Dry Powder Microparticles with Redispersible Clarithromycin Nanocrystals for High Dose Inhalation

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1 Concept

Nanocrystals (NC)

- Clarithromycin is poorly water soluble and needs a high lung dose
- Nanocrystals have an increased dissolution velocity
- In some cases increased saturation solubility

→ Higher bioavailability, lower drug dose for efficient therapy, pulmonal antibiotic therapy possible

Trojan particles (TP)

- Inhalable microparticles with hollow core
- Nanocrystals + matrix material = shell → min. 70 % API
- Release of NC to the lung fluid
- Shall enable high-dose therapy

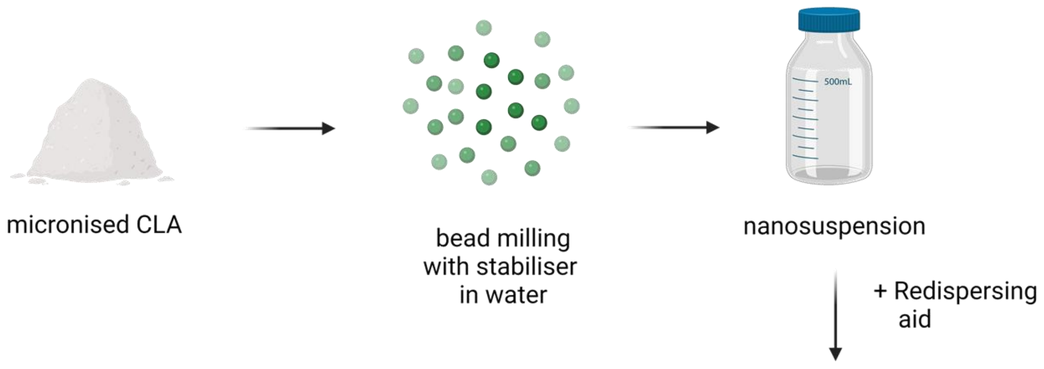
Redispersing aid

- Improving redispersion of Trojan particles
- Has to be lung tolerable

→ Solubilising agents (lyotropic substances, non-ionic surfactants, inclusion complexes)

Initial formulation (IF)	**Optimised formulation (OF)**
Clarithromycin (CLA) = model drug (poorly soluble) Hydroxypropyl methylcellulose (HPMC) = stabiliser during NC preparation and matrix material	CLA HPMC + Redispersing aid

2 Methods



Drying of NC suspension

To investigate multiple additives simultaneously the formulations were freeze-dried. The most promising formulation was spray-dried with the selected additive and further investigated.

Production of lyophilisates:

Drying step	Temperature	Pressure	Duration
freezing	- 30 °C	1 bar	24 h
1st drying	- 10 °C	2.56 mbar	48 h
2nd drying	10 °C	→ 0 mbar	24 h

Freeze dryer: ALPHA 1-4; Martin Christ, Germany

Production of Trojan particles:

Spray-dryer	BÜCHI Mini Spray-Dryer B-290 (Switzerland)
Solid content of feed	2 % solids
Nozzle	Two fluid nozzle, 2 mm inner diameter
Inlet temperature	110 °C
Outlet temperature	59-61 °C
Aspirator rate	100% (35m³ /h)
Airflow	473 l/h

Characterisation

Dynamic light scattering

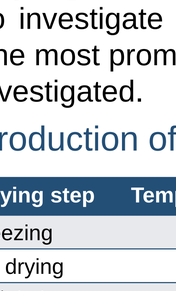
Nanocrystal size:

- Zetasizer Nano ZS (Malvern Instruments Ltd., UK)
- 1:100 dilution with particle-free water

Redispersibility:

- Dried amount of water added
- 1 min stirrring at 1200 rpm
- Size measurement like NC size

Laser diffraction (LD)



- HELOS® (Sympatec GmbH, Germany)
- RHODOS: particle size distribution of the dried powder at 3 bar dispersion pressure
- INHALER: dispersion capability of the device for these powders
- Flow rate of 37.4 L/min ≙ 4 kPa pressure drop
- TwinMax (Hovione Technology Ltd., Ireland) as novel inhalation device for high dose applications
- 20 or 50 mg was filled in one of the cavities with a spatula
- FPF = amount of particles < 5 µm in PSD

Acknowledgements
Thanks to Hovione Technology for providing the TwinMax.
Figures created with BioRender.com.

