Particle Engineering Technologies for Inhalable Biopharmaceuticals

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Use of discrete element modelling in a film coater to optimize the tablet film -coating process

Credit: Liang Li, Elise Vaes and Filip Willemse
Pharmaceutical Product Development & Supply, CPDS

IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

IPAC-RS Workshop:
Inhaled Biologics: Preparing for a Future Beyond Small Molecules

September 4-5, 2024

Johnson&Johnson

Outline

1. **Drying of Biopharmaceuticals**
2. **Particle Engineering – Spray- and Freeze-Drying Technologies**
3. **Examples of Inhalable**
4. **Summary and Q&A**

Slides content previously partly presented at: Formulation Delivery 2023.

Drying of Biopharmaceuticals

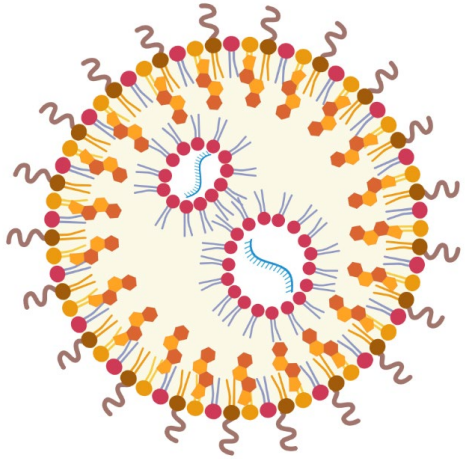
Image: *Multiple myeloma illustration*

Credit: *Johnson & Johnson*

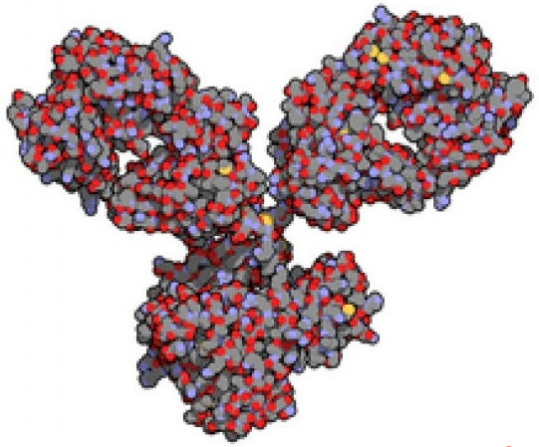
Biopharmaceuticals vs. Small Molecules

Biopharmaceuticals

- Produced by a living organism or derived by a living organism by means of recombinant DNA
- High molecular weight (>1 kDa)
- Function depending on 3D-structure
- Proteins, peptides, RNA and DNA, etc.
- Parenteral delivery/sterile



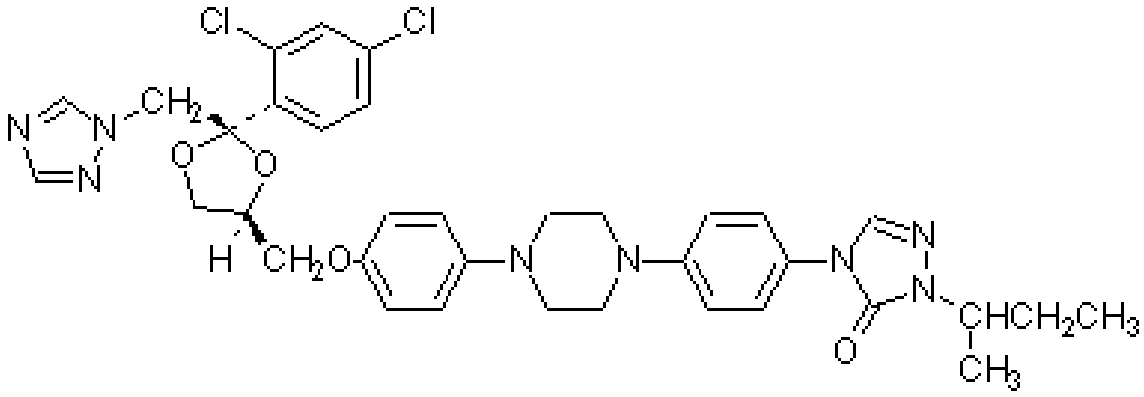
mRNA (280 kDa)



Monoclonal AntiBody (mAb)
Infliximab (144 kDa)

Small Molecules

- Manufactured by controlled and reproducible chemical reactions
- Low molecular weight (<1 kDa)
- Well-defined structure
- Many have low solubility in water
- Oral delivery
- Solid orals, liquid, lyophilized, controlled release (oral and parenteral), inhalation, etc..



Itraconazole (705 Da)

Jung, H.N. et al., "*Lipid nanoparticles for delivery of RNA therapeutics: Current status and the role of in-vivo imaging*", 2022, Theranostics, 12(17), 7509-7531.

Biomolecules vs. Small Molecules 2

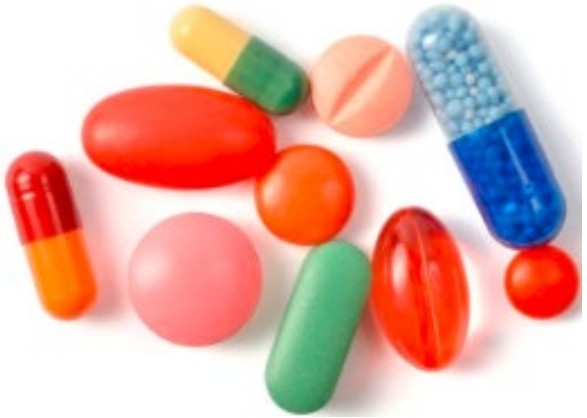
Biomolecules

- Amorphous (typically)
- Highly soluble in water
- *Temperature sensitive*
- High production costs
- Low dose
- Low oral bioavailability
- Parenteral delivery/sterile → **Freeze Drying**

https://www.jnj.com/hiv

Small Molecules

- Crystalline (typically)
- Many have low solubility in water
- Post drying necessary
- High dose
- Low production costs
- High oral bioavailability
- Oral delivery → **Spray Drying**



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Lipid Nanoparticles

Nanoparticles recognized as an enabling technology for both small molecules (poorly soluble) and biopharmaceuticals (DNA, mRNA, etc.)

Lipid nanoparticles

- Biocompatible
- Biodegradable
- Increased penetration-permeation profile
- Low cytotoxicity
- Increased bioavailability

SLN/NLC formulation

- Solid lipid
- Liquid lipid
- Surfactant
- Drying protectant

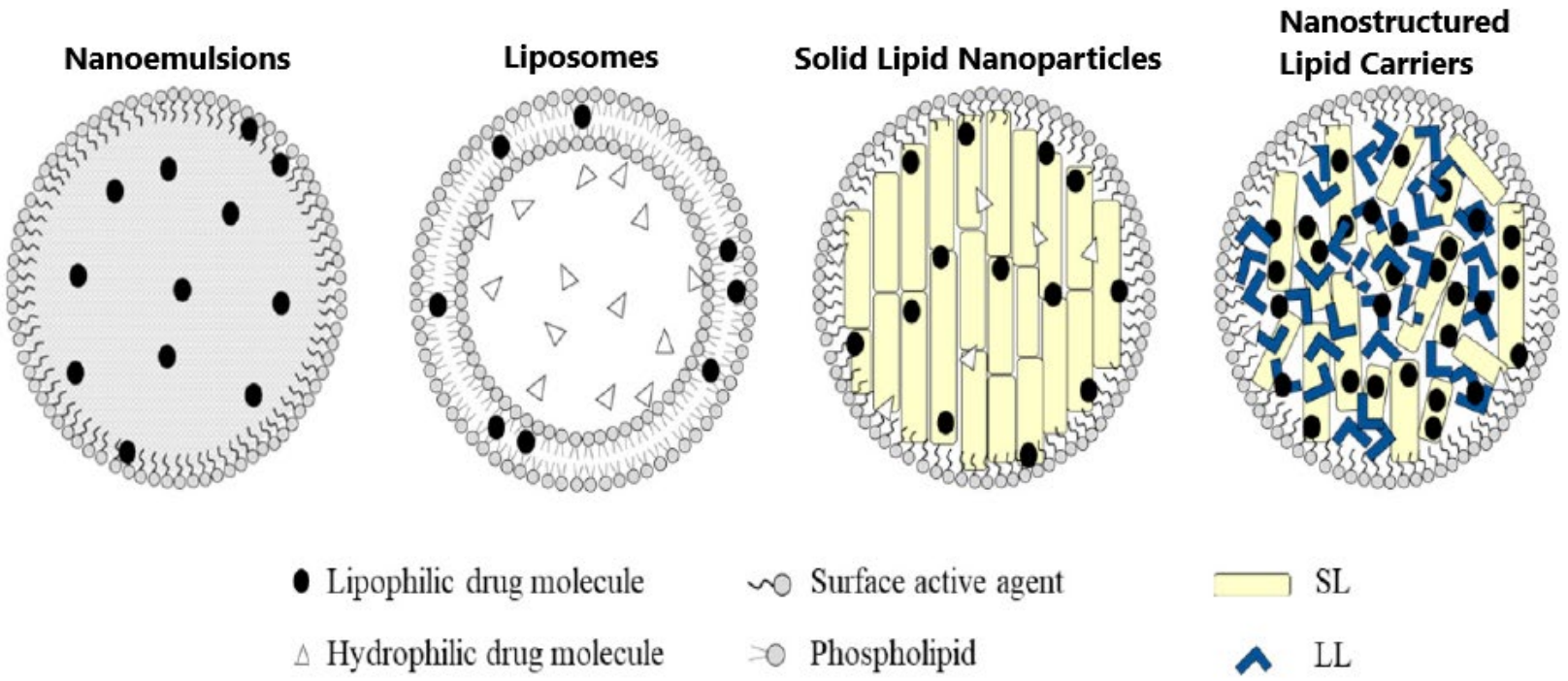


Illustration adapted from Chountoulesi, M. and Demetzos, C., "*Promising Nanotechnology Approaches in Treatment of Autoimmune Diseases of Central Nervous System*", 2020, Brain Sci., V10, 338.
Kuentz et al., "Rational Selection of Bio-Enabling Oral Drug Formulations – A PEARRL Commentary", 2021, J. Pharm. Sci., V110, pp. 1921-1930.
Hou et al., "*Lipid nanoparticles for mRNA delivery*", 2021, Nature Reviews, V6, pp.1078-1094.

Lipid Nanoparticles - Challenges

- Low drug loading
- Drug expulsion
- Stability - Particle size and Polydispersity
- Physical stability - Polymorphic change
- Drug stability

Solid Lipids

Table 1
Solid lipids used in sustained release drug delivery systems.

