New Horizons in Accelerated Stability Modeling-- Tablet Dissolution, Tablet Disintegration and Product Appearance

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Part I: Accelerated Dissolution Stability Determination

Can dissolution changes with time be modeled in an accelerated process?

Solid Dosage Forms

1. Immediate release tablets
2. Capsules
3. Controlled release tablets
    a. Hydrophilic matrix tablets
    b. Coated beads

Solid Dosage Forms

1. **Immediate release tablets**
2. Capsules
3. Controlled release tablets
    a. Hydrophilic matrix tablets
    b. Coated beads

Dissolution Testing

- Stage 1: 6 tablets tested, all >Q+5%
- Stage 2: additional 6 tablets tested; average (of 12) > Q; all tablets >Q-15%
- Stage 3: 12 more tablets tested; average (of 24) >Q; <3 tablets have <Q-15%; 0 tablets <Q-25%

Notes About Stage 1 and Variability

- Many Stage 1 dissolution failures observed on stability studies
- Very few Stage 2 dissolution failures observed

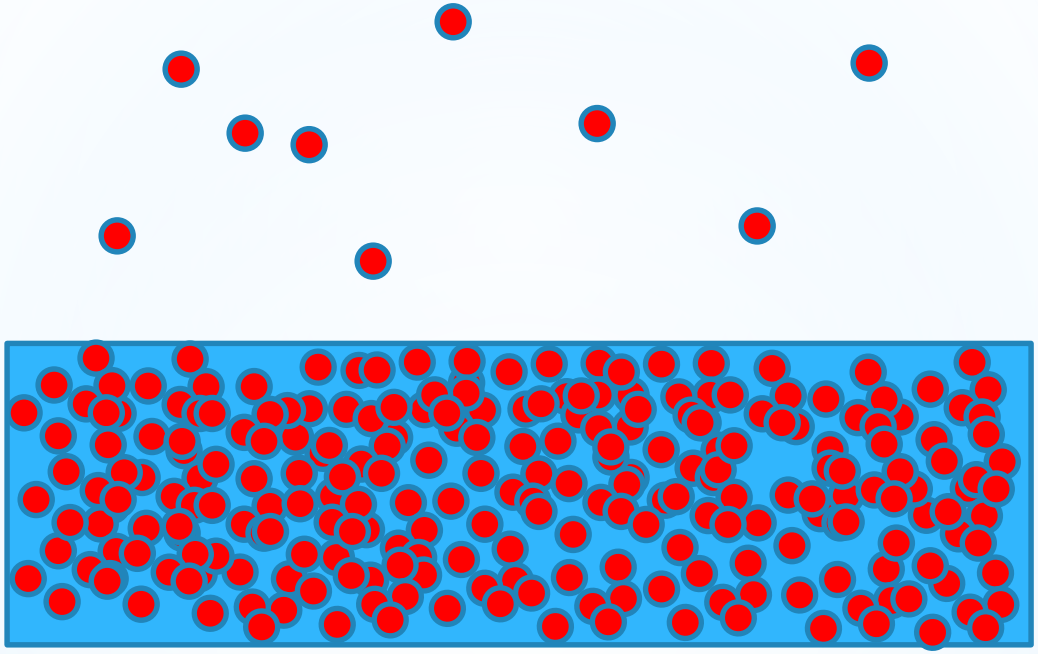
- Stage 1 dissolution requires all 6 tablets have Q+5
- If potency of lot is low, content uniformity leads to random failures (predictably)
- If any loss of potency, makes matters worse (predictably)
- Variability much less likely to cause Stage 2 failure
- Stage 1 failures on stability often investigated, yet not reflective of any dissolution instability!

Notes About Stage 1 and Variability

- ***Example***:
  - Q = 75% (at time *t*)
  - Tablet dissolution variability (content uniformity + measurement variability) = 5%
  - Average amount dissolved at *t* = 95% (for lot with 100% potency)
  - Example lot potency (average) = 97%

  - **Probability of failing Stage 1: 4.4%**
  - **Probability of failing Stage 2: <0.001%**

Critical Relative Humidity (CRH)



Entropy high

Entropy low

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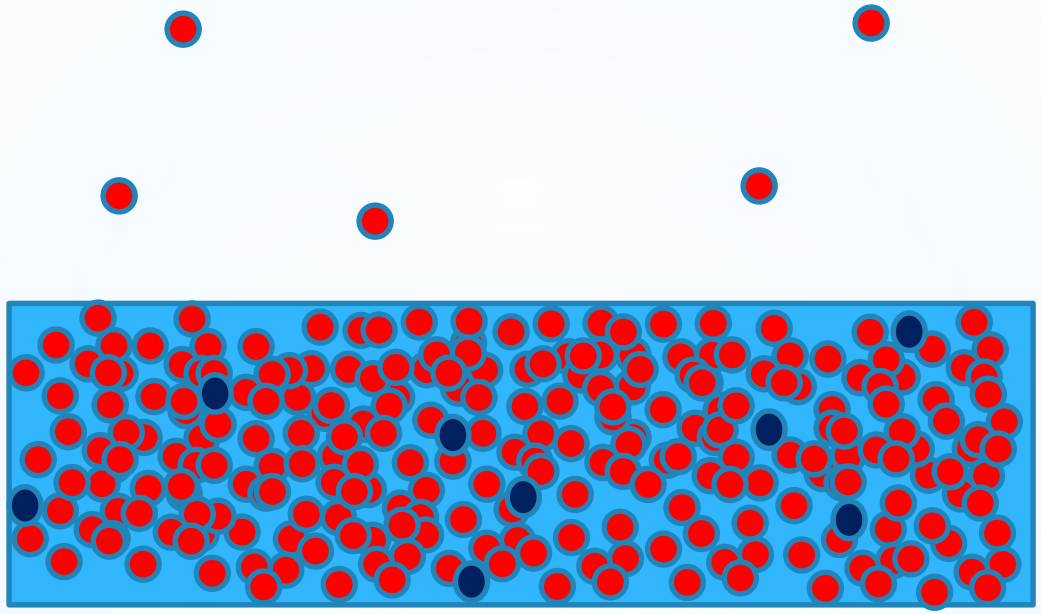
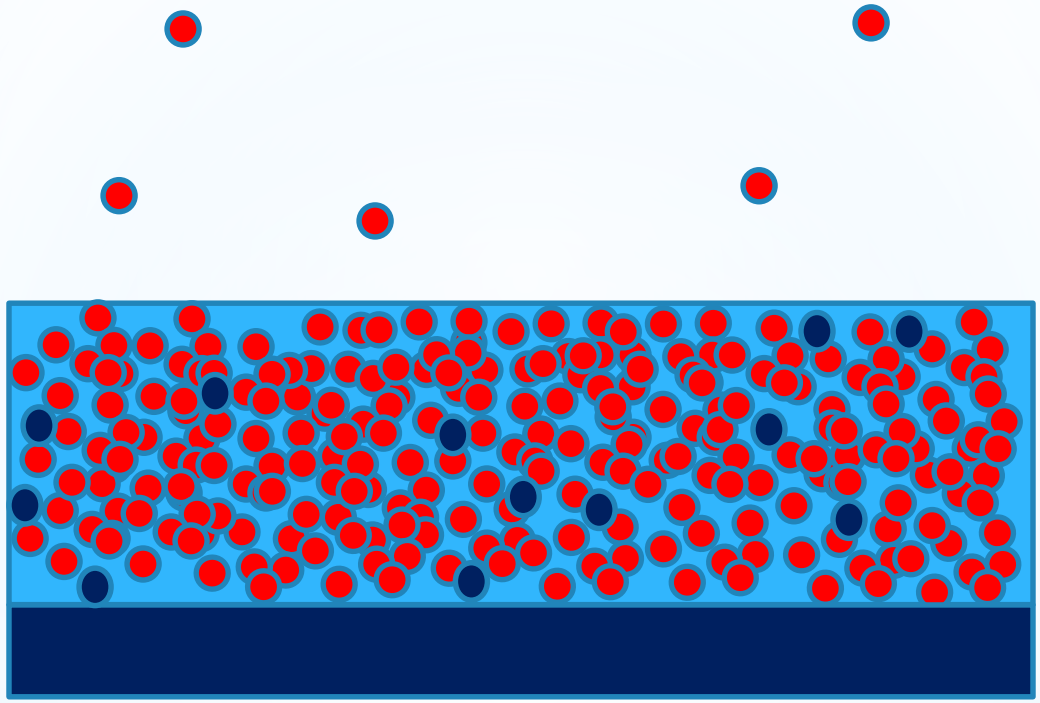
Critical Relative Humidity (CRH)



