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Design of spray-dried TNF-α siRNA-loaded LPNs with high aerosol performance for treatment of COPD

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Introduction:

Therapeutics based on siRNA are highly target-specific and promising for the treatment of chronic obstructive pulmonary disease (COPD)[1,2]. Local delivery of siRNA to the lungs constitutes a promising new area in drug delivery. The aim of the present study was to design inhalable formulations of siRNA-loaded lipidoid-polymer hybrid nanoparticles (LPNs) by spray drying (SD) using the sugars trehalose and dextran as stabilizing excipients and the amino acid leucine as dispersion enhancer.

Hypothesis:

The aerosolization properties of the powder-based solid dosage forms of TNF-α siRNA-loaded LPNs can be improved by using a combination of amino acid and sugars during the spray drying process.

Materials and Methods

TNFα siRNA-loaded LPNs were prepared by the double emulsion solvent evaporation method (DESE)[3]:

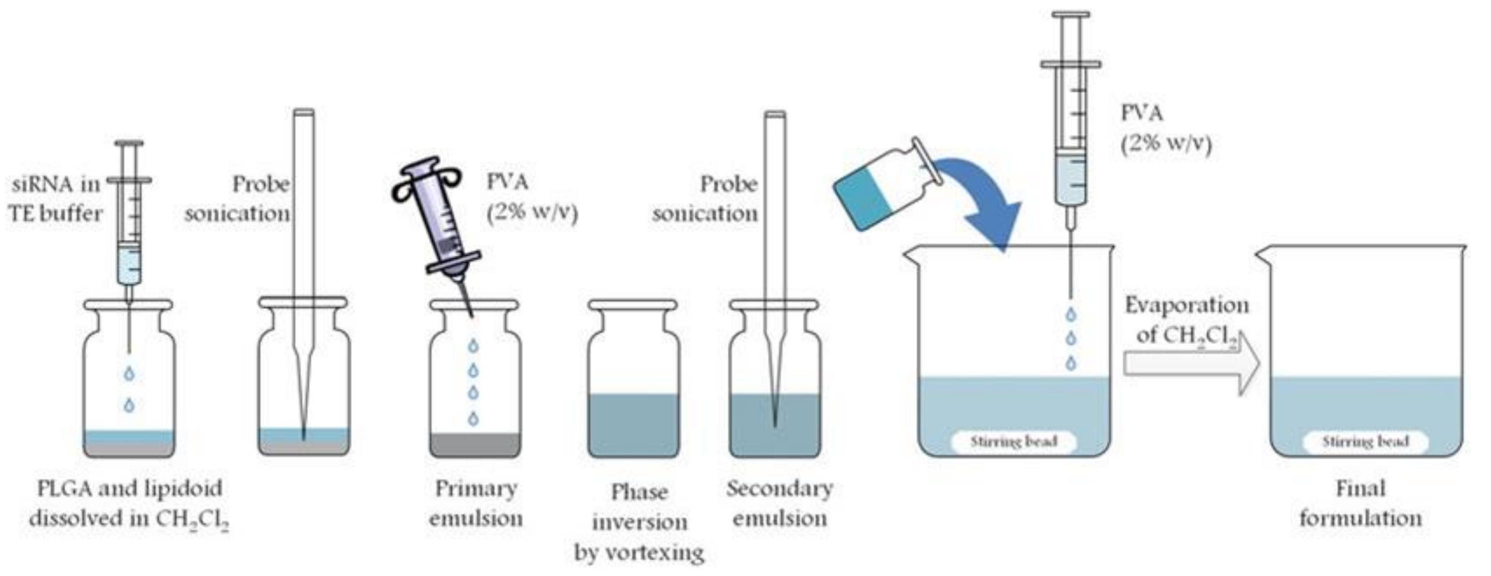

Fig.1. Illustration of the DESE used for the preparation of LPNs.

