The Scientific Basis of QbD

Developing a Scientifically Sound Formulation and Optimizing the Lyophilization Process

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What is Quality by Design?

- **ICH Q8(R):** ***A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management***
- **Quality should be built into the product**
  - **Testing alone cannot be relied on to ensure product quality**
- **Understanding and controlling formulation and manufacturing process variables affecting the quality of a drug product**

Elements of Quality by Design

- Use of Prior Knowledge
  - GFDP "Good Freeze Drying Practice"
  - Preliminary, "scope of problem" experiments
- Use of a formalized risk assessment process
- Due diligence to find "edges of failure"
- Definition of Formulation and Process Design Space
  - using accepted "theory" and generalizations from prior experiments
  - information from "new" experiments

What is "Design Space"?

- (FDA): The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.
  - Working within the design space is not considered as a change.
  - Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process.
  - Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).

Some Quality Attributes for Freeze Drying-not all Critical

- Sterility-critical
- Low endotoxin-critical
- Stability-critical
  - adequate potency
  - absence of toxic degradation products
- Rapid and easy reconstitution
- Cost effective process (i.e., fast)
- Fast development process (speed to market)
- "Elegance"
  - "beauty is in the eye of the beholder"

  • Note: some are impacted by formulation, some by process, and many by both formulation & process

Preliminary Experiment to Assess Magnitude of Problems and Risk

EXAMPLE: Preliminary Freeze Drying Run with recombinant Factor VIII

• Evaluate: two API concentrations (w 8% mannitol) and with Sucrose
  -loss on freezing
  -loss on holding frozen below Tg' and above Tg'
  -loss on drying
  -stability during storage at 40°C

Processing protocol, or step	*% Loss of rAHF activity during step or rate constant*		
	Solution A, 600 IU/mL	Solution B 60 IU/mL	Solution C, 60 IU/mL, with Sucrose
Freezing	3	35	39
Frozen hold at -35°C	2	9	4
Frozen hold at -35°C and -20°C	7	12	5
Drying	20	24	18
Storage Dry Solid @ 40°C, rate constant (k)	1.34±0.16	1.85±0.17	0.45±0.05

Basic Elements of Risk Analysis

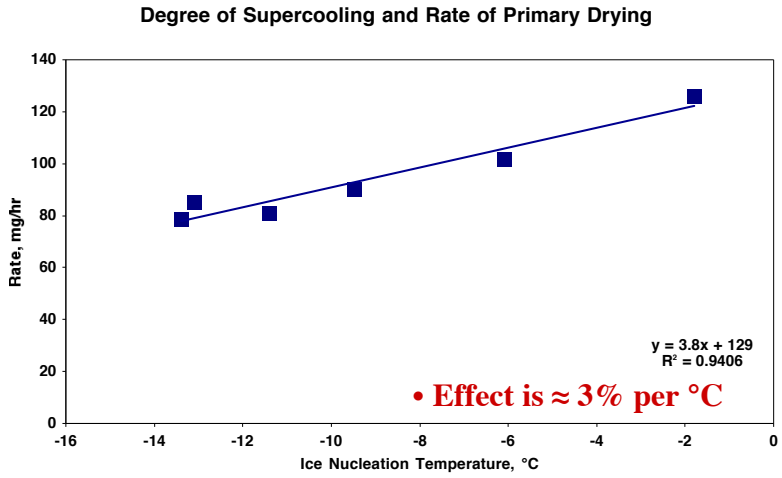
- Define Target Product Profile (TPP)
- Identify aspects of formulation and process that put achieving TPP at risk
  - which are critical, and which are only "desirable"
    - i.e., what is consequence of failure?
- From Prior knowledge, or preliminary experiments, assess Probability of Failure
- If seriousness of failure score multiplied by probability of failure is "high", generally need careful investigation, if not…
  - invoke general rules of GFDP

Keys to Quality Process Design

- Freezing
  - Control the ice nucleation temperature
    - Failure means in-process variation and major scale-up differences
- Primary Drying: Control Product Temperature
  - Normally, a safe margin below the collapse temperature
    - Need to know the collapse temperature
    - Sometimes it is OK to freeze dry above the collapse temperature
- Secondary Drying
  - Residual moisture nearly constant after ≈6 hrs at given temperature
  - Use temperatures well above ambient
    - No harm to product as long as have low moisture when temperature is high.

