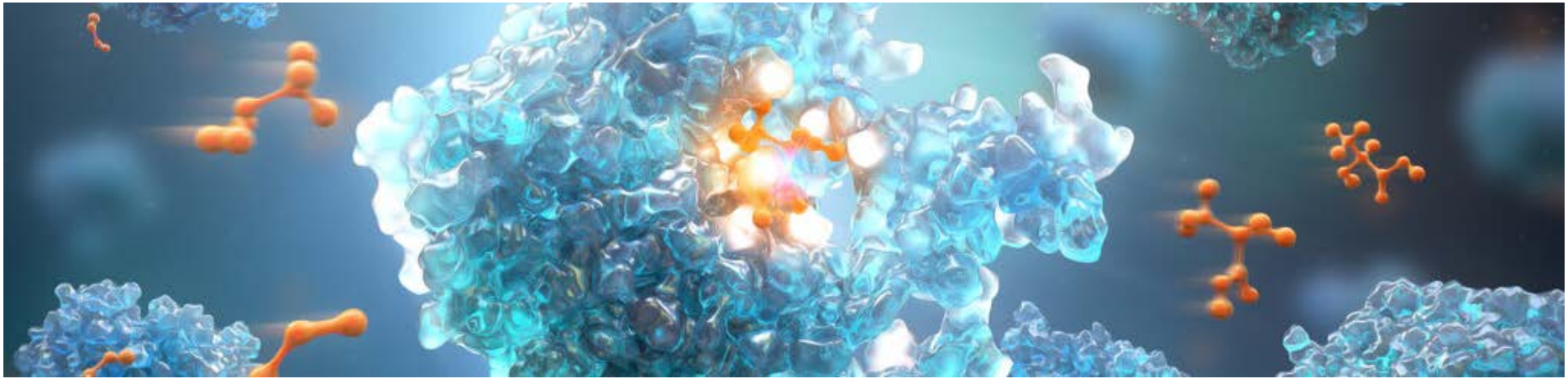
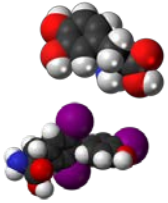
Innovative drug products in the pipeline

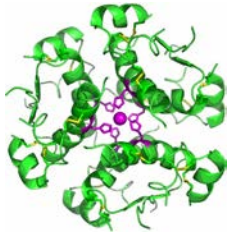
David Lechuga-Ballesteros, Ph.D.
Research Fellow, AstraZeneca Pharmaceuticals



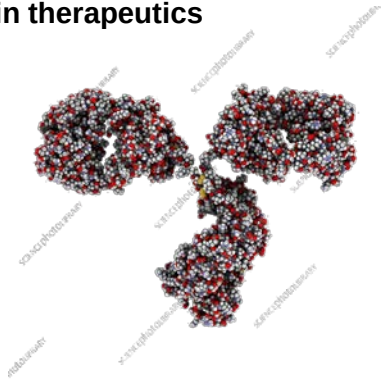
The active pharmaceutical ingredients

Small molecules

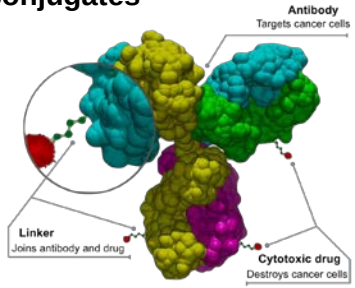




Protein therapeutics

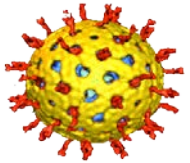


Protein-drug conjugates

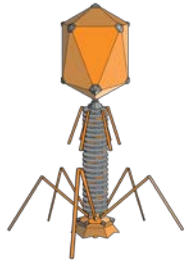


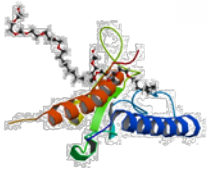
Nanomachines

Viruses

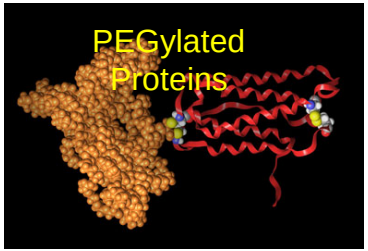


bacteriophage

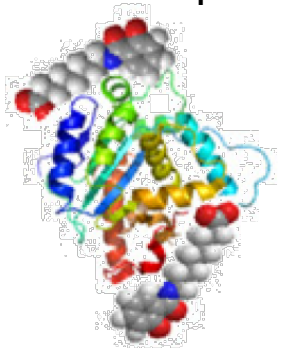




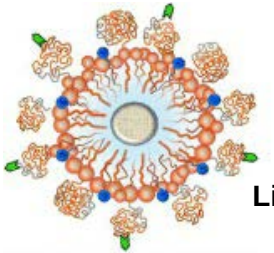
Chemically modified Peptides



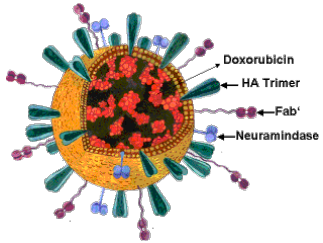
Protein/small molecule complexes



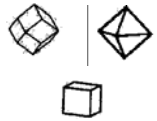
Solid Lipid Nanoparticles



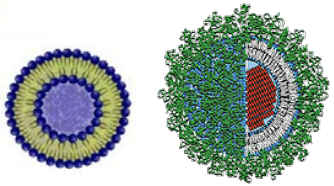
Virosomes



Nanocrystals

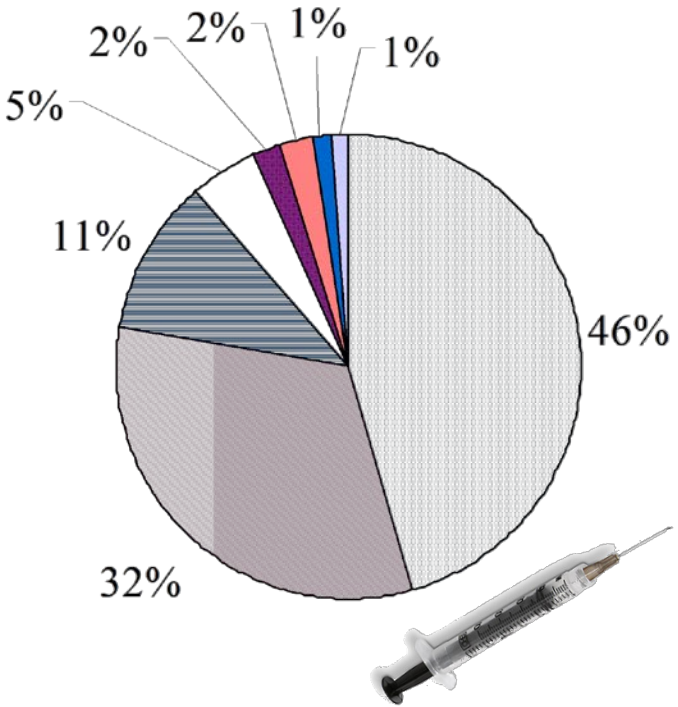


Liposomes



Technological challenges delivery of biologics

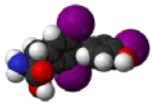
- Parenteral most common route of administration
- Many require refrigeration
- Poor physical stability
- (short and long term), most in dispersion/suspension
- Poor oral bioavailability, most in dispersion/suspension
- Portability challenges transporting solution vs. solid
- (*i.e.*: Cold chain needed for vaccines and most biologics)



Ohtake, S., Lechuga-Ballesteros, D., Truong-Le, V., and Patzer, E. J. (2014) Strategies for Heat Stable Vaccines, in *Vaccine Production and Manufacturing (Wen, E., Ed.), Wiley & Sons.*

