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Inspired Inhalation Innovation™

Increased packing density of fine particles in spray-dried formulations

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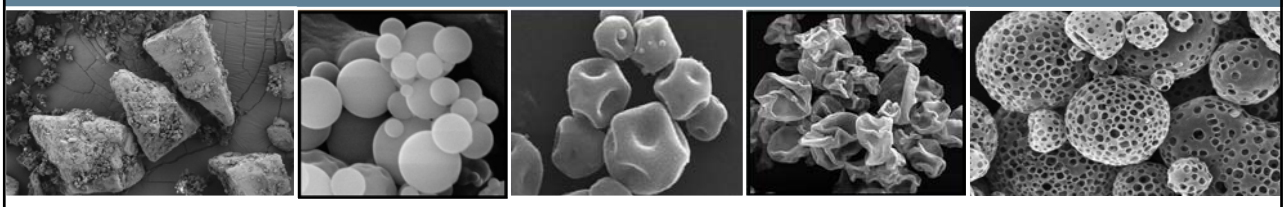

Acknowledgements: Yoen-Ju Son, Daniel Huang

RDD 2020 DIGITAL Respiratory Drug Delivery

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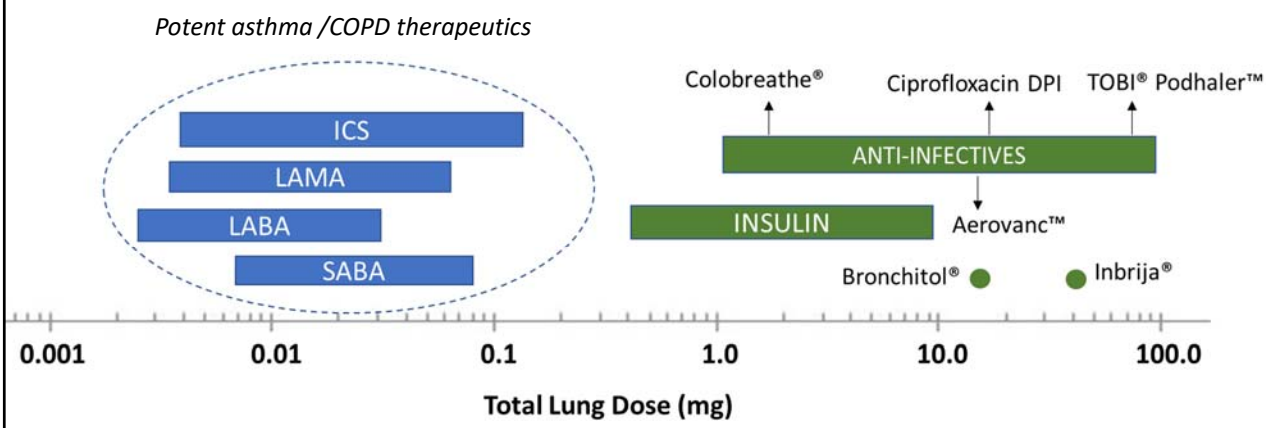
High dose therapeutics require delivery of lung doses 1,000 to 10,000 greater than asthma drugs with a portable inhaler



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The 'product density' is simply a measure of the mass of drug delivered to the lungs for a given receptacle volume

$$\rho_{product} = \frac{TLD}{V_r} = \left(\frac{m_{powder}}{V_r}\right)\left(\frac{m_{drug}}{m_{powder}}\right)\left(\frac{TLD}{m_{drug}}\right)$$

Packing Density | Drug Loading | Aerosol Performance

This talk will focus on a strategy to improve packing density

Source: Son et al: WO 2019/145897 A1

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Current high dose DPI products have product densities up to ~50 mg/mL

$$\rho_{product} = \frac{TLD}{V_r} = \left(\frac{m_{powder}}{V_r}\right)\left(\frac{m_{drug}}{m_{powder}}\right)\left(\frac{TLD}{m_{drug}}\right)$$

Source: Son et al: WO 2019/145897 A1

Drug Product	Packing Density (mg/mL)	Drug Loading (mg/mg)	Aerosol Perf. (mg/mg)	Product Density (mg/mL)
TOBI® Podhaler™	131.1	0.57	0.63	47.1
Ciprofloxacin DPI	135.1	0.65	0.53	46.5
Inbrija®	51.3	0.90	0.5	23.1
Colobreathe®	337.8	0.44	0.12	17.8
Bronchitol®	133.3	1.0	0.40	53.3
OnBrez® Breezhaler®	83.3	0.006	0.34	0.17
Spiriva® Handihaler®	18.3	0.003	0.20	0.012