More Supercooling Means Slower Drying

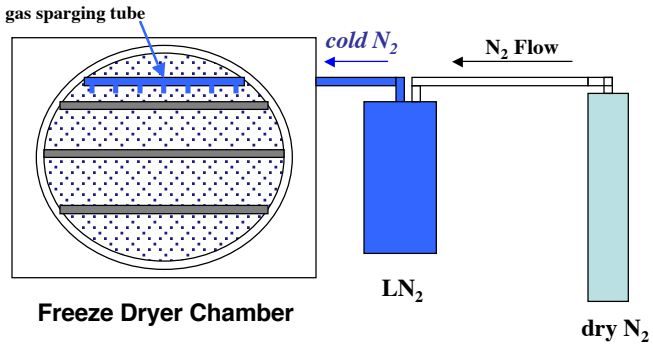
Data From: Searles, et. al., J. Pharm. Sci., 90(7), 2001



Ice Nucleation is Scale-Up Issue

- **Observation**: In laboratory, supercooling much less than in manufacturing (non-TC vials)
  - lower level of ice-nucleating particulates in manufacturing
- **Result:** product runs warmer (≈1-2°C) and 1° drying is longer (≈10-30%) in manufacturing!
- **Solutions:**
  - Set shelf colder (≈3°C) in manufacturing and run ***about*** 30% longer in 1° drying.
    - However, this is "Design by Guess" and "QbA-Quality by Accident"
  - Anneal to increase size of ice crystals and decrease difference between lab and production.
  - Nucleate by "ice-fog" or "depressurization" to fix degree of super-cooling

Nucleation via an Ice Fog

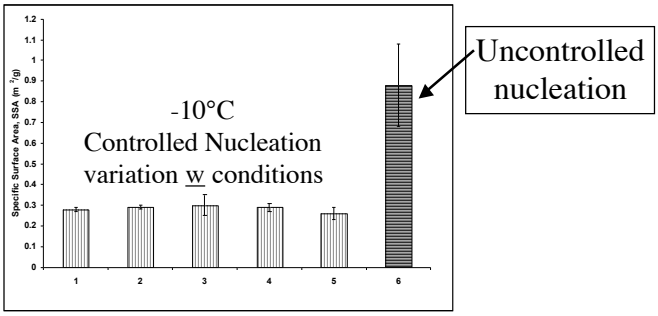


1. Super-Cool product to desired nucleation temperature, but without freezing. Chamber is *Humid* at this point!

2. Reduce pressure, flow nitrogen into freeze dryer, and distribute through sparging tube.

3. Ice forms when cold N_2 hits the humid air in the chamber, ice is pushed into the vials, and ice crystal growth starts.

Sucrose Specific Surface Area (SSA)



Specific surface area with standard deviation bars (n=3) for 5% and 10% sucrose solution for different fill volume and load condition.

KEY: 1: 10% Sucrose, 1 Shelf, 4mL; 2: 10% Sucrose, 1 Shelf, 2mL; 3: 5% Sucrose, 1 Shelf, 4mL; 4: 5% Sucrose, 3 Shelf, 4mL; 5: 5% Sucrose, 1 Shelf, 2mL; 6: 5% Sucrose, 1 Shelf, 5mL fill *without ice fog.*

Note: much smaller (and uniform) stdev bars with ice fog!

Nucleation via Depressurization:

The Praxair Technique

- Novel, patent-pending approach to uniformly and instantaneously induce nucleation within a freeze-dryer via pressurization and depressurization

- Process steps:
  1. Load containers and seal freeze-dryer
  2. Pressurize with inert gas
  3. Cool shelf and containers to target nucleation temperature
  4. Depressurize to induce nucleation
  5. Reduce shelf temperature to complete freezing

- Implementation
  - Simple, low capital retrofit for SIP-rated freeze-dryers
  - Freeze-dryer can operate with or without nucleation control
  - No contaminants or changes to drug formulation

Video of Ice Nucleation

courtesy of Praxair

1. Uncontrolled Nucleation

Nucleation over long time and over large temperature range.

