Simultaneous nasal and lung delivery of antiviral metallodrug using dual targeting powder formulation

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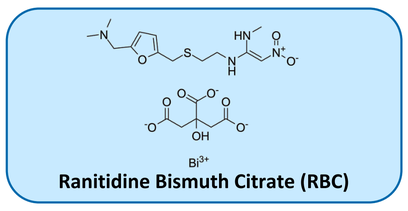
Introduction

Metallodrug - Ranitidine Bismuth Citrate (RBC)

Approved treatment: Helicobacter pylori infection → **Repurposing** → **Proposed treatment:** Anti-SARS-CoV-2 agent[1]

- Well-established safety profile
- Low systemic absorption
- Poor lung distribution[2]



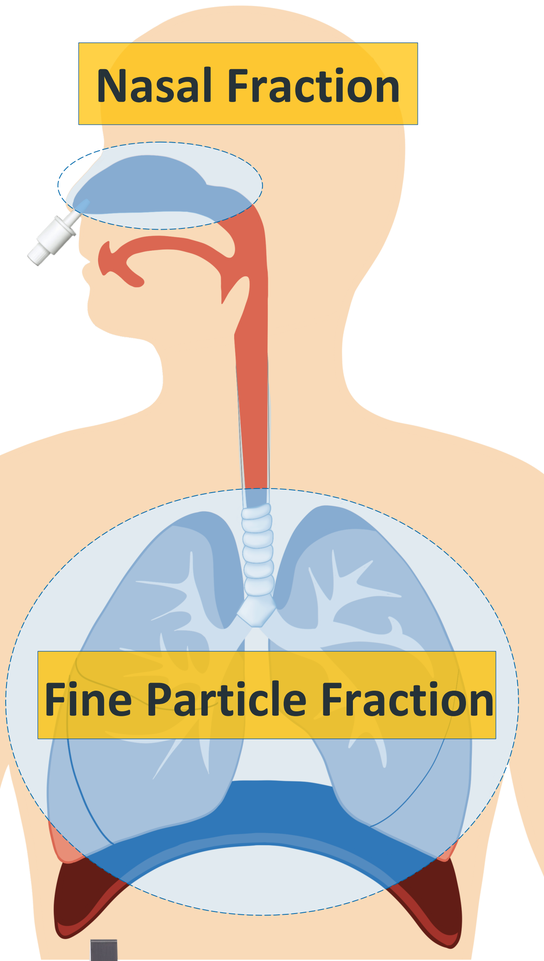
Ranitidine Bismuth Citrate (RBC)

Available dosage form: Oral Tablets → **Reformulation** → **Proposed dosage form:** Intranasal Dry Powder

Objectives

- Develop dual targeting formulation[3] of RBC.
- Determine particle size and aerosol deposition profile.
- Investigate pharmacokinetic profile of RBC in mice by intratracheal administration.

Dual targeting formulation enables simultaneous nasal and pulmonary delivery using nasal powder device.