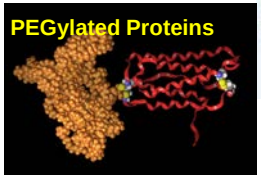
Drug delivery via microparticles

Small Molecule Drugs

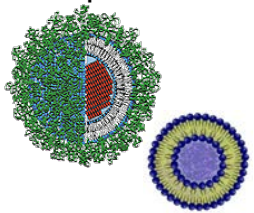


Protein bound drug

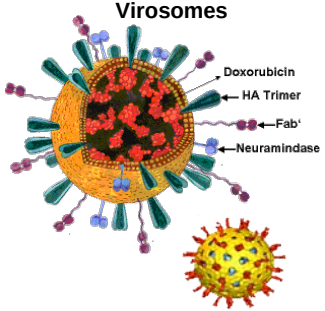
PEGylated Proteins



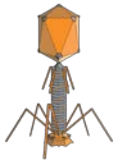
Liposomes



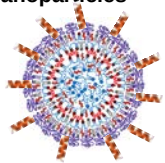
Virosomes



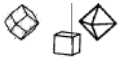
Nanomachines



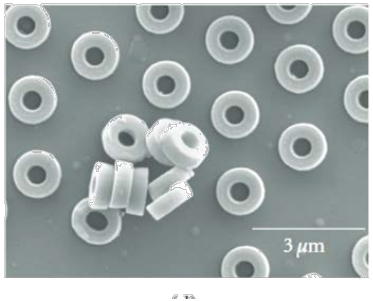
Solid Lipid Nanoparticles



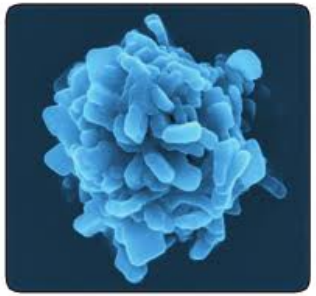
Nanocrystals



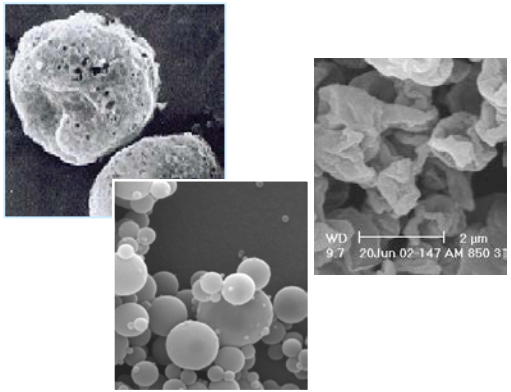
Molded microparticles



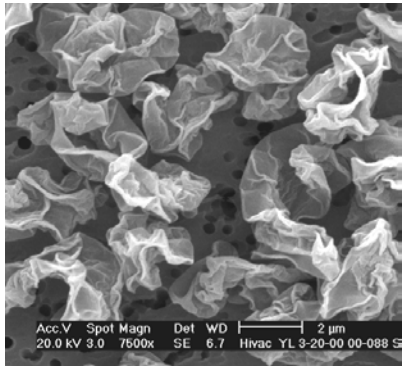
Crystalline protein carriers



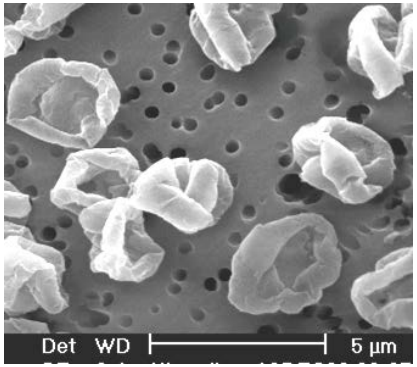
Spray dried microparticles



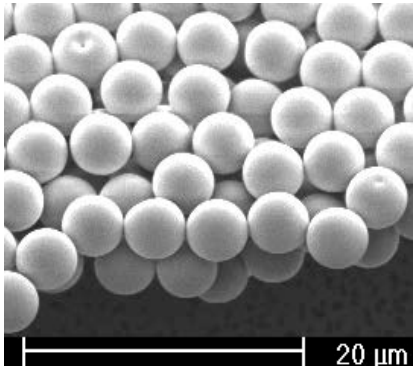
Microparticle Engineering via Spray Drying



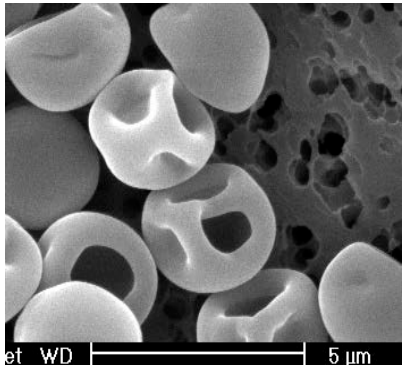
Flakes



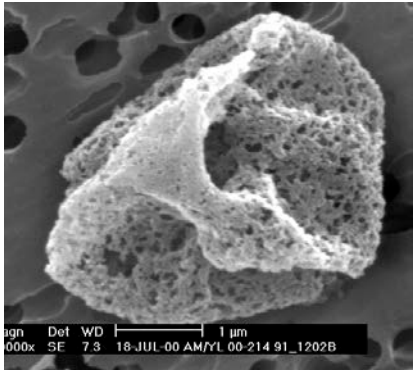
Partially Crystalline



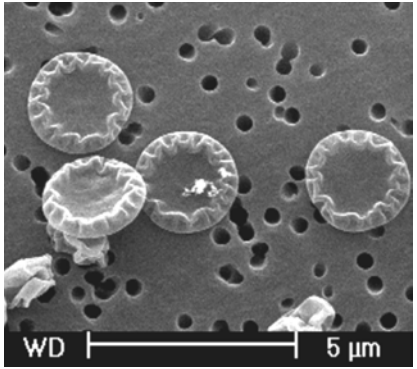
Monodisperse



Smooth Dimpled

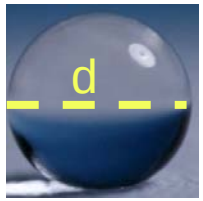


Porous

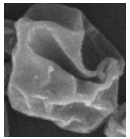


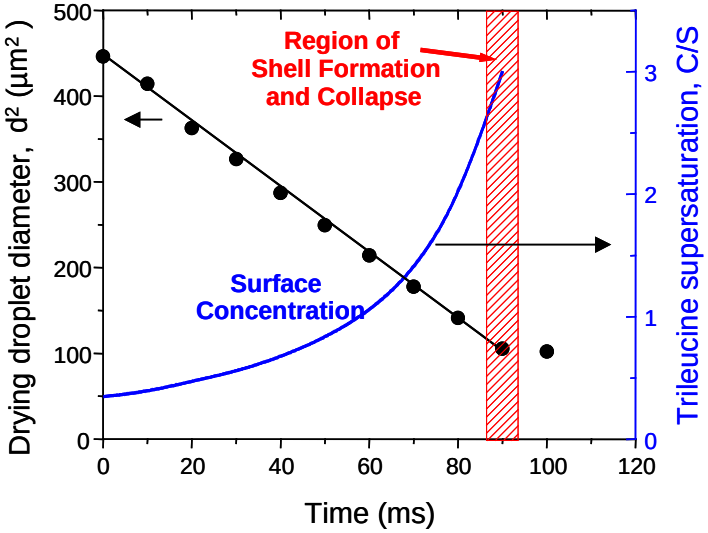
Bottlecaps

Particle design via spray drying based on molecular weight, solubility and surface tension on formulation components



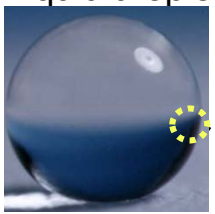
$$d^2(t) = d_0^2 - \kappa t.$$





Formation of a hydrophobic surface is favored by inherent surface activity properties of excipient

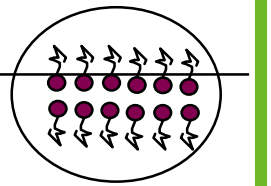
Liquid droplet



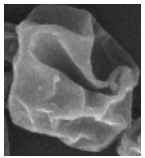
trileucine

Air

Liquid



drying

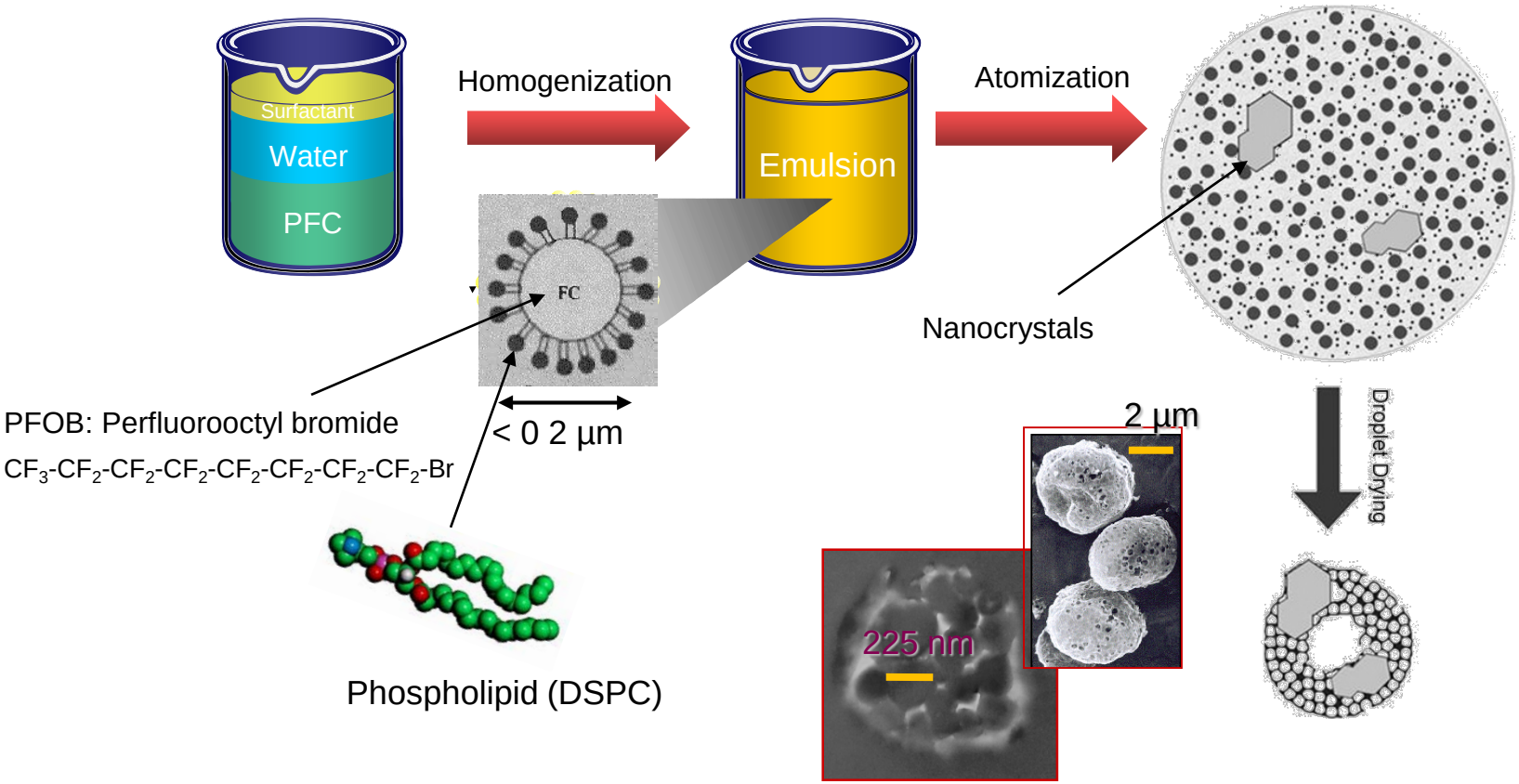


Solid particle

Vehring, R., Foss, W. R., and Lechuga-Ballesteros, D. (2007) Particle formation in spray drying, *J Aerosol Sci 38, 728-746.*

