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DRUG DELIVERY TO THE LUNGS

Microencapsulation of mPEG-PLGA Nanoparticles for Potential Inhalable Anticancer Therapy

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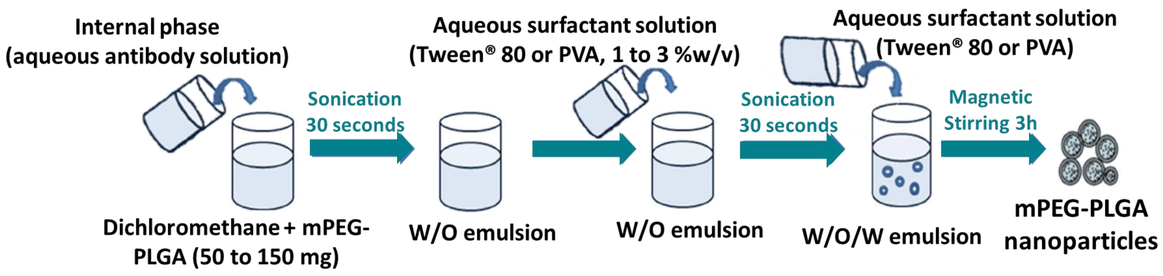
Introduction

Lung cancer has a **high mortality rate** among all common cancers [1]. **Conventional lung cancer therapies** are usually administered intravenously with **low selectivity for tumor cells** and **severe side effects** [2]. **Therapeutic antibodies** are used as an alternative or in combination with chemotherapy, demonstrating benefits due to their **high specificity** and **low toxicity** [3].

The **encapsulation of antibodies into nanoparticles** and **its pulmonary delivery** is a promising strategy which combines **targeted** and **controlled drug delivery** with the **ability to protect antibody structure and bioactivity, improving lung cancer treatment** [4].

Thus, the aim of this work was the **development and optimization of mPEG-PLGA nanoparticles** to reach optimal features for future **therapeutic antibody loading** and the **microencapsulation of nanoparticles by spray-drying to obtain a dry powder** suitable for **inhalable lung cancer treatment**.

Materials and Methods



Nanoparticles formulation
150 mg of mPEG-PLGA

- **DLS:** particle size and PdI
- **ELS:** zeta potential

Characterization

Excipients

- **Lactose, D-trehalose and mannitol 2% (w/v)**
- **L-leucine 0.25-2% (w/v)**

Spray-Drying

T inlet = 170 ºC
Aspiration = 90 %
Feed rate = 2.0 mL/min
Atomizing air flow rate = 473 L/h

Dry powder (microparticles)

Characterization

- **Crystallinity:** X-Ray powder diffraction (XRPD)
- **Morphology:** scanning electron microscopy (SEM)

Figure 1. Schematic diagram of the protocol used to produce and analyse the mPEG-PLGA nanoparticles [3] and for nanoparticles microencapsulation by spray-drying [5-7].

Results and Discussion

Production and optimization of mPEG-PLGA nanoparticles

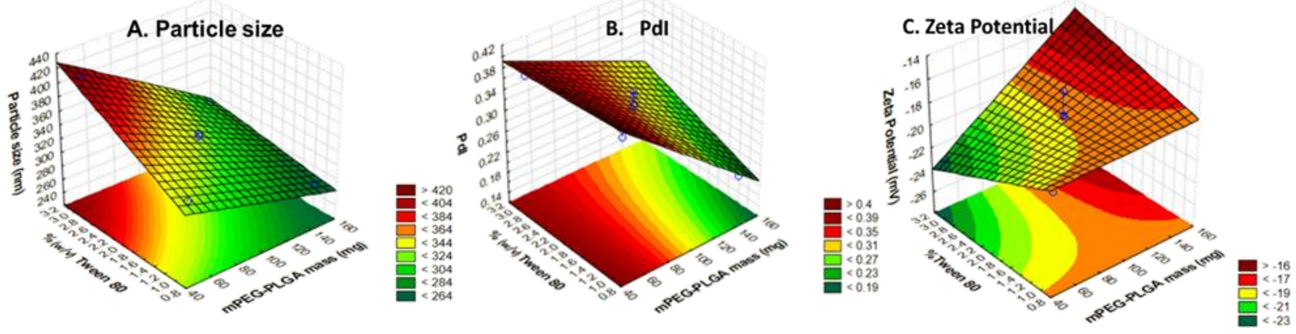


Figure 2. Surface response plots for the dependent variables (A), (B), and (C) as a function of the effect of mPEG-PLGA mass and %Tween®80 (by a Design-of-Experiments approach).

Optimized nanoparticles are aimed at small particle size and good colloidal stability:

- Tween® 80 showed better particle stabilization than PVA.
- Optimal nanoparticle formulation (**Table 1):** 150 mg mPEG-PLGA and 1% Tween® 80.

Table 1. Formulation optimization by a DoE. Predicted value - theoretical values of the responses for the best formulation features. Experimental value was obtained to confirm the predicted value.

