Predicting the Long-Term Dissolution Performance of an Immediate-Release Tablet using Accelerated Stability Studies

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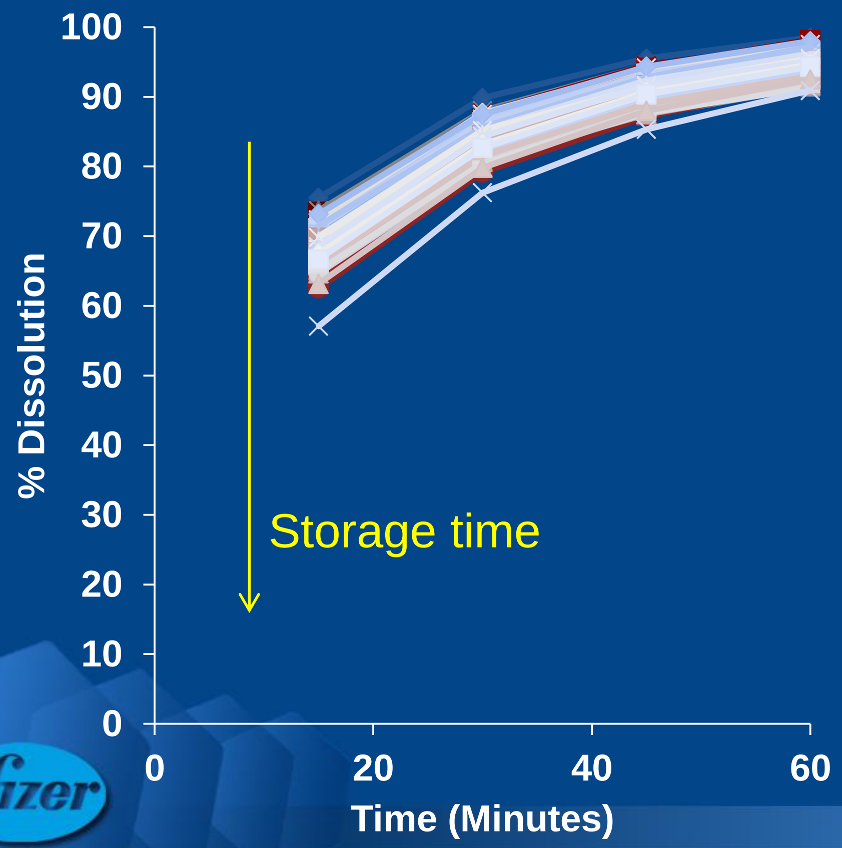
Background

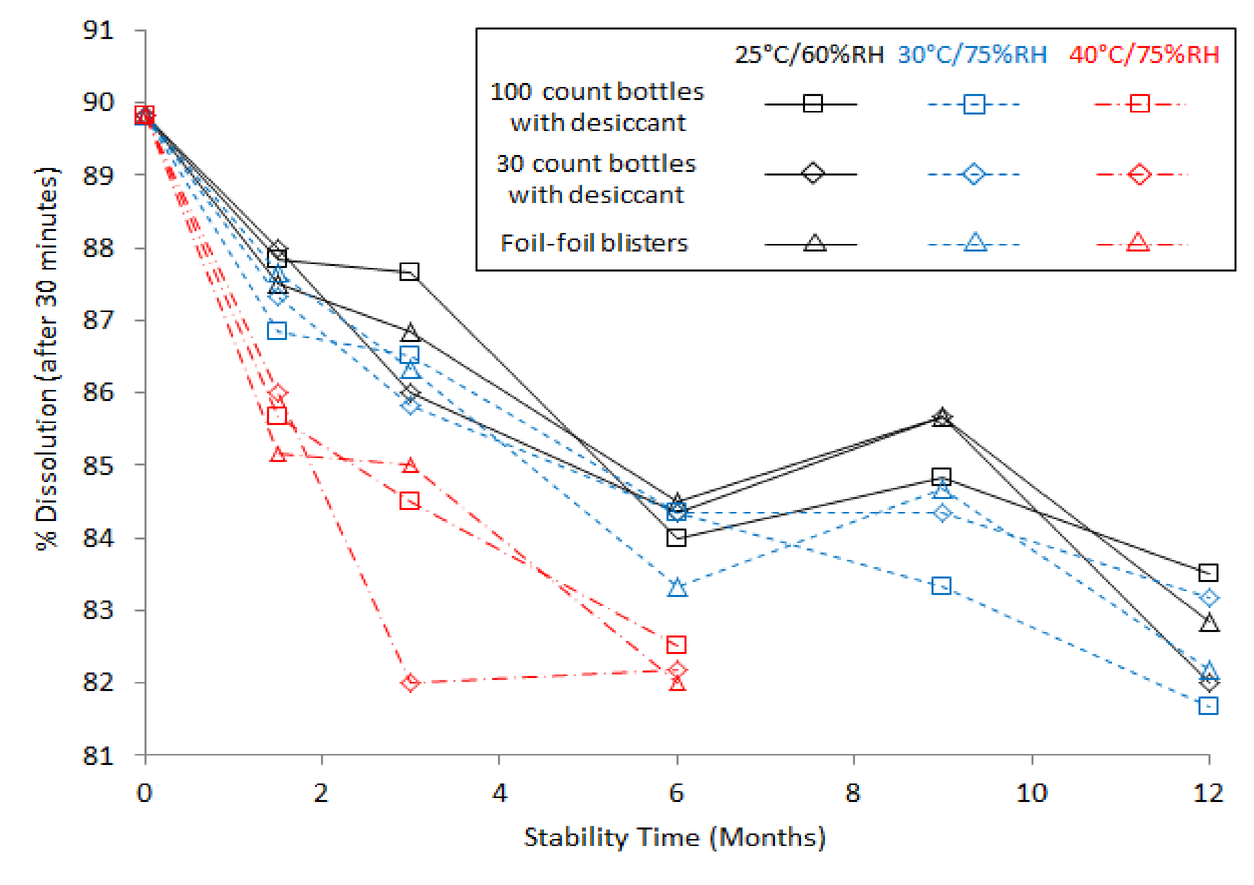
- The dissolution of an IR tablet ‘Product A’ was observed to slow down during registration stability testing



All data up to 12 months:

- 3 different Lots
- 3 pack types: 100 count bottles with desiccant, 30 count bottles with desiccant and foil-foil blisters
- 3 storage conditions: 25°C/60%RH, 30°C/75%RH and 40°C/75%RH

Background



- This presentation outlines our attempts to understand and build a predictive model of the long-term dissolution

Can Long-Term Dissolution Performance be Predicted from Short-Term Accelerated Stability Studies?

- Approach:
  - Expose tablets to a range of different temperature and humidity conditions for a range of different time periods
  - Use elevated temperatures in an attempt to accelerate the degradation processes
  - Model the effects of temperature, humidity and time on the dissolution performance and extrapolate to long-term conditions (and compare to registration stability data)
  - Conduct accelerated protocol on a fresh batch (because registration lots have already aged and may not show any further effects)

Why build a predictive model?:

- Provide Information on the influence of temperature and humidity and help assess the long-term stability risk in different climatic zones.
- Explore if the shelf-life can be extended by using other packaging types, or conversely if the same shelf-life can be obtained without the desiccant or using less expensive blister types.
- Indicate whether the stability trend will continue to (linearly) decrease with time or instead reach a plateau minimum level; this is important to help understand if the product is likely to meet a 2 or 3-year shelf life or longer.
- Provide information on the maximum extent of the problem at future timepoints, which could help with bioequivalence testing and specification setting.
- Provide a rapid screening tool for future lots

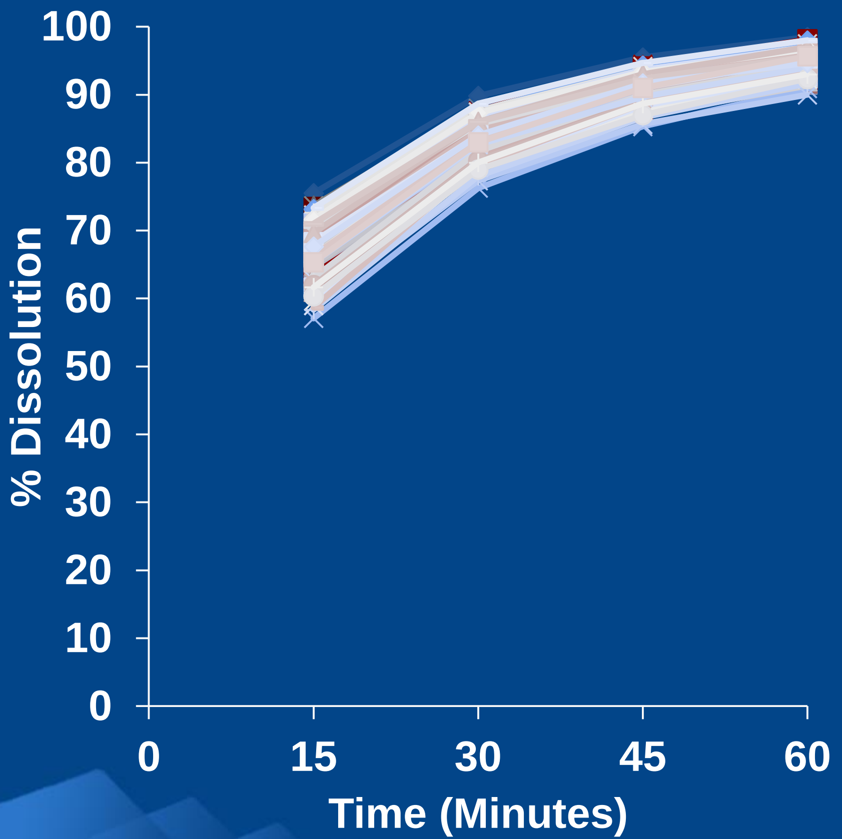
N.B. Activities focused on understanding the mechanism of the slowdown were conducted in parallel with the studies described here, but details of those activities are not the focus of this presentation.

