NANO-IN-MICRO PARTICLES FOR THE PULMONARY DELIVERY OF REMDESIVIR

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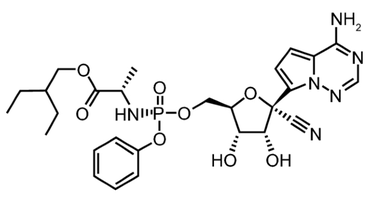
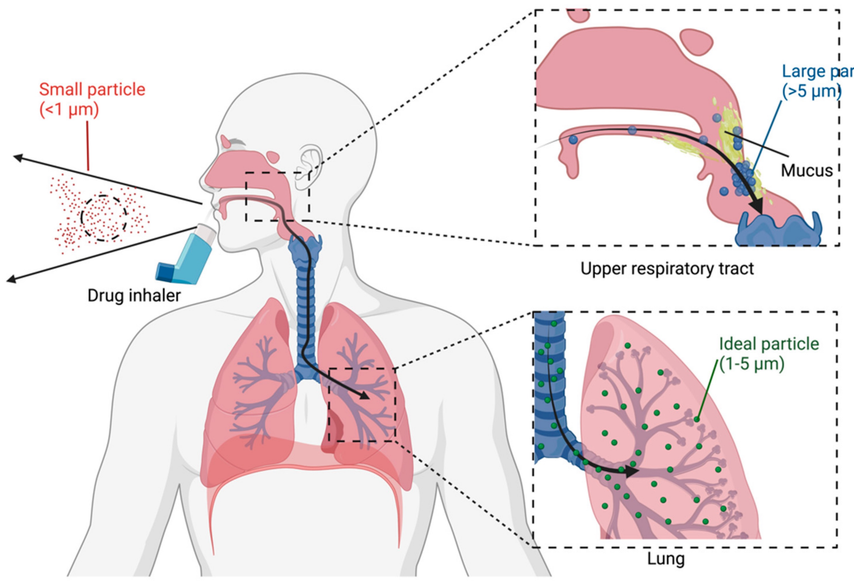
INTRODUCTION AND OBJECTIVE

Remdesivir (RDV) emerged as a potential option to treat COVID-19 in patients with comorbidities (Godwin et al., 2024).



Due to the low oral bioavailability, it must be used IV (2h infusion) and the rapid metabolism may further limit therapeutic efficacy in the lungs (active metabolite is unable to penetrate cell membranes).



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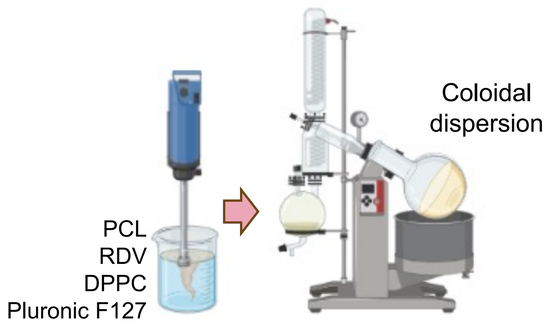
Pulmonary delivery:

- ✓ Avoids first pass metabolism;
- ✓ Large superficial area of the lungs (~100 m^2);
- ✓ Excellent blood supply (~5 L/min);
- ✓ Low enzimatic activity (RASHID et al., 2019).

We developed an inhalable formulation of polycaprolactone (PCL) nanoparticles with DPPC to favor interaction with (NPs) incorporated into microparticles (MPs) for pulmonary delivery of RDV

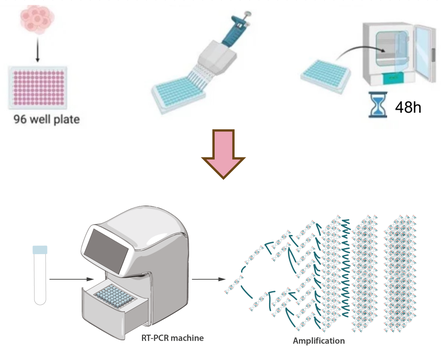
MATERIALS AND METHODS

RDV NANOENCAPSULATION (RDV-PCL-NP)



NPs of PCL were produced by emulsion-diffusion-solvent evaporation and characterized by DLS and zeta potential. DPPC was incorporated to facilitate pulmonary delivery.