Variables	Predicted value	Experimental value
mPEG-PLGA mass (mg)	**150**	150
% (w/v) Tween 80®	**1**	1
Particle size (nm)	**298**	300 ± 10
PdI	**0.233**	0.358 ± 0.025
Zeta potential (mV)	**-19.0**	-24.0 ± 1.1

Values are expressed as a mean ± standard deviation (SD), n = 5.

Dry powder formulation

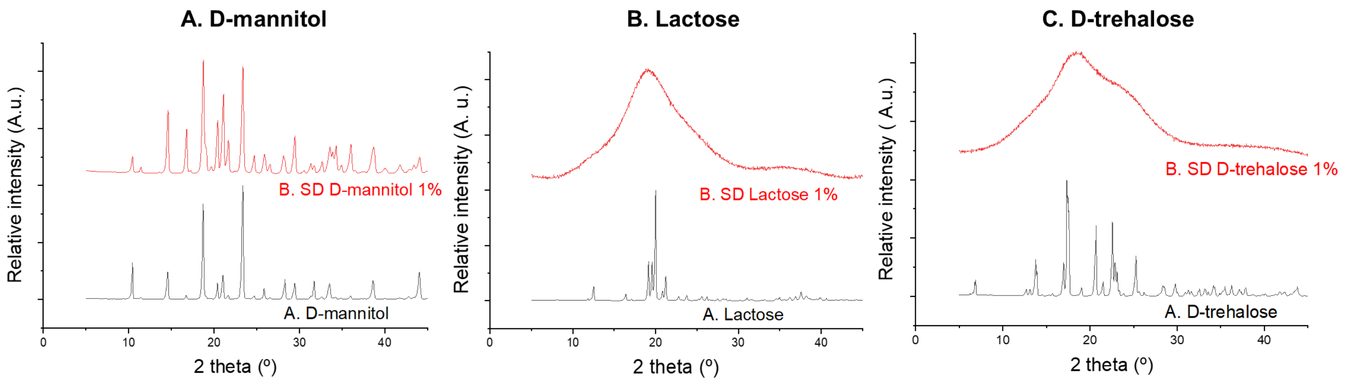


Figure 3. PXRD analysis of excipients and spray-dried (SD) excipients (1% w/v) powders.

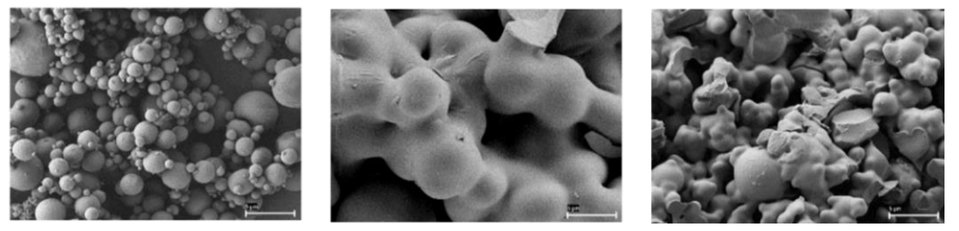


Figure 4. SEM images of spray-dried powders composed of the tested excipients (1% w/v). The scale bar represents 5 µm.

- D-mannitol microparticles showed a dry appearance after drying and had a crystalline structure, while lactose and D-trehalose presented humid and sticky aspect and amorphous structures.

Table 2. Composition of dry powder formulations, spray-drying operating parameters and yield.

Microparticles (Nps/Man/Leu, w/w)	Polymer	Excipients		Total solid content	T outlet	Production yield (%)
	mPEG-PLGA % (w/v)*	D-mannitol % (w/v)*	L-leucine % (w/v)*	Nps+Exc % (w/v)	(ºC)	
20/80/0	0.5	2	-	2.5	127-126	7
20/0/80		-	2	2.5	117-123	47
14/57/29		2	1	3.5	123-126	**59**
15/62/23		2	0.75	3.25	123-125	24
18/73/9		2	0.25	2.75	103-107	23

Exc: excipient(s); Leu: D-leucine; Man: D-mannitol; Nps: nanoparticles;
*Final % in spraying dispersion.

Higher obtained yield

- D-mannitol was selected as the main excipient to proceed, but leucine was further added to improve the spray-drying yield **(Table 2)**.

Figure 5. SEM images of spray-dried microparticles 20/80/0 (A) and 14/57/29 (B) (Nps/Man/Leu, w/w). The scale bar represents 15 µm. Leu - D-leucine; Man - D-mannitol; Nps – nanoparticles.

- L-leucine decreases the inter-particulate forces and results in a low diameter, and also can lead to collapse during the inner water diffusion and evaporation [7].

Conclusions & Future work

- The optimized nanoparticles formulation is produced with 150 mg mPEG-PLGA and 1% Tween® 80.
- Studies to convert nanoparticles into inhalable dry powders are being conducted with D-mannitol and L-leucine allowing reduction of particle agglomeration after spray-drying and satisfactory spray-drying yields.
- Further studies will be done in order to optimize the spray-dried microparticles and the antibody encapsulation keeping its structure and bioactivity.

References:

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