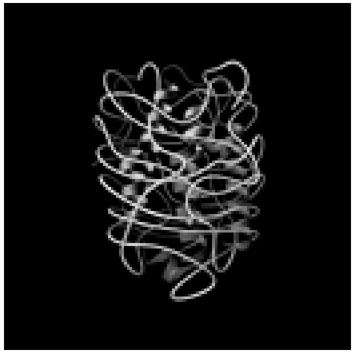
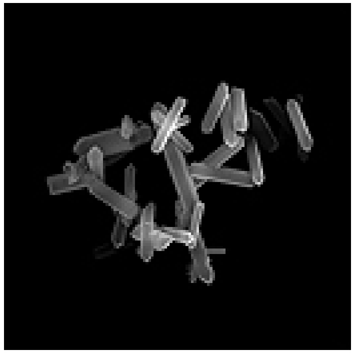
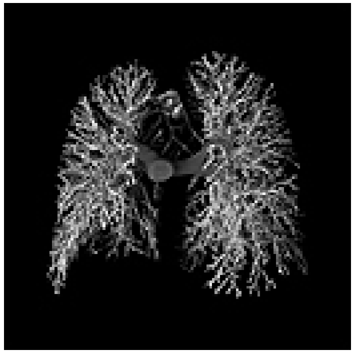
Physical Stabilization of Dry Powders for Pulmonary Drug Delivery

Reinhard Vehring
New Product Evaluation and Development

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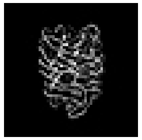
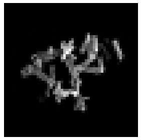
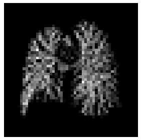
Outline

- Introduction
  - Proteins and peptides in development
  - Selected dry powder technologies
- Stability challenges - Typical failure modes
- Stabilization Strategies
  - Packaging
    - Modeling water uptake
  - Processing
    - Driving crystallization to completion
  - Formulation
    - Increasing the melt temperature of lipids
    - Predicting and increasing the glass transition temperature
    - Predicting and modifying moisture sorption behavior
    - Particle Engineering - Encapsulation
- Conclusion and Outlook

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Proteins and peptides in development for pulmonary delivery

Products that have entered the clinic

Insulin (Qdose)
Leuprolide (Nektar)
hGH (Alkermes)
Interferon-β (Nektar)
α-1-antitrypsin (Nektar)
PTH 1-34 (Nektar)
PTH 1-34 (MannKind)
CC10 (Claragen)
Insulin (Aerogen)
Anti-IgE (Genentech)
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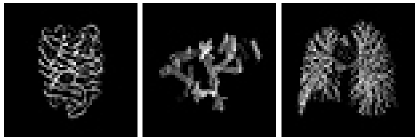
Insulin (Alkermes)
Insulin (MannKind)
Insulin (KOS)
tgAAVCF (TGEN)
α-1-antitrypsin (Arriva)
INS-37217 (Inspire)
Lactoferrin (Agennix)
α-1-antitrypsin (PPL)
Il-4 receptor (Amgen)
INS-365 (Inspire)
RAsOn (Epigenesis)

Insulin (Nektar)
Insulin (Aradigm)
Sinapultide (Discovery Labs)
Cyclosporin (Chiron)
Interferon-γ (Intermune)
rSP-C (Altana)
Leuprolide (TAP)

rhDNase (Genentech)

Dry powder
Liquid



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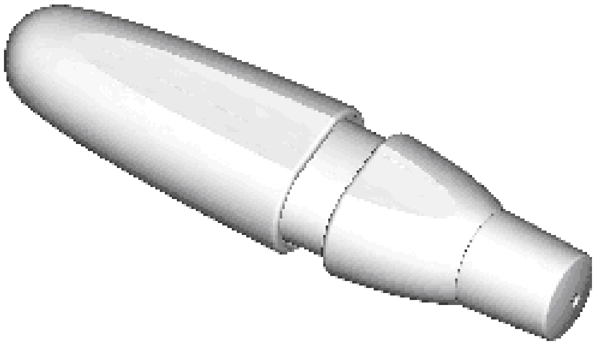
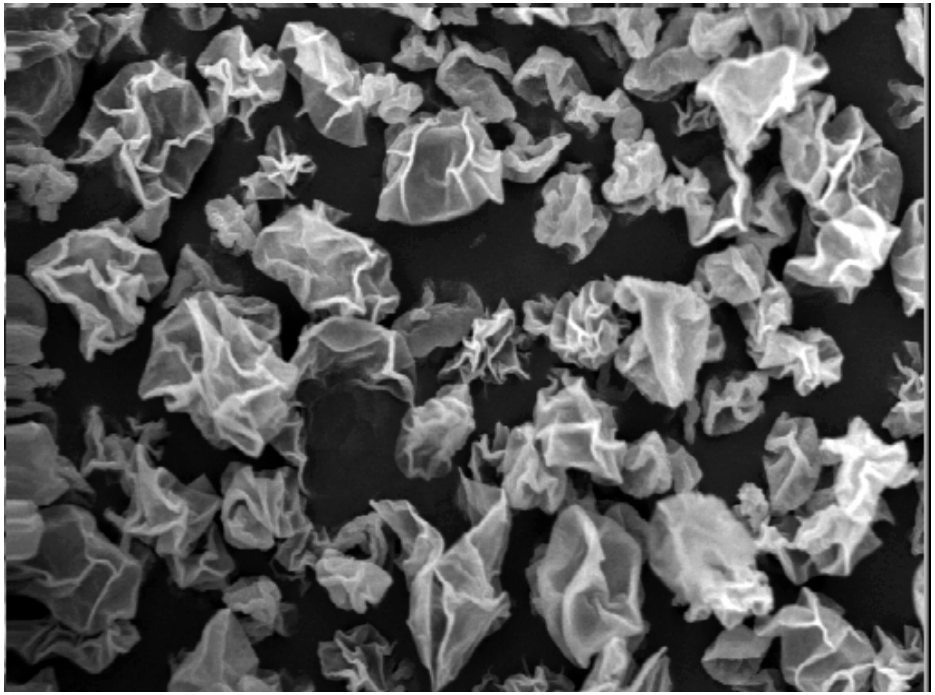
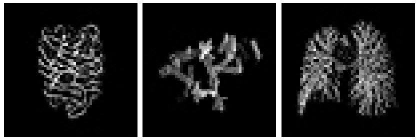
Alkermes AIR® / Device – Dry Powder System



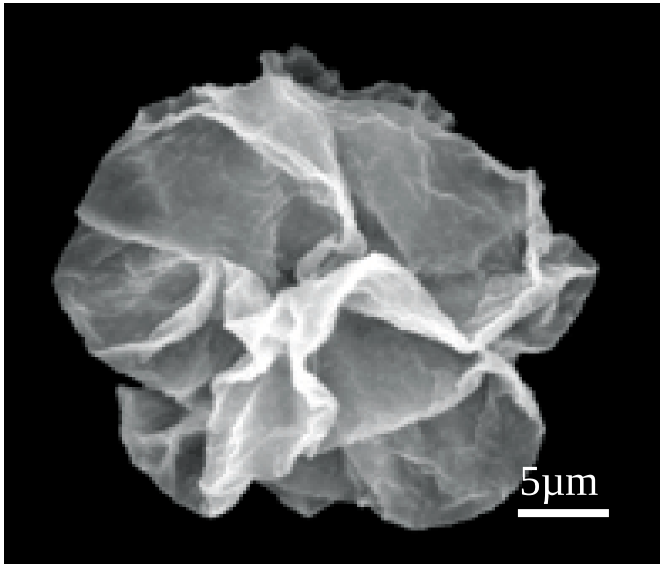
Re-usable, low to medium dose inhaler, capsule based



Large, porous particles



Large porous particles (Alkermes / AIR ®)



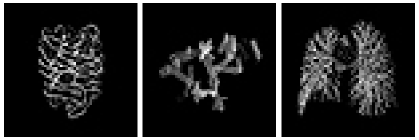
- Large particles with small aerodynamic diameter

$$D_a = D_p \sqrt{\rho_e}$$

- Lipid (DPPC) based
- May use additional excipients such as organic salts

- D_p = 5-30 µm
- D_a = 1-5 µm

Edwards et al. **Large porous particles for pulmonary drug delivery.** *Science* 1997, **276**:1868-1871.



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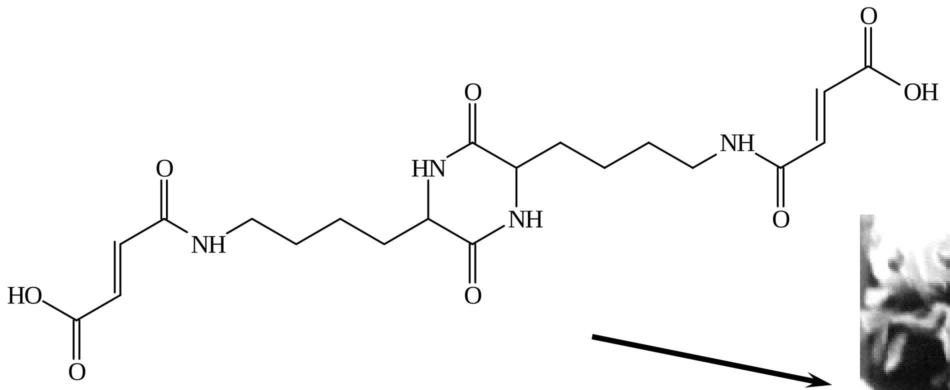
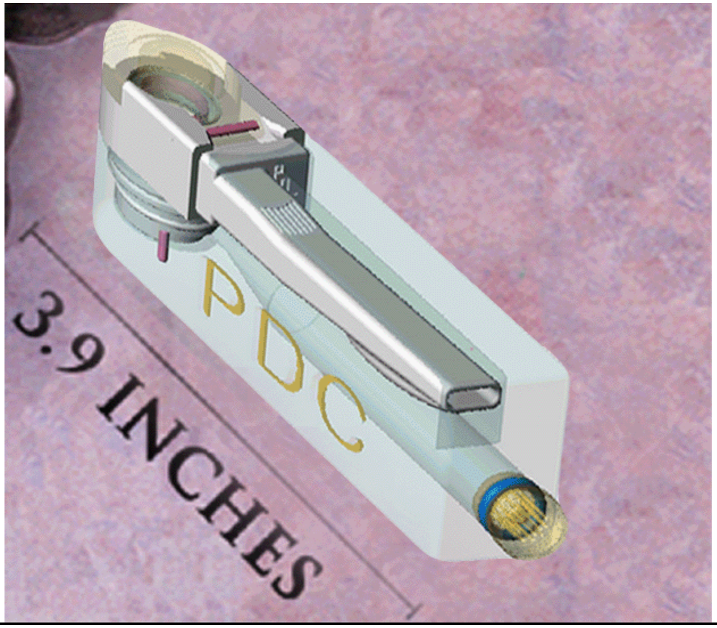
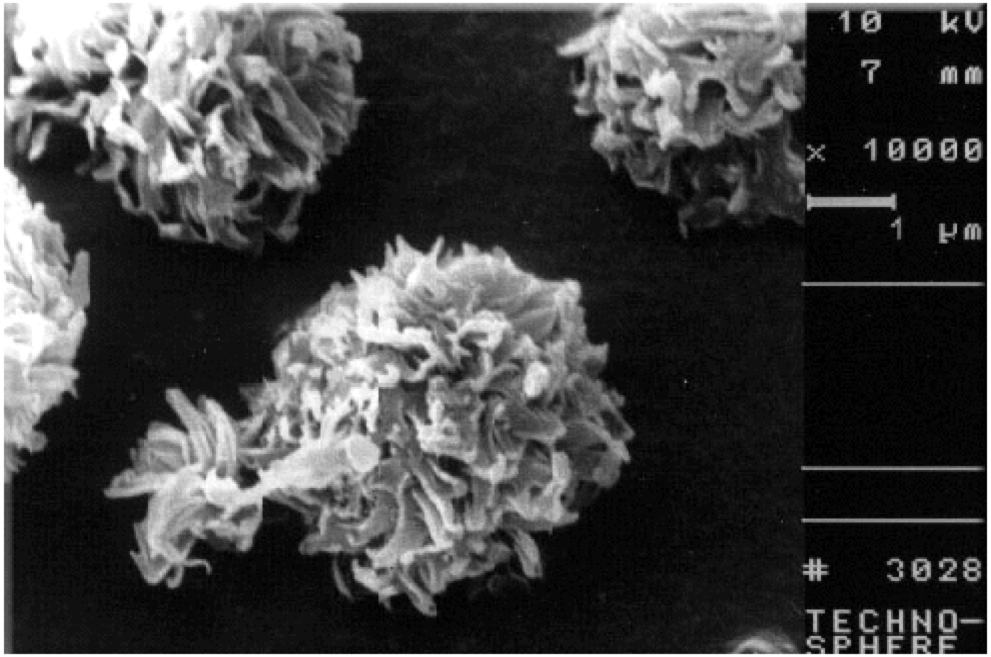
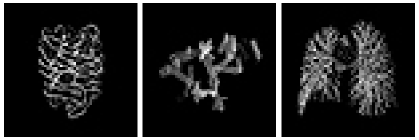
MannKind Device – Dry Powder System