Accelerated Protocol

Condition	Storage Time (days)
Initial	0
61°C/12%RH	6, 9, 21 and 42
62°C/31%RH	6, 9, 21 and 42
61°C/66%RH	6, 9, 21 and 42
61°C/70%RH	6, 9, 21 and 42
52°C/14%RH	9, 21 and 42
52°C/33%RH	9, 21 and 42
51°C/67%RH	9, 21 and 42
50°C/75%RH	9, 21 and 42

- Designed to understand the effects of time, temperature and humidity (t, T and RH)
- Are there any systematic trends that can be modelled? What is the nature of these trends
- Some humidity conditions were different from intended: 50%RH → 66%RH

Analysis of Results from Accelerated Study

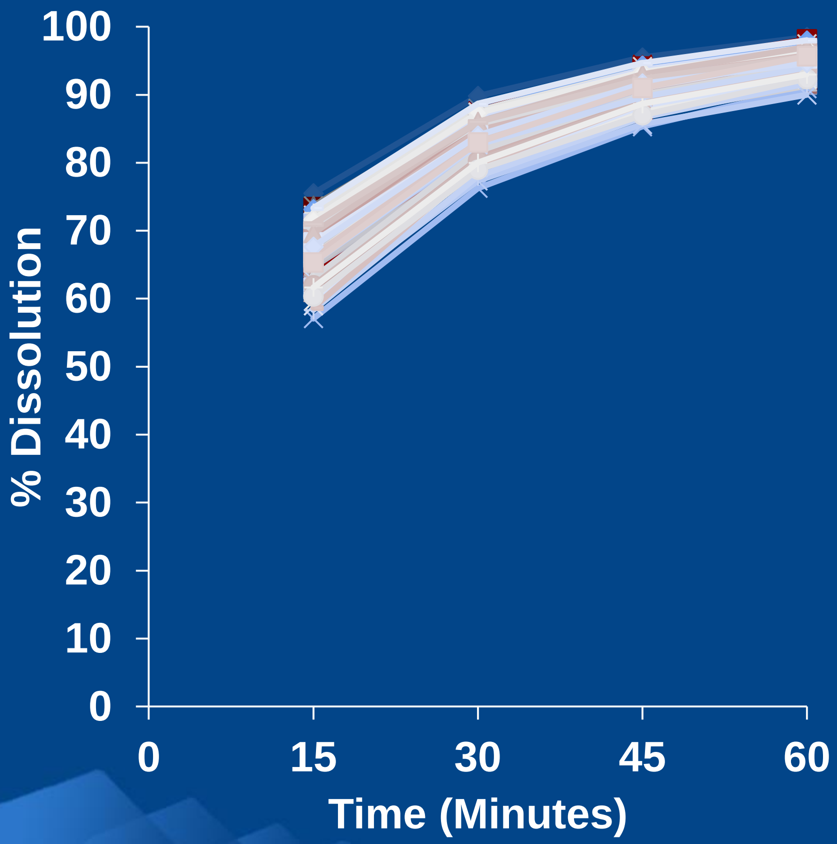


Includes results from accelerated stability study and registration stability study

Dissolution appears to slow down in a very manner to the registration stability (i.e. the dissolution profile has a similar shape)

- Provides some reassurance that the mechanism of the slowdown occurring in the accelerated study is the same as that in the registration study

Modelling the Accelerated Data.
Step 1: Choose 'Response Variable(s)'

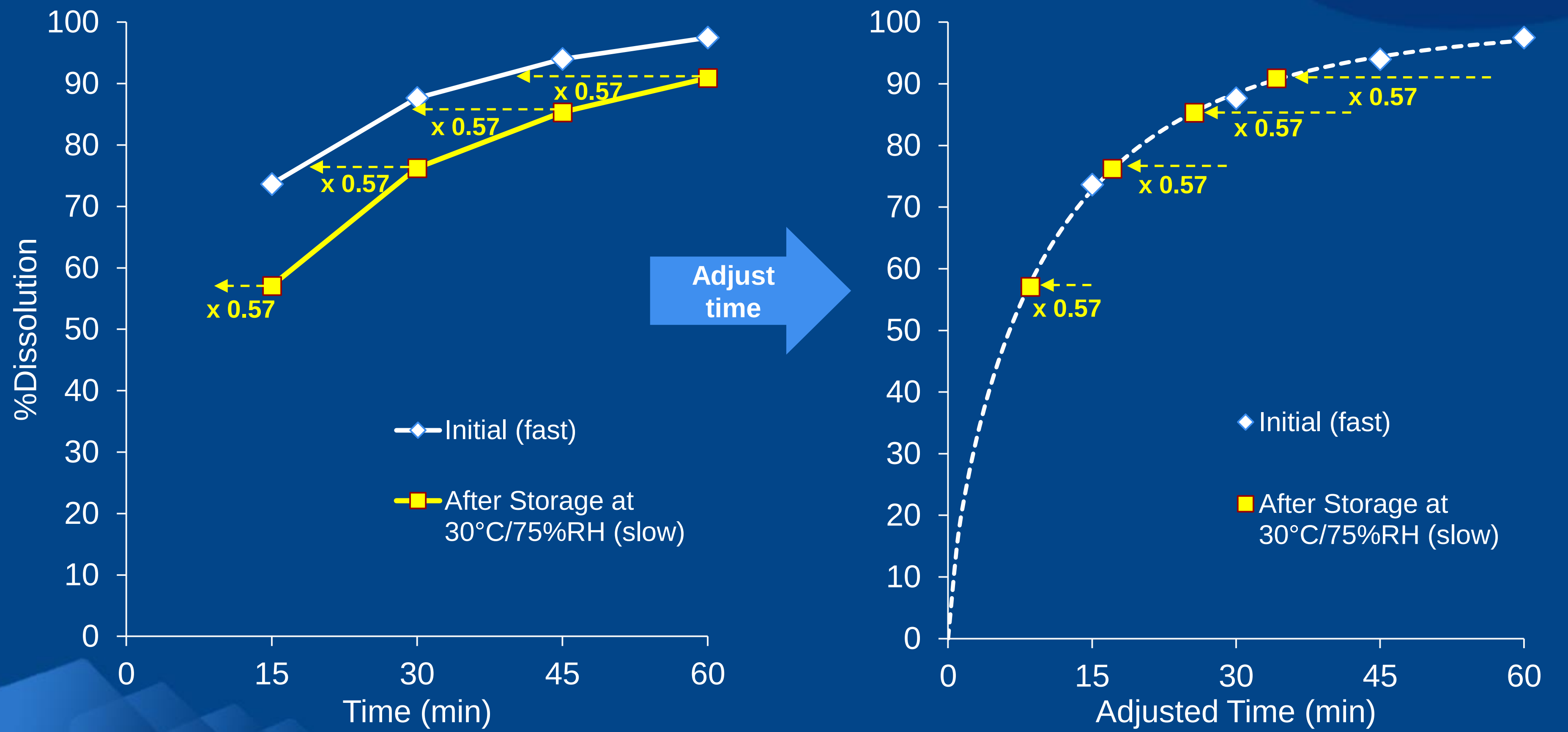


The response variable is something measured from the dissolution results that changes during stability testing

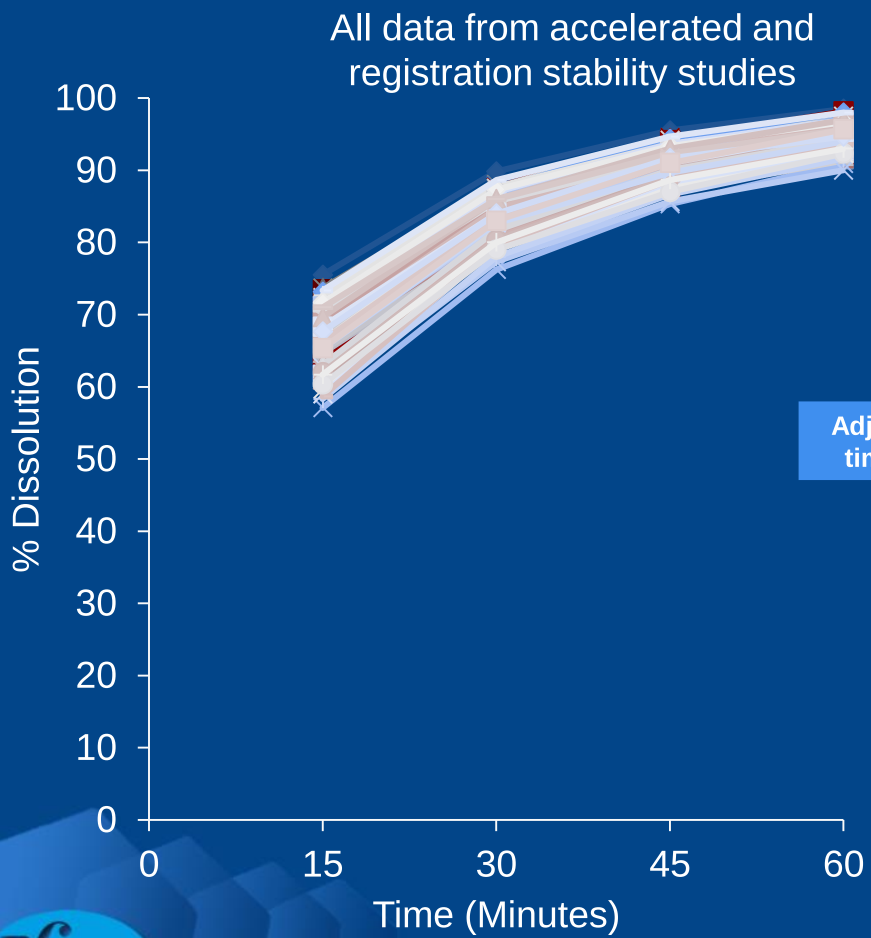
For dissolution, typically this would be %Release after 'X' mins

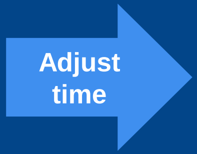
Choosing a Response Variable…

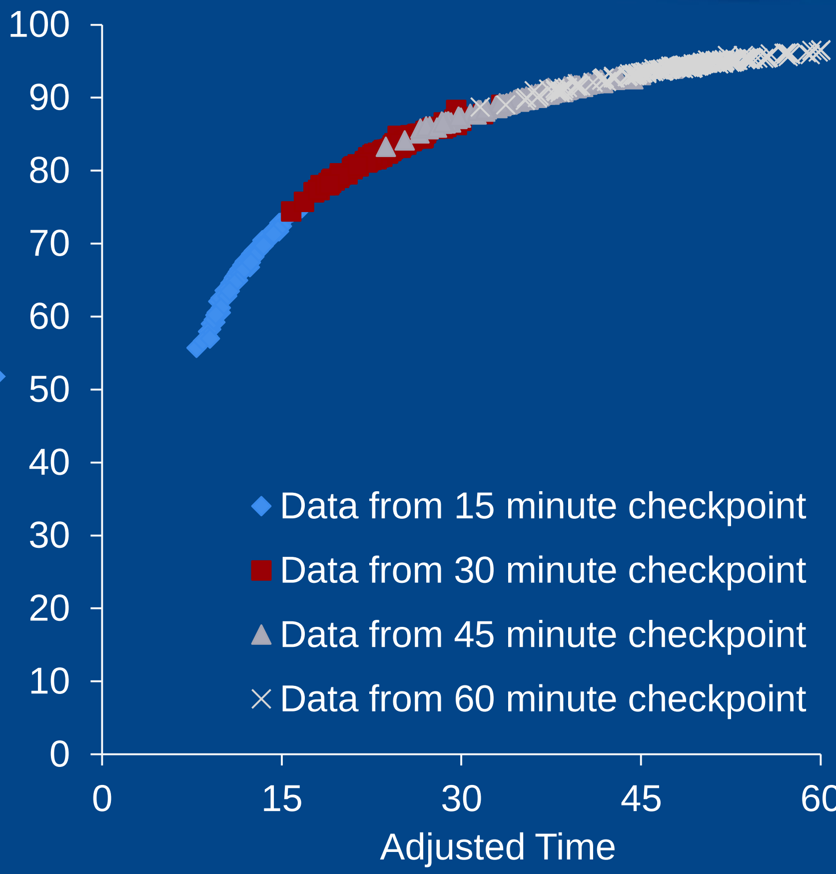
…"Acceleration Factor" (AF)…a measure of the dissolution slowdown



