Monoclonal antibodies Aerosol formulations

Renaud Respaud - 02/07/2015

Challenges for mAbs inhalation therapy

Effect of formulation on the stability of a nebulized antibody

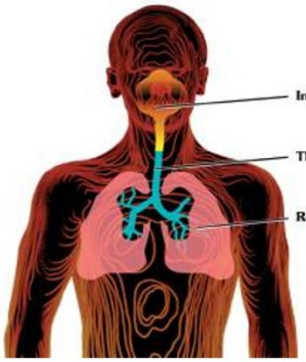
Technical challenges for a successful inhalation therapy

Dependent on:

- Aerosol technology
- Performance of the device

(aerosol output, particle size)

Particle size



> 5µm Upper Respiratory tract

2- 5µm Mid Respiratory tract

0.5-2 µm Alveoli

Technical challenges for a successful inhalation therapy

Dependent on:

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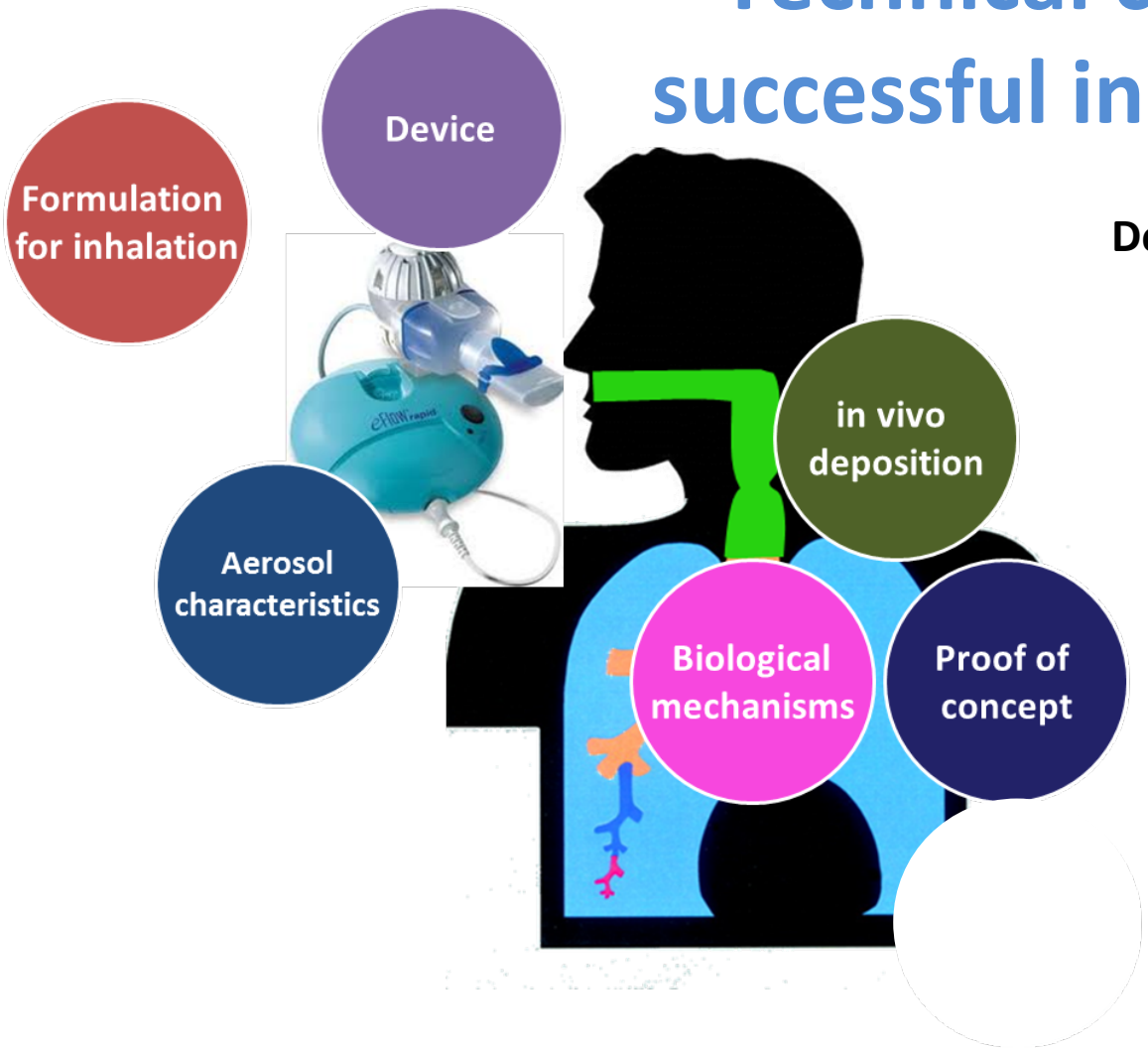
- Performance of the device (aerosol output, particle size)
- Drugs
- Characteristics of drug formulation (concentration, pH, viscosity…)

