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Inhalation Dry Powders of Monoclonal Antibodies Made by Thin-Film Freeze-Drying

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PURPOSE

The present study is designed to assess the feasibility of production of stable, aerosolizable dry powders of monoclonal antibodies (mAbs) for pulmonary delivery.

MATERIALS AND METHOD(S)

MATERIALS

Anti mouse PD-1, Rat IgG2a, Anti-TNF-alpha

METHODS

- **Thin-flim freezing (TFF) and Shelf freeze-drying**

mAbs liquid samples were dropwise applied onto the rotating drum (150 RPM) of a TFF device at −100 ◦C. The primary drying occurred at −40 ◦C for 1200 min, followed by ramping to 25 ◦C for 1200 min. Secondary drying occurred at 25 ◦C for 1200 min. The pressure was held constant at no more than 100 mTorr.

- **Evaluation of aerosol performance**

Dry powder was loaded into a size 3 capsule. The capsule was placed in a Plastiape high resistance RS00 DPI that was then attached to a Next Generation Impactor.

- **Size exclusion chromatography (SEC) and SDS-PAGE**

mAbs samples were reconstituted with an equal volume of water as prior to TFFD, an aliquot was measured with HPLC-SEC and remainder for loaded into SDS-Gel.

- **Micro-Flow imaging (MFI)**
- **Modulated differential scanning calorimetry (mDSC)**
- **X-ray powder diffraction (XRPD)**
- **Scanning electron microscopy (SEM)**
- **Moisture content measurement**

Karl Fischer (KF) was used to measure moisture content in each sample with 5-10 mg of powder

- **Stability study**

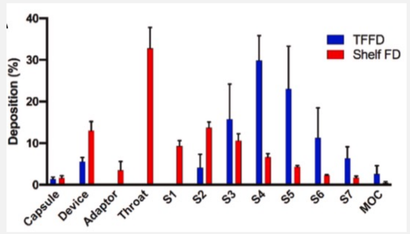
Samples were stored inside a desiccator at the specified temperatures (i.e., 4 ◦C, room temperature, or 40 ◦C). Six or ten weeks later, samples were removed from storage conditions immediately prior to analyzing by SEC, SDS-PAGE, and KF.

- **Antibody binding capacity**

An enzyme-linked immunosorbent assay (ELISA) was used to measure the binding capacity

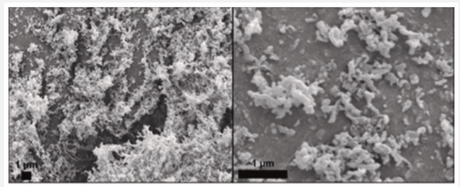
RESULT(S)

TFF mAbs powder showed good aerosol properties

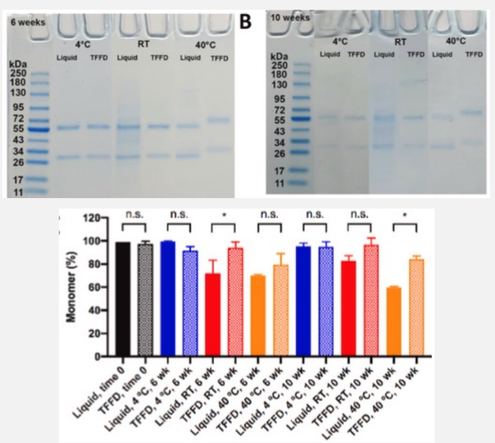


	MMAD (μm)	GSD	FPF delivered [%]
TFFD	1.8 ± 0.4	1.7 ± 0.1	98.2 ± 1.9
Shelf FD	4.2 ± 0.0	2.6 ±1.2	32.4 ± 0.0

TFF mAbs powder contained nanostructured aggregates with a highly porous matrix structure

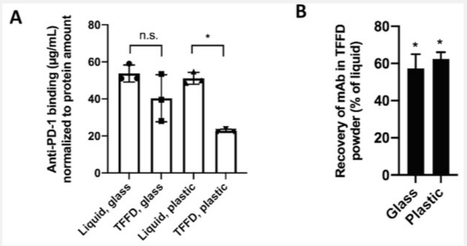


TFF mAbs powder showed a good stability profile of 10 weeks of storage at RT

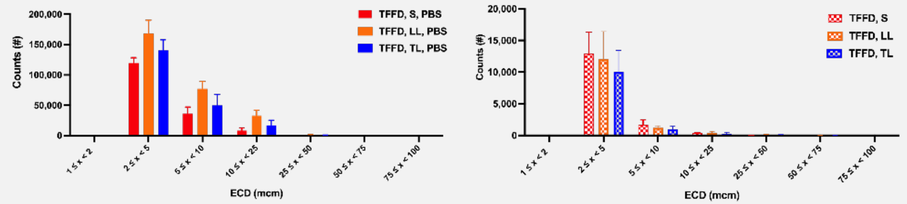


RESULT(S)

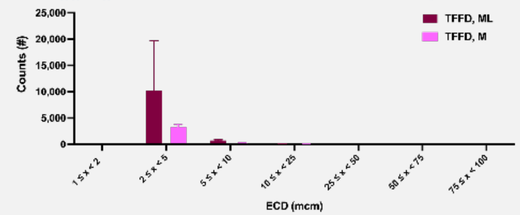
The binding capacity of the TFF mAbs powder was not statistically different than that before TFFD, different materials led a significant difference in the binding capacity of mAbs



Across all the TFF mAbs formulations, salts in PBS buffer caused more mAbs aggregation



The least subvisible aggregation was observed in TFF mAbs powder formulated with mannitol



CONCLUSION

We conclude that TFFD can be applied to produce stable, aerosolizable dry powders of mAbs for pulmonary delivery and that formulations must be optimized to maximize aerosol performance and minimize protein aggregation.

FUNDING

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