Enabling a Healthier World

Excipients for Respiratory Delivery of Large Molecules

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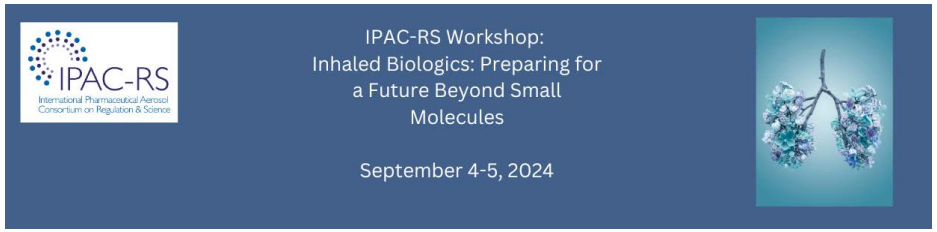


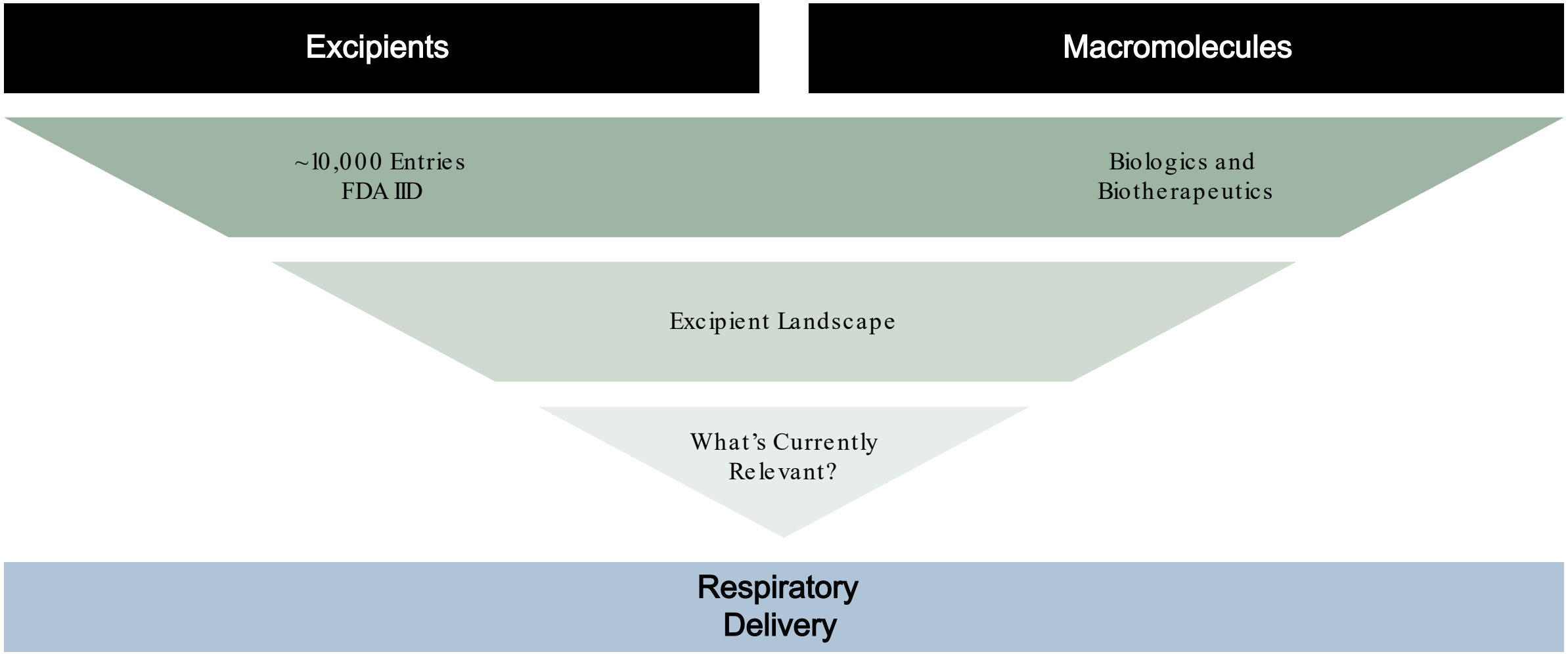
September 2024

Public

Agenda

1. Introduction and definitions
2. Regulatory status of excipients
3. Liquid dosage forms
4. Dry powder dosage forms
5. Challenges and outlook

1 Introduction and definitions



Excipients for Respiratory Delivery of *Macromolecules*

What is most relevant in the current pipeline?

Biologics and Biotherapeutic Macromolecules

- 737 FDA-Approved Biologics (Purple Book Jan2024)
- Biologic Products (Diverse and complex)
  - Recombinant Therapeutic Proteins – mAbs, Insulin
  - Vaccines – MMR, Tetanus, Polio, Seasonal influenza
  - Allergenics – Allergenic extracts from molds, pollens, venoms, etc.
  - Blood and Blood Components - Thrombin and other clotting factors
  - Gene and Somatic Cell Therapies – Activated immune cells for re-infusion, Vector or non-vector introduced gene / knockout
  - Tissues – Bone, Skin, ligaments, heart valves
- Complex structures generally derived from:
  - living material (human, animal, or microorganism; or their components)
  - recombinant technology
- Excipient considerations are a function of biologic characteristics/class
- Scope of this discussion centers around current respiratory-relevant biotherapeutics but it is important to consider the diversity of products which may eventually result in an inhalable product.

Excipients for Respiratory Delivery of *Macromolecules*

Inhalation pipeline landscape

Source: Survey of 163 Molecules in Inhalation Pipeline,PharmaProjects Database 2021

Biologics currently with inhaled therapeutic relevance (pulmonary and nasal)

55% Protein/Polypeptide Biotherapeutics

Antibodies, peptides, recombinant proteins (interferons, interleukins, lung surfactant proteins, hormones, therapeutic enzymes, and others)

30% Nucleic Acid Derivatives

mRNA, ASO, RNAi, miRNAs, siRNA, aptamers

Excipients for Respiratory Delivery of *Macromolecules*

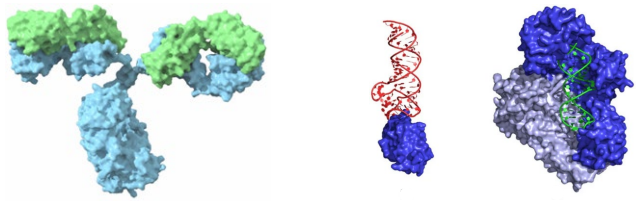
Structure / Function / Stability

Biotherapeutic macromolecules can be challenging due to their complex and diverse molecular structures and close relationship between structure and function.

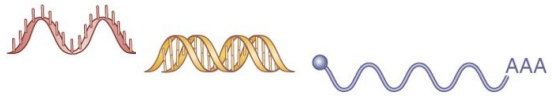
Structure / Function / Stability

mAbs, proteins, peptides, etc...

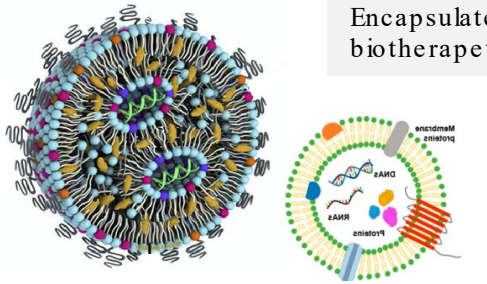
DNA and RNA Aptamers



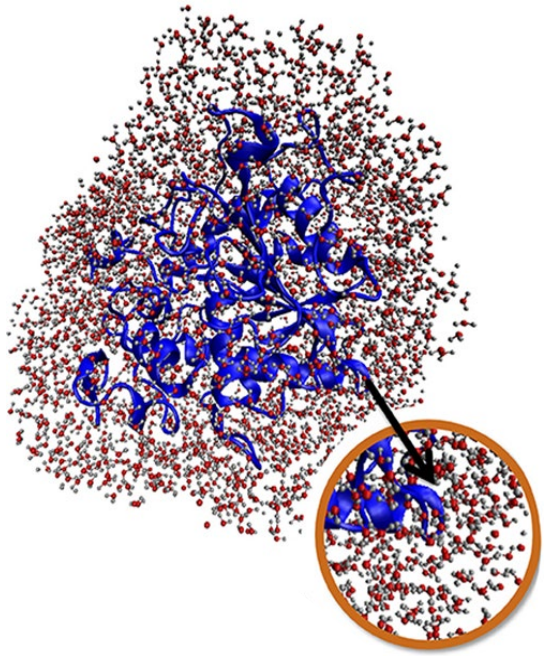
Naked NA therapeutics (ASOs, siRNA, mRNA,...)



Encapsulated biotherapeutics



Dynamic Molecules / Mixtures
Excipients Impact Structure and Function / Physical and Chemical Stability



Solvation of Candida antarctica lipase B CALB (33kDa)

Source: Dahanayake, J, Mitchell-Koch, K. How Does Solvation layer mobility Affect Protein Structural Dynamics? Frontiers in Molecular Biosciences, June 2018.

Table 1. Excipient functional category, class and types used in biologics.

Functional Category[a]	Excipient Class[b]	Types
pH Modifier (Acidifying/Alkalizing/ Buffering Agent)	Buffering Agents	Acetate, Citrate, Tartrate, Histidine, Glutamate, Phosphate, Tris, Glycine, Bicarbonate, Succinate, Sulfate, Nitrate
Tonicity Agent	Tonicity Modifiers	Mannitol, Sorbitol, Lactose, Dextrose, Trehalose, Sodium Chloride, Potassium Chloride, Glycerol, Glycerin
Bulking Agent	Sugars and polyols	Sucrose, Trehalose, Glucose, Lactose, Sorbitol, Mannitol, Glycerol
	Amino Acids	Arginine, Aspartic Acid, Glutamic acid, Lysine, Proline, Glycine, Histidine, Methionine, Alanine,
	Polymers and proteins	Gelatin, PVP, PLGA, PEG, dextran, cyclodextrin and derivatives, starch derivatives, HSA, BSA
Wetting and/or Solubilizing Agent	Surfactants	Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Poloxamer (Pluronic F68 and F127), Triton X-100, Brij 30, Brij 35
Antioxidant	Antioxidant Preservatives	Histamine, methionine, ascorbic acid, glutathione, vitamin E, poly(ethylenimine)
Antimicrobial Preservative	Antimicrobial Preservatives	Benzyl alcohol, metacresol, phenol, 2-phenoxyethanol
Chelating and/or Complexing Agents	Chelator Preservatives	Edetate disodium, diethylenetriamine pentaacetic acid (DTPA), citric acid, hexaphosphate, thioglycolic acid, zinc

[a]Functional category modified from USP-NF 42–37 [8].
[b]Excipient class adapted from "Excipient selection in biologics and vaccines formulation development" [9] and "Excipients Used in Biotechnology Products" [10].

