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Production of Amorphous Solid Dispersions at Low Temperature by Electrostatic Spray Drying

Delivery of Thermolabile Compounds with Enhanced Bioavailability

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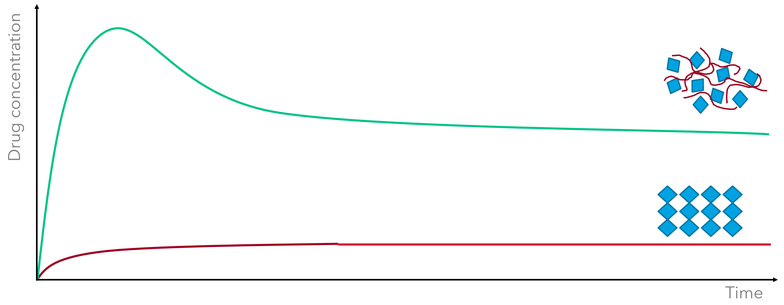
BACKGROUND

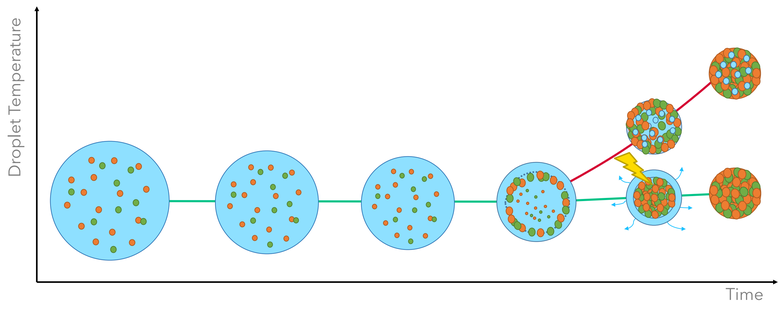
Amorphous solid dispersions (ASDs) have been the subject of attention as a way of increasing the bioavailability of poorly water-soluble therapeutic agents and stabilizing proteins[1].

While the lack of a crystal lattice that must be disrupted increases the dissolution rate, kinetic entrapment and H-bonding provide protein stabilization.



Spray drying is often used to produce amorphous products by solvent evaporation, but the required high temperatures make it unsuitable for thermolabile compounds.

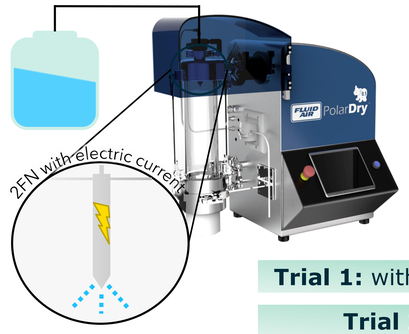
Electrostatic spray drying involves the application of an electric charge during spraying. Since the solvent has usually the largest dipole moment in the mixture, it moves to the outer surface of the drying droplets due to repulsion forces[2]. The process can thereby be carried out at lower temperatures than conventional spray drying since there isn't a decrease in the drying rate after shell formation occurs with solvent still inside.



This approach has shown promising results in the past in monoclonal antibody encapsulation[3], but its application can be extended to the manufacture of spray dried powders of thermolabile compounds for inhalation. As a proof of concept, low temperature spray drying of a trehalose solution with and without electric charge were carried out, and the differences of the products are highlighted.

REFERENCES: [1] AboulFotouh K, Zhang Yi, Maniruzzaman M, Williams III RO, Cui Zhengrong: Amorphous solid dispersion dry powder for pulmonary delivery: Advantages and challenges. International Journal of Pharmaceuticals 2020, 587: 119711 [2] Jayaprakash P, Maudhuit A, Gaiani C, Desobry S: Encapsulation of bioactive compounds using competitive emerging techniques: Electrospraying, nano spray drying, and electrostatic spray drying. Journal of Food Engineering 2023, 339:111260 [3] Mutukuri TT, Maa YF, Gikanga B, Sakhnovsky R, Zhou QT: Electrostatic spray drying for monoclonal antibody formulation. International Journal of Pharmaceuticals 2021, 607: 120942

METHODS



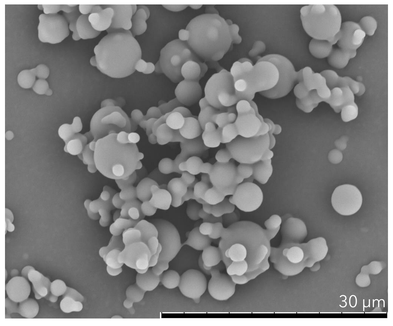
Solutions of 10% w/v of trehalose in water were prepared and spray dried using a PolarDry 0.1 (Fluid Air, France) electrostatic spray dryer, which allows to apply an electric current to its two-fluid nozzle.