Self-Assembling Fumaryl Technosphere™





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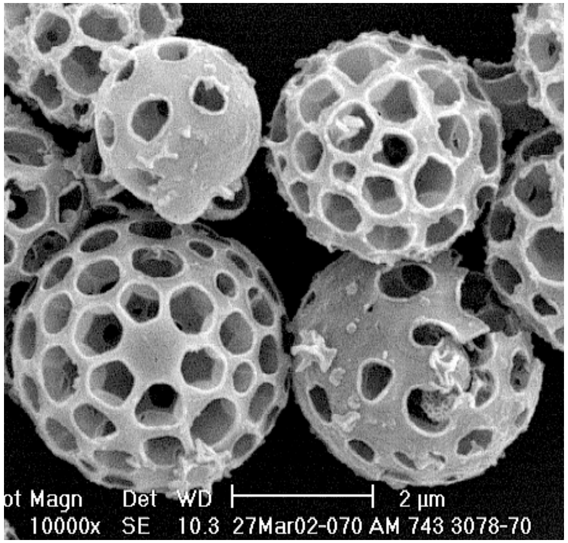
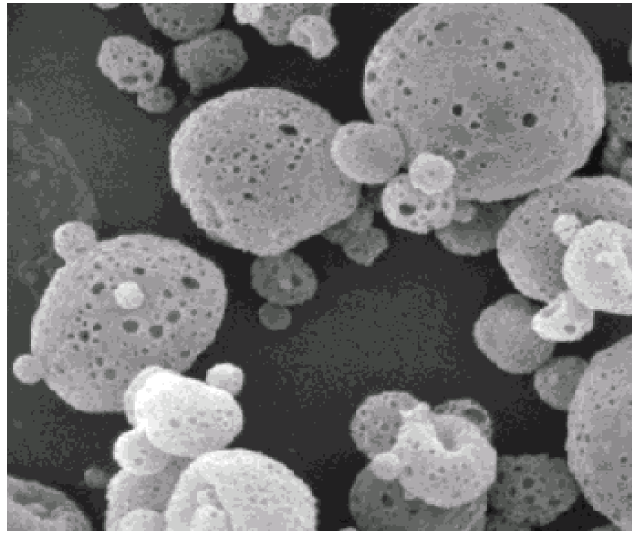
Nektar - lipid based particles





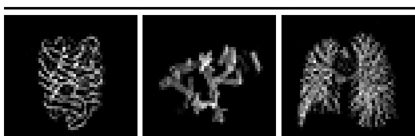
“Small porous particles”

Small Molecule

Calcitonin

Standard capsules
Disposable
Large payloads

MDI
Potent molecules
< 1mg per actuation



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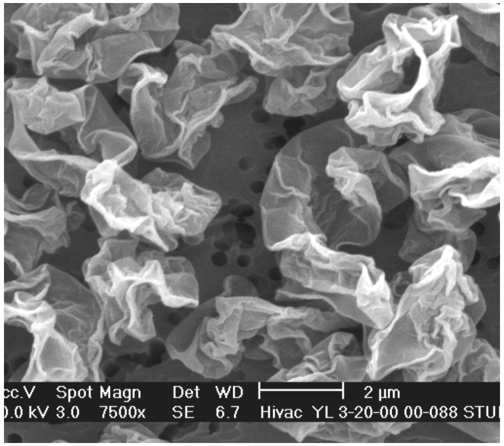
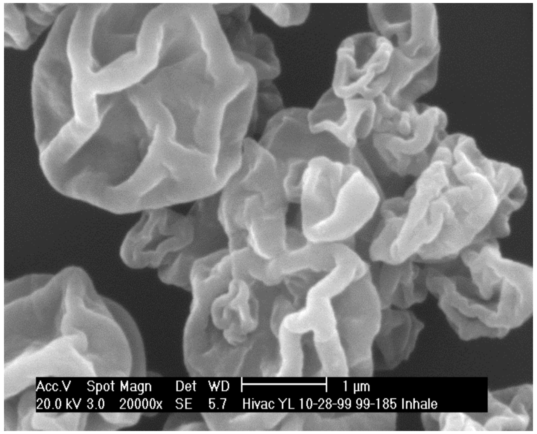
Nektar amino acid / sugar based particles

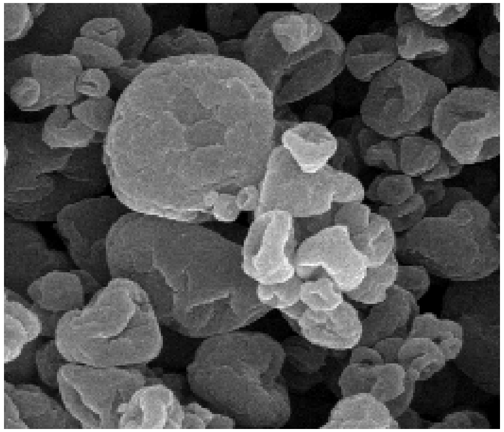
Trileucine



Protein Formulation



Amino Acid



Typical Excipients

- Amino acids, di-, tripeptides
- Sugars
- Organic Salts

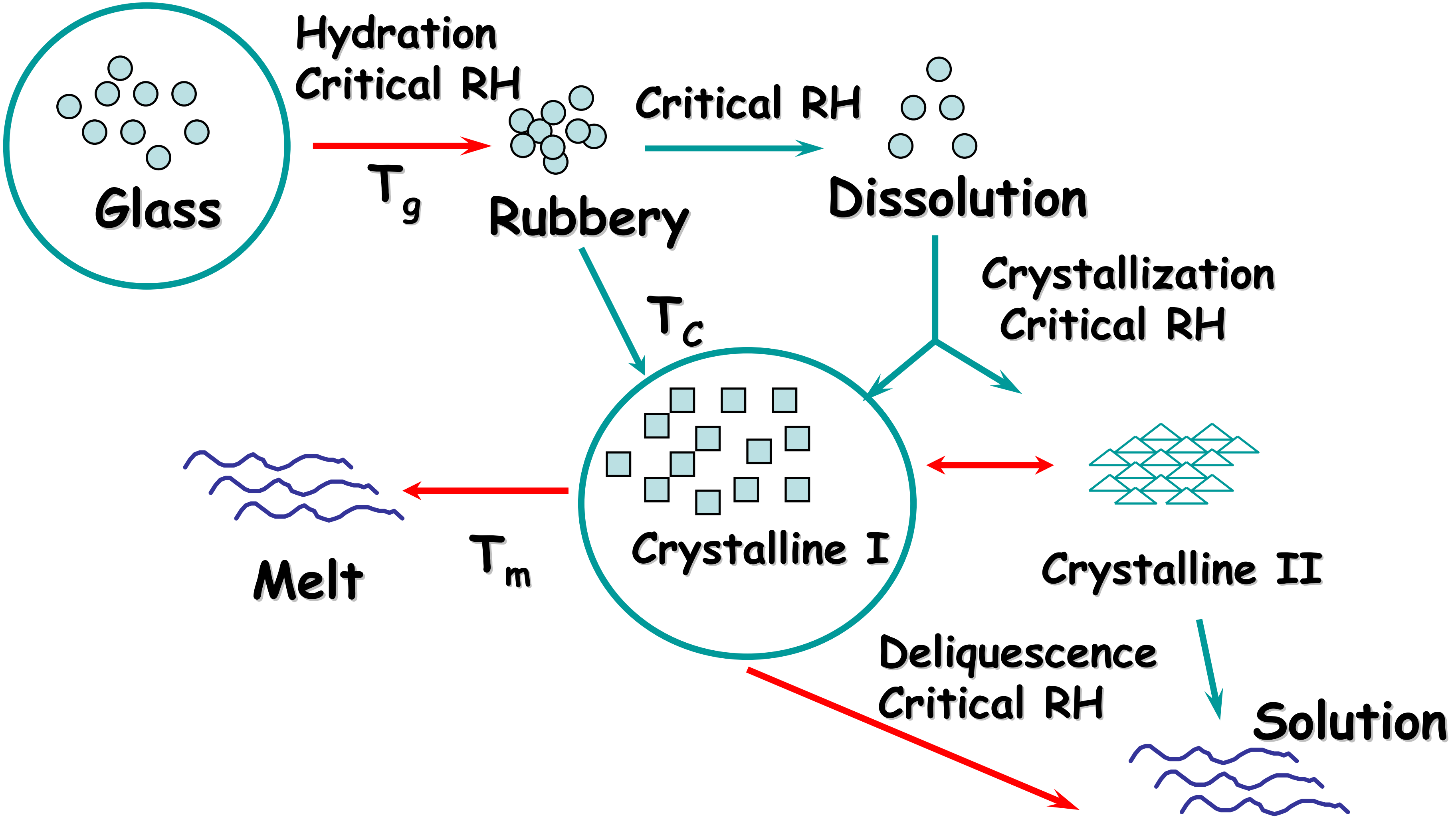
US Pat.: 6,685,967; 6,673,335; 6,589,560; 6,136,346, 6,372,258, 6,518,239

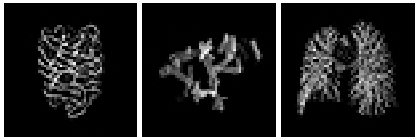
Stability challenges

Manufacture	High T, high RH, very short duration
Storage	Low T, low RH, very long duration
Patient Use	Low T, high RH, moderate duration