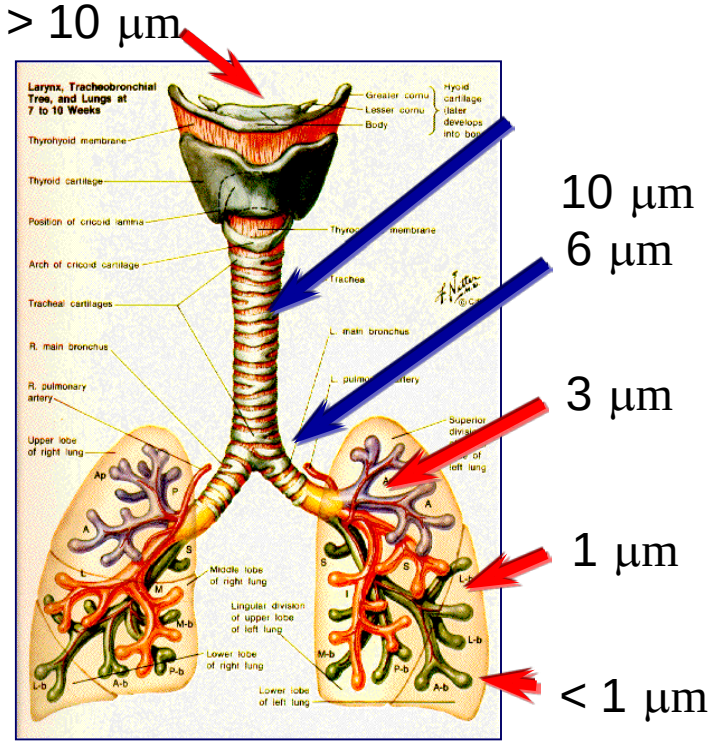
Lechuga-Ballesteros, D., et al., (2008) Trileucine improves aerosol performance and stability of spray-dried powders for inhalation, *J Pharm Sci 97, 287-302.*

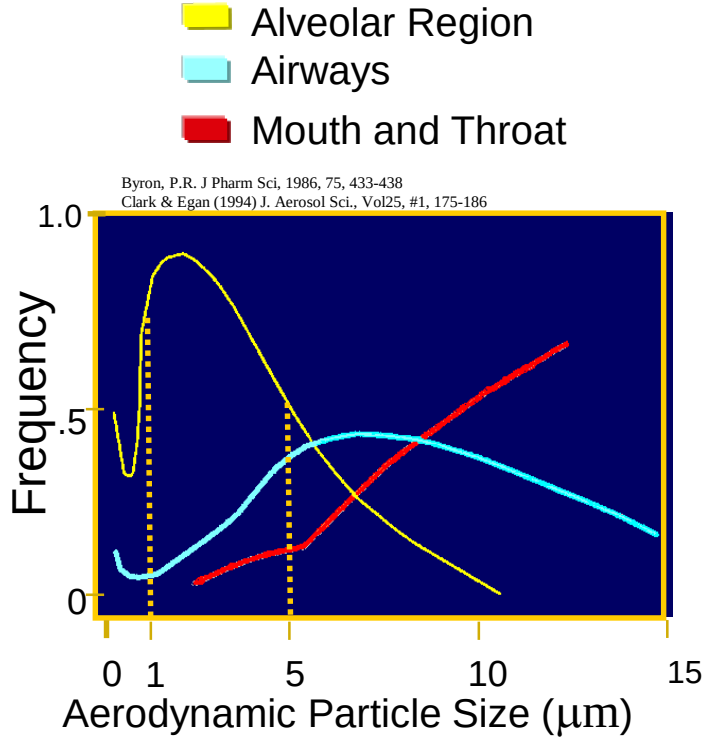
Low density spray dried particles are ideal for pulmonary delivery



Vehring R,.et al. Cosuspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers. Langmuir. 2012 Oct 23;28(42):15015-23. doi: 10.1021/la302281n

Pulmonary deposition is driven by the Aerodynamic Particle Size

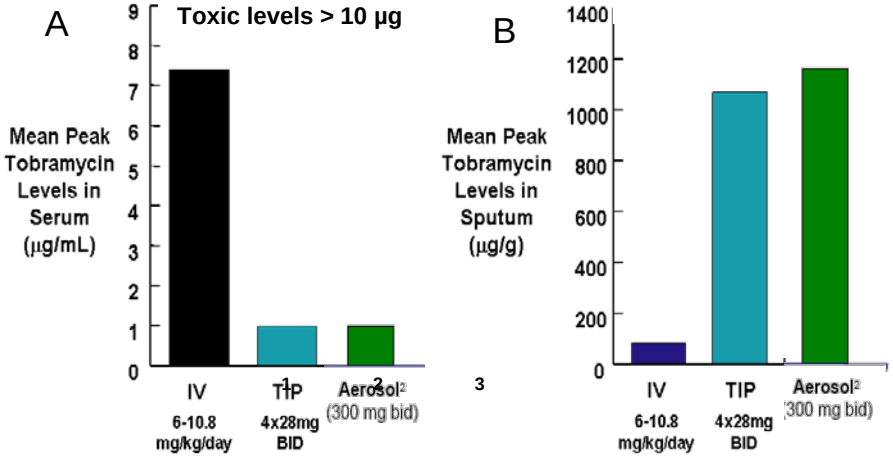




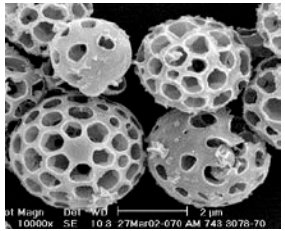
Targeting the lung: Inhaled antibiotics in powder form

Increased efficacy and improved safety profile over IV treatment and improved patient experience with reduced does over nebulized tobramycin solution

Inhalation achieves 10X tobramycin concentrations in sputum and reduces systemic exposure 7X

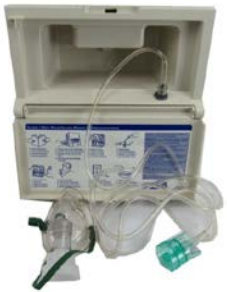


Spray dried tobramycin



Dry powder inhalation: 224 mg/day
8 inhalations over 10 minutes

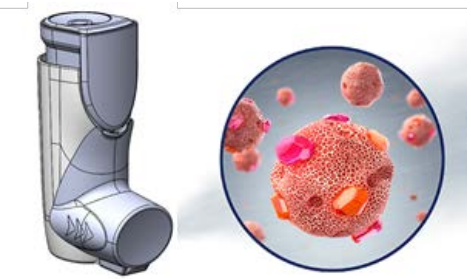
Nebulized solution inhalation: 600 mg/d
2 inhalation sessions over 30 minutes



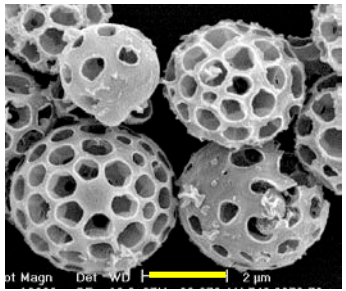
IV infusion: 70 mg/day over 30 minutes

[1]Mendelman PM et al: *Am Rev Respir Dis* 1985, **132**:761-765; [2]Weber, A. et al. *Pediatric Pulmonology* 1997, **23**: 249-260; [3]Geller DE et al: *Pediatr Pulmonol* 2007, **42**:307-313. Geller DE, Weers JG, Heuerding S. *J Aerosol Med and Pulm Drug Delivery,* 2011, **24**(4): 175-182.

Pulmonary drug delivery via spray dried microparticles in a Metered Dose Inhaler

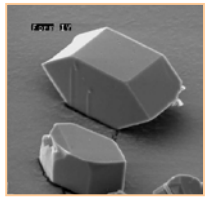


Spray dried particles, carrier



2 µm

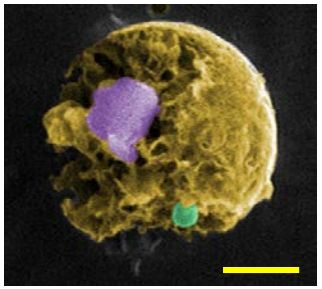
Crystalline API



+

=

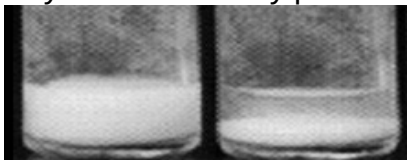
Drug + Carrier



2 µm

Low solubility in propellant (hydrofluoroalkanes) and low adhesive nature of porous particles results in longer flocculation, creaming times.