Technical challenges for a successful inhalation therapy



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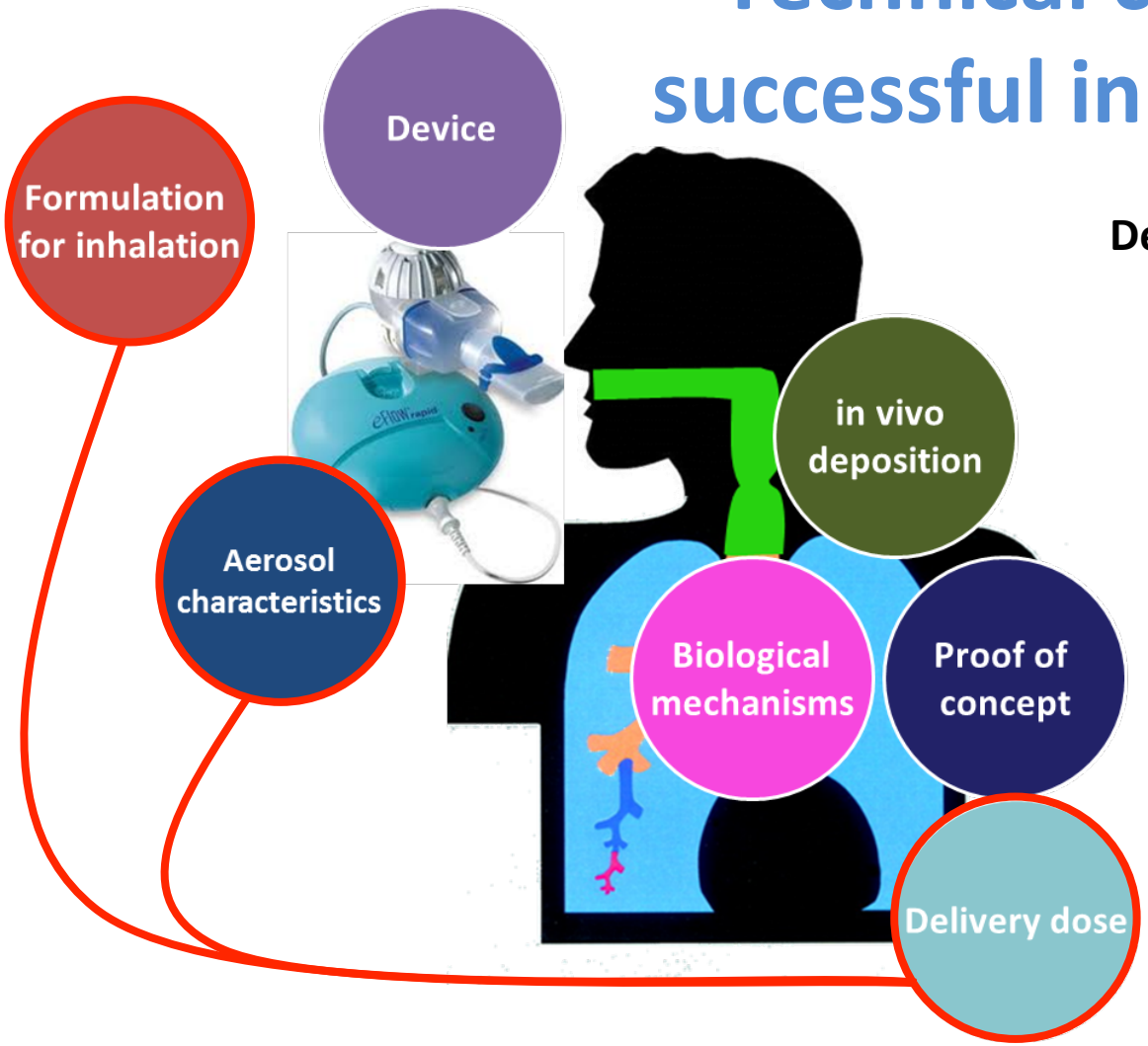
Technical challenges for a successful inhalation therapy



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Strategy of development for a formulation for mAbs inhalation

1. Solid or liquid aerosols ?

Solid or liquid aerosols ?