Spray drying of LPNs into nanocomposite microparticles:

- Investigate the effect of different ratio of sugars and amino acid (n=3)

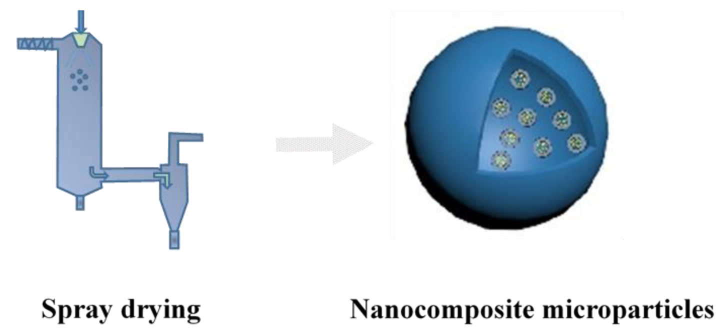

Fig.2. Spray drying

Table 1 Processing Parameters for Spray Drying [4]

Process parameter	Conditions
Outlet temperature	51°C
Inlet temperature	83°C
Feed rate	1.53 ml/min
Atomizing airflow	742 l/h
Feedstock concentration	25 mg/ml
Aspirator	90%
Loading	5%

Results

Powder yield, moisture and aerodynamic properties of the spray-dried LPNs

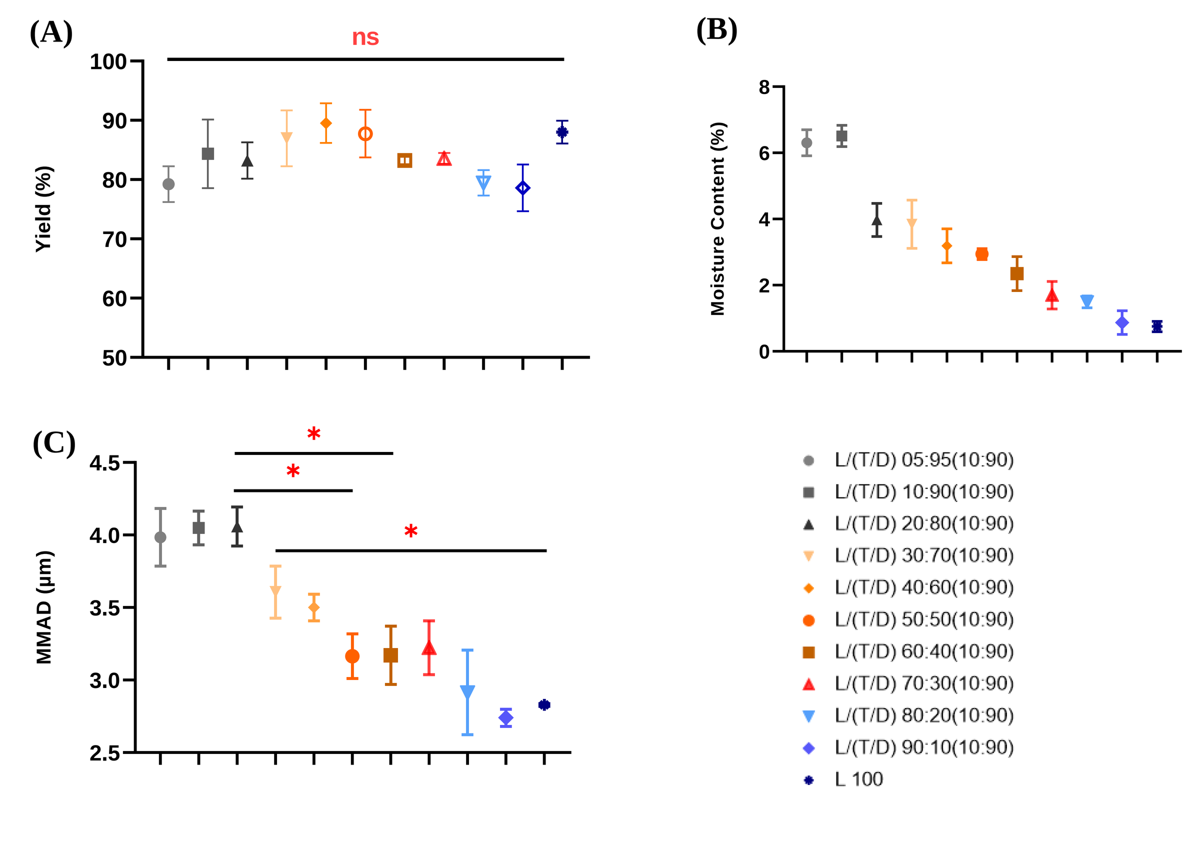

Fig. 3. The yield (A), moisture content (B), and mass median aerodynamic diameter (MMAD) (C) of spray-dried LPNs (mean ± SEM, n=3).