Crystalline API only pMDI



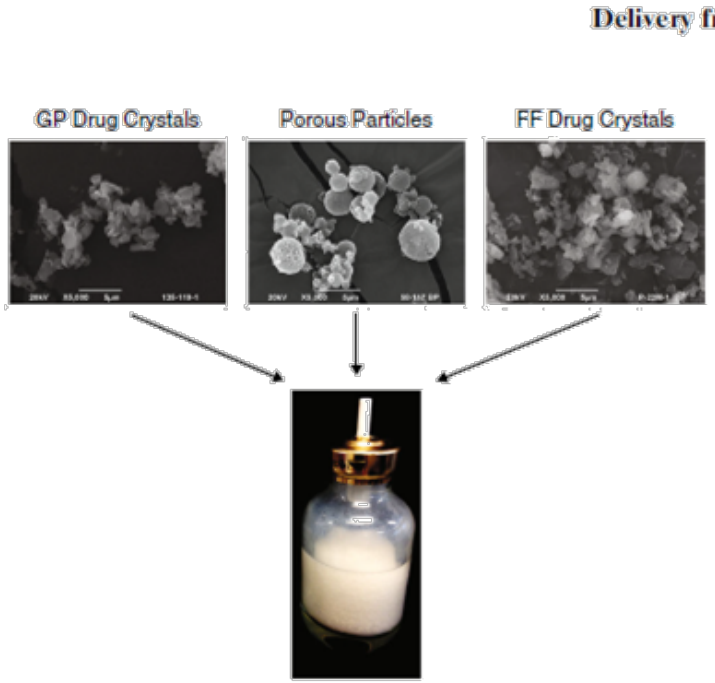
0 seconds → 5 seconds

Co-suspension pMDI

0 seconds → 15 seconds → 30 seconds

Vehring et al. 2015 Langmuir 28 (42), 15015-15023 Co-suspensions of microcrystals and engineered microparticles for uniform and efficient delivery of respiratory therapeutics from pressurized metered dose inhalers,

Co-suspension delivered dose is more robust than drug crystal only suspensions



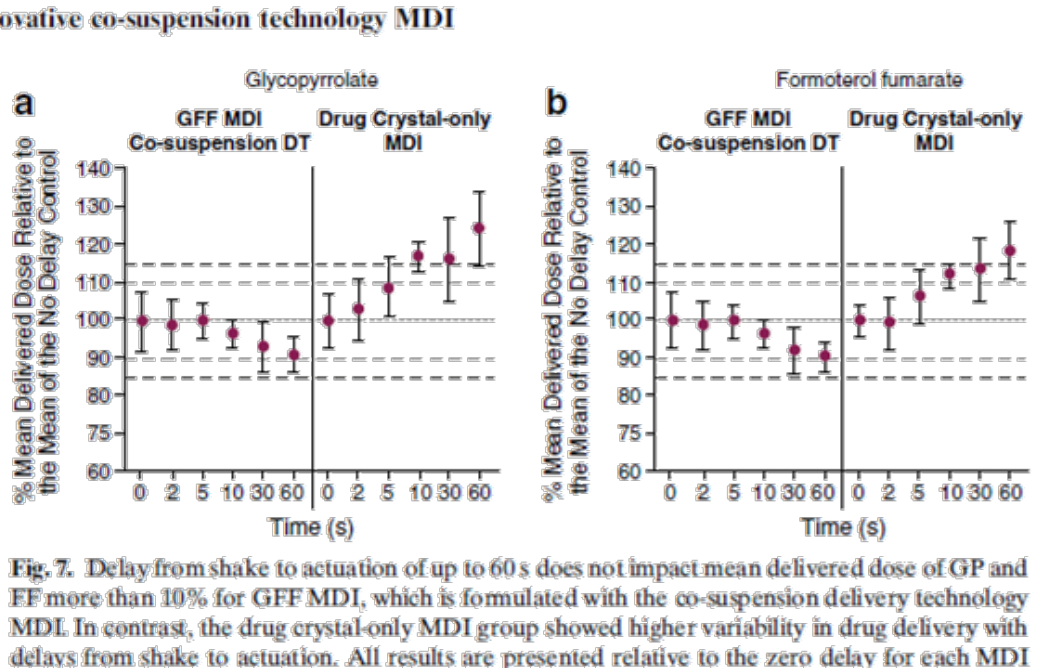
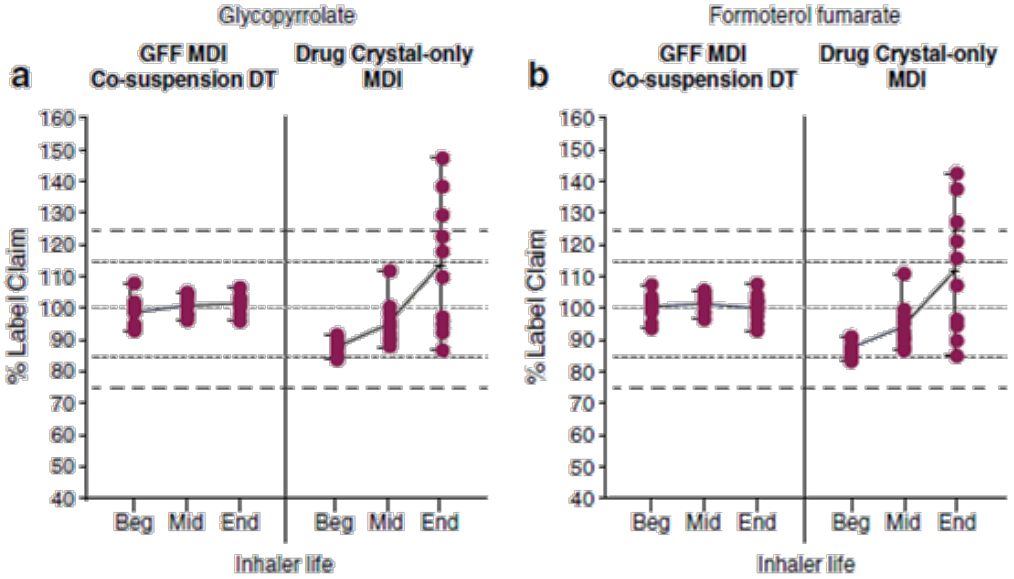
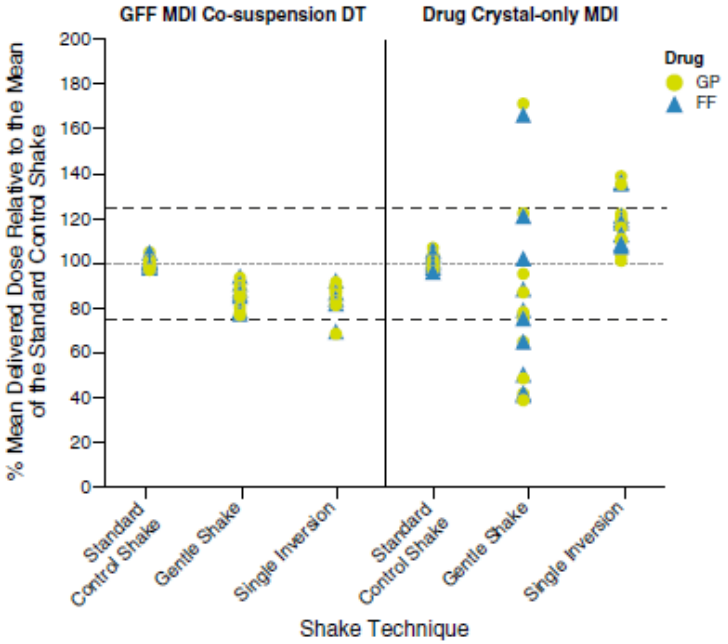


Fig. 7. Delay from shake to actuation of up to 60 s does not impact mean delivered dose of GP and FF more than 10% for GFF MDI, which is formulated with the co-suspension delivery technology MDI. In contrast, the drug crystal-only MDI group showed higher variability in drug delivery with delays from shake to actuation. All results are presented relative to the zero delay for each MDI

Doty et al. 2018 Drug Delivery from an Innovative LAMA/LABA Co-suspension Delivery Technology Fixed-Dose Combination MDI: Evidence of Consistency, Robustness, and Reliability. AAPS PharmSciTech, Vol. 19, No. 2, (# 2017) DOI: 10.1208/s12249-017-0891-1

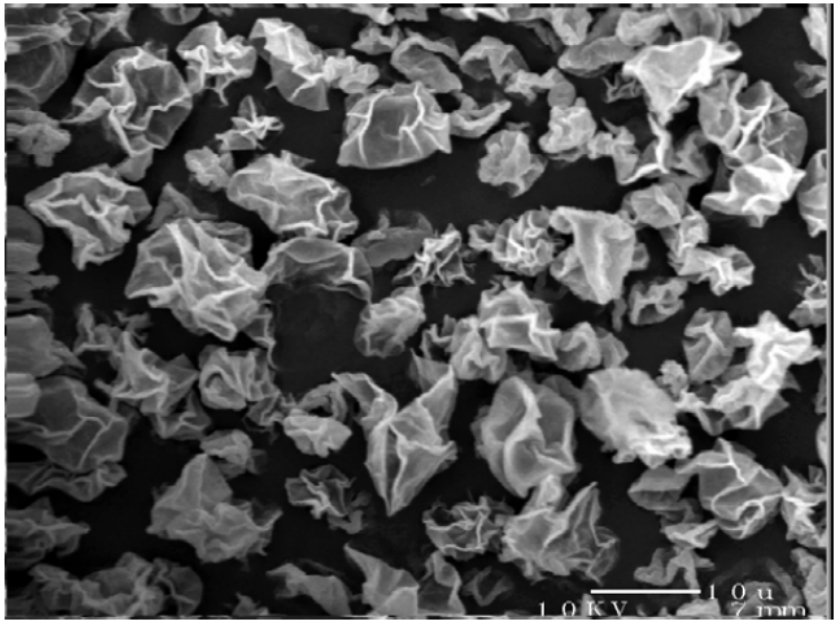
Co-suspension drug delivery is more consistent than drug crystal only suspensions





