Scanning Analysis of Semi-Solvent Impact (SASSI) Assays of naltrexone microparticles Prepared by different manufacturing solvents and conditions

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Introduction

Poly(lactide-co-glycolide) (PLGA) microparticles made of the same formulation composition may have significantly different drug release kinetics and morphology depending on various parameters used in the manufacturing process [1]. The impacts of the different manufacturing conditions on the microparticle properties, however, have not been understood. This study examined whether the microparticles made by different processes can be differentiated by analyzing the scanned surface morphology after treating them with semi-solvents (SASSI).

Methods

Naltrexone (NTX)-loaded microparticles were made using PLGA 75:25 (or 75L) (Evonik, 755S). The PLGA was dissolved either in acetone: dichloromethane (ACE:DCM, 1:9) or in benzyl alcohol:DCM (BZA:DCM, 3:7) to make microparticles by single-emulsion methods [2]. Two different blank microparticles were made using PLGA 75:25 alone and a mixture of PLGA 50:50 (Evonik, RG504H) and PLGA 100:0 (PolySciTech, AP093), i.e., polylithic, after dissolving in DCM. The naltrexone loading and release was assayed by HPLC with the drug release in phosphate buffered saline containing 0.05% polysorbate 20 [3]. A sample of each microparticle powder was attached to a gridded microscope slide by photocurable glue (Loctite 3494) to enable specific tracking of the same particle by location. Samples were exposed to either m-xylene, propylpropionate, 2-methyl tetrahydrofuran, cycloheptanone, or butanone under anhydrous conditions at 0 °C for 1 min followed by drying. The particles were scanned using an Olympus OLS5000 confocal microscope before and after solvent exposure. The 3D scan images were assayed for size and roughness parameters using the Olympus analytical software. The effect of solvent on each particle was determined as percent change ((P_{sol} - P_{dry})/P_{dry})x100) for comparisons between parameters.

Results

Particles 75L+NTX (ACE:DCM) had a loading of 3.3 % w/w drug while 75L+NTX (BZA:DCM) had a loading of 26.1 % w/w drug due to superior solubility of NTX in BZA. **Figure 1** shows cumulative release from each formulation (mg). **Figure 2** shows example images from 3D scans of particles before and after solvent exposure. For each particle – solvent combination, 30 parameters were collected for roughness and a further 5 for dimensions. A small selection of the data set is shown in **Table 1**.

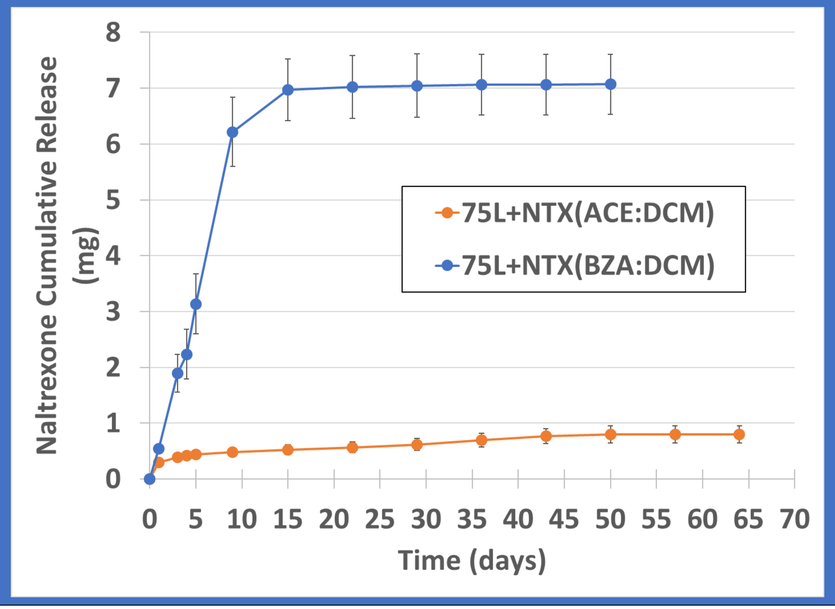

Figure 1. Cumulative NTX release from microparticles prepared by different solvent systems (mean ± SD, N = 3).

