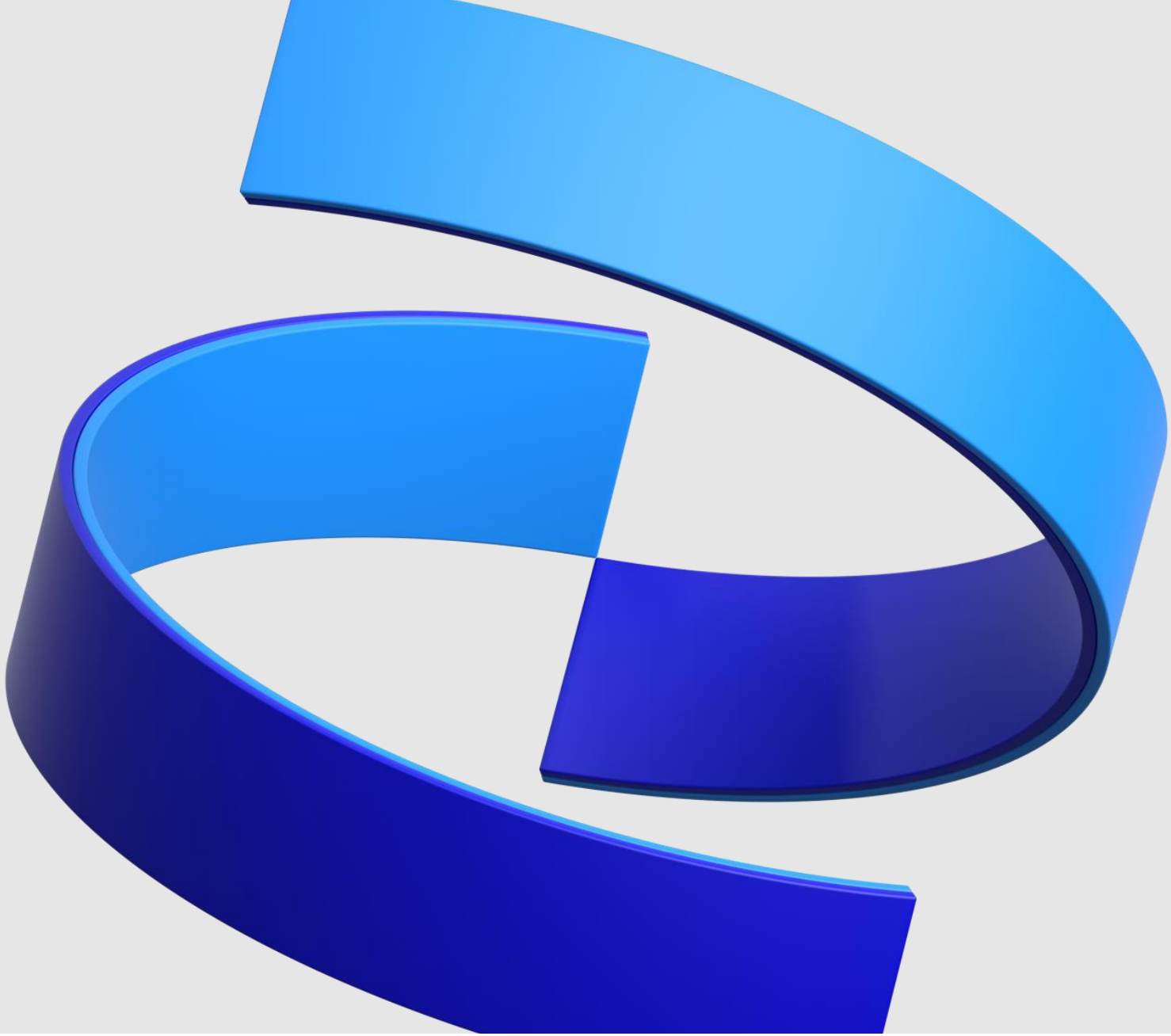
The Effect of Excipient Load on Drug Product Stability



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Science of Stability Conference
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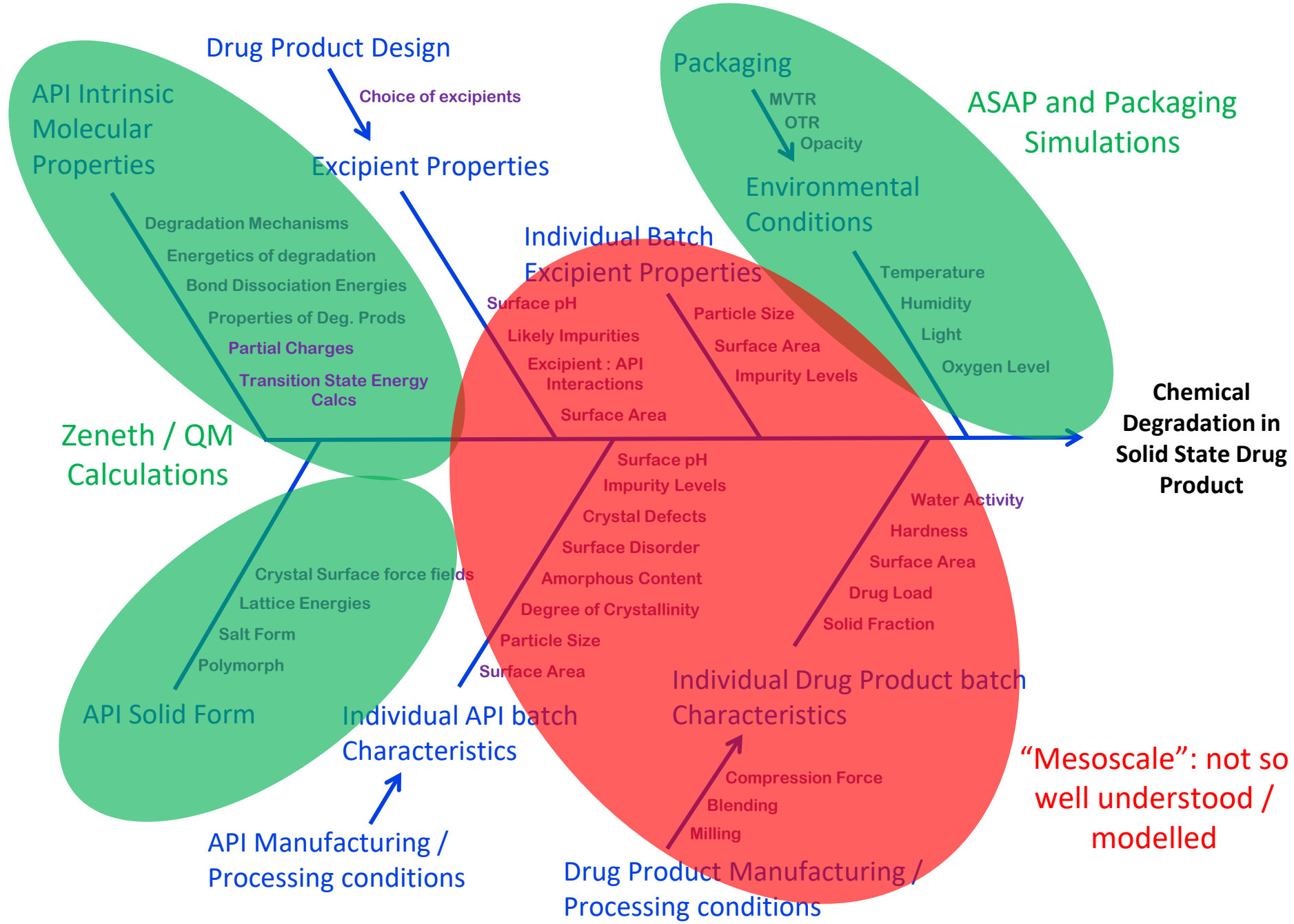
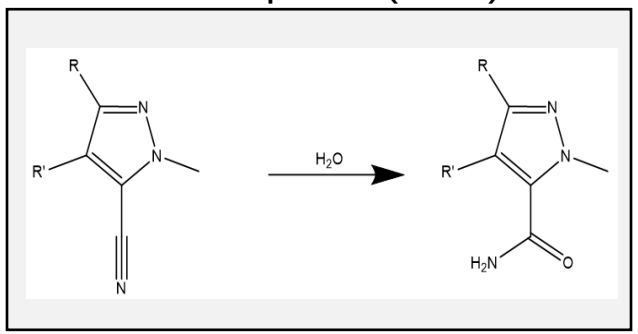
Presentation Outline