Doty et al. 2018 Drug Delivery from an Innovative LAMA/LABA Co-suspension Delivery Technology Fixed-Dose Combination MDI: Evidence of Consistency, Robustness, and Reliability. AAPS PharmSciTech, Vol. 19, No. 2, (# 2017) DOI: 10.1208/s12249-017-0891-1

Levodopa spray dried powder for inhalation



AIR Technology

48 mg/capsule X 2

Inbrija for the treatment of Parkinson’s disease. FDA approved 2018

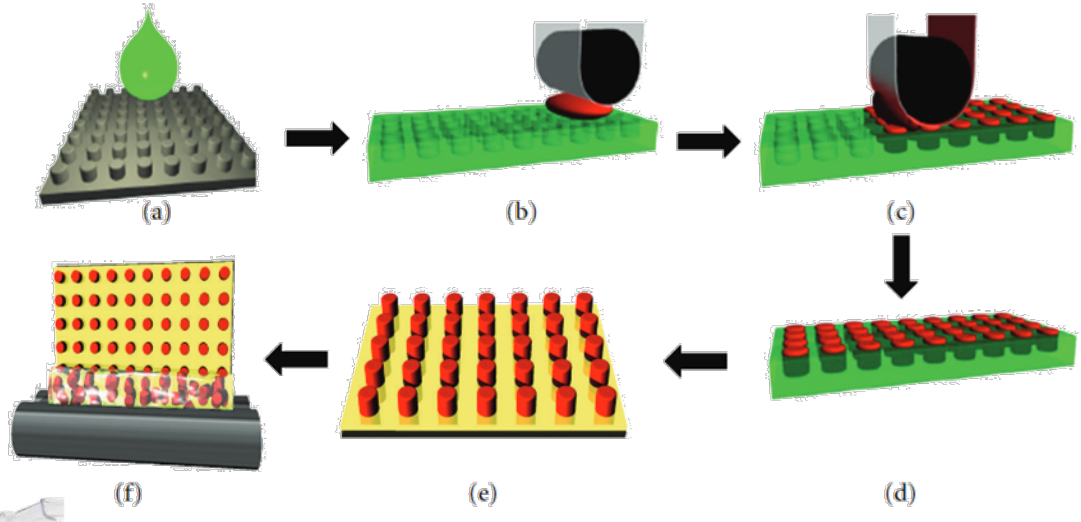
AIR spray dried powder for inhalation scale up

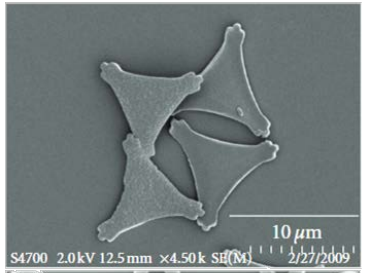
Powder Production Scale-up

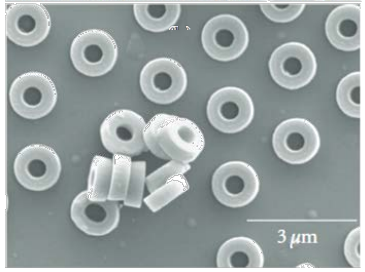
- Approximately 30 minutes of production each
- Scale-up of powder production by > 100,000 times

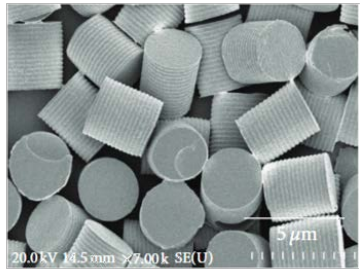
Johnston, Lloyd, 2005 Process Development and Scale-Up of the AIR technology

Molded microparticles, treprostinil powder for inhalation





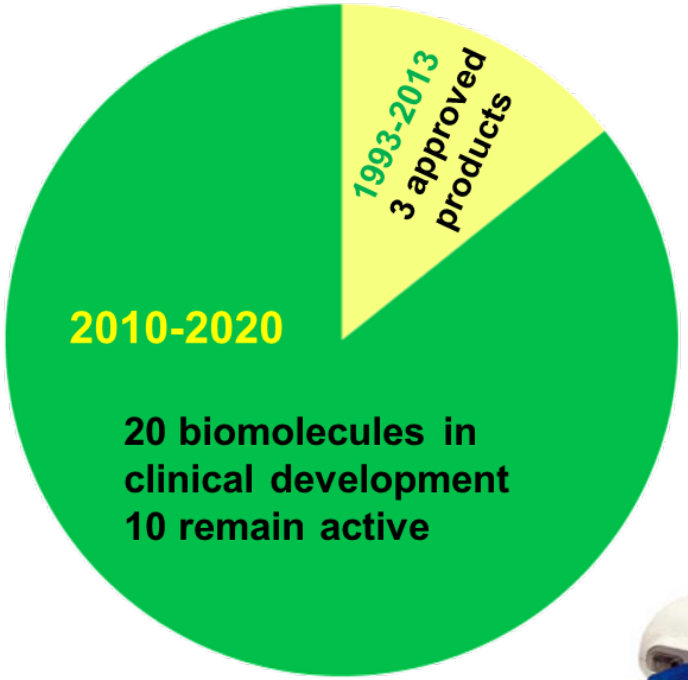




LIQ861, Phase 3, treprostinil DPI
Treatment of PAH

Garcia, Mack et al 2012. Microfabricated engineered particle systems for respiratory drug delivery and other pharmaceutical applications. Journal of Drug Delivery Vol. 2012, doi: 10.1155/2012/941243

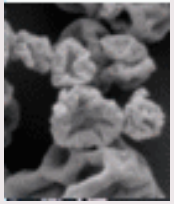
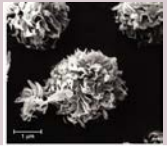
Pulmonary delivery of therapeutic peptides, proteins



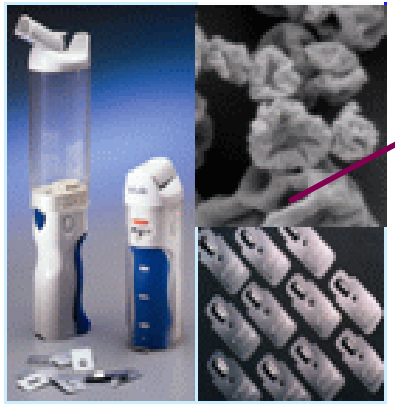
Formulation		Device
Liquid	7	Jet nebulizer
	8	Vibrating mesh
Dry powder	5	Dry powder inhaler

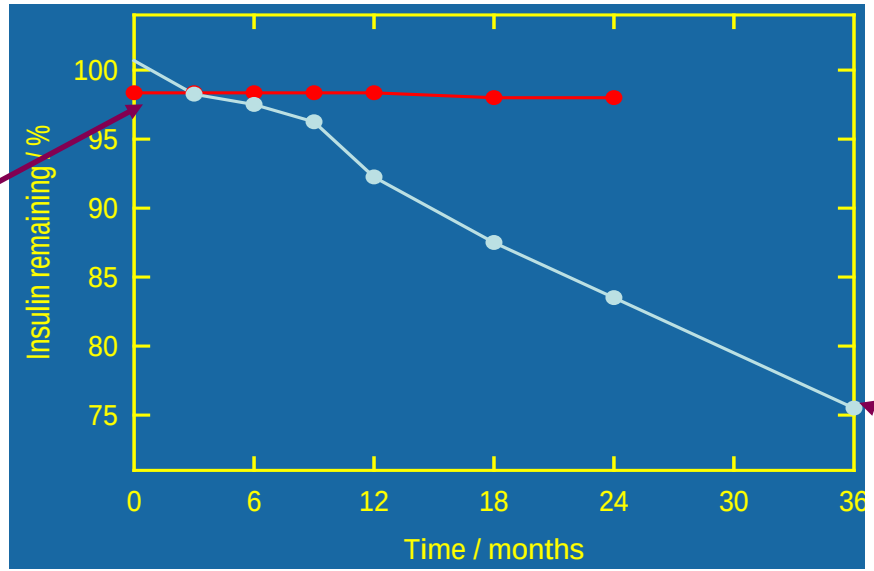
Bodier-Montagutelli et al 2018. Designing inhaled protein therapeutics for topical lung delivery: what are the next steps? Export Opinion On Drug Delivery 15(8) 729-736. doi: 10.1080/17425247.2018.1503251

Pulmonary delivery of therapeutic proteins

Product	Active	Status	Device	Manufacturing	Storage
Pulmozyme	**Dornase alfa**	Available Since 1993	**Nebulizer** 	Liquid blending	Refrigerated
Exubera	**Insulin**	Discontinued 2006-2008	**Dry powder** 	Spray drying 	Room temperature
Afrezza	**Insulin**	Available Since 2013	Dry powder 	Crystallization/ freeze drying 	Refrigerated

Microparticles provides room temperature stability and enable pulmonary delivery for insulin





- Spray dried microparticles have appropriate characteristics for pulmonary deliver
- Proteins are room temperature stable for more than two years in dry amorphous powders

Weers, J. G., Tarara, T. E., and Clark, A. R. (2007) Design of fine particles for pulmonary drug delivery, *Expt Opin Drug Deliv 4, 297-313.*

Insulin liquid formulation data from Oliva et al. Drug Development and Industrial Pharmacy 29(5) 513-521, 2003