2. Controlled Nucleation

Near instantaneous nucleation, at fixed temperature (-5°)

Guidelines for Primary Drying

- Run ≈ "constant" product temperature 2°-5° below collapse temperature; this is the TARGET PRODUCT TEMPERATURE
  - -must know what collapse temperature is
    - -Freeze Drying Microscopy
    - -Better to use Optical Coherent Tomography (see K. Greco)

- Maintain chamber pressure 10-30% of P(H2O)
  - near upper limit of 30% for low collapse temperature (i.e., ≈ -30°C)
  - near lower limit of 10% for high collapse temperature (i.e., ≈ -15°C)

- Heat input must decrease with time to hold at "target" product temperature
  - may often tolerate small (i.e., 2°C-3°C) increase in product temperature
    - if so, maintain constant heat input for simplicity in process design
  - if need to hold constant product temperature, must decrease heat input
    - decrease shelf temperature or decrease chamber pressure

- Determine shelf temperature vs time program (by experiment or calculation)
  - Do experiments: use fill volume and containers of interest!
  - Find appropriate shelf temperature to maintain target product temperature

Simple Steady State Heat and Mass Transfer Theory is Useful in Process Design

- "What if" calculations, for impact of variation in shelf temperature and chamber pressure!
- Design Space Evaluation
  - Scale-Up Calculations
  - Robustness Testing (edge of failure)
- As accurate as experiment!

Simple Steady State Heat and Mass Transfer Theory

Mass Transfer : $\frac{dm}{dt} = A_p \frac{(P_0(T) - P_c)}{\hat{R}_{ps}}$; $\ln P_0 = \frac{-6144.96}{T} + 24.01849$

Heat Transfer : $\frac{dQ}{dt} = A_v \cdot K_v(P_c) \cdot (T_s - T - \Delta T)$; $\Delta T \rightarrow$ function of dm/dt

Coupling : $\frac{dQ}{dt} = \Delta \overline{H}_s \cdot \frac{dm}{dt}$

$$\frac{\Delta \overline{H}_s (A_p / A_v) \cdot (P_0(T) - P_c)}{\hat{R}_{ps}} - K_v(T_s - T - \Delta T) = 0$$

- One Equation, one unknown (T): Solve for T, get dm/dt. and then calculate drying time- Basis of the "Lyo-Calculator"

Experiment and Calculations Agree Well: Blue = Exp., Red = Calc.

Product 5% w/w	*Vial*	*Fill cc*	*Shelf, interior, °C*	*P_c, Torr*	*1° Drying Time, hr*	*Shelf Surface, T_s*	*Mean T_p*	*Max T_p*
PVP	W5816	8	-5	0.1	25.8	-9.6	-27.8	-25.3
					26.9	-9.9	-27.3	-24.6
Mannitol	W5816	8	-5	0.1	33.4	-8.6	-22.4	-20.2
					34.8	-8.9	-22.9	-18.5
Mannitol	W5816	8	+15	0.1	19.2	+6.2	-17.0	-14.2
					19.1	+8.0	-17.0	-11.8
Mannitol	W5816	8	+15	0.4	14.0	+5.7	-13.0	-11.9
					15.8	+6.6	-11.8	-8.0
Mannitol	5303	20	+15	0.4	19.2	+6.1	-14.5	-12.8
					19.0	+8.1	-13.5	-9.7

OLD METHODOLGY: M. Pikal, PDA Journal, 39, 115-138 (1985)

Now available as "Lyo-Calculator"

Role of "Design of Experiments" (DOE) in Primary Drying Design

- **Virtually, no role at all**
  - DOE is useful when mechanistic understanding is poor
  - The physics of primary drying is well understood (i.e. "Lyo-Calculator)
- **General statistics dogma: DOE is an efficient way to generate a "response surface" (or Design Space)**
  - Not true for freeze drying in general, and is very inefficient for primary drying.

DOE: Box-Behnken Design

Independent variables: (3) chamber Pressure, shelf temperature, Ice nucleation temperature

Responses: (3) 1° drying time (hr), mean product temp. maximum product temp in 1° drying, sublimation rate