- Lower API loads almost always have worse stability than corresponding higher API load formulations
- A key part of drug product development is the selection of the composition (excipient compatibility), API particle size specification and API load
- Products often require a range of API loads to meet clinical and commercial demands
- This presentation provides an update on the ‘Contact Surface Area’ model (**SOS 2019**) which helps to understand, model and predict the effects of:
    - API load
    - Particle size
    - Product composition
- Application to N-nitrosamines as ***degradation products*** (**SOS 2021)**
- Factors affecting the rate and extent of nitrosamine formation

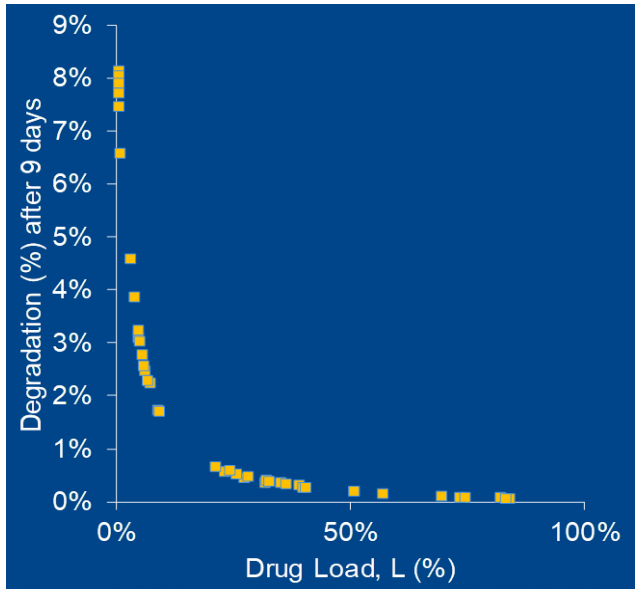

Drug Product Design
Choice of excipients
API Intrinsic Molecular Properties
Excipient Properties
Packaging
MVTR
OTR
Opacity
ASAP and Packaging Simulations
Environmental Conditions
Degradation Mechanisms
Energetics of degradation
Bond Dissociation Energies
Properties of Deg. Prods
Partial Charges
Transition State Energy Calcs
Individual Batch Excipient Properties
Surface pH
Likely Impurities
Excipient : API Interactions
Surface Area
Particle Size
Surface Area
Impurity Levels
Temperature
Humidity
Light
Oxygen Level
Chemical Degradation in Solid State Drug Product
Zeneth / QM Calculations
Crystal Surface force fields
Lattice Energies
Salt Form
Polymorph
Surface pH
Impurity Levels
Crystal Defects
Surface Disorder
Amorphous Content
Degree of Crystallinity
Particle Size
Surface Area
Water Activity
Hardness
Surface Area
Drug Load
Solid Fraction
API Solid Form
Individual API batch Characteristics
Individual Drug Product batch Characteristics
Compression Force
Blending
Milling
API Manufacturing / Processing conditions
Drug Product Manufacturing / Processing conditions
“Mesoscale”: not so well understood / modelled

Background (Recap of SOS 2019 – Binary API:Excipient Mixtures)

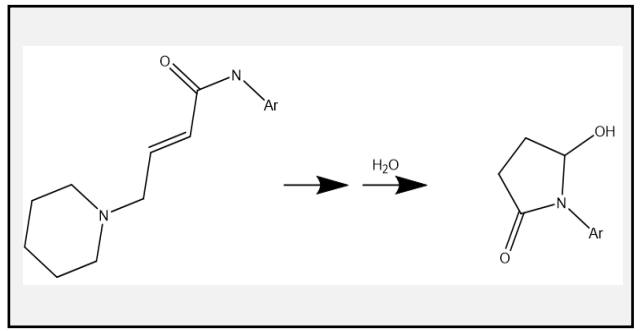
Product A: Dicalcium Phosphate (DCP)



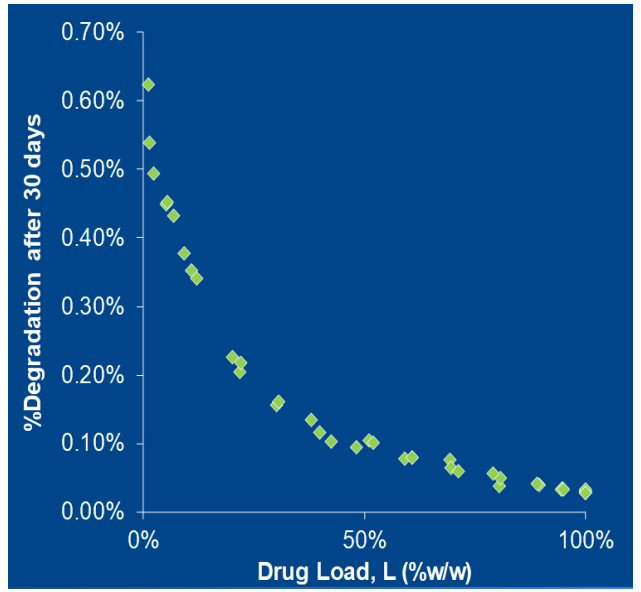
Degradation at 70°C/75%RH



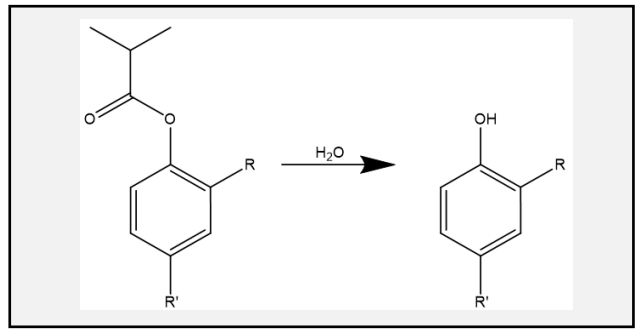
Product B: Avicel (MCC)



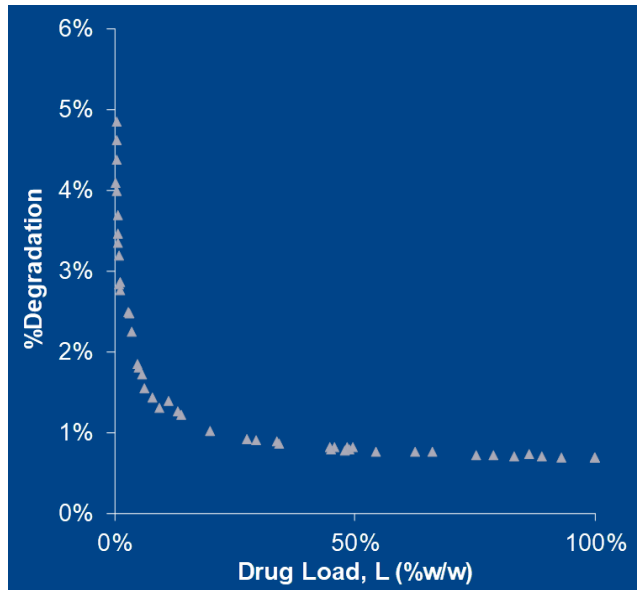
Degradation at 80°C/40%RH



Product C : Avicel (MCC)