Lipid excipients	Chemical composition	Properties	Examples	Process
Waxes	Esters of fatty acids and long chain alcohols	Hydrophobic MP = 62–86 °C	Carnauba wax, candelilla wax, rice bran wax, beeswax, solid paraffin (Sasolwax®6403), cetyl palmitate (Precifac®)	Cold, hot
Vegetables oils	Mixture of triglycerides, free fatty acids, phospholipids	Often digestible MP = 60–71 °C	Hydrogenated cottonseed oil (Lubritab®, Sterotex®), hydrogenated soybean oil (Sterotex® K)	Cold, hot
Polyoxylglycerides	Mixture of glycerides and esters of fatty acid and PEG	Partially digestible MP ≈ 50 °C	Stearoyl polyoxyl-6 glycerides (Gelucire® 50/02), stearoyl polyoxyl-32 glycerides (Gelucire® 50/13)	Hot
Fatty acids	Long chain fatty acids	MP = 60–90 °C	Palmitic acid, stearic acid, behenic acid	Cold, hot
Triglycerides	Monoacid triglycerides	MP = 46–73 °C	Glyceryl tripalmitate (Dynasan® 116), Glyceryl tristearate (Dynasan® 118)	Cold, hot
Partial glycerides	Mixtures of mono-, di-, and triglycerides	MP = 54–74 °C	Glyceryl distearate (Precirol® ATO 5), glyceryl monostearate (Myvaplex™ 600; Imwitor®491), glyceryl behenate (Compritol® 888 ATO)	Cold, hot
Fatty alcohol	Mixture of fatty alcohols	MP = 48–56 °C	Cetostearyl alcohol, cetyl alcohol	Cold, hot

Liquid lipids

- Miglyol 812 (MCT)
- Kollisolv MCT 70 (MCT)
- Labrafac Lipophile WL 1349
- Oleic Acid
- Squalene

Drying Excipients

- Lactose
- Sucrose
- Trehalose
- Mannitol
- PVP
- L-Leucine
- Dextran

Surfactants

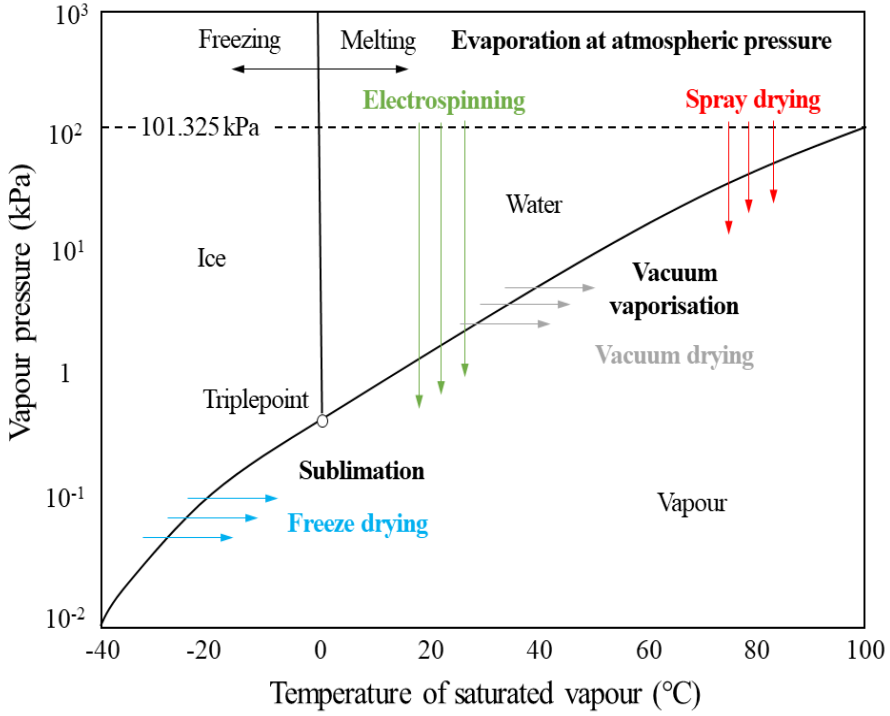
- Polysorbate 80
- Poloxamer 188
- Phosphatidylcholine (soy, egg)
- Poloxamer 407

Table from Rosiaux et al., "*Solid lipid excipients—Matrix agents for sustained drug delivery*", 2014, J. Cont. Release, V188, pp.18-30.
Doktorovova, S., Shegokar, R. and Souto, E.B., "*Role of Excipients in Formulation Development and Biocompatibility of Lipid Nanoparticles (SLNs/NLCs)*", 2017, Nanostructures for Novel Therapy, Ch. 30, pp. 811-843.
Salminen et al., "*Influence of spray drying on the stability of food-grade solid lipid nanoparticles*", 2019, Food Res. Int., V119, pp. 741-750

Drying of Pharmaceuticals – Potential Approaches

Drying of Pharmaceuticals – Why?

- Pharmaceuticals are more stable in the solid state
- Reduction of transportation costs
- Ease of handling and storage



Spray Drying

- *Investment/Operating costs: 5-8 times lower than FD*
- Organic solvents feasible
- High capacity & Continuous Process
- Particle Engineering
- PAT might be applied

Freeze Drying

- Injectables/Parenterals
- Sterile manufacturing
- High yields
- Small volumes

Spray Drying feasible for:

- Powder properties important for functionality e.g. Oral Dosage Forms, **Inhalable Particles**
- Large volumes
- Low/Medium Heat sensitive products

Freeze Drying feasible for:

- Injectables/Parenterals/Sterile products
- Small volumes
- Heat sensitive products

Vass et al., "*Drying Technology Strategies for Colon-Targeted Oral Delivery of Biopharmaceuticals*", 2019, J. Cont. Rel., Vol. 296, pp.162-178.
Walton and Mumford, 1999, "*Spray Dried Products – Characterization of Particle Morphology*", Trans IChemE, V77, pp. 21-38.