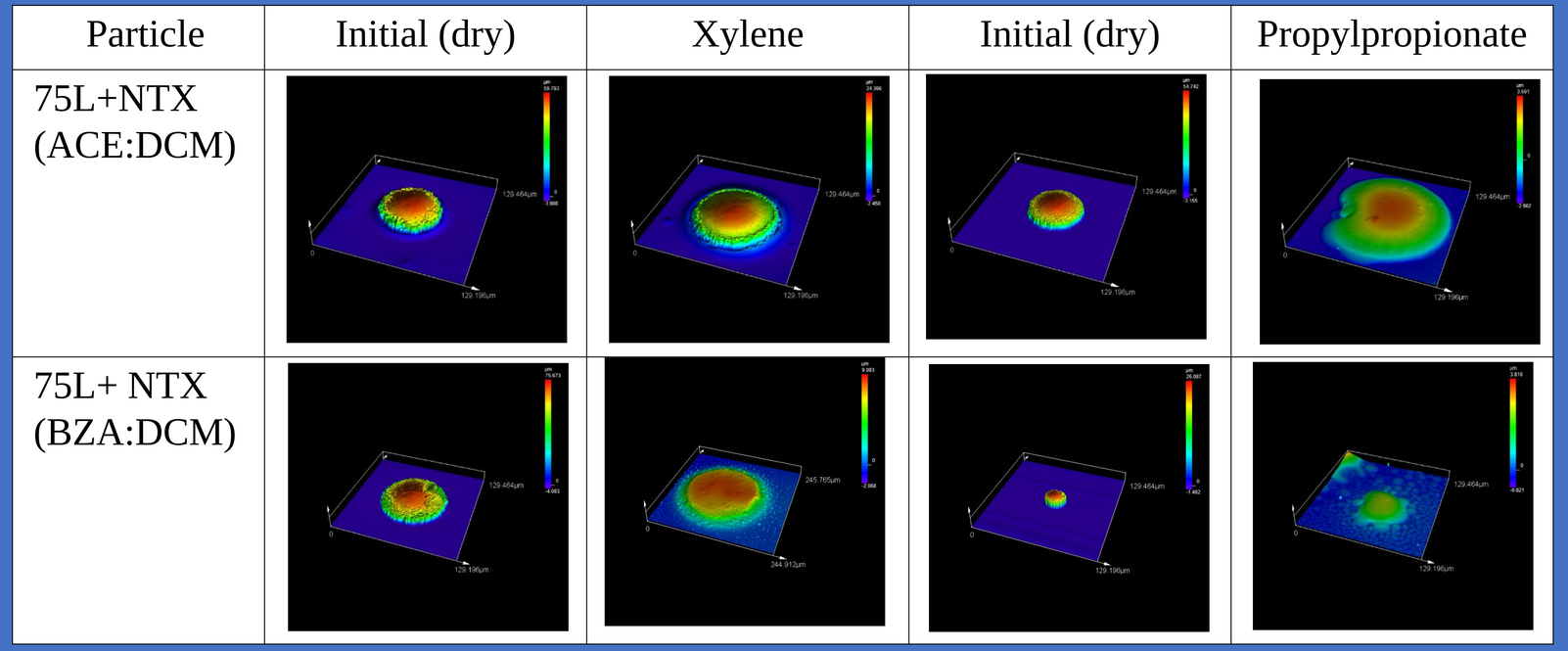

Figure 2. Examples of 3D scans of microparticles before and after exposure to indicated solvent.

Table 1. Examples of roughness parameters, dimensional parameters, and % change after exposure to indicated solvents.

Particle / Solvent (N) (mean ± SD)	Sa[µm] (arithmatical mean height)	Vmc[µm³/µm²] (core material volume)	Surface area ratio (Surface area/volume)
75L+NTX (BZA:DCM) (N = 27) (Dry, initial)	4.7 ± 4.0	1.6 ± 1.2	4.9 ± 1.5
Xylene Exposed (N = 6)	0.8 ± 0.5	0.8 ± 0.4	1.1 ± 0.0
Change	-53% ± 35%	-8% ± 56%	-80% ± 5%
Propylpropionate Exposed (N = 5)	0.2 ± 0.2	0.3 ± 0.2	1.0 ± 0.0
Change	-85% ± 22%	-75% ± 30%	-76% ± 7%
75L+NTX (ACE:DCM) (N = 30) (Dry, initial)	2.3 ± 1.1	1.4 ± 0.8	4.9 ± 1.5
Xylene Exposed (N = 6)	1.2 ± 1.2	0.6 ± 0.3	2.4 ± 1.2
Change (%)	-56% ± 37%	-58% ± 26%	2% ± 38%
Propylpropionate Exposed (N = 3)	0.2 ± 0.1	0.2 ± 0.0	1.0 ± 0.0
Change (%)	-636% ± 156%	-375% ± 63%	-428% ± 57%

Student's t-test was performed to evaluate the strength of statistical significance between the parameter change and the solvent used for NTX-loaded PLGA 75:25 microparticles manufactured using either ACE:DCM or BZA:DCM (**Table 2**). Depending on the solvent used, the parameters varied between the formulations showing either no statistical difference or statistically significant increases ($p < 0.05$). Polypropionate (10 mg/mL dissolution transition at the 80% lactide content, or 80% L) exhibited the strongest significant differences between the two microparticle batches made using different solvents and manufacturing conditions (**Fig 3**). This is thought to be due to its transition at 80% L being close to the lactide content of the PLGA (75% L). Use of a solvent which has a low solubility for the batches leads to minimal impact and the good solvents simply dissolve the microparticles, making the differentiation difficult.