Entropy increases

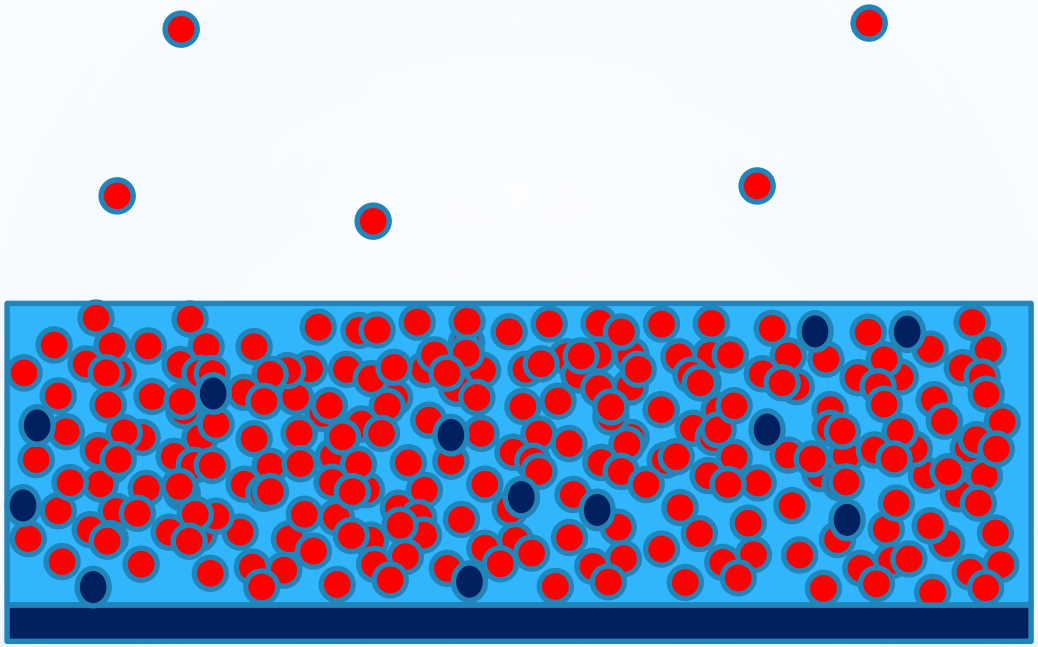
Dissolved solute increases entropy: decreases advantage of going into vapor phase. Result: saturated vapor pressure in air reduced

Critical Relative Humidity (CRH)



Saturated solution (i.e., when solid present at equilibrium with its solution) has a single activity (entropy and enthalpy)
Air above has a single partial pressure of water (saturated, but lower than that above pure water)

Critical Relative Humidity (CRH)



If more water added, more solute dissolves, but concentration remains saturated therefore vapor pressure remains saturated

Critical Relative Humidity (CRH)

- If solid placed in air at RH > CRH, condensation (deliquescence) will occur since above water's saturation partial pressure (though not above that over pure water)
- Deliquescence is not absorption: liquid water is condensed from the air
- CRH is a sharp point: below this RH, not saturated so no condensation occurs
- Ability to lower the partial pressure of saturated air depends on ability to raise entropy of liquid water solution
  - Only depends on moles of species in solution
  - Will change with temperature if saturated solubility changes
  - Note, most compounds increase solubility as a function of temperature

Critical Relative Humidity (CRH) and Dissolution

- Many tablets will dramatically change dissolution after deliquescence
- Packaging and storage conditions will predict when this abrupt transition occurs
- Can use ASAP*prime*® to determine shelf-life: time before deliquescence occurs

Example Issue

- NaCl 75%RH (40°C)
- Sorbitol 69%RH (40°C)
- Fructose 64%RH (40°C)

Note

- Some polymers behave like deliquescing materials even when not technically dissolving: sections of the polymer “dissolve” to alter water’s entropy and lower CRH

