State-of-the-Art Pharmaceutical Research & Health Economics

Presentation:

The Challenge of Protein Drugs

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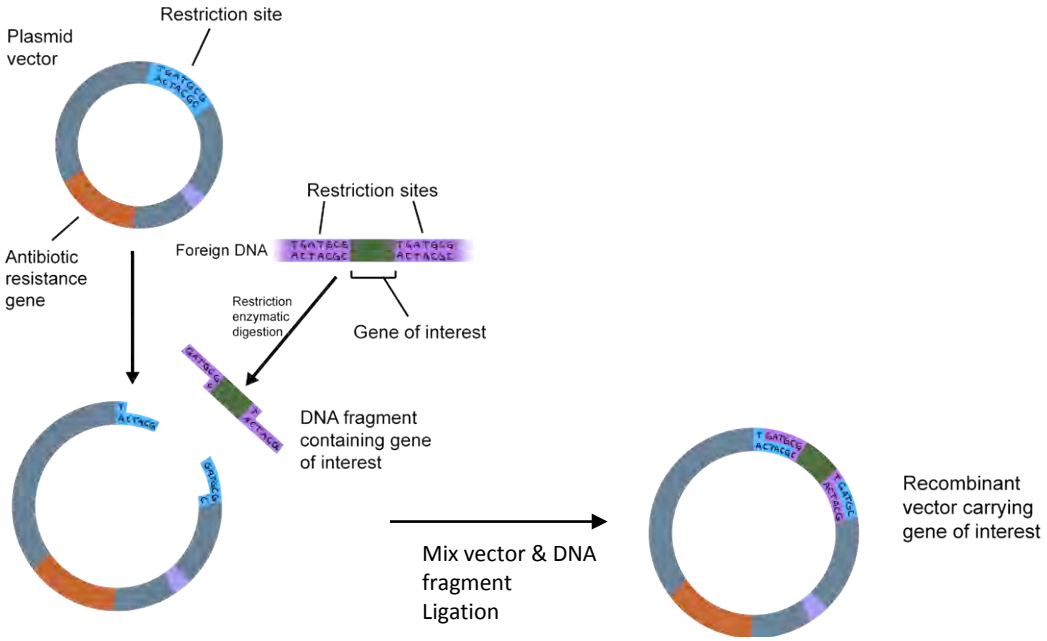
The Challenge of Protein Drugs

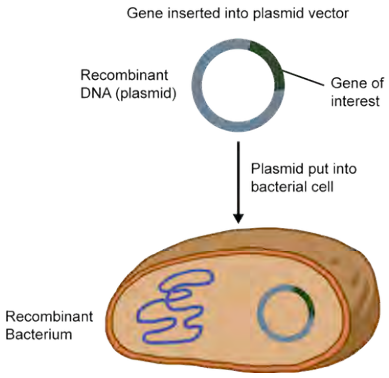
What will I be talking about ?

1. What are protein drugs ?
2. What is the challenge ?
3. What is the current solution ?
4. What are the potential alternative solutions using *protein powders* ?
5. Research: Ultrasonic levitation during protein powder formation

1.1 What are Protein Drugs ?

- Before 1980 there were but few protein drugs available
  insulin, growth hormone = extracts of animal or human origin
- Development of *recombinant DNA technology* has made possible their synthesis
- Since 1980 more than 100 recombinant protein drugs have been introduced





1.2 What are Protein Drugs ?

Some examples of the many *recombinants*:

1. Recombinants that replaced animal or human sources:

   - Human growth hormone (rHGH)
   - Human insulin (BHI)
   - Follicle-stimulating hormone (FSH)
   - Factor VIII

2. Recombinants as only source

   - Erythropoeitin (EPO)
   - Granuloycte-colony stimulating factor (GCSF)
   - Alpha galactosidase A
   - Dornase alpha DNase
   - Tissue plasminogen actvator (TPA)
   - Interferon (IF)
   - Insulin-like growth factor (IGF-1)

1.3 What are Protein Drugs ?

Recombinants are a substantial part of total drug products sales

Table I: Combined global prescription sales for the top 50 pharmaceutical companies (excluding generic-drug companies) by molecule type (2009–2014).

	Sales ($ billion)						
Molecule type	2009	2010	2011	2012	2013	2014	Difference in sales between 2009 and 2014
Small molecule	411	414	415	405	394	394	–4%
Therapeutic protein	65	68	70	72	74	76	17%
Monoclonal antibody	38	43	48	53	58	62	63%
Vaccine	21	22	24	25	27	28	33%

Sources: Datamonitor, PharmaVitae Explorer, January 2010, and company-reported information.

2. What is the Challenge of Protein Drugs ?

Two problems need to be considered during protein drug development:

- Proteins show only limited *stability in aqueous solution*

  - Gibbs free energy of unfolding & denaturation is low 50 kJ/mol
  - a small change in condition (e.g. temperature, solvent) can cause unfolding
  - unfolding is enthalpically unfavorable, but entropically favorable
  - an aqueous solution has therefore limited storage stability

  → *Why is this a problem* ? (process; drug product)

- Proteins have very poor *bioavailability* on oral administration

  - peptides & proteins are readily denatured under the physiological conditions in the gastero-intestinal tract (GIT)
  - cannot therefore be given as, for example, a tablet
  - narrow therapeutic range

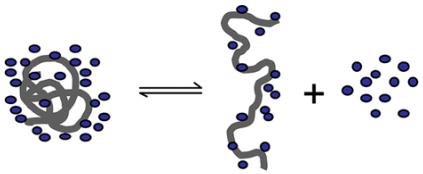
  → *Why is this a problem* ?

3.1 What is the Current Solution ?

Solutions to the problem of *storage stability*: making a storage stable form

- Formulation measures in solution

  - some proteins can be stabilized in aqueous solution using particular adjuvants
    i) preferential excludants: sugars, polyols, amino acids
    sucrose & trehalose can be very effective:



    ii) surfactants can reduce protein aggregation and adsorption to interface
    competitive adsorption, binding to protein
    iii) bulk storage as frozen solution = floor space problem

- Freeze Drying

  - if all else fails, then a solution is freeze dried to a solid
  - applicable to bulk storage = expensive technology
  - drug product reconstituted with WFI immediately before application

3.2 What is the Current Solution ?

Solutions to the problem of low *oral bioavailability*

- Protein drug products are given parenterally (exception: some few nasal sprays)

  - Application according to requirements on pharmacokinetic profile
    intra veneous (rapid onset) or extra veneous (prolonged therapeutic effect)

  - parenterals have some disadvantages
    generally viewed as ‚unpleasant'; can be painful
    in most cases requires trained personal
    very high demands on manufacturing process & product quality

- It is possible to avoid needle injection ?