Solvent (t-value)	Ssk	Sku	Sz [µm]	Sa [µm]	Sal [µm]	Smr(c) [%]	Sk [µm]	Vvc [µm³/µm²]	Vmc [µm³/µm²]	Spd [1/mm²]	Volume [µm³]	Surface Area [µm²]	Area [µm²]	Maximum height [µm]	Surface area ratio
Xylene (df = 10)	**1.0**	**-1.0**	**-0.6**	**0.2**	**4.7**	**1.0**	**2.6**	**2.0**	**2.0**	**0.5**	**-1.5**	**2.3**	**6.0**	**-7.8**	**-5.2**
Propylpropionate (df = 6)	**1.0**	**1.7**	**2.1**	**6.1**	**1.3**	**-0.4**	**4.9**	**6.8**	**7.7**	**1.8**	**0.9**	**0.9**	**2.9**	**2.6**	**10.7**
MTHF (df = 10)	**1.5**	**2.0**	**-3.7**	**-3.9**	**-4.0**	**-3.7**	**-2.0**	**-1.7**	**-2.1**	**-1.7**	**-0.5**	**0.1**	**-0.1**	**0.2**	**0.4**
Cycloheptanone (df = 4)	**-1.6**	**-0.6**	**-1.5**	**-1.5**	**0.3**	**1.4**	**-1.0**	**-1.3**	**-1.0**	**-1.2**	**0.9**	**1.1**	**1.2**	**-0.5**	**-0.9**
Butanone (df = 5)	**0.04**	-1.6	-1.6	-1.2	**2.9**	**2.6**	**-0.2**	**-0.3**	**-0.9**	**-9.2**	**-2.1**	**-1.2**	**8.2**	**-2.1**	**-1.7**

Acronyms: Skewness (Ssk), Kurtosis (Sku), Max height (Sz), autocorrel length (Sal), areal material ratio (Smr(c)), core height (Sk), core void volume (Vvc), peak density (Spd).

Table 2. t-scores for change (%) due to SASSI effect for selected parameters. Red indicates parameters significantly decreased for BZA:DCM relative to ACE:DCM, Blue is for parameters significantly increased for BZA:DCM relative to ACE:DCM, Parameters showing insignificant differences ($p \geq 0.05$) are in black. (Degrees of freedom (df) are specified in first column.)

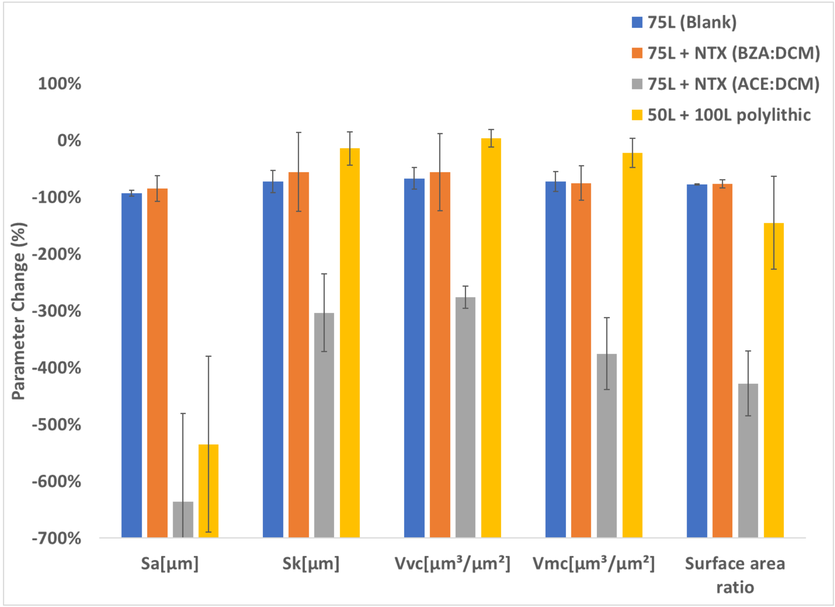

Figure 3. Roughness/dimensional parameter changes (%) after exposure to semi-solvent polypropionate for 1 min at 0 °C, mean ± SD, N = 3~6.

Conclusion

Measuring the particle morphology changes upon semi-solvent exposure can be used to evaluate manufacturing differences. This process is most effective if the selected semi-solvent has a transition L:G ratio close to that of the PLGA used to make the microparticles.

References

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