Opportunities in Analytical Approaches to Spray Drying of Solid Dosage Forms

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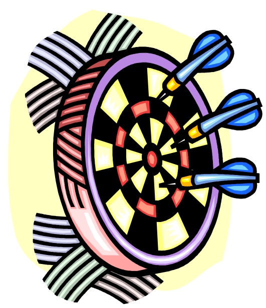
MECHANICAL ENGINEERING

Spray Drying Process Development by Trial and Error ?

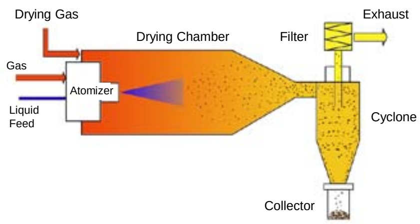


There must be a better way.

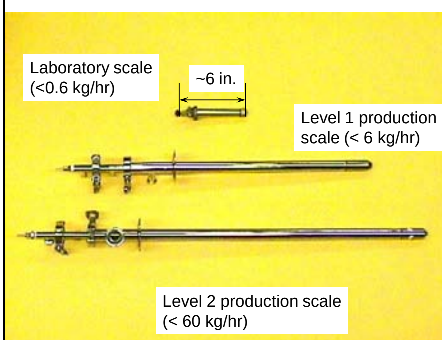
Outline

- **Atomization – droplet formation**
  - Experimental determination of droplet size distribution
  - Theoretical descriptions
    - Droplet size
    - Distribution of suspended material
- **Droplet Evaporation**
  - Numerical model
  - Simplified analytical description
- **Particle Formation**
  - Predicting Size
  - Predicting Morphology
- **Collection and Outlet Conditions**
  - Cyclone cutoff
  - Global mass and energy balance

Introduction: The Spray Drying Process



Two-Fluid Atomizers: Examples



How can the droplet size distribution be predicted?

Pneumatic Atomization, Theory

Mean diameter:

$$\bar{d} = \frac{A}{\left(\rho_g \Delta v^2\right)^{\alpha}} + B\left(\frac{\dot{m}_g}{\dot{m}_l}\right)^{\beta}$$

Depends on relative velocity at nozzle head and the ratio of the gas and liquid mass flows.

A, B, α, β are functions of the nozzle design and liquid properties.

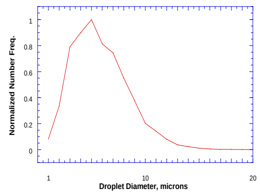
Droplet size distributions for a specific nozzle need to be determined experimentally

Masters, K.: Spray Drying. CRC Press, Cleveland, 1972

Atomizer Testing With Phase Doppler Methods

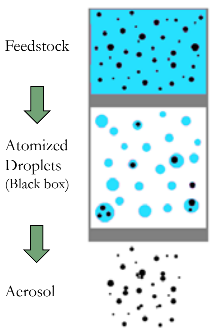
Atomizer Test Facility

Provides droplet size distributions for various process conditions:



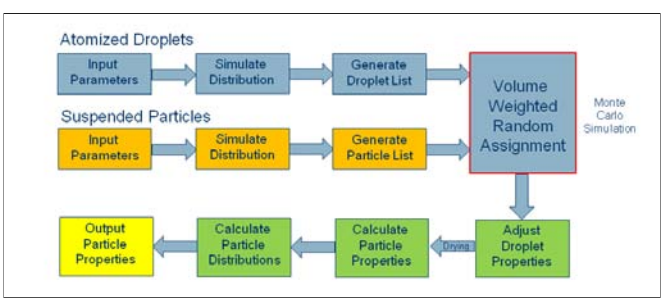
Snyder, et al., 12th Annual Conf. on Liquid Atomization and Spray Systems. Indianapolis, 1999

Spray Drying of Suspensions



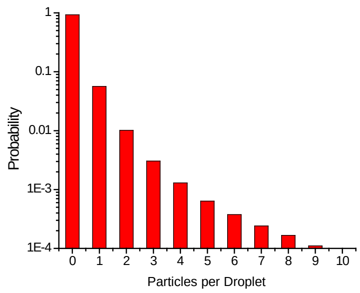
How do particle size distribution and concentration of suspended particles and atomized droplet size affect the composition and particle size distribution of the final powder?

Stochastic Model of Suspension Atomization



Ivey, J. W., Vehring, R. AAPS Workshop on Utilization of Process Modeling and Advanced Process Control, Baltimore, 2009.