Particle Engineering using Spray- and Freeze-Drying Technologies

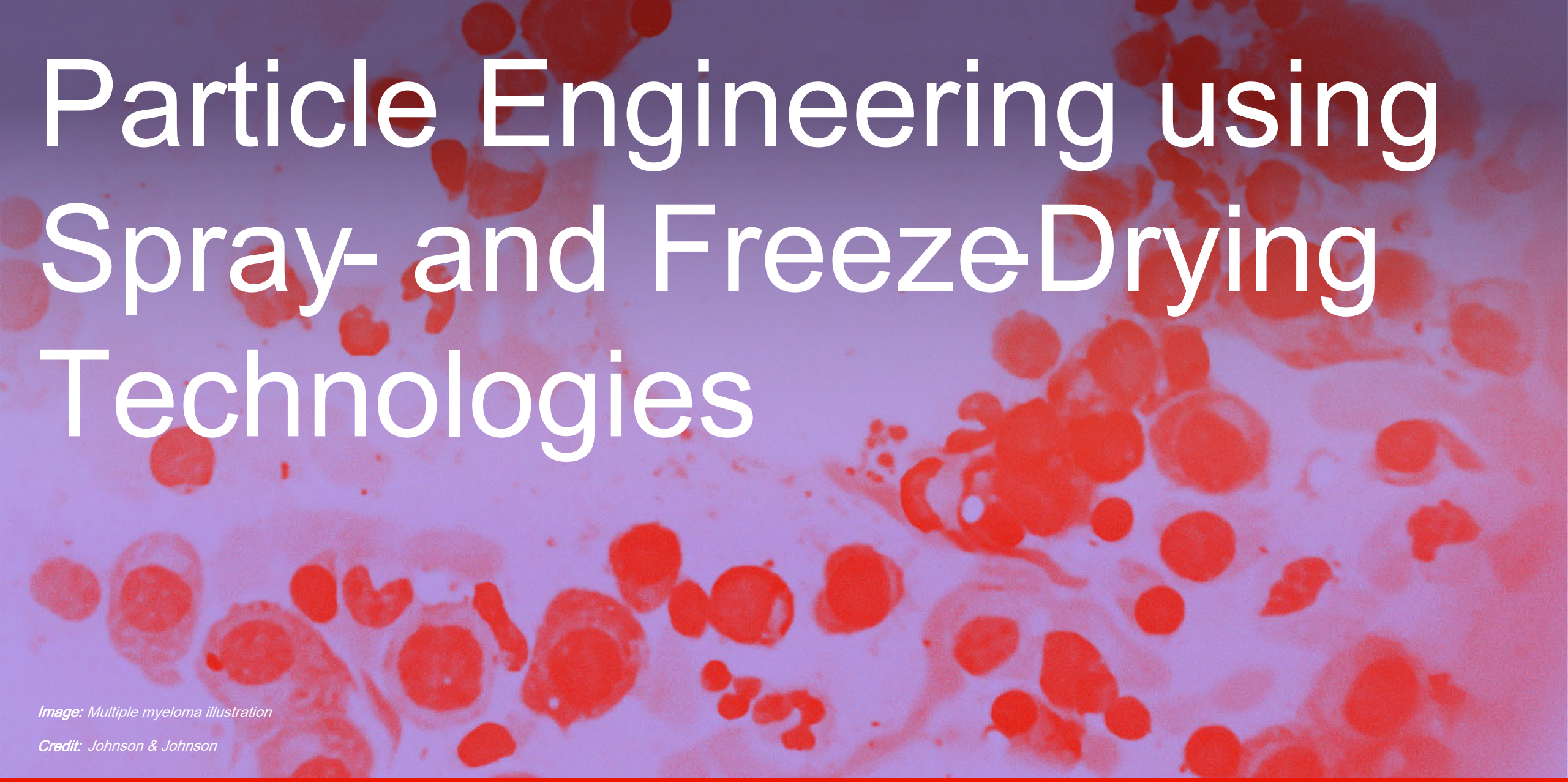


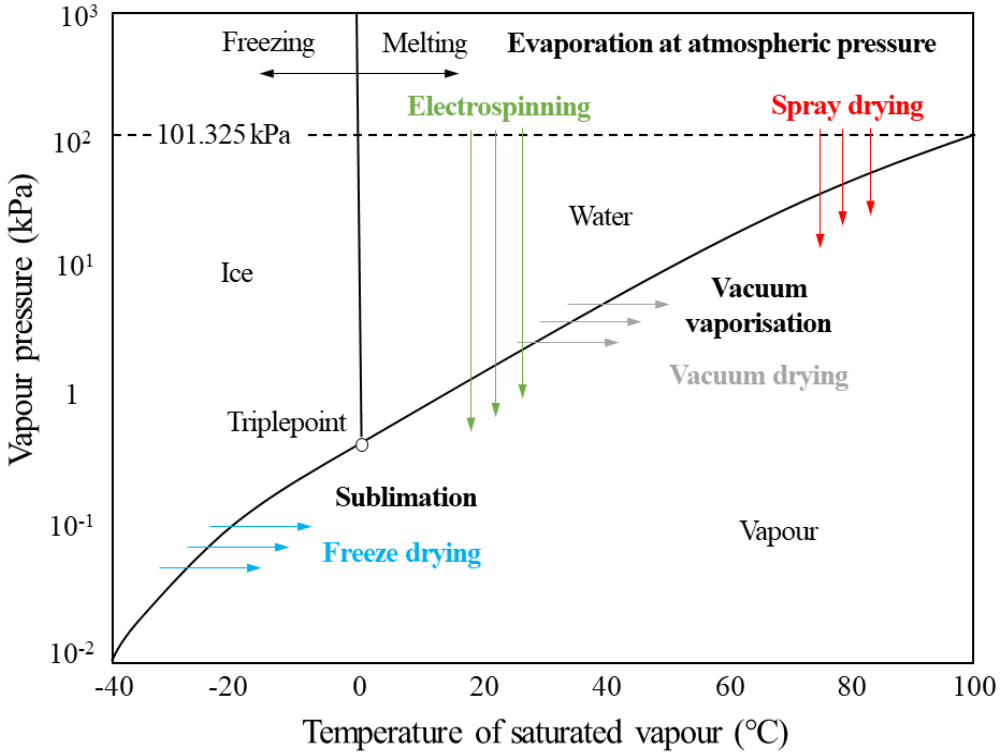
Image: *Multiple myeloma illustration*

Credit: *Johnson & Johnson*

Drying Processes for Inhalable Biopharmaceuticals

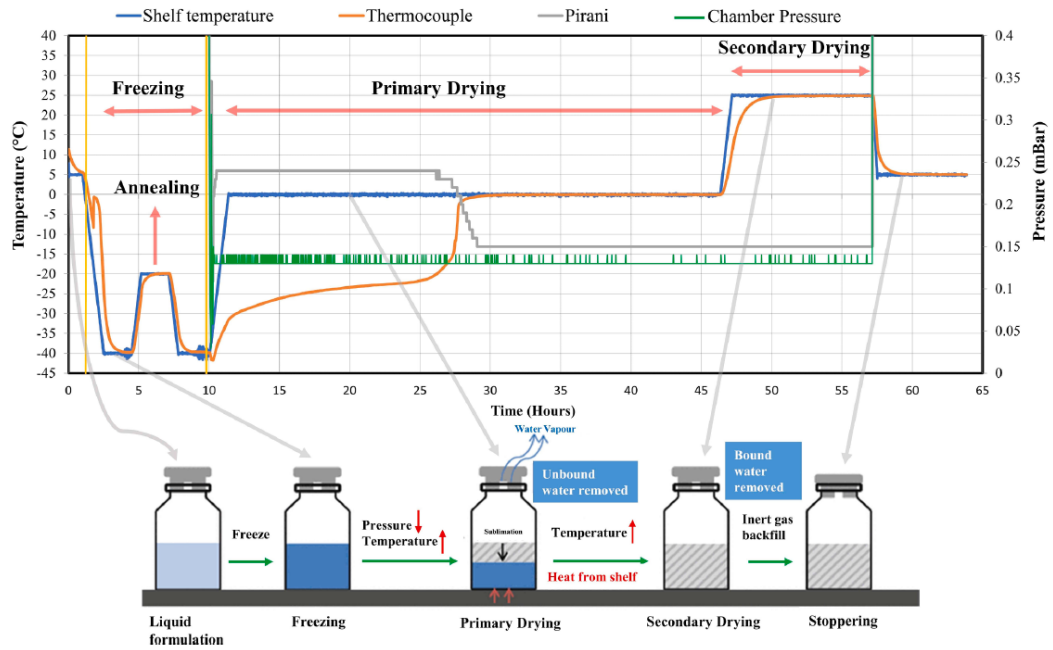
Drying ± Milling (+ Powder Filling)

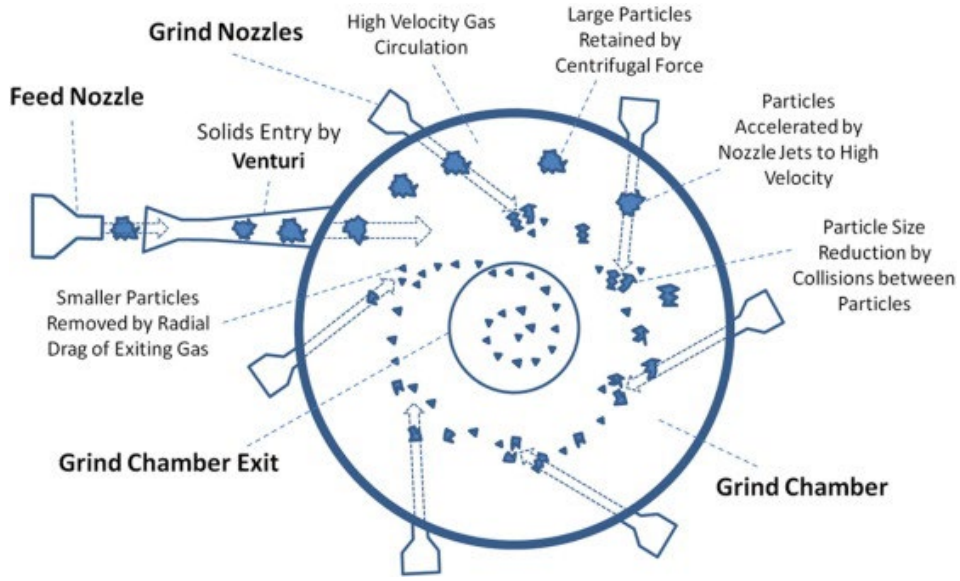
1. Spray Drying
2. Electro-spraying/-spinning + Milling (spinning)
3. Spray-Freeze Drying
4. Supercritical Drying
5. Continuous Bulk Freeze Drying + Milling
6. Active Freeze Drying + Milling
7. Thin Film Freeze Drying
8. Drying (particles) + Atomic Layer Deposition
9. .....



Walters et al., 2014, "*Next Generation Drying Technologies for Pharmaceutical Applications* ", J. Pharm Sci., V103, pp. 2673-2695.
Vass et al., 2019, "*Drying Technology Strategies for Colon-Targeted Oral Delivery of Biopharmaceuticals*", J. Cont. Rel., Vol. 296, pp.162-178.
Sharma et al., 2021, "*Innovative Drying Technologies for Biopharmaceuticals*", Int. J. Pharm., V609, Article 121115.
Samborska et al., 2022, "*Innovations in spray drying processes for food and pharma industries*", J. Food Eng., V321, Article 110960.

Freeze Drying + Jet Milling





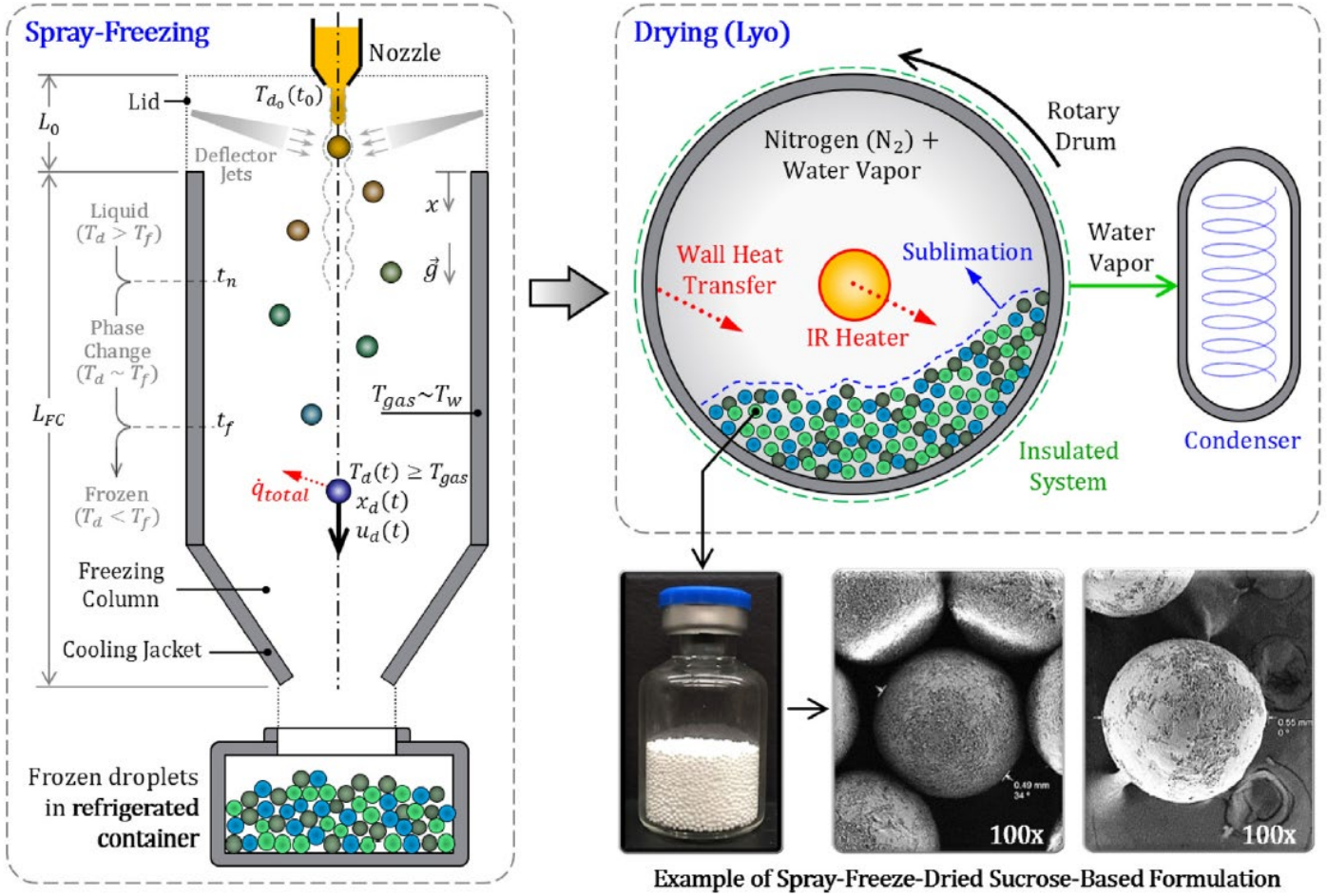
- **Advantages**
  - + Low temperature drying
  - + High yield
  - + Sterile manufacturing *(Pharma)*
  - + Preservation of shape *(Food)*

- **Challenges**
  - Long drying times
  - Expensive
  - *Difficult to scale -up*
  - Stresses during freeze drying (freezing and dehydration) and milling (mechanical)

Sharma et al., 2021, "*Innovative Drying Technologies for Biopharmaceuticals*", Int. J. Pharm., Vol. 609, Article 121115.
C. Ratti, 2013, "*Freeze drying for food powder production*", in Handbook of Food Powders, Woodhead Publishing, DOI : 10.1533/9780857098672.1.57, pp. 57-84.
Yang et al., 2024, "*Characterization and biological activity evaluation of water-soluble resveratrol complexes obtained by spray drying, ball milling and jet milling*", J. Drug Del. Sci. Tech. V100, doi.org/10.1016/j.jddst.2024.106075.
Macdonald et al., 2016, "*The spiral jet mill cut size equation*", Powder Tech. V299, pp. 26-40, dx.doi.org/10.1016/j.powtec.2016.05.016.