Solid aerosols: DPIs - Dry Powder Inhalers

- **Advantages :** user friendly / no cleaning / quick delivery
- **Disadvantages :** manufacturing process (gas-liquid interface, thermal stress) / drug and device development / Quantity of drugs

Liquid aerosols:

- MDIs - Metered Dose Inhalers
- Nebulizers
  - US
  - Jet
  - Mesh

Strategy of development for a formulation for mAbs inhalation

1. Solid or liquid aerosols 

2. Type of nebulizer ?

Type of nebulizer ?

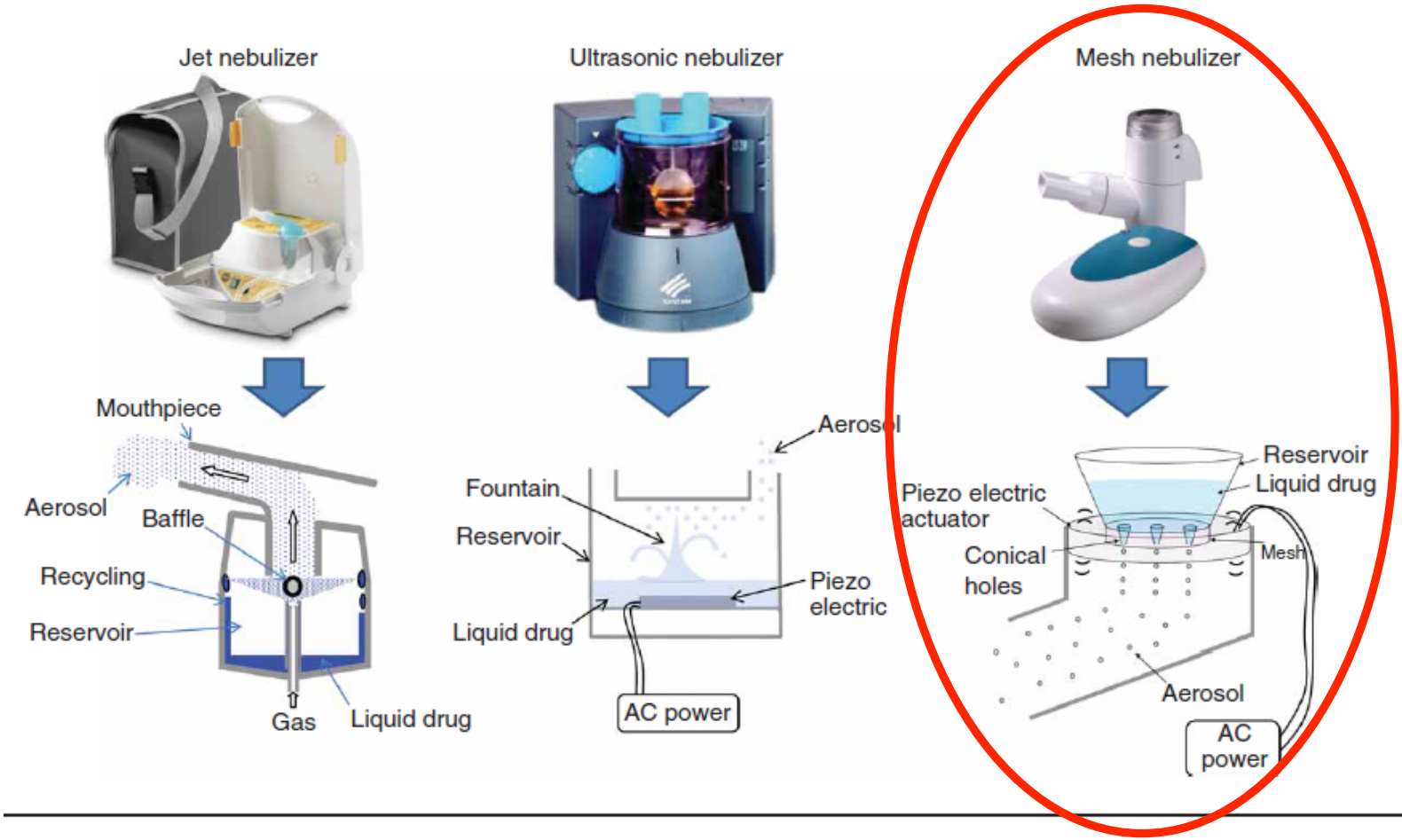


Figure 2. Mechanisms of action of nebulizers.