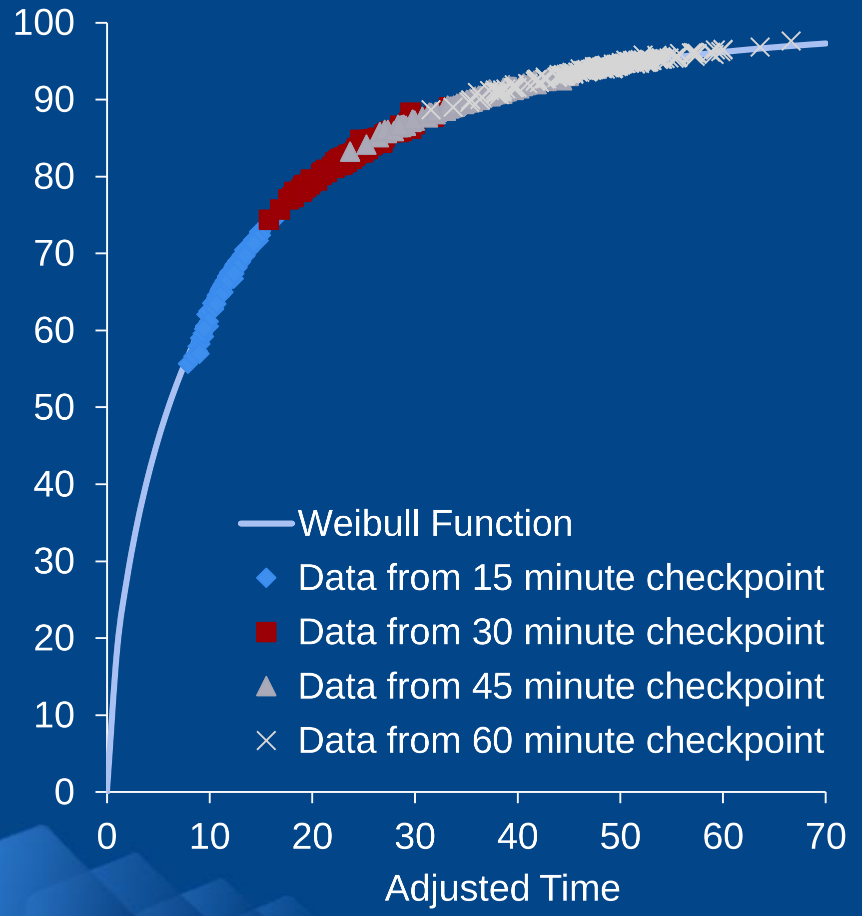
AF = 0.57


All data from accelerated and
registration stability studies
100
90
80
70
60
50
40
30
20
10
0
% Dissolution
0
15
30
45
60
Time (Minutes)


Adjust
time


100
90
80
70
60
50
40
30
20
10
0
0
15
30
45
60
Adjusted Time
Data from 15 minute checkpoint
Data from 30 minute checkpoint
Data from 45 minute checkpoint
Data from 60 minute checkpoint

1. Fit a Curve to the Data
2. Fit an Equation to the Curve



Weibull function fits the data very well

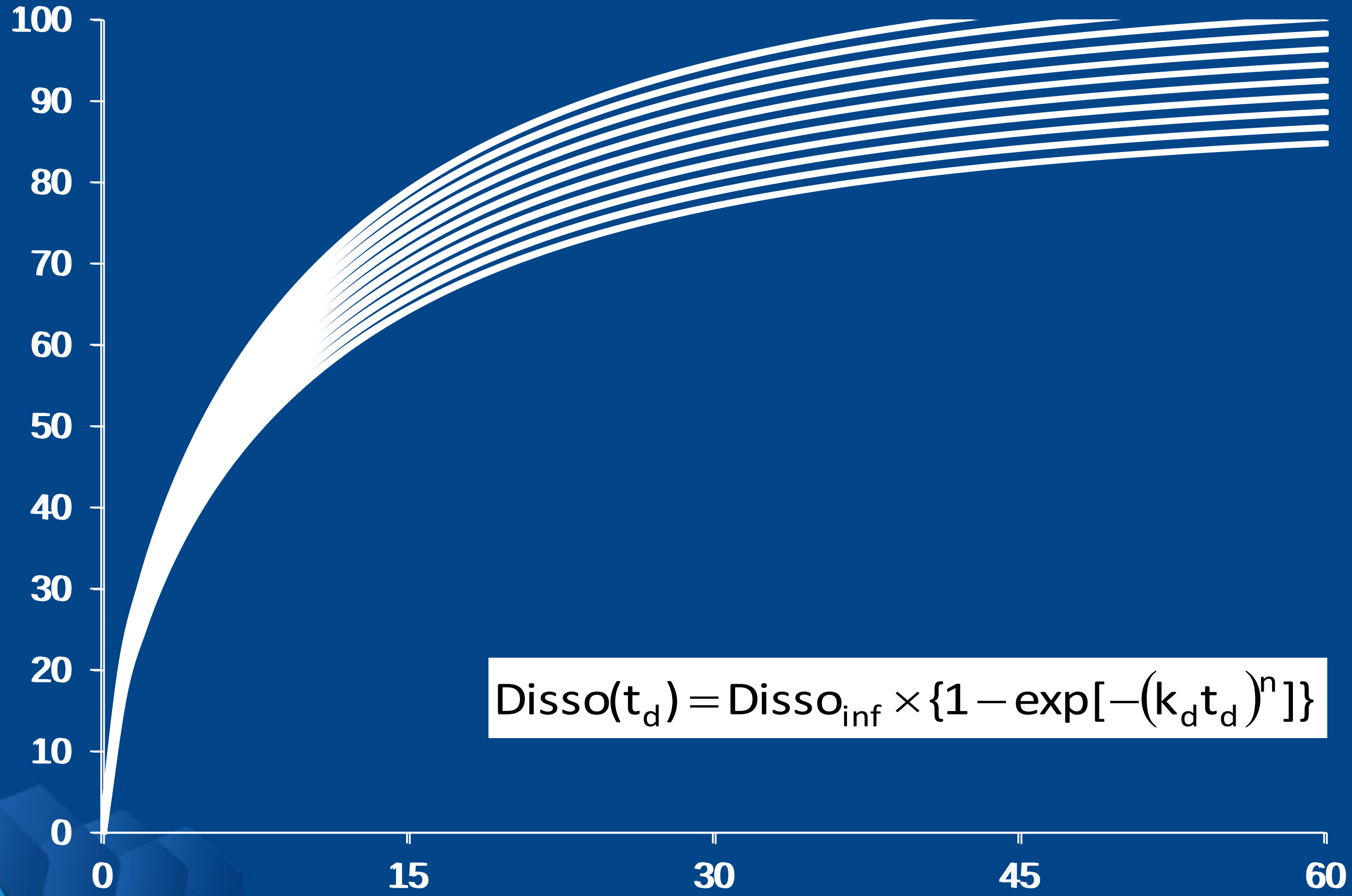
$$\mathrm{Disso}(t_d) = \mathrm{Disso}_{inf} \times \{1 - \exp[-(k_d t_d)^n]\}$$

- The 'Shape Factor' (n) is fixed for all dissolution curves of Product A (n=0.67)
- The only factor that changes during stability testing is 'k_d'

No mechanistic implications: the Weibull function merely provides a convenient means of calculating the AF value from a set of data and for generating a curve from an AF value

$$\mathrm{AF} = \frac{k_d \text{ (Dissolution Curve A)}}{k_d \text{ (Dissolution Curve B)}}$$

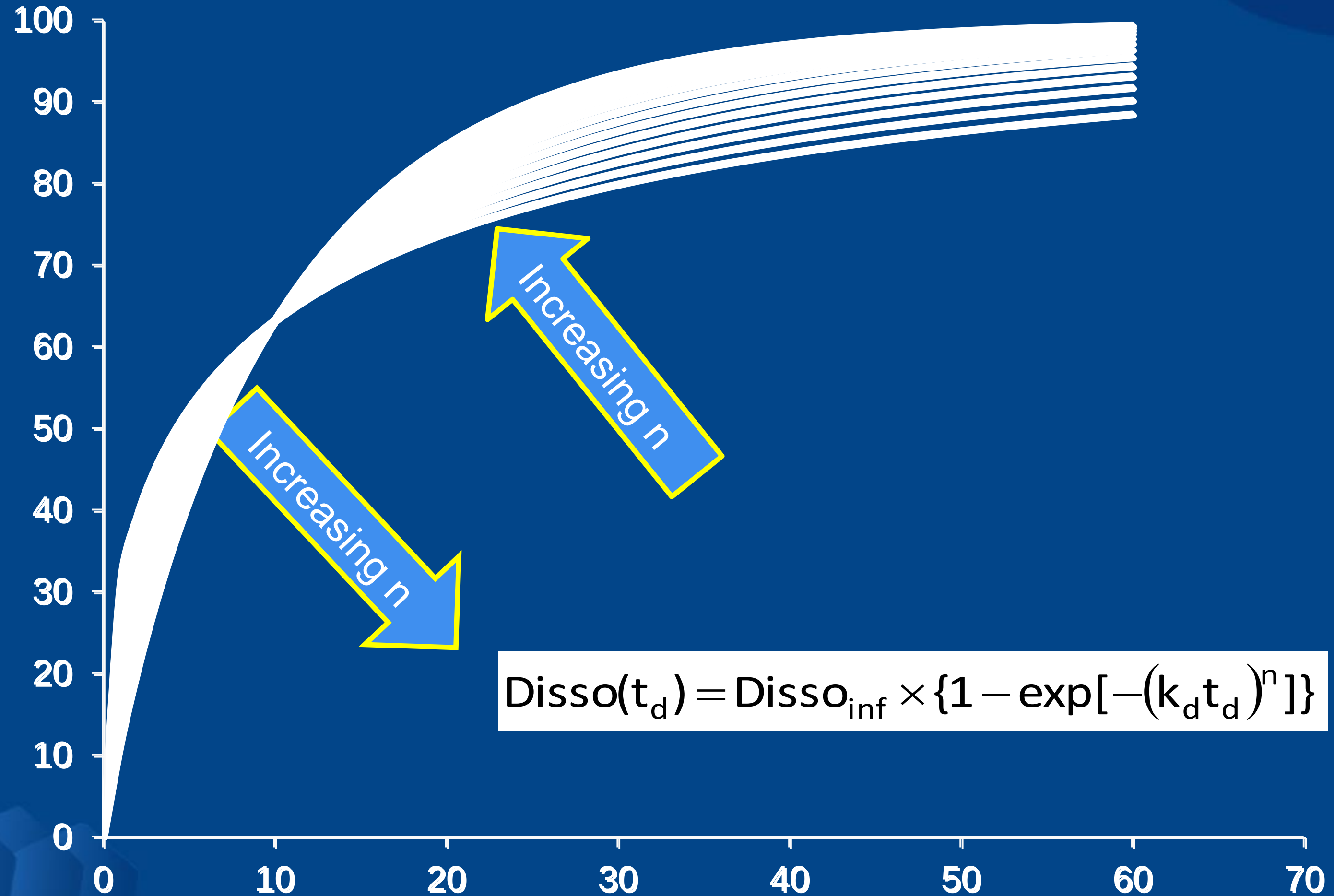
Effect of $Disso_{inf}$



$$Disso(t_d) = Disso_{inf} \times \{1 - \exp[-(k_d t_d)^n]\}$$

Stretch / Contract in y-axis

Effect of 'n'