Exp. #	Pattern	Pchamber	T shelf	Ice Nucl. Temp	1° dry hr	Tp mean	Tp(max)	mean dm/dt
1	/+−0	0.4	-5	-12.5	33.9	-18.7	-15.1	0.228
2	/0−+	0.25	-5	-5	31.4	-21.3	-17.2	0.246
3	/++0	0.4	15	-12.5	16	-13.8	-8.2	0.483
4	/−−0	0.1	-5	-12.5	35.5	-23.6	-18.6	0.218
5	/000	0.25	5	-12.5	22.1	-17.8	-12.6	0.350
6	/0+−	0.25	15	-20	17.3	-14.4	-8.2	0.447
7	/−+0	0.1	15	-12.5	19.4	-18.4	-11.8	0.398
8	/0−−	0.25	-5	-20	35	-19.9	-15.6	0.221
9	/−0−	0.1	5	-20	26.4	-19.8	-13.8	0.293
10	/000	0.25	5	-12.5	22.4	-18.3	-13.4	0.345
11	/+0+	0.4	5	-5	21.1	-16.8	-12.3	0.366
12	/+0−	0.4	5	-20	23	-15.2	-10.4	0.336
13	/000	0.25	5	-12.5	21.2	-17.2	-12	0.365
14	/0++	0.25	15	-5	16.1	-16.5	-10.6	0.480
15	/−0+	0.1	5	-5	24.1	-21.9	-16.1	0.321

- **15 freeze drying experiments, average 2 days per experiment---> 30 days run time**
- **Physics Driven: do runs in green, 4 runs--> 8 days**

Using Physics

- **Vial Heat Transfer Coefficients**
  - **Previously determined for all vials used by company, vs. Pressure-3 days required for each vial type**
- **Dry Layer Resistance- 4 experiments!**
  - **Unique to formulation and ice nucleation temperature**
  - **Need runs at three ice nucleation temperatures**
    - **See GREEN on previous slide**
      - **Rp evaluated from MTM data and/or cycle product temperatures.**
  - **Prudent to do one of the runs that give high product temperature to compare with center point temp.**
    - **Provides two replicate runs for Rp @ center point ice nucl.**
    - **Provides validation of calculations in extreme case**
      - **Resistance normally independent of temperature, but not near collapse temperature!**

- **Total Run Time of 8 days, save 22 d, $66MM**

DOE: Central Composite Design

- Independent variables:(2) chamber pressure and shelf temperature (ice nucleation temperature fixed)
- Responses:(3) 1° dry time, max product temp., minimum controllable pressure (Torr)

Exp. #	Pattern	Pchamber	T shelf	1° dry hours	Tp(max)	Pmin
1	/A0	0.25	10	19.1	-10.9	0.059
2	/0A	0.15	25	14.3	-8.2	0.082
3	/++	0.25	25	13.1	-6.7	0.092
4	/00	0.15	10	20.5	-12.3	0.056
5	/0a	0.15	-5	33.9	-17.6	0.053
6	/−−	0.05	-5	39.1	-20.1	0.036
7	/00	0.15	10	21	-13	0.056
8	/+−	0.25	-5	33.1	-16.4	0.039
9	/a0	0.05	10	25.1	-15	0.046
10	/−+	0.05	25	18.1	-11.1	0.061

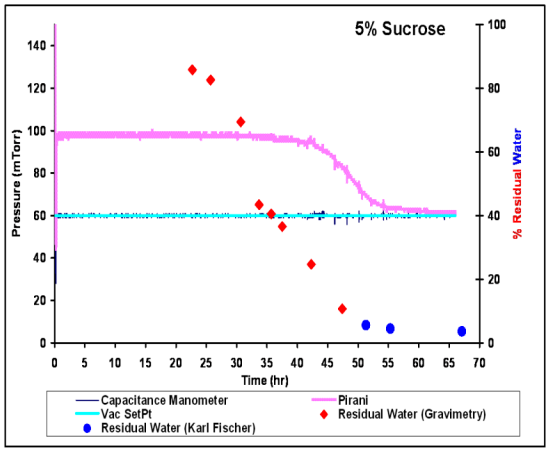
Physics Driven

- Three runs (in green) to evaluate dry layer Resistance.
- Savings of 14 days, $42MM
- Also can predict other variations beyond selected range

PAT in Freeze Drying

Determination of End Point of 1° Drying

Pirani Pressure



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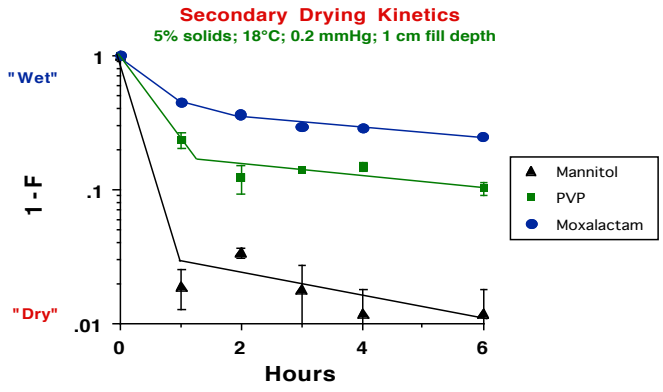
Secondary Drying:
Water Desorption in Secondary Drying