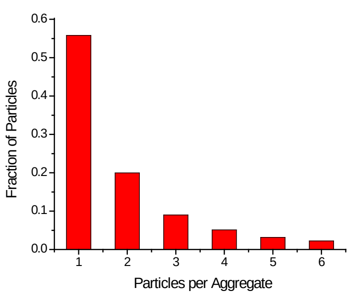
Example: Distribution of Particles in Droplets



Droplets:
VMD: 9 µm, GSD 1.8

Suspended Particles:
VMD: 4.6 µm, GSD 1.6
Concentration: 2.45 g/l

Example: Prediction of Powder Properties

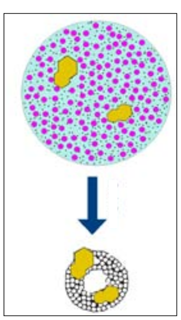


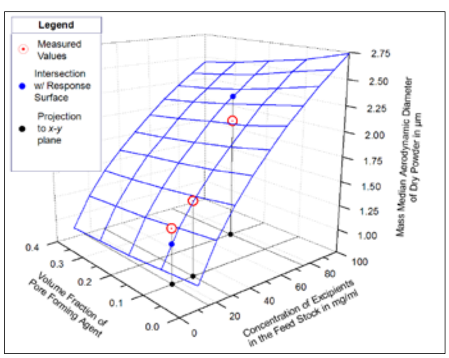
Propellant:
VMD: 9 µm, GSD 1.8

Suspended Particles:
VMD: 4.6 µm, GSD 1.6
Concentration: 2.45 g/l

Aerosol:
VMD: 5.2 µm, GSD 1.58

Application Example: Porous Particles With Suspended Crystals





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Full Numerical Model

Weight fraction of species i (w_i) in droplet and gas:

$$\rho \frac{\partial w_i}{\partial t} + \rho v \frac{\partial w_i}{\partial r} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \rho D_i \frac{\partial w_i}{\partial r}\right) \quad \text{and} \quad \sum_{i=1}^{n} w_i = 1$$

Weight fractions at gas/droplet interface:

$$\left[\rho D_i \frac{\partial w_i}{\partial r} + \rho w_i\left(\frac{\partial R}{\partial t} - v\right)\right]_R^{(drop)} = \left[\rho D_i \frac{\partial w_i}{\partial r} + \rho w_i\left(\frac{\partial R}{\partial t} - v\right)\right]_R^{(gas)}$$

$$\text{and} \quad a_i(w_i)_R^{(drop)} = \left.\frac{p_i}{p_i^{sat}}\right|_R^{(gas)} \quad \text{where } a_i \text{ is the activity of species } i$$

Droplet size (R) and radial velocity (v) in droplet and gas:

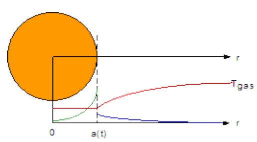
$$\frac{\partial R}{\partial t} = \left[\frac{(\rho v)^{(drop)} - (\rho v)^{(gas)}}{\rho^{(drop)} - \rho^{(gas)}}\right]_R \quad \text{and} \quad v = -\frac{1}{r^2 \rho}\int_0^r \xi^2 \frac{\partial \rho}{\partial t} d\xi$$

Gas temperature (T):

$$\rho \hat{C}_p \frac{\partial T}{\partial t} + \rho \hat{C}_p v \frac{\partial T}{\partial r} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 k \frac{\partial T}{\partial r}\right) + \sum_{i=1}^{n}\left(\bar{H}_i \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \rho D_i \frac{\partial w_i}{\partial r}\right)\right)$$

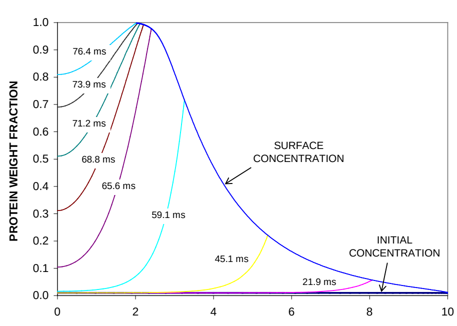
Droplet temperature (T_{drop}):

$$\frac{R \rho C_p}{3}\frac{\partial T_{drop}}{\partial t} = \left[k \frac{\partial T}{\partial r} + \rho \sum_{i=1}^{n} H_i D_i \frac{\partial w_i}{\partial r} + \rho H\left(\frac{\partial R}{\partial t} - v\right)\right]_R^{(gas)} + \rho^{(drop)} \Delta H_{vap} \frac{\partial R}{\partial t}$$

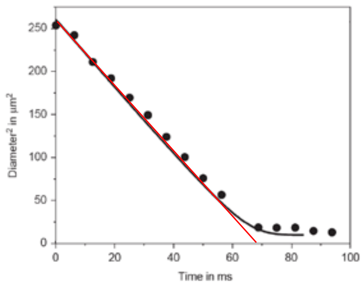


Foss, W. R., Vehring, R., 23rd Annual AAAR Conference, Atlanta, GA, USA, 2004.