Formulation stability is a major factor determining product cost

Moisture and temperature induced solid state transformations





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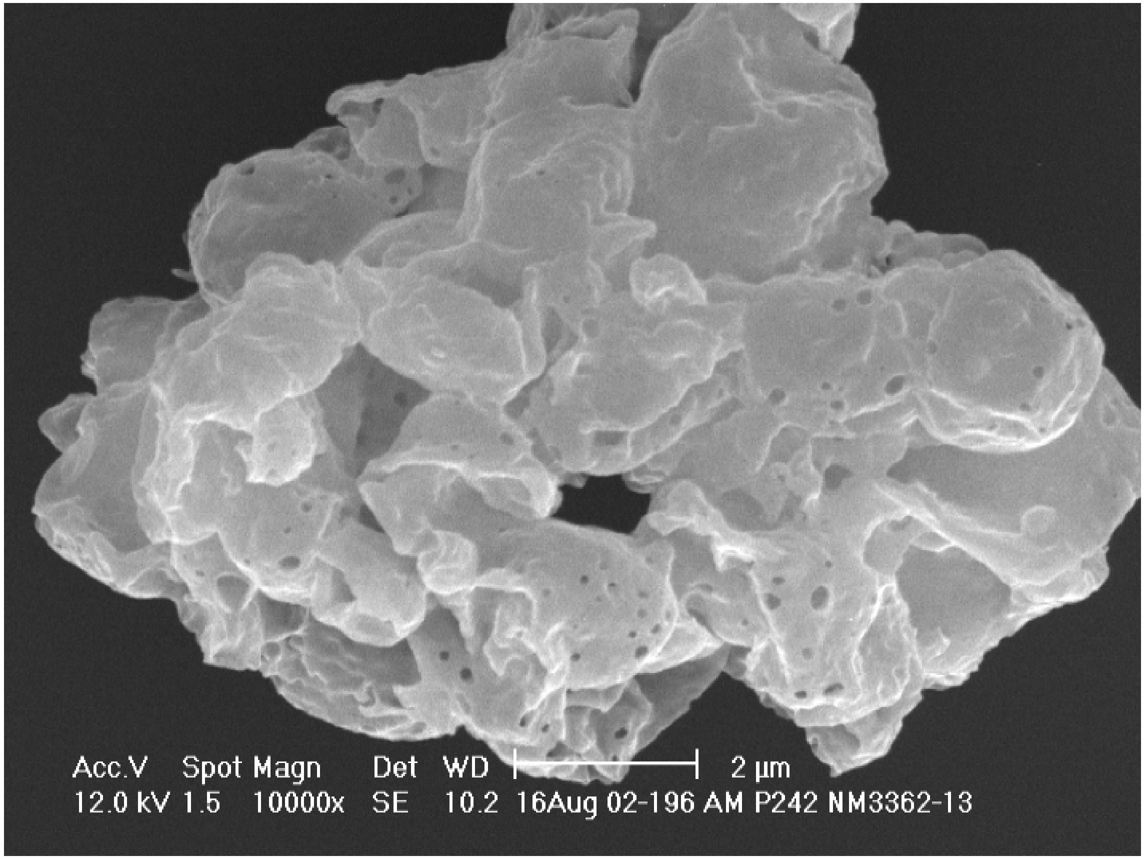
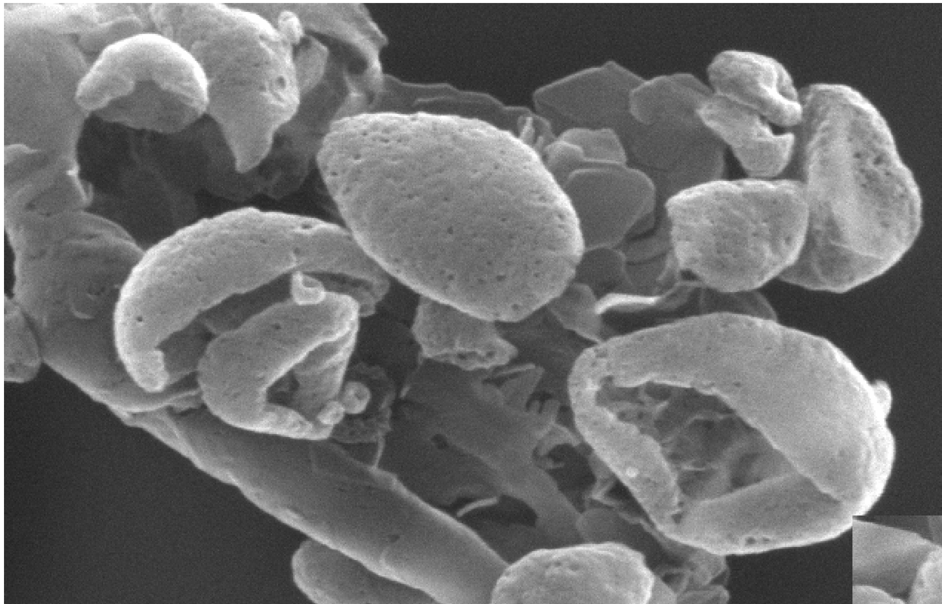
Failure modes - Lipid melting

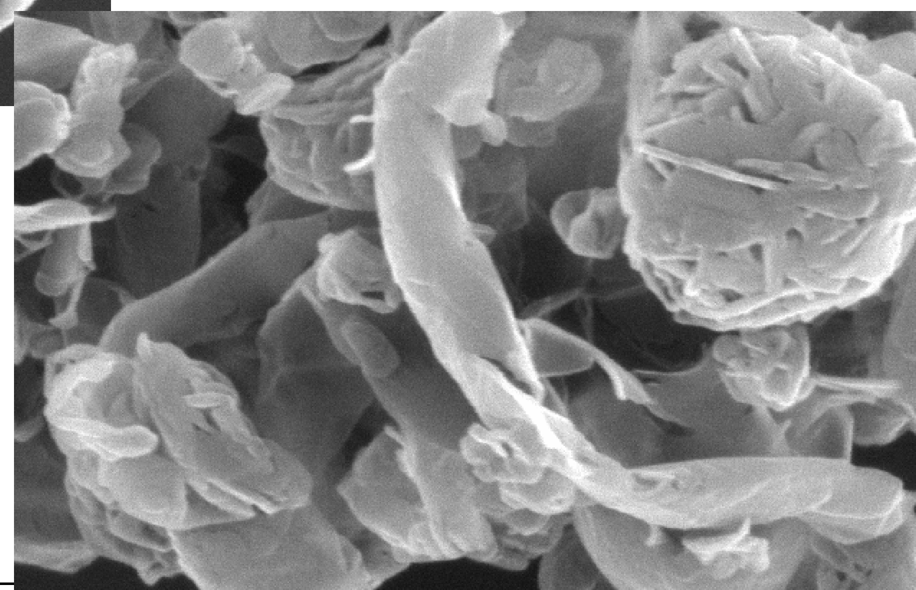
Particles with depressed lipid melting temperature fused during collection in the cyclone



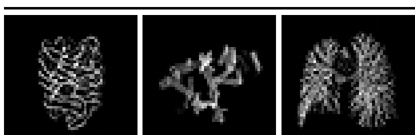
Failure mode - Recrystallization



Spray-dried amino acid
95 % very small crystals



After storage at 40˚C for 2 weeks
100 % crystalline



Failure mode – Structural collapse

Sucrose formulation stored at

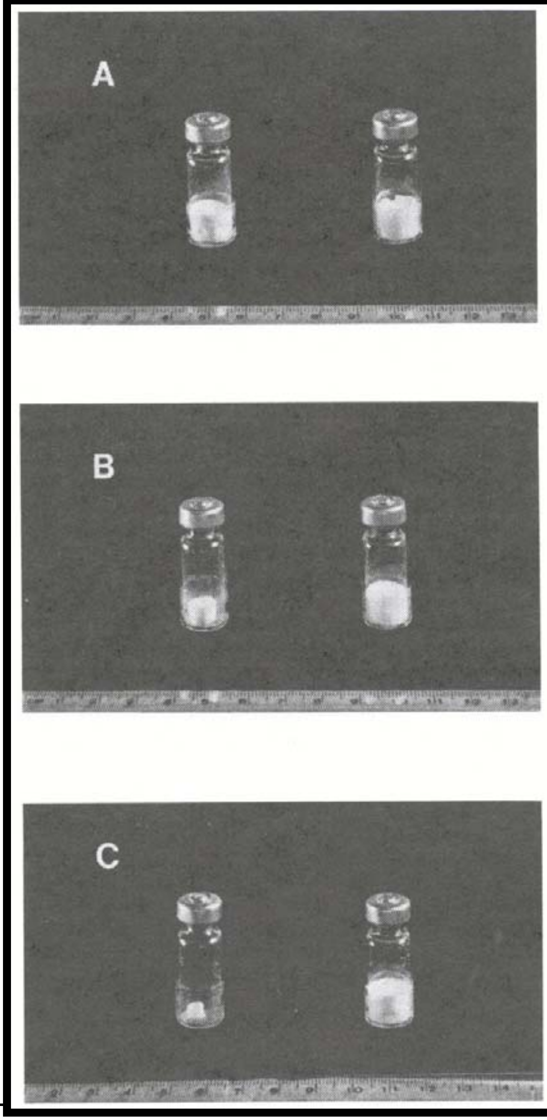
40 °C

Tg = 59 °C

50 °C

55 °C

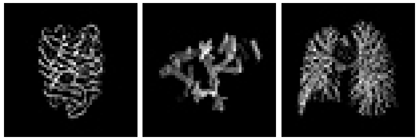
for 1 month



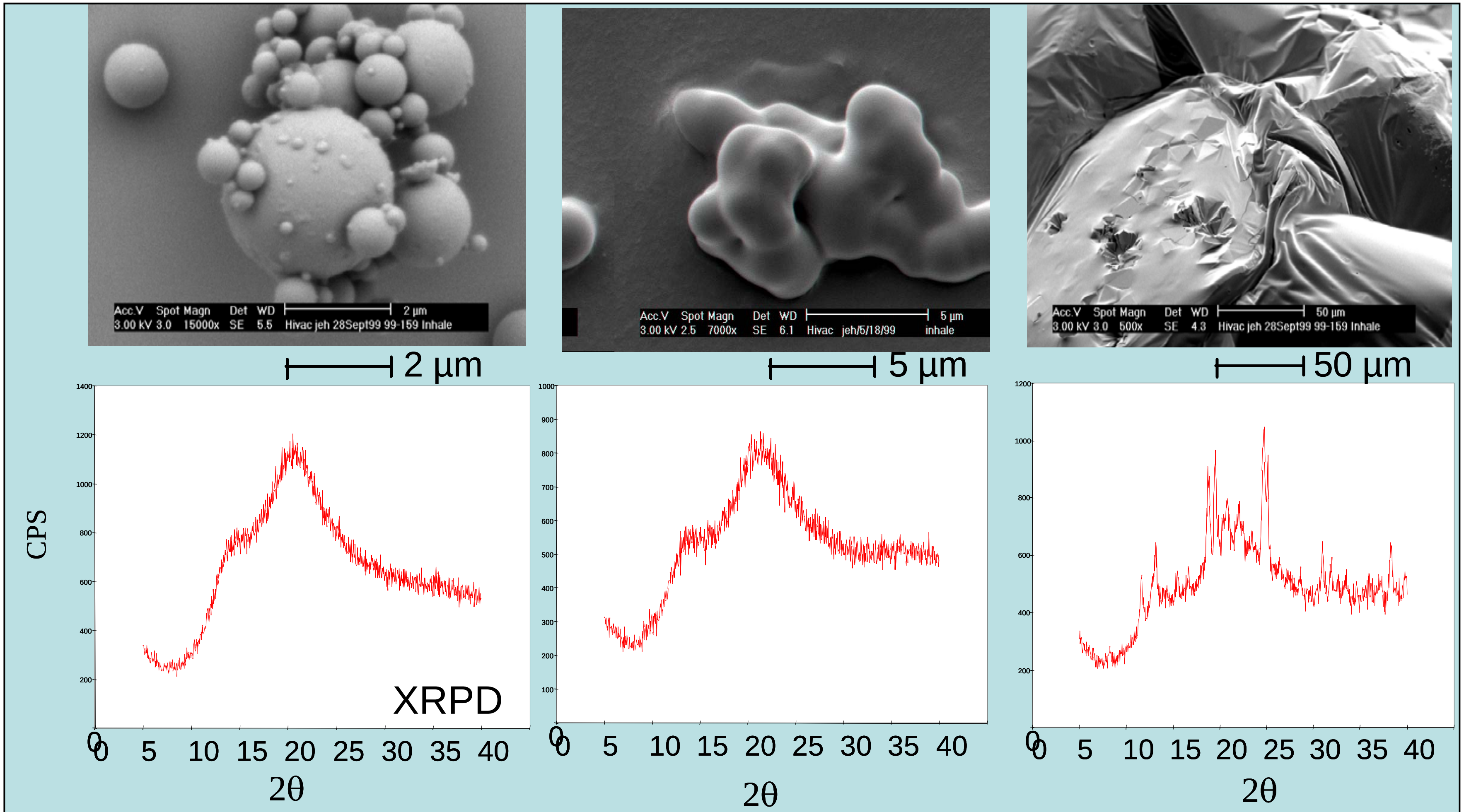
Tg = 80 °C

High Tg control

Duddu et al., Pharm Res 14 596, 1997



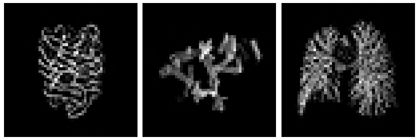
Moisture induced particle fusion and crystallization: Sucrose