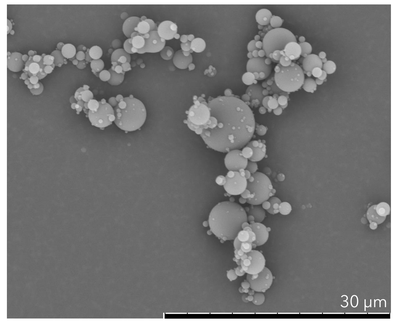
Trial 1: without applied voltage (regular SD)

Trial 2: applied voltage of 15 kV

F_{drying} = 6 m³/h
F_{feed} = 1.7 g/min
$d_{nozzle\ tip}$ = 0.7 mm
P_{nozzle} = 1.25 bar
T_{in} = 90 °C
T_{out} = 35 °C

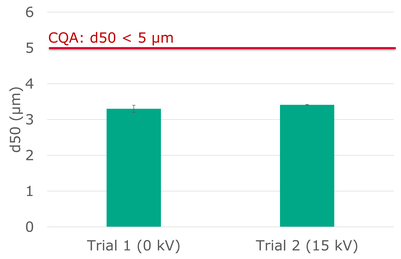
Particle size by dry laser diffraction
Residual water content by gravimetry in vacuum dryer
Particle morphology by SEM
Crystallinity after 40 days by XRPD

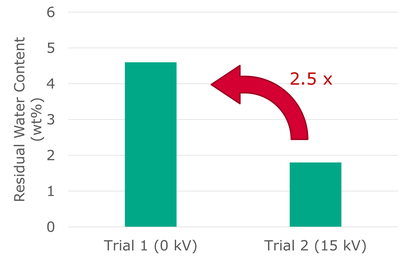




- SEM pictures of Trial 1 (left) show fused particles suggesting incomplete drying in contrast with Trial 2 (right), where perfectly spherical particles can be observed.

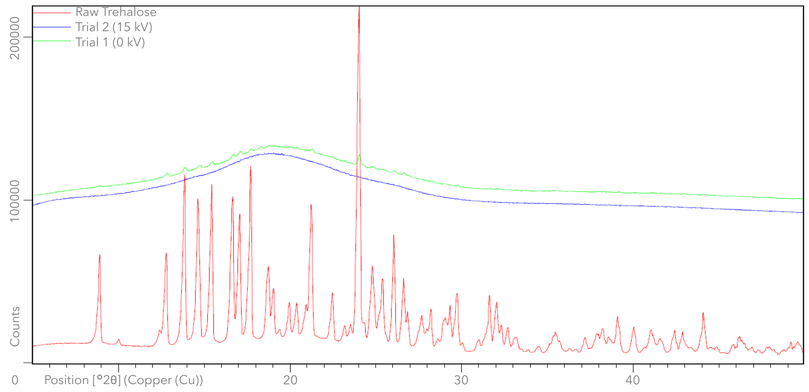
RESULTS





- Both trials exhibit a particle size suitable for inhalation: d_{50} of 3.30 µm for Trial 1 and 3.41 µm for Trial 2.
- Significant difference in residual water content: 4.6 wt% in Trial 1 vs 1.8 wt% for Trial 2.

Water has a plasticizing effect, promoting crystal growth and ASD instability!



- XRPD diffractogram after 40 days at 5 °C shows trehalose crystallinity peaks for Trial 1 (green), but not for Trial 2 (blue) → **stable amorphous product by ESD!**

CONCLUSIONS AND FUTURE WORK

- Dry amorphous powders were obtained by electrostatic spray drying with an outlet temperature of 35 °C, whereas traditional spray drying was not capable of providing fully dry particles.
- Electrostatic spray drying with trehalose (high glass transition temperature non-reducing sugar) can be looked at as the basis for a platform to produce ASDs for inhalation with thermolabile compounds (and potentially biologics).
- Moisture uptake prevention at room conditions can be achieved by improving the formulation with a surface modifier such as an amino acid or a lipid.
- The optimization of electrostatic spray drying and the formulation platform for the production of amorphous solid dispersions for inhalation should be carried out envisioning its broad applicability through a quality by design approach.

ACKNOWLEDGEMENTS

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