CYTOTOXICITY AND ANTIVIRAL ACTIVITY

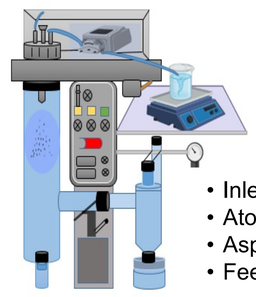


Vero E6 cells pretreated with samples for 1h:

- Cytotoxicity by LDH after 48h
- infected with SARS-CoV-2 (Wuhan strain) - viral RNA quantified by RT-qPCR after 48h.

NANO-IN-MICROPARTICLES POWDER FORMULATION (RDV-PCL-MP)

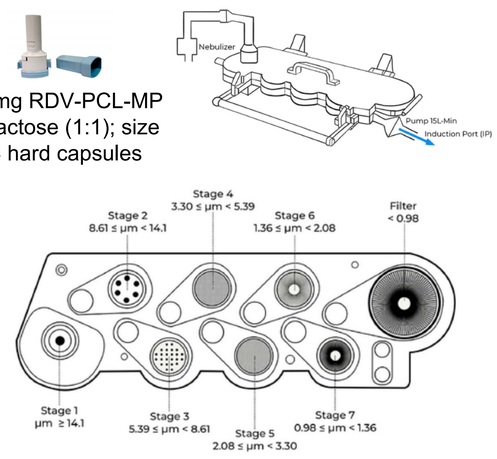
NPs spray-dried with lactose (Lactohale® LH206). Powder formulations characterized by SEM, laser diffraction, infrared spectroscopy (FTIR), X-ray diffraction, DSC, TG.



Mini B190 (Büchi)

- Inlet T = 100 °C
- Atomizing air flow = 600 L/h
- Aspirator air flow = 70%
- Feed rate = 4.5 mL/min

IN VITRO AEROSSOLIZATION PERFORMANCE (NGI)



25mg RDV-PCL-MP + lactose (1:1); size 4 hard capsules

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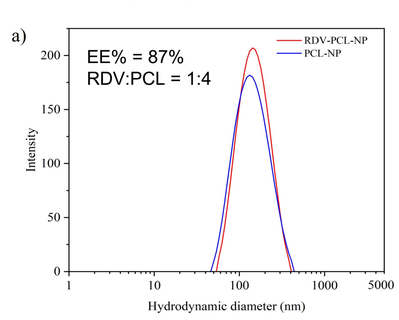
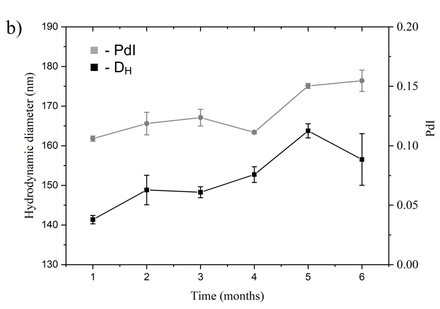
RESULTS

NANOPARTICLES PRODUCTION AND STABILITY

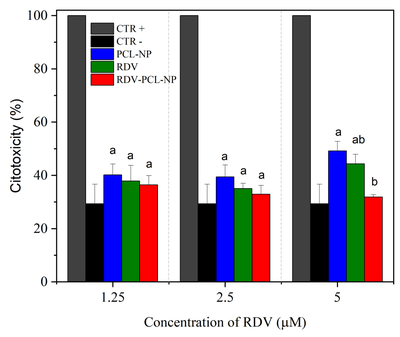


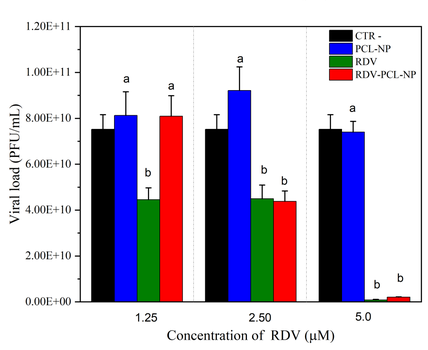


Coloidal dispersion	Zeta Potential (mV)
NP-PCL-RDV	-4.94 ± 0.100
NP-PCL-Placebo	-5.10 ± 0.120