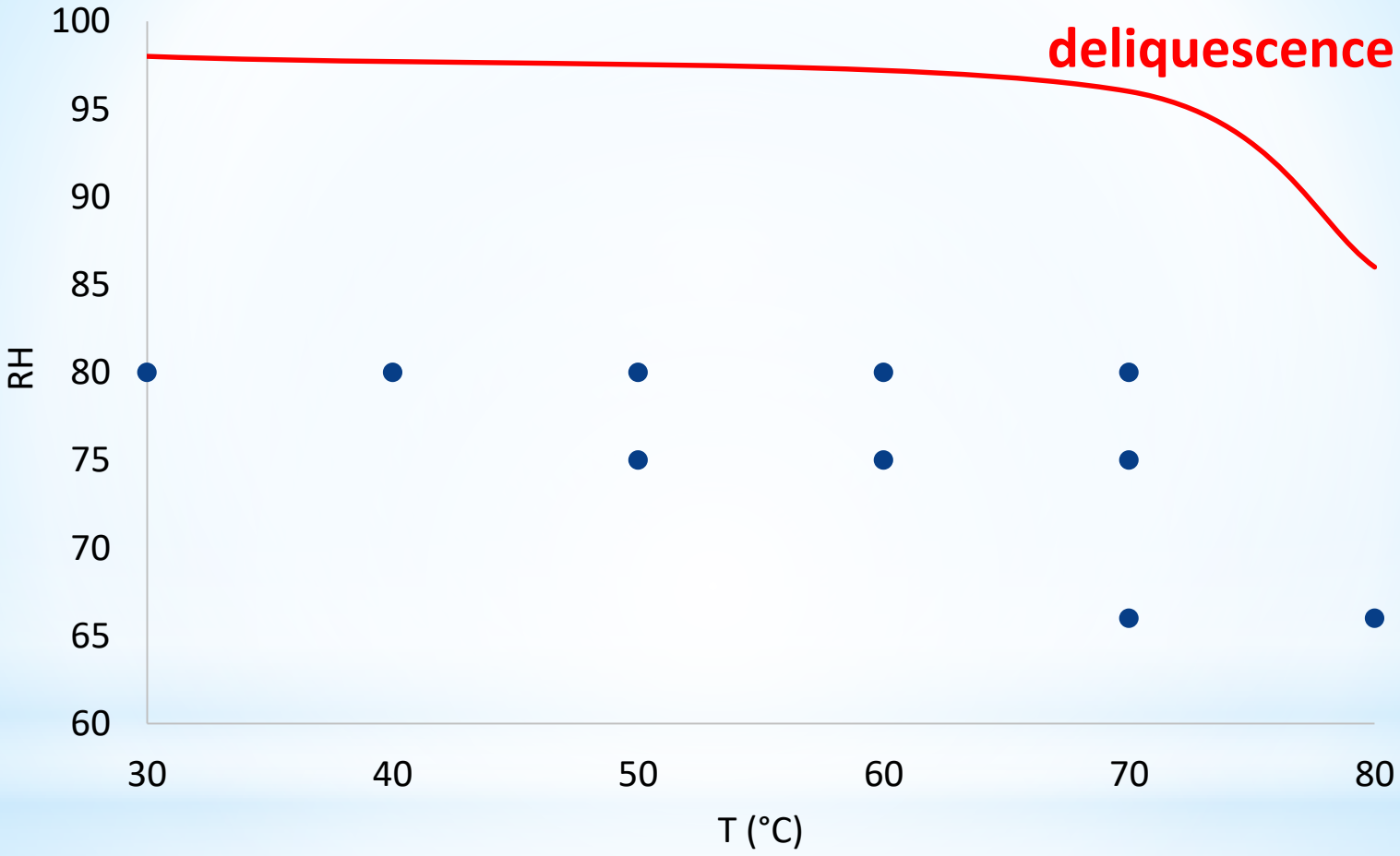
- Example: croscarmellose sodium

Immediate Release Tablet Dissolution Stability when Storage <CRH

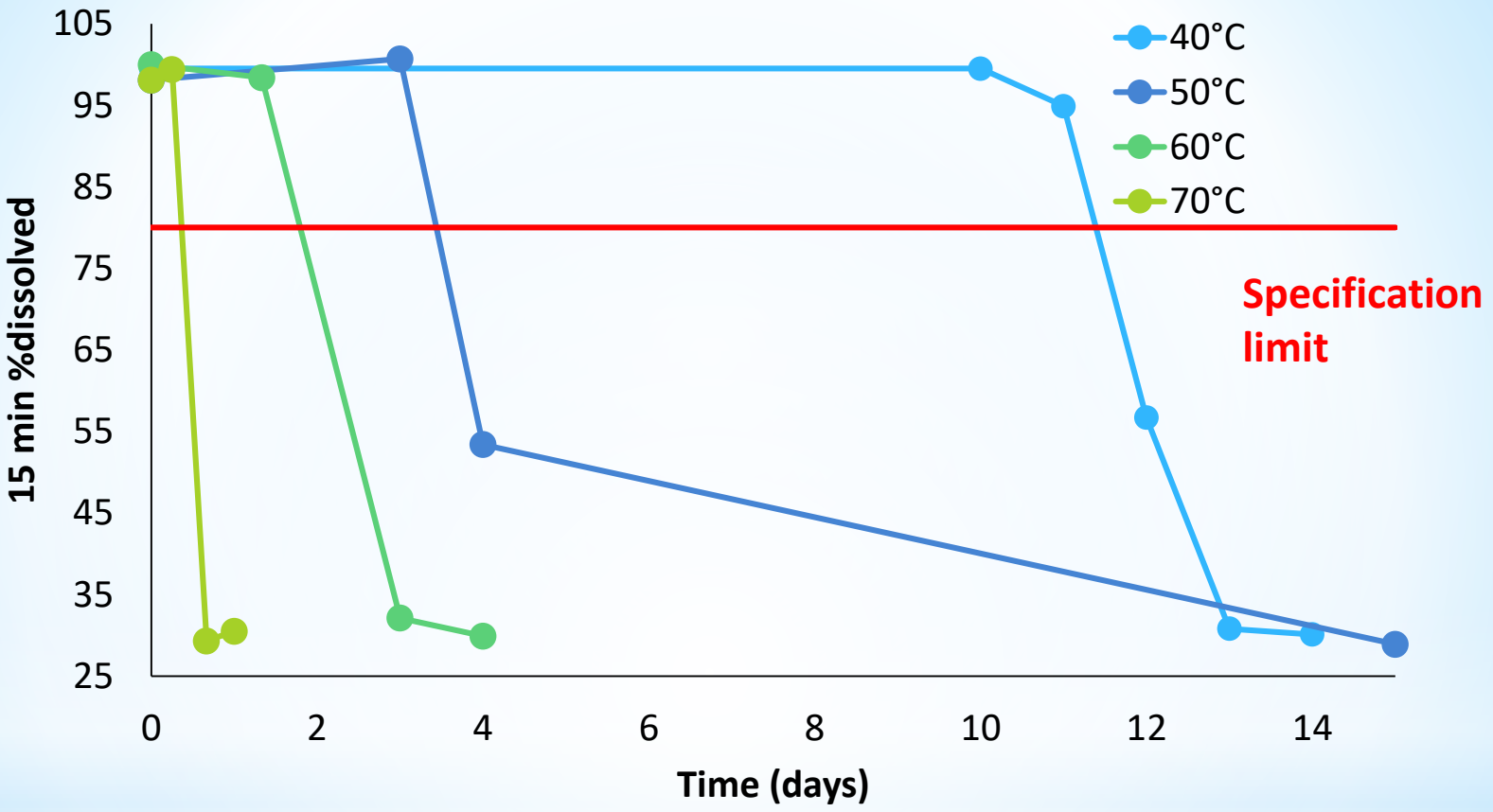
Step 1: Critical Relative Humidity (CRH) Screen

- Screen for deliquescence point (CRH) from 60-80°C
- Accelerated dissolution stability studies need to stay below CRH

Disso Stability Design for Drug Product I



General Behavior



Dissolution behavior for Drug Product I at 15-min as a function of time at specified temperatures (80%RH)

Drug Product I: General Behavior

- Change in disso not gradual: discontinuous function
- Cannot assign a rate of change
- Can still assign a storage ***time to failure***