Spray-Freeze Drying

"2-step production of a dry powder by 1) Atomization of a liquid into droplets and freezing the droplets by a cold gas, liquid or surface, and 2) freeze drying the frozen particles"



Example of Spray-Freeze-Dried Sucrose-Based Formulation

Advantages

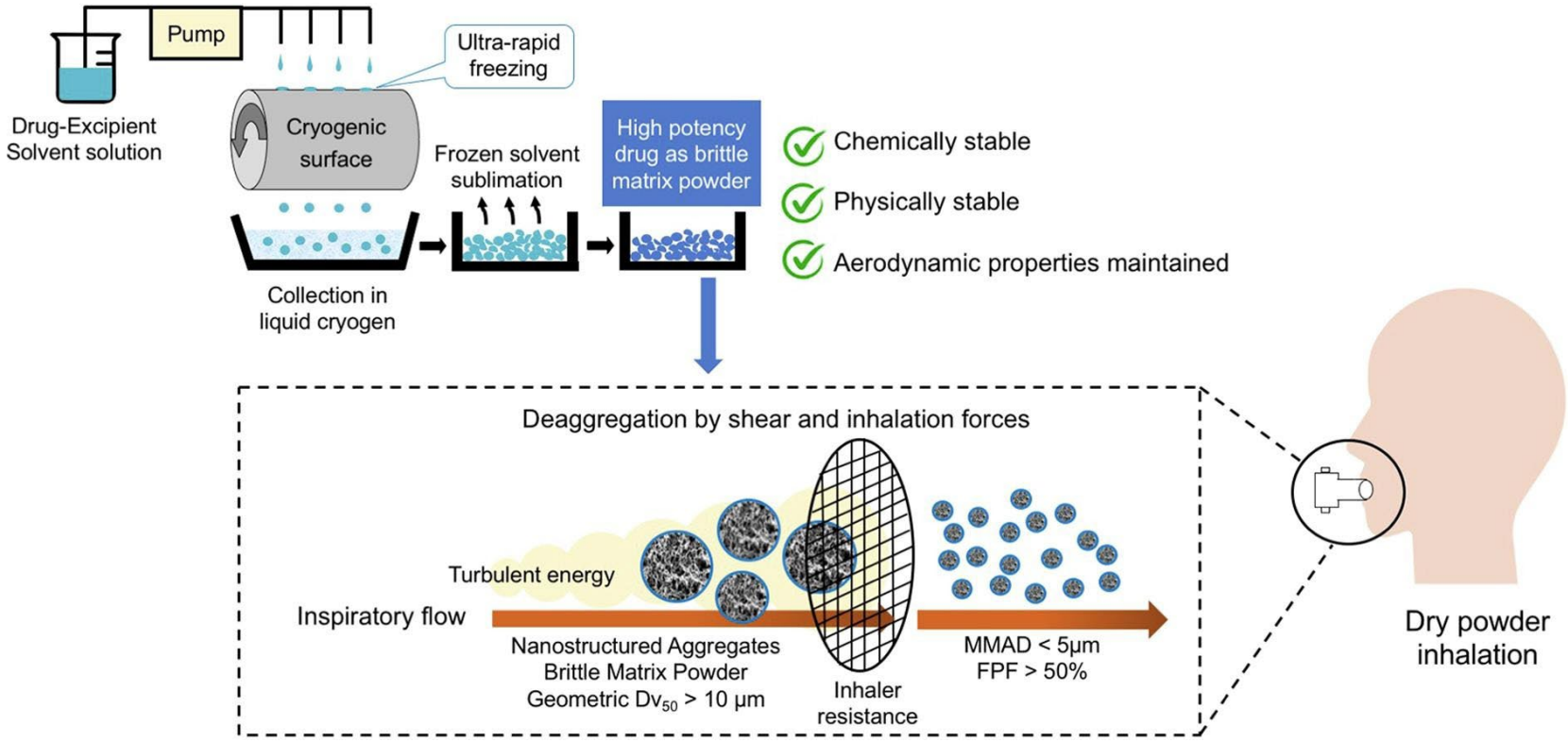
+ Ideal for heat sensitive proteins
+ High yield

Challenges

- Scale-up challenging
- Capacity
- Freezing and dehydration stresses

I.B. Sebastiao et al., 2019, "*Bulk Dynamic Spray Freeze-Drying Part 2 - Model-Based Parametric Study for Spray-Freezing Process Characterization*", J. Pharm Sci., Vol. 108, pp.2075-2085.
Chang et al., 2021, "*Dry powder pharmaceutical biologics for inhalation therapy*", Adv. Drug Del. Reviews, V172, pp. 64-79.
Farinha et al., 2023, "*Spray Freeze Drying of Biologics: A Review and Applications for Inhalation Delivery*", Pharm. Res., V40, doi.org/10.1007/s11095-022-03442-4.

Thin-Film Freeze-Drying Technology for Inhalation



Advantages

+ Ideal for heat sensitive proteins
+ Minimal air/water interface

Challenges

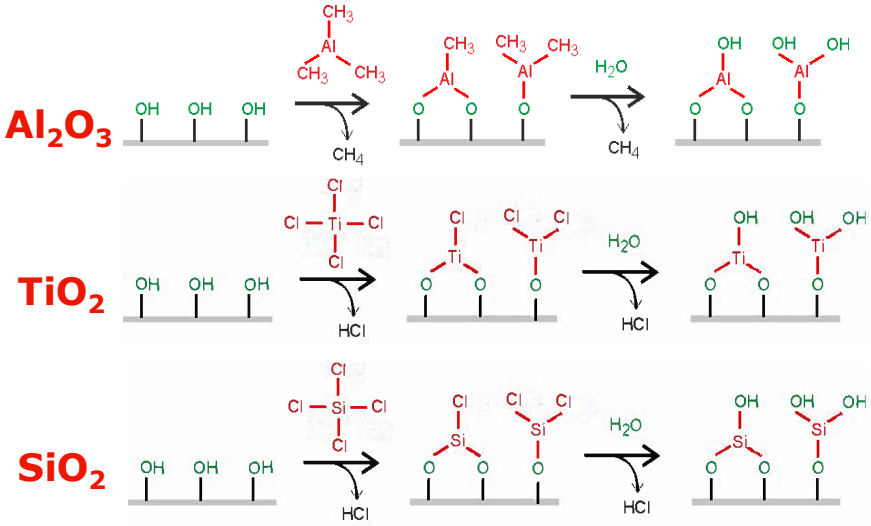
- High specific surface area
- Low density particle
- Freezing and dehydration stress

Sahakijpijam et al., "*Using thin film freezing to minimize excipients in inhalable tacrolimus dry powder formulations*", 2020, Int. J. Pharm., V586, 119490.
Chang et al., "*Dry powder pharmaceutical biologics for inhalation therapy*", 2021, Adv. Drug Del. Reviews, V172, pp. 64-79.

Atomic Layer Deposition

- Technology from the semiconductor industry
  - Layer is well-controllable in nm-size range
  - Nonconformal object are uniformly coated

- Idea/Purpose:
  - Improve powder processability (i.e. dispersibility, flowability)
  - Improved stability against water and oxygen



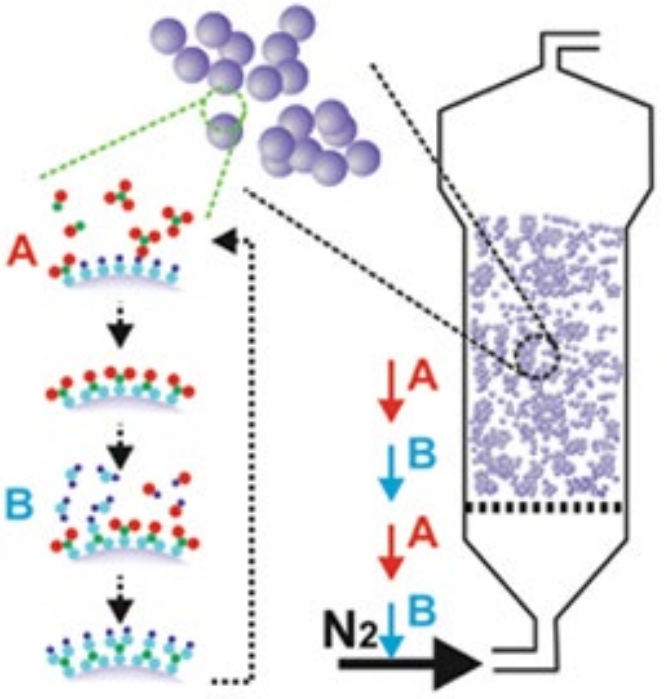
Advantages

+ Improved dispersibility and flowability

+ Small excipient amount (typically 1-5 wt.%)

Challenges

- New technology (supplier, benefits, …)
- *Mainly metaloxides as coatings*
- Toxicology
- ….

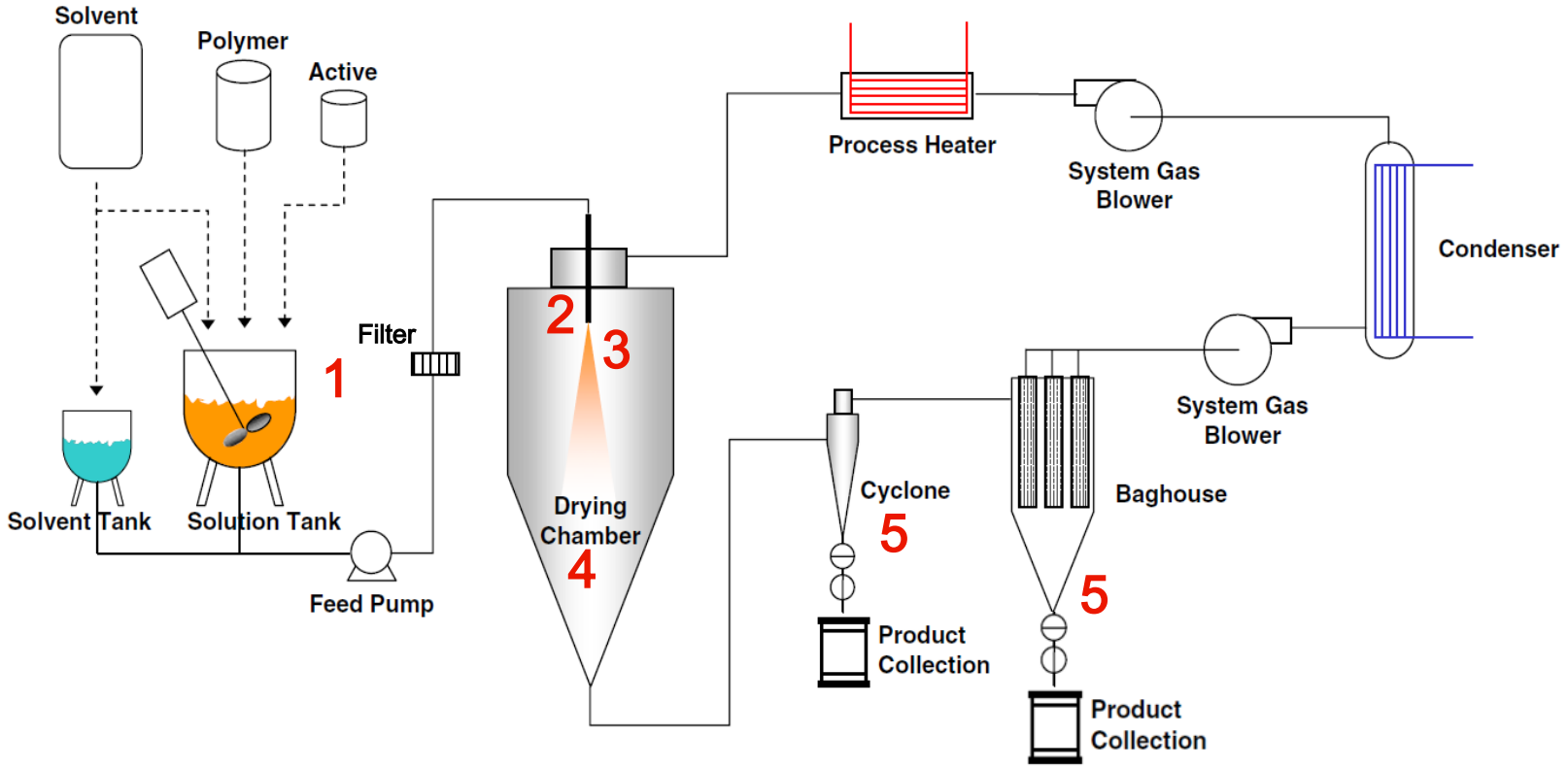


La Zara et al., 2021, "*Controlled Pulmonary Delivery of Carrier-Free Budesonide Dry Powder by Atomic Layer Deposition*", ACS Nano, V15, doi.org/10.1021/acsnano.0c10040.
R. van Ommen, 2020, "ALD on particles - Scalable production of nanostructured materials", NEVAC Blad, 58(2); https://nevac.nl/archief_pdf/pdf_194.pdf.