RH < 10 %, years

RH 33 %, hours

RH 75 %, minutes



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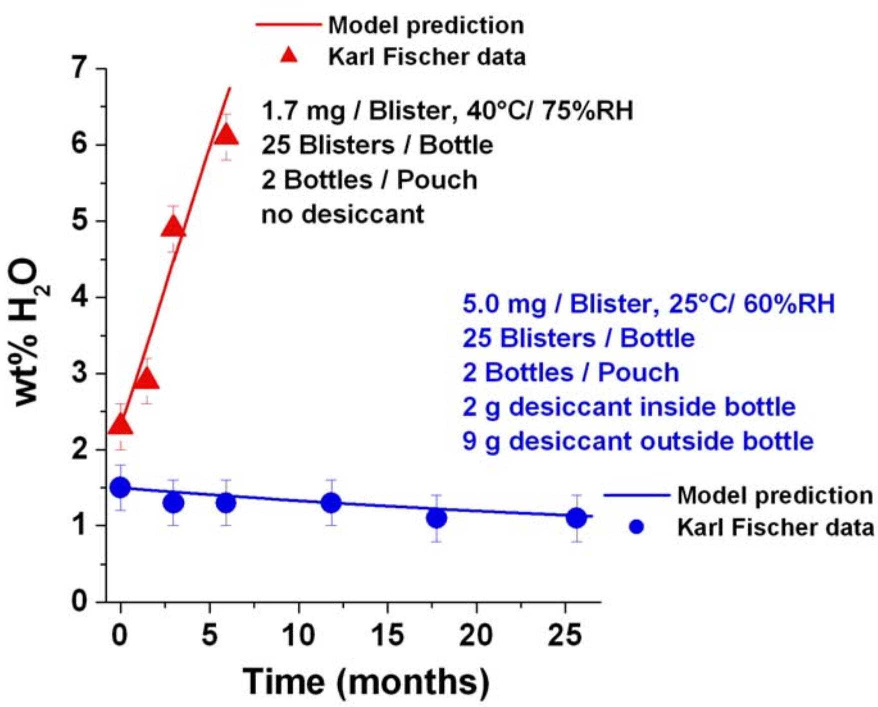
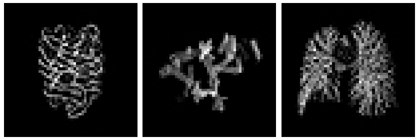
Stabilization through packaging

Prevent moisture exposure - blister packaging



- Required package configuration can be determined by moisture permeation modeling
- Numerical model of water permeation through packaging provides moisture content as a function of time => prediction of shelf life



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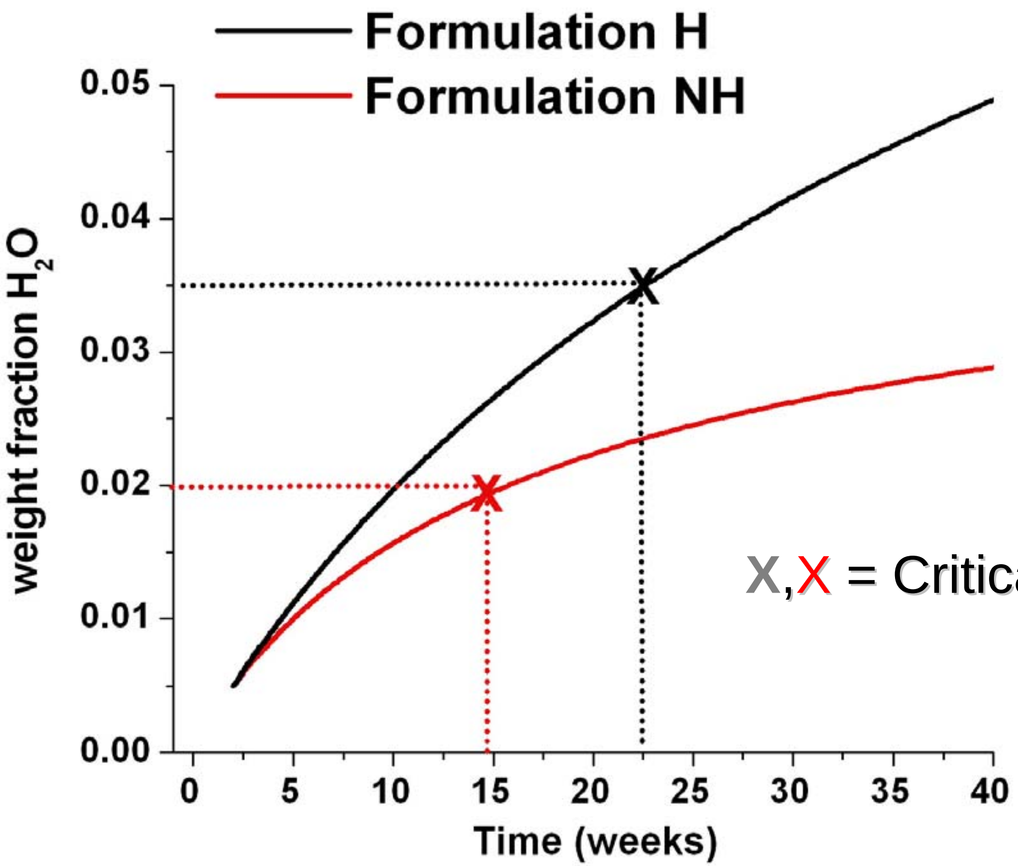
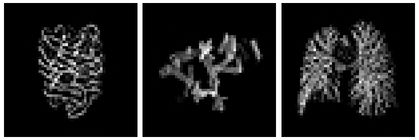
Shelf life predictions



Shelf life depends on multiple factors

X,X = Critical moisture criteria

Model allows to rank-order formulations and predict shelf life



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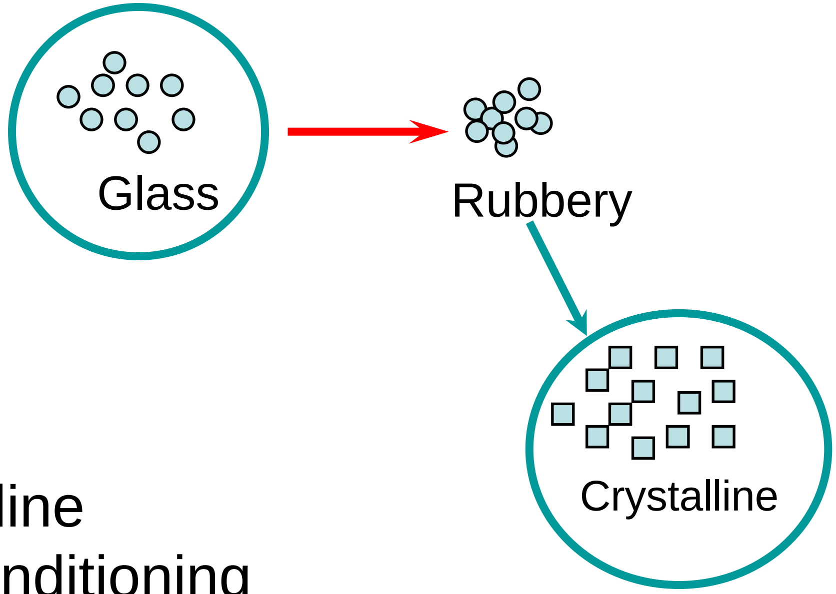
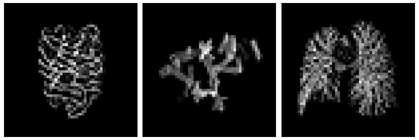
Stabilization through processing

Driving crystallization to completion prevents transition to rubbery state



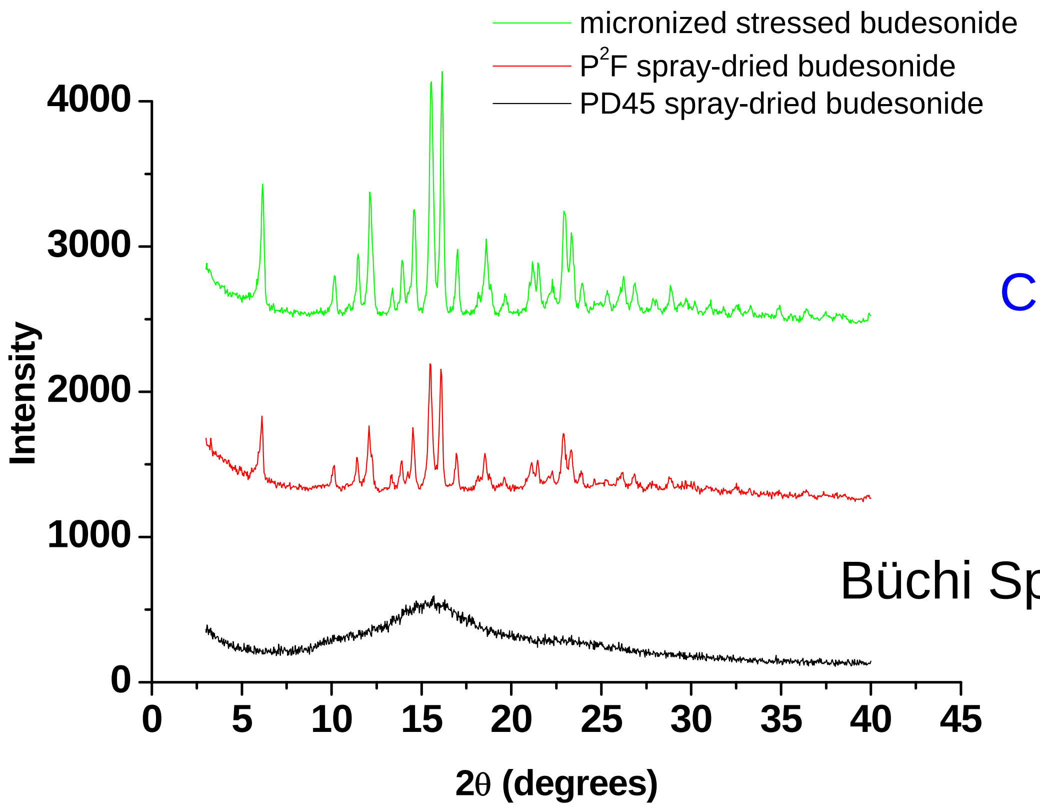
- Amorphous-to-crystalline transformation in a conditioning zone of the spray dryer
- Conditioning occurs prior to collection to prevent particle fusing