Respaud R. *et al*. Expert Opin Drug Deliv. 2015 Jan 5:1-13

Strategy of development for a formulation for mAbs inhalation

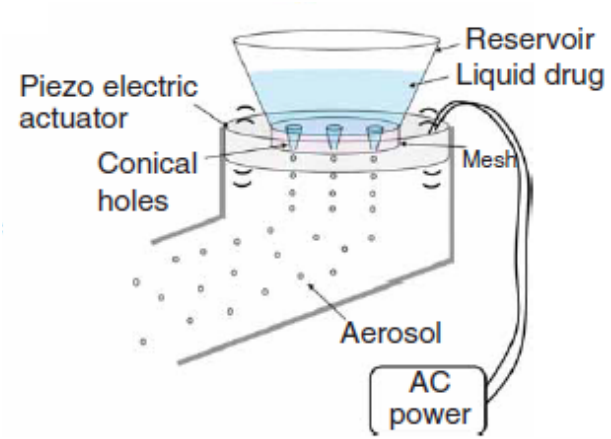
1. Solid or liquid aerosols 

2. Type of nebulizer 

3. Limitation of nebulizer regarding mAbs ?

Limitation of nebulizer = physical stresses

Mesh nebulizer



Respaud *et al.* 2015

Dispersion/suspension of liquid droplets in a gaseous medium

- Heat
- Shearing
- Air-liquid interface ++++++ +

Strategy of development for a formulation for mAbs inhalation

1. Solid or liquid aerosols 

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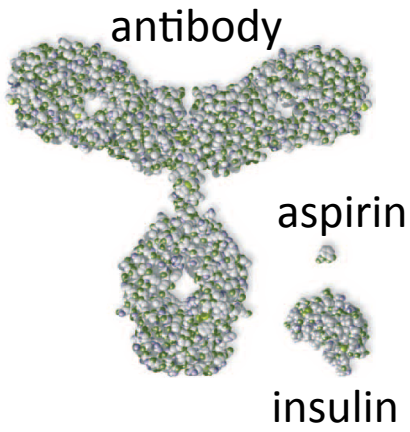
4. Formulation challenges ?

Formulation Challenges



Prone to various types of physical and chemical degradation

- Denaturation, deamidation, oxidation
- **Non-covalent/covalent aggregation ++++**

- **Antibody concentration:** known to affect aggregation
- **Buffer dilution and pH:** PBS, citric acid, histidine…
- **Excipients:**
  - **Surfactants (Polysorbate…):** protect mAbs at the air-liquid interface
  - **Sugars (sucrose, trehalose…):** cryoprotection
  - **Amino-acids (glycine, lysine, isoleucine…):** stabilizers

Strategy of development for a formulation for mAbs inhalation

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Challenges for mAbs inhalation therapy

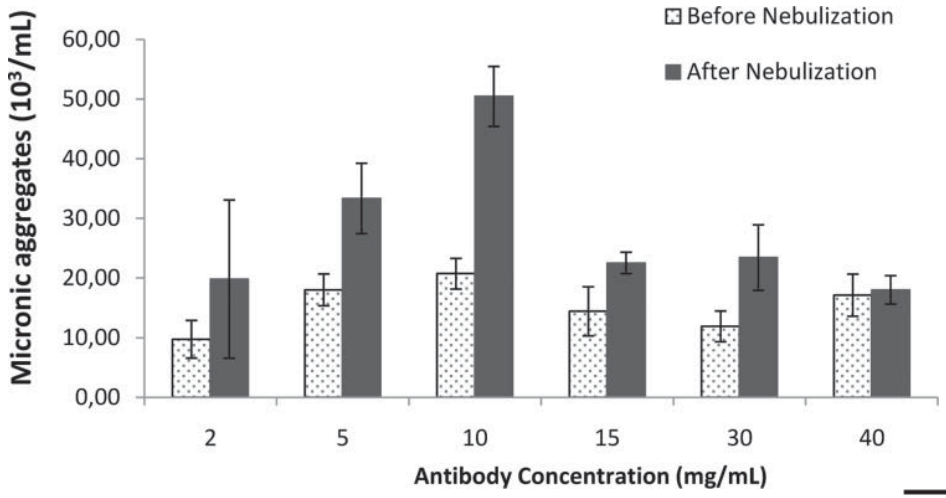
Effect of formulation on the stability of a nebulized antibody

Context

- Drug & device for the rapid delivery into the alveoli of anti-ricin mAb
  - Drug : IgG1 43RCA-G1 in PBS pH 7.2
  - Device : mesh nebulizer
  - Formulation ???

