A RATIONAL APPROACH TO SPRAY DRYING MULTI-COMPONENT FORMULATIONS CONTAINING LOW-SOLUBILITY ACTIVES

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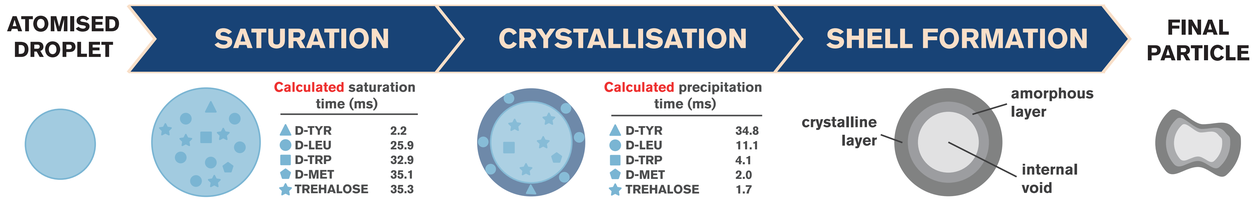
01 INTRODUCTION

- Complex formulations with design constraints are costly to develop.
- In this study, an *in silico* approach is taken to the design of multi-component D-amino acid formulations, to assist formulation development *a priori*.
- An equimolar quaternary D-amino acid formulation containing D-Leucine (D-Leu), D-Methionine (D-Met), D-Tryptophan (D-Trp) and D-Tyrosine (D-Tyr) has been found to have *in vitro* activity against *Pseudomonas aeruginosa* biofilm[1]. This will be used as a model formulation.

02 PREDICTED PARTICLE FORMATION

For this formulation, particle formation theory[2,3] predicts (see right):

- D-Tyr and D-Leu achieve saturation early on the surface, and crystallise;
- Trehalose remains amorphous;
- The final particle will likely have a crystalline shell that deforms or collapses.



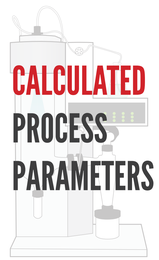
03 PROCESS DEVELOPMENT

Step A. Set design targets (right).

Step B. Apply particle formation and spray drying process models to design targets.

Step C. Adjust formulation and process design according to boundary conditions (far right).

1. **PRIMARY PARTICLE MMAD = 2µm**
2. **HIGH DISPERSIBILITY**
   - Rugose, hollow particles
   - Crystalline D-Leu as dispersibility agent
3. **LUNG DOSE FRACTION > 40%**
4. **> 5nM D-AMINO ACID CONCENTRATION ACHIEVED THROUGHOUT THE AIRWAYS SURFACE LIQUID**
5. **BIOPHARMACEUTICAL STABILITY AND PROTECTION**
   - Amorphous trehalose

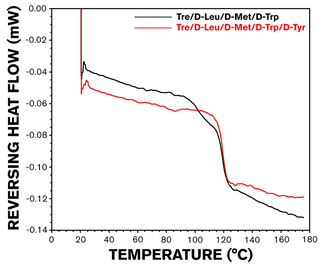


	Tre/D-Leu/D-Met/D-Trp (60:30:5:5 %w/w)	Tre/D-Leu/D-Met/D-Trp/D-Tyr (60:30:3.3:3.3:3.3 %w/w)
Inlet temperature (°C)	90	90
Outlet temperature (°C)	45	44
Drying gas flow rate (std L/min)	425	425
Atomising gas flow rate (std L/min)	32	9
Feed flow rate (mL/min)	3	3
Feed concentration (mg/mL)	27	10

04 RESULTS

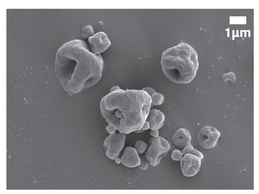
▶ **mDSC.** A glass transition associated with amorphous trehalose was identified at ~120°C.