Source: Ionova Y, Wilson L (2020) Biologic excipients: Importance of clinical awareness of inactive ingredients. PLoS ONE 15(6): e0235076. https://doi.org/10.1371/journal.pone.0235076

Manufacturing

↓

Storage/Stability

↓

Delivery

Excipients are vital in formulating the dosage form by enhancing the manufacturability, stability, and delivery of the drug product.

2 Regulatory Status

Excipients / Inactive Ingredients

US Food and Drug Administration

21 CFR 210.3(b)(8)

- Inactive ingredient means any component other than an active ingredient.

European Medicines Agency

Article 1(3b) of Directive 2001/83/EC, as amended by Commission Directive 2011/62/EU

- Excipient is any constituent of a medicinal product other than the active substance and the packaging

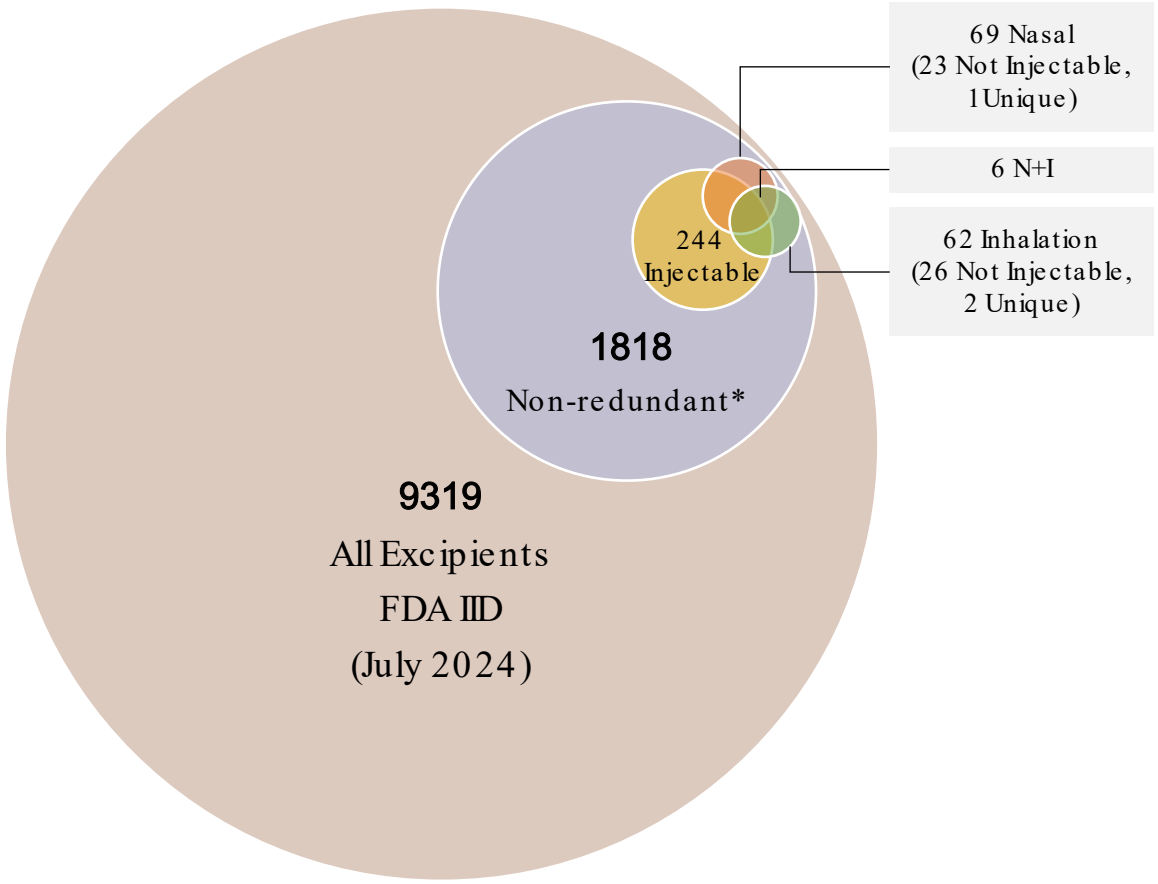
- 60 Functional Categories in USP-NF Excipient List
- Nearly 10,000 entries in the US FDA Inactive Ingredient Database (IID)

US Pharmacopeia and National Formulary – Excipient Functional Categories									
Acidifying or Alkalizing Agent	Adhesive	Air Displacement	Alcohol Denaturant	Antifoaming or Defoaming Agent	Antimicrobial Preservative	Antioxidant	Anti-tack Agent	Biodegradable Polymer	Buffering Agent
Bulking Agent	Capsule Shell	Carrier	Chaotropic Agent	Chelating Agent	Coating Agent	Colloid Stabilizing Agent	Crystallization Inhibitor	Desiccant	Diluent
Disintegrant	Drag-Reducing Agent	Dry Binder	Emollient	Emulsifying Agent	Filler	Film-Forming Agent	Filtering Aid	Flavors and Fragrance	Free Radical Scavenger
Gelling Agent	Glidant and/or Anticaking Agent	Humectant	Liposome Forming Agent	Lubricant	Muco-Adhesive	Ointment Base	Opacifier	Permeation Enhancer	Pharmaceutical Water
Physical-Chemical Identifiers	pH Modifier	Plasticizer	Polymeric Membrane	Polymers for Ophthalmic Use	Printing Ink Component	Propellant	Protein Stabilizer	Reducing Agent	Release-Modifying Agent
Solubilizing Agent	Solvent	Sorbent	Stabilizer	Stiffening Agent	Sugar-Coating Agent	Suppository Base	Surfactant	Suspending and/or Viscosity-Increasing Agent	Sweetening Agent
Tonicity Agent	Transfer Ligand	Vehicle	Viscosity-Lowering Agent	Water-Repelling Agent	Wet Binder				

*USP-NF 2024 Excipient Monograph (as of 01Aug2024)

Excipients for Respiratory Delivery of Macromolecules

Survey of FDA Inactive Ingredient Database (IID)



*Non-Redundant Entries: Reduced to remove redundancies in chemical entities (CAS #) across all routes / concentrations

Limited selection of approved excipients for nasal and inhalation routes*

- 105 FDA-approved excipients for nasal and inhalation routes
- Significant overlap with injectable routes of administration
- Existing resources and literature on excipients rarely distinguish the use of excipients among different drug types, such as small molecule synthetic drugs and biotechnology-derived drugs
- Are these 105 respiratory excipients relevant relative to approved excipients for biotherapeutics?

*Includes: Endosinusial, Endotracheal, Intrapleural

Excipient Landscape for Protein and NA Biotherapeutics

FDA-Approved Protein (397) and NA Formulations (21)

Protein Biotherapeutics and NA Biotherapeutics

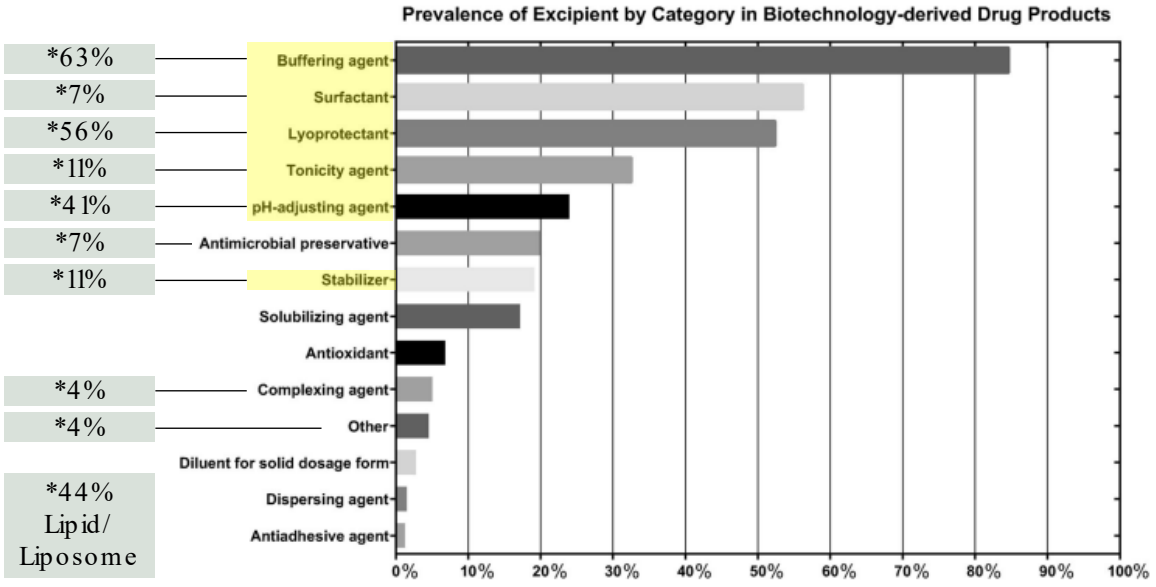


Fig. 1 Prevalance of excipient by category in biotechnology-derived drug products

Source: Rao VA, Kim JJ, Patel DS, Rains HE, Estoll CR. A Comprehensive Scientific Survey of Excipients Used in Currently Marketed, Therapeutic Biological Drug Products. Pharm Res. 2020 Sep 24;37(10):200. doi: 10.1007/s11095-020-02919-4. Erratum in: Pharm Res. 2022 Apr;39(4):825. doi: 10.1007/s11095-022-03253-7. PMID: 32968854; PMCID: PMC9010397.

Source: Ingle, Rahul G. and Wei-Jie Fang. "An Overview of the Stability and Delivery Challenges of Commercial Nucleic Acid Therapeutics." *Pharmaceutics* 15 (2023).