Pat.: WO 01/00312 A1

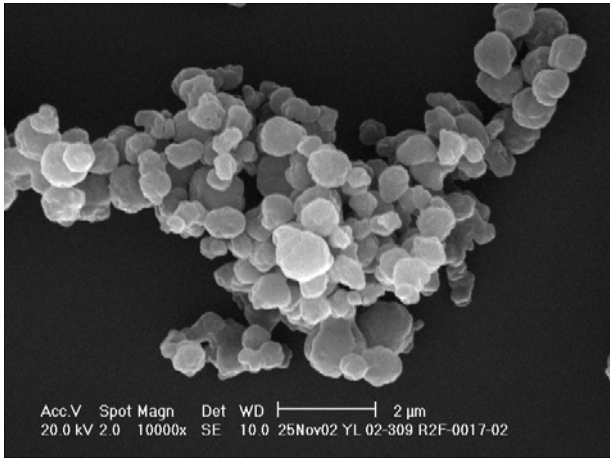


Crystalline budesonide manufactured in a stage dryer

Stage Spray Drier

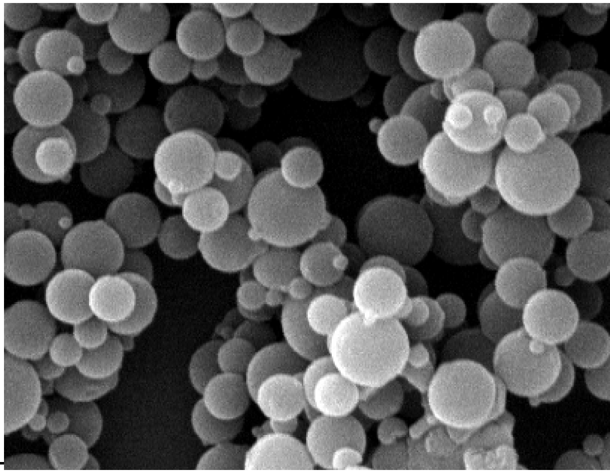


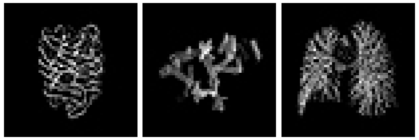
Crystalline



Büchi Spray Drier

Amorphous





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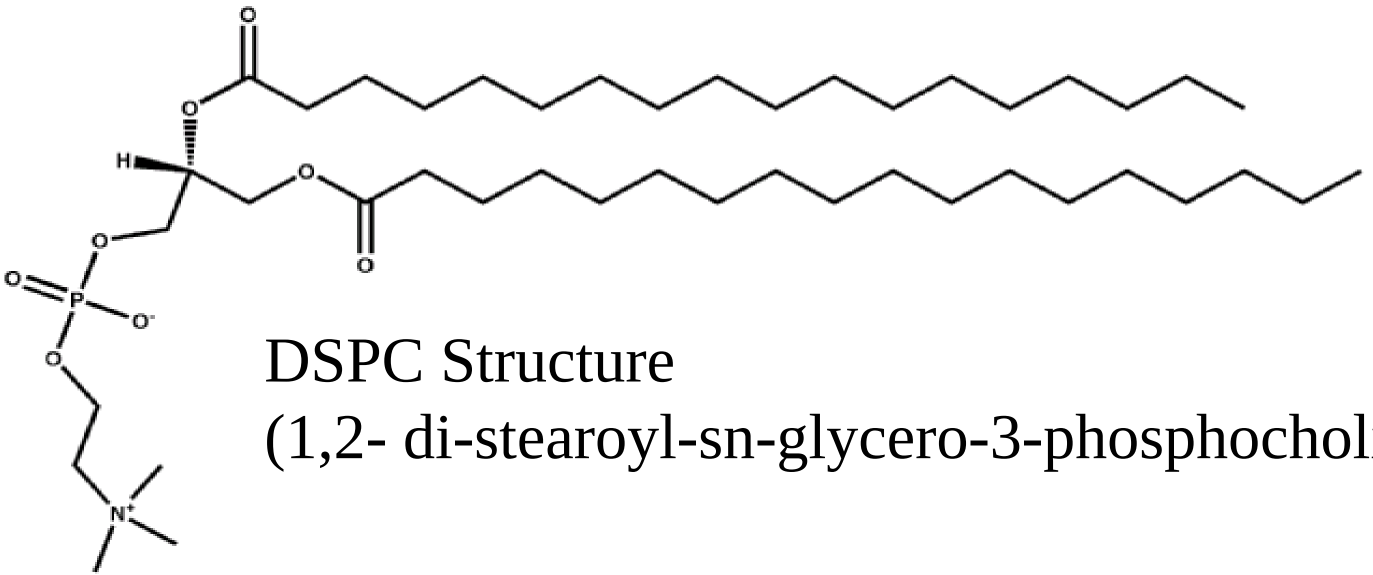
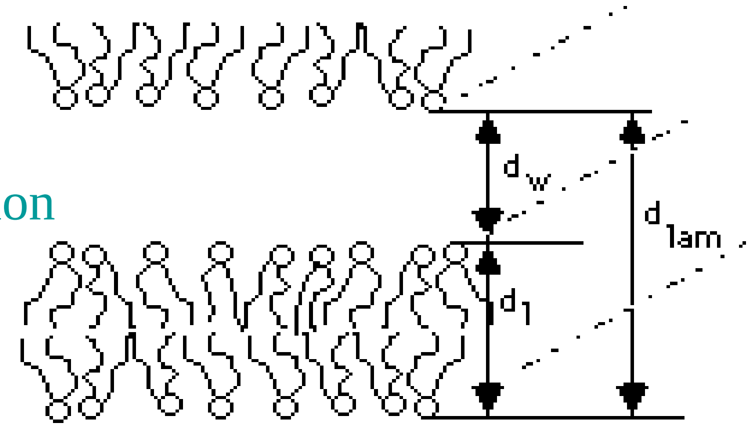
Stabilization through formulation – Phospholipid modifications

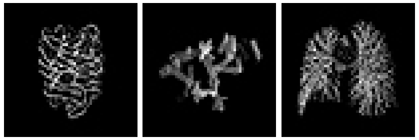


DSPC Structure
(1,2- di-stearoyl-sn-glycero-3-phosphocholine)

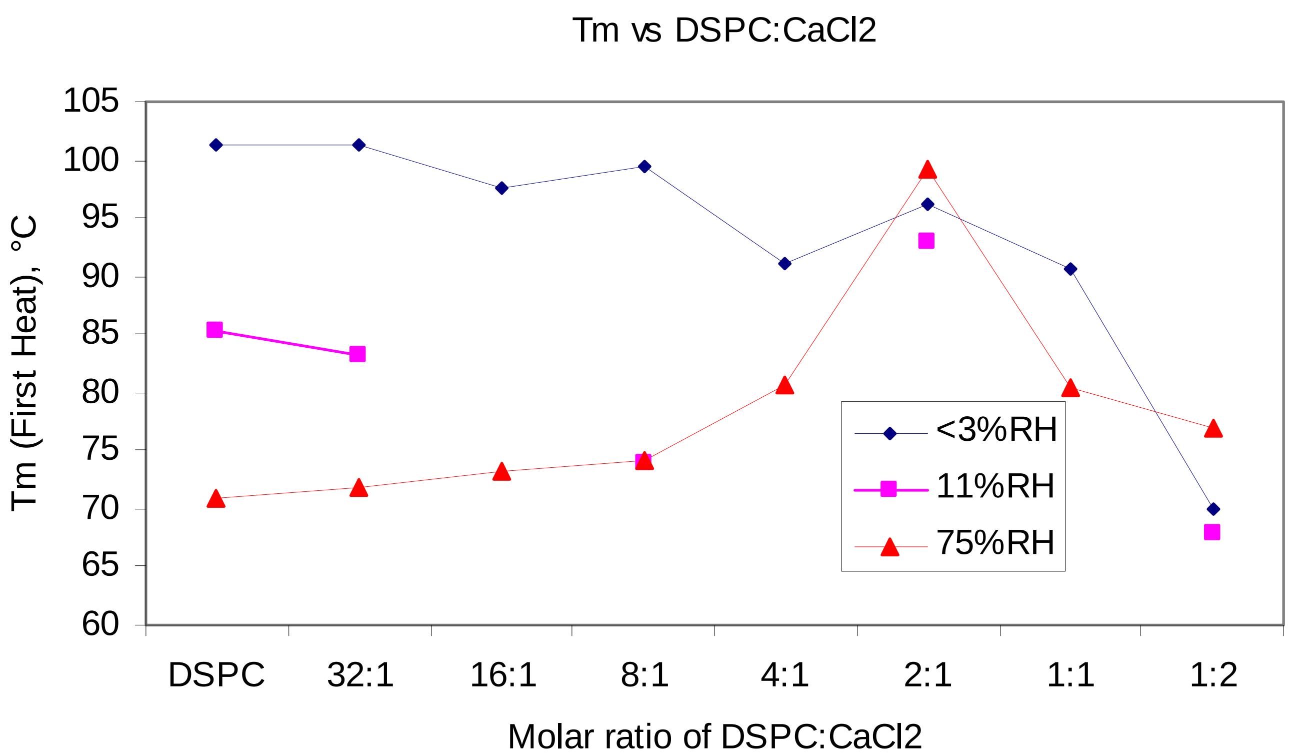
Addition of Ca+

- ➢Changes the head group geometry
- ➢Influences chain packing and lamellar separation
- ➢Reduces water sorption

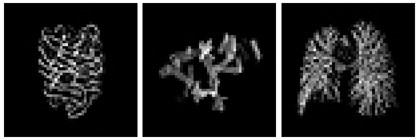




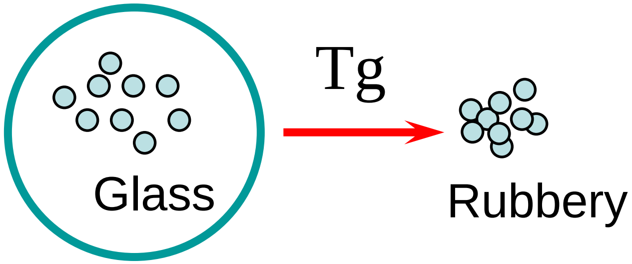
Increasing the melting temperature of phospholipids with calcium cations



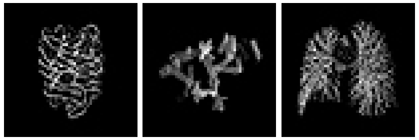
Effect of $CaCl_2$ on the Tm of DSPC at various RH
The phase transition temperature (Tm) was measured using DSC heating scan at 1°C/min



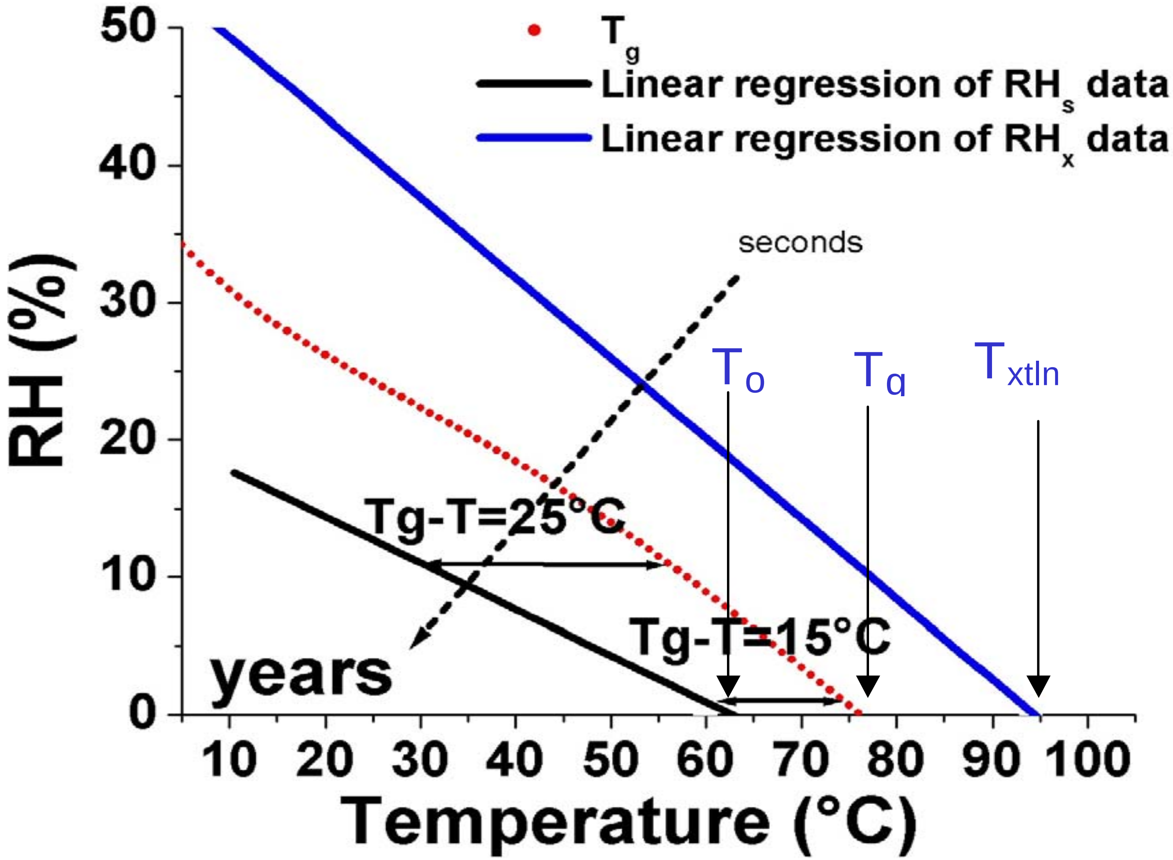
Glass stabilization



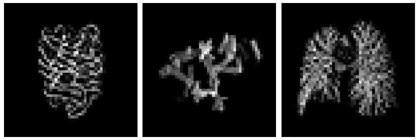
- Increase glass transition temperature
- Improve plasticization properties



