Addition of leucine to trehalose-containing microparticles enhances environmental robustness against moisture for nasal vaccination applications

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Introduction

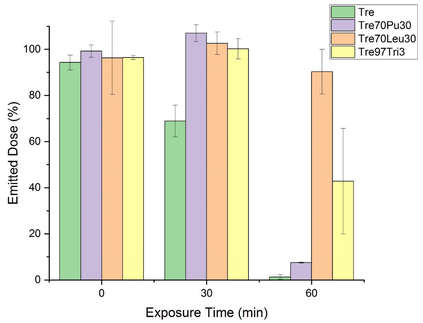
- Nasal dosage forms, e.g. nasal dry powder vaccines, have attracted increasing research interest due to their needle-free administration, no need for preservatives, and low storage and transportation requirements.
- High environmental robustness of dry powder vaccines is important to ensure efficacy is maintained when powders are exposed to humid environments during use.
- This study investigated the environmental robustness of various two-component excipient systems when exposed to high humidity environments.

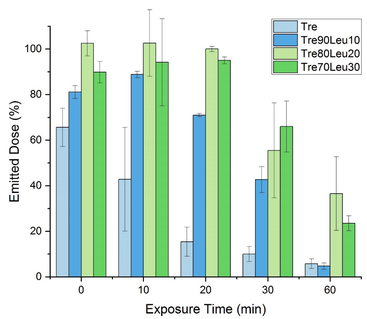
Materials & Methods

- Three two-component excipient systems – **trehalose/leucine**, **trehalose/trileucine**, and **trehalose-pullulan** – were selected as the candidate systems for enhanced environmental robustness compared with pure trehalose. According to the particle formation theory, leucine, trileucine and pullulan are expected to form protective outer shell covering the inner trehalose core, leading to enhanced environmental robustness.
- A monodisperse spray drying setup which was recently scaled up using a dual-orifice plate was used to manufacture the model particles for this study [1]. The inlet temperature was 80 ± 1 °C and outlet temperature was 56 ± 1 °C. The predicted outlet relative humidity (RH) was ~2%. The moisture contents of all spray-dried particles before exposure to moisture were expected to be minimal in this study [2].
- The sample powders were filled into size 3 hydroxypropyl methylcellulose capsules (Quali-V®-I, Qualicaps, Inc., Madrid, Spain) in a dry environment. The powder mass in each capsule was in the range of 20 - 40 mg. The filled capsules were closed and kept in a dry envirnment or in a humid environment (90% RH and 25 °C) for 10, 20, 30 and 60 min before emitted dose measurements.
- Powder dispersibility of the preconditioned samples was characterized using the emitted dose from a dry powder inhaler (Seebri® Breezhaler®, Novartis International AG, Basel, Switzerland). The actuation flow rate was set to a constant value of 60 or 15 L/min for 2.4 s. The capsules were pierced manually in the dry powder inhaler before actuation. Emitted dose, defined as the mass fraction of the emitted powders over the total filled powders, was measured.
- Particle morphology was analyzed by scanning electron microscopy (SEM). Solid phase of the material in the spray-dried particles was analyzed by Raman spectroscopy.

Results

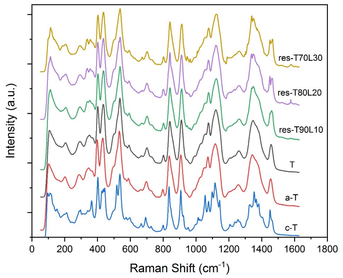
Emitted dose measurements



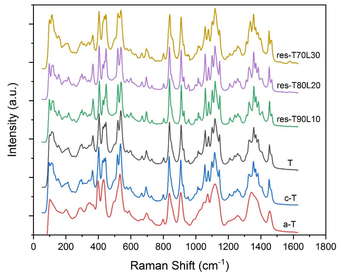


- **Trehalose/leucine maintained the highest emitted doses when exposed to moisture among the three two-component excipient systems**
- **10% leucine fraction enhances powder dispersibility against moisture after only 10 min exposure to 90% RH and 25 °C**

Solid phase analysis



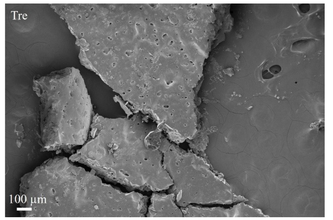
30 min exposure to 90% RH and 25 °C



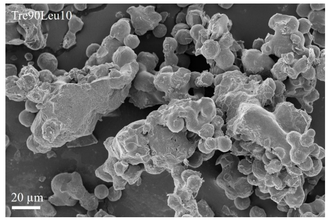
60 min exposure to 90% RH and 25 °C

Particle morphology analysis

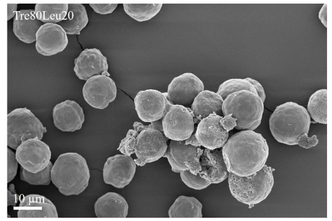
60 min exposure to 90% RH and 25 °C



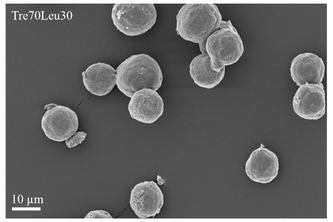
Trehalose



Trehalose(90%)/leucine(10%)



Trehalose(80%)/leucine(20%)



Trehalose(70%)/leucine(30%)

- **Compared with pure trehalose, there was less material bridging and fusing between trehalose/leucine particles, explaining their higher emitted doses**
- **Higher leucine fraction reduces the material bridging and fusing further, leading to better protection against moisture**
- **Trehalose remained amorphous for all formulations after 30 min exposure to moisture (left), but became crystalline for all formulations after 60 min exposure to moisture (right)**
- **The addition of leucine does not prevent the crystallization of trehalose under the chosen conditions**

Conclusions

- **Trehalose/leucine** system was the most promising excipient system in providing environmental robustness for particles in a size range suitable for nasal delivery of vaccines.
- As low as **10%** leucine fraction enhances powder dispersibility after only **10 min** exposure to 90% RH and 25 °C; higher leucine fraction provides better protection against moisture.
- Leucine may not prevent the crystallization of trehalose, but it can still enhances powder dispersibility even at a high moisture content by reducing the material bridging and fusing between particles.

References

1. Wang, Z., Ordoubadi, M., Wang, H., & Vehring, R. (2021). Morphology and Formation of Crystalline Leucine Microparticles from a co-Solvent System using Multi-Orifice Monodisperse Spray Drying. *Aerosol Science and Technology*, (just-accepted), 1-21.
2. Wang, Z., Wang, H., & Vehring, R. (2021). Leucine Enhances the Dispersibility of Trehalose-Containing Spray-Dried Powders on Exposure to a High-Humidity Environment. *International Journal of Pharmaceutics*, 120561.

Acknowledgements

Particle Engineering
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