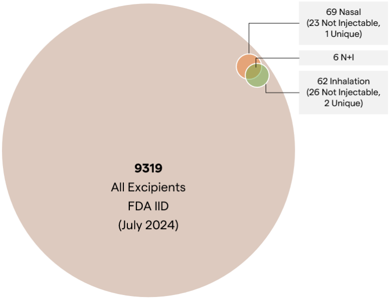
Table 4 Common Excipients Among Unique Formulations for All Biotechnology-derived Drug Products

Excipients	Percentage of unique formulations (n = 397)	(n = 21)
Sodium phosphate	39.04%	Sodium Phosphate 52%
Polysorbate 80	32.49%	Sodium Chloride 52%
Sodium chloride	32.24%	Sodium Hydroxide 43%
Sucrose	23.68%	Hydrochloric Acid 38%
Sodium hydroxide	20.15%	Potassium Phosphate 33%
Mannitol	19.40%	Potassium Chloride 19%
Polysorbate 20	17.63%	DSPC 14%
Histidine	17.38%	Cholesterol 14%
Hydrochloric acid	14.36%	Sucrose 10%
Metacresol	12.34%	

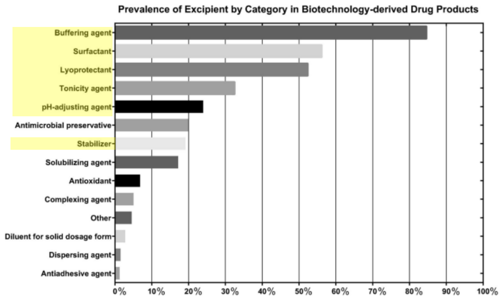
Current Respiratory Excipient Toolbox

Protein and NA Biotherapeutics

105 Inhalation and Nasal Excipients



~67% (70) are Protein/NA-relevant Excipients



~48% (50) represented in most prevalent biotherapeutic -excipient categories

- **Buffering (and pH -Adjusting Agents), Salts**
  - pH and salt concentration are critical for controlling folding state and minimize physical and chemical degradation.
  - Most commonly utilized buffer is sodium phosphate with some level of sodium or potassium chloride.
- **Surfactants**
  - These agents act to stabilize against interfacial tension and to reduce aggregation or protein - protein interactions.
  - Most commonly utilized surfactants included polysorbate 80, polysorbate 20, and poloxamer 188.
- **Stabilizers, Lyophilizing / Bulking Agents**
  - They act to maintain molecular structure in both the liquid and solid state affecting physical stability.
  - Most commonly utilized stabilizers and lyoprotectants are sugars - sucrose, mannitol, and trehalose.

Category	Present	Absent
Buffering Agent	ACETIC ACID, ANHYDROUS CITRIC ACID, CALCIUM CARBONATE, CITRIC ACID MONOHYDRATE, GLYCINE, MONOBASIC POTASSIUM PHOSPHATE, SODIUM BICARBONATE, SODIUM PHOSPHATE, SODIUM PHOSPHATE, DIBASIC (ANHYDROUS, DIHYDRATE, DODECAHYDRATE, HEPTAHYDRATE), TROMETHAMINE	SODIUM ACETATE, SODIUM SUCCINATE, ARGININE, ALANINE, ASPARTIC ACID, GLUTAMIC ACID, LYSINE, HISTIDINE
pH-Adjusting Agent	ACETIC ACID, ANHYDROUS CITRIC ACID, ANHYDROUS TRISODIUM CITRATE, ASCORBIC ACID, CITRIC ACID MONOHYDRATE, HYDROCHLORIC ACID, NITRIC ACID, SODIUM BICARBONATE, SODIUM HYDROXIDE, SULFURIC ACID	PHOSPHORIC ACID
Tonicity Agent	ANHYDROUS DEXTROSE, DEXTROSE, DEXTROSE MONOHYDRATE, GLYCERIN, MANNITOL, POTASSIUM CHLORIDE, SODIUM CHLORIDE	

Category	Present	Absent
Surfactant	BENZALKONIUM CHLORIDE, CETYLPYRIDINIUM CHLORIDE, POLYSORBATE 20, POLYSORBATE 80, PROPYLENE GLYCOL, SODIUM LAURYL SULFATE	POLOXAMER 188, TRIPALMITIN, PALMITIC ACID, COLFOSCERIL PALMITATE, DISMYRISOTYL GLYCEROL

Category	Present	Absent
Lyoprotectant / Bulking Agent	GLYCINE, LACTOSE, MANNITOL	SUCROSE, TREHALOSE
Stabilizer	BUTYLATED HYDROXYTOLUENE, CELLULOSE MICROCRYSTALLINE/CARBOXYMETHYLCELLULOSE SODIUM, EDETATE DISODIUM, FERRIC OXIDE, GLYCINE, HYDROXYETHYL CELLULOSE (2000 MPA.S AT 1%), HYPROMELLOSE, MANNITOL, POLYETHYLENE GLYCOL 3350, POLYETHYLENE GLYCOL 400, POLYSORBATE 20, POLYSORBATE 80, SILICON DIOXIDE, SODIUM METABISULFITE, SORBITOL, TITANIUM DIOXIDE	ALBUMIN, ARGININE, ALANINE, ASPARTIC ACID, GLUTAMIC ACID, LYSINE, HISTIDINE

Category	Present	Absent
Antimicrobial Agent	ALCOHOL, BENZALKONIUM CHLORIDE, BUTYLATED HYDROXYANISOLE, CALCIUM CHLORIDE, CETYLPYRIDINIUM CHLORIDE, CHLOROBUTANOL, GLYCERIN, METHYLPARABEN, PHENYLETHYL ALCOHOL, PHENYLMERCURIC ACETATE, PHENYLMERCURIC NITRATE, POTASSIUM SORBATE, PROPYLENE GLYCOL, PROPYLPARABEN, SODIUM BISULFITE, SODIUM METABISULFITE, THIMEROSAL, THYMOL, ZINC OXIDE	METACRESOL
Solubilizing Agent	BENZALKONIUM CHLORIDE, CETYLPYRIDINIUM CHLORIDE, GLYCINE, HYPROMELLOSE 2906 (4 MPA.S), HYPROMELLOSE 2910 (4000 MPA.S), HYPROMELLOSE 2910 (5 MPA.S), LANOLIN, POLYSORBATE 20, POLYSORBATE 80, PROPYLENE GLYCOL, SODIUM LAURYL SULFATE, SORBITAN MONOLAURATE, SORBITAN TRIOLEATE	ISOPROPYL ALCOHOL, MYIONOSITAL
Antioxidant	ASCORBIC ACID, BUTYLATED HYDROXYANISOLE, BUTYLATED HYDROXYTOLUENE, CITRIC ACID MONOHYDRATE, SODIUM BISULFITE, SODIUM METABISULFITE, THYMOL	METHIONINE
Complexing Agent	EDETATE DISODIUM	MAGNESUM CHLORIDE
Diluent for Solid Dosage Form	CASTOR OIL, MAGNESIUM STEARATE, POLYETHYLENE GLYCOL 3350, POLYETHYLENE GLYCOL 400	
Dispersing Agent	CELLULOSE MICROCRYSTALLINE/CARBOXYMETHYLCELLULOSE SODIUM, HYPROMELLOSE	
Lipids and Liposome Forming Agents		(6Z,9Z,28Z,31Z)- heptatriaconta-6,9,28,31 tetraen-19-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA), 1,2-distearoyl-sn-glycero-3- phosphocholine (DSPC), α-(3O-{[1,2- di(myristyloxy)propanoxy] carbonylamino}propyl)-ω-methoxy, polyoxyethylene (PEG 2000 C-DMG), 2[(polyethylene glycol)-2000]-N,N ditetradecylacetamide, (4-hydroxybutyl)azanediyl)- bis(hexane-6,1-diyl)bis(2- hexyldecanoate), SM-102, Cholesterol

Liquid Dosage Forms

September 2024

3 Liquid Dosage Forms

make up the **majority** of inhaled large molecule formulations…

…marketed, under clinical…

Table 4. Selected clinical studies and marketed products of inhaled biologic therapy.

Name	API	Development Stage	Company/Sponsor	Clinical Application	Delivery Device	Formulation	Reference, Year & Clinical Trial Number
Inhaled proteins							
Afrezza®	Insulin, 5.7 kDa	Marketed in 2014	MannKind	Diabetes mellitus	Dreamboat® inhaler	Technosphere® insulin inhalation powder	[187,188] 2014
Alpha-1 HC	Human α_1-PI, 52 kDa	Phase II	Grifols Therapeutics	CF	AKITA² APIXNEB® nebuliser system	Inhaled solution	[158] 2016, NCT01684410
AZD1402/PRS-060	IL4 mutein (IL-4Rα antagonist), ~18 kDa	Phase I	AstraZeneca & Pieris Pharmaceuticals	Asthma	InnoSpire Go mesh nebuliser	Inhaled solution	[164,165] 2019, NCT03384290 and NCT03574805
Alteplase	rt-PA, 70 kDa	Phase II	University of Michigan & Genentech	Acute plastic Bronchitis	Nebuliser	Inhaled solution	[175] 2017, NCT02315898
ALX-009	OSCN-/bLF, 80 kDa	Phase I	Alaxia SAS	P. aeruginosa and Bcc infection in CF	Nebuliser	Inhaled solution	[174] 2018, NCT02598999
Aliodornase alfa (PRX-110, AIR Dnase™)	rhDNase I, 37 kDa	Phase I	Protalix	CF	Philips Respironics I-neb AAD inhaler system	Inhaled solution	[155] 2017, NCT02605590
Dornase alfa (Pulmozyme®)	rhDNase I, 37 kDa	Marketed in 1993	Genentech	CF	Jet nebuliser/air compressor combinations	Inhaled solution	[189] 1996
Dornase alfa	rhDNase I, 37 kDa	Phase IV	Erasmus Medical Centre-Sophia Children's Hospital	CF	AKITA² APIXNEB® nebuliser system	Inhaled solution	[128] 2011
Dornase alfa	rhDNase I, 37 kDa	Phase IV	PARI	CF	eRapid™ nebuliser system	Inhaled solution	[124] 2015, NCT01712334
DAS181 (Fludase®)	Recombinant sialidase fusion protein, 46 kDa	Phase I/II	Ansun BioPharma	Parainfluenza infection	Cyclohaler® DPI	Dry powder	[154,167] 2015, NCT01037205, NCT01924793 NCT01113034
		Compassionate use/Phase III	Renmin Hospital of Wuhan University & Ansun BioPharma	COVID-19	Nebuliser	Inhaled solution	NCT04324489 NCT03808922
Exubera®	Insulin, 5.7 kDa	Marketed in 2006; withdrawn in 2007	Pfizer/Nektar Therapeutics	Diabetes mellitus	Exubera® DPI inhaler	SD powder	[190] 2004
EpoFc	Epo Fc-fusion protein	Phase I	Syntonix Pharmaceuticals	Anemia	Aeroneb® Pro nebuliser	Inhaled solution	[117] 2005
GM-CSF (Leukine®, Sargramostim)	rhuGM-CSF, 14 kDa	Phase I	Milton S. Hershey Medical Center	RASP	Nebuliser	Inhaled solution	NCT02601365
		Phase II	Children's Hospital Medical Center, Cincinnati	PAP	Nebuliser	Inhaled solution	NCT01511068
		Phase II	Peking Union Medical College Hospital	PAP	Nebuliser	Inhaled solution	NCT02243228
					PARI eFlow® nebuliser	Inhaled solution	[160] 2009
					PARI eFlow® nebuliser	Inhaled solution	[161] 2017, NCT04204252
					PARI LC Plus nebuliser	Inhaled solution	[163] 2007, NCT00535031
					Nebuliser	Inhaled solution	[173] 2000, NCT01590069
					MiniHeart jet nebuliser	Inhaled solution	[191] 2019, NCT02294630
					Nebuliser	Inhaled solution	[168,170] 2014, NCT01126177
					Nebuliser	Inhaled solution	[169] 2019
					Nebuliser	Inhaled solution	[171] 2020, NCT04385095
ALX-0171	Anti-F protein trivalent Nanobody®, 42 kDa	Phase II	Ablynx	RSV infection	FOX-Flamingo inhalation system	Inhaled solution	2017, NCT02979431 and NCT03418571
CSJ117	Anti-TSLP antibody fragment, 46 kDa	Phase I/II	Novartis	Asthma	Concept1 device (single dose DPI)	PulmoSol™ engineered powder	[181] 2020, NCT03138811 and NCT04410523
E25	Omalizumab, 149 kDa	Phase III	Genentech/Novartis	Asthma	PARI IS-2 nebuliser	Inhaled solution	[35] 1999
GSK1995057	Anti-TNFR1 dAb, 13 kDa	Phase I	GSK	Acute lung injury	PARI eFlow® nebuliser	Inhaled solution	[38] 2018, NCT01587807
GSK2862277	Anti-TNFR1 dAb, 13 kDa	Phase II	GSK	Postoperative lung injury	PARI eFlow® nebuliser	Inhaled solution	[93] 2020, NCT02221037
VR942/ CDP7766	Anti-IL-13 mAb fragment	Phase I	UCB Pharma	Asthma	Multidose F1P DPI	Dry powder	[45] 2018, NCT02473939