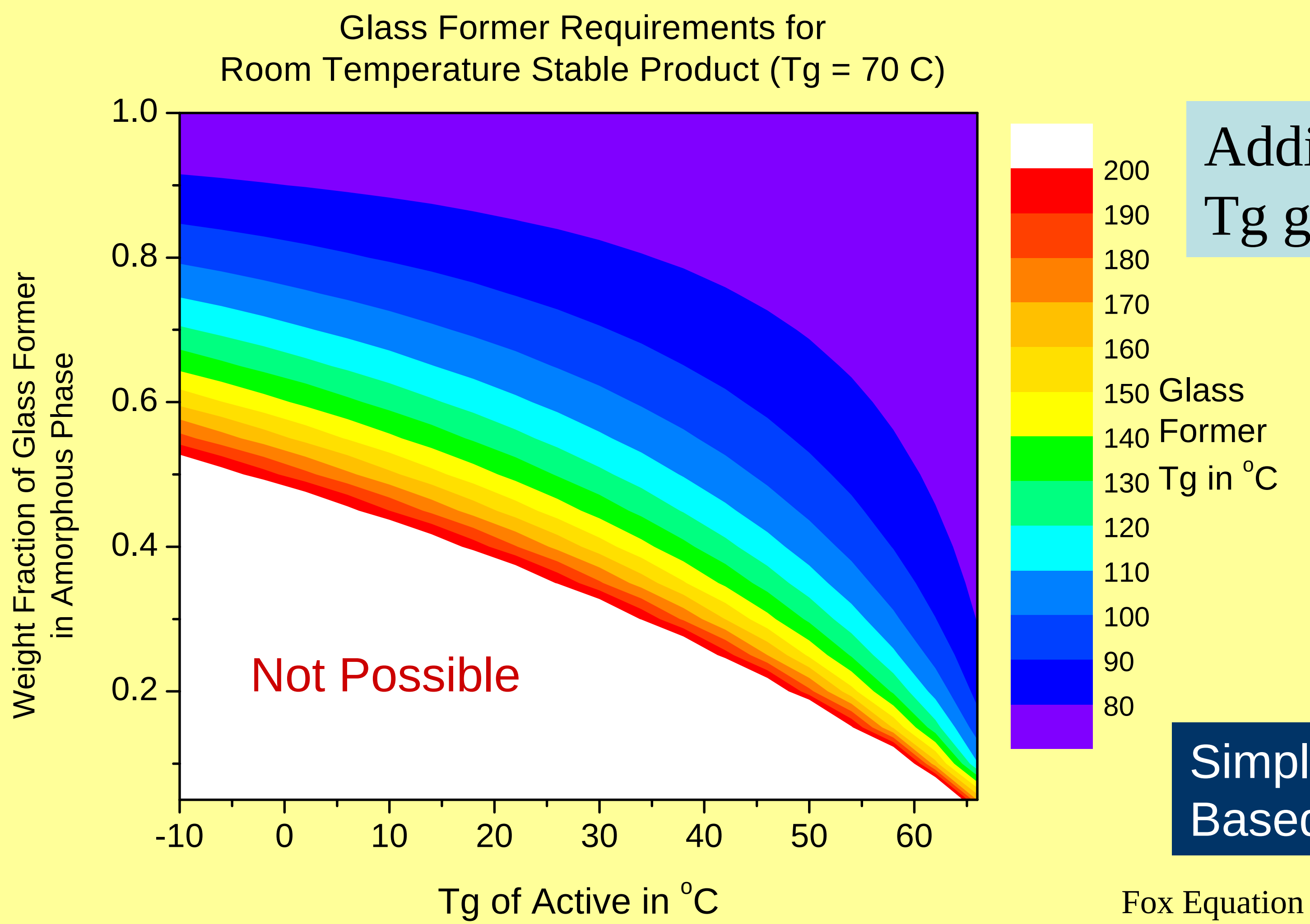
Glass Transition Temperature and Structural Relaxation Time



Long term stability at Tg-T = 50 ˚C



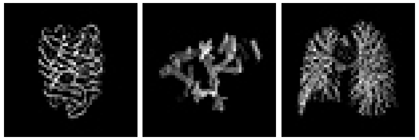
Increasing the glass transition temperature



Addition of a high Tg glass former

Simple mixing rule
Based on dry Tg

Fox Equation



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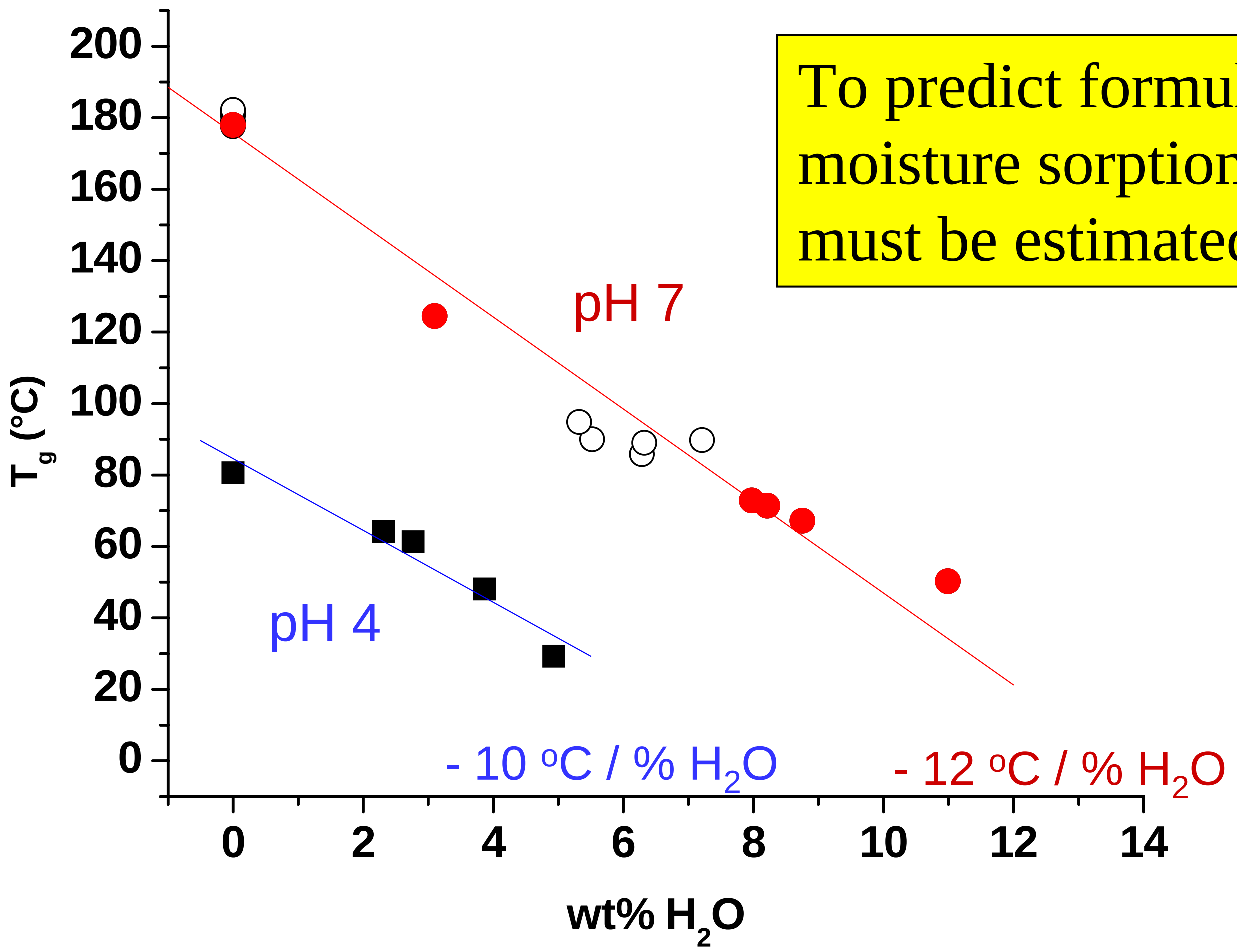
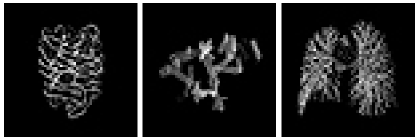
Water depresses the Tg



To predict formulation Tg, moisture sorption and plasticization must be estimated

Example: Plasticization of amorphous sodium citrate.



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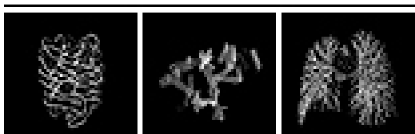
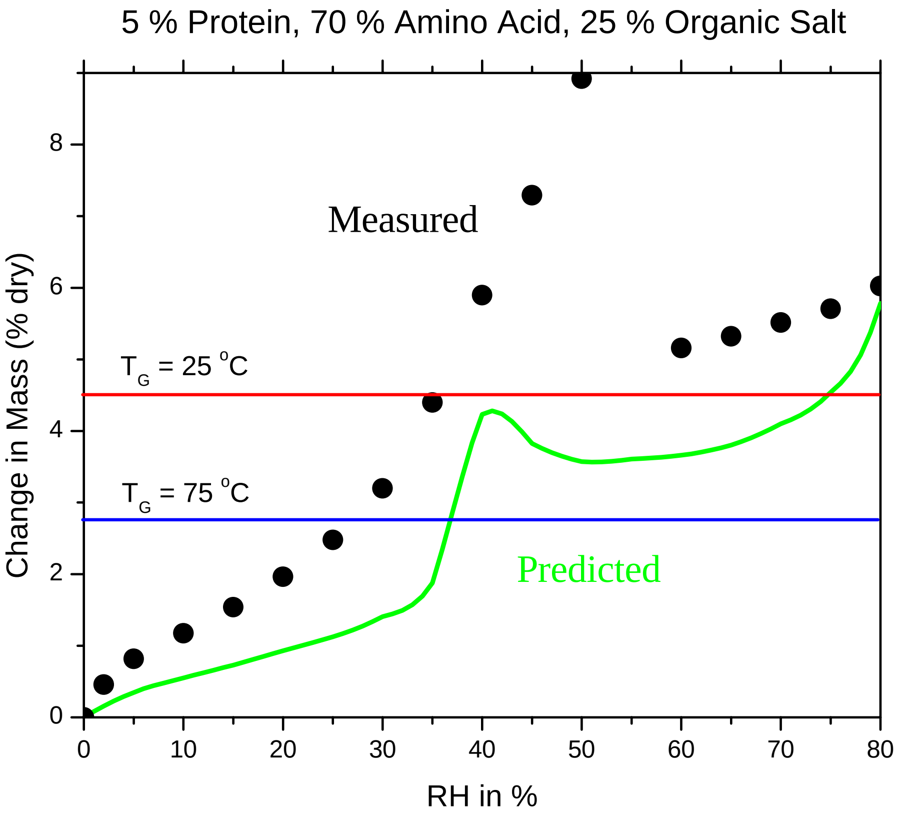
Formulator tool predicts glass transition

Nektar has developed a predictive tool for moisture sorption behavior and Tg of formulations as a function of excipient ratios and pH.