Higher content of leucine influences the surface morphology and solid state characteristics of spray-dried LPNs

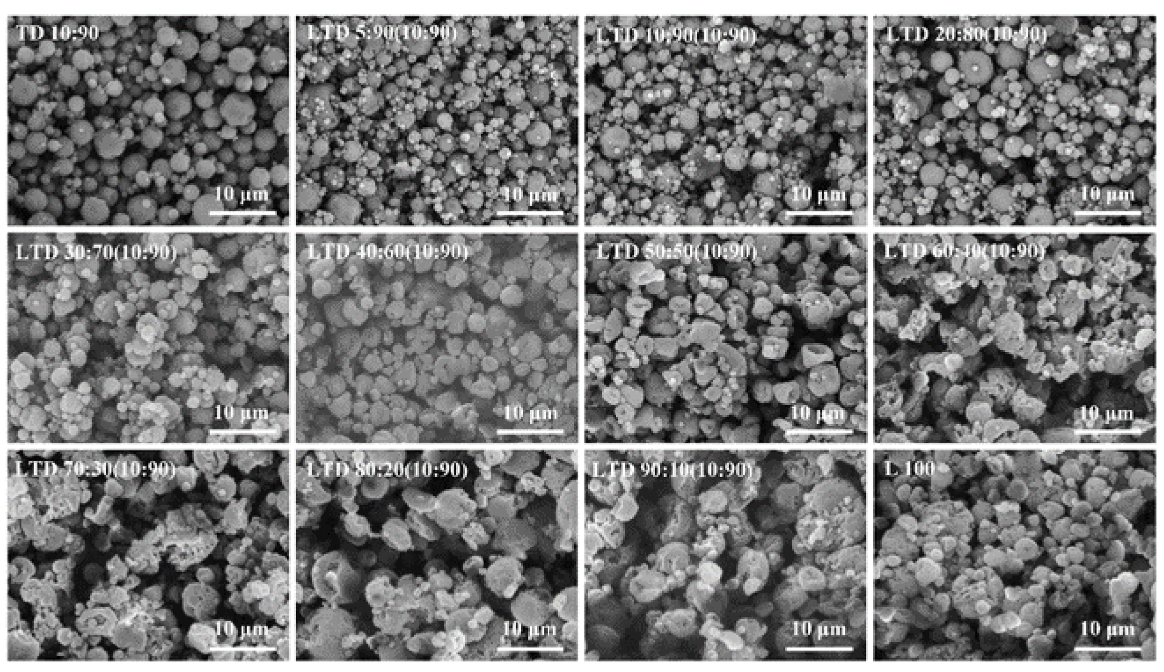

Fig. 5. Scanning electron microscope images of spray-dried LPNs. The scale bare represent 10 µm.