Degradation at 50°C/30%RH



Modelling the Degradation – Drug Load Relationship

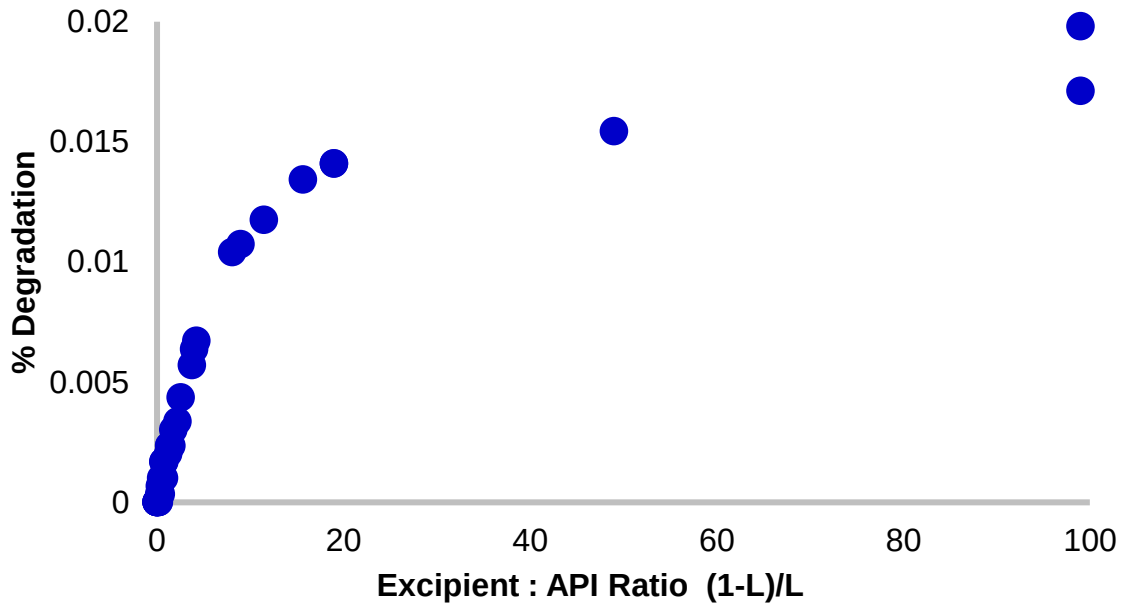
- Degradation products are measured as %API

$$\%Deg = \frac{\text{Amount of Deg}}{\text{Amount of API}} \times 100$$

- Maybe the amount of Deg is constant, and only the denominator is changing?

$$\%Deg \propto \text{Excipient : API ratio} = \frac{(1 - L)}{L}$$

$\frac{(1 - L)}{L}$ ← Excipient Load / API Load



“Contact Surface Area” Model

%Deg is proportional to the amount of API in contact with excipient

$$\text{Deg} \propto \frac{\text{Surface area of the excipient in a sample}}{\text{Total surface area of the sample}} = \frac{(1-L)\times S_E}{(L\times S_{API}) + (1-L)\times S_E}$$

‘Available’ surface area of API in sample

‘Available’ surface area of excipient in sample

Divide top and bottom of this equation by S_E to give:

$$\text{Deg} \propto \frac{1 - L}{R_{ASA}.L + 1 - L}$$

$$\text{Deg} = \text{Deg}_{Limit} \times \left(\frac{1 - L}{R_{ASA}.L + 1 - L} \right)$$

Two parameters (Deg_{Limit} and R_{ASA}) need to be fitted to data (determined experimentally)

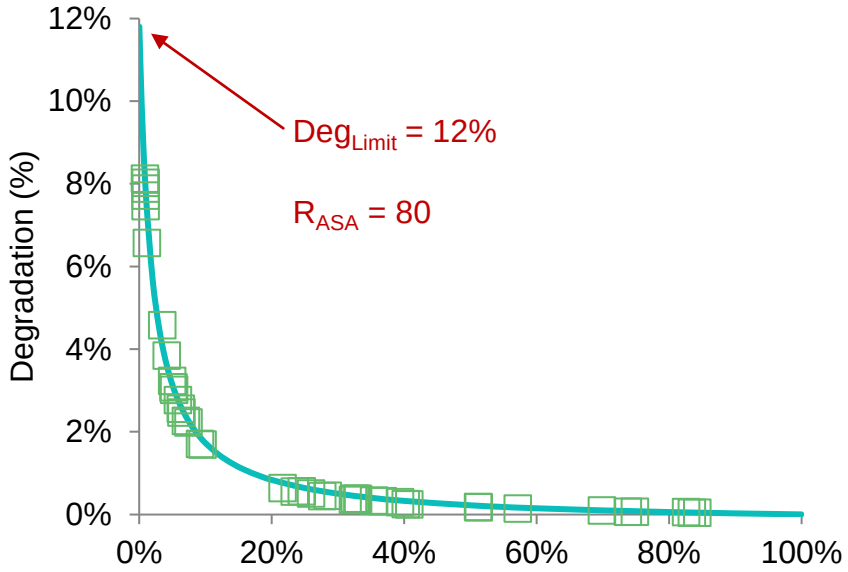
L is drug load (between 0 and 1)

S_E and S_{API} are the ‘available’ surface areas of the excipient and API; measured in units of m^2/g.

R_{ASA} = ratio of ‘available’ surface areas (S_{API}/S_E)

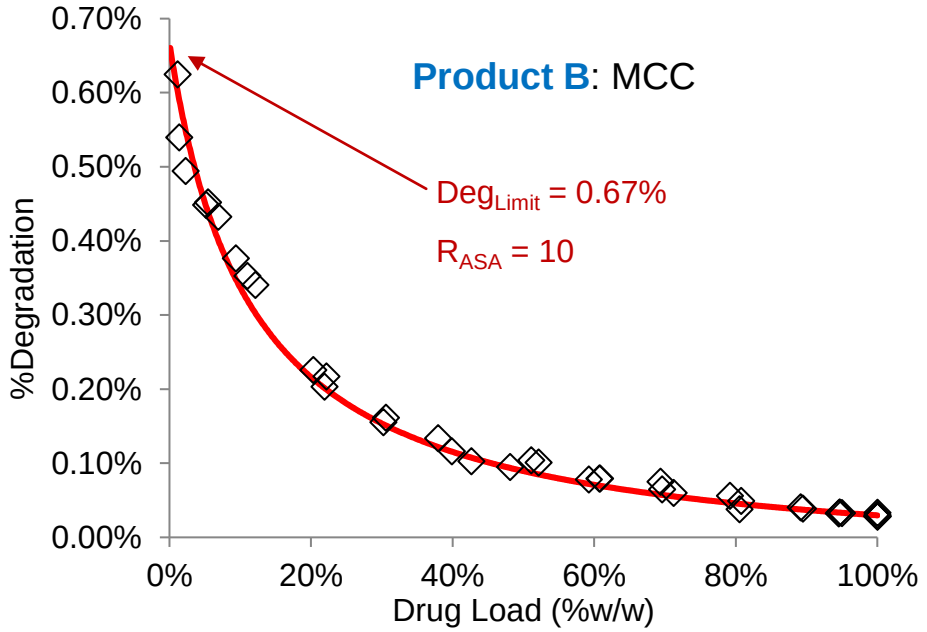
Deg_{Limit} = Degradation at the lowest possible drug load (i.e. maximum degradation)

Product A: Dicalcium Phosphate (DCP)

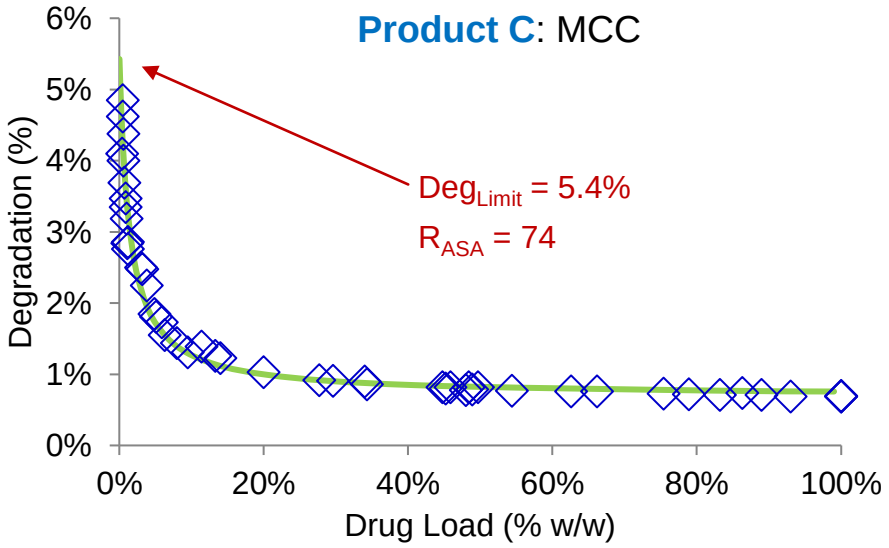


Data from at least 2 different drug loads are required to generate the curve because there are 2 parameters (Deg_{Limit} and R_{ASA}) that need to be fitted