- Aggregation of a nebulized polyclonal IgG and IgG1 43RCA-G1
  - Effect of Antibody concentration
  - Influence of the device
  - Effect of surfactants

High concentration seems to protect polyclonal antibodies



Fluorescence Microscopy (Nile Red)
Large aggregates > 2µm

DLS: Dynamic Light Scattering
Medium-size aggregates < 1µm

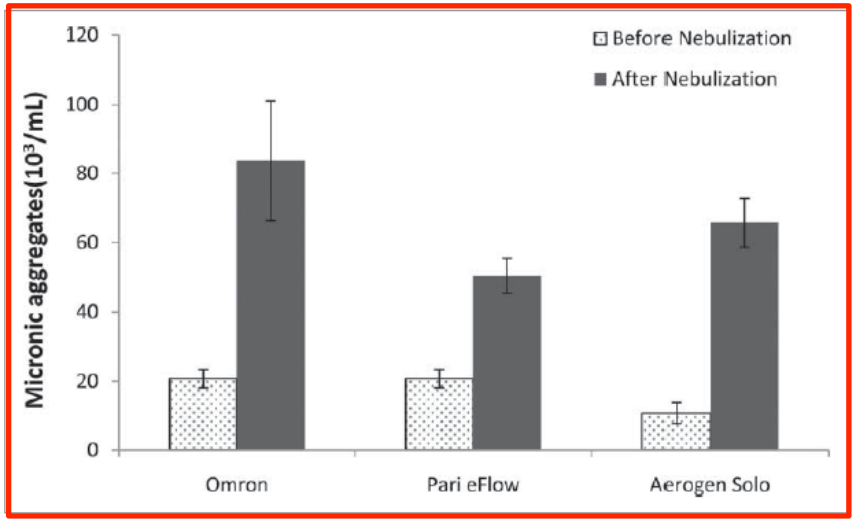
Antibody concentration (mg/ml)	Hydrodynamic diameter (nm ± SD)	Percentage monomers (mean% mass)
2	NA	NA
5	NA	NA
10	NA	NA
15	12.6 ± 1.42	94.4 ± 9.0
30	11.9 ± 0.06	99.6 ± 0.2
40/45	12.6 ± 0.35	99.6 ± 0.5

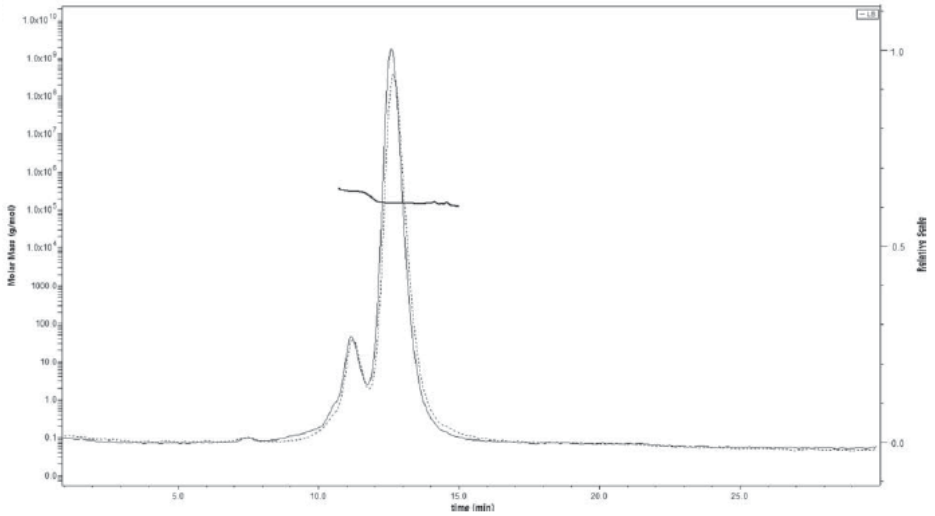
Respaud R et al. 2014

Device has influence on large aggregates

Table 1. Characteristics of a 10 mg/ml solution of antibody in PBS pH 7.2 after nebulization with three nebulizers. Each result is the mean (± SD) of three nebulizations

Nebulizer	Hydrodynamic diameter (nm ± SD)	Percentage monomers (% mass)	Size exclusion chromatography (% monomers/% other aggregates)	VMD (μm) (mean ± SD)	Flow rate (ml/min ± SD)
Omron	NA	NA	91.1 ± 0.6 / 8.9 ± 0.5	5.6 ± 0.1	0.23 ± 0.04
Aerogen Solo	NA	NA	91.3 ± 2.5 / 8.7 ± 1.9	4.1 ± 0.1	0.50 ± 0.01
PARI eFlow	NA	NA	90.6 ± 0.5 / 9.5 ± 0.6	3.8 ± 0.3	0.45 ± 0.05