API: active pharmaceutical ingredient; AAT: alpha-1-antitrypsin; AATD: alpha-1-antitrypsin deficiency; bLF: bovine lactoferrin; Bcc: burkholderia cepacia complex; CF: cystic fibrosis; COPD: Chronic obstructive pulmonary disease; dAb: domain antibody; DPI: dry powder inhaler; Epo: erythropoietin; RDS: respiratory distress syndrome; RSV: respiratory syncytial virus; rhDNase I: recombinant human deoxyribonuclease I; IL-2: interlukin-2; OSCN-: Hypothiocyanite; PAP: pulmonary alveolar proteinosis; P. aeruginosa: pseudomonas aeruginosa; rt-PA: recombinant tissue plasminogen; rhuGM-CSF: recombinant human granulocyte-macrophage colony stimulating factor; RASP: respiratory virus-associated severe pneumonia; RVI: respiratory viral infection; SD: spray dried; TNFR1: tumour necrosis factor receptor-1; IL-4Rα: interleukin-4 receptor alpha; IL-13: interleukin-13; PI: protease inhibitor; TSLP: thymic stromal lymphopoietin.

…and pre-clinical development.

Table 3. Selected preclinical studies on inhaled biological therapy for local and systemic disorders.

Drug	Target Disease	Formulation	Animal	Target/Format	Administration/Device	Reference & Year
Aldesleukin	Pulmonary metastases	Liposome	Dogs	IL-2	Puritan Bennet™ twin-jet nebuliser	[109,110] 1997
ALX-0171	RSV infection	Inhaled solution	Cotton rats	Anti-Fusion protein trivalent Nanobody®	AKITA² APIXNEB® nebuliser	[27,96] 2016
ALX-0171	RSV infection	Inhaled solution	New born lambs	Anti-Fusion protein trivalent Nanobody®	Aeroneb® Solo system	[97] 2018
Anti-IL-17A PEG40-F(ab')$_2$ and Anti-IL-13 PEG40-Fab'	Asthma	Inhaled solution	NMRI mice	Anti-IL-17A F(ab')$_2$ and Anti-IL-13 Fab	Intranasal instillation	[111] 2014
Anti-IL-17A PEG40-Fab'	Asthma	Inhaled solution	Mice, rats and rabbits	Anti-IL-17A Fab	Intratracheal instillation	[37] 2017
Anti-IL-17A PEG20-Fab', Anti-IL-17A PEG40-Fab' and Anti-IL-13 PEG40-Fab'	Asthma	Inhaled solution	Mice	Anti-IL-17A and anti-IL-13 Fab	Intratracheal instillation	[60] 2018
Cetuximab	Lung tumour	Inhaled solution	Balb/c nude mice	Anti-EGFR mAb	Aeroneb Pro™ mesh nebuliser	[22,33] 2011
Cetuximab	Lung tumour	Inhaled solution	Balb/c nude mice and cynomolgus macaques	Anti-EGFR mAb	Microsprayer® IA-1b aerosoliser	[21] 2014
CA154_582	Asthma	Inhaled solution	Balb/c mice	Anti-IL-13 Fab	inExpose nebulisation system	[88] 2012
CDP7766	Asthma	Inhaled solution	Cynomolgus macaques	Anti-IL-13 Fab	PARI eFlow® mesh nebuliser	[89] 2017
EpoFc	Anemia	Inhaled solution	Cynomolgus monkeys	Erythropoietin Fc-fusion protein	Aeroneb Pro® nebuliser	[57] 2004
FSHFc	Infertility	Inhaled solution	Cynomolgus monkeys	FSH Fc-fusion protein	Aeroneb Pro™ nebuliser	[81] 2005
GSK1995057	Acute lung injury	Inhaled solution	Cynomolgus monkeys	Anti-TNF receptor-1 dAb	Intratracheal instillation	[38] 2018
hGH	Growth hormone deficiency	SD powder	Wistar rats	hGH	Dry Powder Insufflator™	[65] 2004
Influenza subunit vaccine	Influenza	SD and SFD powder	Balb/c mice	Surface glycoprotein haemagglutinin	Dry Powder Insufflator™	[112] 2010
IFNβFc	Multiple sclerosis	Inhaled solution	Cynomolgus monkeys	IFNβ Fc-fusion protein	Aeroneb Pro® mesh nebuliser	[82] 2012
IgG 43RCA-G1	Ricin intoxication	Inhaled solution	Balb/c mice/cynomolgus macaques	Anti-ricin mAb derived from scFv 43RCA	Micropipette tip and Aerogen® Solo mesh nebuliser	[36] 2016
Infliximab	Asthma	SD powder	Balb/c mice	Anti-TNFα mAb	Dry Powder Insufflator™	[34] 2019
p55-specific dAb	Ventilator-induced lung injury	Inhaled solution	C57BL6 mice	Anti-p55 TNF receptor dAb	Intratracheal instillation	[91] 2012
PEG-rhα$_1$-PI	Hereditary emphysema	Solution	CD1 mice	α1-PI	Intranasal instillation	[113] 2002
PEG12-IFNαPEG40-IFNα	Cancer or fibrosis	Inhaled solution	SD rats	PEGylated IFNα	Intratracheal instillation	[114] 2014

dAb: domain antibody; EGFR: epidermal growth factor receptor; FSH: follicle-stimulating hormone; hGH: human growth hormone, IFNβ: interferon beta; IL: interleukin; PEG: polyethylene glycol; RSV: respiratory syncytial virus; rhα$_1$-PI: recombinant α$_1$-proteinase inhibitor, scFv: single-chain variable fragment; SD: spray dried; SFD: spray freeze dried; TNF: tumour necrosis factor.

Source: Liang W. et al., Pharmaceutics 2020, 12, 1025; doi: https://doi.org/10.3390/pharmaceutics12111025

3 Liquid Dosage Forms

generally include **solutions** or **suspensions** that can be administered via

Nebulizers

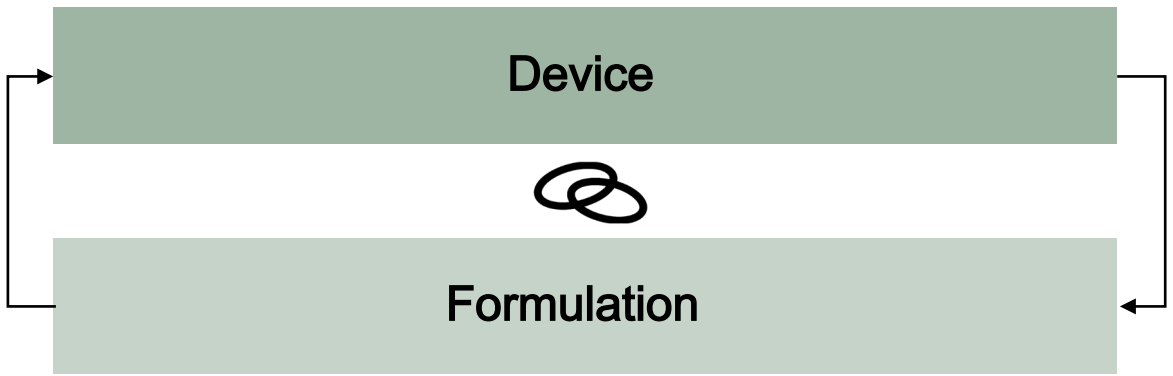
Soft mist inhalers

Nasal sprays

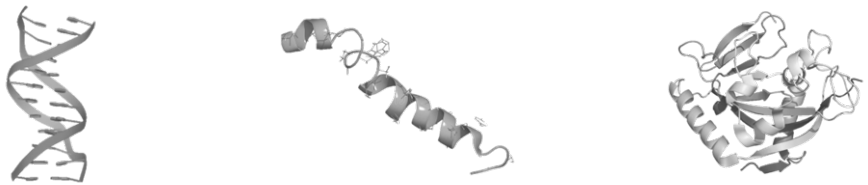
3 Liquid Dosage Forms

Formulation considerations

- Type of device, tailored for a specific administration route, and class of biologic (at least) will determine the formulation pathway – Device and formulation design to be carried out in parallel



- Formulation excipients kept to a minimum.



3 Liquid Dosage Forms

Formulation considerations

Excipient selection drivers to enable a safe and effective liquid -based drug product

- Retaining biologic conformational structure (if applicable) and/or potency/activity,
- Meeting spray characteristics and aerodynamic performance targets (might be different as per administration route),
- And preserving formulation sterility,

across drug product shelf -life.

Retaining biologic conformational structure and/or potency/activity

Conformational structure and potency/activity can be affected by physical (non-covalent) and/or chemical (covalent) degradation.

Retaining biologic conformational structure and/or potency/activity

Conformational structure and potency/activity can be affected by **physical (non -covalent)** and/or chemical (covalent) degradation.

Physical degradation

- Interfacial adsorption.
- Aggregation.

$$P \overset{K}{\longleftrightarrow} P^* \overset{k}{\longrightarrow} A$$

Lumry-Eyring framework of protein aggregation reaction in a bulk solution

P- Native form of the protein
*P**- Aggregation competent non-native form
A- Aggregate

Source: Gokarn Y. et al., Chapter 17, 2006, CRC Press 1st edition; doi: https://doi.org/10.1201/9781420004137
Chi, E.Y. et al., *Pharm Res* 20, 1325–1336, 2003; doi: https://doi.org/10.1023/A:1025771421906

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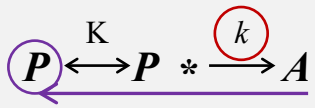

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*P** - Protein transition state preceding the formation of an aggregation intermediate

- Select excipients that modulate solution conditions
  - favoring the native form, *P*,
  - and lowering the kinetic reaction rate constant (*k*).

