Levothyroxine dry powder formulation for the treatment of idiopathic pulmonary fibrosis

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Background

Local delivery of medications can be advantageous in some pulmonary disease. Idiopathic pulmonary fibrosis (IPF) is defined as a chronic condition in which the normal lung anatomy is altered. These changes in lung architecture cause an irreversible decrease in oxygen diffusion and lung function, rapidly leading to death. IPF is a complex disease in which aging related abnormalities, such as mitochondrial morphology abnormality, reduction of fusion process and mitophagy[1] have been observed. The activity of thyroid hormone in mitochondrial biogenesis regulation has been experimentally demonstrated[2] and a recent study proposes the possibility to reverse the fibrotic state in bleomycin-induced fibrotic mice model by thyroid hormone aerosolization[3].

AIM

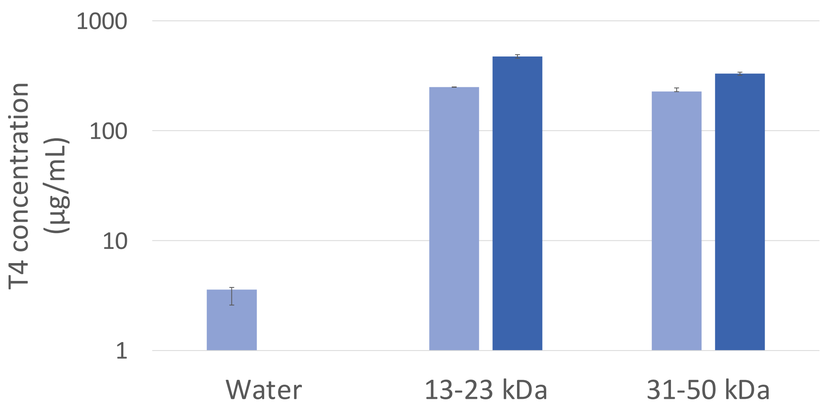
The aim of this work is the development of a dry powder for the lung administration of levothyroxine (T4) based on PVA nano embedded microparticles as a novel treatment for IPF.

Method

The solubility of T4 in polyvinyl alcohol (PVA) aqueous solution was evaluated adding an excess of T4, stirred for 24h at 25°C and quantified by HPLC Agilent 1200 series. PVA at two molecular weights (13-23 and 31-50 kDa) was tested at two different concentrations (1% and 3.5% w/v).
Dynamic light scattering analysis showed the presence of highly polydisperse systems in the PVA-T4 suspensions with different T4 concentrations (from 0.99 to 3.38 w/w)
A reduction of size and polydispersity index (PDI) was obtained by applying 15 cycles of high pressure homogenization (400 Bar). The obtained suspension was dried by spray drying and the powder were characterized by thermogravimetric analysis, particle size distribution, particle size recovery after resuspension. Morphology was studied by SEM images.
A preliminary aerodynamic assessment was performed by fast screening impactor (FSI).

Results

T4 apparent solubility



HPLC analysis shows an increase of levothyroxine apparent solubility in presence of PVA, but this increase does not seem to be related to PVA molecular weight and concentration (ligh blue 1% and blue 3.5% w/v).

PVA-T4 nano-suspensions

PVA Molecular weight (kDa)	PVA concentration (%)	Sample	T4 (% w/w)
13 - 23	1	S1	0.99
		S2	1.48
		S3	1.96
		S4	2.91
		S5	3.38

Suspension homogenization and powders production

Sample	Size (nm)	PDI
S1	648.3	0.48
S2	636.3	0.48
S3	674.4	0.41
S4	917.3	0.65
S5	602.4	0.41

High pressure Homogenization

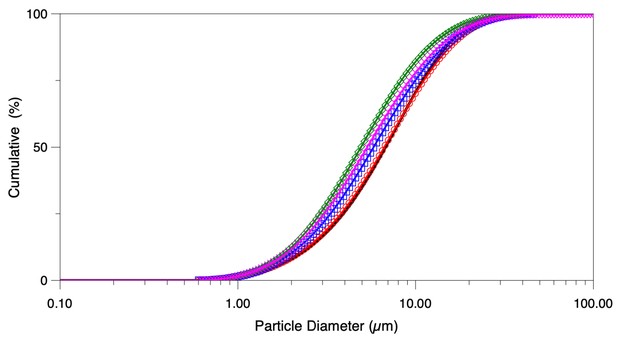
Sample	Size (nm)	PDI
S1	422.7	0.29
S2	429.8	0.30
S3	436.3	0.25
S4	481.7	0.33
S5	436.4	0.35

Spray Drying

The homogenization process give a particle size and polydispersity reduction after that a spray drying process was applied.

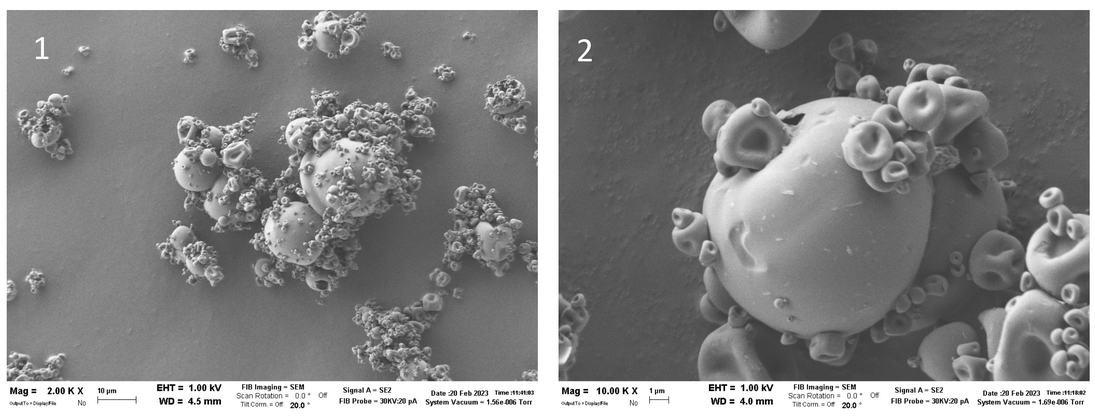
Powders characterization

Sample	Powder particle size (µm)	Residual humidity (%)	Size after resuspension (nm)	PDI
S1	7.33± 0.53	1.79	448.7	0.26
S2	6.9± 0.44	2.37	429.8	0.26
S3	6.43 ± 0.64	3.07	449.8	0.26
S4	5.04 ± 0.11	2.20	501.7	0.38
S5	5.52 ± 0.67	1.70	450.5	0.32



Aerodynamic assessment

SEM images show the presence of aggregates (1), particles have a spherical shape and seem empty (2)



Sample	Emitted Dose (%)	Fine Particle Fraction (%)
S1	95.37	39.34
S2	97.05	51.94
S3	92.78	45.14
S4	94.41	41.87
S5	97.23	38.27

Conclusions

PVA increases T4 apparent The homogenization process allow a size reduction before powder production; this particle size was re-obtained after resuspension of the powder. Looking at the pulmonary administration, the presence of aggregates could explain the low fine particle fraction.

References:
[1] Bueno M, Lai YC, Romero Y, et al. *J Clin Invest*. 2015;125(2):521-538; [2] M Yen et all. Autophagy. 2015 [3] Yu G. et al. *Nat Med*. 2018;24(1):39-49.