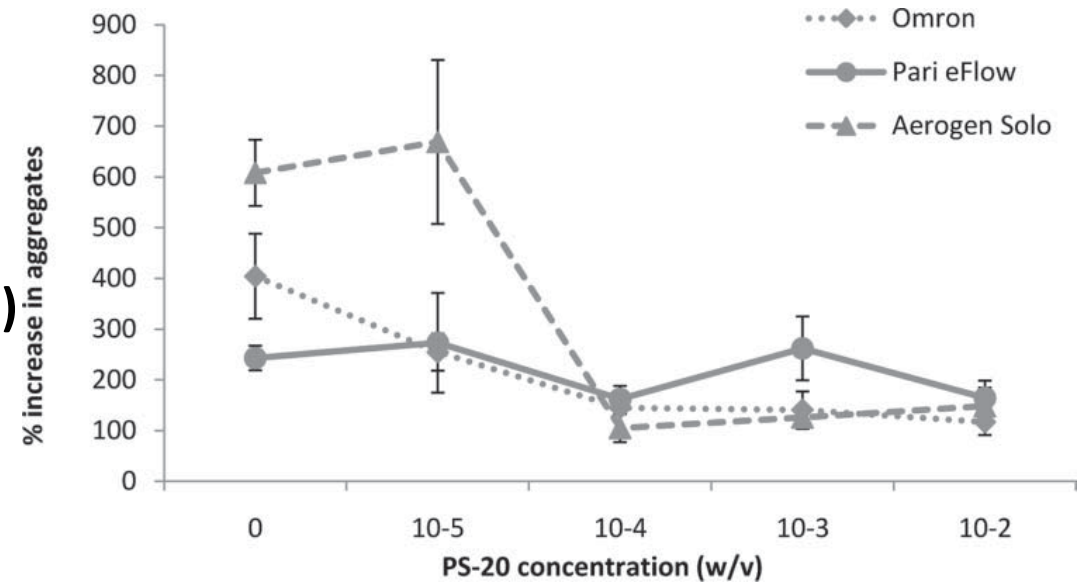
Respaud R et al. 2014

Surfactants protect polyclonal antibodies during nebulization

PS-20 concentration% (w/v)	Hydrodynamic diameter (nm ± SD)	Percentage monomers (% mass ± SD)
0%	NA	NA
0.00001%	NA	NA
0.0001%	NA	NA
0.001%	11.4 ± 0.5	99.9 ± 0.2
0.01%	11.2 ± 0.3	99.9 ± 0.2