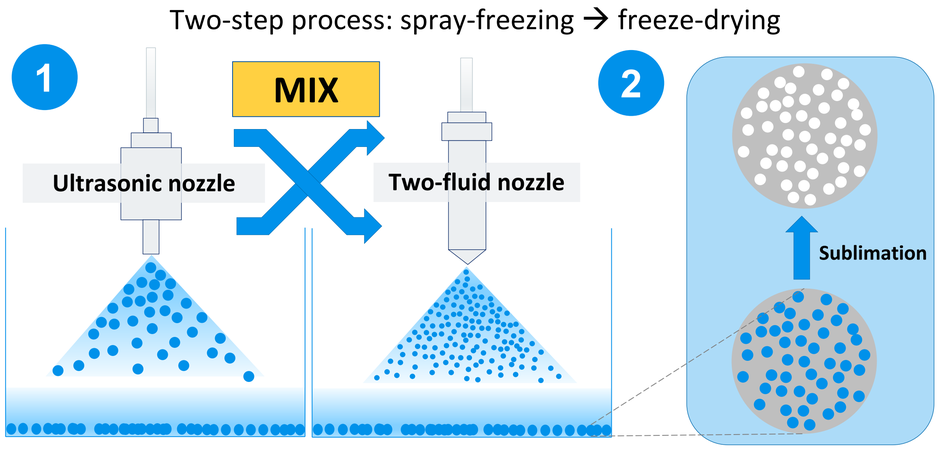


Methods

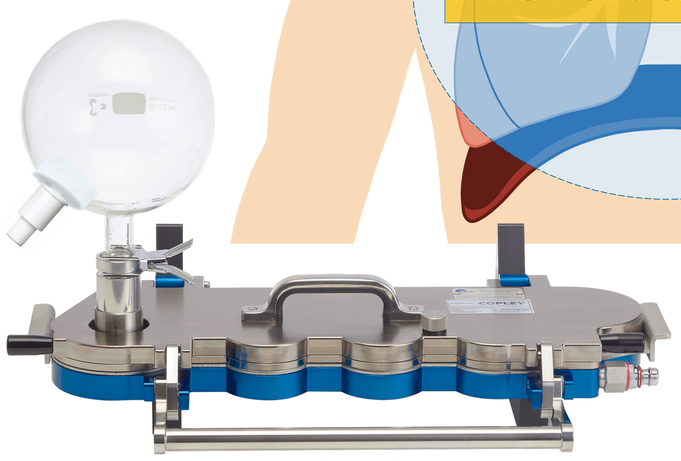
Parameters	Formulation
RBC content	20 % w/w
Mannitol	70% w/w
L-leucine	10 % w/w
Total solute concentration	2 % w/v
Primary drying temperature	-40 °C for 40 h
Secondary drying temperature	20 °C for 20 h

Spray freeze drying (SFD)

Two-step process: spray-freezing → freeze-drying



Mixed at a 1:1 mass ratio using Turbula® shaker-mixer type T2F



Aerosol performance
Dispersed with Aptar UDS Powder Nasal Spray

Results

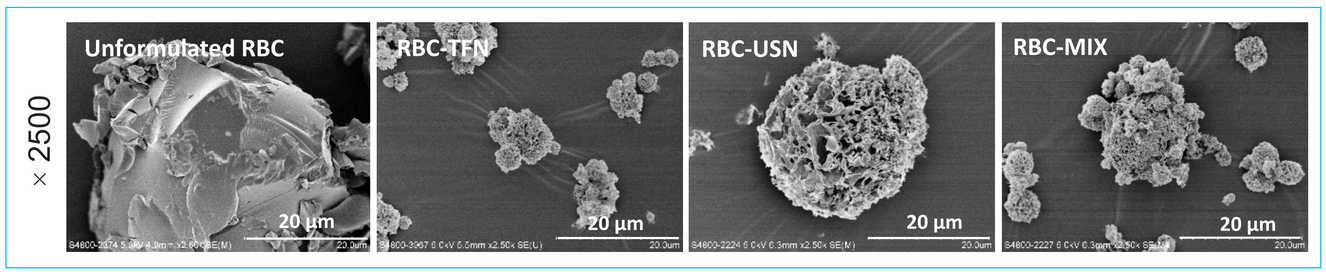
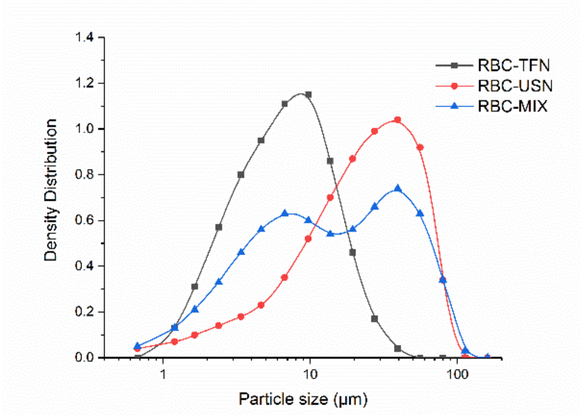
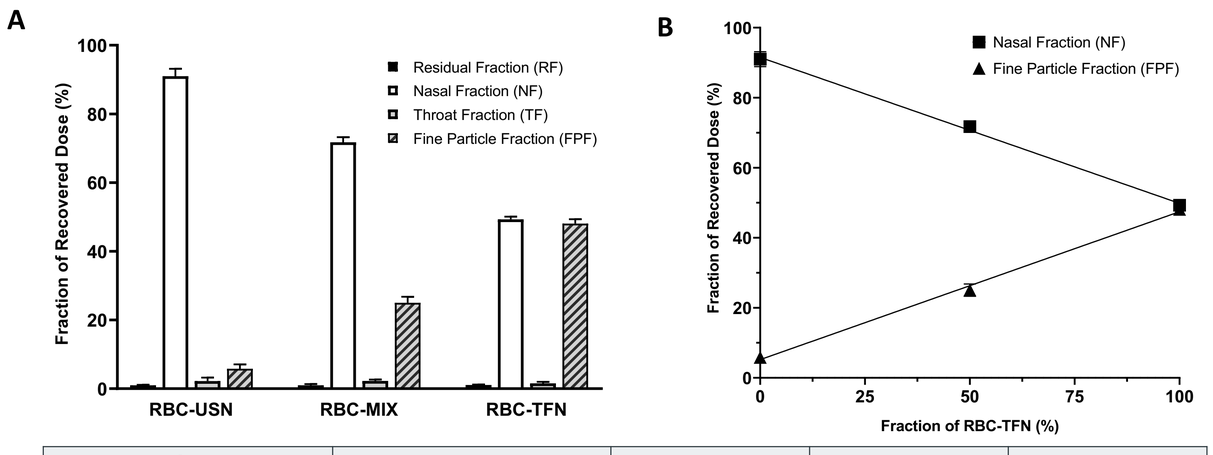