  - more comfortable
  - this might make protein drug products cheaper
  - it might improve therapy via control of drug plasma levels

4.1 What are the Potential *Alternative* Solutions Using Protein Powders ?

Use of Protein Powders as Intermediate Storage & Drug Application Forms

- Protein powders have some useful atributes
- Enhancing stability

  - protein stabilized in dry state
  - flowable powder suitable as intermediate storage form

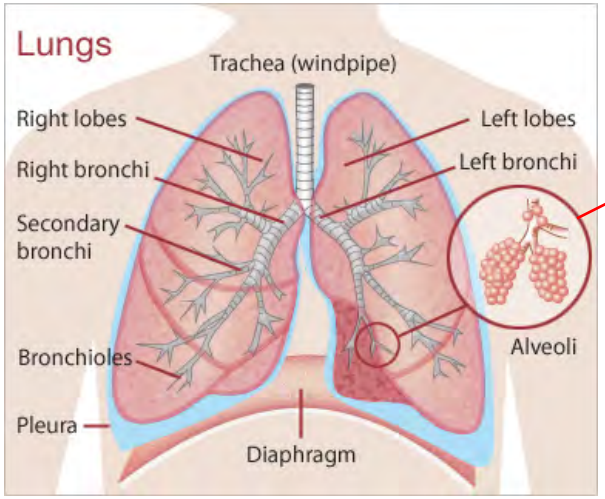
- Avoiding needle injection

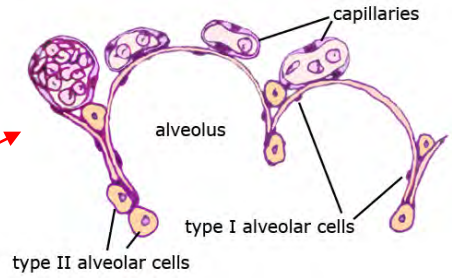
  - inhalation powders
  - ballistic injection powders

4.2 What are the Potential *Alternative* Solutions Using Protein Powders ?

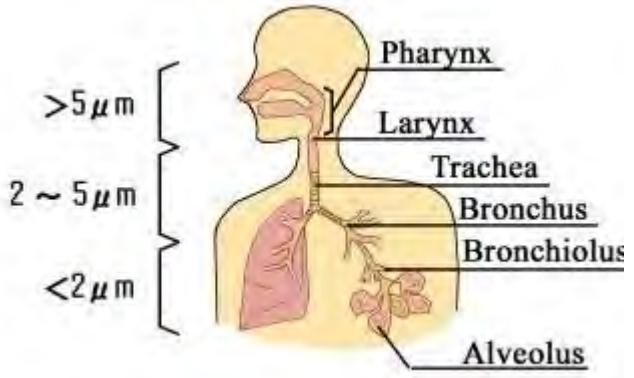
Alternative # 1: Inhalable Protein Powders

- The lungs are an excellent place for absorption into plasma





- But the drug particles have to have the correct size for deep lung penetration
  - aerodynamic diameter of < 2 µm; $d_{aer} = d \cdot \sqrt[2]{\rho}$

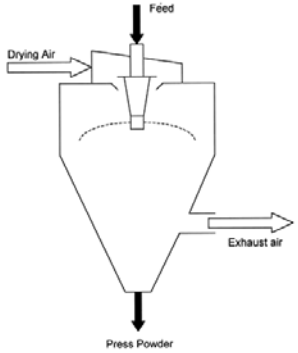


- Require a *particle* manufacturing technique

4.3 What are the Potential *Alternative* Solutions Using Protein Powders?

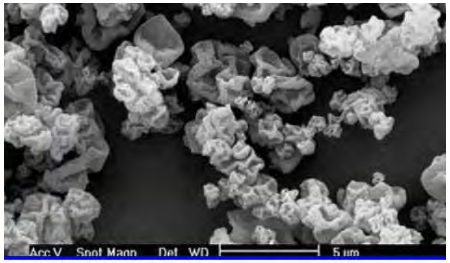
Inhalable human insulin: Exhubera (Pfizer; 2006 – 2008)

- Inhalable microparticles prepared by spray drying (Tin/Tout = 180/87°C):



- Formulation:
  - 60 % recombinant human insulin
  - 30 % Na citrate
  - 10 % mannitol, glycine & NaOH

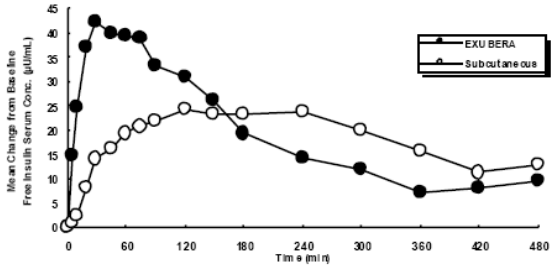
- Product: irregular microparticles with approx. 2 % water, Tg = 80°C
  - storage at room temperature



4.4 What are the Potential *Alternative* Solutions Using Protein Powders ?

Inhalable human insulin: Exhubera (Pfizer; 2006 – 2008)

- Pharmacokinetic results were comparable to extravasal injection
  - plasma levels of rhI



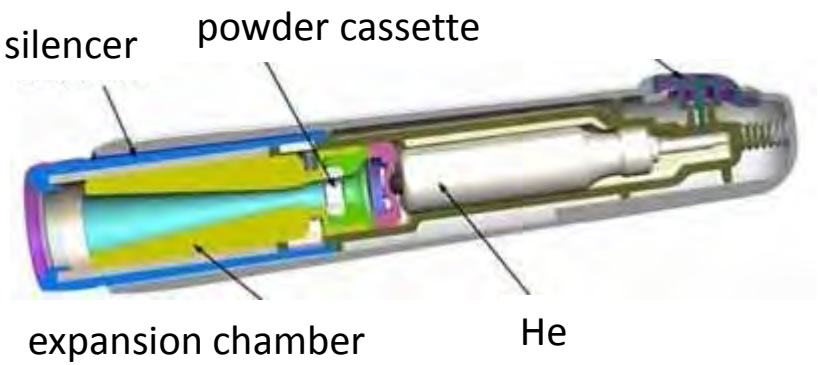
- Inhalation device poorly designed: patient acceptance low
  - hardly a ‚pocket' device