- Note: potency not changed significantly during any of the challenge conditions

Dissolution Stability: Product 1

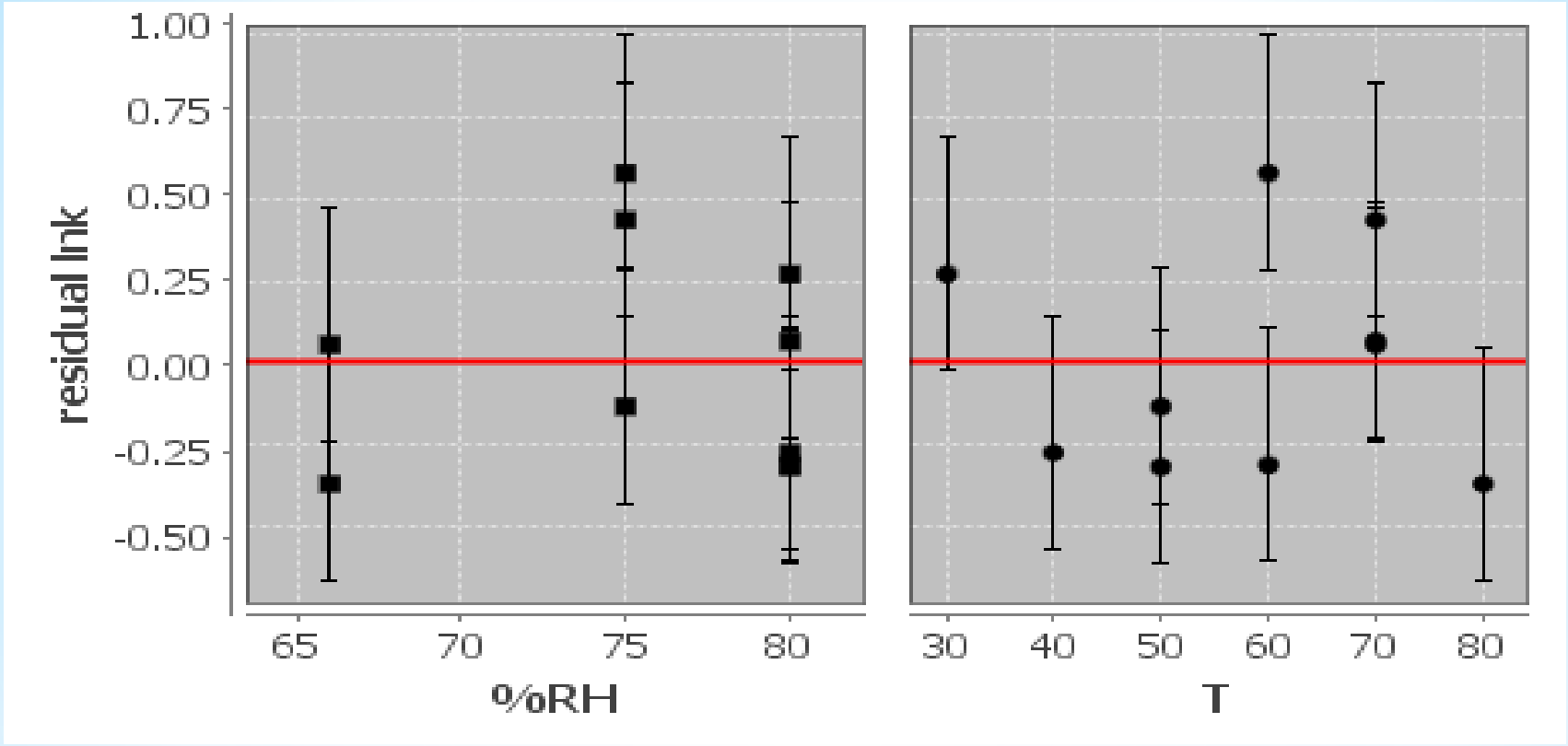
- Shows both temperature and RH dependencies of storage time to fail
- Can fit with ASAP*prime*® modified Arrhenius equation:

$$\ln \frac{1}{t_{failure}} = lnA - \frac{E_a}{RT} + B(RH)$$

Error Bars

- Can assign maximum and minimum storage times to failure at each condition
- Assign an approximate average and standard deviation to each failure time
  - Default to 50%RSD

Drug Product I Time to Dissolution Failure Residuals



ln A = 12.7 ± 2.7

E_a = 21.4 ± 2.3 kcal/mol

B = 0.24 ± 0.03

R^2 = 0.932

Q^2 = 0.869

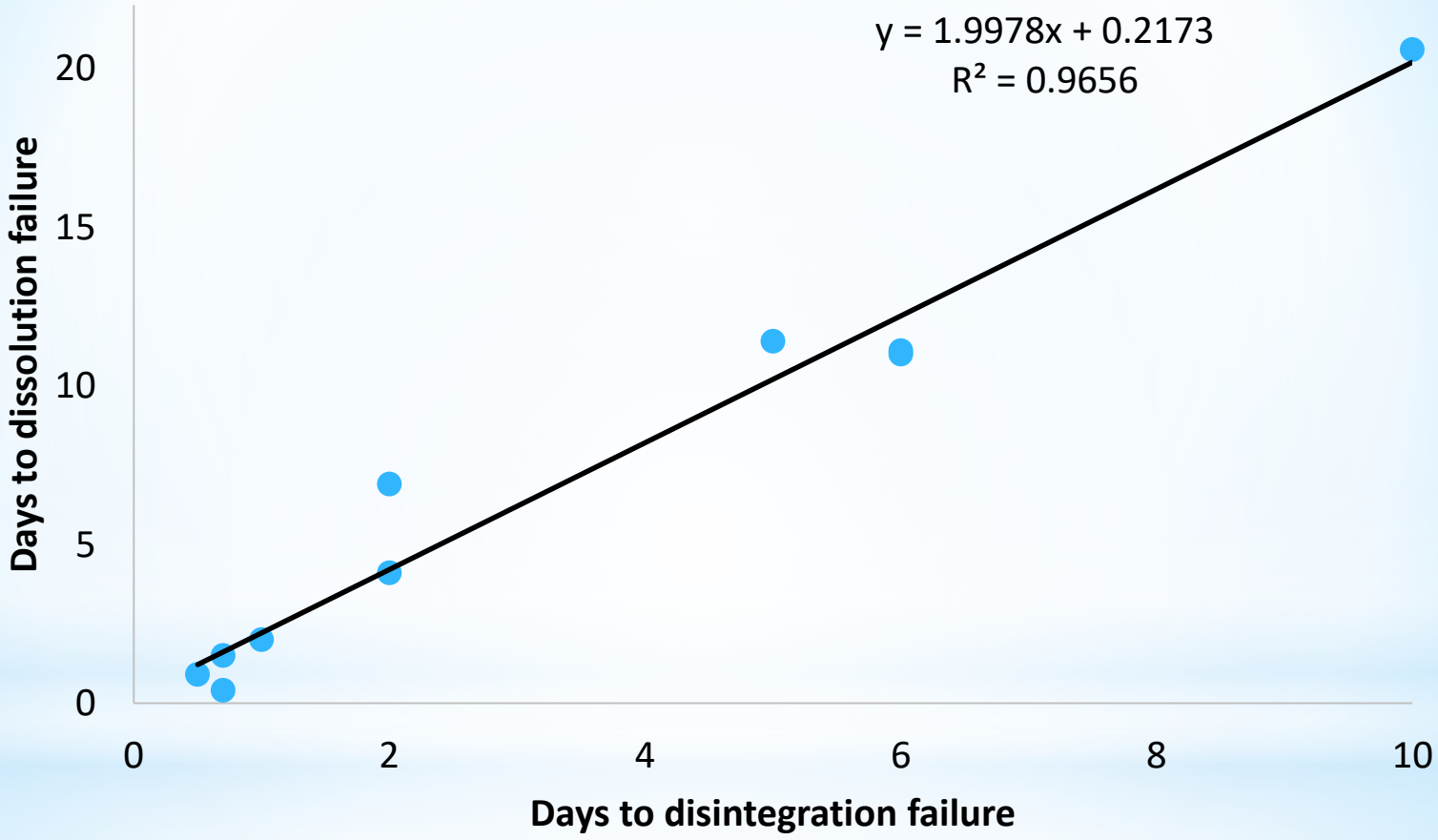
Observations

- ASAP*prime*® fitting model consistent with observed data
- Remarkable that Arrhenius-type description can be used here (with the “isoconversion” concept)
- May indicate that the change in dissolution involves motion having a barrier (impacted by activation—temperature; and mobility—RH)

