N-acetylcysteine spray dried powders with antioxidant activity for pulmonary delivery

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Introduction

N-acetylcysteine (NAC), the acetylated form of L-cysteine, a sulphur containing amino acid, is primarily used as a mucolytic agent and as an antidote for acetaminophen poisoning[1]. Beyond established therapeutic purposes, NAC presents a multifaceted pharmacological activity, including antioxidant and anti- inflammatory properties, which support the recent repurposing as adjuvant treatment for chronic pulmonary diseases[2].
Despite the low oral bioavailability[3], NAC is currently marketed in oral dosage forms, while additional formulations are available as solutions for oral inhalation.

Aim of the study

This study aims to investigate a formulation strategy for the development of NAC spray dried powders suitable for pulmonary administration.
The antioxidant activity of NAC following SD process was assessed and SD powders were tested after 6 months storage in terms of solid state and aerosol performance.

Materials and methods

1) Formulation study

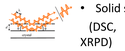
Spray dryer Mini B290 (Büchi, Switzerland)

L-leucine
- Surface active agent

Sodium hyaluronate
- High molecular weight polymer
- High biocompatibility

2) Powders characterization

- Drug content

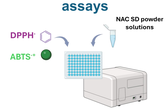



- Solid state (DSC, XRPD)

- Particles' morphology (SEM)

- Aerodynamic particle size distribution (APSD)

3) Radical scavenging activity assays



4) Stability studies conditions

- **Long term: 6 months at 25°C-60% RH**
- **Accelerated: 6 months at 40°C-75% RH**

(Images were created with Biorender.com)

Results

Spray drying process

Table I. Spray dried powders composition, process yields and drug contents (mean value± st.dev, n=3)

Powders	NAC (% w/w)	NaHyal (% w/w)	L-leu (% w/w)	Outlet Temp (°C)	Yield (%)	Drug content (%)
#1	50	50	0	74	54.8±6.5	49.4±0.3
#2	50	30	20	73	70.5±1.2	49.7±1.3
#3	50	20	30	71	75.1±4.0	48.5±0.7
#4	50	0	50	76	20.0±8.8	49.9±0.3

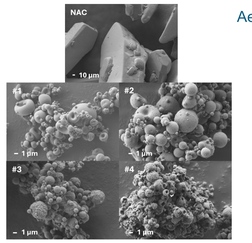


Figure I. SEM images 5000x of NAC raw and SD powders #1, #2, #3 and #4.

Aerodynamic parameters at time zero (T0)

Powder #2
MMAD: 4.0±0.1
GSD: 2.8±0.1
RF (%): 58.1±0.1

Powder #3
MMAD: 5.7±2.0
GSD: 2.5±0.5
RF (%): 44.6±0.2

Aerodynamic particle size distribution (APSD)

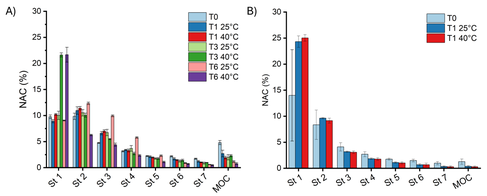


Figure III. APSD stability of SD powder #2 (A) over 6 months, SD powder #3 (B) over 1 month.

Radical scavenging activity assays

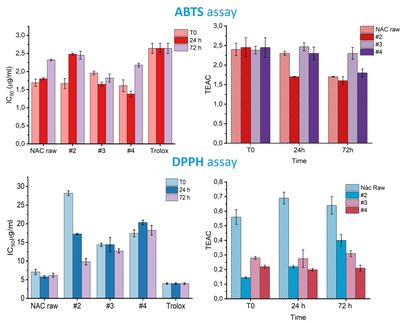


Figure II. Radical scavenging activity by ABTS and DPPH assays.

Solid state stability

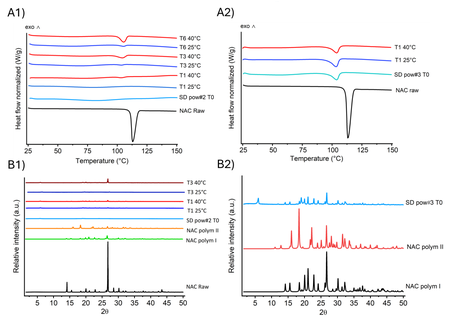


Figure IV. DSC of SD powder #2 (A1) and powder #3 (A2), XRPD of SD powder #2 (B1) and SD powder #3 (B2).

Conclusions

- In this study an organic solvent free formulation approach was successfully investigated for the development of high payload NAC spray died powders, suitable for pulmonary delivery.
- NAC exhibited in vitro selective radical scavenging activity, with higher efficacy in inhibiting ABTS than DPPH radical (Figure II).
- SD powder #2, containing the highest polymer ratio, was stable for at least 6 months of storage at 25°C (Figure III, IV).

References:
[1] Sahasrabudhe S., et al. Antioxidants. 2023. 1316. [2] Calzetta L., et al Expert Rev. Respir. Med. 2018. 639-708. [3] Sadowska A.M. Ther Adv Respir Dis 2012. 127-135