→ withdrawn from market
→ loss: some 2.3 billion US dollars

4.5 What are the Potential *Alternative* Solutions Using Protein Powders ?

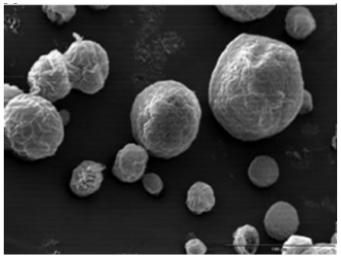
Alternative # 2: Needle-Free Powder Injectors (Powderject®)

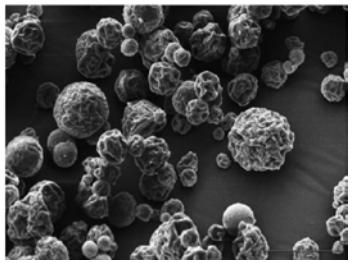
- Powder dose (1 – 2 mg) accelerated into epidermis by He expansion (40 bar)



- Powder particles require correct size and density for epidermal penetration
  - diameter 40 – 60 μm; density: high; > 1.5

- Ballistic particles prepared by spray drying or spray freeze drying

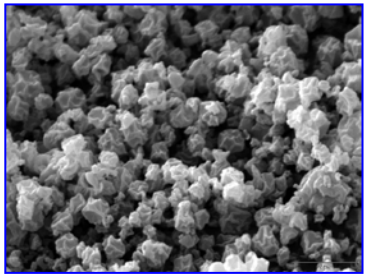




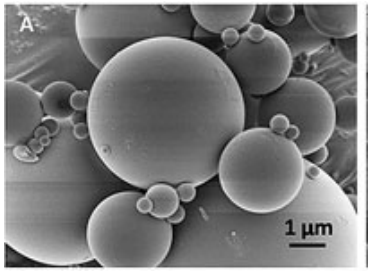
4.6 What are the Potential *Alternative* Solutions Using Protein Powders ?

Two Essential Properties of Protein Particles are Determined during Formation

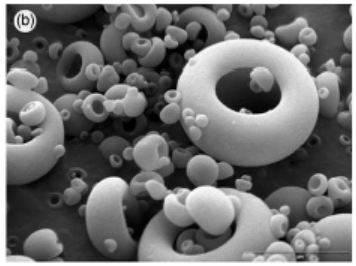
- Particle *shape* = f(liquid feed concentration; process conditions)



Small peptide



Bovine serum albumin
(CK Kwock, Hong Kong)



Immunglobulin G
Maury et al, 2006

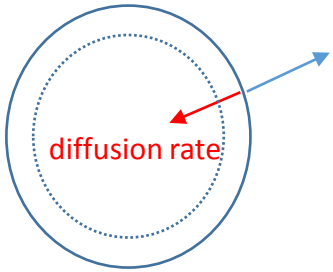
- *Damage* to protein molecule during the process

  - arises from atomization and heat stresses
  - protein molecules in solution can partially unfold and aggregate
  - loss of activity & enhanced immunogenic effects of aggregates

4.7 What are the Potential *Alternative* Solutions Using Protein Powders ?

Particle Shape Based on Peclet Number, Pe

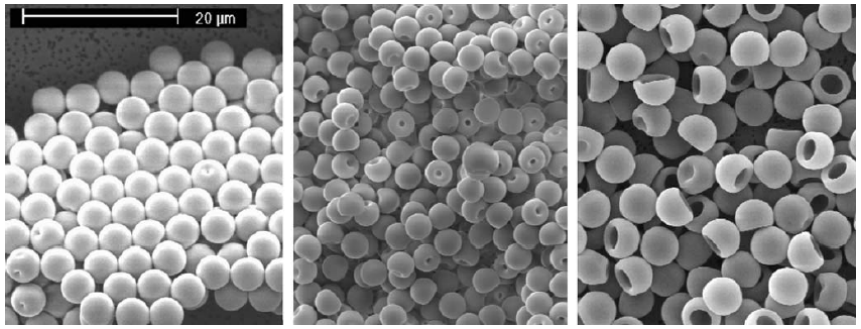
- Shape determined by relative rates of evporative drying and solute diffusion:



$$r(t)^2 = r_0^2 - \kappa t$$

$$Pe = \frac{drying\ rate}{diffusion\ rate} = \frac{\kappa}{8D}$$

- low Pe: diffusion faster than interface retraction = solid spheres
- high Pe: interface retraction faster than diffusion = surface enrichment



Vehring, Pharm Res (2007)

4.8 What are the Potential *Alternative* Solutions Using Protein Powders ?

Protein Damage assesed in Final Particle

- Small peptide (Tin/Tout = 130°C/80°C) suffers little aggregation:

	Peptide purity [%]	Impurity ≥ 0.5% [%]
liquid feed	98.54	0.71
redissolved SD powder	98.51	0.79

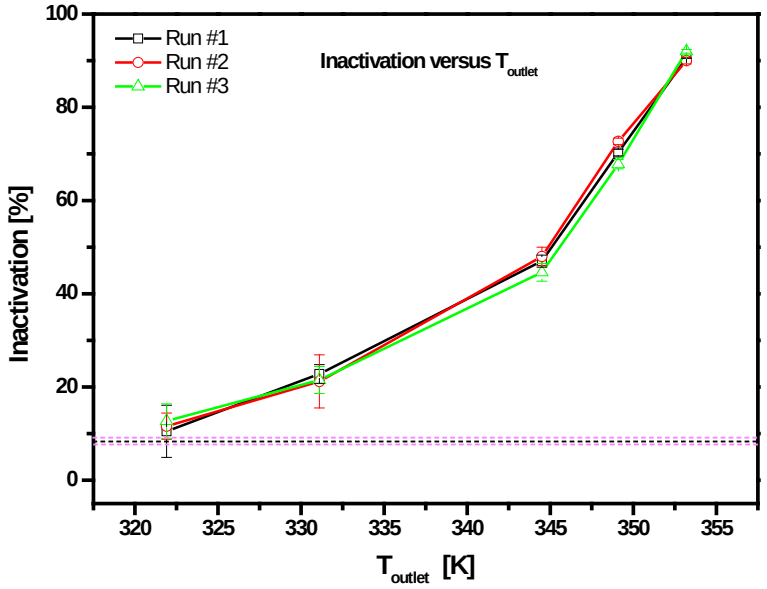
- Large protein (IgG) shows massive changes in aggregation:

treatment	Peak	RT [min]	MWt [kDa]	AUC [%]	assignation
liquid feed (dialyzed)	1 2	13.9 15.6	646 167	0.7 99.3	aggregates monomer
redissolved SD powder	1 2	10 – 14.8 15.5	- 165	17.3 82.7	aggregates monomer