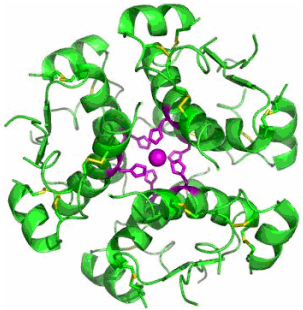
Spray drying manufacturing process

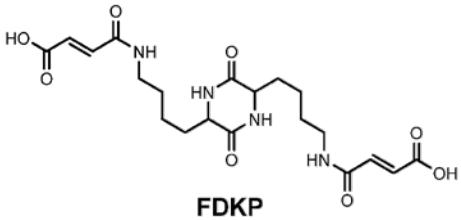
Preclinical

Clinical

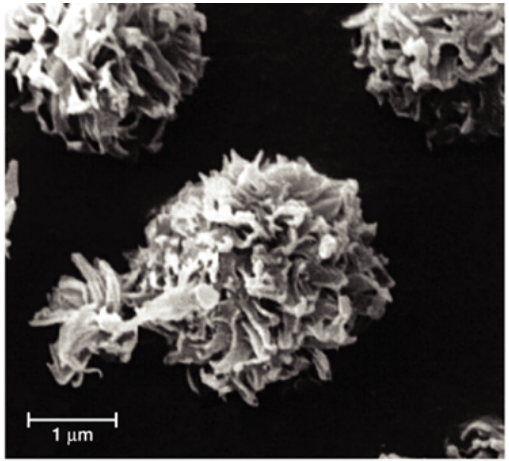
Commercial

Crystalline microparticles manufactured via crystallization followed by freeze drying enable insulin pulmonary delivery





fumaryl diketopiperazine

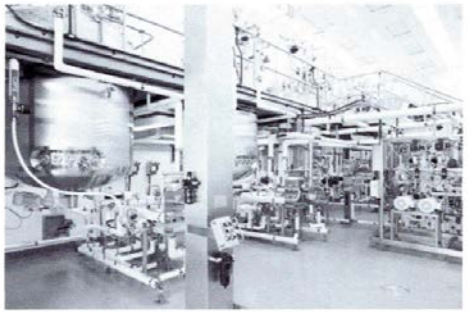


Technosphere

Rendell, 2014 Technosphere inhaled insulin. Drugs Today (Barc.) 50(12):813-27. doi: 10.1358/dot.2014.50.12.2233894

Technosphere manufacturing process

Tanks for tangential flow diafiltration

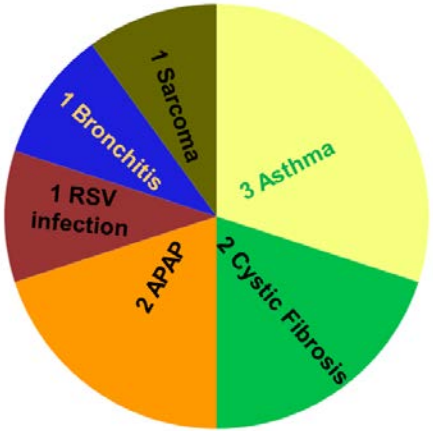


Formulation suite showing tanks and reactor used for manufacture of Technosphere particles

Cryogranulator used to form Technosphere Insulin pellets prior to lyophilization

 https://pdfs.semanticscholar.org/0dce/ab26cd902cbfb46c3a922810e42698dfe75d.pdf

Current pulmonary products cover topical indications



	Active ingredient	Indication	Clinical Phase	Dose	Formulation	Process
ALX-0171/VR465	Trivalent RSV F-Protein	RSV Infection	Phase 2b	[illegible]	Liquid	Liquid blending
Aidornasa alfa PRX-110	Actin-inhibition resistant deoxyribonuclease (37kD)	Cystic Fibrosis	Phase 2	2.5 mg/d	Liquid	Liquid blending
ALX-009 Lactoferrin	antibacterial blycoprotine (80 kD)	Cystic Fibrosis	Phase 1	4 mg/mL	Liquid	Liquid blending
Alteplase	Tissue plasminogen activator (tPA) (70kD)	Plastic bronchitis	Phase 2	5 mg every 6h	Liquid	Liquid blending
Molgramostim	rh-GM-CSF	APAP	Phase 3	300 µg/d	Liquid	Liquid blending
GM-CSF	GM-CSF (14kD)	APAP	Phase 2	150 µg/d	Liquid	Liquid blending
VR942/UCB4144	Anti-IL-13 Fab	Asthma	Phase 1	0.5 to 20 mg/d	Dry powder	Spray drying
AZD1402/PRS-060	Anticalin (18 kD) IL-4Rα	Asthma	Phase 1b	BUSCAR	Liquid	Liquid blending
CSJ117	Anti TSLP Fab (46kD)	Asthma	Phase 2	BUSCAR	Dry powder	Spray drying

APAP: Autoimmune Pulmonary Alveolar Proteinosis

Bodier-Montagutelli et al 2018. Designing inhaled protein therapeutics for topical lung delivery: what are the next steps? Export Opinion On Drug Delivery 15(8) 729-736. doi: 10.1080/17425247.2018.1503251

Nasal Delivery via Microparticles

Examples of nasal microparticle powders.

Drug	Microparticle type	Excipient/s	Manufacturing method	Ref.
Gentamicin	Microsphere	Hyaluronic acid Chitosan glutamate Hyaluronic acid/chitosan glutamate	Solvent evaporation	(Lim et al., 2000)
	Microparticle	Chitosan hydroglutamate Hyaluronic acid Chitosan hydroglutamate/hyaluronic acid	Solvent evaporation	(Lim et al., 2002)
Granisetron	Microparticle	Hydroxypropyl-β-cyclodextrin Hydroxypropyl-β-cyclodextrin and sodium carboxymethylcellulose	Freeze drying	(Cho et al., 2010)
Insulin	Microparticle	Thiolated chitosan-4-thiobutylamidine	Emulsification solvent evaporation	(Krauland et al., 2006a)
	Microsphere	Starch with lysophosphatidyl choline Starch with glycodeoxycholate Starch with sodium taurodihydroxyfusidate	Freeze drying	(Illum et al., 2001)
Lorazepam	Microparticle	Hydroxypropyl-β-cyclodextrin + mucoadhesive polymer (hydroxypropylmethylcellulose and/or carbomer)	Spray drying	(Jug and Bećirević-Laćan, 2008)
	Microparticle	Poly(vinylalcohol) Poly(vinylpyrrolidone)	Spray drying	(Zhao et al., 2012)
Metoclopramide	Microsphere	Sodium alginate Chitosan hydrochloride Sodium alginate/chitosan hydrochloride	Spray drying	(Gavini et al., 2005)
Ropinirole	Microparticle	Poly(lactic-*co*-glycolic)acid/dipalmitoylphospatidylcholine/trimethylchitosan	Spray drying	(Karavasili et al., 2016)
Tacrine	Microparticle	Chitosan/pectin polyelectrolyte	Spray drying	(Saladini et al., 2013)
Verapamil	Microsphere	Chitosan	Spray drying and precipitation	(Abdel Mouez et al., 2014)

Tiozzo Fasiolo 2018 Opportunity and challenges of nasal powders: drug formulation and delivery. European J. Pharm. Sci. 113:2-17. doi 10.1016/j.ejps.2017.09.027

Nasal Sumatriptan Dry Powder Delivery

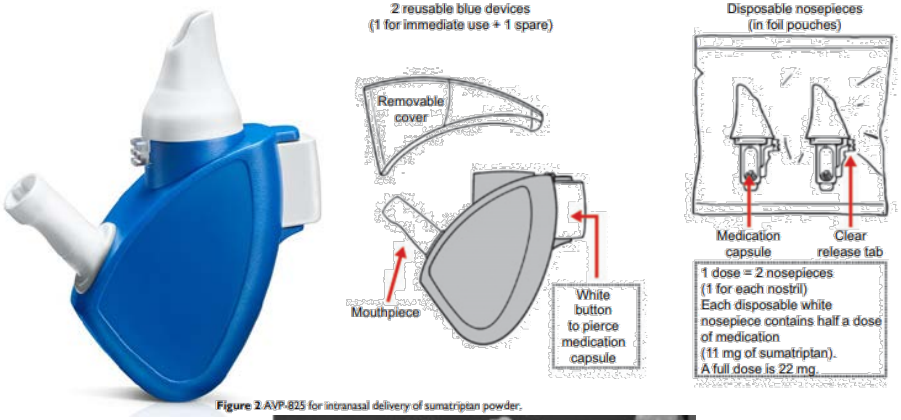
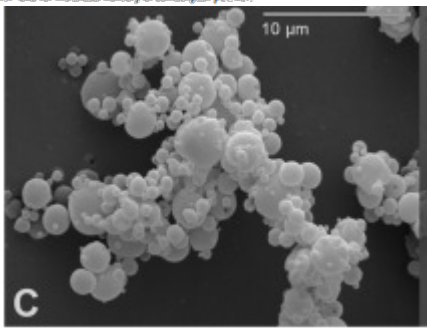


Figure 2 AVP-825 for intranasal delivery of sumatriptan powder.