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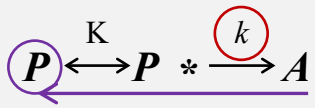

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Buffering agents control pH

- Organic and amino acids, phosphates and Tris

Buffering agent	pK_a	Previously approved for
Citrate	pK_{a1} = 3.1, pK_{a2} = 4.8, pK_{a3} = 6.4	IV, Pulmonary, Nasal
Acetate	4.8	ID, IM, IV, SC, Nasal
Succinate	pK_{a1} = 4.8, pK_{a2} = 5.5	IV
Histidine (imidazole)	6.0	IV, SC, Nasal
Phosphate	pK_{a1} = 2.15, pK_{a2} = 7.2, pK_{a3} = 12.3	IM, IV, Nasal
Tris	8.1	IV, SC

ID – Intradermal; IM – Intramuscular; IV – Intravenous; SC - Subcutaneous

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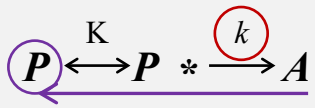

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Salts, Amino acids, Sugars and Polyols

- Stabilization of ***P*** by
  - binding to charged residues on the protein's surface,
  - shielding repulsive electrostatic interactions between residues within the protein,
  - and/or by preferential exclusion.
- Stabilization of ***P**** by binding to the peptide groups along the protein backbone.

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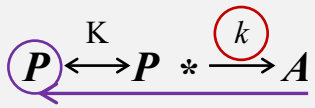

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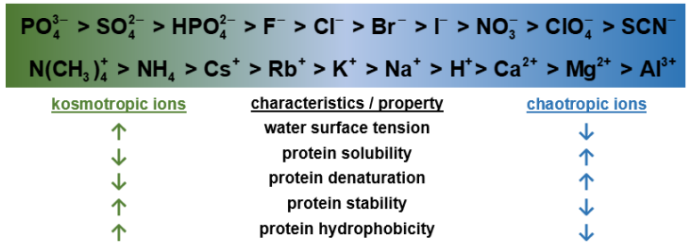
Salts

Salts	Previously approved for
Sodium chloride	ID, IM, IV, SC, Pulmonary, Nasal,
Potassium chloride	IM, IV, Pulmonary (powder), Nasal
Sodium sulfate	IV, Pulmonary

ID – Intradermal; IM – Intramuscular; IV – Intravenous; SC - Subcutaneous



Hofmeister series of anions and cations and their influence on protein solution properties.

Source: Kurac T, Polakovic M., Membranes 12, 1173, 2022; doi: https://www.mdpi.com/2077-0375/12/12/1173

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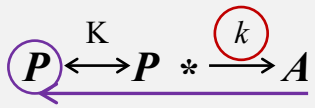

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Amino acids, Sugars and Polyols

Amino acids	Previously approved for
Glycine	ID, IM, IV, SC, Pulmonary (powder)
Proline	IV
Serine	IV
Alanine	IV
Arginine	IM, IV

ID – Intradermal; IM – Intramuscular; IV – Intravenous; SC - Subcutaneous

Sugars and polyols	Previously approved for
Sucrose	IV, SC
Trehalose	ID, SC
Mannitol	IM, IV, SC, Nasal, Pulmonary (powder)
Sorbitol	IM, IV, SC, Nasal

ID – Intradermal; IM – Intramuscular; IV – Intravenous; SC - Subcutaneous

Retaining biologic conformational structure and/or potency/activity

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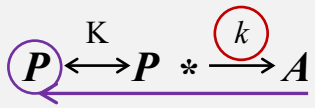

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Surfactants

- Stabilization of ***P**** by out-competing proteins for interfacial positions, preventing adsortion.

Surfactants	Previously approved for
Benzalkonium chloride	IM, Pulmonary, Nasal
Polysorbate 20	IM, IV, SC, Nasal
Polysorbate 80	IM, IV, SC, Pulmonary, Nasal
Palmitic acid	IV
Poloxamer 188	IM, IV
Sodium lauryl sulfate	Pulmonary (powder)

IM – Intramuscular; IV – Intravenous; SC - Subcutaneous

Retaining biologic conformational structure and/or potency/activity

Conformational structure and potency/activity can be affected by physical (non-covalent) and/or **chemical (covalent)** degradation.

Chemical degradation

- Non-reducible cross linking.
- Deamidation.
- Formation of basic or acidic species.
- Glycation.
- Isomerization.
- **Oxidation.**
- Fragmentation.
- C-terminal clipping.
- Reduction.
- Hydrolysis.
- Racemization.

Antioxidants and chelating agents

- Ablating active oxygen species in solution or
- Binding trace metal contaminants that promote free radical formation.

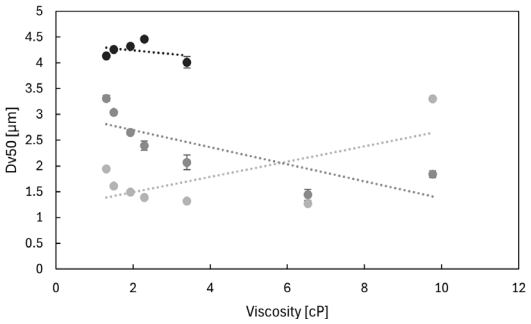
Antioxidants and chelating agents	Previously approved for
EDTA	IM, IV, SC, Pulmonary, Nasal
DTPA	IV
Histidine	IV, SC
Methionine	IV, SC
Ethanol	IM, Pulmonary, Nasal

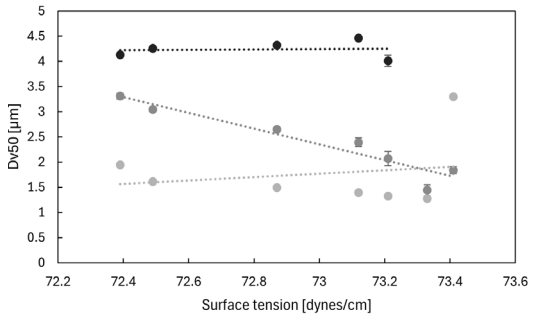
IM – Intramuscular; IV – Intravenous; SC - Subcutaneous

Meeting spray characteristics and aerodynamic performance targets

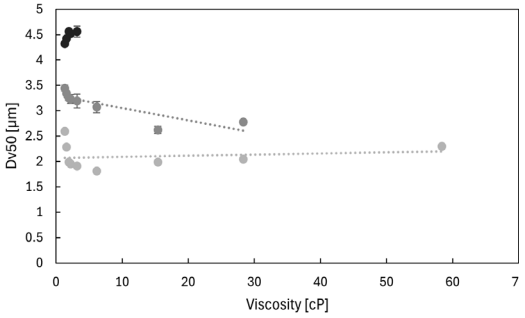
Governed by the combined effect of device atomizing system with formulation viscosity and surface tension.

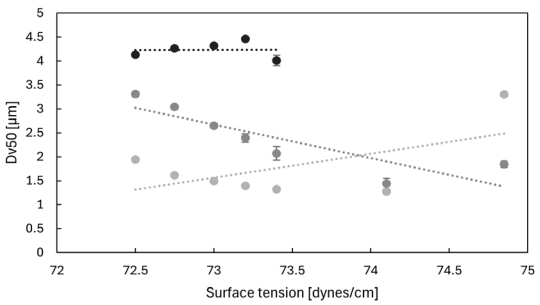
Sodium citrate solutions
7-36% (w/v)





Sucrose solutions
10-60% (w/v)





Nebulizers

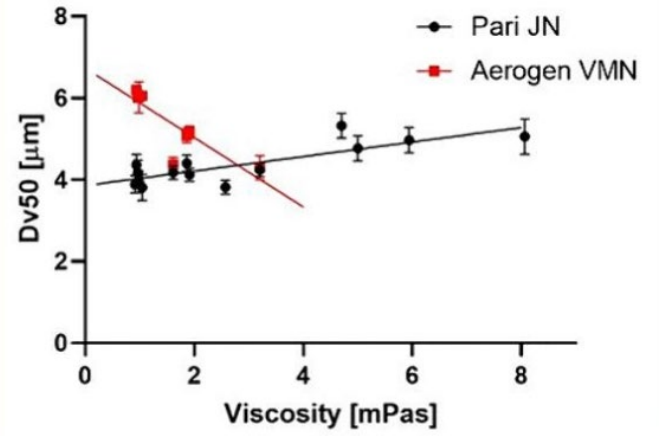
- Pari LC
- Medix A II
- Medix Electronic Nebulisers

Source: MC Callion ONM and Patel MJet al., International Journal of Pharmaceutics 1996, 130,124390; doi: https://doi.org/10.1016/j.ijpharm.2024.124390

Meeting spray characteristics and aerodynamic performance targets

Governed by the combined effect of device atomizing system with formulation viscosity and surface tension.

Antisense oligonucleotides solutions in nebulizers



Source: Seidl LL. et al., International Journal of Pharmaceutics 2024, 661, 124390; doi: https://doi.org/10.1016/j.ijpharm.2024.124390

Small RNA (sRNA) solutions in the soft mist inhaler Softhaler ®

sRNA [mg/ml]	50	50	75	75
Benzalkonium chloride [mg/ml]		0.1		0.1
Dv10 (µm)	2.2	2.2	3.1	2.1
Dv50 (µm)	6.0	5.9	8.0	5.6
Dv90 (µm)	13.3	13.9	17.0	16.4
Span	1.9	2.0	1.8	2.6

Source: Lopes IS, Fernandes DA, Rawert J, Journal of Aerosol Medicine and Pulmonary Drug Delivery via DDLconference 2024 (submitted)

Surfactants, ethanol

Decrease formulation surface tension, allowing for smaller droplets to be formed.

