Scanning analysis of semi-solvent impact using sequential solvent vapor (SASSI-SSV): Assay of poly(lactide-co-glycolide)-naltrexone (PLGA-NTX) microparticles

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Introduction

The microstructural arrangement of PLGA microparticles is a critical facet of their drug release performance. Combining the selective solubility of semi-solvents with advanced imaging techniques allows analysis of PLGA microparticle structural arrangement based on morphological changes to the particles in response to semi-solvent exposure [1]. It was found that a series of semi-solvent vapors can be used to dissolve PLGA layers from the surface for rapid, automated tracking of particle morphological (related to the microparticle structural) changes.

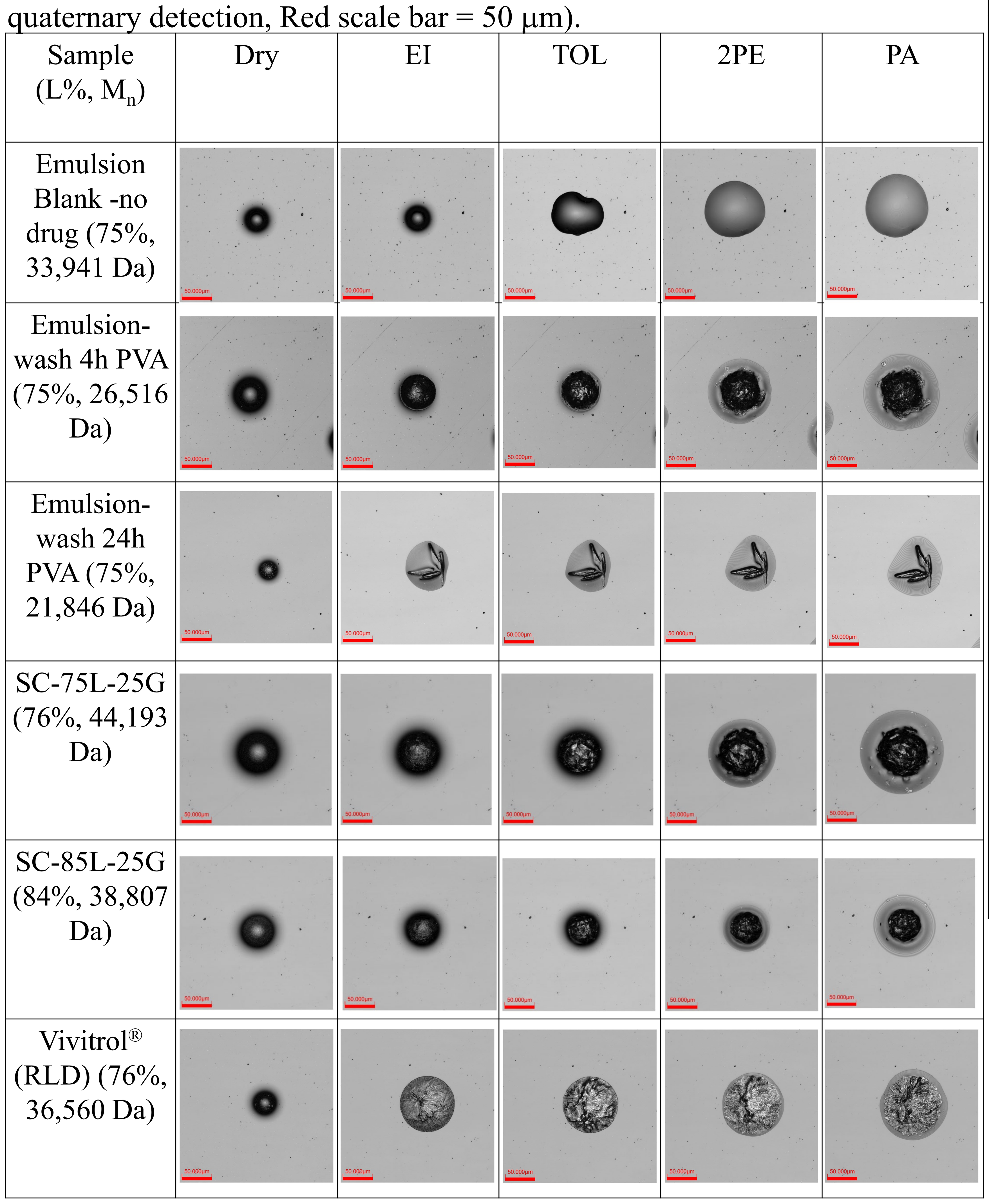
Methods

PLGA-NTX microparticles were manufactured by an emulsion method with controlled processing parameters. Additionally, Naltrexone XR Inj, the reference listed drug (RLD), Vivitrol®, and samples of particles generated by semi-continuous (SC) manufacturing [2] were also assayed for comparison. Each sample was spread across a microscope slide, and a series of particles were imaged using laser scanning confocal microscopy (LSCM) with particle locations programmed in for future imaging. The particles were warmed to 30°C and exposed to the horizontal flow of argon (40 mL/min) carrying 95±18 mg of a semi-solvent for 10 minutes. Afterward, the particles were imaged, and then the particles were exposed to the next semi-solvent in the sequence. The semi-solvents used were ethyl isobutyrate (EI, PLGA solubility threshold of 85% lactide content, or 85L), toluene (Tol, 78L), 2-pentanone (2PE, 69L), and propyl acetate (PA, 63L) (**Fig 1**). Profilometry was performed using LEXT (Olympus) software.