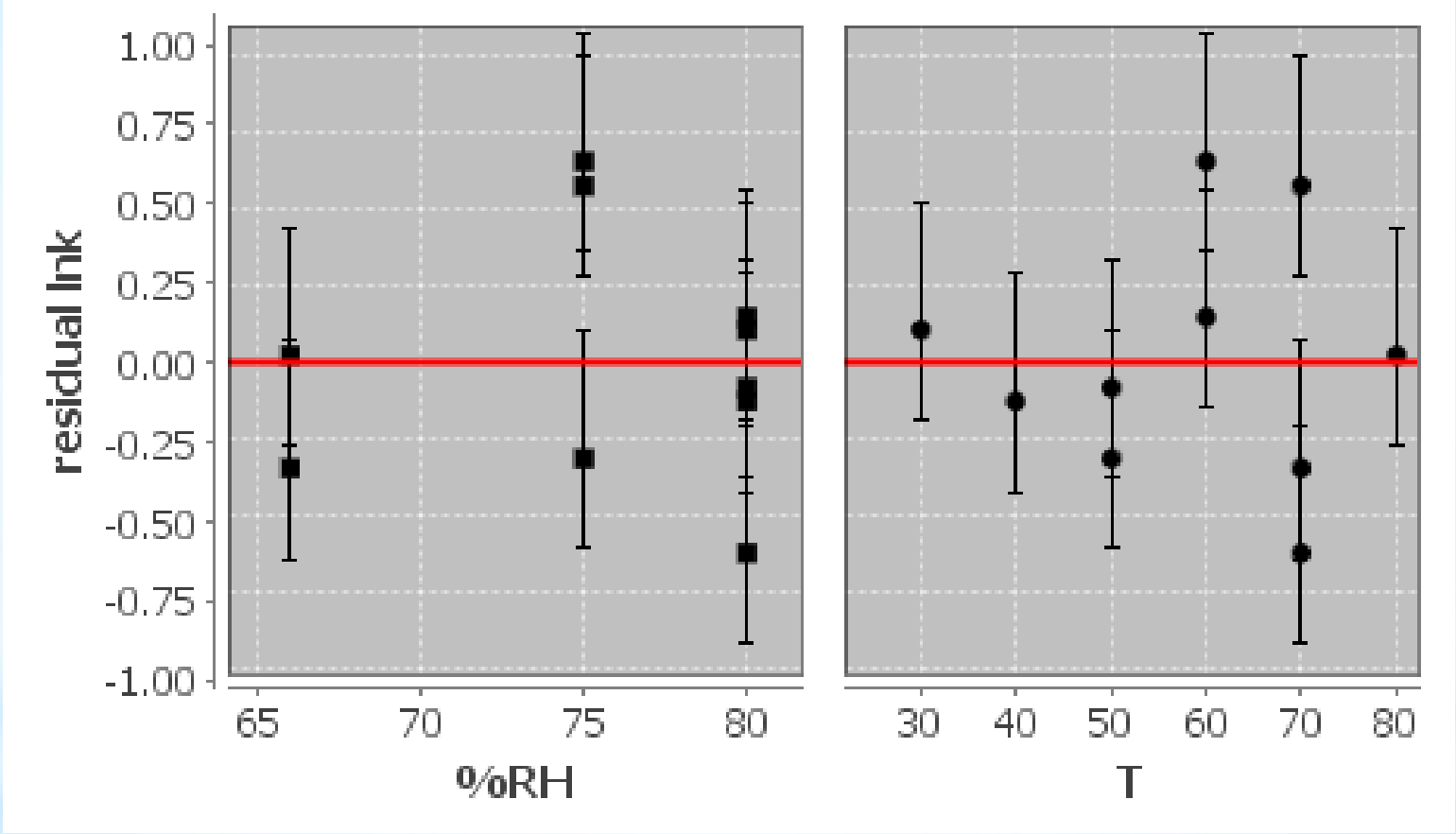
Very High B Term Observed

- B terms for chemical stability usually range from 0.00-0.10
- B term for product 1 dissolution stability = 0.24
- Means small change in RH will lead to large change in stability
- Can be mistaken for a threshold or critical RH: in fact, appears continuous

Dissolution vs. Disintegration Product I



Drug Product I Time to Disintegration Failure Residuals



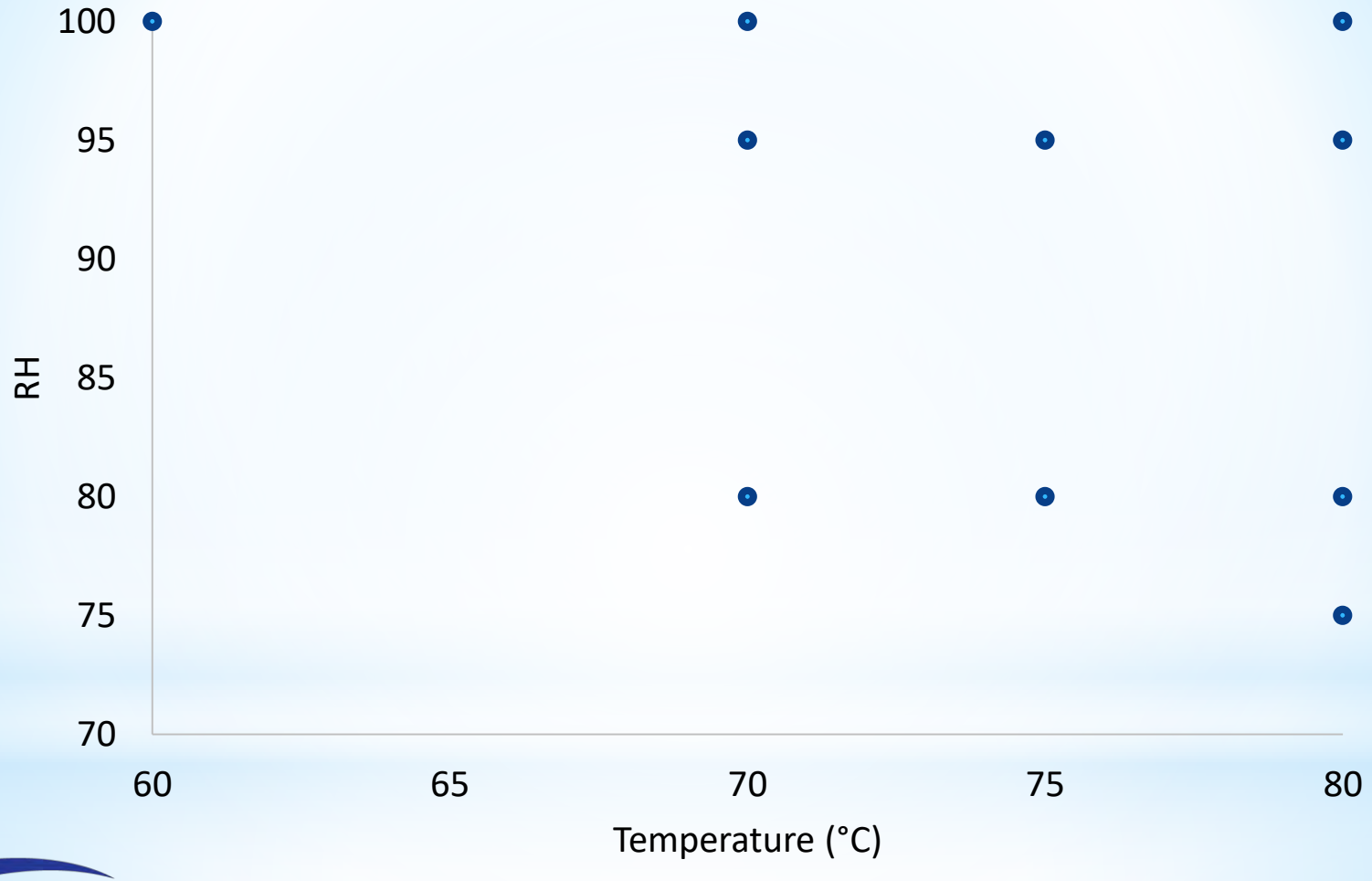
Dissolution vs. Disintegration Product I