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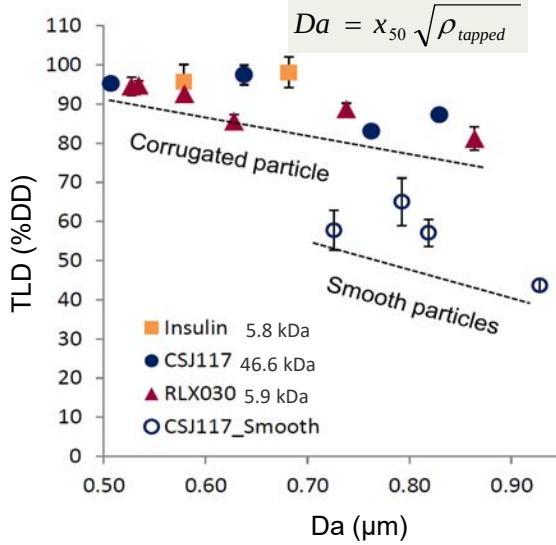
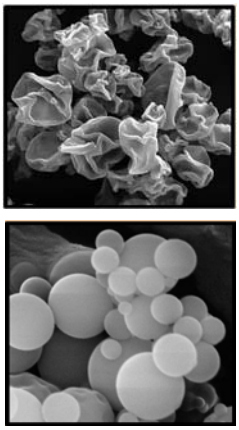
Extrafine corrugated particles with median aerodynamic diameters less than ~0.7 μm enable total lung doses > 90%

$$Da = x_{50}\sqrt{\rho_{tapped}}$$





But unfortunately, highly corrugated particles have a low packing density

For gravitationally stable particles > 100 μm, spherical particles have the highest packing density

Is this true for 1-5 μm cohesive powders?

Source: Weers J et al: Idealhalers versus realhalers: is it possible to bypass deposition in the upper respiratory tract? J Aerosol Med Pulm Drug Deliv. 2019,32:55-69.

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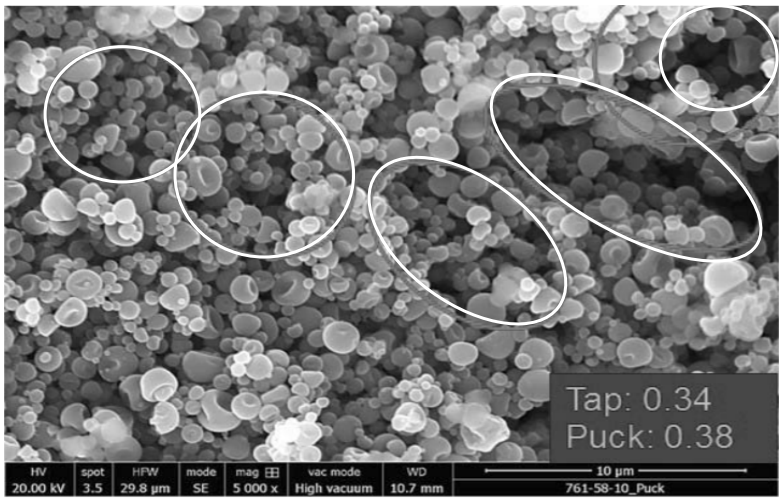
Interparticle cohesive forces between fine drug particles leads to void spaces in the powder bed for smooth spheres



- **SEM of 'compressed puck' for smooth spherical particles of CSJ117**
- **No shell-forming excipient**

Fine spherical particles do not have a high packing density

Source: Son et al: WO 2019/145897 A1

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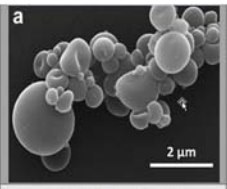
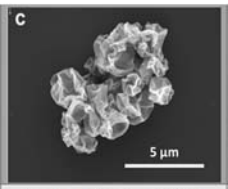
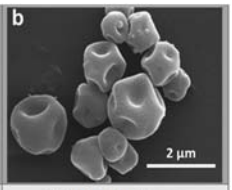
For cohesive powders, the maximum packing density is observed for particles with low surface corrugation

TSLP Antibody Fragment (CSJ117)			
Morphology	Smooth spheres	Corrugated particles	Dimpled spheres
Trileucine (%w/w)	0	15	2.5
Drying conditions	Fast	Fast	Slow
x50 (µm)	1.19	1.36	1.43
SSA (m^2/g)	6.35	14.90	6.01
Bulk density (g/cm^3)	0.21	0.10	0.29
Tapped density (g/cm^3)	0.34	0.15	0.57
Puck density (g/cm^3)	**0.38**	**0.28**	**0.64**
Compressibility Index (inh)	10.5	46.4	10.9

Low Peclet spray-dried particles with low corrugation exhibit higher densities

Source: Son et al: WO 2019/145897 A1

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Spray-dried CSJ117 with a dimpled morphology can achieve product densities of 150 mg/mL or more

$$\rho_{product} = \frac{TLD}{V_r} = \left(\frac{m_{powder}}{V_r}\right)\left(\frac{m_{drug}}{m_{powder}}\right)\left(\frac{TLD}{m_{drug}}\right)$$

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Bronchitol®	133.3	1.0	0.40	53.3
CSJ117	**405.4**	**0.50**	**0.74**	**150**

Conclusion: A small degree of surface corrugation is needed to reduce interparticle cohesive forces and optimize packing density

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