4.9 What are the Potential *Alternative* Solutions Using Protein Powders ?

Protein Damage assesed in Final Particle

- Enzymes show loss in activity dependent on process conditions:

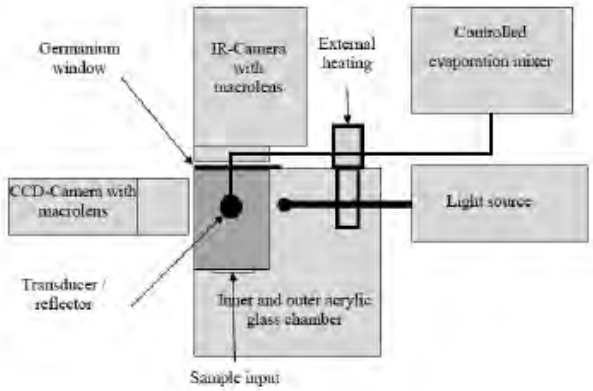


- Measurements performed on final particle after redissolution
- What do we require ? A technique to examine changes in protein *during* particle formation

5.1 Research: Single Droplet Drying with Acoustic Levitator

Allows Examination of Particle *Formation* Process and Kinetics of Protein *Damage*

- Droplet/particle levitated in standing sound wave



Wulsten & Lee, Chem Eng Sci (2009)

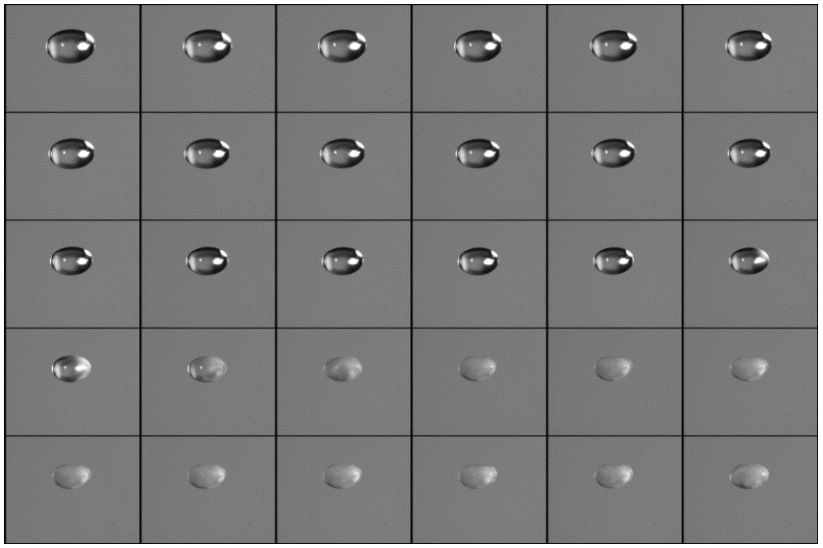
v = 58 kHz
λ = 5.71 mm
D∞ = 4 mm
RH = 0 – 100%
Qdg = $\geq$ 2 L/min

Schiffter & Lee, J Pharm Sci (2006)

5.2 Research: Single Droplet Drying with Acoustic Levitator

A Kinetic Picture of *Particle Formation and Shape*

- Droplet/particle is taken up on video camera



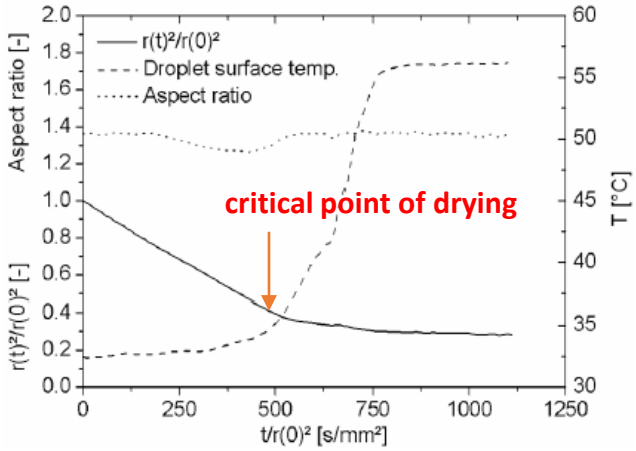
- sphere equivalent radius, r(t)
- aspect ratio, r_{hor}/r_{vert}
- surface temperature, T_s

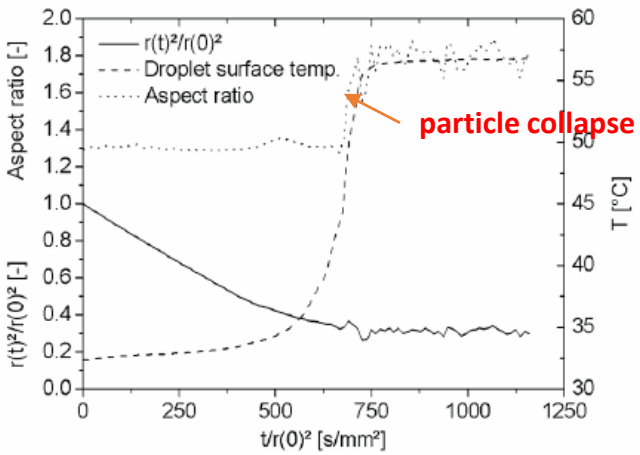
- Result: plots of $r(t)^2/r^2_0$ (drying rate), aspect ratio (shape), and T_s versus drying time

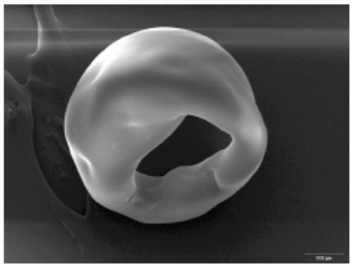
5.3 Research: Single Droplet Drying with Acoustic Levitator

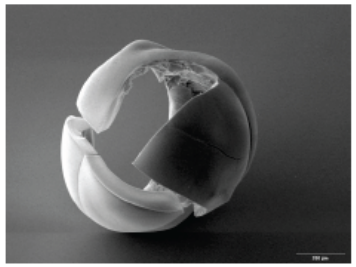
Application #1: A Kinetic Picture of *Particle Formation and Shape*