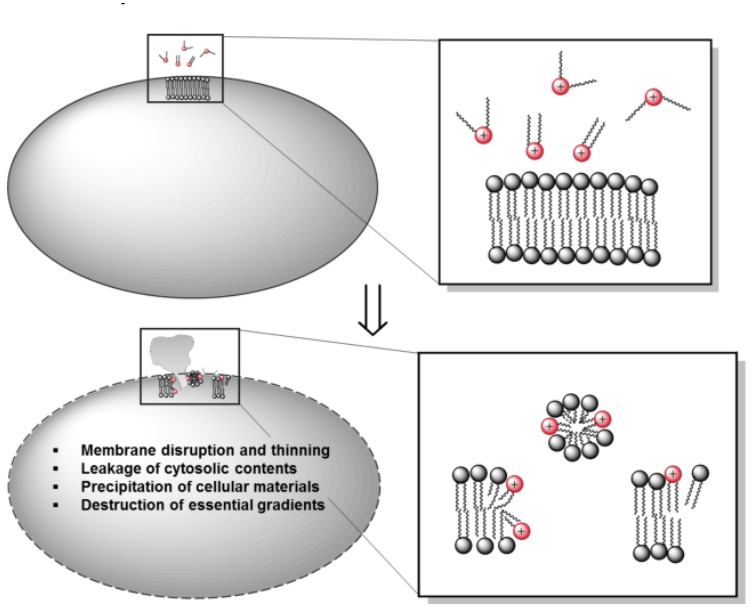
Preserving formulation sterility

Preservatives

- Added to multidose formulations to prevent microbial growth.
- Antimicrobial activity typically dependent on pH.
- Prevalence of Quaternary ammonium (QAC) and Phenolic (PC) compounds.

Preservatives	Previously approved for
Benzalkonium chloride	IM, Pulmonary, Nasal
Cetylpyridinium chloride	Pulmonary
Metacresol	ID, IM, IV, SC
Phenol	ID, IM, IV, SC

ID – Intradermal; IM – Intramuscular; IV – Intravenous; SC – Subcutaneous



Source: Jennings MC. et al., ACS infectious diseases 2015, 17;doi: https://pubs.acs.org/doi/10.1021/acsinfecdis.5b00047

QAC and PC antimicrobial activity maximized according to their lateral chain length.

Previously reported hypersensitive reactions – Use discouraged by current relevant guidances.

Preservative efficacy test studies to fine-tune amount in formulation.

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Self preserving/low water activity agents, as an alternative

- Reduce the free water in the formulation that otherwise would be available for microbial growth.

Self-preserving agents	Previously approved for
Ethanol	IM, Pulmonary, Nasal
EDTA	IM, IV, SC, Pulmonary, Nasal
Propylene glycol	IM, IV, SC, Pulmonary, Nasal
Glycerin	ID, IM, IV, SC, Pulmonary, Nasal
Glycerol	IM, IV, SC
Sorbitol	IM, IV, SC, Nasal
Xylitol	-

ID – Intradermal; IM – Intramuscular; IV – Intravenous; SC – Subcutaneous

Solid Dosage Forms

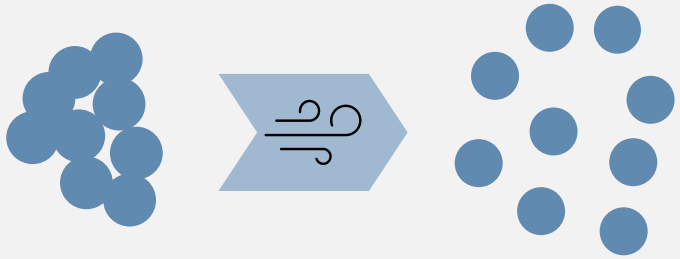
September 2024

Designing an effective dry powder particle

100% active would be nice, but rarely works

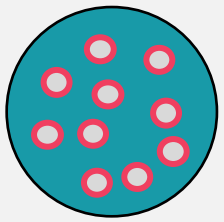
1 Respirable & Dispersible

- Particle engineering only works if dry powders can be redispersed to their primary size on emission from inhaler
- Small particles are cohesive!
- Usually, a dispersibility-enhancing excipient is needed to achieve this, leucine and tri - leucine are most common, and often compatible with bio APIs

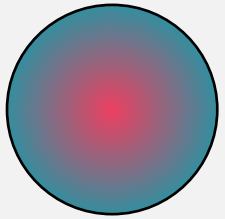


2 API stability

- Maintain activity of the API: different metrics for different API classes
  - Primary structure intact
  - Protein unfolding and aggregation
  - mRNA encapsulation
- Most APIs need some help from stabilizers, surfactants, buffers, etc.
- Have had some success with un-stabilized ASOs, achieving high active loading



Nano-in-micro



Amorphous dispersion

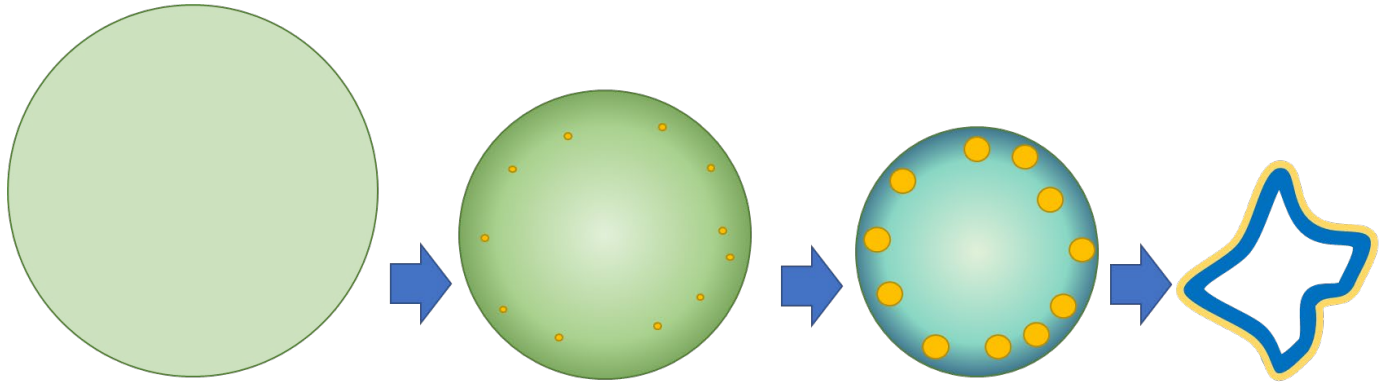
3 Physical stability

- Solid form of the particle must not change over time, whether amorphous or crystalline
- Target storage conditions at ambient temperature
- Low water content is often important

Leucine: Dry powder delivery's favorite amino acid

- In previous discussion, amino acids are employed as stabilizers for protein and other liquid formulation
- Leucine is one of those, but is used differently in dry powder formulations
- Used as a dispersibility-enhancer for dry powders to improve aerosol properties and solid-state stability
- Hypotheses that increased particle roughness and reduced hygroscopicity contribute
- Leucine must be at the particle's surface, not in contact with API
- Tri-leucine also of interest, works by different mechanism

Overview of leucine surface enrichment



Liquid droplet: Homogeneous concentration

Drying droplet: At surface, leucine reaches its solubility

Skinned droplet: Phase separated leucine domains concentrate at the surface

Particle: Surface enriched with crystalline leucine

Investigated extensively by: Vehring, Lechuga-Ballesteros, Boraey, Ordoubadi, Alhajj, Feng, Mangal and others!

API stability in the solid state

Mechanisms of instability during drying

- Denaturation/unfolding: unfolded state becomes more thermodynamically stable than folded
  - Protein/peptide secondary and tertiary structure
  - RNA/DNA secondary structure
- Aggregation: intermolecular interaction
  - Noncovalent via hydrophobic interaction
  - Covalent via thiol and/or disulfide linkages in proteins
- De-amidation
- Oxidation
- Maillard reaction (proteins)
- Aggregation of encapsulated materials

Chang and Pikal J Pharm Sci 2009
Lechuga-Ballesteros, Miller, Duddu 2005

Stabilization mechanisms for drying

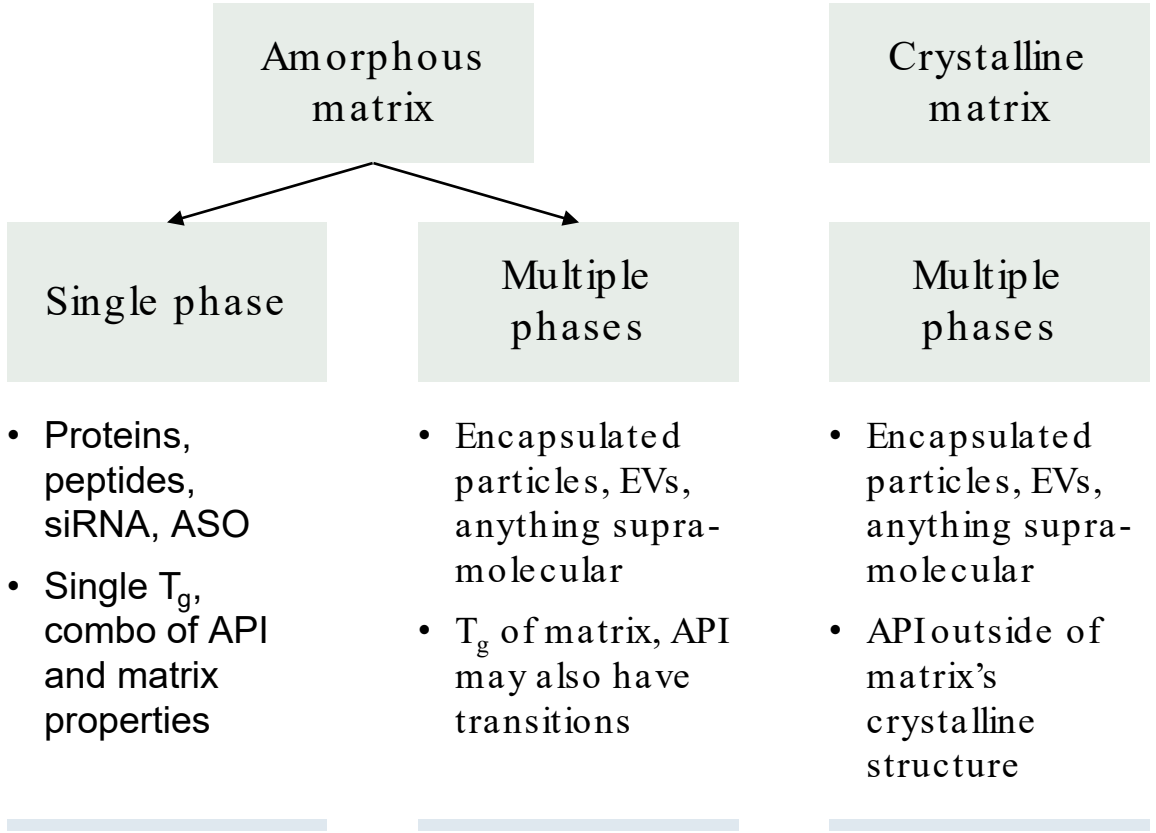
- Water replacement theory
  - Hydrogen bonding with water shifts thermodynamics in favor of native (folded) state
  - As water leaves, sugar/sugar alcohol hydrogen bonding replaces this need
- Glass stabilization
  - Diluting the molecule in a high T_g matrix physically locks in API structure
  - T_g needs to be far (preferably > 50°C) higher than storage conditions to prevent gradual rearrangement
  - Sufficient dilution of encapsulated API systems also helpful for nanoparticle reconstitution

What do we mean by stability here?