- Dissolution and disintegration storage times to failure linearly correlated
- Implies that the change in dissolution directly linked to change in disintegration
- Slope >1 (failure more readily seen for disintegration)
  - Hypothesis: higher shear in disso test requires greater changes in tablet before observable

Tablet 1 Dissolution/Disintegration Stability

- Disintegrant in Tablet 1 is croscarmellose sodium
- Reportedly works by wicking plus swelling
  - Wicking weakens interparticle forces
  - Swelling provide shear to break up tablet
- Does aging reduce wicking, swelling or affect the interparticle interactions themselves?
  - Research ongoing

Drug Product 2—Design



Product 2 Tablet Dissolution

- Change in disso again discontinuous
- Can again assign storage times to dissolution failure

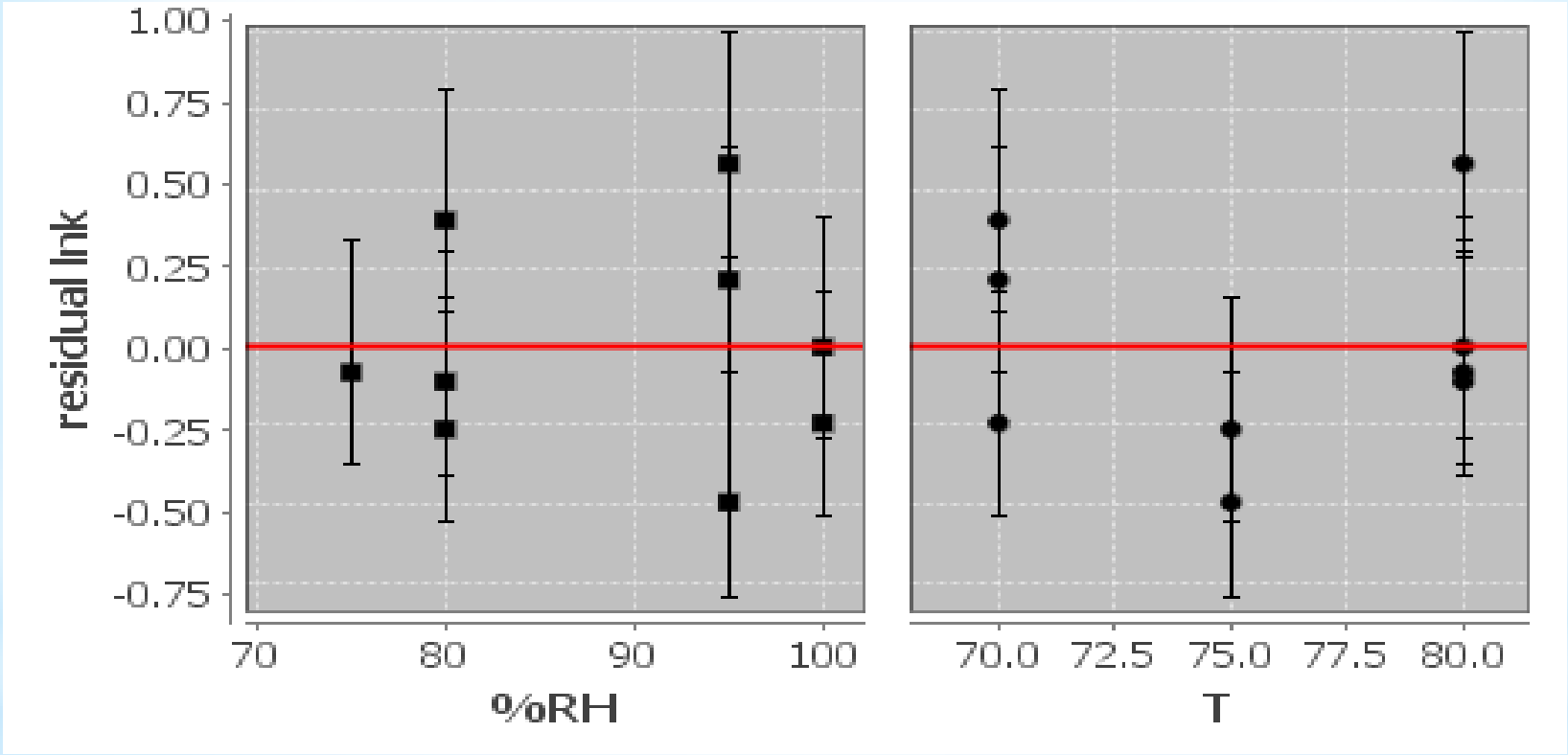
Tablet 2 Storage Time to Dissolution Failure—Residual Graphs