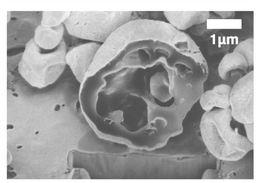
✓ Design Target #5

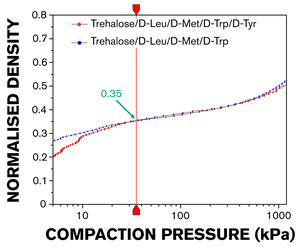


▼ **Focused Ion Beam Milling and SEM.** Rugose and hollow particles were produced, as predicted by particle formation theory.

✓ Design Target #2

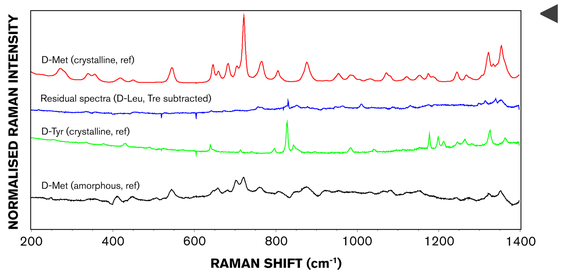






▲ **Compressed bulk density.** The normalised bulk densities are 0.35 for both formulations at 35.3 kPa, indicating the presence of an internal void space or porosity.

✓ Design Target #2



◀ **Raman spectroscopy.** The spectra for the formulation was deconvoluted using the majority components (trehalose and D-Leu), leaving a low intensity residual spectra.

- D-Leu was crystalline
- Indications that D-Tyr was crystalline.

✓ Design Target #2

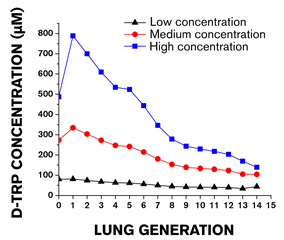
▶ **Aerosol properties.** The primary particle MMAD for both formulations are close to 2µm. The delivered lung dose fraction was high for both formulations, exceeding 40% of the loaded dose. D-Leu, with a mass fraction of 0.30, is an effective dispersibility agent.

✓ Design Targets #1,2 and 3

	TRE/D-LEU/D-MET/D-TRP	TRE/D-LEU/D-MET/D-TRP/D-TYR
$MMAD_{primary}$ (µm)	2.09 ± 0.14	2.60 ± 0.05
Emitted dose (% loaded dose)	53.8 ± 8.4	65.2 ± 8.0
Alberta Throat deposition (% loaded dose)	6.8 ± 1.7	9.1 ± 1.4
Lung dose fraction (% loaded dose)	47.0 ± 6.9	56.1 ± 7.2

▼ **Numerical lung deposition model.** Simulated deposition of the minority components (D-Trp, D-Met, D-Tyr) were predicted to exceed 5nM throughout lung generations 0-14 by at least three orders of magnitude, regardless of mucus production rate and mucociliary rates.

✓ Design Target #4



05 CONCLUSIONS

- An *in silico* approach to aerosol formulation and spray dryer process development was successful.
- The powders achieved all design targets, thus no further empirical iterations were required.
- This eliminates significant experimental work for complex formulations.

CHARACTERISATION METHODS

Modulated Differential Scanning Calorimetry	Modulation ± 0.618°C per 60s, temperature equilibration at 20°C for 30 mins, temperature ramp from 20 to 180°C at 2°C/min.
Low-frequency-shift Raman spectroscopy	Custom instrumentation[4]
Compressed bulk density	Uniaxial low-pressure compaction of powder samples at 35.3 kPa. Results normalised for true density of the formulation.
Primary particle aerodynamic diameter	Powder entrained into Venturi air flow by disperser unit, and into the Aerodynamic Particle Sizer.
In vitro aerosol deposition	Alberta Idealised Throat assembled with a filter unit. 20mg of powder loaded into an Aeroliser dry powder inhaler, and discharged into the throat-filter assembly at a flow rate of 60 L/min ($n = 3$).

ACKNOWLEDGMENTS

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