- Two different proteins: bovine serum albumin (10%) and lactate dehydrogenase (10%)





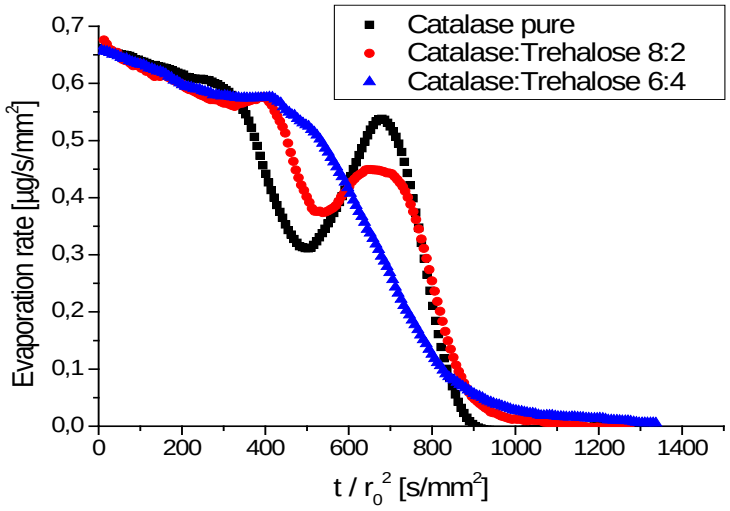


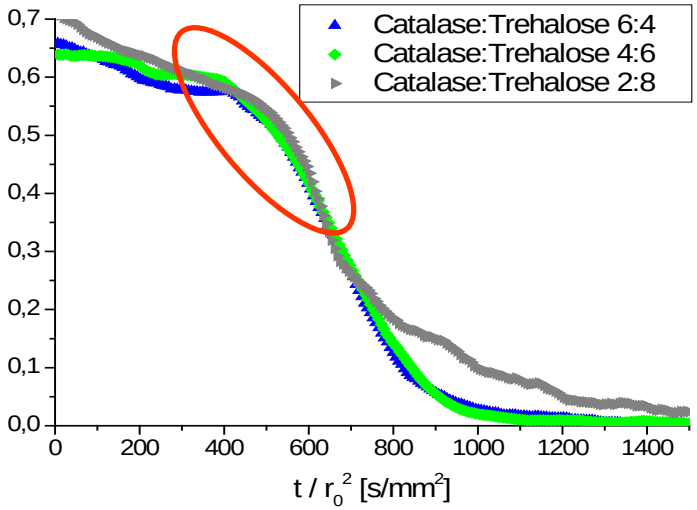


- Don‘t forget differences in dimension between spray drying & levitation

5.3a Research: Single Droplet Drying with Acoustic Levitator

Application #1: A Kinetic Picture of *Particle Formation and Shape*

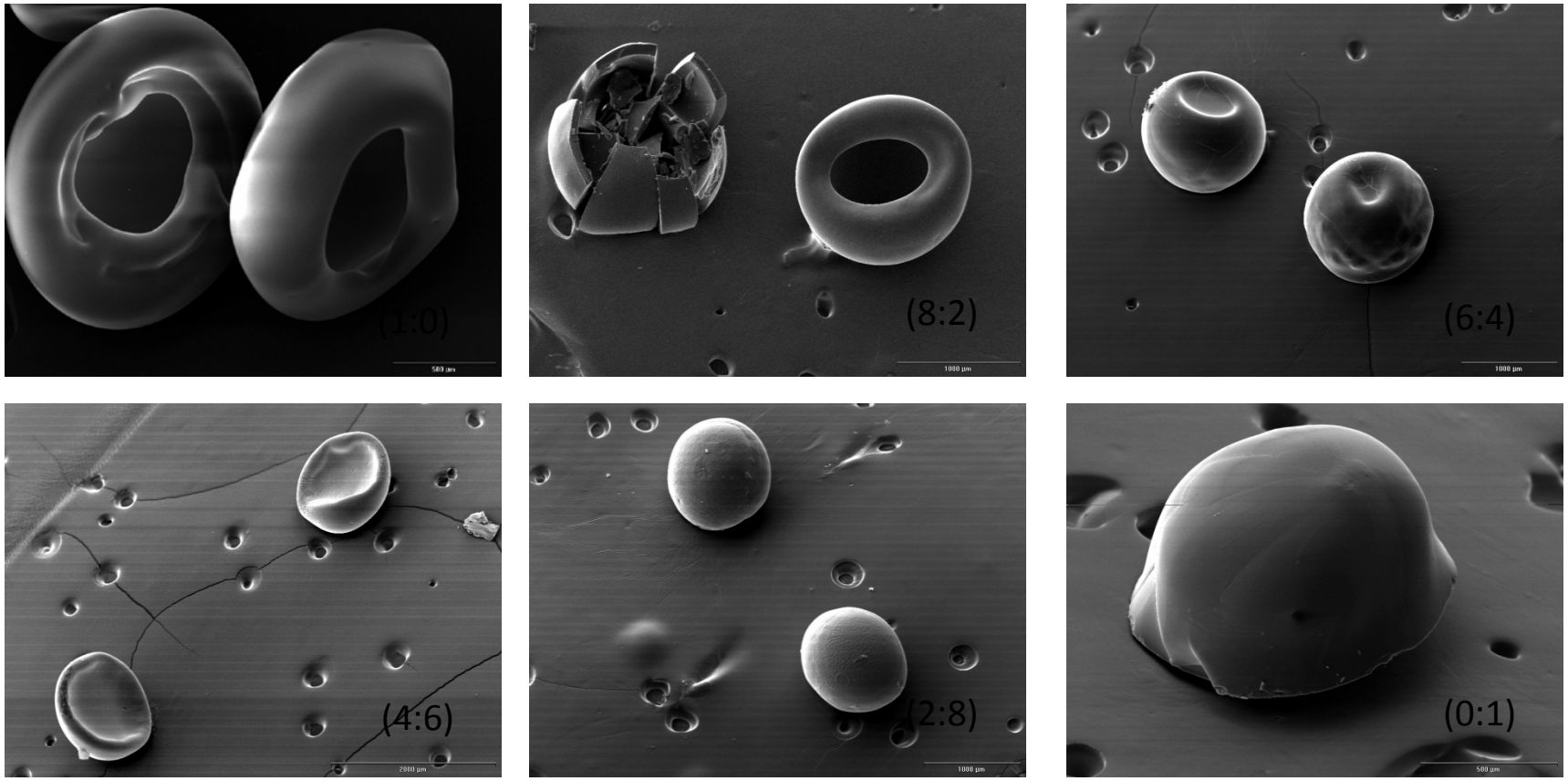




Catalase/Trehalose Mixtures (1:0) – (0:1): 60°C – 5% RH – 10% w/v

5.3b Research: Single Droplet Drying with Acoustic Levitator