Figure 1 - Scanning electron microscopy (SEM) images of RBC formulations; RBC-TFN – produced with two-fluid nozzle; USN – produced with ultrasonic nozzle, RBC-MIX – 1:1 mix of RBC-USN:RBC-TFN.



	Volumetric diameter			
	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	Span
RBC-USN	4.78 (0.52)	23.76 (1.72)	58.95 (1.57)	2.29 (0.12)
RBC-TFN	2.36 (0.07)	7.46 (0.70)	18.97 (2.19)	2.22 (0.08)
RBC-MIX	2.63 (0.23)	14.62 (2.67)	54.47 (5.46)	3.59 (0.47)

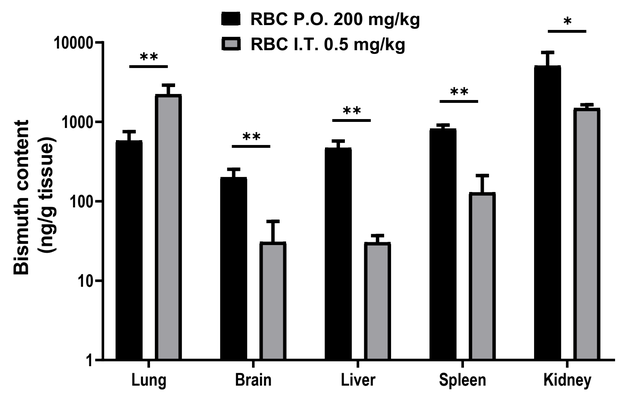
Figure 2 - Volumetric particle size distribution of RBC powder formulations measured by laser diffraction. Volumetric diameter are presented as mean (standard deviation).



Deposition fractions	RF	NF	TF	FPF
Aerodynamic diameter	Remaining in nasal spray	> 10.0 µm	5.0 – 10.0 µm	< 5.0 µm

Figure 3 - (A) Aerosol performance of RBC powder formulations evaluated by Next Generation Impactor (NGI) coupled with 1 L glass expansion chamber. (B) Linear regression of NF and FPF plotted against fraction of RBC-TFN in the formulation.

- Bimodal size distribution of RBC-MIX (Mixing ratio 1:1 of RBC-USN:RBC-TFN).
- NF:FPF ratio of RBC-MIX is the average ratio of individual formulations.
- Linear trend for NF:FPF ratio as mixing ratio is varied.
- Intratracheal administration of RBC-TFN resulted in 3.8-fold increase in RBC concentration in the lungs compared to oral administration.



P.O – Oral
I.T. – Intratracheal

Figure 4 - Biodistribution profile in mice when administered unformulated RBC by oral administration (200 mg/kg) or RBC-TFN powder by intratracheal administration (0.5 mg/kg). Bismuth concentration was quantified 24 h post-administration. **p < 0.01, *p < 0.05.

Conclusions

- SFD formulations of antiviral metallodrug were produced with distinct particle sizes using the ultrasonic nozzle and the two-fluid nozzle.
- The dual targeting formulation RBC-MIX exhibited customizable nasal and lung aerosol deposition profile when dispersed using nasal powder device.
- In vivo studies showed improved drug delivery to the lungs with lower dose and reduced systemic absorption and distribution.
- Antiviral efficacy in animal models following intranasal and pulmonary administration will be examined in future studies.

References

1. Yuan S. et al. Nat Microbiol 2020; 5: pp1439-1448.
2. Wang R. et al. Chem Sci 2022; 13: pp2238-2248.
3. Seow H.C. et al. Int J Pharm 2022; 619: pp121704.