Spray Drying – Concept & Elements

"1-step production of a dry powder by atomization of a liquid into droplets with simultaneous exposure to a hot gas, whereby the liquid is evaporated"

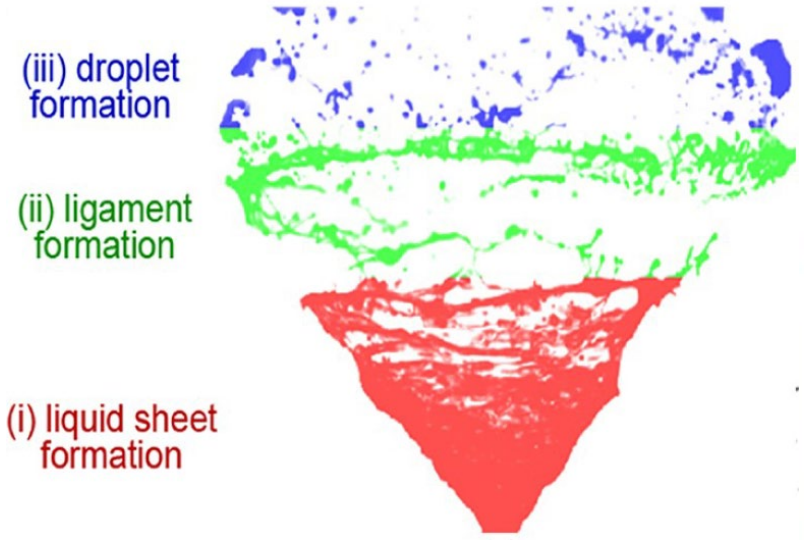
1. Solution Preparation including Filtration
2. Atomization
3. Mixing of droplets and the drying gas
4. Drying
   - Inlet 80-200 °C
   - Outlet 30-80 °C
5. Separation of particles and gas

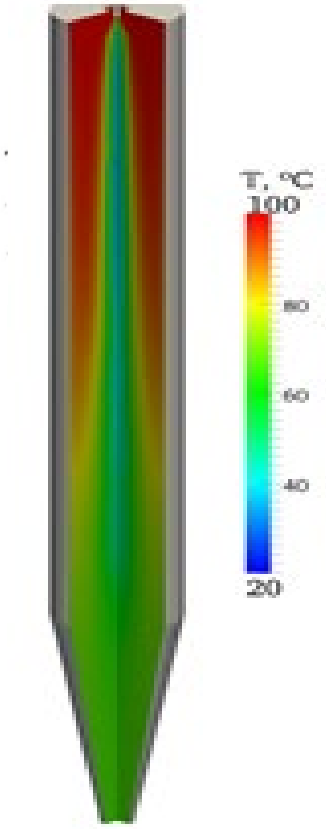


Dobry et al. "*A Model-Based Methodology for Spray-Drying Process Development*", J. Pharm. Innov., 2009, Volume 4, pp. 133-142.

Stresses in Spray Drying

- **Atomization stresses:**
  - Shear forces
- **Thermal stresses:**
  - Inlet & outlet temperature
  - Residence time
  - Formulation (proteins at the Air-Water interface)
- **Powder recovery system:**
  - Temperature
  - Humidity
  - Residence time





CFD simulation shown courtesy Hovione FarmaCiencia S.A.

Atomization illustration from Shrestha et al., "*Primary break-up and atomization characteristics of a nasal spray*", 2020, PLOS ONE., V15(8):e0236063.

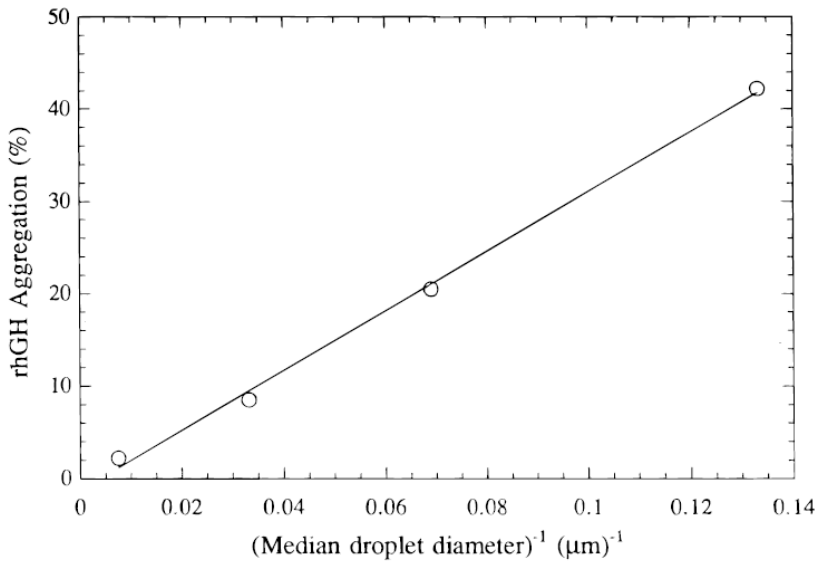
Degradation Examples

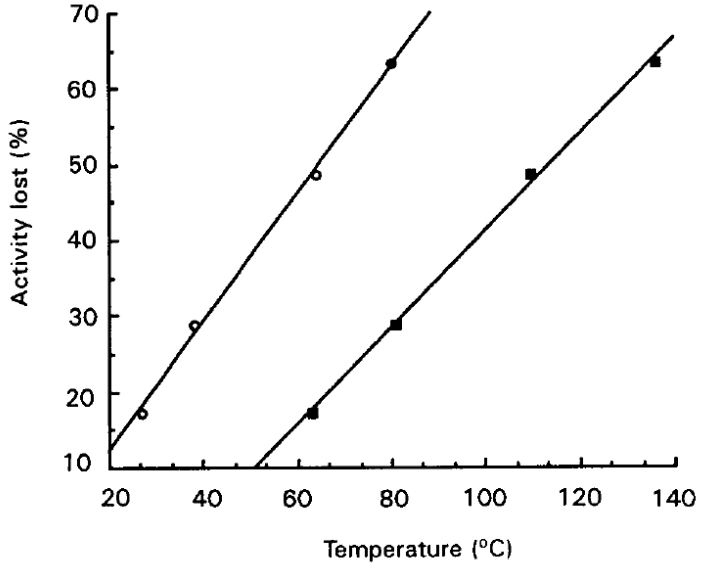
▪Human Growth Hormone

- Degradation by Air-Water interface exposure i.e. high atomization force (small droplets)
- Degradation reduced by use of surfactant (Tween20)

▪ β-Galactosidase

- Degradation by temperature (same atomization conditions)
- Degradation reduced by use of excipients (Sucrose, Trehalose)





Broadhead et al., "*The effect of process and formulation variables on the properties of spray dried b-galactosidase",* J. Pharmacy and Pharmacology, 1994, V46, pp. 458–467.
Mumenthaler et al., "*Feasibility study on spray-drying protein pharmaceuticals: recombinant human growth hormone and tissue-type plasminogen activator"*, 1994, Pharm. Res. V11, pp. 12-20
Maa et al., "*Spray-Drying of Air-Liquid Interface Sensitive Recombinant Human Growth Hormone"*, 1998, J. Pharm. Sci., V87(2), pp. 152-159.

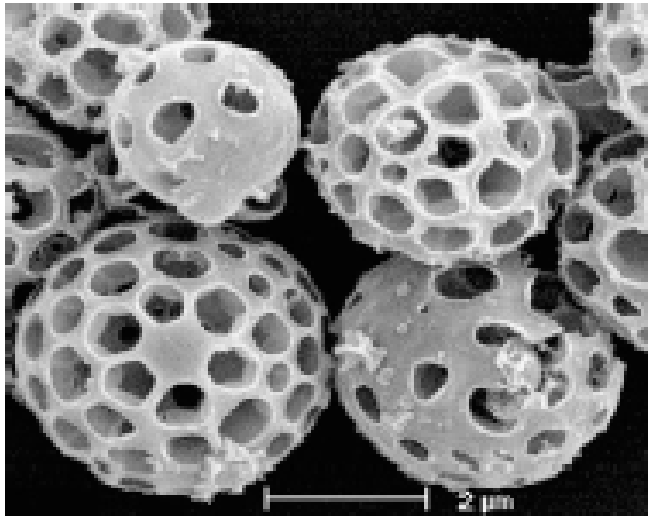
Spray Drying Quality-by-Design – Prior Knowledge, Impact on CQA's, and Critical Process Parameters

1. **Formulation** impacts physical and chemical properties
   - Concentration, Viscosity and Solvent(s) choice, Polymer type, API:polymer (sugar) ratio
   - Viscosity: Atomizer type & Droplet size
2. **Atomisation** (droplet size) impacts primarily Particle Size and Solvent Cont.
   - Specific atomizer design
   - *2-Fluid Nozzle:* Liquid & Atomisation Gas flow rate, Ratio between flow rates
   - *Pressure Nozzle:* Pressure (Liquid flow rate)
3. **Droplet -Gas Contact** impacts primarily Morphology and Density
   - Drying Gas flow rate
   - Gas disperser design (fixed)
4. **Drying** impacts Solvent Cont., Activity, Purity, HMWP, T_g
   - Drying Gas flow rate
   - Inlet temperature
   - Liquid flow rate
   - Condenser temperature
   - Outlet temperature = func. (Inlet T, Liquid flow rate, Drying gas flow rate, Condenser T and Liquid properties)
   - Relative Saturation = func. (Inlet T, Liquid flow rate, Drying gas flow rate, Condenser T and Liquid properties)
5. **Collection** impacts Solvent Cont., Activity, Purity, HMWP, T_g
   - Collector design: Cyclone vs. Bag-filter
   - Residence time
6. **Post Drying** impact Solvent Cont.
   - Temperature
   - Time

Formulation, Process Understanding and CQAs

Process understanding – Spray Drying & Formulation:

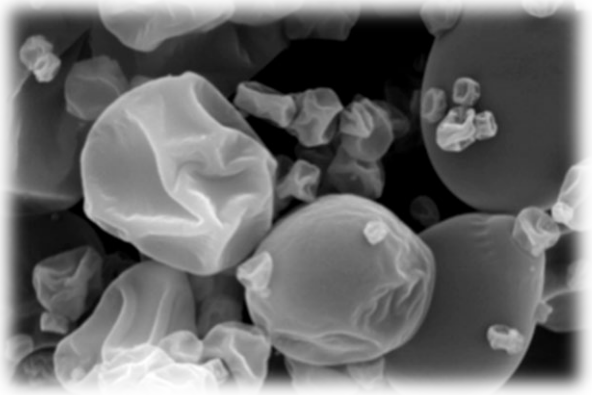
- Impact of spray drying parameters on the Critical Quality Attributes (CQAs)
- Interaction between process parameters
  - E.g. through Design-of-Experiments (DoE)
- Critical Material Attributes impact on CQAs
  - Solution composition (solvents)
  - Excipients (polymers, sugars)
  - Surfactants



Pulmospheres™
Vehring, R. "Pharmaceutical Particle Engineering via Spray Drying", 2008,
DOI: 10.1007/s11095-007-9475-1.