ln A = 81.0±10.1

E_a = 65.2±7.1 kcal/mol

B = 0.132±0.014

R^2 = 0.908



Very High B Term Observed

- B terms for chemical stability usually range from 0.00-0.10
- B term for Product 2 dissolution stability = 0.13
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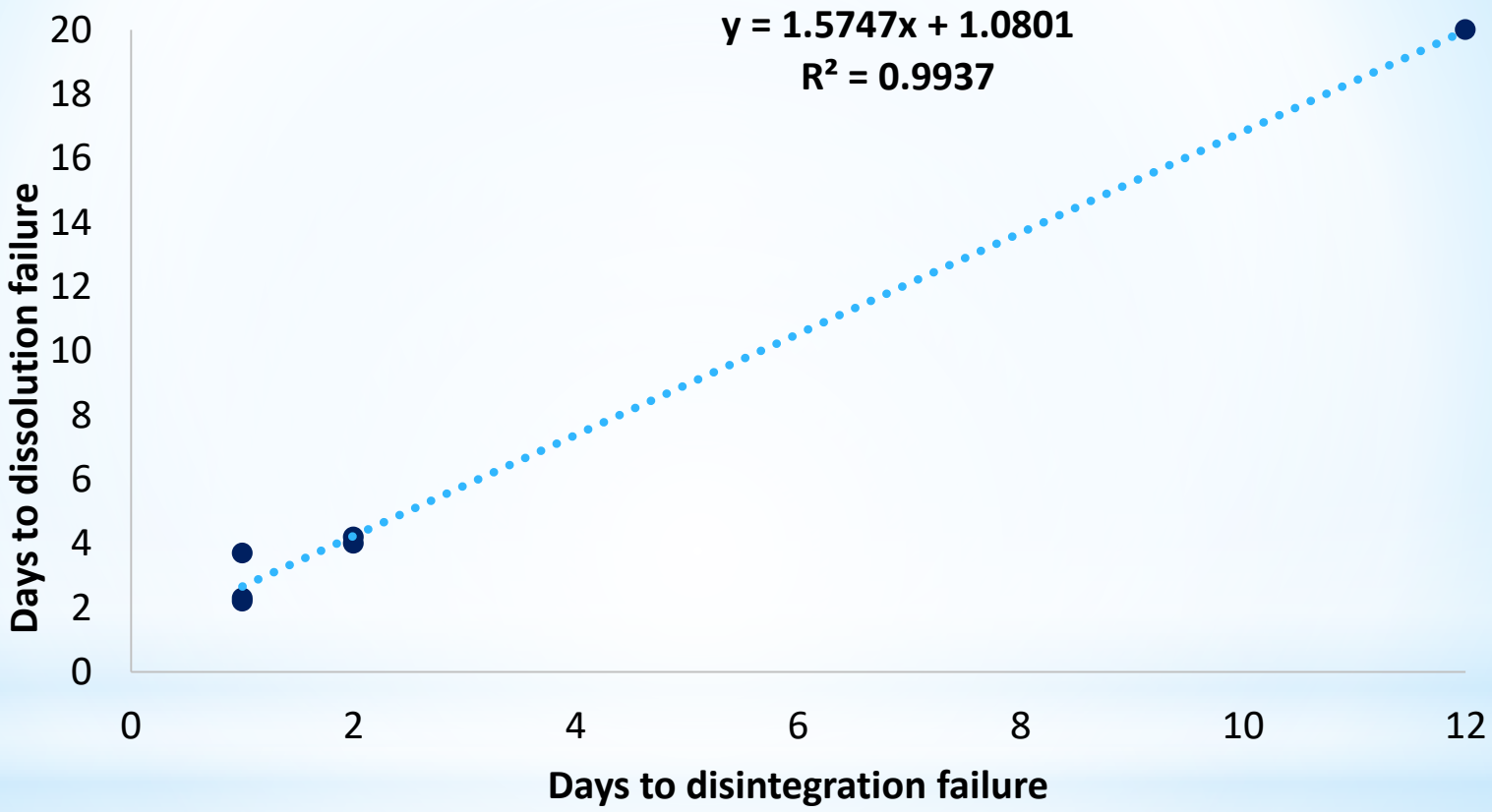
Dissolution vs. Disintegration Product 2



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Tablet 2 Dissolution/Disintegration Stability

- Disintegrant in Tablet 1 is sodium starch glycolate
- Reportedly works by swelling
  - Swelling provide shear to break up tablet
- Does aging reduce swelling or affect the interparticle interactions themselves?
  - Research ongoing

Solid Dosage Forms

1. Immediate release tablets
2. Capsules
3. Controlled release tablets
    a. **Hydrophilic matrix tablets**
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Hydrophilic Matrix Controlled Release Tablets

- Viscous “gel” formed from high molecular weight, water soluble polymer
- Drug release controlled by combination of erosion + slowed drug diffusion
- As ages, MW reduces (polymer strand degradation)
- This chemical process follows ASAP*prime*® model
- Results in faster drug release upon aging, which **can be modeled effectively**

Appearance Stability

- In some cases, shelf-life is limited by changes in the appearance of a product
- For tablets different factors:
  - Color
  - Mottle
  - Cracking, etc.

Appearance Stability

- In some cases, shelf-life is limited by changes in the appearance of a product
- For tablets different factors:
  - ***Color***
  - Mottle
  - Cracking, etc.

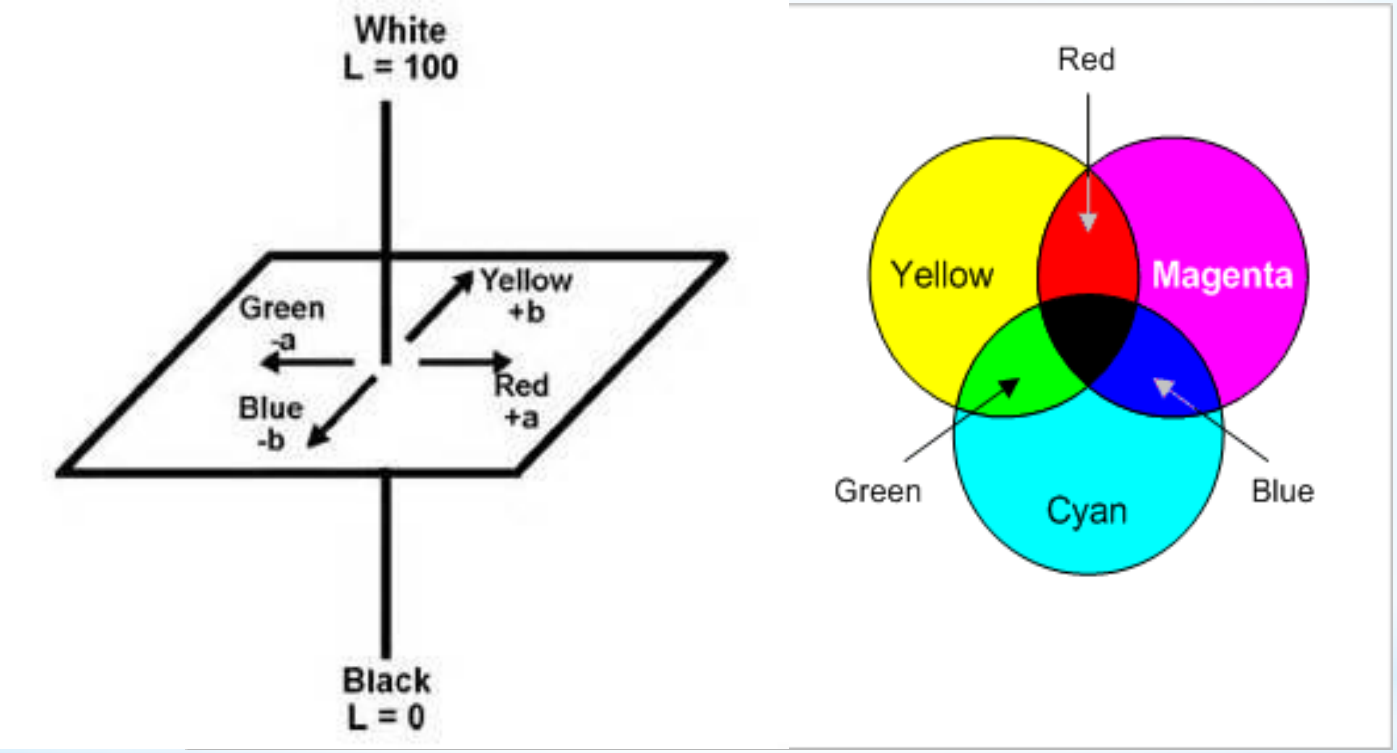
Tablet Color Stability

- Root causes
  - Chemical degradation
  - Migration
- Can we model these in accelerated process?