DLS: Dynamic Light Scattering
Medium-size aggregates < 1µm

Fluorescence Microscopy (Nile Red)
Large aggregates > 2µm



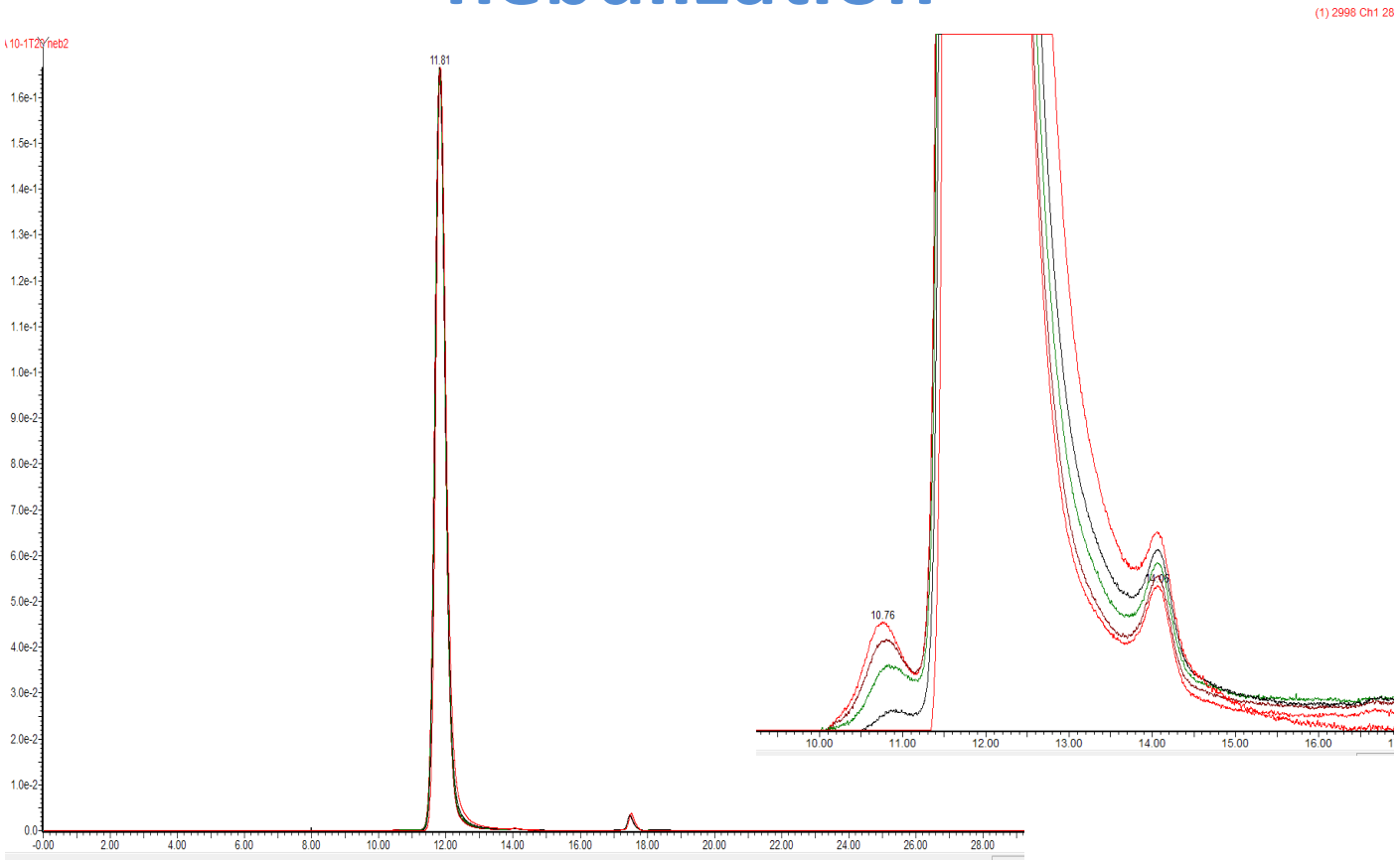
Respaud R et al. 2014

Does surfactants protect monoclonal antibodies during nebulization ?

Characteristics of solutions of IgG 43RCA-G1 15 mg/mL in buffer 25 mM, NaCl 135 mM, with various concentration of PS20, before and after nebulization. Each result is the result of 1 nebulization

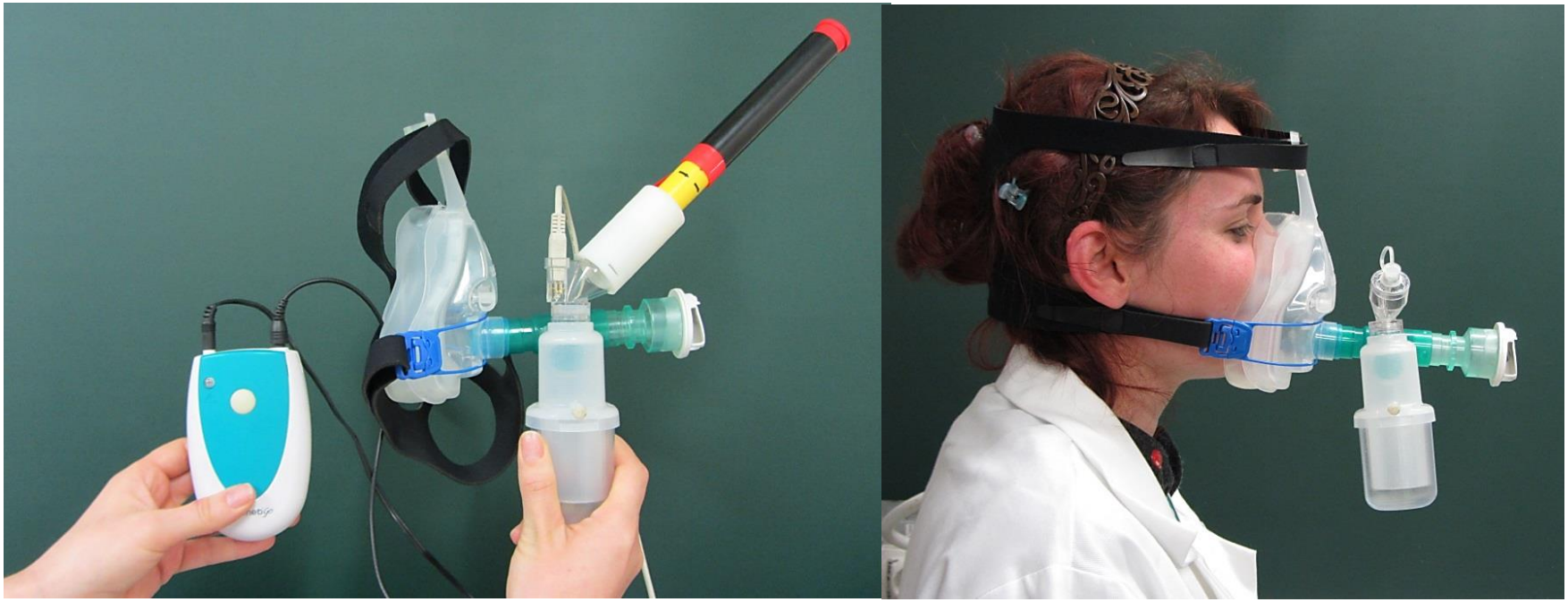
Nebulizer	Surfactant (PS20) concentration (% w/v)	SEC (% of monomer / % of other species)		DLS (% of monomer)		Large antibody aggregates (10^3/mL)	
		Before nebulization	After nebulization	Before nebulization	After nebulization	Before nebulization	After nebulization
Aerogen solo	0	100 / 0	100 / 0	99.6	99.1	85.6	128.8
	0.01	100 / 0	99.9 / 0.1	99.2	98.6	27.9	45.9
	0.1	100 / 0	99.8 / 0.2	99.9	100	33.3	29.7