Typical Critical Quality Attributes:

- Impurity profile / High Molecular Weight Protein
- Residual Solvent
- Particle size
- Powder density
- Flowability (*inc. with particle size and density*)
- Particle shape (inhalation)
- API form (crystalline vs. amorphous)
- Yield (process quality attribute)



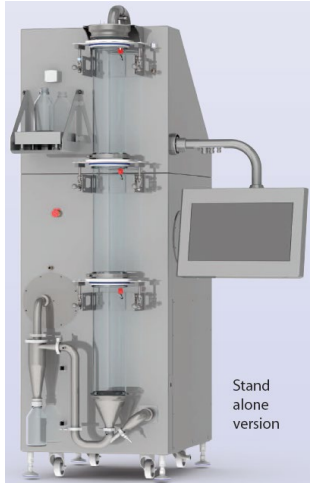
The strategy for scaling up a spray drying process will depend on the specific product:

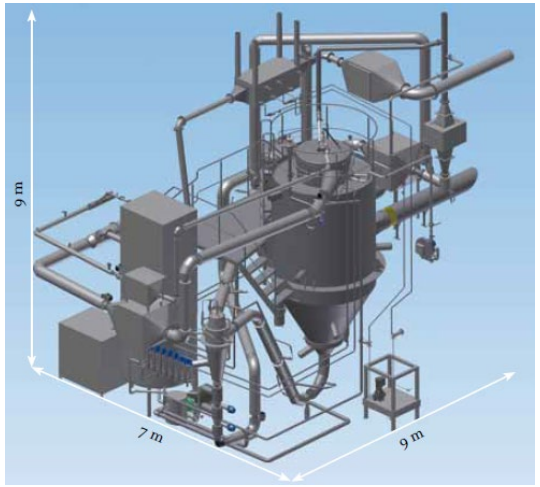
- **Pulmonary** — **Particle size maintained**
- **Solid Dosage Form** — **Increase particle size/flowability**

Spray Drying Platforms- Inhalation

Spray Dryer Size	Drying Gas Flow Rate	Powder Production Rate [1]	Residence Time	Particle Size (D_{v50})	Yield	
					Cyclone	Bag Filter
Lab (Buchi)	30 kg N_2/h	0.005 kg/h	2 s	2 – 15 µm	50-90%	NA
Lab (ProCepT)	30 kg N_2/h	0.005 kg/h	5 s	2 – 50 µm	50-90%	NA
Small Pilot/Commercial (PSD-1)	100 kg N_2/h	0.05 kg/h	25 s	2 – 40 µm	40-80%	≥80%
Commercial (PSD-4)	1.250 kg N_2/h	1 kg/h	45 s	2 – 120 µm	40-80%	≥80%
Commercial XL (PSD-7)	10.000 kg N_2/h	8 kg/h	45 s	2 – 120 µm	40-80%	≥80%

[1] 2 wt.% aqueous solution





Examples of Inhalable Biopharmaceuticals

Image: *Multiple myeloma illustration*

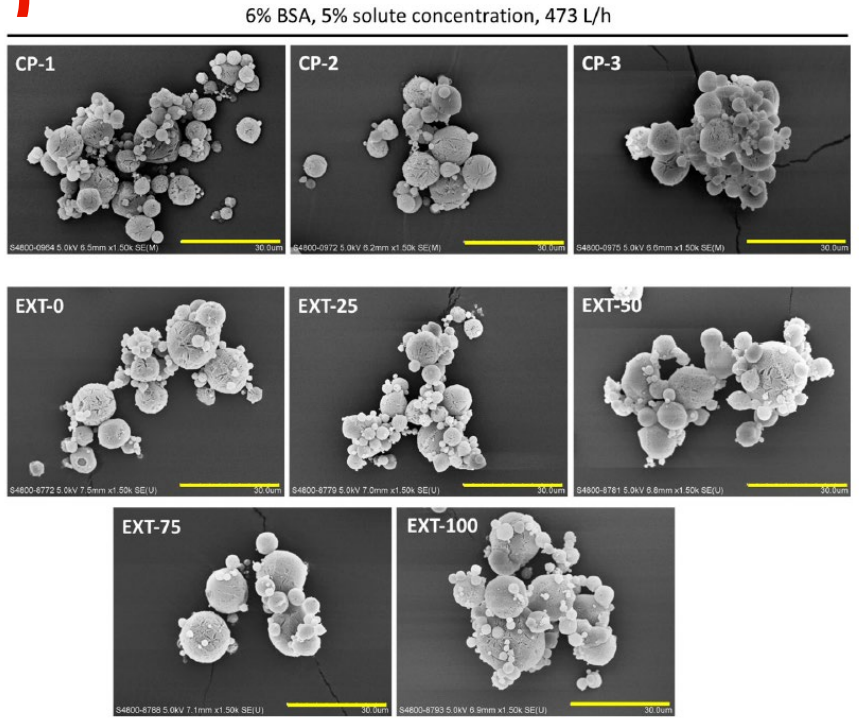
Credit: *Johnson & Johnson*

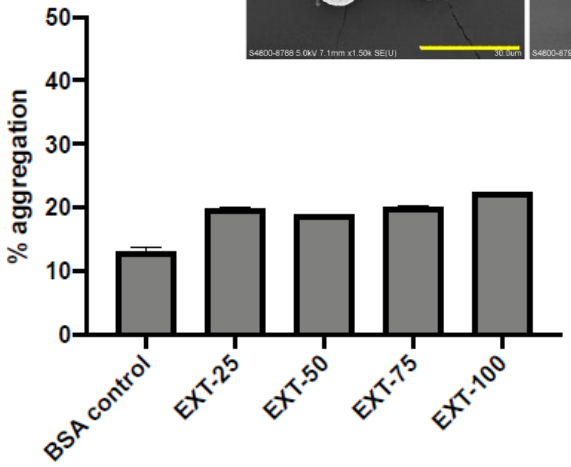
Spray-Freeze Drying of BSA with HP-β-CD

- BSA protein with HP-β-CD
- 5 wt.% total solids in water
- **Spray-Freeze Drying:** 2-fluid nozzle into liquid nitrogen
- Good aerodynamic properties, but BSA aggregation
- Atomization gas flow rate critical for aerodynamic properties and aggregation

Formulation	Volumetric Diameter				EF (%)	FPF (%)	MMAD (μm)
	D_{10} (μm)	D_{50} (μm)	D_{90} (μm)	Span			
CP-1	4.3 ± 0.1	10.8 ± 0.3	24.7 ± 1.0	1.9 ± 0.0	96.5 ± 0.5	60.4 ± 6.4	2.1 ± 0.5
CP-2	4.3 ± 0.1	10.8 ± 0.2	24.8 ± 0.3	1.9 ± 0.0	95.4 ± 0.9	59.8 ± 8.1	2.0 ± 0.8
CP-3	4.3 ± 0.0	10.6 ± 0.1	24.4 ± 0.3	1.9 ± 0.0	95.7 ± 1.1	61.1 ± 8.7	1.5 ± 0.2
EXT-0	3.9 ± 0.1	9.9 ± 0.3	24.4 ± 0.9	2.1 ± 0.0	98.5 ± 0.6	60.5 ± 2.7	1.8 ± 0.2
EXT-25	4.0 ± 0.0	10.4 ± 0.2	25.5 ± 0.5	2.1 ± 0.0	100 *	65.5 ± 1.7	1.4 ± 0.0
EXT-50	4.1 ± 0.0	11.1 ± 0.3	27.2 ± 1.2	2.1 ± 0.1	100 *	63.6 ± 1.8	1.4 ± 0.1
EXT-75	3.9 ± 0.1	10.8 ± 0.7	27.2 ± 1.9	2.2 ± 0.0	98.3 ± 0.7	54.7 ± 3.3	2.1 ± 0.3
EXT-100	3.8 ± 0.0	11.7 ± 0.5	31.1 ± 2.0	2.3 ± 0.1	98.4 ± 0.4	52.3 ± 4.7	2.5 ± 0.6

* The amount of protein in the capsule and inhaler was below the lower limit of the standard curve (i.e., unrecoverable from the capsule and inhaler).

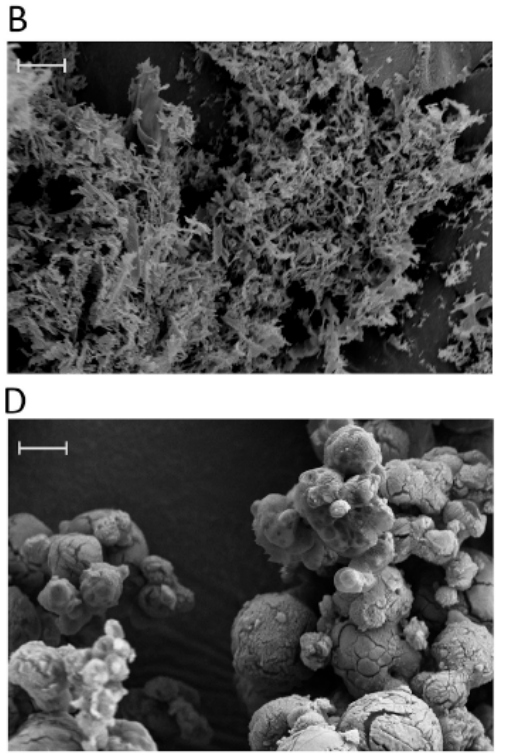


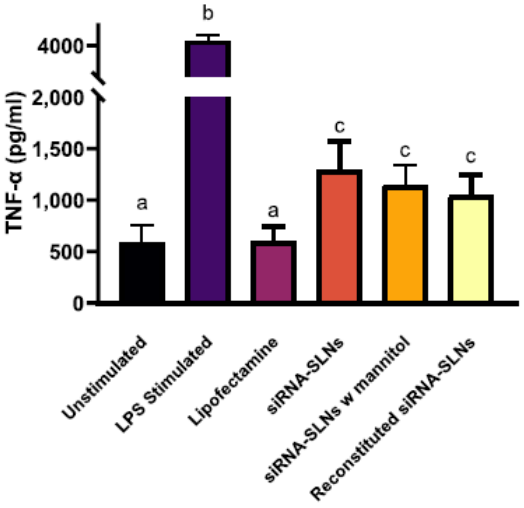


Lo, J.C.K., Pan, H.W. and Lam, J.K.W., 2021, "*Inhalable Protein Powder Prepared by Spray-Freeze-Drying Using Hydroxypropyl-Cyclodextrin as Excipient*", Pharmaceutics, V13, doi.org/10.3390/pharmaceutics13050615

