ± 52	0.5 ± 0.2	16 ± 5
EI	4.2 ± 4.7	37 ± 31	1.0 ± 1.3	24 ± 8	0.4 ± 0.3	15 ± 5
TOL	2.7 ± 4.2	32 ± 33	1.2 ± 1.6	23 ± 8	0.4 ± 0.2	15 ± 5
2PE	1.9 ± 2.9	23 ± 31	1.1 ± 1.7	19 ± 9	0.4 ± 0.2	13 ± 4
PA	2.0 ± 2.6	20 ± 25	0.8 ± 1.0	17 ± 9	0.4 ± 0.2	12 ± 4

Conclusion

NTX hydrolysis of PLGA is a driving factor in long-acting injectable release performance. The use of the surface analysis of (sequential semi-solvent) vapor impact (SAVI) method sequentially melts polymer layers away and allows for observation of differences in particle microstructure. It can be a valuable tool for testing the structural changes of NTX-PLGA microparticles upon sequential exposure to semi-solvent vapors.

References

[1]Wang, Yan, et al.: FDA's poly (lactic-co-glycolic acid) research program and regulatory outcomes. The AAPS Journal 23 (2021) 92.

[2] Hua, Yabing,et. al. Key factor study for generic long-acting PLGA microspheres based on a reverse engineering of vivitrol®. Molecules 26, no. 5 (2021): 1247.

Acknowledgements

This work was supported by BAA Contract # 75F40119C10096 from the U.S. Food and Drug Administration (FDA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the FDA.