- Water in Amorphous Phase Must Decrease from about 25% to "dryness" of <1%
- Rate is fast at first, but slows greatly later as the product dries
- Much faster at higher temperature
  - usually use temperatures between 25°C and 50°C
- How fast depends on product
  - dilute solutions are moderately fast (high surface area), but concentrated solutions (i.e., >10% solids) are often slow.
- How fast does NOT depend on chamber pressure (at least in range below 0.2 Torr)
  - rate determining step is diffusion in solid and/or evaporation at solid:vapor boundary

Drying Kinetics are Highly Non-Linear

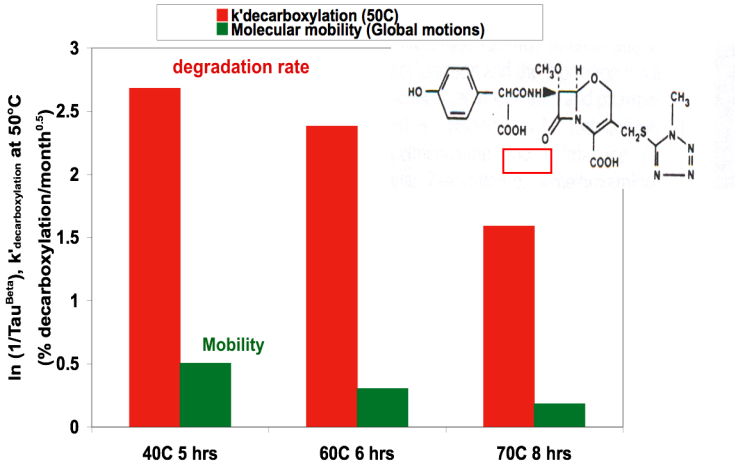
1-F = fraction of initial water content



Effects of Thermal History: Annealing a Glass

- Hold sample at T<Tg for given time(s)
- Energy decreases,
- Structure Increases,
- Free volume decreases,
- Relaxation time increases,
- If relaxation dynamics is a predictor of pharmaceutical stability,
  - Much evidence suggest it is, so…
- **Stability improves!**
- **Lesson: HIGH SECONDARY DRYING TEMPERATURE MAY STABILIZE!**

The Annealing Effect for Moxalactam Disodium

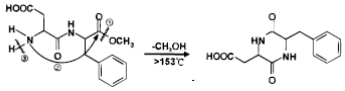


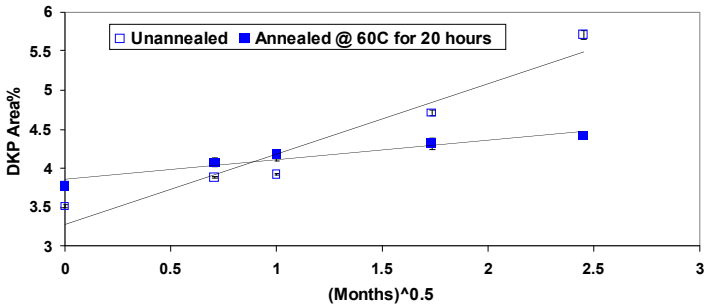
Annealing decreases mobility (enthalpy relaxation) and decreases Degradation rate: "HIGH TEMPERATURE Stabilizes"

Annealing Can Improve Purity at end of Storage

Appearance of DKP Degradation Product as a function of time at 50°C storage temperature.