Product B: MCC



Product C: MCC



Case Studies: Applications of Model

A) To Multicomponent Formulations

Product D

ASAP Data obtained for development lots:

API Load (mg)	MCC (mg)	Lactose (mg)	Glycerol Dibehenate (mg)	PVP (mg)	Capsule Size	API Surface Areas (m^2/g) by BET
48	13	13	4.0	2.4	4	0.283 & 1.097
80	21	21	6.7	4.0	3	0.500
160	43	43	13.3	8.0	1	0.283 & 1.097
80	113	113	16.7	10.0	0	0.147, 0.223, 0.626 & 0.878
160	35	35	12.5	7.5	0	0.147, 0.223, 0.626 & 0.878

1:1 5:3

Objective: to understand and predict product shelf life:

Dimer is key deg

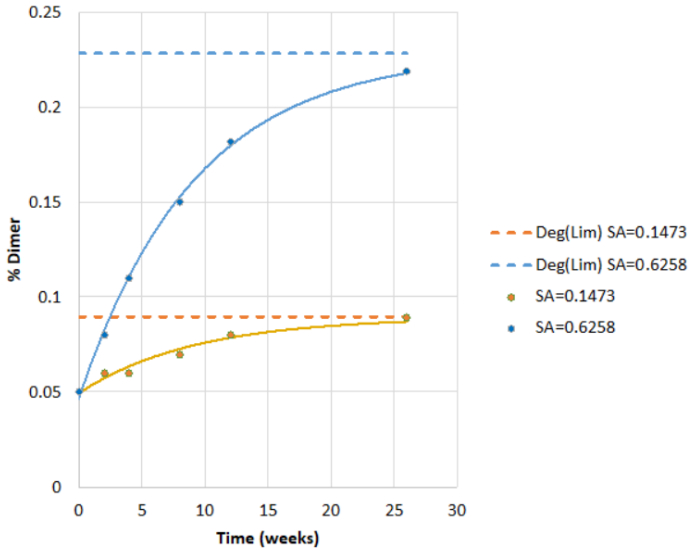
Different drug loads (& different excipient ratios); capsule formulation

Different API particle sizes (surface areas)

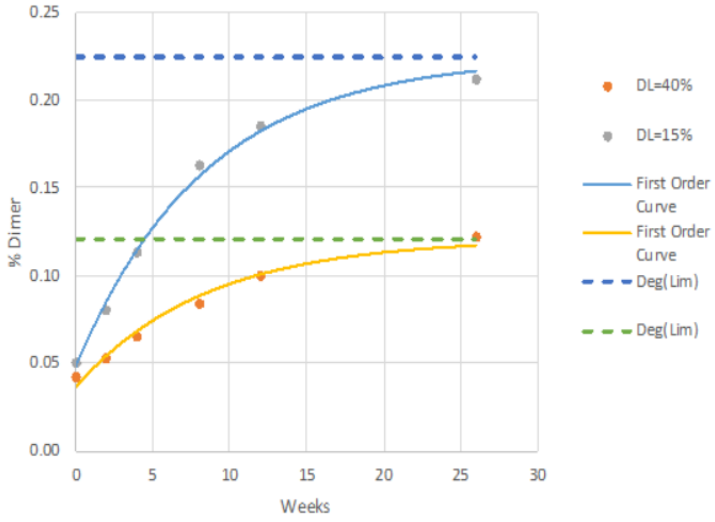
Different storage conditions (Temperature and Humidity)

Case Studies: Product D

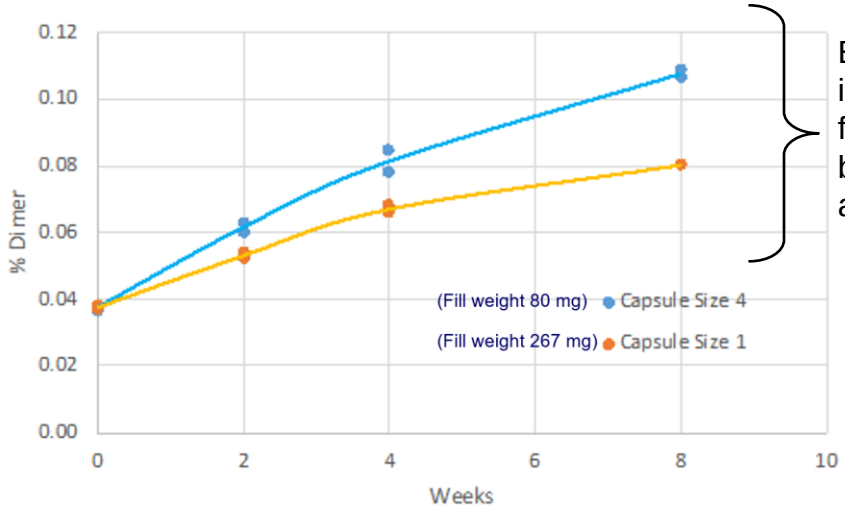
Effect of API particle size (surface area):



Effect of Drug Load

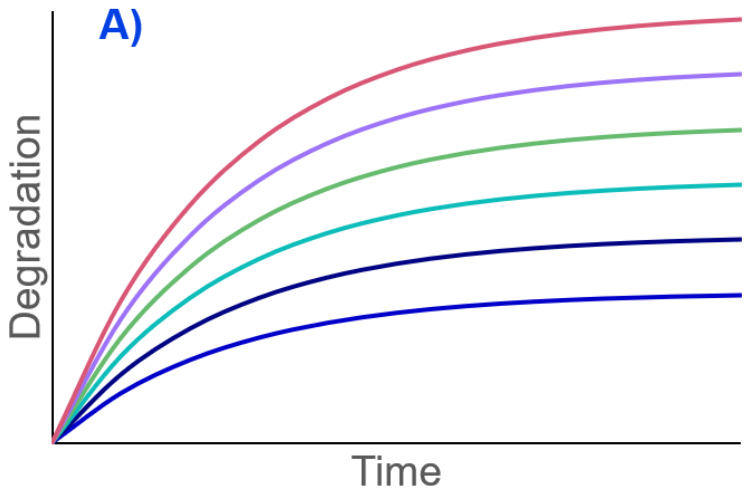


Effect of Capsule Size & Fill Weight



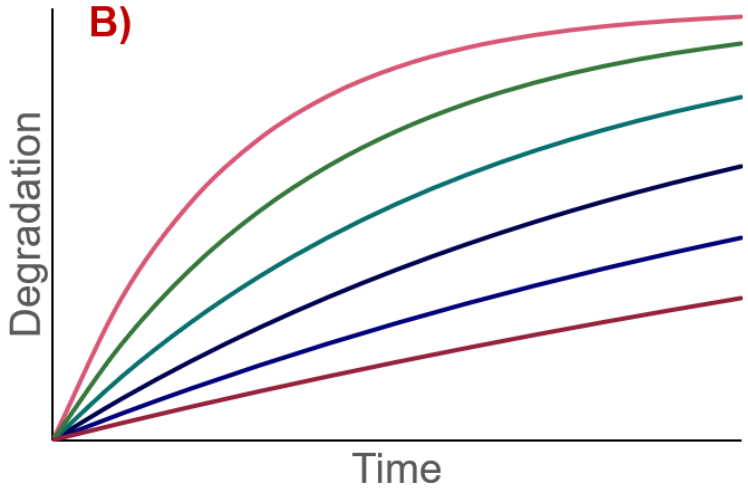
Even though the capsule shell is not mixed in with the other formulation components, the blend:capsule ratio appears to affect the stability.