Tablet Color Stability

1. Need analytical method
2. Need specification limit

Quantifying Color



Tristimulus L,a,b color space

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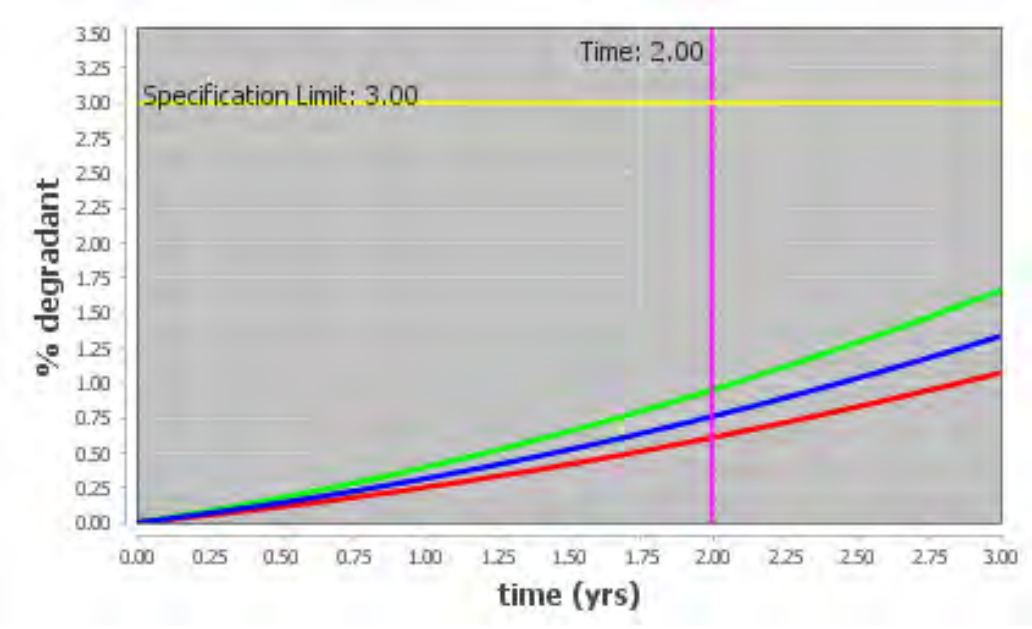
Color Quantification

- Tristimulus measurements allow for good quantification of tablet color using commercial equipment
  - Need custom holder for each sample

Setting Specifications

- Often done qualitatively
- Switch to quantitative (line up tablets)

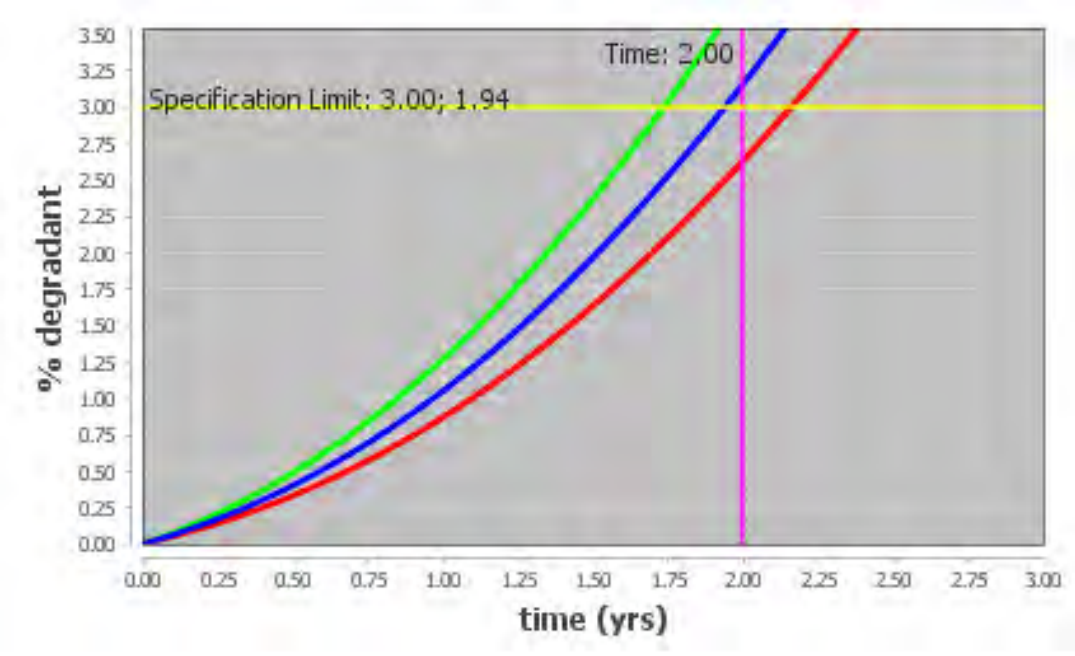
Product Behavior



60 cc-HDPE bottle
30 tablets with
200 mg MCC + 100 mg spray-dried lactose
ASAP*prime*® using diffusion modeling

25°C/60%RH

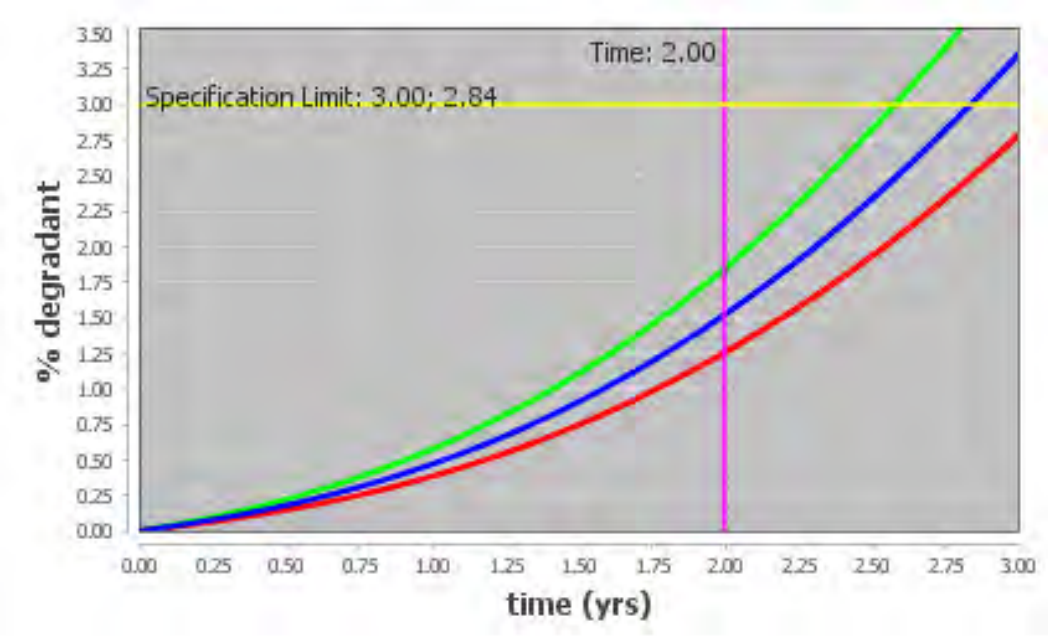
Product Behavior



60 cc-HDPE bottle
30 tablets with
200 mg MCC + 100 mg spray-dried lactose
ASAP*prime*® using diffusion modeling

30°C/75%RH

Product Behavior



60 cc-HDPE bottle
30 tablets with
200 mg MCC + 100 mg spray-dried lactose
ASAP*prime*® using diffusion modeling

Add 0.5 g silica gel desiccant

30°C/75%RH

New Horizons Summary

- For IR tablets, current data support
  - Storage time-to-failure approach validity
  - Storage failure times accelerated by both T + RH in continuous manner (no T/RH cross-term): follows modified Arrhenius equation of ASAP*prime*®
  - Use of disintegration vs. dissolution testing
- For hydrophilic matrix CR tablets, can use ASAP*prime*® since loss of control a chemical process
- Can underwrite disso stability with short-term studies
- ASAP*prime*® can be applied to color changes
  - Need to use tristimulus measurements
  - Need to establish specification limits