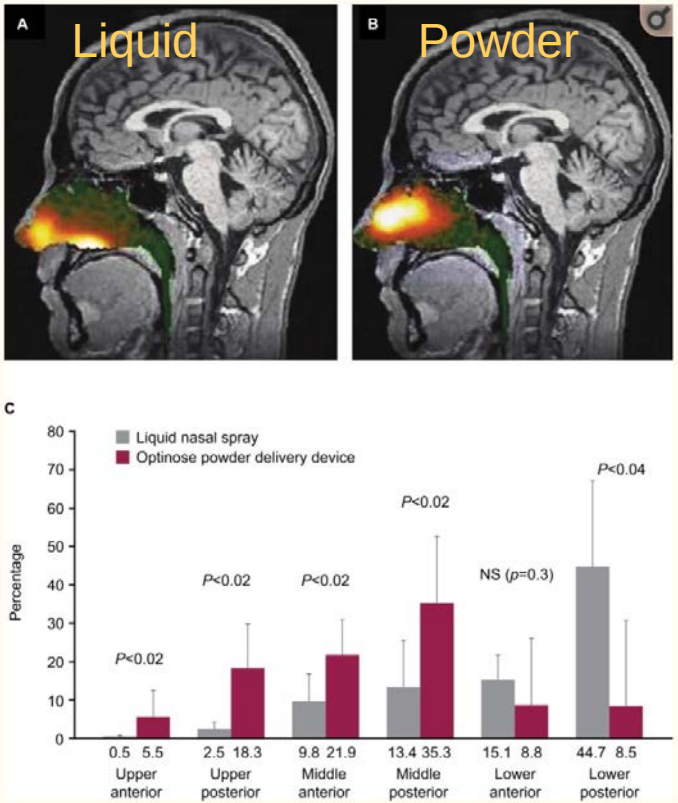
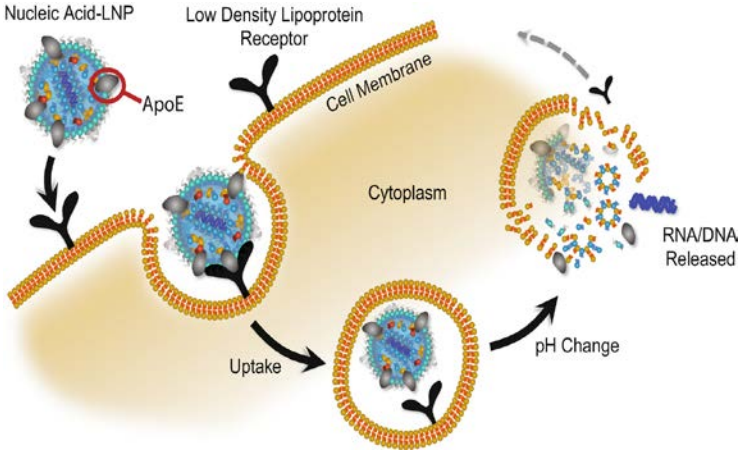


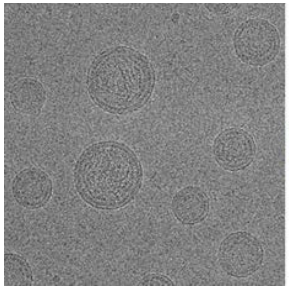
Figure 1

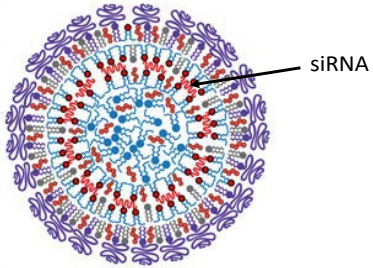
Imaging of intranasal delivery of (A) conventional liquid spray (radiolabeled diethylene triamine pentaacetic acid) vs (B) powder (radiolabeled lactose) with the breath-powered device and (C) quantification of deposition patterns.

Tepper and Johnstone 2018. Breath-powered sumatriptan dry nasal powder: an intranasal medication delivery system for acute treatment of migraine. Medical Devices: Evidence and Research 2018:11 147–156

Gene delivery: transfection of human cells via SLNP

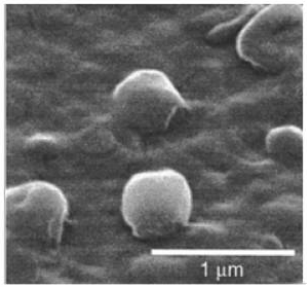






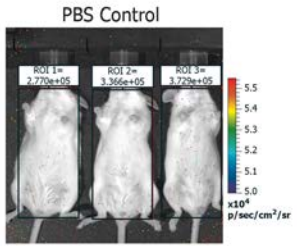
Positively charged ionizable lipid
Neutral ionizable lipid
PEG-lipid
Cholesterol
DSPC
siRNA

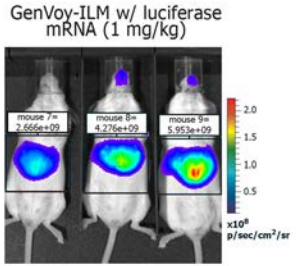
Kulkarni et al, ACS Nano 2018



Garcia-Pinel B, Porras-Alcalà C, Ortega-Rodríguez A, et al. Lipid-Based Nanoparticles: Application and Recent Advances in Cancer Treatment. *Nanomaterials (Basel)*. 2019;9(4):638. Published 2019 Apr 19. doi:10.3390/nano9040638

Deliver mRNA for gene expression



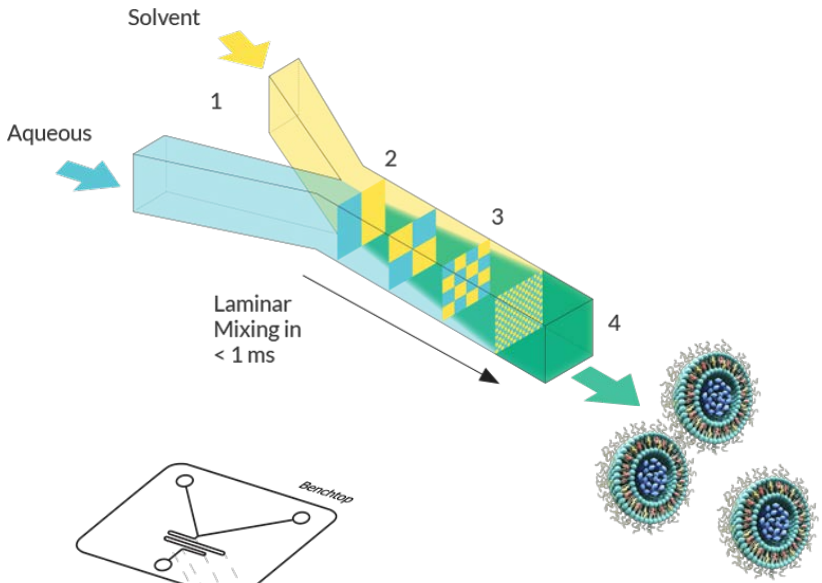


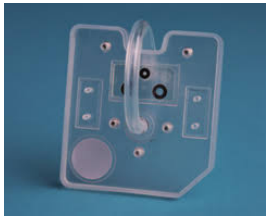
Precision Nanosystems website

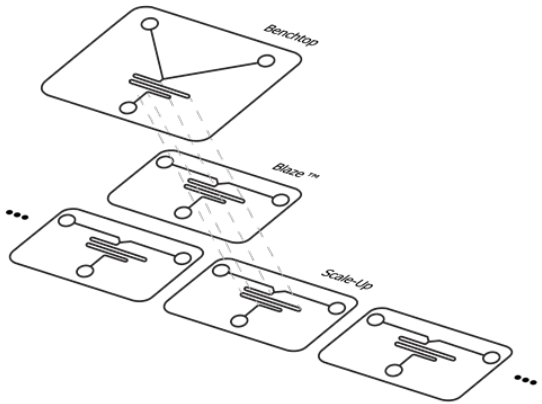
A single injection of GenVoy-ILM Luciferase mRNA-LNP was administered to mice via the tail vein at an RNA dose of 1 mg/mL. Luciferase expression was measured 6-hours post-mRNA-LNP administration.

25

SLNP manufacturing process

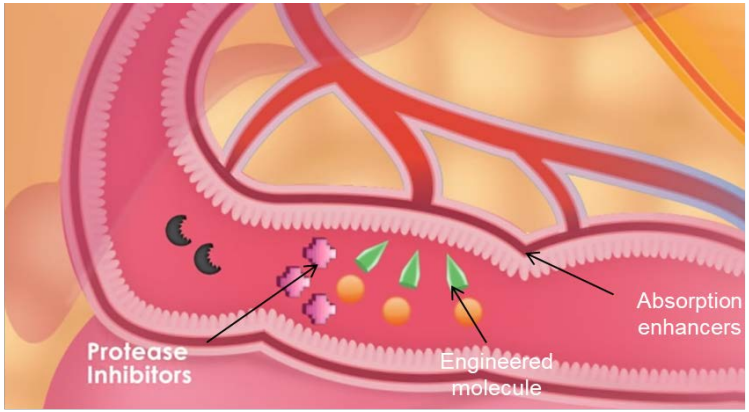




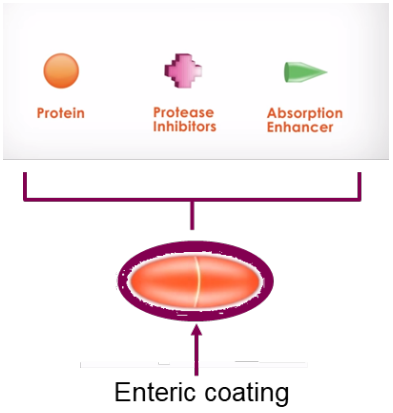


https://www.precisionnanosystems.com/

Oral delivery of peptides and proteins, biologics



Miriam Kidron, http://www.oramed.com/
https://www.youtube.com/watch?v=p3LOiZsSSOU



Challenge	Peptide modification/Formulation
Stomach: Increase stability	D-amino acids, lipid particles, PEG
Small intestine: Increased stability	Cyclization, PEG, lipidization, d-amino acid, polymer matrices, nanoparticles. N-acetylation
Enzyme inhibitors	Soybean trypsin inhibitor, aprotinin, bacitracin, puromycine
Absorption enhancers	Chitosan, faty acids, lectines, liposomes, emulsions, muchoadhesive particles, lipid particles
Circulation Increased stability	PEG. Hyper glycosilation, liposomes, nanoparticles