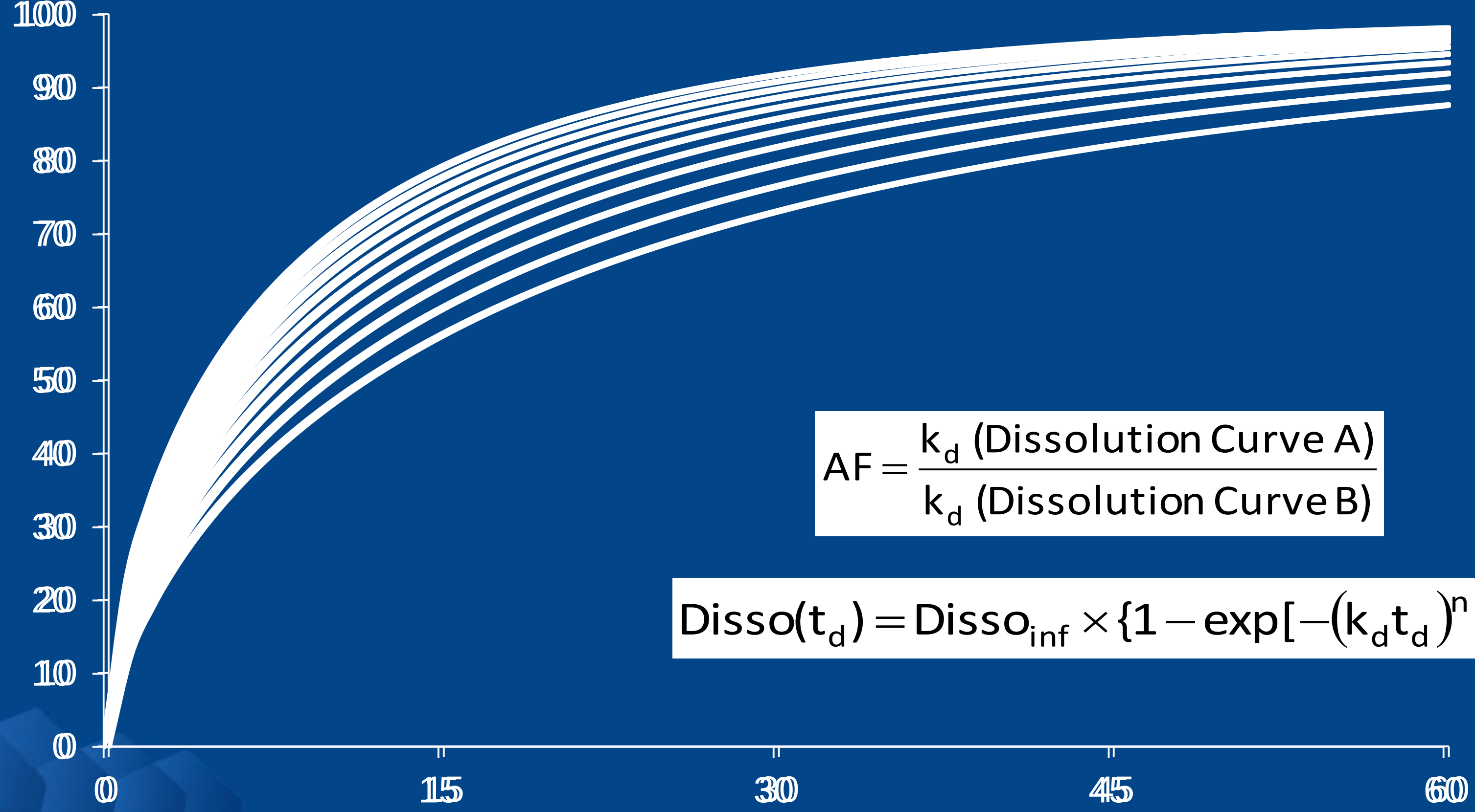


$$Disso(t_d) = Disso_{inf} \times \{1 - \exp[-(k_d t_d)^n]\}$$

Effect of k_d (AF)

Only this parameter appears to change during stability testing

Stretch / Contract in x-axis



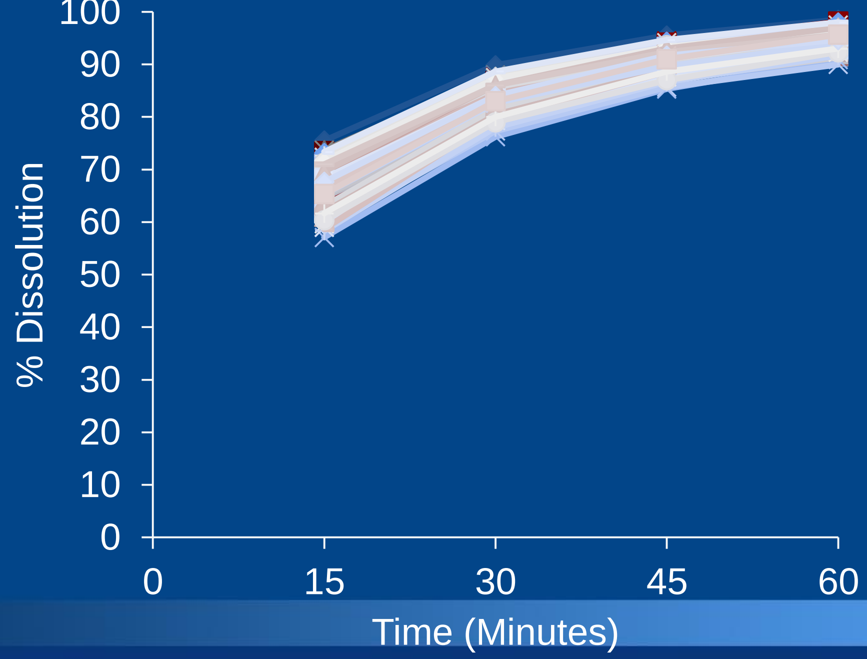
$$AF = \frac{k_d \text{ (Dissolution Curve A)}}{k_d \text{ (Dissolution Curve B)}}$$

$$Disso(t_d) = Disso_{inf} \times \{1 - \exp[-(k_d t_d)^n]\}$$

Advantages of Modelling AF (k_d)

(as opposed to modelling % release after X min)

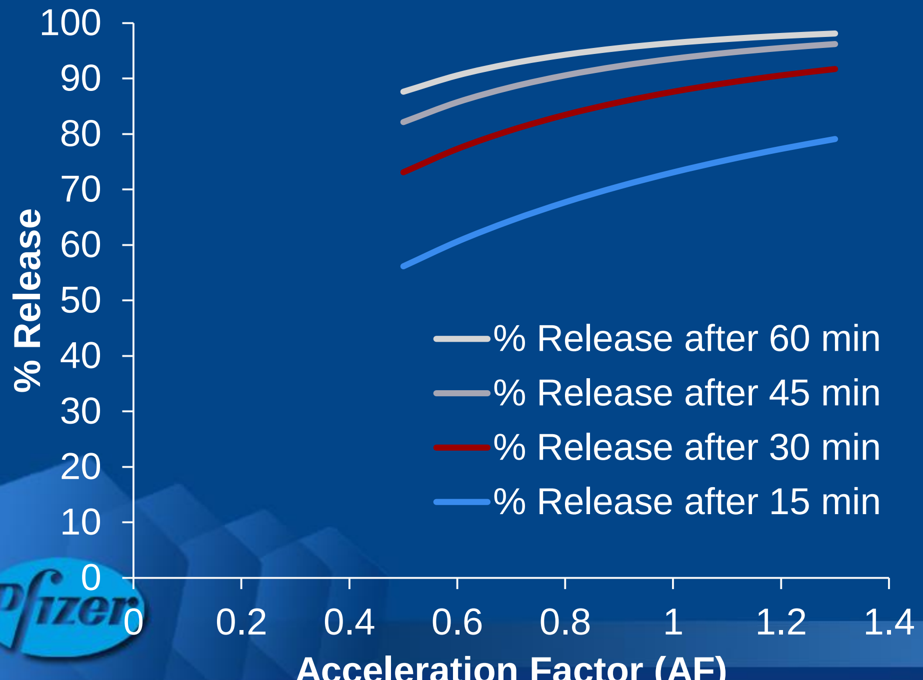
- Data from all dissolution timepoints are used to calculate a single AF value => less vulnerable to experimental variability One model can be used to predict any dissolution timepoint; ability to model whole curve
- Appears to be the best description of what occurs during stability testing:



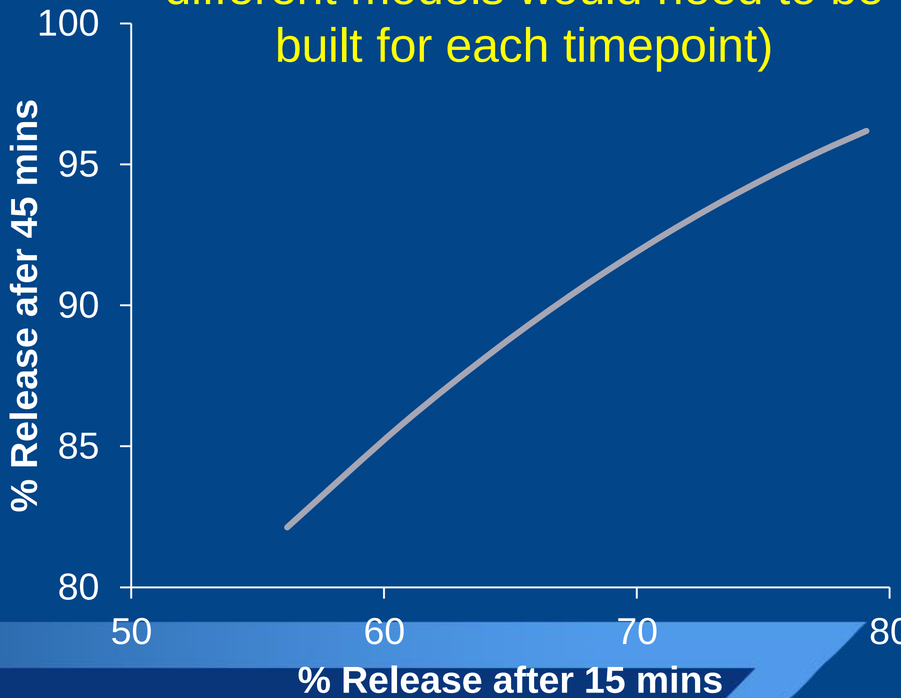
Advantages of Modelling AF (k_d)
(as opposed to modelling % release after X min)