Thin-Film Freeze-Drying of Inhalable SLN with siRNA

- **Formulation:**
  - Lecithin, Cholesterol, Stearoyl Hydrazone PEG, DOTAP, TNF-α siRNA, Mannitol
  - Particle size = 150-200 nm
- **Powders produced by TFFD, Spray Drying, and Freeze Drying**
  - After Freeze Drying SLN particle size not preserved
  - SLN particle size preserved after TFFD and Spray Drying
- TFFD powder had the best aerosolization properties and preserved siRNA functionality



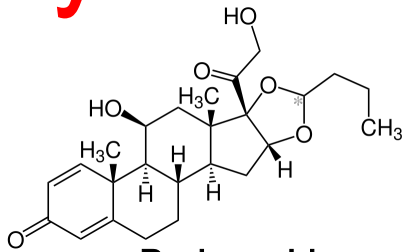


	Spray dried	TFFD	Shelf freeze-dried
Specific surface area (m^2/g)	0.92 ± 0.12	19.34 ± 2.57*	ND
Moisture content (%)	1.17 ± 0.04	0.23 ± 0.07*	0.35 ± 0.12*
FPF%	22.42 ± 12.88	37.01 ± 4.52*	ND
MMAD (μm)	5.97 ± 1.73	3.96 ± 0.97*	ND
GSD	2.30 ± 0.49	3.25 ± 0.61	ND

Wang et al., "*Aerosolizable siRNA-encapsulated solid lipid nanoparticles prepared by thin-film freeze-drying for potential pulmonary delivery*", 2021, Int. J. Pharm., V596, 120215.

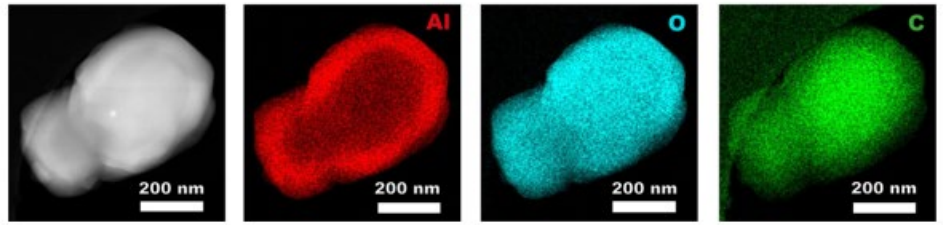
Inhalable Budesonide by Atomic Layer Deposition

- **Formulation:**
  - Budesonide coated with SiO_2, TiO_2 and Al_2O_3 with varying thicknesses
- Coating improves FPF 2-fold
- Type of metal oxide seems to impact cell viability
- Release can potentially be tailored through layer thickness
- Atomic Layer Deposition seems to be a viable technique for controlled pulmonary delivery

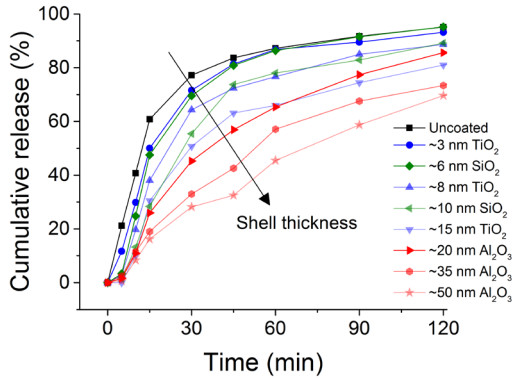


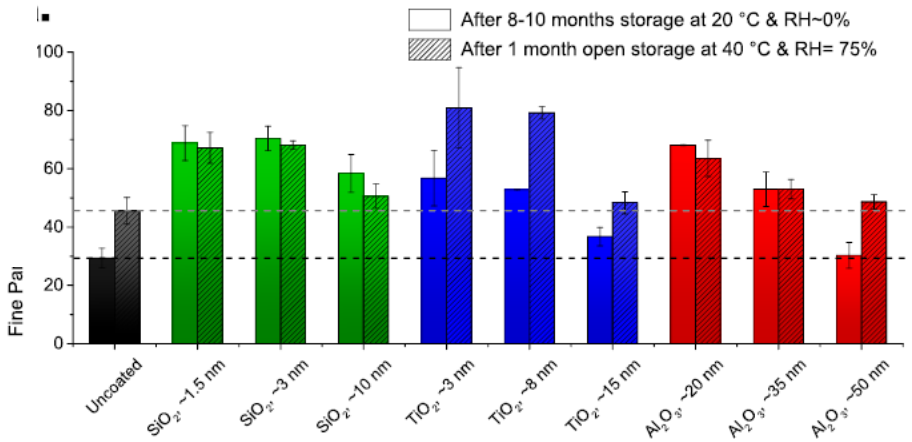
Budesonide

Al_2O_3



sample		loading (wt %)	ALD time (h)	t50 *in vitro* (min)	FPF (%)	cell viability (%)
uncoated budesonide		100		12.3	29.4	98.7 ± 4.6
SiO_2/ budesonide	6 nm	95.9	9.4	16.7	68.3	
	10 nm	93.2	18.8	27.0	58.4	86.2 ± 19.6
TiO_2/ budesonide	3 nm	96.2	1.9	15.0	56.8	
	8 nm	89.3	4.8	21.8	52.8	
	15 nm	78.9	9.6	29.5	36.7	81.2 ± 4.0
Al_2O_3/ budesonide	20 nm	93.9	2	36.1	68.1	
	35 nm	85.6	5	52.6	53.0	
	50 nm	81.3	10	61.6	30.3	95.0 ± 10.0

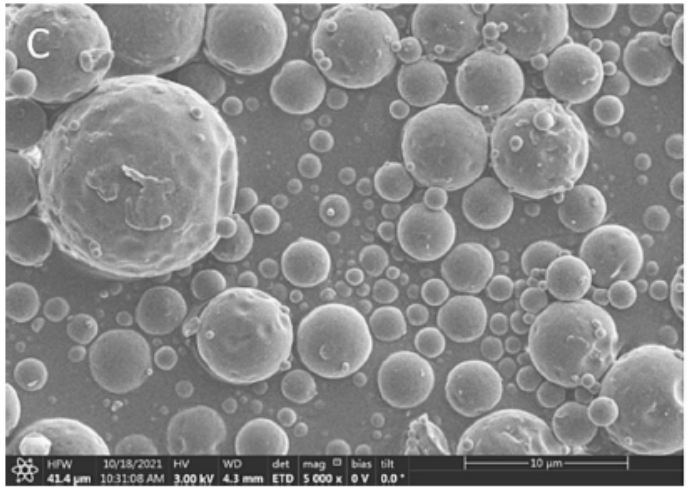


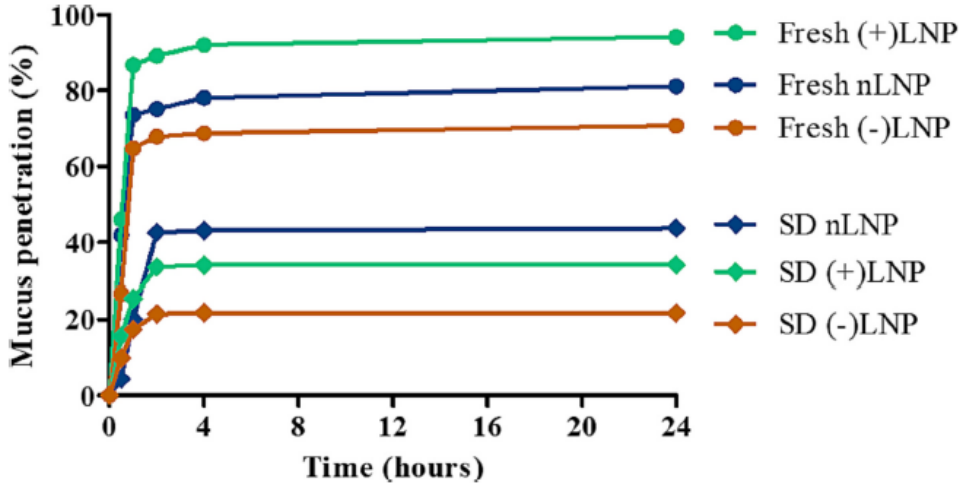


La Zara et al., 2021, "*Controlled Pulmonary Delivery of Carrier-Free Budesonide Dry Powder by Atomic Layer Deposition*", ACS Nano, V15, doi.org/10.1021/acsnano.0c10040.
Moseson et al., 2022, "*Atomic Layer Coating to Inhibit Surface Crystallization of Amorphous Pharmaceutical Powders*", ACS Appl. Mater. Interfaces, V14(36), doi.org/10.1021/acsami.2c12666.

Spray Drying of Lipid NP for Inhalation – siRNA

- **Formulation:**
  - siGFP, Ionizable cationic lipid (analog of DLin-MC3-DMA), Cholesterol, PEG-DMG, Lactose
  - Particle size = ~150 nm
- **Spray drying at Buchi B-290:**
  - Yield = ~65%
  - Outlet temperature = 62°C and 72°C (deg.)
  - Particle size similar before/after SD
  - Moisture content = 3-4 wt.%
  - MMAD = 2.9 µm
  - Fine Particle Fraction = 28%
- Spray dried LNPs penetrated lung mucus
- Bioactivity with 90% protein downregulation
- 50% gene silencing of GADPH