Application Example: Surface Enrichment of Protein



More Practical: Constant Rate Assumption



● : Experiment
— : Numerical Model
— : Constant Rate

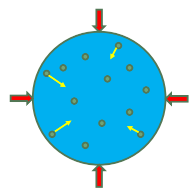
$$d^2(t) = d_0^2 - \kappa t$$

Vehring, R.: *Particle Design using Spray Drying*. The Fine Particle Society, Int. Conf. on Bio and Pharm. Science and Techn., San Diego, 2006.

Dimensionless Numbers: Peclet Number and Surface Enrichment

Peclet Number: $\mathrm{Pe}_i = \frac{\kappa}{8D_i}$

Describes balance between velocity of surface recession and diffusion



Surface Enrichment: $E_i = \frac{c_{s,i}}{c_{m,i}}$

Ratio of surface concentration to average concentration

$$E_i = 1 + \frac{\mathrm{Pe_i}}{5} + \frac{\mathrm{Pe_i^2}}{100} - \frac{\mathrm{Pe_i^3}}{4000}$$

Vehring, R. *Expert Review: Pharmaceutical Particle Engineering via Spray Drying*. Pharm. Res. **25**: 999, 2008.

How to Estimate Evaporation Rate

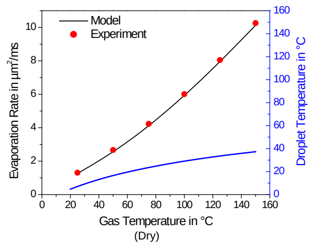
Approximation: $\kappa = 8D_g \frac{\rho_g}{\rho_l}\left(Y_s(T_e) - Y_\infty\right)$

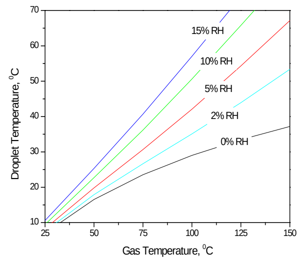
Vapor Pressure: $\log P_{sat} = A - \frac{B}{T + C}$

A = 10.113
B = 1685.6
C = - 43.154
T in K, P in Pa

Wet bulb temperature: $T_{\mathrm{wb}} = 137\left(\frac{T_{\mathrm{b}}}{373.15}\right)^{0.68} \log(T_{\mathrm{G}}) - 45$

Even Simpler: Use Published Results





Vehring, R., Foss, W. R., Lechuga-Ballesteros, D.: *Particle Formation in Spray Drying.* J. Aerosol Science **38**: 728, 2007.

Characteristic Times: Droplet Drying Time

Droplet drying time: $$\tau_D = \frac{d_0^2}{\kappa}$$

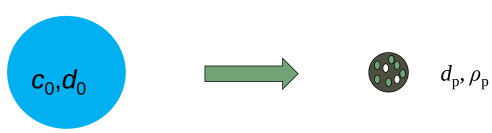
Can be used to estimate necessary residence time in dryer.

Examples:

a) Pulmonary drug delivery, active not labile, d_0= 5 µm, κ= 5 µm²/ms: **τ_D= 5 ms**

b) Nasal drug delivery, active labile, d_0= 30 µm, κ= 2 µm²/ms: **τ_D= 0.45 s**

Mass Balance Allows Prediction of Size



- Geometric Diameter $$d_p = \sqrt[3]{\frac{c_0}{\rho_p}} d_0$$
- Aerodynamic Diameter $$d_a = \sqrt[6]{\frac{\rho_p}{\rho^*}} \sqrt[3]{\frac{c_0}{\rho^*}} d_0$$

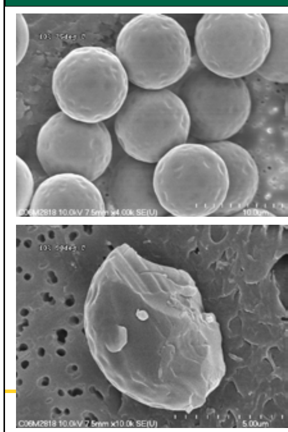
Predicting Particle Morphology: Sequence of Precipitation