- Very similar (but not identical) predictions would be obtained if '% release after X min' were modelled instead of AF

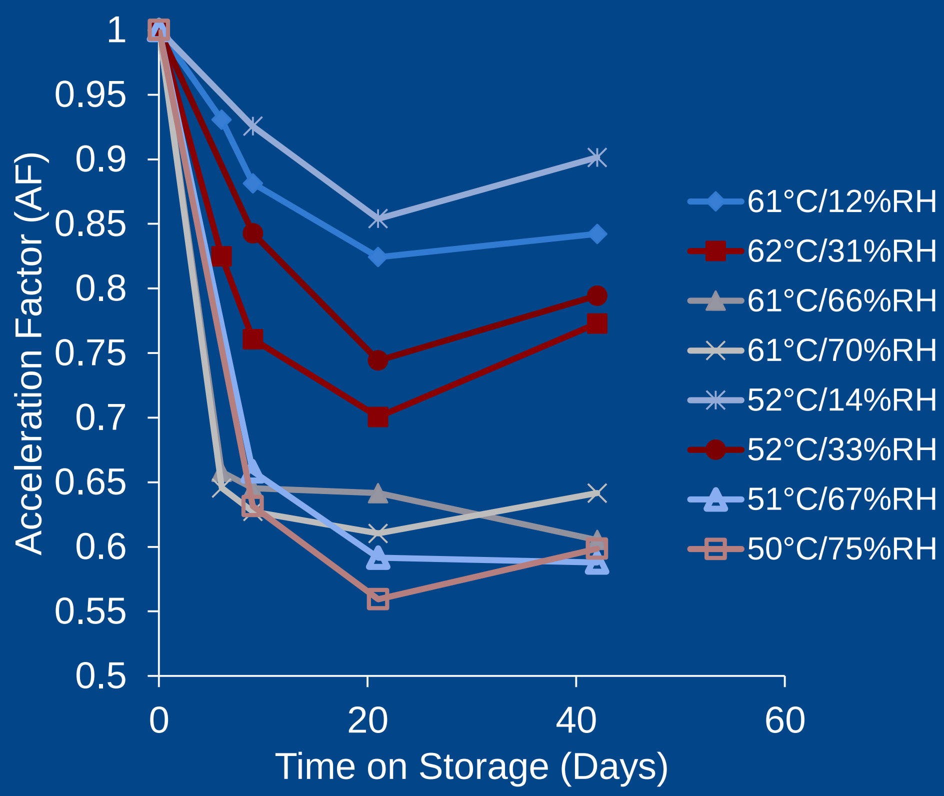
Identical models would be obtained if %Release after X mins were linearly correlated with AF…(but they are not)…

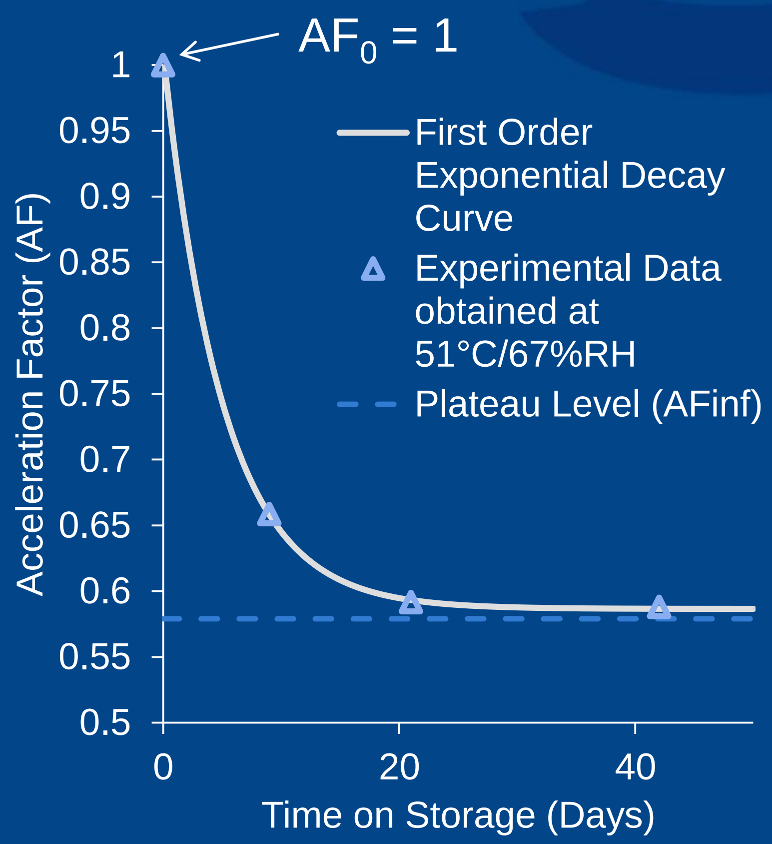


Note that the %Release at different timepoints are also not linearly correlated with each other (so different models would need to be built for each timepoint)



Effect of Temperature and Humidity on AF

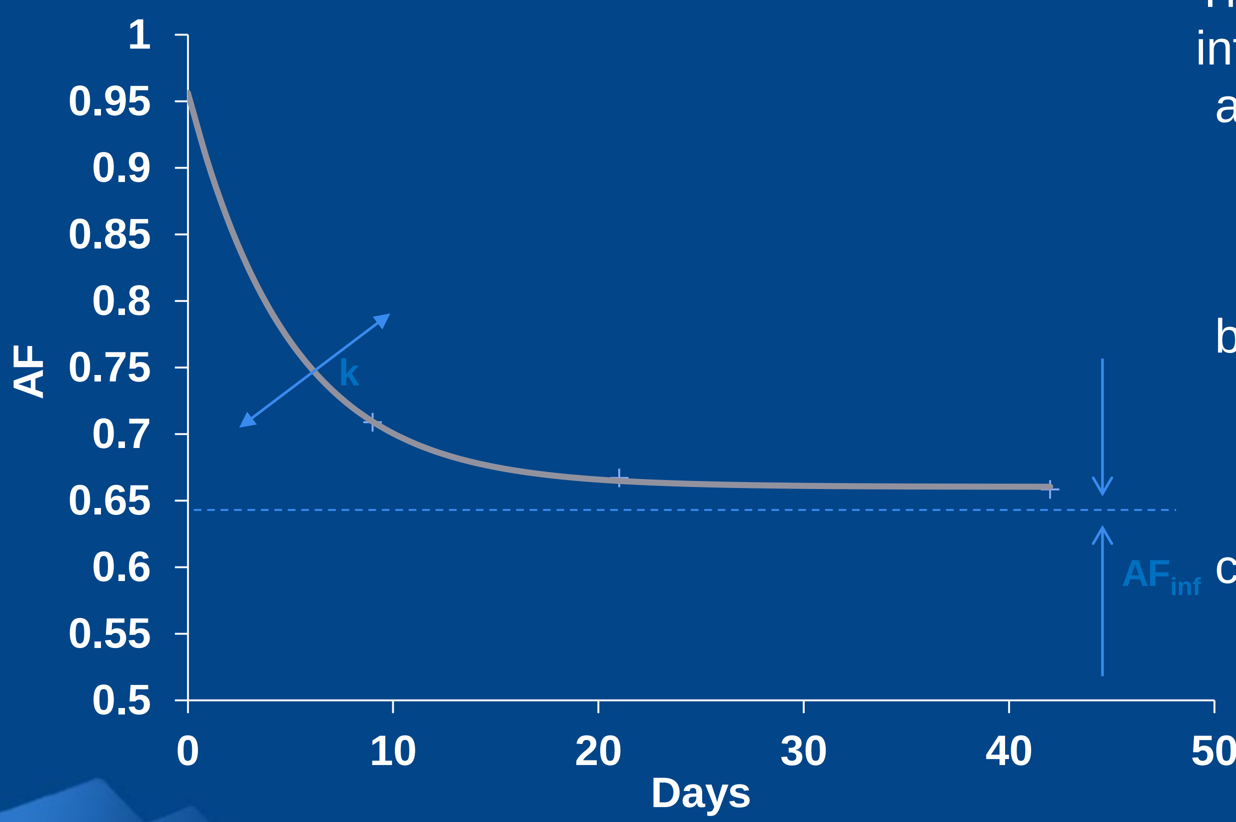




$$\text{First Order Exponential Decay:} \quad AF_t = AF_0 + (AF_{inf} - AF_0) \times [1 - \exp(-k_s t_s)]$$

Interpretation of Accelerated data

Looking beyond the scatter in the data ☹



Three key pieces of information:

a) What is the plateau level (i.e. how bad can the dissolution get) under these conditions? – "AF_{inf}"

b) What is the rate constant for this process (i.e. how fast does it tend towards AF_{inf})? – "k"

c) What is the curve shape for this stability process.? In view of scatter and lack of data, the simplest plateauing model was selected (a 'first order' curve shape)

$$AF_t = AF_0 + (AF_{inf} - AF_0) * (1 - \exp(-kt))$$

Effect of Temperature and Humidity

- The dissolution slowdown appears to tend towards a ‘limit’ value (AF_{inf})
- Temperature and humidity appear to affect both:
  - The limiting value of the dissolution slowdown (AF_{inf}), and
  - The rate constant at which the dissolution tends towards this limit (k_s)

Temperature (°C)	RH (%)	AF_{inf}	k_s (day^{-1})
60	12	0.836	0.113
60	31	0.747	0.209
60	66	0.637	0.501
60	70	0.643	0.573
50	14	0.897	0.144
50	33	0.788	0.144
50	67	0.588	0.173
50	75	0.569	0.187

Modelling AF_{inf} and k_s as functions of Temperature and Humidity

- Multiple models were evaluated, e.g.:
  - Empirical Models
  - Physically Relevant Models
  - Models where humidity is input as %RH
  - Models where humidity is input as vapour pressure
  - Models with and without a Temperature-humidity 'cross term'
- 'Adjusted R^2' and minimising the RMSE were used to evaluate which model matched the experimental data best (in previous slide)

$$\text{Property (i.e. } AF_{inf} \text{ or } k_s) = C_0 + C_1 \cdot f_a(T) + C_2 \cdot f_b(H) + C_3 \cdot f_c(T,H)$$

or

$$\text{Ln(Property)} = C_0 + C_1 \cdot f_a(T) + C_2 \cdot f_b(H) + C_3 \cdot f_c(T,H)$$

$$f_a = T \quad \text{or} \quad f_a = 1/T$$

$$f_b = H, \quad \text{or} \quad f_b = \text{Ln}(H)$$

$$f_c = \{\text{null}\}, \quad f_c = T \times H, \quad f_c = H/T, \quad f_c = T \times \text{Ln}(H) \quad \text{or} \quad f_c = \text{Ln}(H)/T$$

Modelling AF_{inf} and k_s as functions of Temperature and Humidity

- The best fit was obtained with the following models:

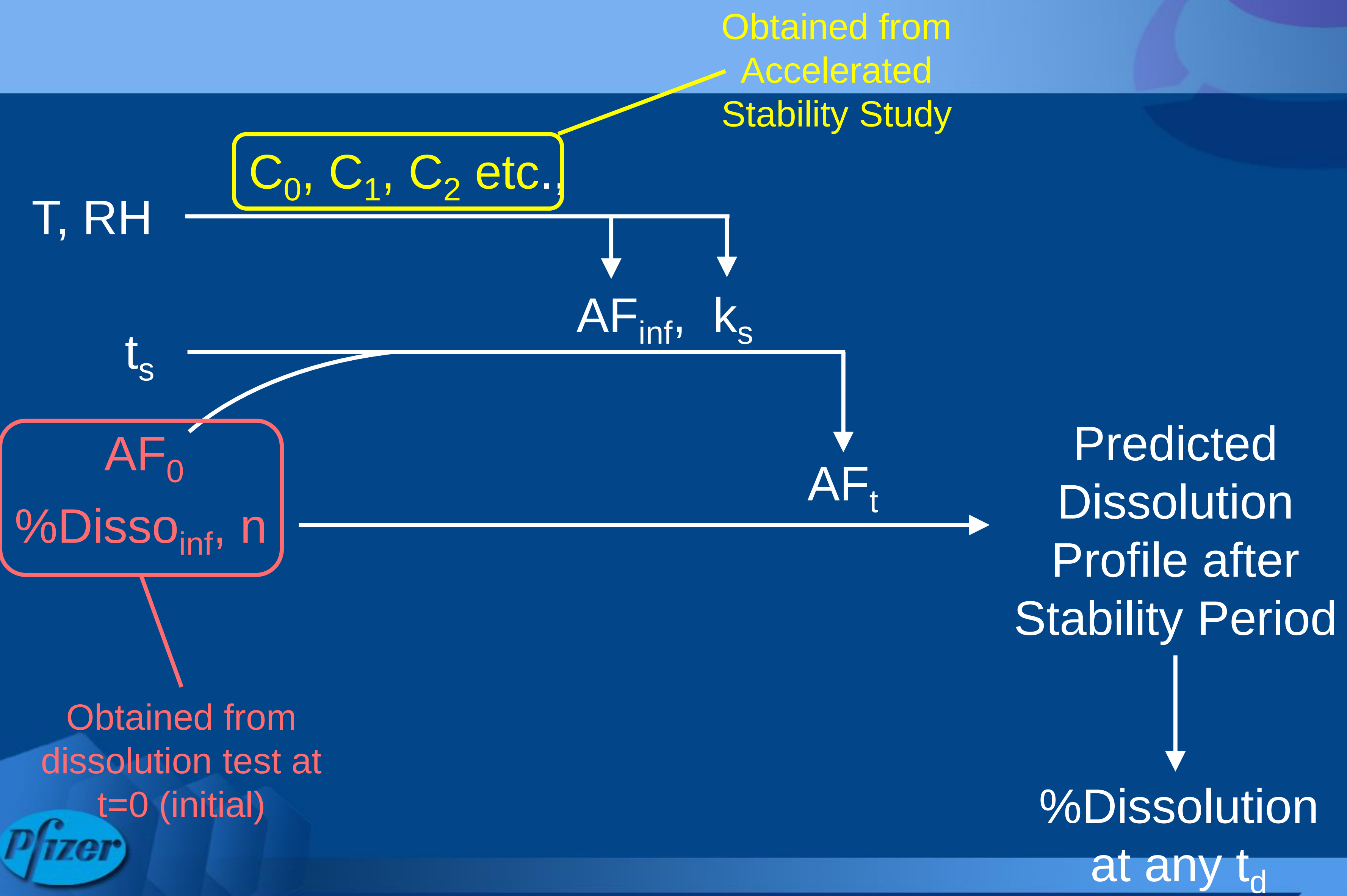
$$\mathrm{Ln}(AF_{inf}) = C_0 + \frac{C_1}{T} + C_2(RH)$$

$$\mathrm{Ln}(k_s) = C_3 + \frac{C_4}{T} + C_5(RH)$$

- These models are quite familiar…
  - Similar relationships are common in kinetics and thermodynamics
- Somewhat reassuring that a completely 'data-led' analysis resulted in these familiar-looking equations

$C_0 = 0.6750$, $C_1 = -244.0$, $C_2 = -0.006225$,
$C_3 = 19.07$, $C_4 = -7040$, $C_5 = 0.0168$

Summary of Model – A series of nested models



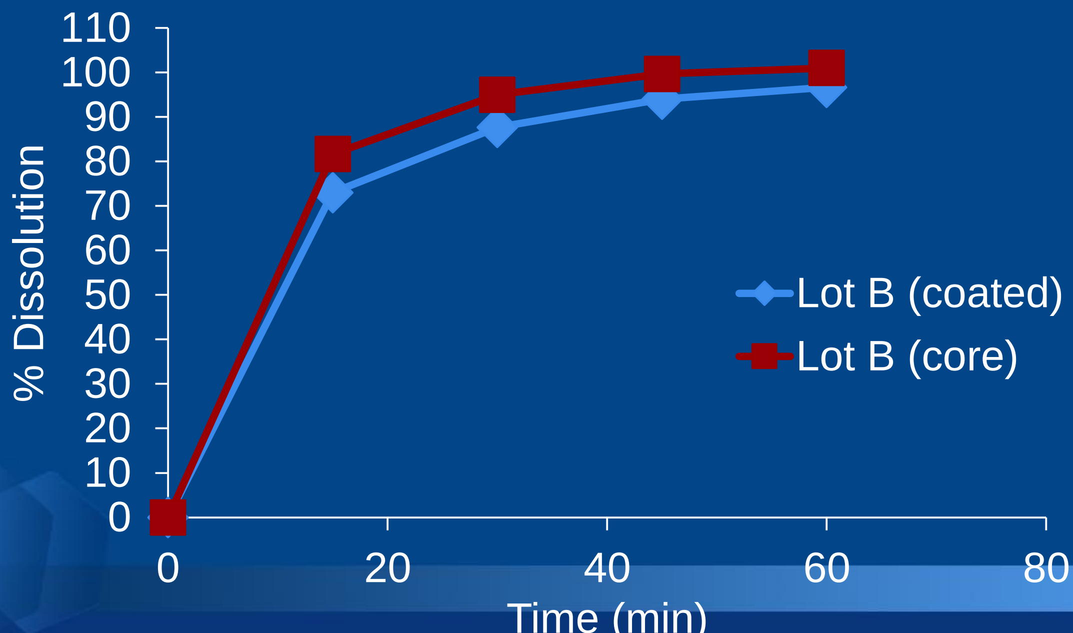
Model Evaluation

1. Ability to predict dissolution of three freshly made batches stored at various temperatures and humidity levels.

2. Ability to predict dissolution for registration stability batches
   – Need to account for constantly changing RH inside packaging

Model Evaluation

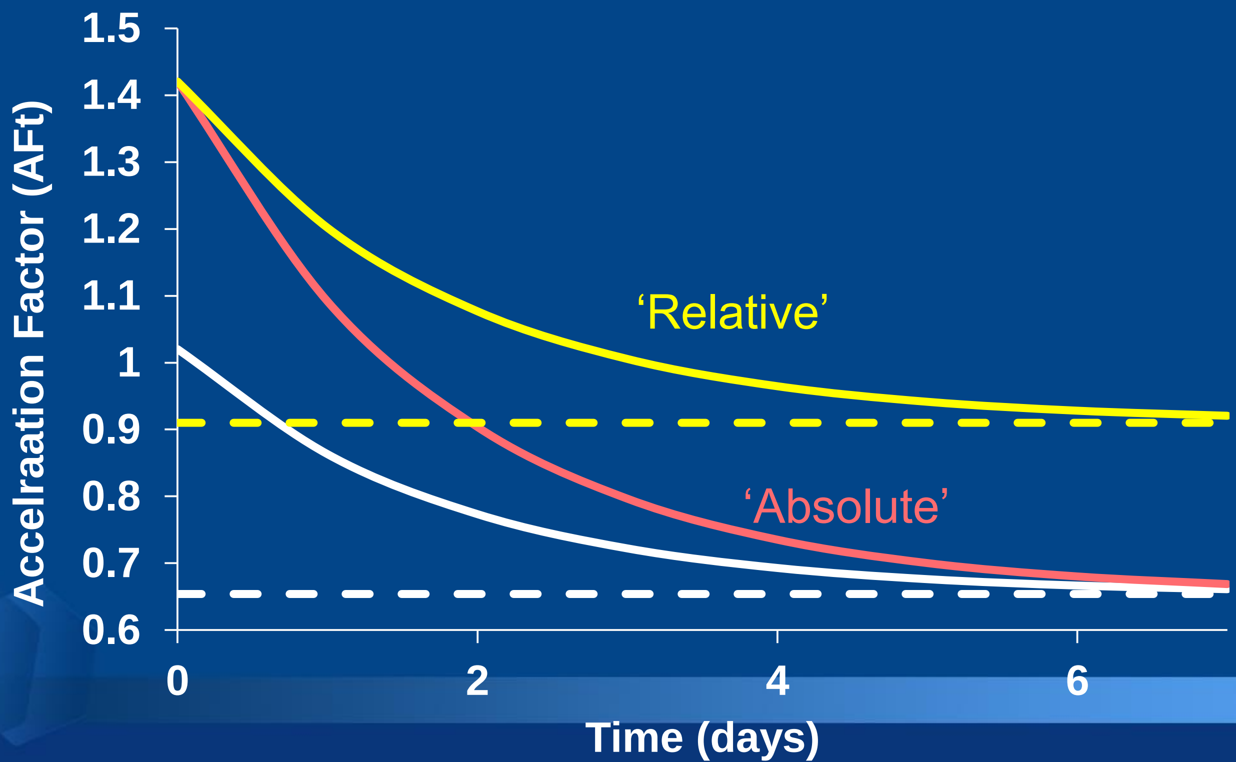
- Predicted dissolution was compared to actual dissolution for:
  - Three freshly manufactured batches were stored for 7 days in an open dish at 40°C/75%RH, 50°C/75%RH, 60°C/75%RH, 50°C/10%RH and 60°C/10%RH
  - Two of the batches were film-coated, and one batch was one of the corresponding uncoated cores.