3 Results

Redispersibility of lyophilisates with various additives

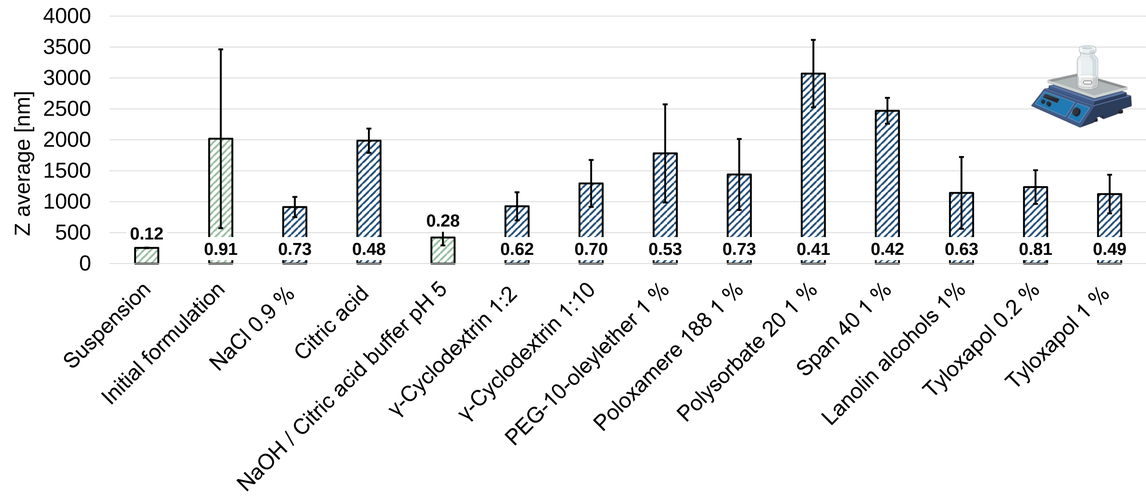


Figure 1: Z average of the redispersed lyophilisates. n=3, labelling = PDI, bars = SD.

→ The lower the Z average, the PDI and the SD the more effective the additive

It is presumable, that sodium citrate as a lyotropic salt enhances the hydrophobicity of the HPMC. The more hydrophobic HPMC as stabiliser of the nanosuspension in turn interacts more intensively with the CLA nanocrystals and stabilises them more efficiently.

Redispersibility of the Trojan particles

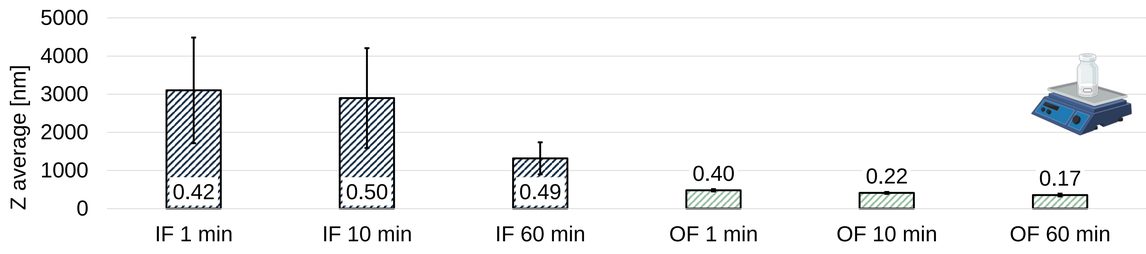


Figure 3: Z average of the redispersed spray-dried formulations, labelling = PDI, n=3, bars = SD

- Even after one hour no dispersion of the initial formulation
- Properties of HPMC not useful to guide the disintegration of the primary microparticles in NC
- After one hour the particles of the OF (355 nm) are in the same size range as the fresh nanosuspension (254 nm) and the redispersed lyophilisate (422 nm)

This proved an adequate redispersing capability of the buffer and showed that results were transferable from freeze-drying to spray-drying.

Morphology of the Trojan particles

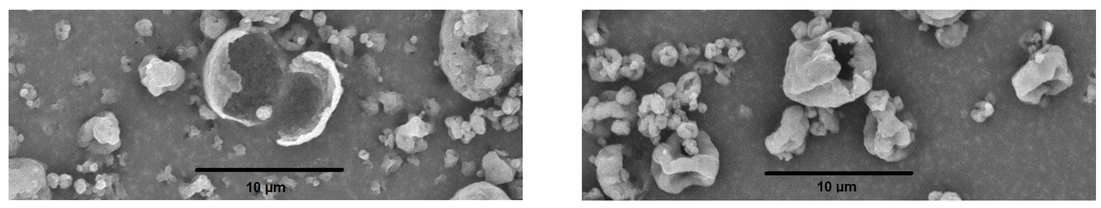


Figure 2: SEM picture of the spray-dried IF (left) calc. API amount: 88 %, OF (right) calc. API amount 71 %

→ IF & OF contain TP, mostly spherical particles, more particles of OF are wrinkled

Particle size and fine particle fraction (FPF)

Measurement	X_{10} [µm]	X_{50} [µm]	X_{90} [µm]	FPF [%]
Lyophilisate OF RHODOS	3.69	24.66	93.47	13.90
IF RHODOS	0.60	1.99	4.87	90.93
OF RHODOS	0.61	2.58	6.26	81.83
IF INHALER TwinMax 20 mg	1.69	4.45	50.27	54.47
OF INHALER TwinMax 20 mg	2.95	12.17	43.16	27.21
IF INHALER TwinMax 50 mg	6.20	47.03	114.14	22.21
OF INHALER TwinMax 50 mg	5.20	38.49	99.56	15.05

Table 2: Particle size and fine particle fraction (FPF, particle fraction < 5 µm) determined by laser diffraction, n=3

- OF results in lower FPF, needs optimisation
- For both formulations, the FPF determined with 50 mg powder was lower than the one determined with 20 mg

Higher amounts of powder are more difficult to disperse. The FPF measured with LD should not be equated to an FPF determined by aerodynamic characterisation. Hollow particles behave in the airflow like a dense particle with a much smaller diameter, leading to possibly higher aerodynamic FPF.

Conclusion + outlook

Adding buffer to the nanosuspension facilitates proper redispersion of the dried nanosuspension. The API amount was reduced from 88% (IF) to 71% (OF) due to the addition of further excipients, but is still suitable for a high-dose formulation.
The FPF measured by LD decreased with the addition of the buffer salts. This could be caused by stronger hydrophilic interactions of the TP or the slightly larger particle size after spray-drying. Ongoing work focuses on aerodynamic characterisation and optimisation of FPF.

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