Aside: Degradation Curve Shapes



Type A)

- Same rate constant (k)
- Different endpoints (plateau levels) → different amount of API in 'reactive state'



Type B)

- Different rate constants (k)
- Same endpoint (plateau level) → same amount of API in 'reactive state'

Examples: API Load, API Particle Size

Temperature

Humidity *can* affect both rate constant and endpoint

Isoconversion approaches more applicable to Type B

Non-linear degradation curves usually approximate well to 'first order' curve

1st order = consistent with depleting reactant (observed rate ∝ amount of reactant remaining)

Contact Surface Area Model:

Extension to Multicomponent Formulations (proposed in SOS 2019)

$$Deg = Deg_{Limit,E1} \times \frac{\text{Surface area of Excipient 1 in sample}}{\text{Total surface area of the sample}} + Deg_{Limit,E2} \times \frac{\text{Surface area of Excipient 2 in sample}}{\text{Total surface area of the sample}} + \text{Etc.}$$

$$Deg = \frac{S_{DS} \times (D_{E1} \cdot L_{E1} \cdot S_{E1} + D_{E2} \cdot L_{E2} \cdot S_{E2} + D_{E3} \cdot L_{E3} \cdot S_{E3})}{L_{DS} \cdot S_{DS} + L_{E1} \cdot S_{E1} + L_{E2} \cdot S_{E2} + L_{E3} \cdot S_{E3}}$$

Surface area of Excipient 1 in sample

Surface area of Excipient 2 in sample

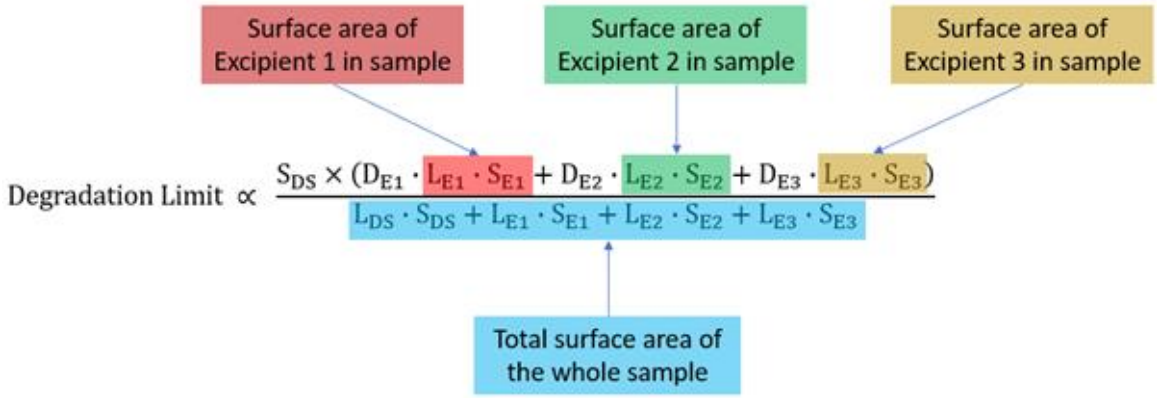
Surface area of Excipient 3 in sample

Model assumes the degradation is proportional to the surface area of the drug substance

Total surface area of the whole sample

Contact Surface Area Model:

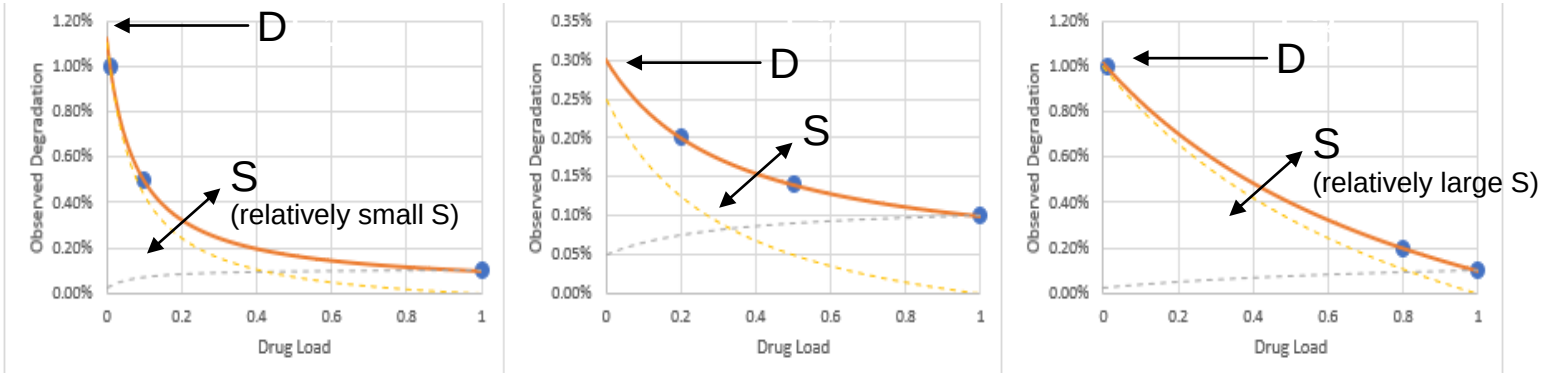
Extension to Multicomponent Formulations



In this model, each excipient has 2 fitted parameters “S” and “D”

“S” : loosely based on its **S**urface area. Perhaps better thought of as its ‘reactive surface area’ or ‘available surface area’.

“D” : based on the **D**egradation extent. This is the degradation extent at maximum dilution of the API in the excipient:



Case Study: Product D

Excipient 1 = Diluent A + Diluent B (1:1)

Excipient 2 = Lubricant + Disintegrant (5:3)

Excipient 3 = Capsule Shell

$$Deg = \frac{S_{DS} \times (D_{E1} \cdot L_{E1} \cdot S_{E1} + D_{E2} \cdot L_{E2} \cdot S_{E2} + D_{E3} \cdot L_{E3} \cdot S_{E3})}{L_{DS} \cdot S_{DS} + L_{E1} \cdot S_{E1} + L_{E2} \cdot S_{E2} + L_{E3} \cdot S_{E3}}$$

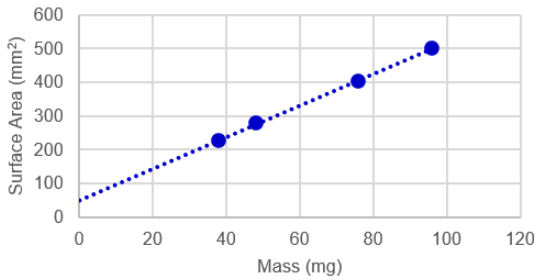
Surface area of Excipient 1 in sample

Surface area of Excipient 2 in sample

Surface area of Excipient 3 in sample

Total surface area of the whole sample

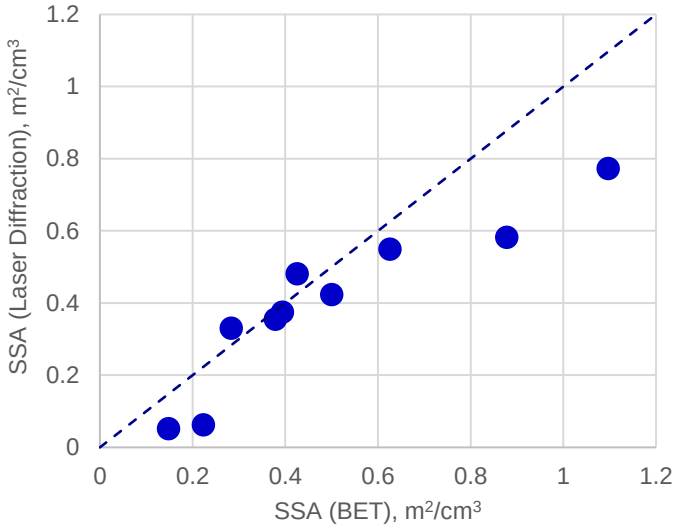
'L' is the loading for each excipient (units e.g. mass)
The loading for the capsule shell could be input as either mass or surface area (based on geometry/dimensions of the shell):



Capsule Size	Mass of Gelatin (mg)	Surface area of Shell (mm^2)
0	96	500
1	76	404
3	48	278
4	38	227