No dimer (<0.5%) of IgG1 43RCA-G1 during nebulization



Size exclusion chromatography of a 15 mg/ml 43RCA-G1 IgG1 solution in developed buffer with various concentration of PS20 before and after nebulization with the Aerogen Solo. UV signal

Does surfactants protect monoclonal antibodies during nebulization ?



Drug & device for the rapid delivery into the alveoli of anti-ricin mAb

Conclusion and perspectives

• Utility of **adding surfactants** and **increasing protein concentration** to stabilize antibody formulations during nebulization

• Optimization for **each "drug and device" pairing** (specifications of the device and **properties of the mAb molecule)**

• Chemical modifications of mAbs during nebulization

• Toxicity of excipients used to stabilize mAbs during nebulization

Thank you for your attention

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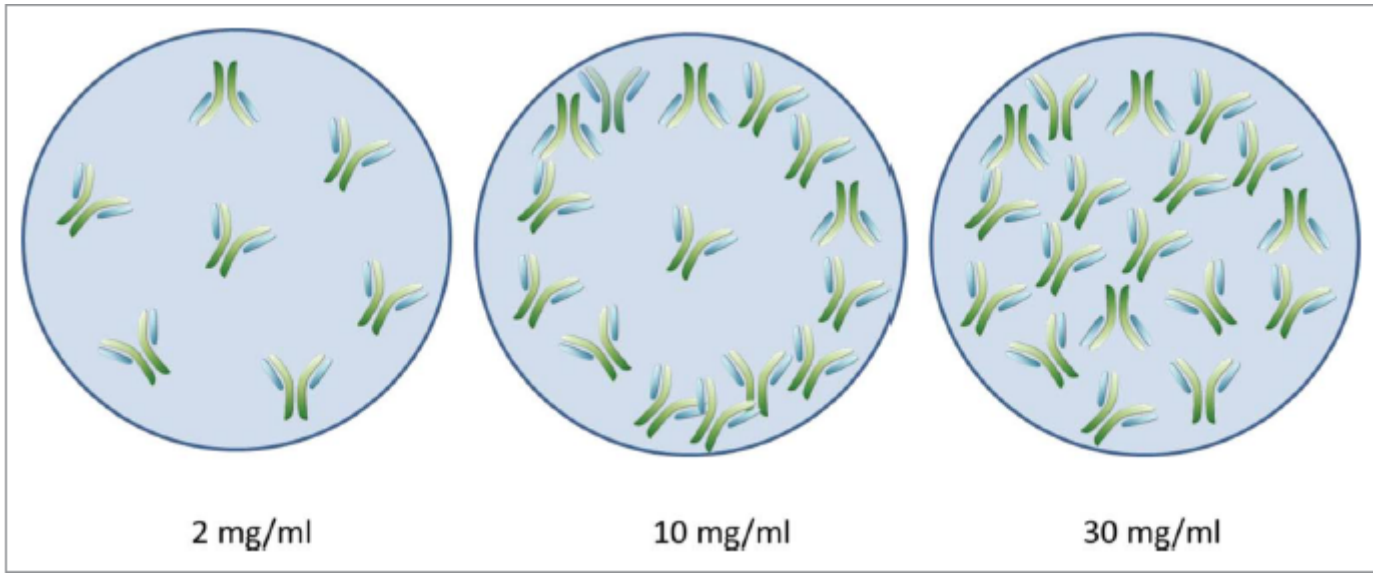
Plateforme de physicochimie des Biomédicaments



Model of the spatial distribution of antibodies in aerosol droplets as a function of antibody concentration

Respaud R et al. 2014