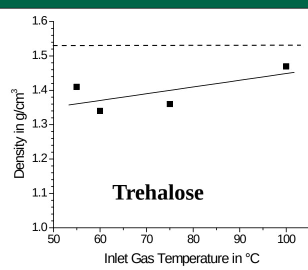
Dimensionless Number: $S_{0,i} = \frac{c_{0,i}}{c_{pre,i}}$ Initial concentration / Precipitation concentration

Time to precipitation: $\tau_{pre,i} = \tau_D \left(1 - \left(S_{0,i} \cdot E_i\right)^{\frac{2}{3}}\right)$

$\tau_{pre,A} < \tau_{pre,B}$ $\tau_{pre,B} < \tau_{pre,A}$

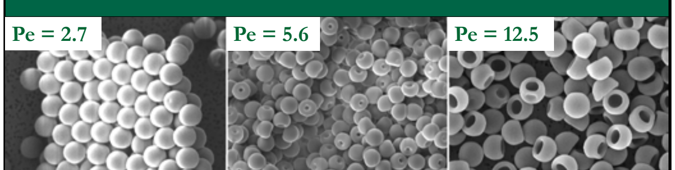
Predicting Particle Density: Low Peclet Number



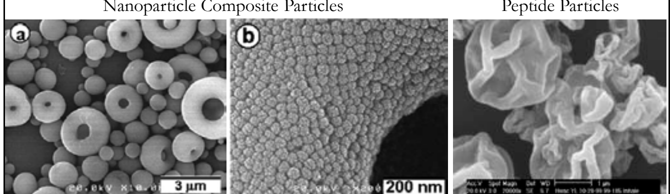


Low Peclet Number (<2) and high solubility lead to solid particles

Predicting Particle Density: High Peclet Number



Nanoparticle Composite Particles Peptide Particles



Vehring, R., Foss, W. R., Lechuga-Ballesteros, D.: *Particle Formation in Spray Drying*. J. Aerosol Science **38**: 728, 2007.
F. Iskandar et al. Journal of Colloid and Interface Science **265**, 296, 2003.
J. S. Patton US Patent 6,685,967, 2004.

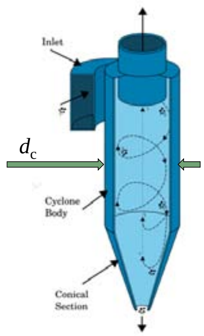
Cyclone Separation

Cyclone cutoff (Leith / Licht model):

$$d_{a,50} = k\sqrt{\frac{18\mu d_c^3}{\dot{V}}}$$

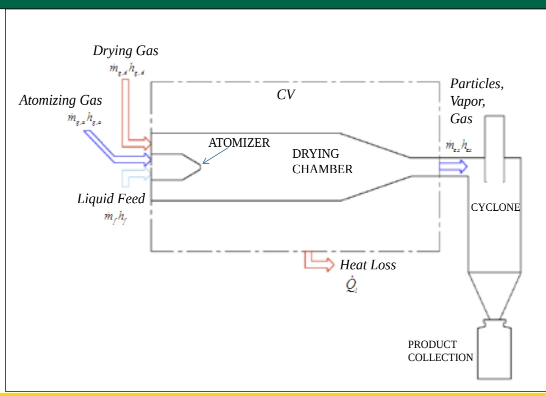
μ: Gas viscosity
d_c: Cyclone diameter
$\dot{V}$: Gas flow
k: Configuration factor

Cutoff needs to be verified experimentally



http://aerosol.ees.ufl.edu/cyclone

Global Mass and Energy Balance



Prediction of Outlet Temperature

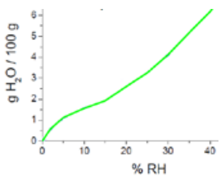
(Graph removed)

Measured and predicted outlet temperatures agree within ± 2 °C.

Prediction of Powder Moisture Content

(Graph removed)

Combining outlet RH with moisture sorption data allows accurate estimate of powder moisture content



Conclusions

- The individual steps of the spray drying process are fairly well understood and can be described theoretically.
- The spray drying process should be treated as a series of sub-processes.
- Experimental work should focus on the unknown aspects of the process.
- Many process and powder attributes can be predicted and don't need to be determined empirically
- Using analytical approaches to spray drying saves time and cost and allows theoretical identification of key process and formulation variables leading to prudent investment in process control measures.
- Differences between observed and predicted behavior point to areas of future development and provide IP opportunities.

Outlook