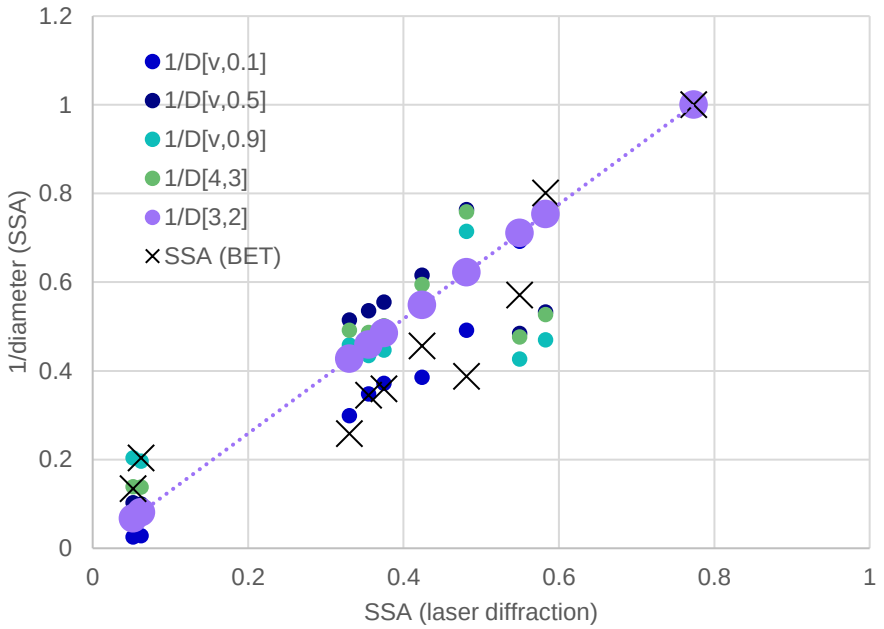
Case Study: Product D

API surface area input data: BET or Laser Diffraction?
Both techniques can output volume specific surface area (m^2/cm^3)



- 1/D[v,0.1] worked almost as well

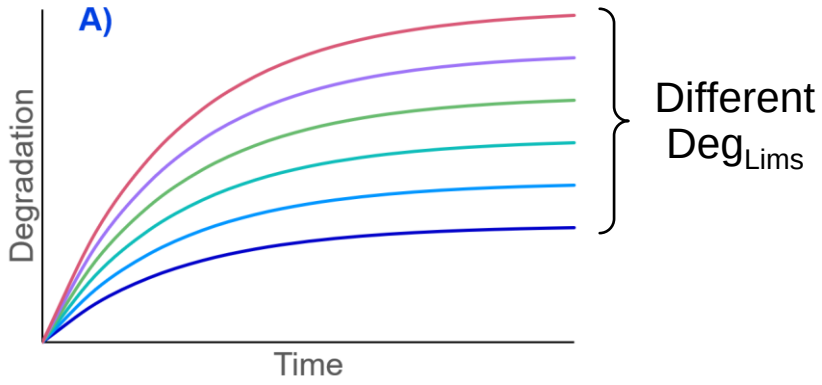
- Degradation model fit better using laser diffraction surface areas
- Volume specific surface area is not a default output from laser diffraction software, but using 1/D[3,2] as the surface area gives identical model.



Case Study: Product D

The full model, taking into account, T, RH, time, API particle size, formulation composition and capsule shell size:

$$Deg_t = Deg_0 + (Deg_{Lim} - Deg_0) * [1 - exp(-k.t)]$$



Where

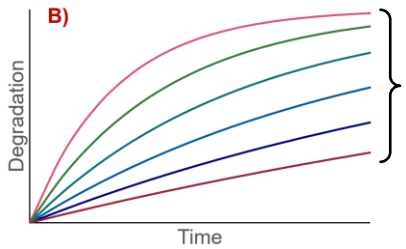
$$Deg_{Lim} = \exp\left[\text{Ln } A_{D\_E1} + \frac{E_{a,D}}{R}\left(\frac{1}{T}\right) + B_D(RH) + C_D(RH)^2\right] \times \frac{S_{DS} \times \left(L_{E1} \cdot S_{E1} + f_{E2/E1} \cdot L_{E2} \cdot S_{E2} + f_{E3/E1} \cdot L_{E3} \cdot S_{E3}\right)}{L_{DS} \cdot S_{DS} + L_{E1} \cdot S_{E1} + L_{E2} \cdot S_{E2} + L_{E3} \cdot S_{E3}}$$

Temperature coefficient (E_a) is relatively small: Temperature has a small effect on Deg_{Lim}

Contact surface area model: Drug product composition only affects Deg_{Lim} (not rate)

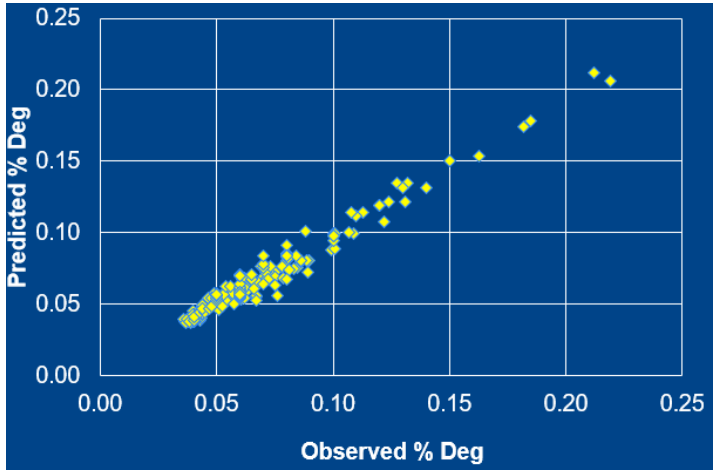
$$k = Exp[\text{Ln } A_k - E_{a,k}/R(1/T) + B_k(RH) + C_k(RH)^2]$$

Rate constant is affected by temperature and humidity

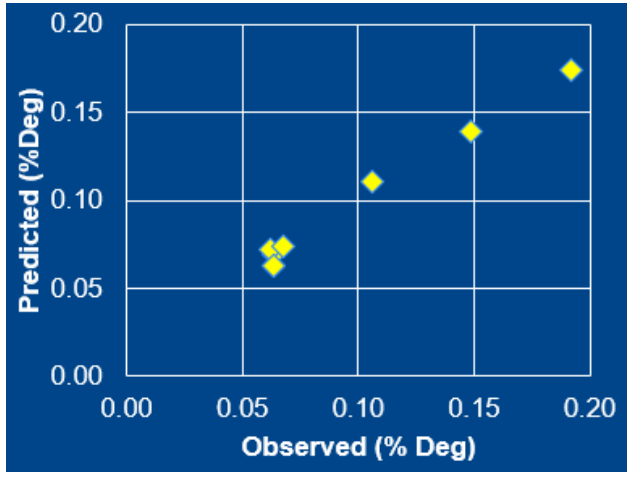


Different ‘k’s

Case Study: Product D

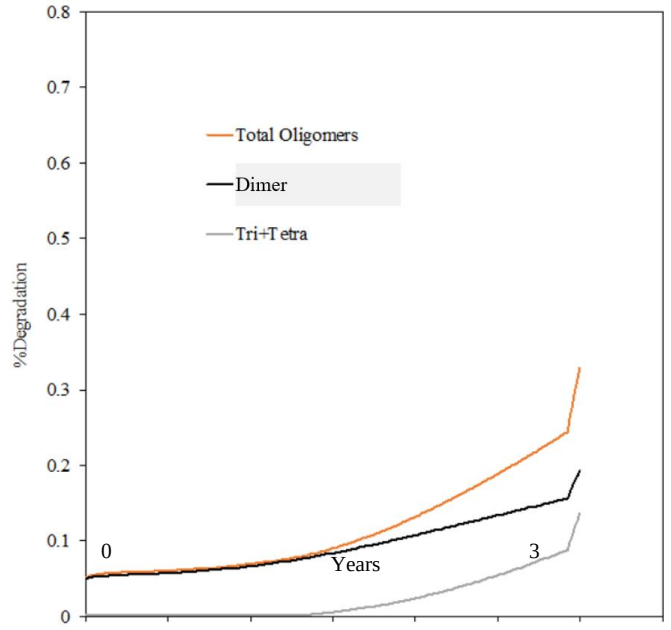


External validation of the model using paediatric formulations made later:



Coupling the model to packaging simulation to make real-world predictions:

Temp /ºC	**30**	Dose Strength	30
%RH	**75**	Volume specific surface area, Sv (m2/cm3)	0.4
Duration (Months)	**60**	Drug Load %w/w (mgA)	37.5
Initial Water activity	**0.36**	Initial total Oligs (%)	0.051
Initial Water Content (%w/w)		Initial PF-06757444 (%)	0.05
Inner Packaging	**60 cc Bottle**	Capsule Size	4
Outer Packaging	**None**	Water Activity of Shell	0.36
Unit count (e.g. 1 for blister)	**28**	Water Activity of Contents	0.36
Grams of desiccant (in inner packaging)	**1**	Capsule Shell Loading Metric	Capsule Surface Area (mm2)



Case Study: Product E

Objective: to understand and predict product shelf life as a function of:

- Time
- Temperature
- RH
- Drug Load
- API particle size
- Solid Fraction

3 Main Degs: Dimer, Diol, Pruv Adduct
Model was built for Total Degs, Dimer, Diol, Pruv Adduct and RRT 3.4
Essentially the **same model** used for Product D was used for Product E:

$$\mathbf{Deg(t) = Plateau\ Level * [1 - exp(-(A \,.\, exp(-E_a / RT + B \,.\, RH) \,.\, t)]}$$

$$\text{Plateau Level} = \text{Exp}(\text{LnA}_P - E_{a,P}/RT + B_P.RH) * S_{DS} * (1 - L) / (L * S_{DS} / S_E + 1 - L) * SF$$

Where SF is the solid fraction.

Contact Surface Area Model Component

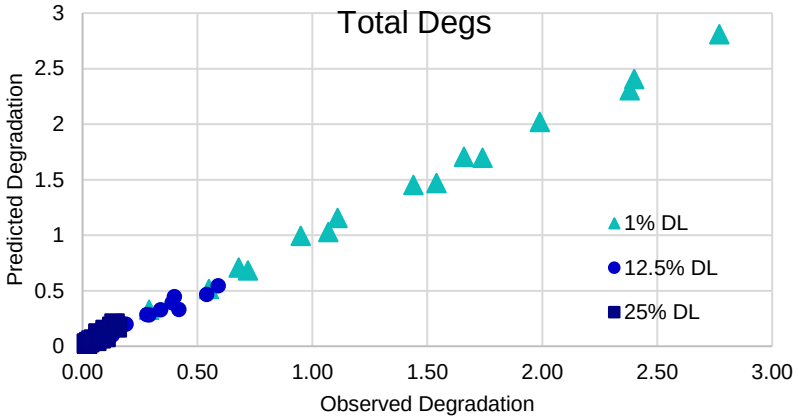
Correcting for SF in this way brought about a minor improvement to model fit

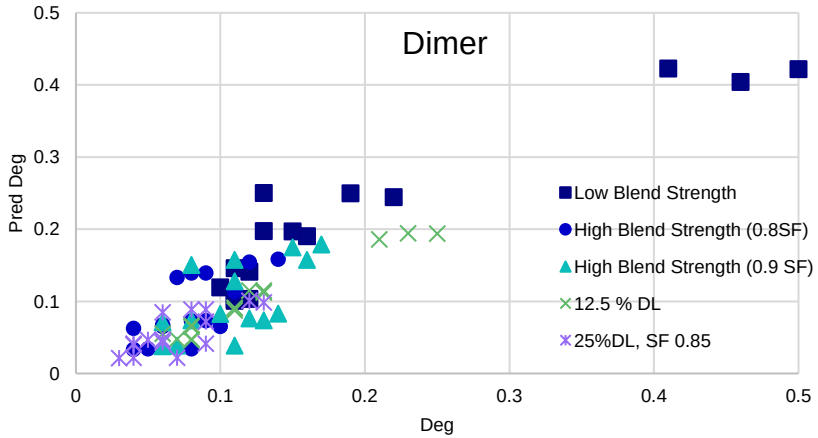
The rate constant, k, is dependent on temperature and humidity in the usual 'ASAP' way: $k = A.\exp\left(\frac{-E_A}{RT} + B.RH\right)$

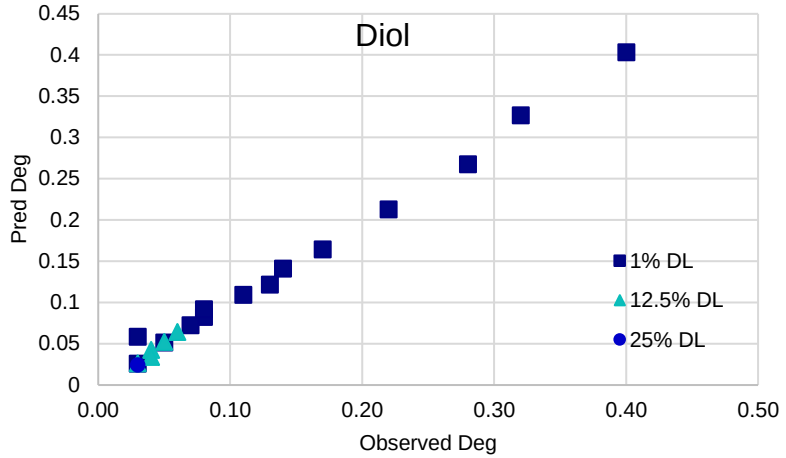
Case Study: Product E

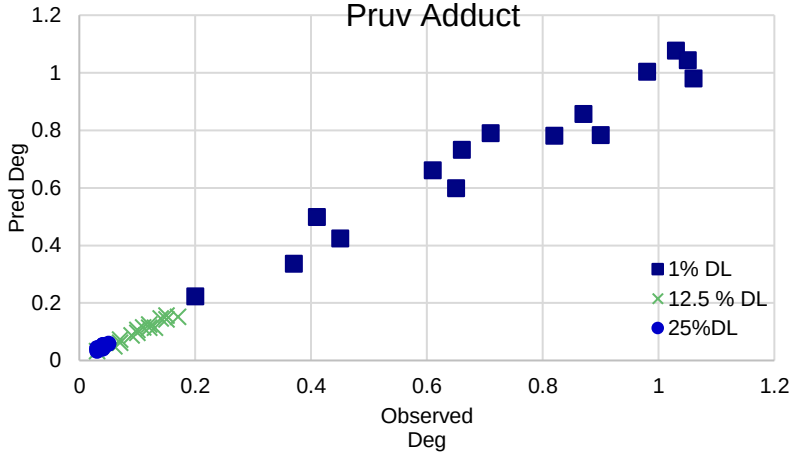
ASAP study with conditions at:

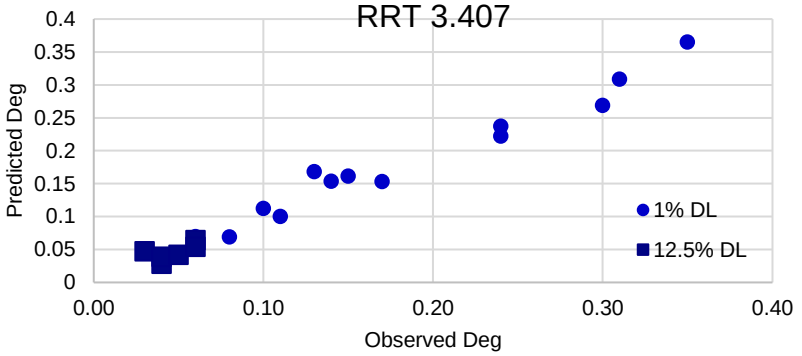
- 50°C/30%RH
- 50°C/75%RH
- 60°C/40%RH
- 60°C/50%RH
- 70°C/10%RH