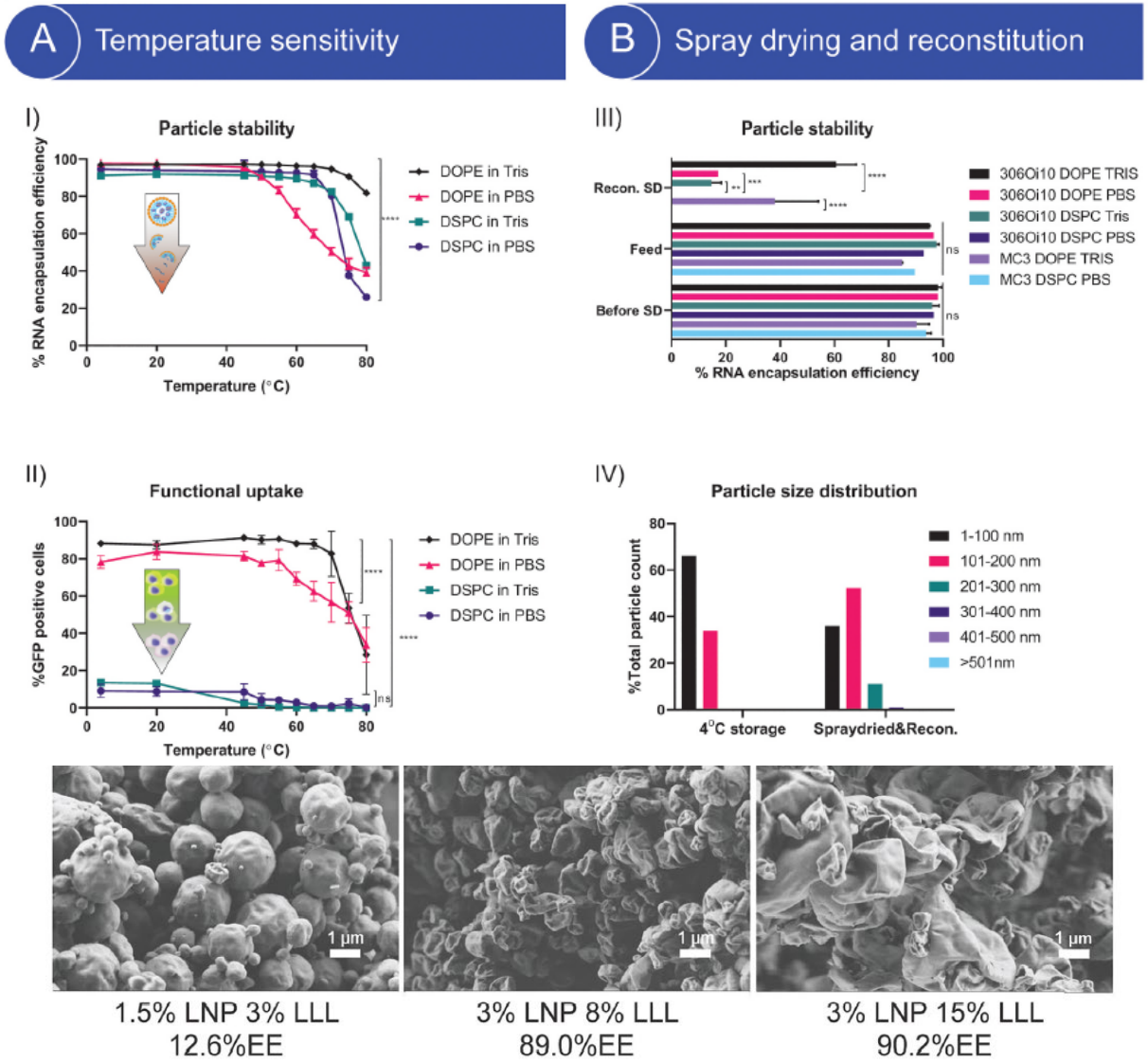




Zimmerman et al., "*Spray drying siRNAlipid nanoparticles for dry powder pulmonary delivery*," 2022, J. Cont. Rel. V36:142.

Spray Drying of Lipid NP for Inhalation – mRNA

- **Formulation:**
  - eGFP, DSPC, DOPE, 306Oi10 (Cationic lipid), Trehalose, TriLeucine
  - Particle size = <200 nm
- **Spray drying at Buchi B-290:**
  - Yield >80%
  - Encapsulation Efficiency ≥90%
  - Temperature (In/Out) = 90°C/54°C
- New LNP formulation was stable at higher temperatures and had higher encapsulation efficiency

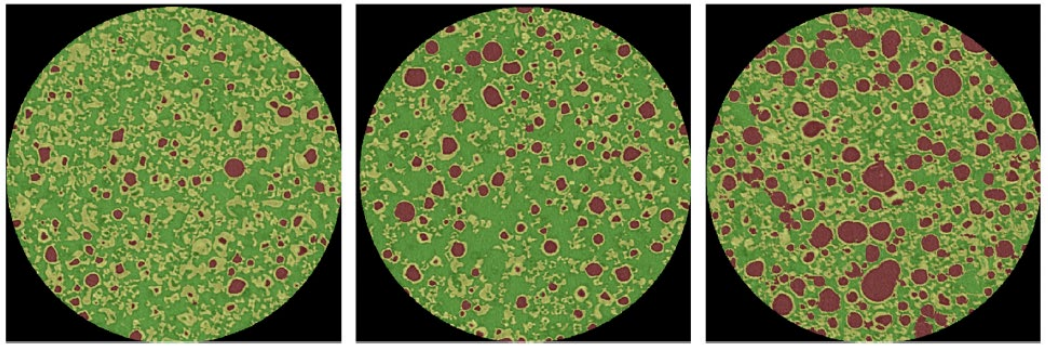


Friis et al., "*Spray dried lipid nanoparticle formulations enable intratracheal delivery of mRNA*", 2023, J. Cont. Rel., V363, pp. 389-401.

Spray Dried Particle Properties – Towards Understanding the Structure

Going from bulk properties towards resolution on particle level

- Use of imaging techniques like FIB-SEM, XRM and MFV-SEM
- Application of ML/AI algorithms to images to characterize properties like particle size, surface area, pore size distribution, chemical composition, wall/shell thickness, etc.
- Enables quantification of spray dried particle morphology in spheres vs. raisins/shrivelled fractions
  - Spheres: Low density and good compressibility
  - Raisins: High density and lower compressibility
- Potential tool to better understand how to protect sensitive molecules during spray drying through increased knowledge of component distribution and particle structure



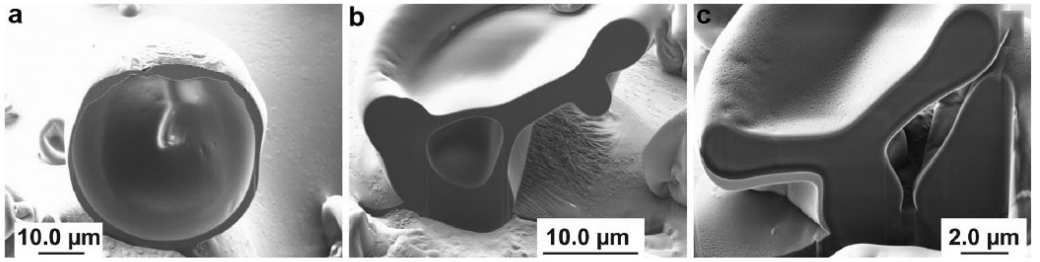


Fig. 2. FIB-SEM reveals the cross-section of MK-A SDP with different morphologies: (a) Sphere; (b) Raisin-like particle; (c) Small solid particle.

Zi et al. (2020), "*Characterizing the Impact of Spray Dried Particle Morphology on Tablet Dissolution Using Quantitative X -Ray Microscopy*", J. Pharm Sci., V109, pp.3404-3412. https://doi.org/10.1016/j.xphs.2020.07.032
Zhang et al. (2021), "*Characterizing the Impact of Spray Dried Particle Morphology on Tablet Dissolution Using Quantitative X -Ray Microscopy*", Eur. J. Pharm Sci., V165, https://doi.org/10.1016/j.ejps.2021.105921

Summary/Conclusions

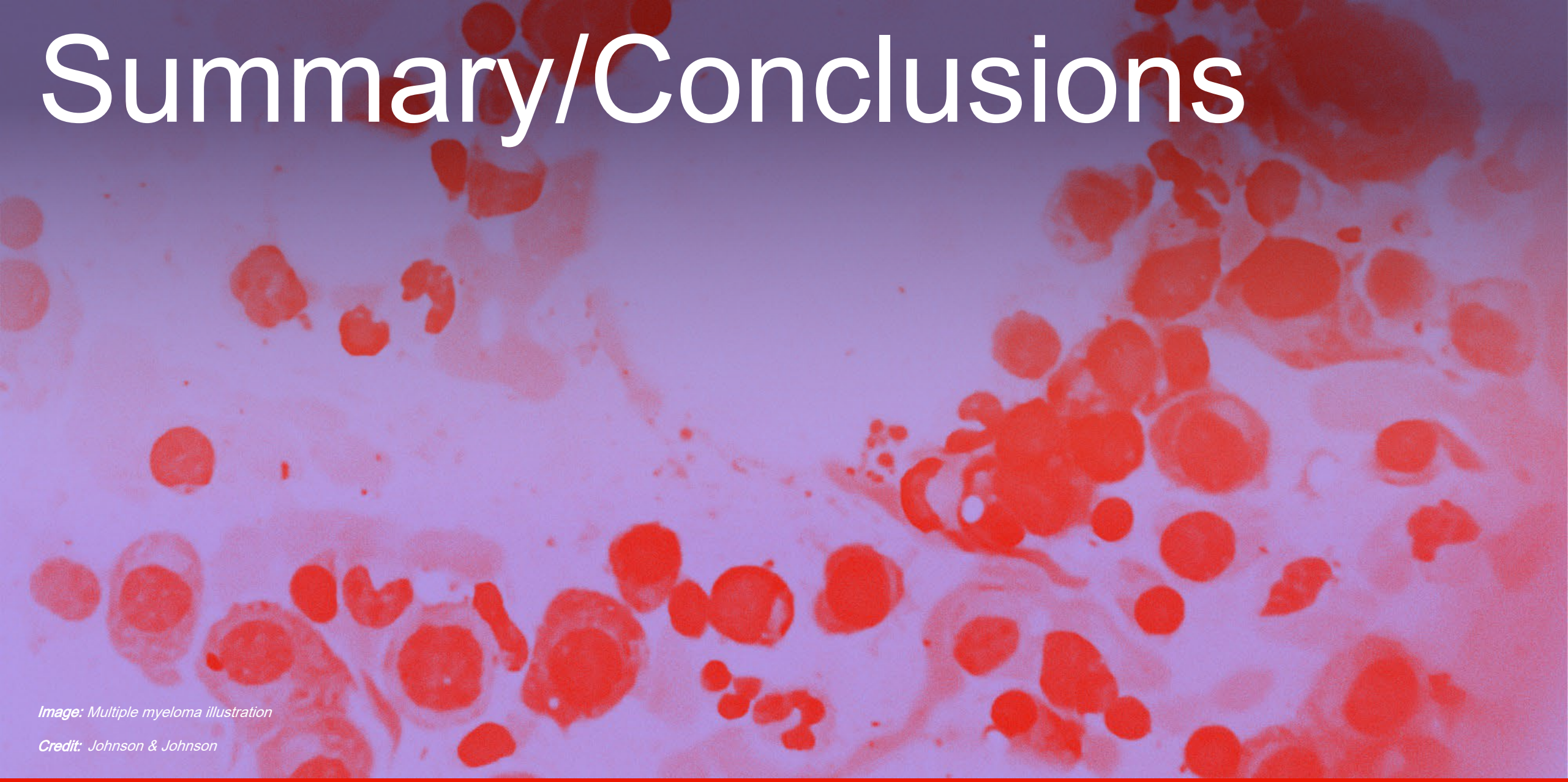


Image: Multiple myeloma illustration

Credit: Johnson & Johnson

Summary/Conclusions

- Biopharmaceuticals are sensitive to formulation and drying conditions:
  - Thermal stress through the drying temperature, equipment scale, shear stress, choice of solid lipid (T_m), and wall/matrix-former
- Several Spray- and Freeze-Drying based technolgies are feasible for manufacturing inhalable biopharmaceuticals; Alternative technologies for „formulation“ like Atomic Layer Deposition are being researched
- Inhalation is seen as a viable route for biopharmaceuticals with multiple studies having demonstrated the feasibility for example for siRNA/mRNA
- New characterization techniqes are becoming available to give new insights into particle properties
- **Production of biopharmaceuticals for inhalation by Spray -Drying and Freeze-Drying is feasible, however, still require significant formulation development work and optimization of drying conditions**

Thank you!

Johnson&Johnson

If you have more questions, please contact:
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