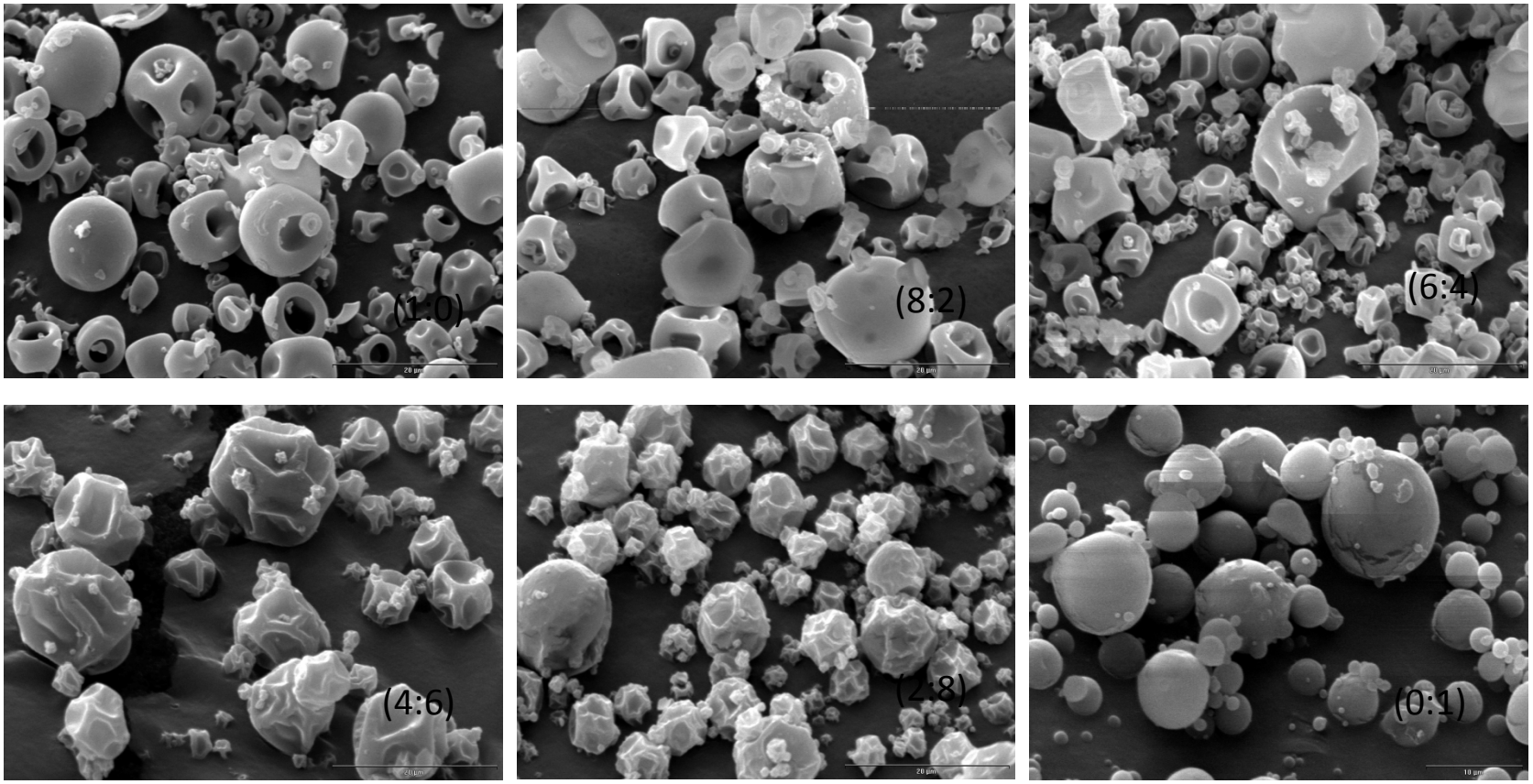
Application #1: A Kinetic Picture of *Particle Formation and Shape*



Catalase/Trehalose Mixtures (1:0) – (0:1): 60^{o}C – 5% RH – 10% w/v

5.3c Research: Single Droplet Drying with Acoustic Levitator

Application #1: A Kinetic Picture of *Particle Formation and Shape*



Catalase/Trehalose Mixtures (1:0) – (0:1): T_{out} = 60°C – 10% w/v: Comparison with spray-dried particles

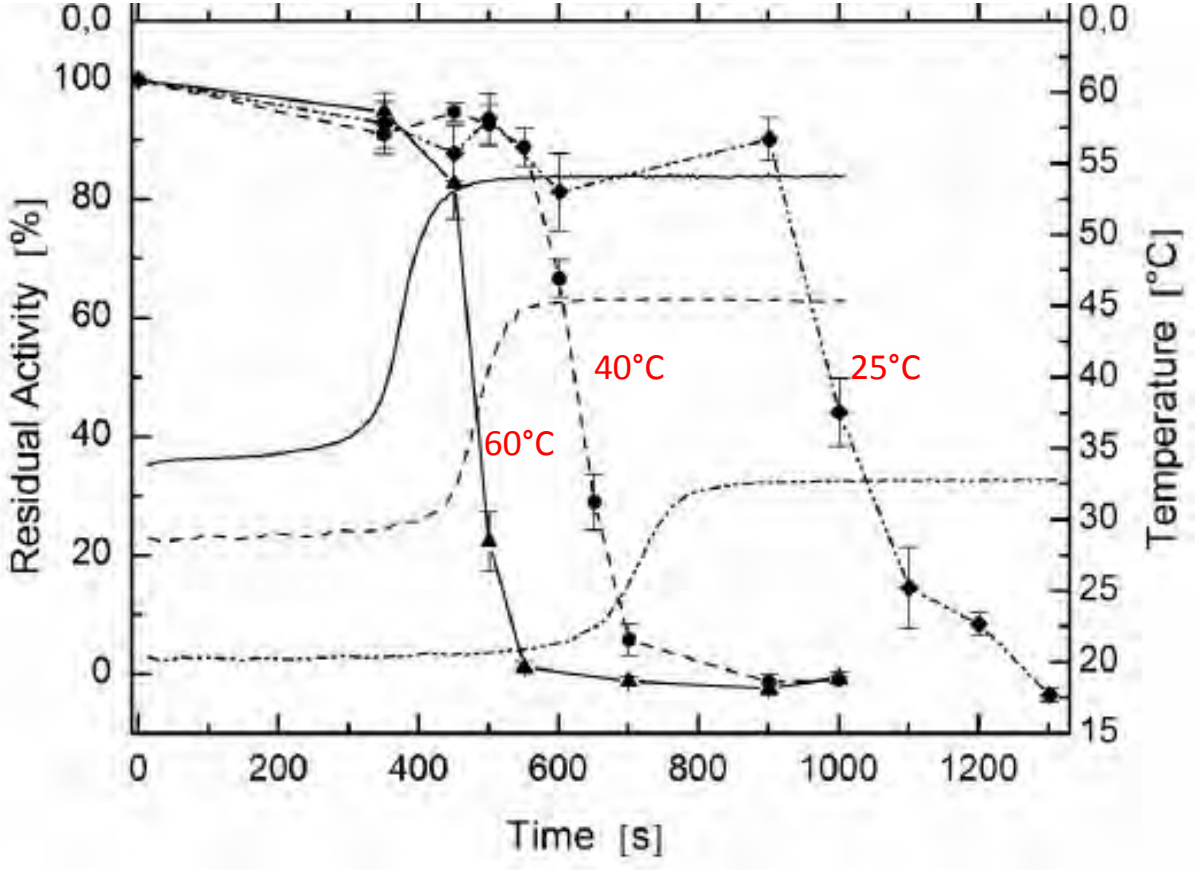
→ Don‘t forget differences in dimension between spray drying & levitation