Two sides to solid state stability

- Stabilization of the API structure and activity via excipient matrix
  - In liquid formulations, API and excipients mix freely
  - In solid formulations, they are not necessarily in intimate molecular contact
- Also, stabilizing the solid form of the dry powder. Relevant solid form questions include
  - Is the matrix amorphous or crystalline?
  - Is the formulation one phase or multiple?
  - Is there any polymorphism of crystalline components?
  - For amorphous components, is the T_g far enough above storage conditions?
  - How does water content/humidity impact all this?

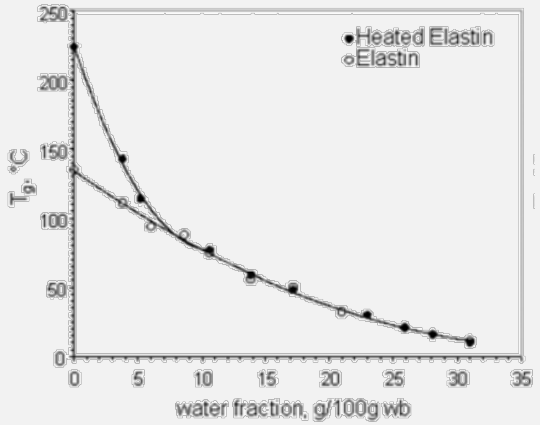
Solid form possibilities



Plasticization of amorphous formulations

T_g dependence on water content

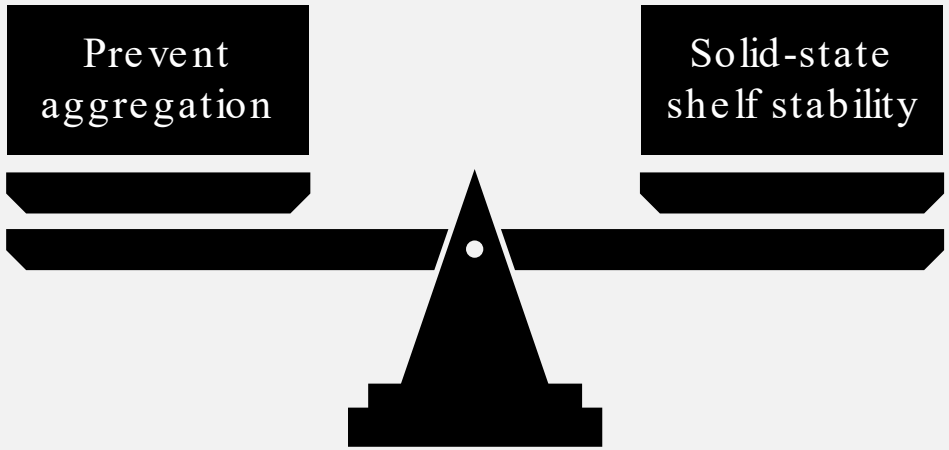
- Glass transition temperature decreases with increasing water (or other solvent) content
- Water content is critical to success of dry powder formulations



Lechuga-Ballesteros, Miller, Duddu 2005

Surfactants can also be plasticizers

- Surfactants typically have very low glass transition temperature
- Increasing presence of surfactants often leads to lower physical stability of the dry powder



Favorite matrix formers for dry powder bios

A biased list

Trehalose

- High dry T_g reduces molecular mobility of solid state, "locks in" a non-aggregated structure
- Stable at low humidity in the amorphous form
- Can form a single dispersion phase with API
- Non-reducing sugar
- Strong hydrogen bonding for water replacement
- Not **yet** in FDA inactive ingredients list for pulmonary or nasal delivery
- Extensively precedented in clinical trials for pulmonary delivery

Mannitol

- Precedented in the lung
- Usually crystalline after drying process, but has multiple polymorphs
- Can be amorphous when mixed with other carriers, but has low T_g
- Most useful when a phase-separated morphology is desired

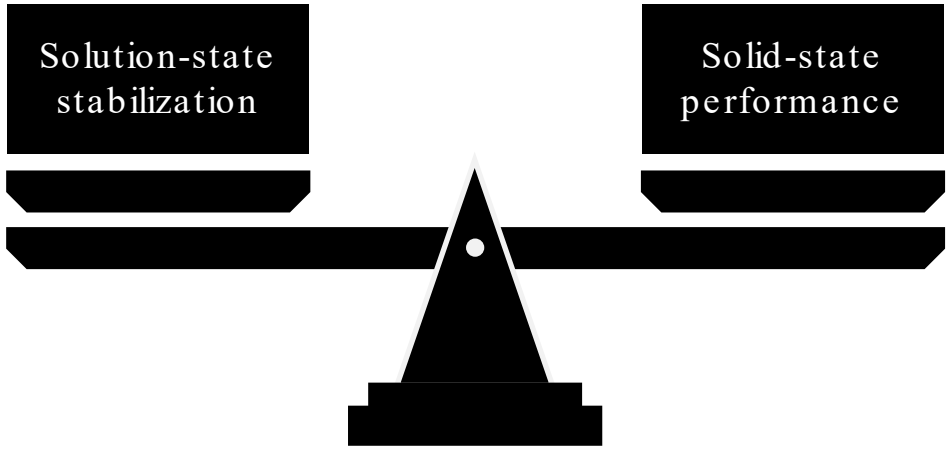
…and the rest

- Inulin, naturally-occurring high-T_g polysaccharide
- Sucrose, investigated but generally not preferred due to low T_g
- Cyclodextrans (beta, HP-beta in particular) have been studied, still need work for lung compatibility
- Sorbitol has a lower T_g, but has been successfully used to stabilize IgG spray dried powders (Maury et al)
- Lactose is approved for lung use, but appears less valuable as a stabilizer than other sugars

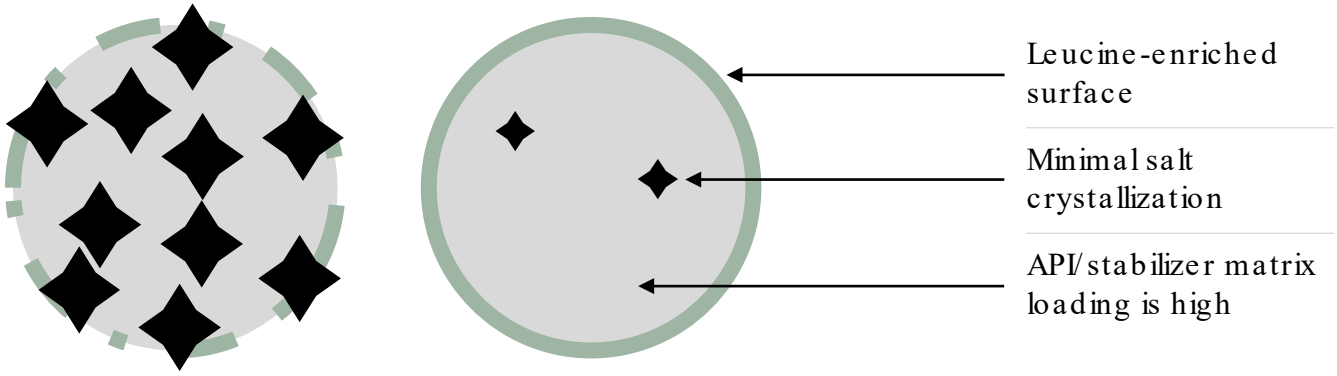
Buffers and other salts

- Buffer salts are important for stabilizing many pH-sensitive APIs

- Once in solid form, buffer salts can get in the way if concentrations are high:
  - Hygroscopic material
  - Can compete with leucine for surface
  - Phase separated from API



Component	IV formulation	Spray solution	Powder composition
mAb	30 mg/mL	4 mg/mL	40% wt
Trehalose	60 mg/mL	4 mg/mL	40% wt
Leucine	0	2 mg/mL	20% wt
Surfactant	0.04% wt	~0	~0
Buffer	50mM	1mM	~1% wt

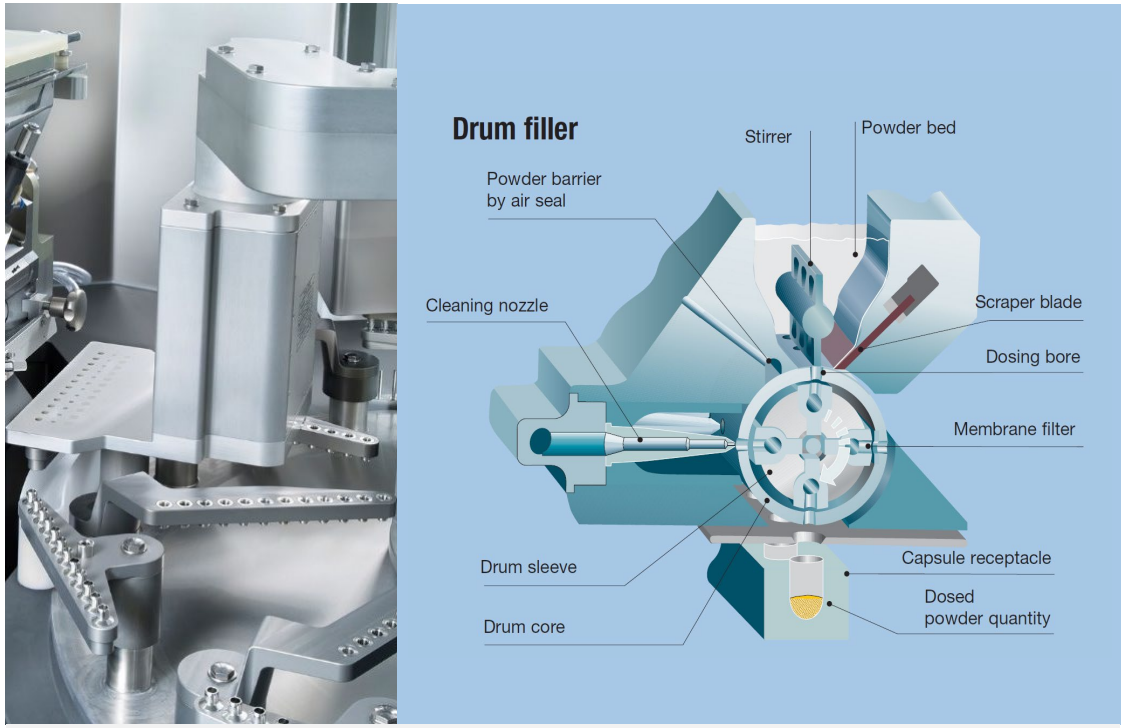


Shepard et al, AAPS PharmSciTech 2021

Downstream impact of formulations

Dry powders still need to be filled into their device (capsule, reservoir or blister)

- Spray dried pulmonary powders tend to have poor to extremely poor flow properties
- Drum filling helps, but every formulation is different
- Formulation-related variables which impact downstream operations:
  - Hygroscopicity of excipients
  - Particle size (nasal vs. pulmonary)
  - Surface characteristics of particles
  - Particle shape and rugosity



Example drum filler for capsules, Harro Höfliger

Outlook

5 Gaps, Challenges, Outlook

Excipient Toolbox is still Growing

- Increasing complexity of molecules / mixtures
  - Risk of not using optimal excipients if limited to currently-approved excipients
  - Will likely require exploring novel excipients
- Novel Excipients and Approval Requirements (next slide)

Other Gaps and Challenges

- Ambiguous excipient categories (overlapping) may cause confusion
- Interaction of excipient and API resulting in decreased effect of excipient, or complexing of API resulting in decreased efficacy.
- Stabilization-centric excipients; excipients for improving drug delivery, absorption, targeting.
  - Carriers, targeting agents, muco-adhesives (ex. Chitosan, gellan gum, PEG, PVA. currently PEG3350 is approved)

Opportunity? Consortium of Respiratory Developers for Excipients of Interest ?