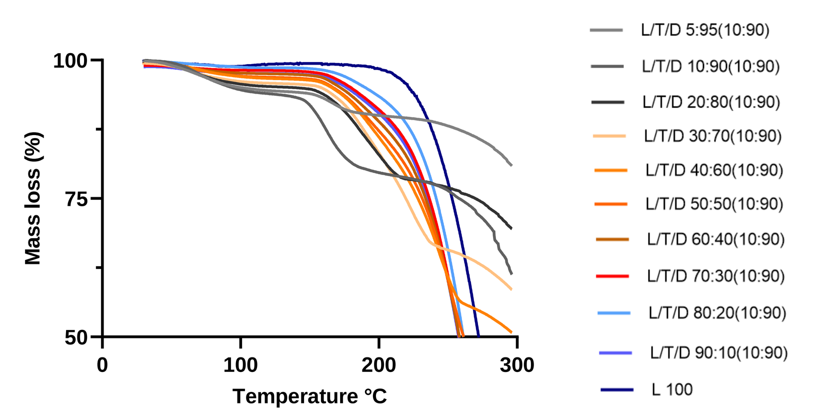

Fig. 6. Thermal gravimetric analysis of the spray-dried LPNs

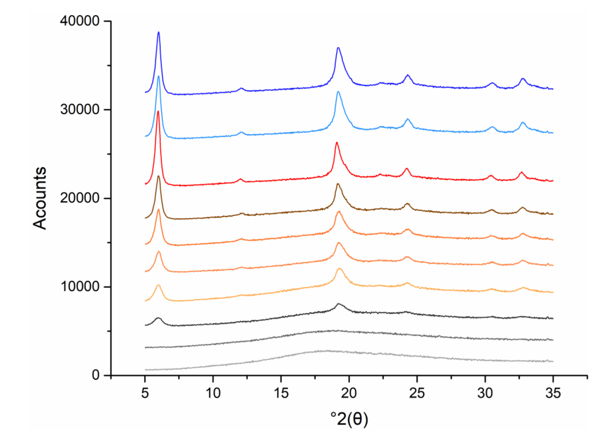

Fig. 7. X-ray powder diffraction profiles of spray-dried LPNs

Spray drying influences the physicochemical properties of the LPNs

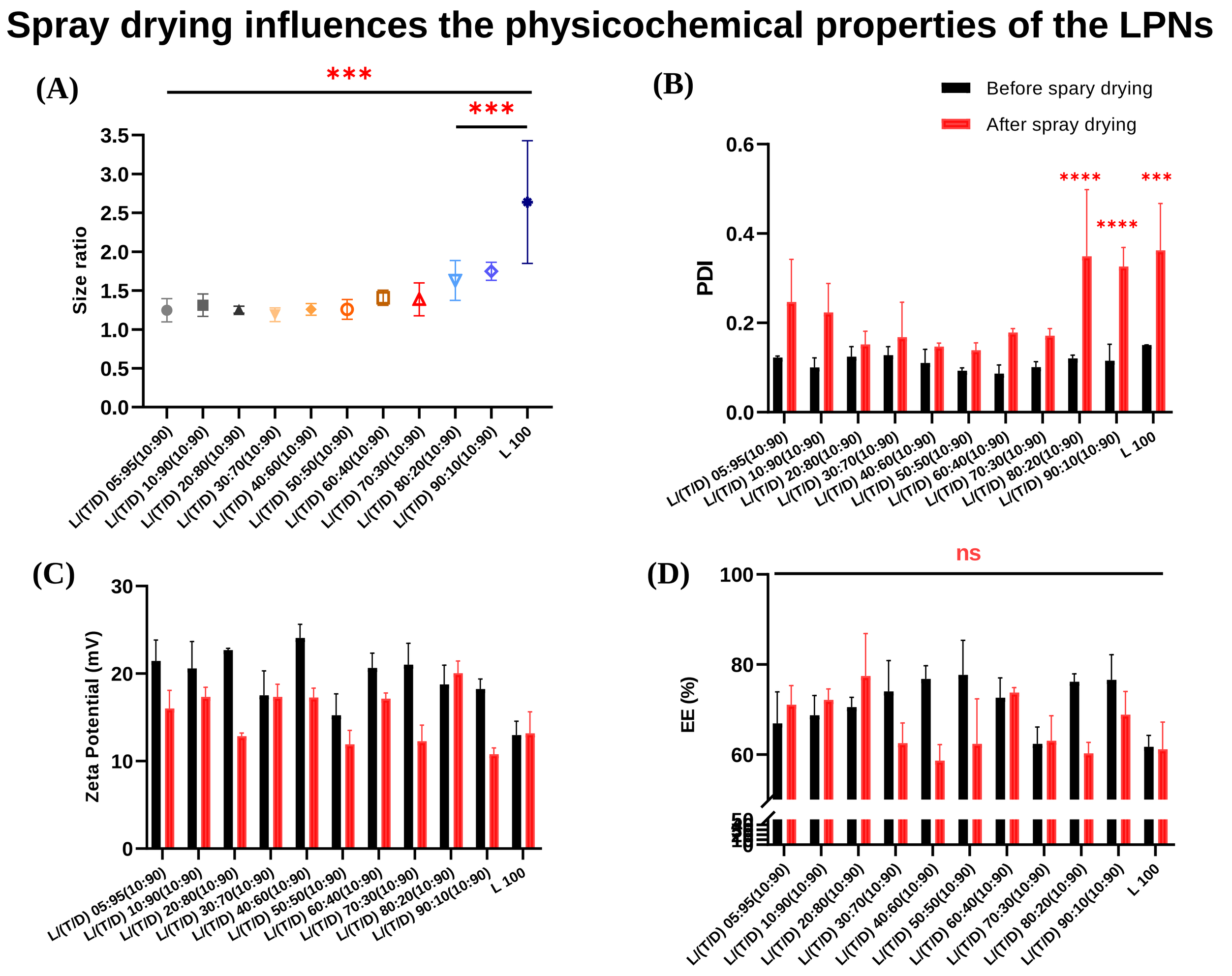

Fig. 4. The size (A), PDI (B), zeta potential (C) and encapsulation efficiency (D) before and after spray drying of LPNs (mean ± SEM, n=3).

The flyability of the powder was enhanced with the leucine and sugars combination