5.4 Research: Single Droplet Drying with Acoustic Levitator

Application #2: A Kinetic Picture of *Damage* to Protein Molecule

- Effects of drying air temperature

Lorenzen & Lee, J Pharm Sci (2012)

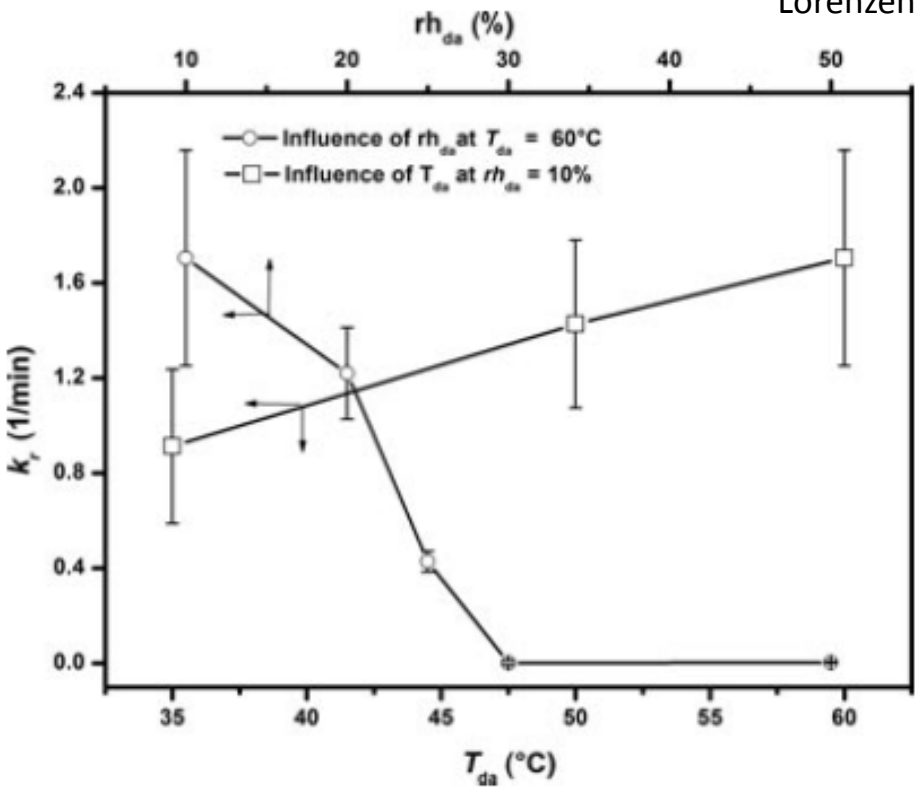


5.5 Research: Single Droplet Drying with Acoustic Levitator

Application #2: A Kinetic Picture of Damage to Protein Molecule

- Effects of drying air temperature & RH on first order rate constant

Lorenzen & Lee, J Pharm Sci (2012)

