Designing macromolecule particles to manufacture an inhaled formulation

V Carli, Ph.D(1), L Menu-Bouaouiche, Ph.D(2), P Cardinael, Prof(3), G Coquerel, Prof(3)

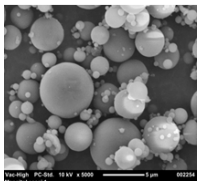
(1) IDD-Xpert International Drug Development Xpert, 453 rue de l'Industrie, 27000 Evreux, FRANCE

(2) Rouen-University Laboratoire Glyco-Mev EA-4358, 76821 Mont Saint Aignan, France

(3) Normandie Univ, France, UR, EA3233, Sciences et méthodes Séparatives, IRCOF, 1 rue Tesnière, 76821 Mont Saint Aignan Cedex, France

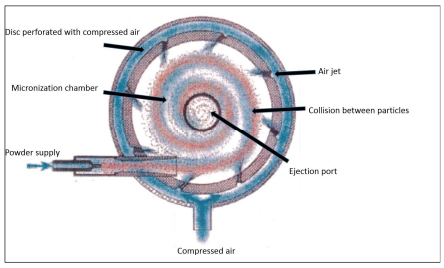
INTRODUCTION

Improved knowledge of the biological molecules and their therapeutic benefit contributed to the development of a new drug generation based on biopharmaceutical products. Most biopharmaceutics are administrated by injection, however this parenteral administration route is an invasive method which often requires medical assistance. The pulmonary dosage form offers an attractive alternative to avoid this medical requirement. The objective of this study is to design particles to manufacture inhaled formulation. Protein particles were produced with two manufacturing processes: Co-spray drying and micronization. The goal being to formulate the particles obtained in pressurized Metered Dose Inhaler (pMDI).



Main challenges

- To preserve the biological activity
- To reach the pulmonary target established: « the Mass Median Aerodynamic Diameter must be (MMAD) between 3 and 5µm »
- To avoid formation of side products and remain chemically and physically stable in time

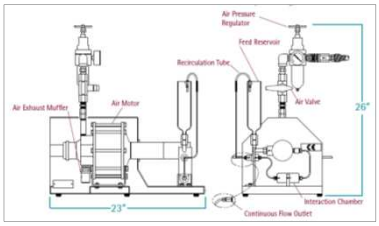


PROCESSING DESIGNED TO COMPLY WITH THESE CHALLENGES:

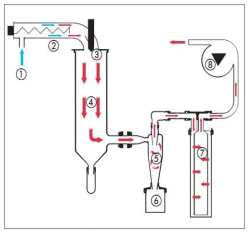
Micronization

Dry way

Liquid way



Spray drying

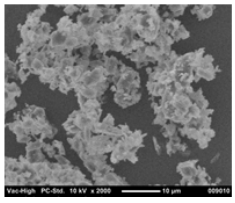


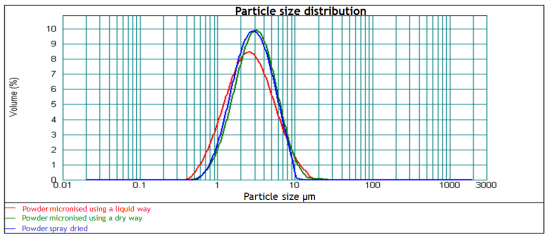
The mini Spray Drier B-191 functions according to the same principle as the co-current flow atomizer, the sprayed product and drying air flow are in the same direction.

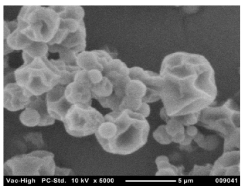
① Air intake
② Heater
③ Nozzle
④ Flow stabilizer intake into the drying chamber
⑤ Cyclone, the product is separated from the air flow here
⑥ Container for collecting finished product
⑦ Filter
⑧ Aspirator

RESULTS

➢ Measuring the particle size distribution of particles obtained from the different processes shows that the narrowest particles size distribution is reached with the spray drying process. Moreover this process provides particles with more suitable morphology (less dense) appropriate for an inhaled formulation.

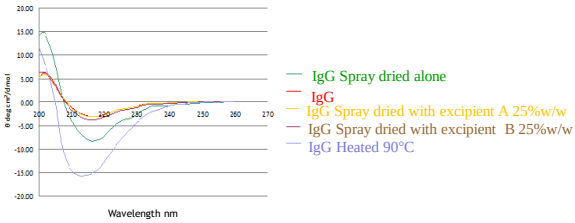






➢ The activity of the macromolecule is tested from different methods: Circular dichroism and Slotblot methods are used to control IgG activity while an HPLC method has been developped for protein product assay. The results show that the IgG is unaltered when spray dried with excipient . These methods confirm the integrity and the activity of the protein micronised or spray dried with the processes developped.

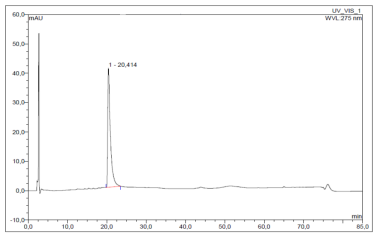
Circular dichroism method



Slot blot method

Well number (10µg)	1	2	3	4	5
Product	IgG Ref	IgG spray dried alone	IgG spray dried with excipient A	IgG spray dried with excipient B	IgG Heated at 90°C

HPLC method



➢ The performance of the inhaled formulation is evaluated using the MMAD value (Mass Median Aerodynamic Diameter) generated just after manufacturing and after 1 month at 40°C/75%RH. The results show that the micronization performed with process A gives better results than process B . In the case of the results obtained with the spray drying process, excipient B provides a better stability in time.

Process	Trial	MMAD µm	
		Initial	1 month 40°C/75%RH
Micronization	Process A	3.5	3.4
	Process B	4.5	4.5
Spray drying	IgG Excipient A	4.1	5.1
	IgG Excipient B	4.6	4.7

CONCLUSION

This study demonstrates that an atomization process in presence of excipient or a micronization process can be used to design macromolecule particles manufactured in inhaled formulation while maintaining their biological activity.

Reference: Thesis of Véronique CARLI, « Etude des moyens de réduction de taille de particules de macromolécules dans le but de fabriquer une formulation pharmaceutique par voie inhalée. »