Figure 1. Confocal Microscope mounted with Scanning Analysis Vapor Impact (SAVI) assembly on the platform.

Results

Figure 2. Example images in laser-intensity mode of selected microparticles. (Lactide% by HNMR and M_n by Gel Permeation Chromatography quaternary detection, Red scale bar = 50 μm).



Particles were imaged (**Fig 2**), and LEXT software parameters were characterized for root mean square height (Sq, roughness), core height (Sk, bulk height variance), kurtosis (Sku, peak sharpness), 10 point height (S10z, tallest 5 peaks minus lowest 5 valleys), and area ratio (Ar, surface area/contact area) (**Table 1**). Reduced roughness (Sq) of PLGA blank after Tol exposure relative to all other samples reflects the smoother surface of the drug-free sample relative to drug-loaded samples. Area ratio (Ar) indicates the collapse of the particle, and the SC-85L-25G exhibited higher degree of collapse relative to SC-75L-25G, likely due to more soluble 85L PLGA. Additionally, Emulsion with 4 h in the PVA bath exhibited less collapse in EI and TOL relative to the emulsion with 24 h in the PVA bath. This correlated to the difference in measured number average molecular weight (M_n) of the formulations as extra time in the emulsion bath led to increased hydrolysis of the sample with lower M_n and more susceptibility to collapse. The Vivitrol® RLD exhibits significantly higher kurtosis (Sku) across EI, TOL, and 2PE relative to both Emulsion-4H and SC-75L ($P < 0.01$). Kurtosis is related to peak sharpness and can be affected by the presence of NTX, which presents as poorly soluble cubic crystals that poke up from the melting polymer and provide a blocky structure. This exhibits a different Sku relative to the valleys and ravines structures observed for NTX in Vivitrol ®.

Table 1. Selected parameters from samples (average ± standard deviation, N indicated for each sample)