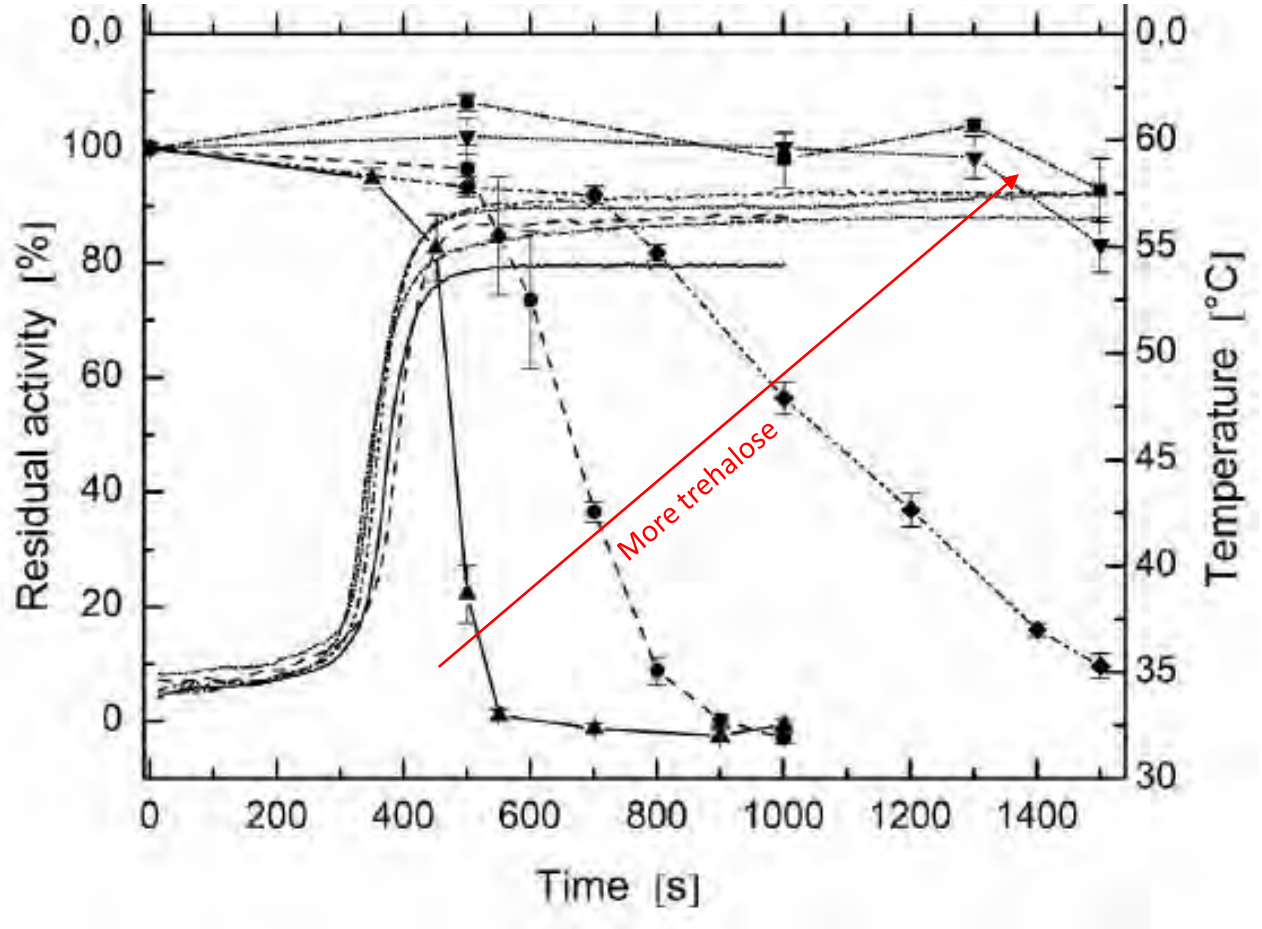


5.6 Research: Single Droplet Drying with Acoustic Levitator

Application #2: A Kinetic Picture of Damage to Protein Molecule

- Effects of added trehalose

Lorenzen & Lee, J Pharm Sci (2013)

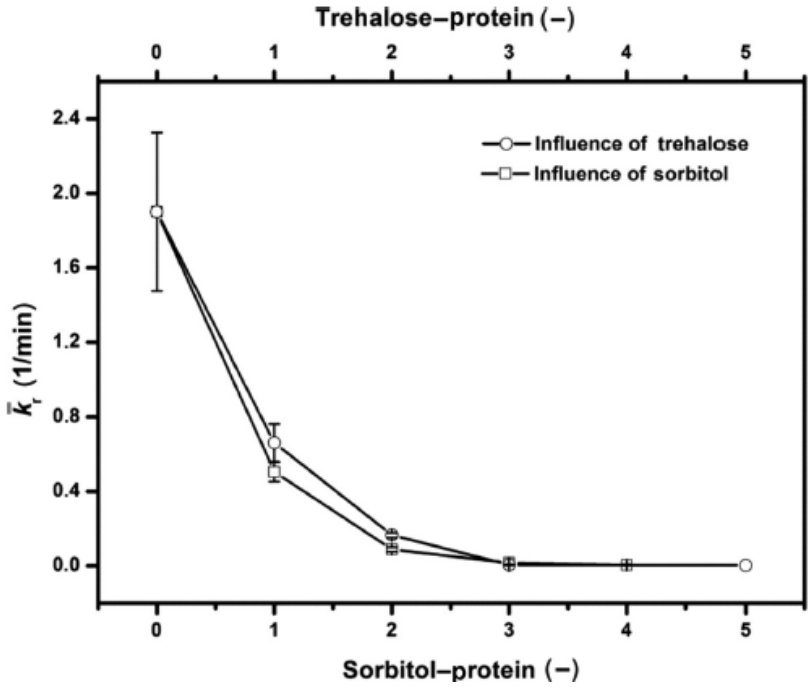


5.7 Research: Single Droplet drying with Acoustic Levitator

Application #2: A Kinetic Picture of Damage to Protein Molecule

- Effects of added trehalose on first order rate constant

Lorenzen & Lee, J Pharm Sci (2013)

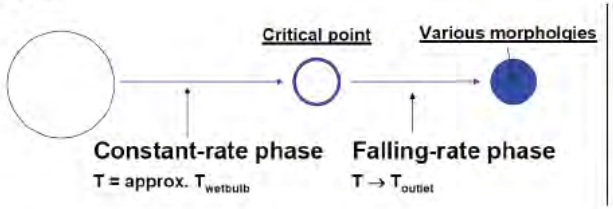


- Correction for particle size is possible SD/levitator; prediction ?

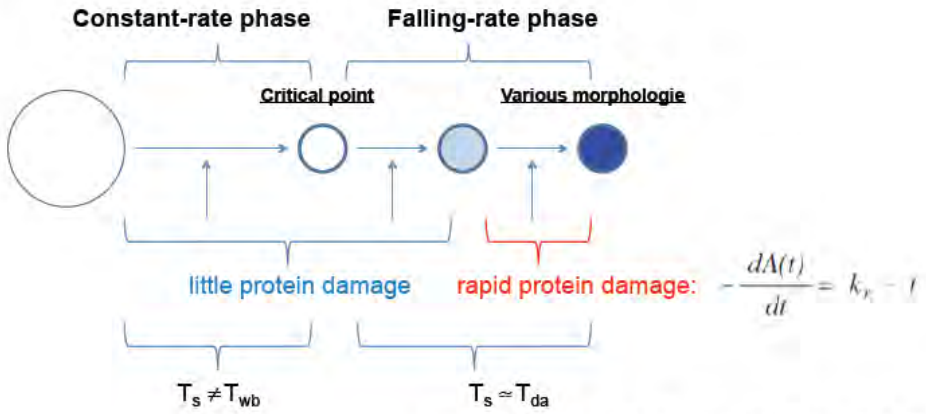
5.8 Research: Single Droplet Drying with Acoustic Levitator

The levitator gives a picture of process of drying and protein damage

Sherwood's model:



Levitator result:



is residual moisture content decisive ?
difficulties ?

Meeting One of the Challenges of Protein Drugs using Stable Particles

- Inhalation powders are still a viable delivery form for proteins
- Flowable protein powders can solve some difficuties in intermediate storage of bulk
- Levitation of single droplets allows visualisation of particle formation
- Kinetics of damage to a protein can be examined in detail