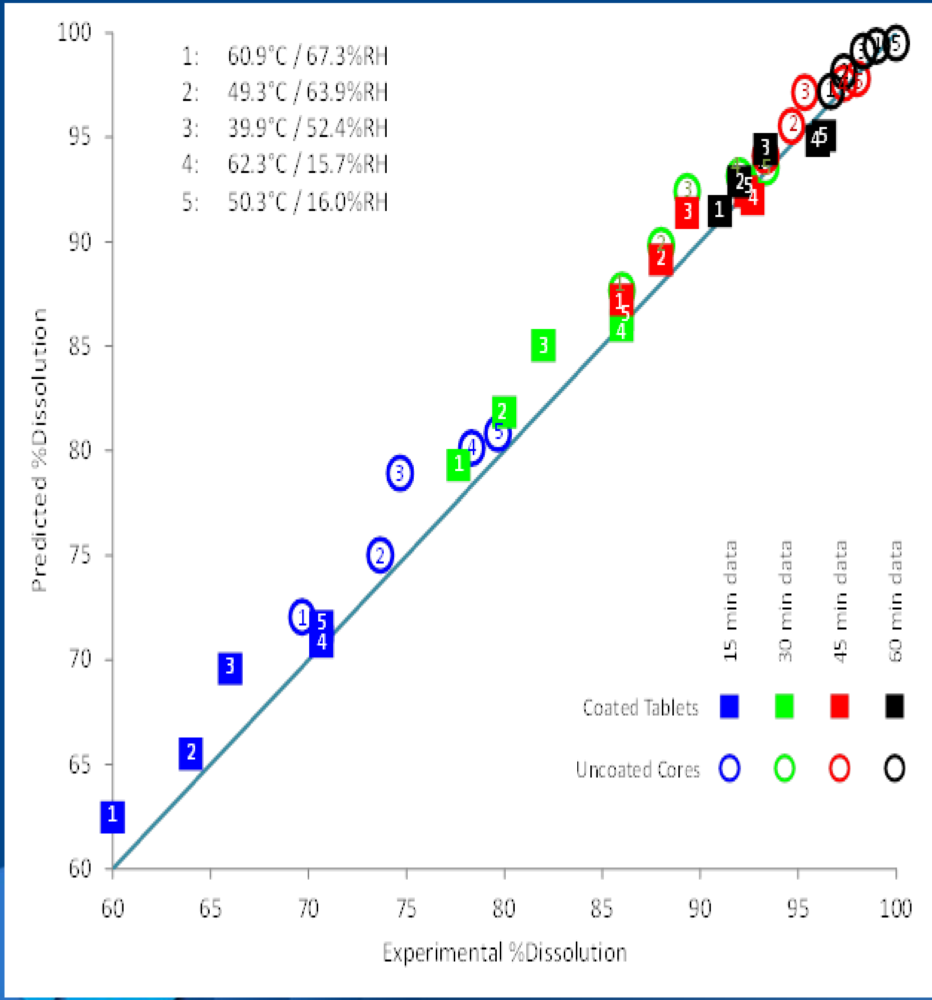
…focus on one of the batches and its corresponding core: they have different rates at stability initial….

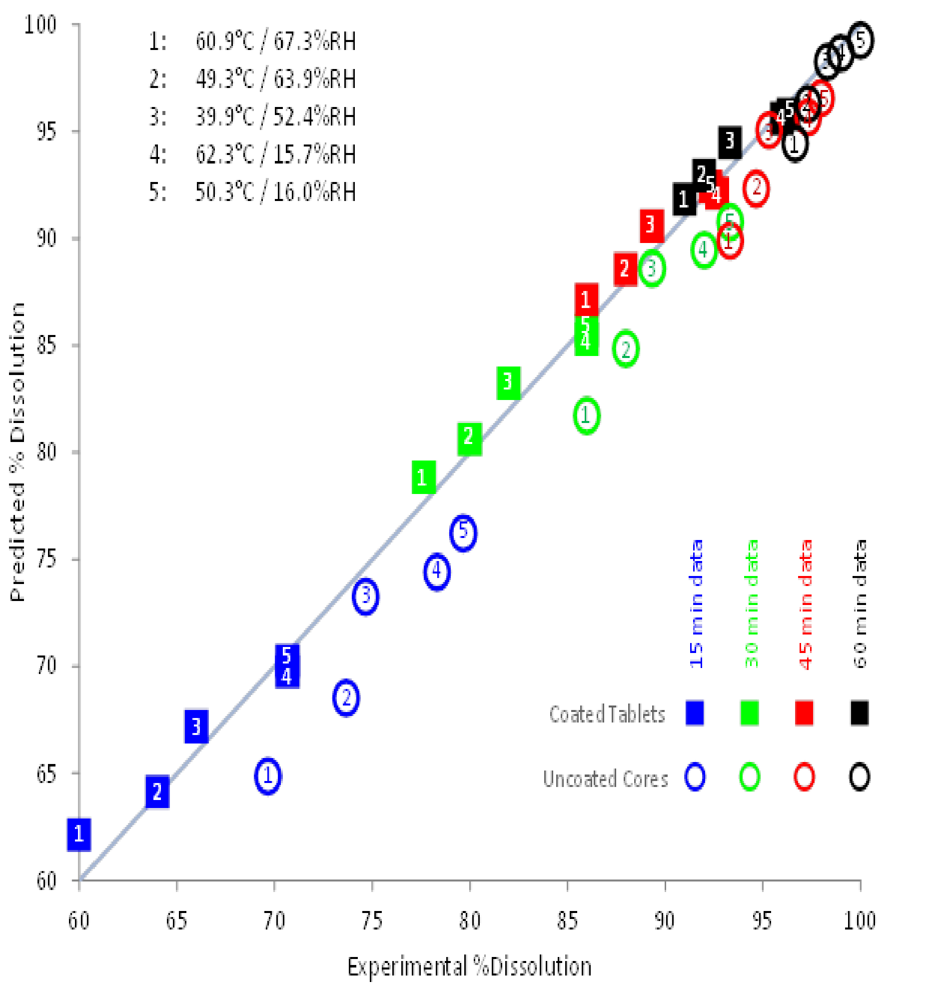
Predicting for other batches

- If the accelerated stability study is conducted on the batch to be predicted then this not an issue
- The tablet cores have a faster dissolution release than coated tablets (prior to stability)
- We can use the model to make predictions in 2 different ways:



Better predictions were obtained when the slowdown was modelled to be *relative* to the stability initial





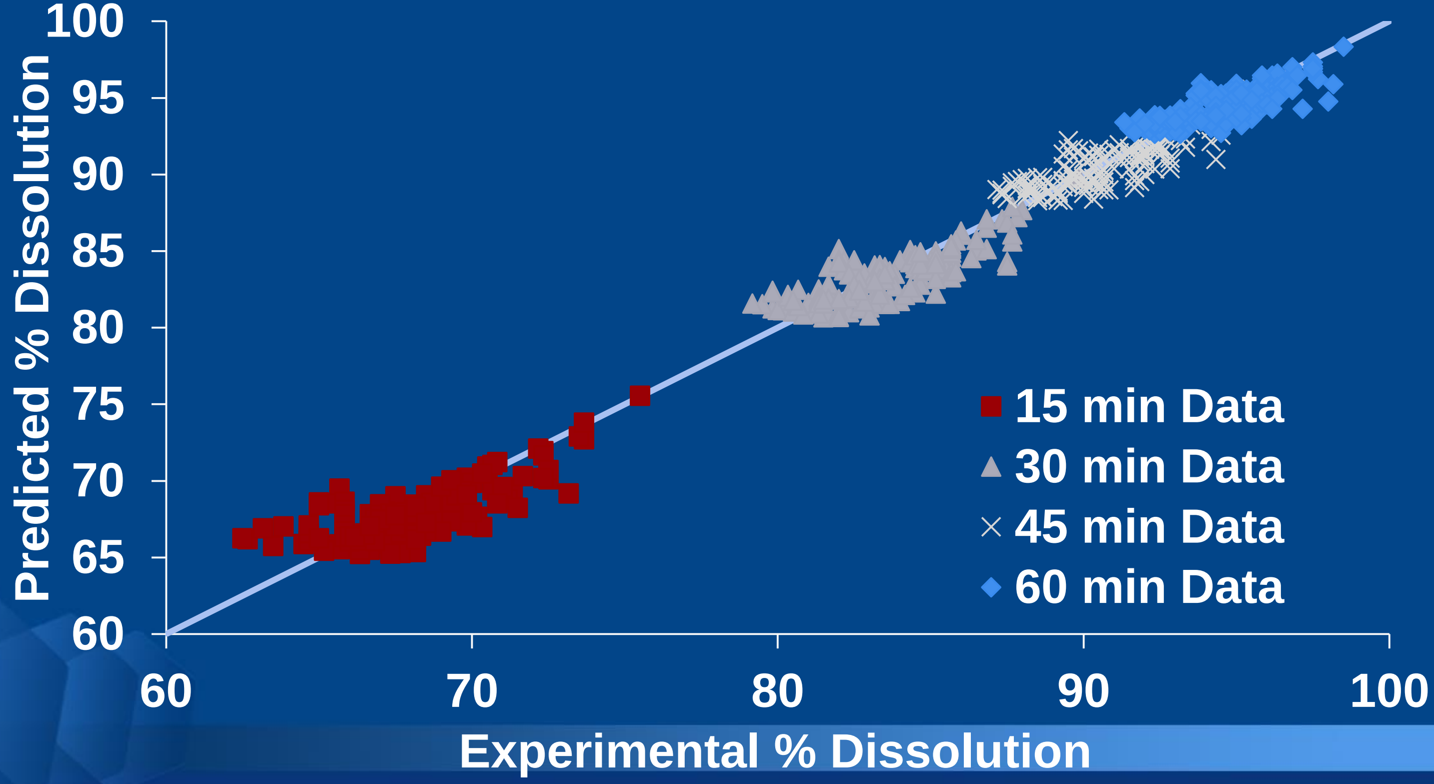
Prediction of Registration Stability Lots

- The samples are **packaged**:
  - The humidity inside the packaging is not fixed
  - The relative humidity (RH) inside packaging vs time can be simulated using established methods
  - Predictions are made by considering a very small duration of time (δt), over which time the humidity is approximately fixed
  - The model can now calculate how much the dissolution slows down during this very small duration
  - The slowdown that occurs over the total storage period is obtained from the accumulation of multiple 'δt' periods

Registration Data: Observed vs Predicted

All data up to 12 months

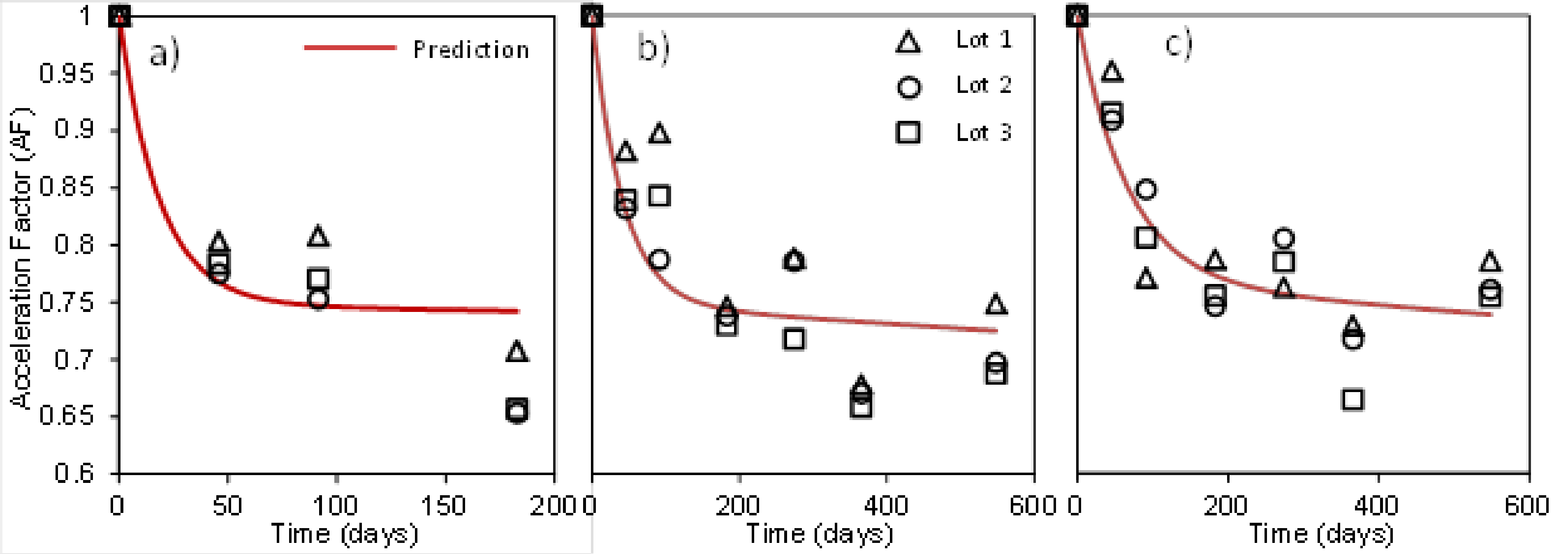
- 3 different Lots
- 3 pack types: 100 count bottles with desiccant, 30 count bottles with desiccant and foil-foil blisters
- 3 storage conditions: 25°C/60%RH, 30°C/75%RH and 40°C/75%RH