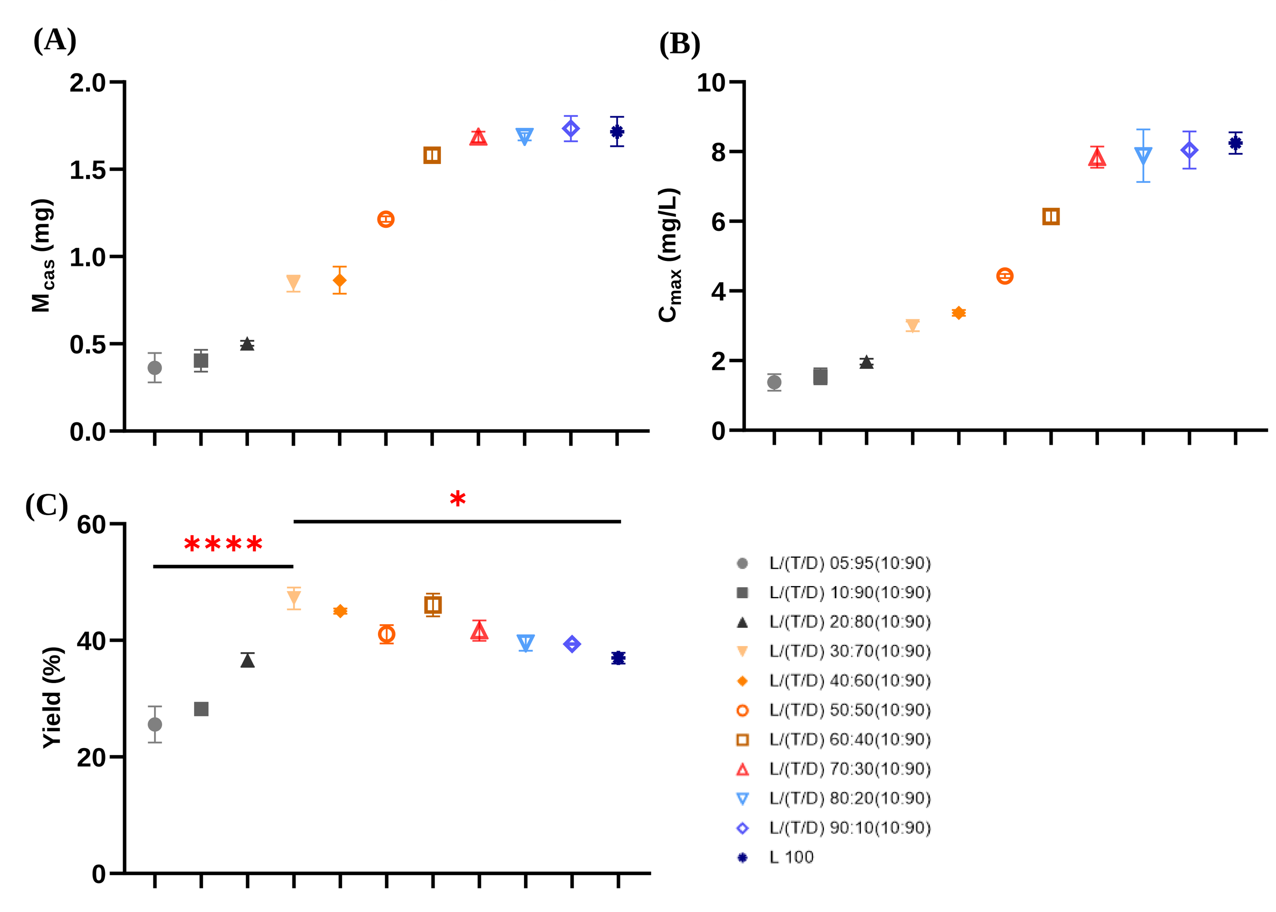

Fig. 8. The accumulated dose (M_{cas}) (A), the maximum concentration in Casella (C_{max}) (B), and yield in PreciseInhale™ (PI) system

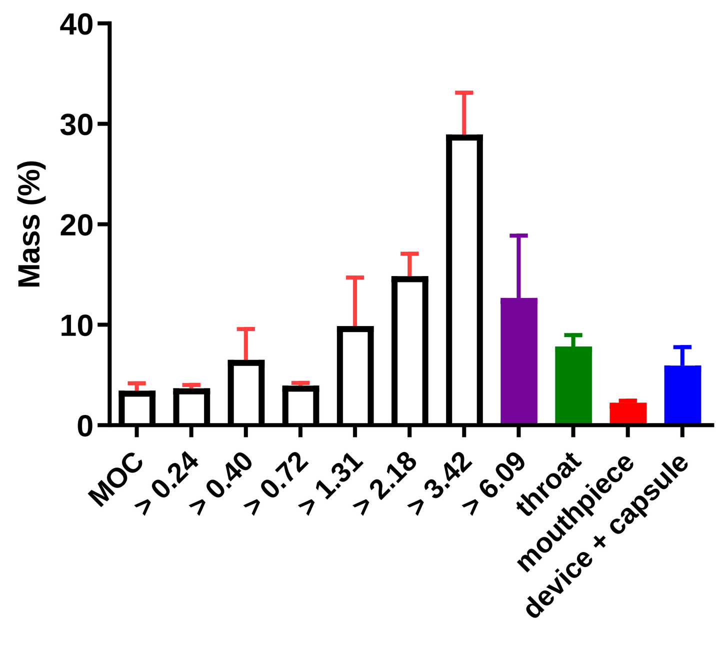

Fig. 9. Deposition of L/(T/D) 40:60(10:90) in different stages of the Next Generation Impactor (NGI) at an air flow rate of 100 L/min (mean ± SEM, n=3).

Results of NGI

- Emitted dose: 96%
- Fine particle fraction: 71%.

Conclusions

1. Inclusion of the dispersion enhancer leucine into the trehalose:dextran sugar mixture of spray dried excipients enhances the aerosol performance of the resulting powders in PreciseInhale system.
2. The leucine content should be kept below 60% because leucine influences the particle size and distribution after spray drying, as well as the surface morphology.
3. The highest aerosol performance was achieved for the formulation containing 40% leucine and 60% Trehalose/Dextran (10:90), hence it is promising for *in vivo* lung powder deposition studies.

References:
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3. Thanki, Kaushik, et al. Springer New York. (2019), 141-52.
4. Dormenval, Cypriane, et al. Pharm. Res. 36.10 (2019): 142.

Acknowledgements: We gratefully acknowledge the financial support from the Novo Nordisk Foundation, Denmark (grant no. NNF17OC0026526) and Independent Research Fund, Denmark (grant no. DFF-4184-00422). We acknowledge the China Scholarship Council (CSC) for the Scholarship to You Xu (201906210064).