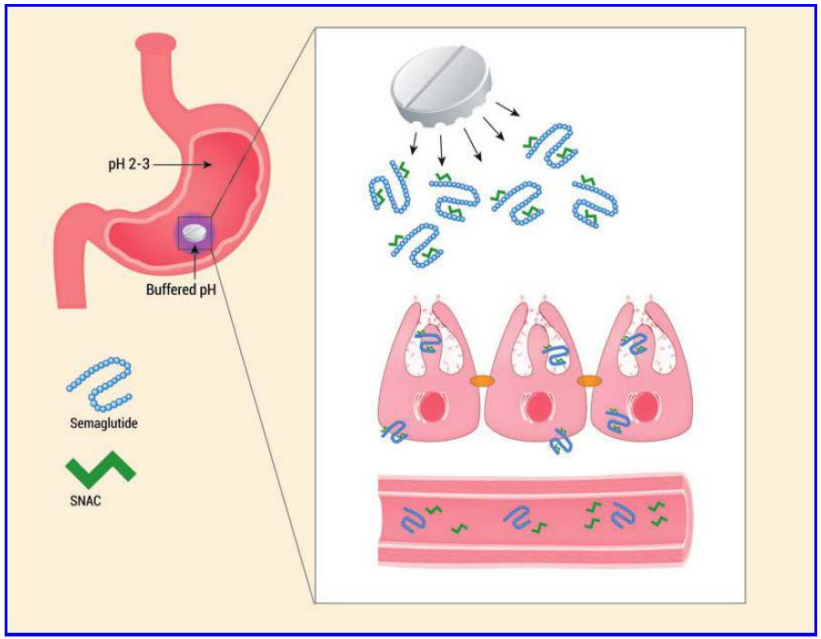
Oral delivery of protein and peptides: Current clinical trials

	Product	Active ingredient	Formulation	Indication	
Marketed	Neoral	Cyclosporine	SEDDS	Transplant rejection	
Approved	Rybelsus	Semaglutide	Eligen SNAC	T2DM	
Phase 1	ORMD-0901	Exenatide	Soft gelatine capsule enteric coating	T2DM	Israel
Phase 2	ORMD-0801	Insulin	Soft gelatine capsule enteric coating	T2DM	NCT03467932
Phase 2	Ovarest	Leuprolide	Peptelligence	Endometriosis	NCT02807363
Phase 2	CR845	Difelikefalin	Peptelligence	CKD, pruritis	NCT03617536
Phase 3	Mycapssa	Octreotide	Transient permeability enhancer	Acromegaly	NCT0352353
Phase 3	SMC021	Salmon Calcitonin	Elgen 5-CNAC	Osteoarthritis	NCT00704847
Phase 3	TBRIA	Salmon Calcitonin	Peptelligence	Postmenopausal osteoporosis	NCT02807363

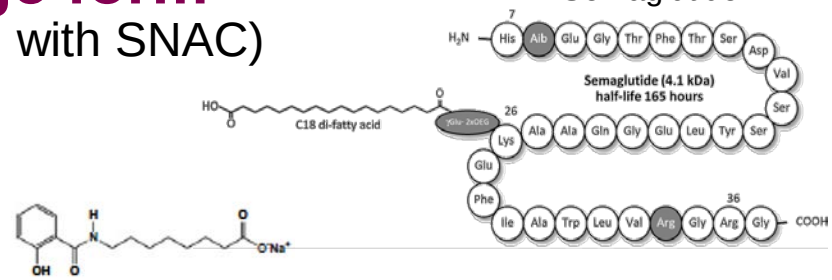
Brown, T.D., Whitehead, K.A. & Mitragotri, S. Materials for oral delivery of proteins and peptides. Nat Rev Mater 5, 127–148 (2020). https://doi.org/10.1038/s41578-019-0156-6

First approved GLP-1 oral dosage form

Rybelsus (semaglutide complexed with SNAC)



Semaglutide



SNAC: sodium *N*-[8-(2-hydroxybenzoyl)amino] caprylate

TABLE 1. PHARMACOKINETICS OF ORAL AND SUBCUTANEOUS SEMAGLUTIDE[11,12,16]

Parameter	*Oral semaglutide*	*Subcutaneous semaglutide*
AUC (nmol×h/L)	284	3026
Cmax (nM)	15	10
Tmax (h)	1	66
$T_{1/2}$ (h)	152	168

AUC, area under the curve; Cmax, maximum plasma concentration; Tmax, time to reach Cmax; $T_{1/2}$, terminal half-life.

10 mg semaglutide/SNAC 300 mg

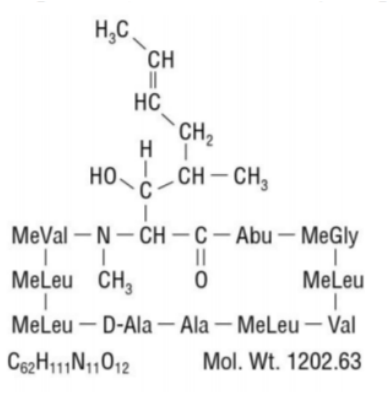
0.5-1 mg semaglutide subcutaneous (Ozempic)

Bucheit JD, Pamulapati LG, Carter N, Malloy K, Dixon DL, Sisson EM Oral Semaglutide: A Review of the First Oral Glucagon-Like Peptide 1 Receptor Agonist. Diabetes Technol Ther. 2020 Jan;22(1):10-18. doi: 10.1089/dia.2019.0185.

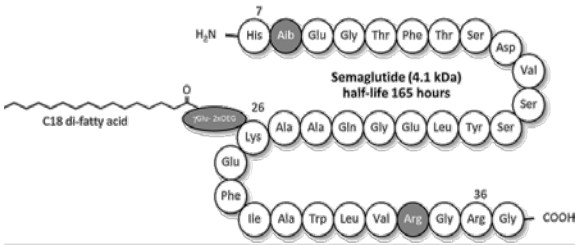
Approved peptide oral dosage forms

Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-αtocopherol USP, gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine, and other ingredients

Cyclosporine



Semaglutide



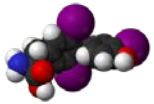
magnesium stearate, microcrystalline cellulose, povidone and salcaprozate sodium (SNAC).

Each tablet contains
3 mg, 7 mg or 14 mg of semaglutide

Bucheit JD, Pamulapati LG, Carter N, Malloy K, Dixon DL, Sisson EM Oral Semaglutide: A Review of the First Oral Glucagon-Like Peptide 1 Receptor Agonist. Diabetes Technol Ther. 2020 Jan;22(1):10-18. doi: 10.1089/dia.2019.0185.

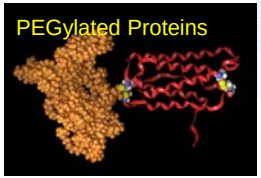
Drug delivery via microparticles contribute to an innovative pipeline

Small Molecule Drugs

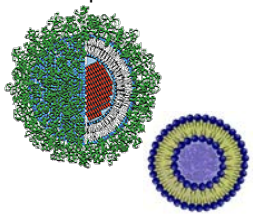


Protein bound drug

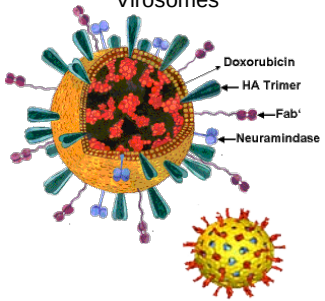
PEGylated Proteins



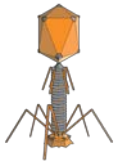
Liposomes



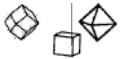
Virosomes



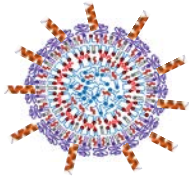
Nanomachines



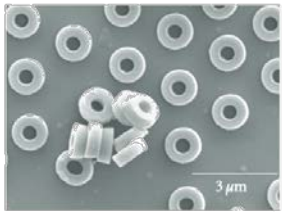
Nanocrystals



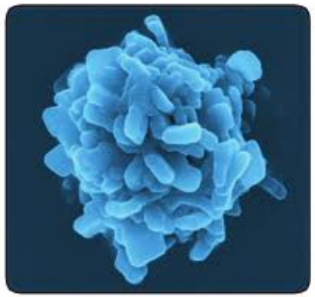
SLNP



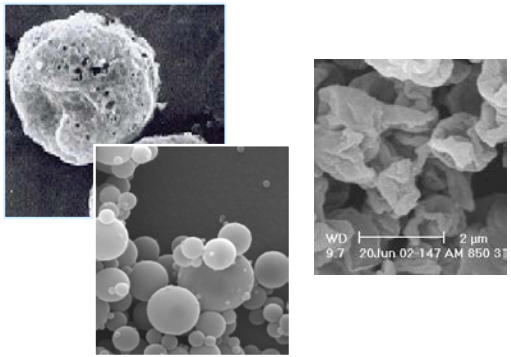
Molded microparticles



Crystalline protein carriers



Spray dried microparticles



Outlook

- Many innovative products for the delivery of proteins and peptides in the pipeline
  - Pulmonary delivery for topical applications
  - Nasal delivery for local as well as applications targeting the brain
  - Oral delivery of proteins and peptides is a reality

- Well established processes such as freeze drying and spray drying enable manufacture of specialty formulations

- Microparticle molding may emerge as a platform process

- Lipid based drug delivery systems require customized processes which are emerging as the need arises

Thank you for your attention