Condition	Sq	Sk	Sku	S10Z	Ar
PLGA (75L) blank (N = 29)					
Dry	5.77 ± 3.9	3.09 ± 2.3	17.17 ± 60.5	15.66 ± 16.6	5.1 ± 0.88
EI	3.61 ± 2.6	4.45 ± 3.7	5.82 ± 5.3	12.04 ± 7.9	4.4 ± 0.41
TOL	0.72 ± 0.5	0.56 ± 0.5	9.80 ± 5.9	6.77 ± 3.7	1.4 ± 0.14
2PE	0.16 ± 0.1	0.11 ± 0.1	21.18 ± 54.6	2.34 ± 1.3	1.0 ± 0.01
PA	0.13 ± 0.1	0.11 ± 0.1	12.94 ± 18.5	2.45 ± 1.6	1.0 ± 0.01
Emulsion-wash (4H PVA/8H ETOH) (N = 30)					
Dry	4.17 ± 1.1	4.80 ± 2.7	2.37 ± 0.9	13.41 ± 8.6	5.1 ± 0.41
EI	4.22 ± 1.2	4.25 ± 1.4	3.61 ± 3.3	27.30 ± 10.8	4.6 ± 0.74
TOL	5.66 ± 1.6	9.32 ± 4.3	2.96 ± 1.5	30.29 ± 7.4	4.1 ± 1.06
2PE	4.48 ± 1.7	8.11 ± 5.2	3.29 ± 0.9	25.79 ± 8.5	2.2 ± 0.45
PA	4.16 ± 1.9	8.16 ± 5.6	3.92 ± 1.2	22.86 ± 8.3	1.8 ± 0.23
Emulsion-wash (24H PVA/8H ETOH) (N = 40)					
Dry	4.15 ± 1.6	3.94 ± 3.1	2.08 ± 0.9	11.06 ± 6.7	5.2 ± 0.57
EI	1.07 ± 0.7	1.38 ± 1.2	7.95 ± 4.8	9.35 ± 5.9	1.5 ± 0.52
TOL	1.22 ± 0.7	1.63 ± 1.3	9.23 ± 15.1	10.48 ± 5.9	1.5 ± 0.49
2PE	1.28 ± 0.9	1.47 ± 1.8	12.42 ± 20.6	10.58 ± 6.6	1.4 ± 0.37
PA	1.25 ± 0.8	1.23 ± 1.5	13.93 ± 25.0	10.58 ± 6.6	1.4 ± 0.32
Semi-Cont (75L, 25G) (N = 30)					
Dry	5.26 ± 1.6	4.23 ± 2.2	2.88 ± 1.1	10.15 ± 5.7	4.2 ± 0.18
EI	6.80 ± 1.4	7.17 ± 2.4	3.34 ± 1.0	23.40 ± 11.5	5.0 ± 0.32
TOL	7.88 ± 1.5	9.63 ± 2.9	2.85 ± 1.0	31.85 ± 10.7	5.2 ± 0.47
2PE	6.15 ± 1.9	13.35 ± 3.9	2.75 ± 0.5	29.15 ± 9.4	2.3 ± 0.50
PA	4.90 ± 2.3	10.74 ± 5.6	3.27 ± 0.8	25.35 ± 9.3	1.9 ± 0.39
Semi-Cont (85L, 25G) (N = 30)					
Dry	4.90 ± 1.6	5.14 ± 2.7	2.84 ± 1.3	13.83 ± 10.0	4.1 ± 0.61
EI	4.66 ± 2.4	5.72 ± 2.5	3.23 ± 1.2	21.85 ± 14.4	3.9 ± 1.07
TOL	6.36 ± 3.4	11.05 ± 6.1	3.09 ± 1.4	31.45 ± 19.4	3.7 ± 1.39
2PE	3.14 ± 2.8	4.05 ± 6.5	7.46 ± 4.0	20.46 ± 13.7	1.5 ± 0.44
PA	2.68 ± 2.4	2.49 ± 5.5	9.30 ± 4.7	19.05 ± 11.4	1.4 ± 0.31
Vivitrol (RLD) (N = 40)					
Dry	5.97 ± 2.2	6.47 ± 2.6	2.80 ± 0.9	18.95 ± 7.9	5.2 ± 0.93
EI	3.43 ± 3.2	4.91 ± 5.1	5.70 ± 3.0	21.47 ± 14.3	3.2 ± 1.67
TOL	3.66 ± 3.3	5.90 ± 5.1	5.01 ± 1.4	24.07 ± 14.6	3.4 ± 1.82
2PE	4.56 ± 4.9	9.12 ± 9.5	4.25 ± 1.6	26.65 ± 21.6	2.6 ± 1.61
PA	4.51 ± 4.7	9.62 ± 10.4	4.53 ± 2.2	24.41 ± 18.8	2.2 ± 1.12

Conclusion

The SAVI method sequentially melts polymer layers away and allows for observation of differences in particle microstructure. It can be a valuable tool for testing long-acting injectable formulations as part of research and quality control applications.

References

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