Aspartame: sucrose (1:10) formulation





Good Freeze Drying Practice (GFDP)

General Rules for Formulation

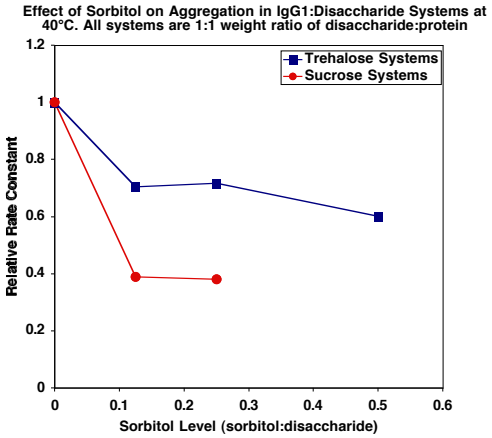
- **Minimize amount of buffer**
- **Avoid high levels of salts**
  - Recent data suggest low levels may stabilize!
- **Maximize Collapse Temperature**
  - Without crystalline bulking agent, need to keep $T_p < T_c$
  - Exceeding T_c does not always damage product quality!
    - Check to see the impact on quality
- **With proteins, add stabilizer**
  - sucrose or trehalose
- **With good stability and low dose drug**
  - use bulking agent: mannitol (or) glycine

Levels of Bulking Agent and Stabilizer

- **Principles**
  - Total solids: ≥ 3% but ≤10% for ease of drying & good cake
  - Stabilizer:drug weight ratio: 1:1 to 10:1
  - Bulking agent
    - to allow crystallization: 3:1 weight ratio of bulking agent to other (amorphous) components
- **Low Dose Drug**
  - possible use of both bulking agent and stabilizer
    - more robust formulation
- **High Dose Drug**
  - use of stabilizer limited by total solids constraint

Addition of Small Amount of "Small Molecule" Stabilizes

Stability of an IgG1 Antibody at 50°C in Disaccharide Based Systems



- **Small amounts of sorbitol (and other small molecules) stabilize!: WHY???**

Role of DOE in Formulation Design

- **Can be useful in screening and optimization, however…**
  - **Choose your formulation components and ranges based on prior knowledge (GFDP)**
    - **Much knowledge has been gained over the past two decades.**
  - **Beware of non-linearity**
  - **Beware that effects impacted by component crystallization may not reproduce well (or scale-up well)**

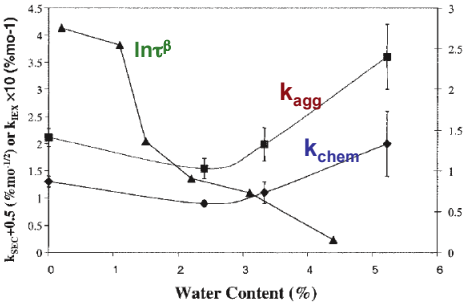
The Natural World is often Neither Linear nor Monotonic

Choose your ranges with care!

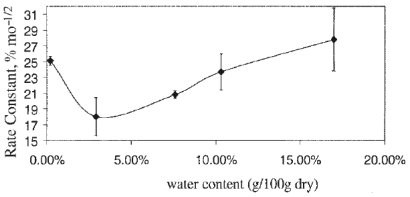
Non-Linearity in Residual Water Impact

The Effect of Residual Water on Storage Stability of an IgG1 MAB at 50°C

Protein:Sucrose 1:1



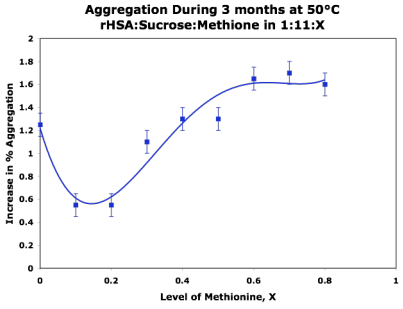
Pure Protein

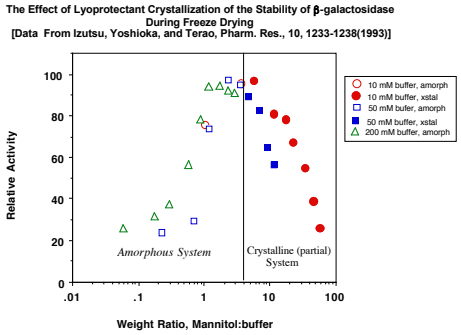


Note: error bars are standard errors estimated from the fit, and are unusually large in some cases due to marginal quality of the fit. The same trends are obtained using % degradation at a given time point.

- **Seems to be minimum in degradation rate at "intermediate" water content,… anti-plasticization?**

Non-Linear Formulation Effects





- **T_g is decreased**
- **Role of "Fast Dynamics"**
  - **small amount "anti-plasticizes**
- **mannitol crystallizes**
- **crystalline not effective as stabilizer**