Prediction of Registration Stability Lots

Snapshot across different packaging and conditions

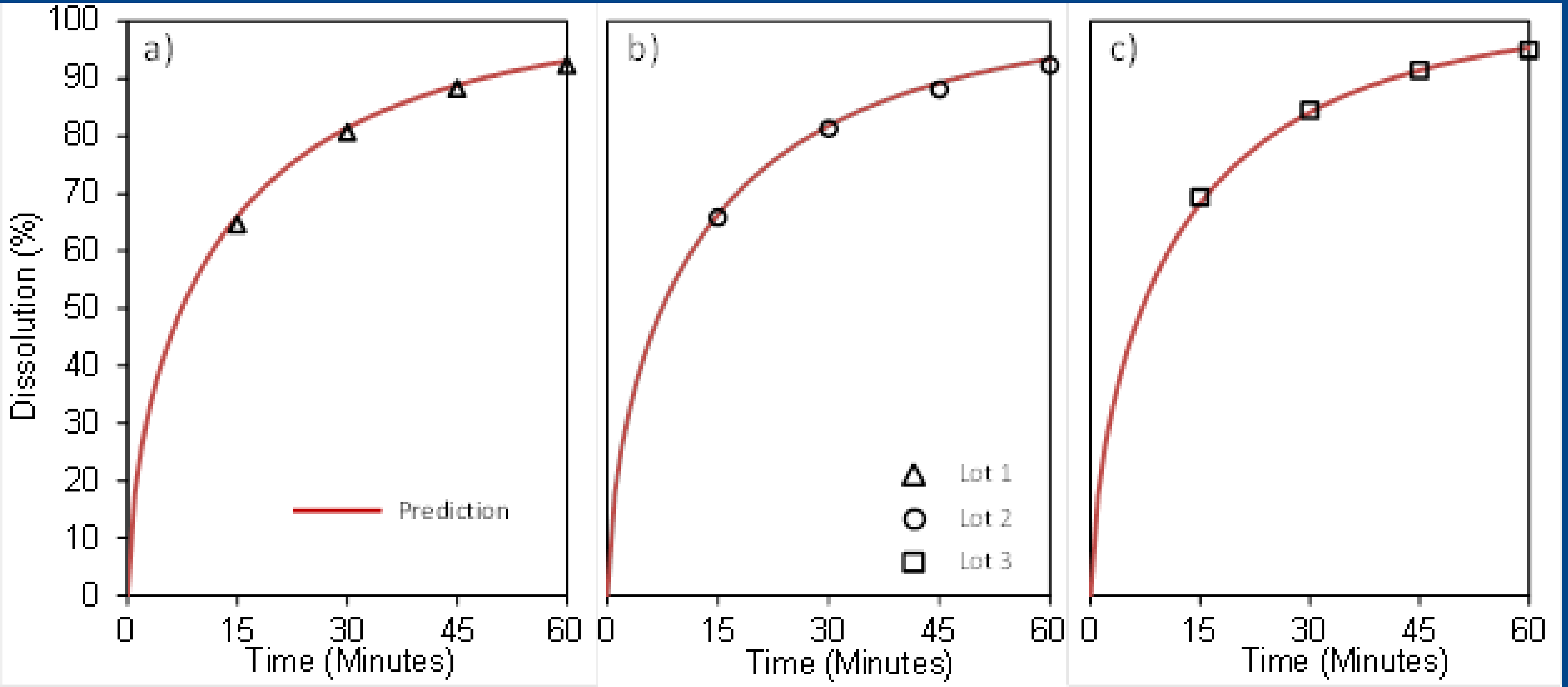
Foil-Blisters 40°C/75%RH	100 count bottles+1g desiccant 30°C/75%RH	30 count bottles+1g desiccant 25°C/60%RH



Prediction of Registration Stability Lots

Snapshot across different packaging and conditions

Foil-Blisters 40°C/75%RH 6 months	100 count bottles+1g desiccant 30°C/75%RH 18 months	30 count bottles+1g desiccant 25°C/60%RH 18 months

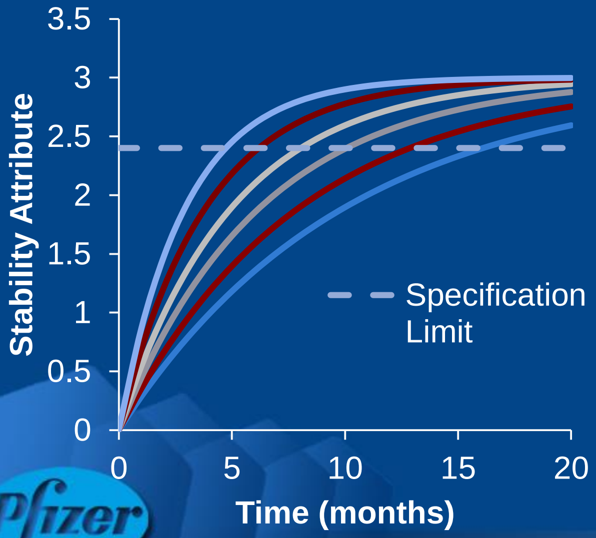


Discussion

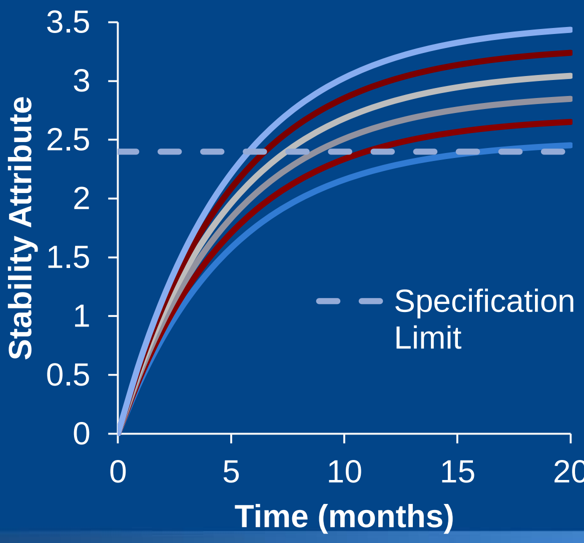
Q Would a simpler approach (e.g. time to failure) have worked?

A Disso stability trend was non-linear; the rate and maximum extent (limit) were both affected by temperature and humidity

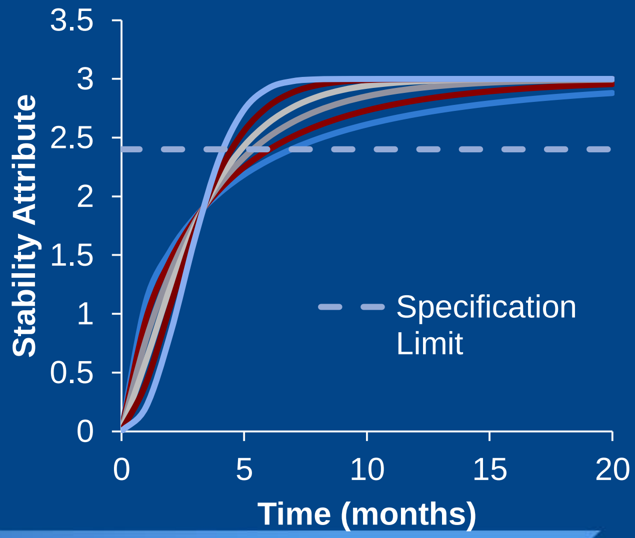
✓
Rate



✓/x
Maximum Extent



x
Shape



Summary

- Long-Term Dissolution can be reasonably predicted from short-term accelerated data
  - A useful screening protocol has been devised (less elevated temperatures)
- The model predicts that the dissolution should not significantly further slowdown in future timepoints
  - Confirmed with later checkpoints
- The model quantifies the effects of temperature and humidity on the dissolution stability
  - The long-term dissolution performance can be predicted for any packaging type and in any climatic zone

Thank you for your attention

Acknowledgements

- Hasan Bozkina
- Mark McAllister
- Gerald Segelbacher
- Neil Clayton
- Jon Beaman

Back Up Slides

Summary of Model – A series of nested models

Weibull Model

AF_{inf} model

k_s model

$$\%\text{Dissolution} = \text{Disso}_{inf} \times \left\{ 1 - \exp\left[-\left(\left\{ AF_0 + \left(\exp\left[C_{0,AF} + \frac{C_{1,AF}}{T} + C_{2,AF}(RH) \right] - AF_0 \right) \times \left[1 - \exp\left(-\exp\left[C_{0,k} + \frac{C_{1,k}}{T} + C_{2,k}(RH) \right] t_s \right) \right] \right\} k_d t_d \right)^n \right] \right\}$$

Exponential Decay Model for AF_t

Background Info

Product Information

Each tablet of Product A consists of:

- Active ingredient
- Microcrystalline cellulose
- Anhydrous calcium phosphate
- Sodium starch glycolate
- Magnesium stearate
- Opadry™ film coat

Dissolution Procedure

USP Apparatus II (rotating paddles) stirred at 100 rpm in 900 mL pH 4.5 acetate, 0.1M. Samples withdrawn for testing after 15, 30, 45 and 60 min.

Accelerated Predictive Stability Protocol

- Humidity-controlled ovens set at 60°C/75%RH and 50°C/75%RH; samples stored in open glass petri dishes
- Saturated salt solutions of LiCl, $MgCl_2$ and NaBr were used to achieve humidity levels of ~11%RH, ~30%RH and ~50%RH respectively; samples stored in airtight bell jars along with the saturated salt solutions
- In all cases the temperature and humidity conditions were measured using data loggers kept in close proximity to the samples.