CDER Conversation: Novel Excipient Review Pilot Program

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FDA's Center for Drug Evaluation and Research's (CDER) Office of New Drugs (OND) recently launched a pilot program on Novel Excipient Review. The pilot program offers a new pathway for drug manufacturers to obtain FDA review of certain novel excipients (inactive ingredients) before the excipients are used in drug formulations.

On December 5, 2019, a Request for Information (RFI) was posted in the Federal Register to gather input from industry to evaluate interest in developing a pilot program and to identify potential challenges. FDA considered this public feedback in developing this pilot.

5 Gaps, Challenges, Outlook

Requirements for Novel Excipients

Any excipient that is not fully supported by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration.

- Proper planning during early development is important to prevent delays in product approval.
- FDA and EMA outline requirements for novel excipient approval.
- FDA Novel Excipient evaluation oulined in *"Section IV. Recommended strategies to support marketing of new excipients in drug products"* including:

A Safety Pharmacology (ICH Guidance S7A)

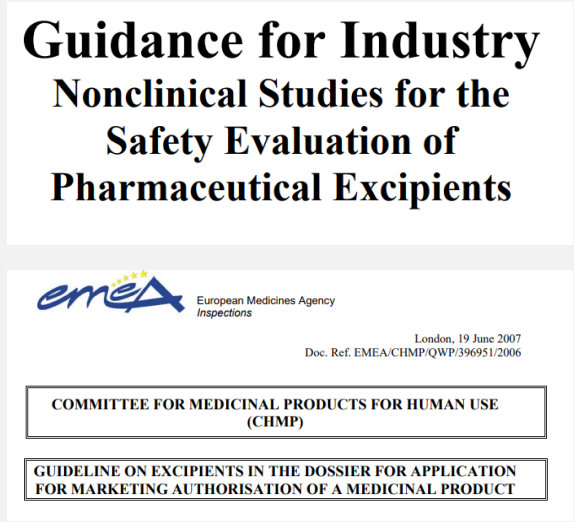
B Intended for Short-Term Use (14 day treatment window)
- Acute Toxicology and Nonclinical Safety Studies, 2 species (1 rodent and 1 non-rodent) (CDER Guidance Single *Dose Acute Toxicity Testing for Pharmaceuticals,* ICH Guidance M3)
- Toxico- and Pharmacokinetics (ICH Guidelines S3A and S3B)
- Genotoxicity (ICH Guidance S2B)
- 1-month repeat-dose toxicology studies - 2 species Reproductive toxicology (ICH Guidelines S5A and S5B)

C Intended for Intermediate Use (14 day – 3 months)
- IV. A and B + 3-month repeat-dose toxicology studies (2 species)

D Long-Term Use (> 3 months)
- IV. A, B, and C + 6 month repeat-dose toxicology study (rodent)
- 6 month or up to 9-12 month chronic (non-rodent)
- Carcinogenic potential (ICH Guidance S1A and S2B)

E For Intranasal and Pulmonary Products
- IV. A, B, C, or D + Sensitization (Immunotox.) (CDER Guidance *Immunotoxicology Evaluation of Investigational New Drugs)*
- If systemic exposure observed, additional toxicology studies by oral or parenteral routes

F Photosafety (CDER Guidance *Photosafety Testing)*



Thank you!

Q&A

Addendum Slides

September 2024

Appendix: Buffering Agents and Salts

Excipients for Protein and Nucleic Acid Therapeutics

pH and salt concentration are critical for controlling folding state and minimize physical and chemical degradation. The most commonly utilized buffer is sodium phosphate with some level of sodium or potassium chloride.

Category	Present	Absent
Buffering Agent	ACETIC ACID, ANHYDROUS CITRIC ACID, CALCIUM CARBONATE, CITRIC ACID MONOHYDRATE, GLYCINE, MONOBASIC POTASSIUM PHOSPHATE, SODIUM BICARBONATE, SODIUM PHOSPHATE, SODIUM PHOSPHATE, DIBASIC (ANHYDROUS, DIHYDRATE, DODECAHYDRATE, HEPTAHYDRATE), TROMETHAMINE	SODIUM ACETATE, SODIUM SUCCINATE, ARGININE, ALANINE, ASPARTIC ACID, GLUTAMIC ACID, LYSINE, HISTIDINE
pH-Adjusting Agent	ACETIC ACID, ANHYDROUS CITRIC ACID, ANHYDROUS TRISODIUM CITRATE, ASCORBIC ACID, CITRIC ACID MONOHYDRATE, HYDROCHLORIC ACID, NITRIC ACID, SODIUM BICARBONATE, SODIUM HYDROXIDE, SULFURIC ACID	PHOSPHORIC ACID
Tonicity Agent	ANHYDROUS DEXTROSE, DEXTROSE, DEXTROSE MONOHYDRATE, GLYCERIN, MANNITOL, POTASSIUM CHLORIDE, SODIUM CHLORIDE	

*Underlined entries represent overlap between protein and NA therapeutic excipients.

Appendix: Surfactants

Excipients for Protein and Nucleic Acid Therapeutics

Most commonly used surfactants included polysorbate 80, polysorbate 20, and poloxamer 188. These agents are used not only to stabilize against interfacial tension but also to reduce aggregation or protein -protein interactions.

Category	Present	Absent
Surfactant	BENZALKONIUM CHLORIDE, CETYLPYRIDINIUM CHLORIDE, POLYSORBATE 20, POLYSORBATE 80, PROPYLENE GLYCOL, SODIUM LAURYL SULFATE	POLOXAMER 188, TRIPALMITIN, PALMITIC ACID, COLFOSCERIL PALMITATE, DISMYRISOTYL GLYCEROL

*Underlined entries represent overlap between protein and NA therapeutic excipients.

Appendix: Lyoprotectants and Stabilizers

Commonly used lyoprotectants and stabilizers are sugars - sucrose, mannitol, and trehalose. They act to maintain molecular structure in both the liquid and solid state affecting physical stability.

Category	Present	Absent
Lyoprotectant / Bulking Agent	GLYCINE, LACTOSE, MANNITOL	SUCROSE, TREHALOSE
Stabilizer	BUTYLATED HYDROXYTOLUENE, CELLULOSE MICROCRYSTALLINE/ CARBOXYMETHYLCELLULOSE SODIUM, EDETATE DISODIUM, FERRIC OXIDE, GLYCINE, HYDROXYETHYL CELLULOSE (2000 MPA.S AT 1%), HYPROMELLOSE, MANNITOL, POLYETHYLENE GLYCOL 3350, POLYETHYLENE GLYCOL 400, POLYSORBATE 20, POLYSORBATE 80, SILICON DIOXIDE, SODIUM METABISULFITE, SORBITOL, TITANIUM DIOXIDE	ALBUMIN, ARGININE, ALANINE, ASPARTIC ACID, GLUTAMIC ACID, LYSINE, HISTIDINE

*Underlined entries represent overlap between protein and NA therapeutic excipients.

Appendix: Other

Category	Present	Absent
Antimicrobial Agent	ALCOHOL, BENZALKONIUM CHLORIDE, BUTYLATED HYDROXYANISOLE, CALCIUM CHLORIDE, CETYLPYRIDINIUM CHLORIDE, CHLOROBUTANOL, GLYCERIN, METHYLPARABEN, PHENYLETHYL ALCOHOL, PHENYLMERCURIC ACETATE, PHENYLMERCURIC NITRATE, POTASSIUM SORBATE, PROPYLENE GLYCOL, PROPYLPARABEN, SODIUM BISULFITE, SODIUM METABISULFITE, THIMEROSAL, THYMOL, ZINC OXIDE	METACRESOL
Solubilizing Agent	BENZALKONIUM CHLORIDE, CETYLPYRIDINIUM CHLORIDE, GLYCINE, HYPROMELLOSE 2906 (4 MPA.S), HYPROMELLOSE 2910 (4000 MPA.S), HYPROMELLOSE 2910 (5 MPA.S), LANOLIN, POLYSORBATE 20, POLYSORBATE 80, PROPYLENE GLYCOL, SODIUM LAURYL SULFATE, SORBITAN MONOLAURATE, SORBITAN TRIOLEATE	ISOPROPYL ALCOHOL, MYIONOSITAL
Antioxidant	ASCORBIC ACID, BUTYLATED HYDROXYANISOLE, BUTYLATED HYDROXYTOLUENE, CITRIC ACID MONOHYDRATE, SODIUM BISULFITE, SODIUM METABISULFITE, THYMOL	METHIONINE
Complexing Agent	EDETATE DISODIUM,	MAGNESUM CHLORIDE
Diluent for Solid Dosage Form	CASTOR OIL, MAGNESIUM STEARATE, POLYETHYLENE GLYCOL 3350, POLYETHYLENE GLYCOL 400	
Dispersing Agent	CELLULOSE MICROCRYSTALLINE/CARBOXYMETHYLCELLULOSE SODIUM, HYPROMELLOSE	
Lipids and Liposome Forming Agents		(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31tetraen-19-yl-4-(dimethylamino)butanoate (DLin-MC3-DMA), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), α-(30-{[1,2-di(myristyloxy)propanoxy] carbonylamino}propyl)-ωmethoxy, polyoxyethylene (PEG 2000 C-DMG), 2[(polyethylene glycol)-2000]-N,N ditetradecylacetamide, (4-hydroxybutyl)azanediyl)-bis(hexane-6,1-diyl)bis(2-hexyldecanoate), SM-102, Cholesterol

*Underlined entries represent overlap between protein and NA therapeutic excipients.