(n=3 plus standard deviation)

NANOPARTICLES CYTOTOXICITY AND VIRAL LOAD



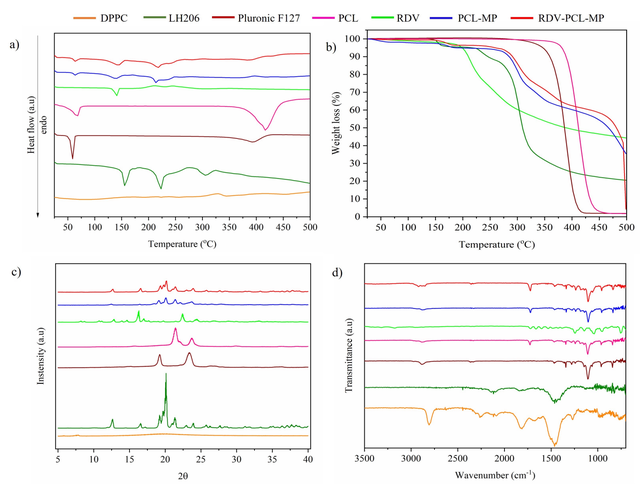


Values represent mean ± SD and correspond to data from two independent biological experiments, each conducted in triplicate. Different letters indicate statistical differences among columns at the same time ($p < 0.05$).

CHARACTERIZATION OF THE RDV-PCL-MP INHALABLE POWDER

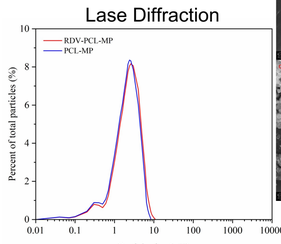
RDV-PCL-MP
Process yield = 63%

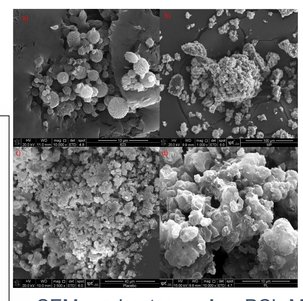
PCL-MP
Process yield = 61%



a) DSC, **b)** TG, **c)** DRX, and **d)** FTIR, illustrating the thermal transitions, stability, crystallinity and molecular interaction of excipients: DPPC, LH206, Pluronic F127, RDV and formulations containing or not RDV: PCL-MP and RDV-PCL.

Lase Diffraction





SEM: **a**-Lactose, **b**- PCL-MP (1000 x), **c**- RDV-PCL-MP (2500 x), **d**- RDV-PCL-MP (10000 x)

Sample	D (0.1) (µm)	D (0.5) (µm)	D (0.9) (µm)	Span
RDV-PCL-MP	1.20 ± 0.06	2.36 ± 0,02	4.11 ± 0,71	1.63
PCL-MP	0.92 ± 0.01	2.59 ± 0,03	4.88 ± 0,53	1.78

IN VITRO AEROSSOLIZATION (NGI)

- Mean Mass Aerodynamic Diameter (MMAD) = 4.08 µm
- ED = 85%
- Fine particle fraction (FPF) = 40% (< 5 µm)
- Respirable fraction (RF) = 39% (between 1 and 5 µm)

CONCLUSIONS

The nano-in-micro particles developed correspond to a promising alternative for pulmonary delivery of RDV, with the potential to be adapted to other drugs and contribute to therapeutic advances in the fight against respiratory diseases. Compared to previously described RDV-PCL-Pluronic-NP (Fouad et al., 2024), the nano-in-micro particles contains DPPC as a biocompatible stabilizer and lactose, providing a more robust polymeric matrix.

ACKNOWLEDGMENTS

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