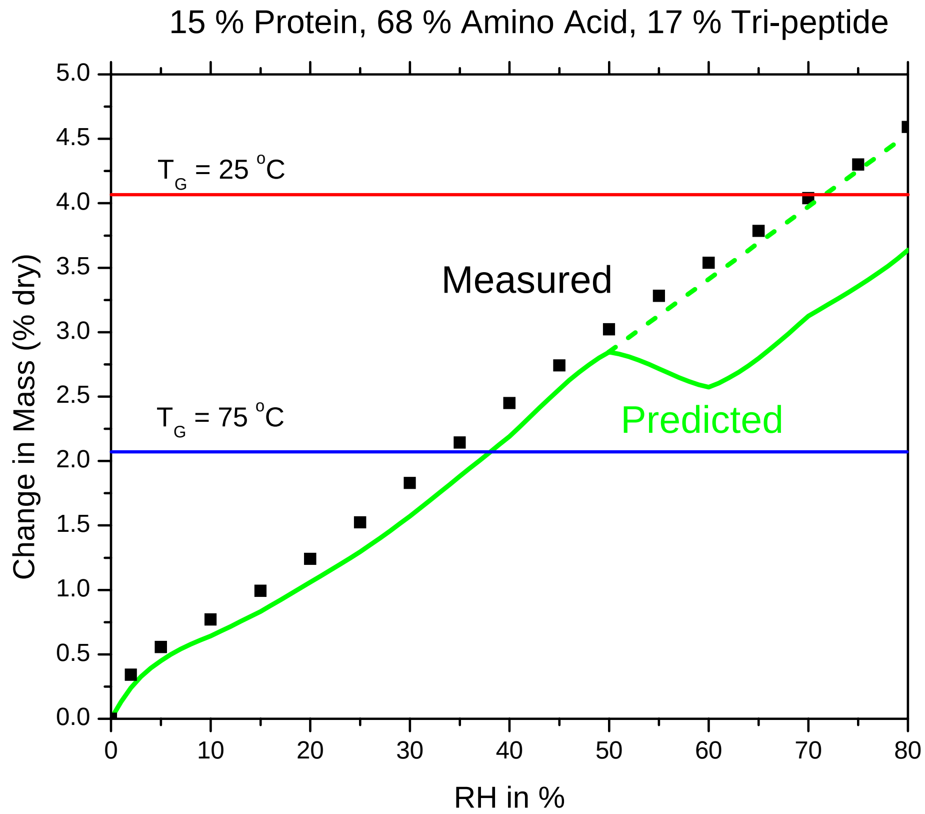
- Uses an extensive database of excipient properties and interactions in binary and tertiary mixtures.
- Coefficients for Tg models have been determined for typical Nektar formulation systems.



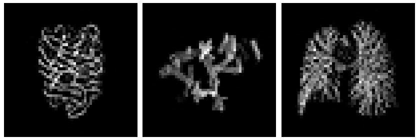
Designing the amorphous phase



Crystallization at moderate RH



Much improved out-of-package stability



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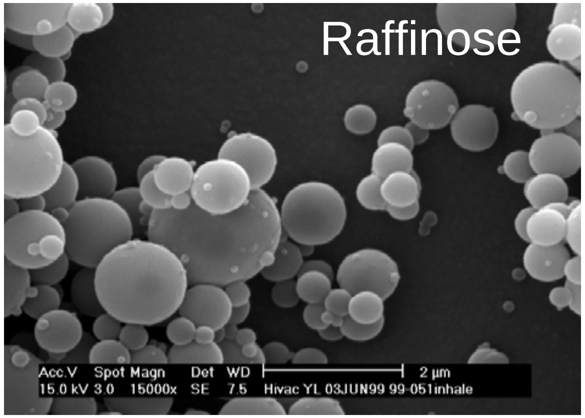
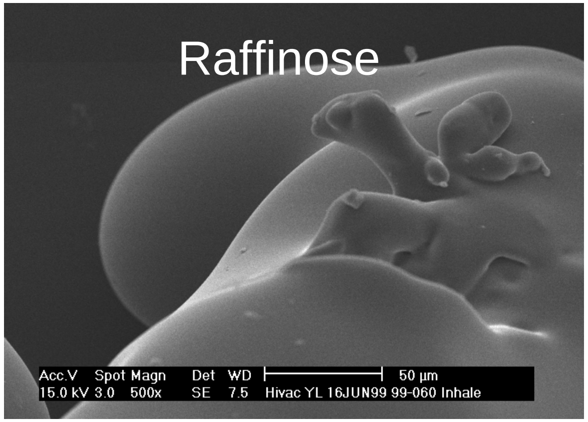
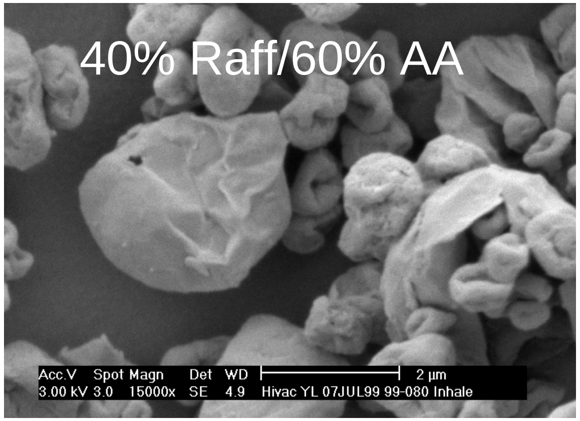
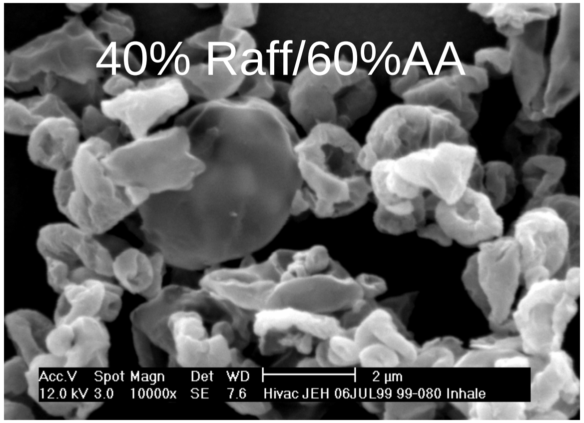
Glass stabilization with a high Tg amino acid



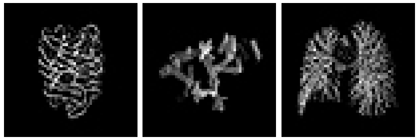






Spray dried and kept dry

After exposure at RH = 50% for 4 hours



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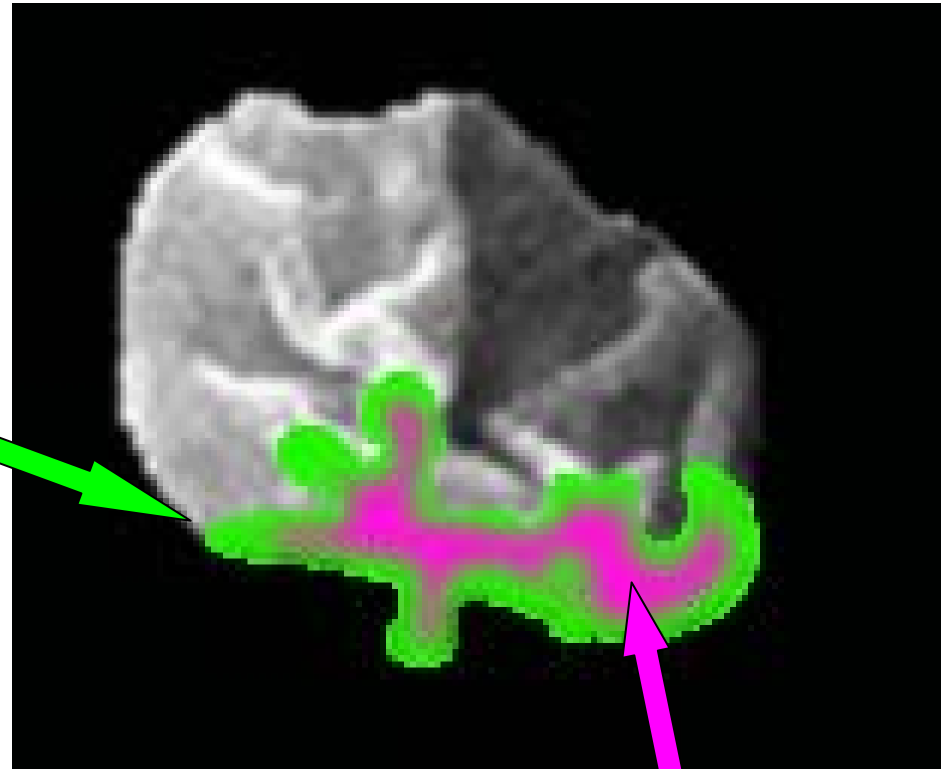
Stabilization by particle engineering - Encapsulation

Shell:

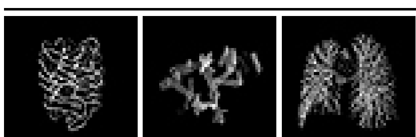
Dispersibility enhancers

-Tri-peptides
-Amino acids
-Lipids

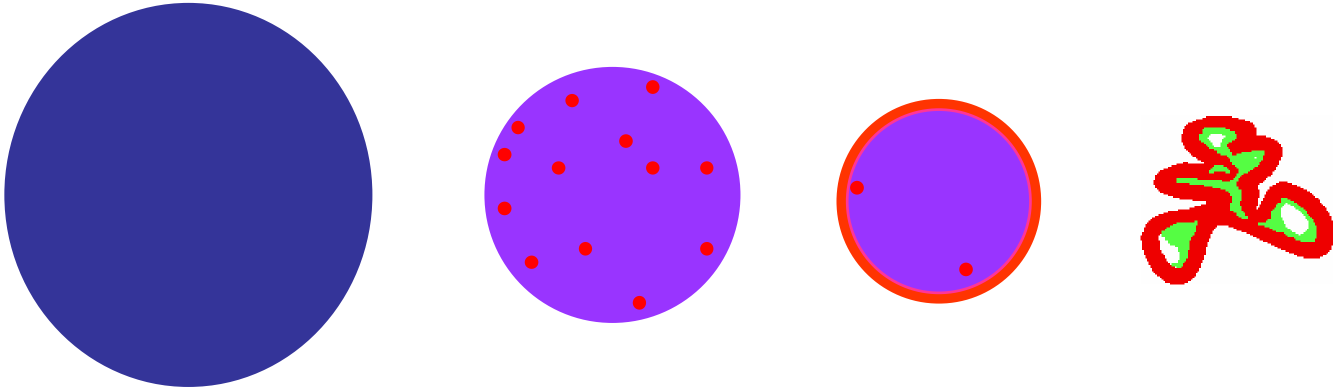


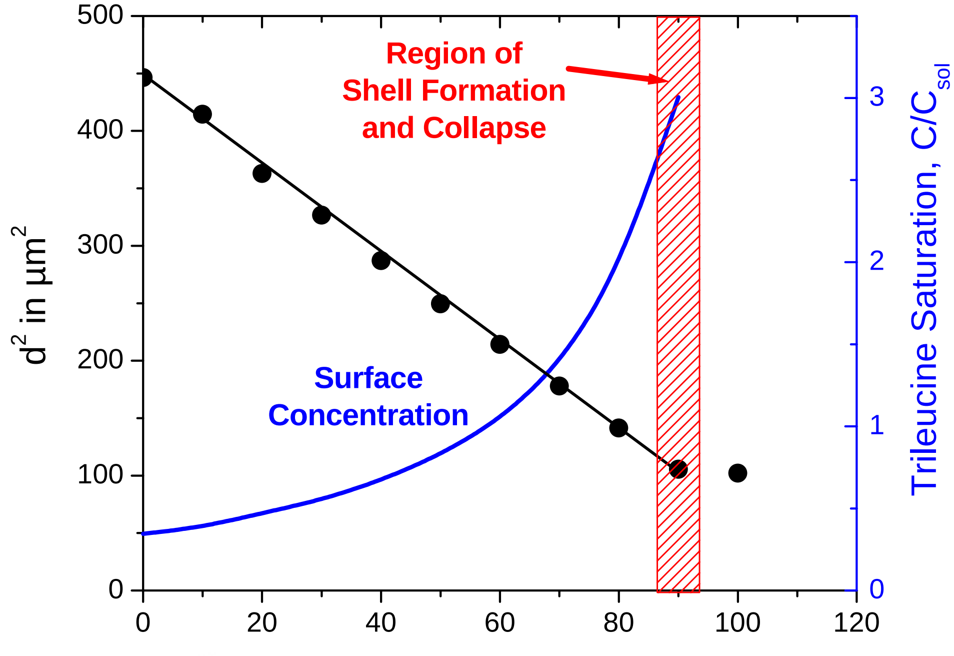
Core:

Protein – Protein stabilizer – Glass stabilizer

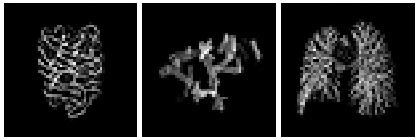


Mechanism of encapsulation





Numerical model in combination with experimental data allows predictions of the required amount of excipient for encapsulation



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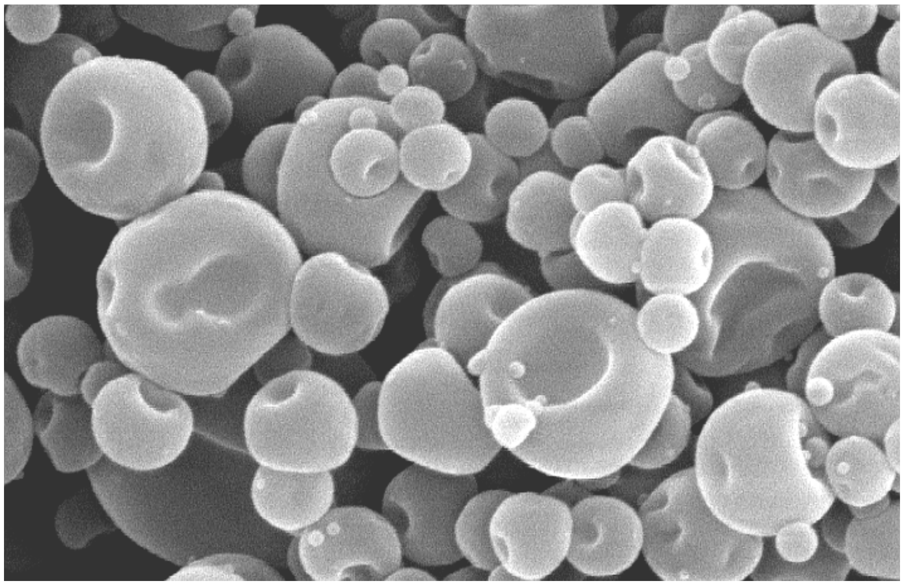
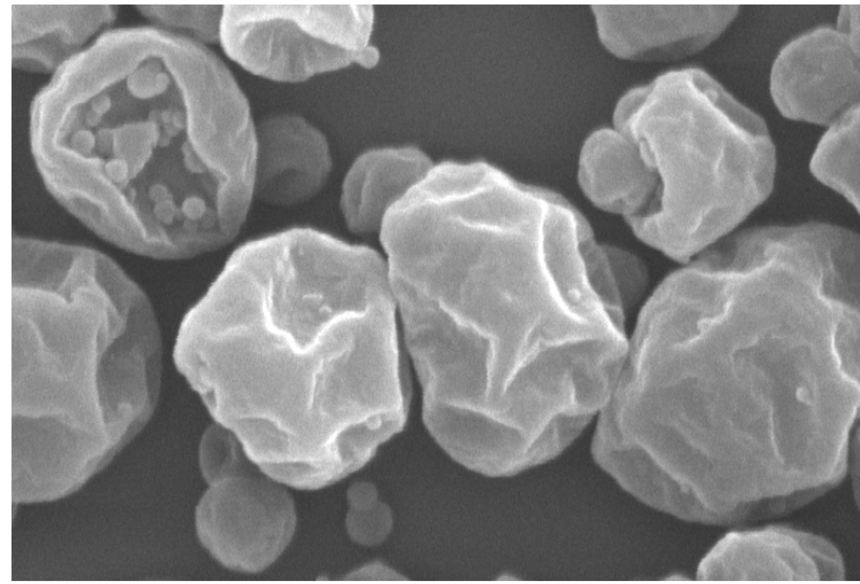
Successful encapsulation of a model molecule

Spray-dried from a co-solvent system:

100 % PVP K17



90 % PVP, 10 % Amino Acid



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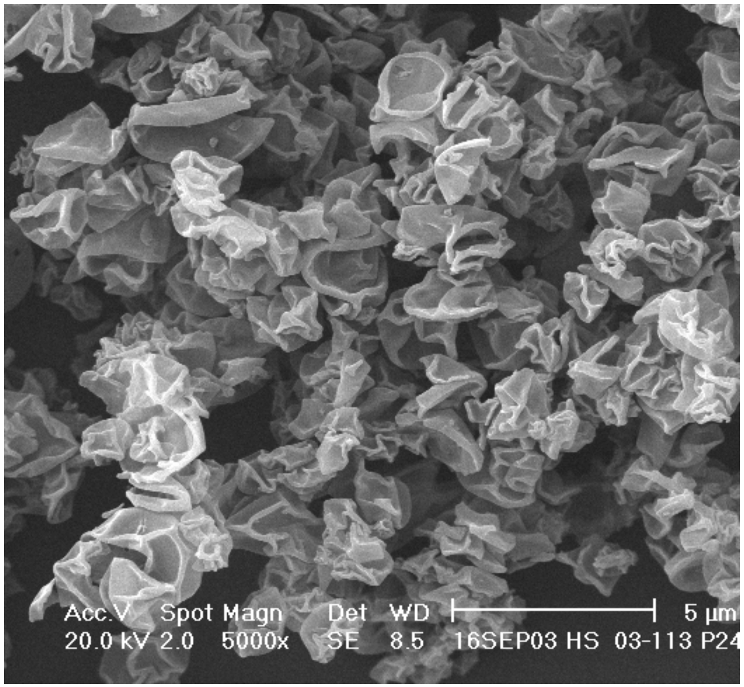
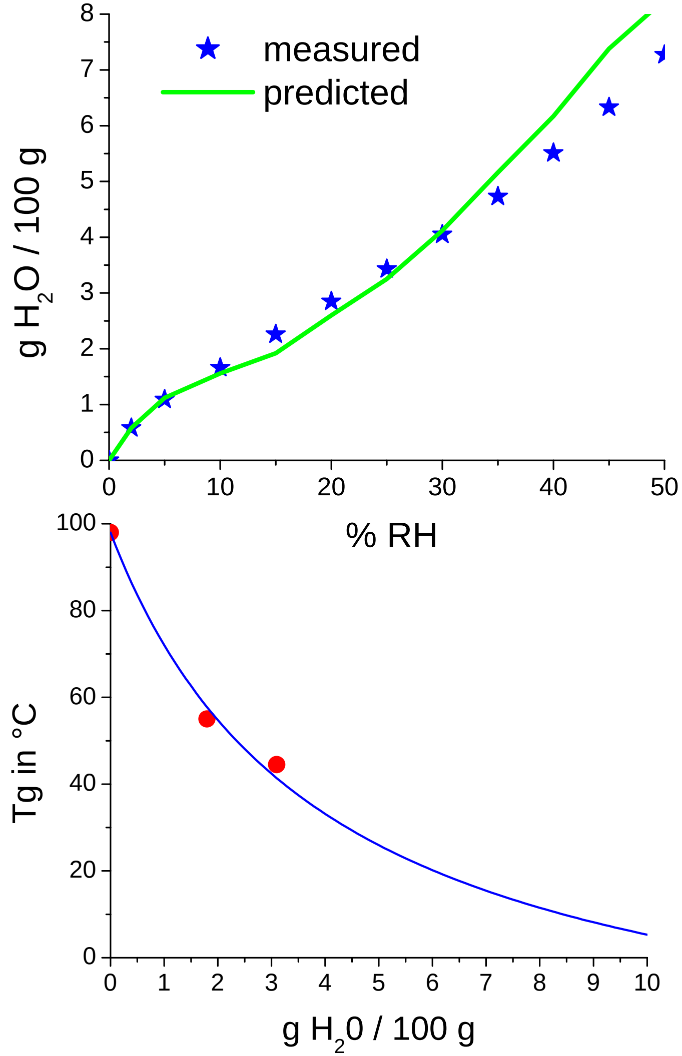
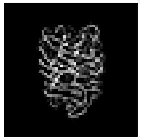
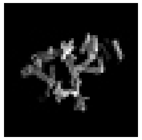
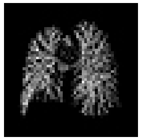
Protection by encapsulation





Plasticized core protected by a shell

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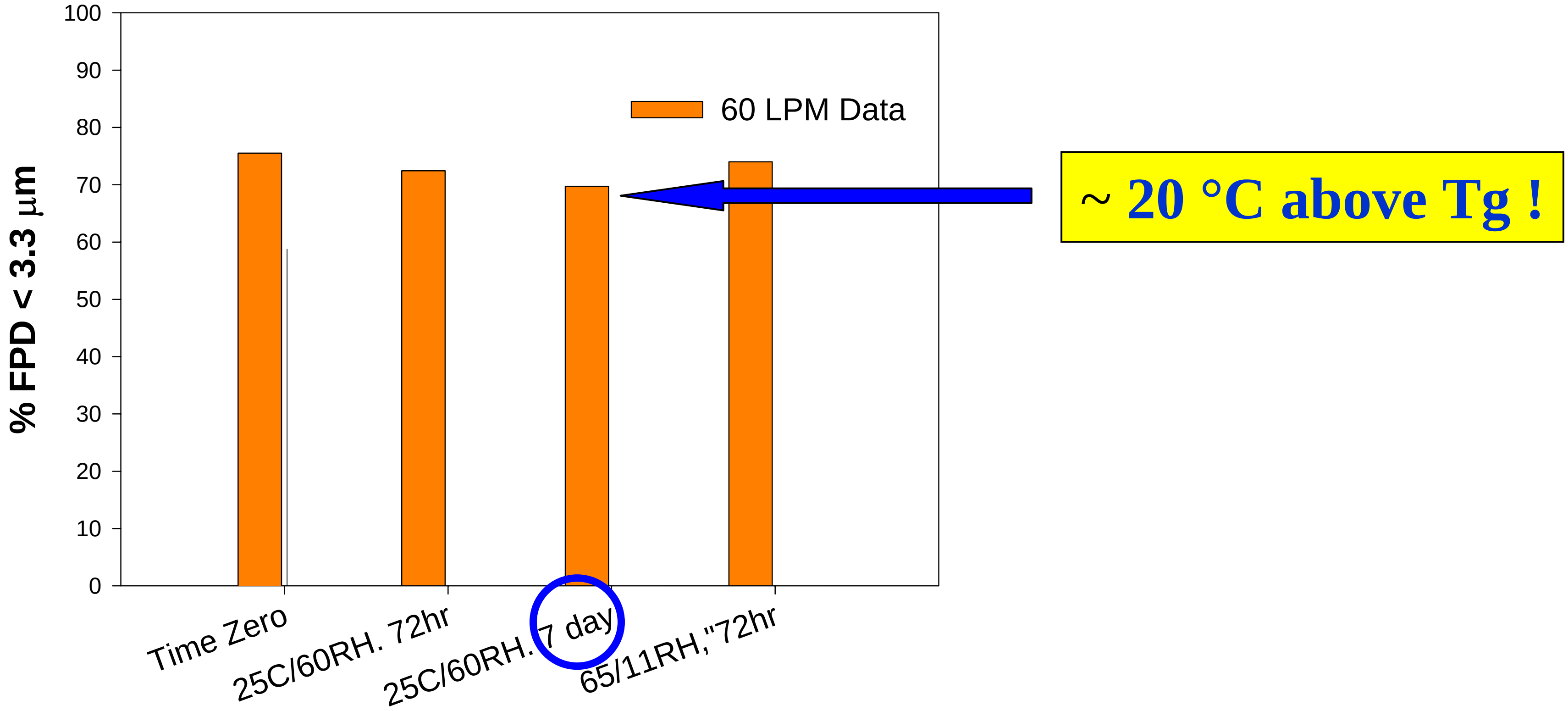
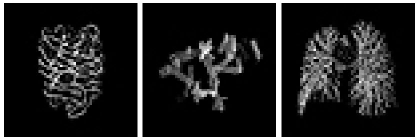
Excellent out-of-package stability

56 % Encapsulation excipient, 20 % Saccharide
20 % low Tg API, 4 % organic salt

Lot 3909- 67





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Conclusion and outlook

- Glass stabilization enhances the stability of protein and peptide formulations and provides room temperature stable products in most cases
- Predictive tools for the design of packaging configurations, processing conditions, and formulation compositions allow rapid development and optimal product performance
- New excipients and particle engineering approaches show the potential for designing highly stable dry powders, further reducing device and packaging cost.