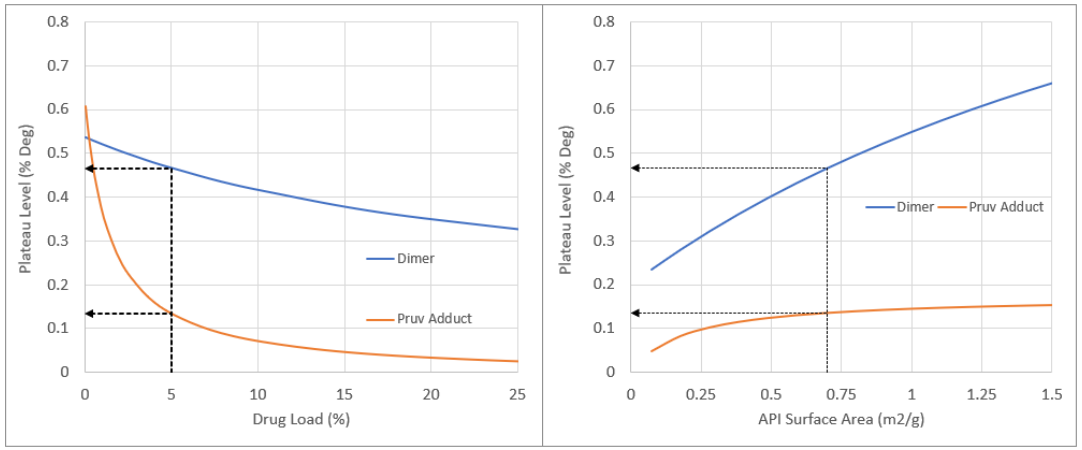




Case Study: Product E

…Benefits of developing a model

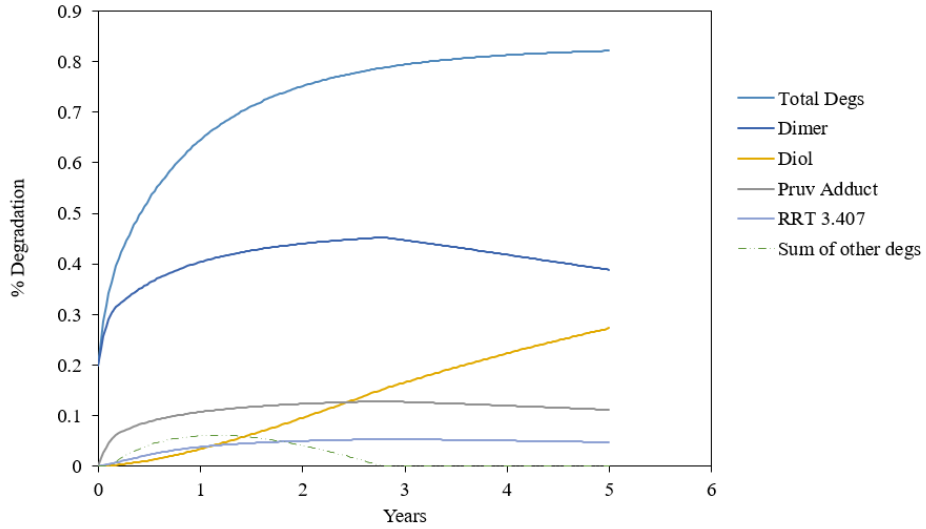
Understanding the Effects of Drug Load and API Particle Size



Coupling to packaging simulation to predict long-term packaged stability

Dimer at t=0 (%)	0.2
Pruv adduct at t=0	0
DL(%)	5
Solid Fraction	0.85
% Conf	80
API Surface Area by Laser Diffraction	0.7

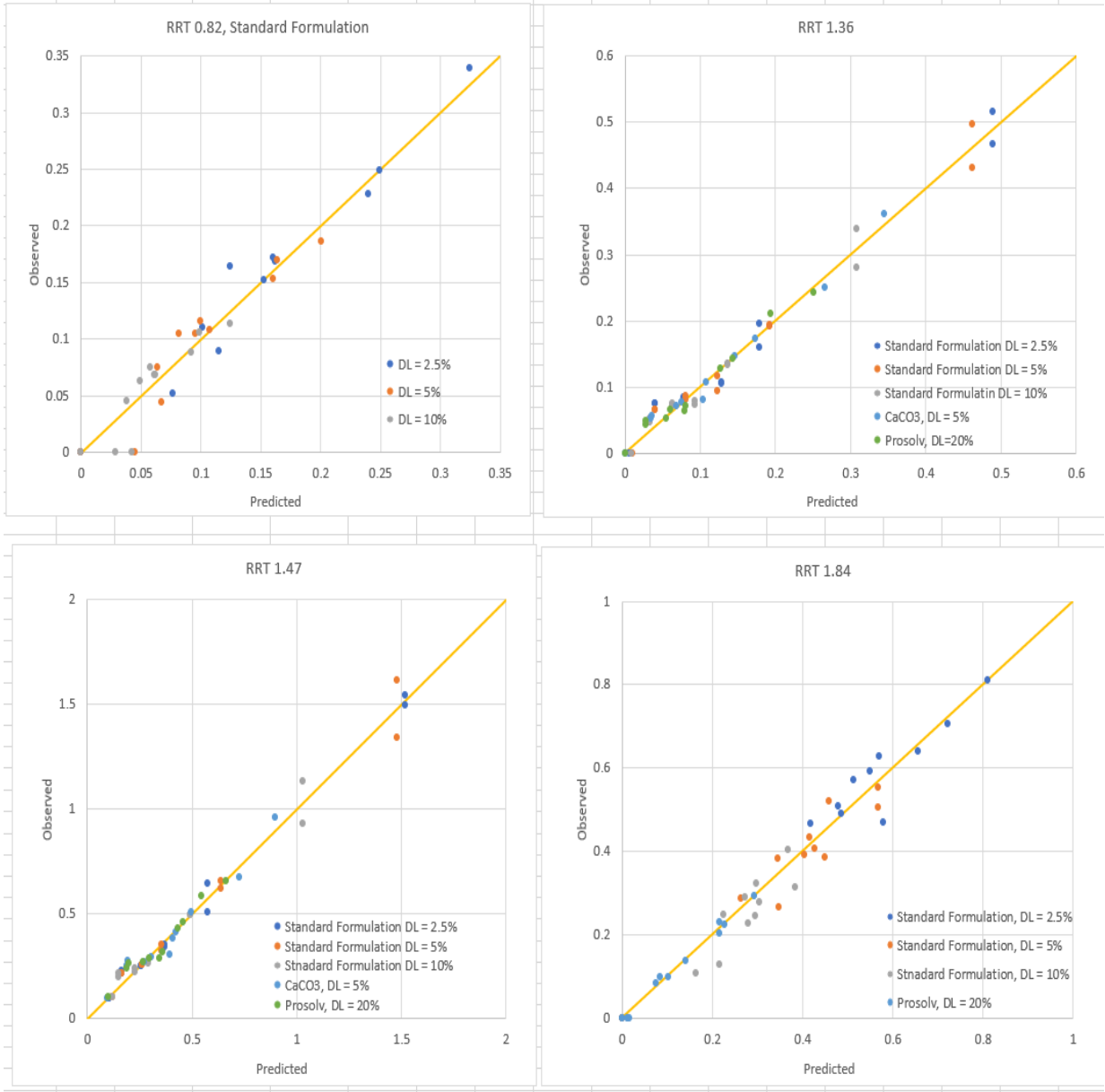
Temp /°C	30
%RH	75
Duration (Years)	5
Initial Water activity	0.3
Initial Water Content (%w/w)	
Inner Packaging	Aclar 2000 Blister
Outer Packaging	None
Unit count (e.g. 1 for blister)	1
Grams of desiccant (in inner packaging)	0



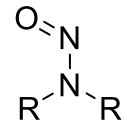
Case Study: Product F

Objective: to understand and predict product shelf life as a function of:

- Time
- Temperature
- RH
- Three Different Formulations
  - One formulation at 3 different drug loads (2.5%, 5% and 10%)
- 4 Main Degs
- ASAP data at 50°C/75%RH, 60°C/40%RH, 70°C/10%RH, 70°C/40%RH and 70°C/75%RH
- Same model used again



Application to Nitrosamine Formation in Drug Products

"Vulnerable amine" + Nitrosating agent + Favourable conditions → 

'*N*-Nitrosamine'

E.g. API

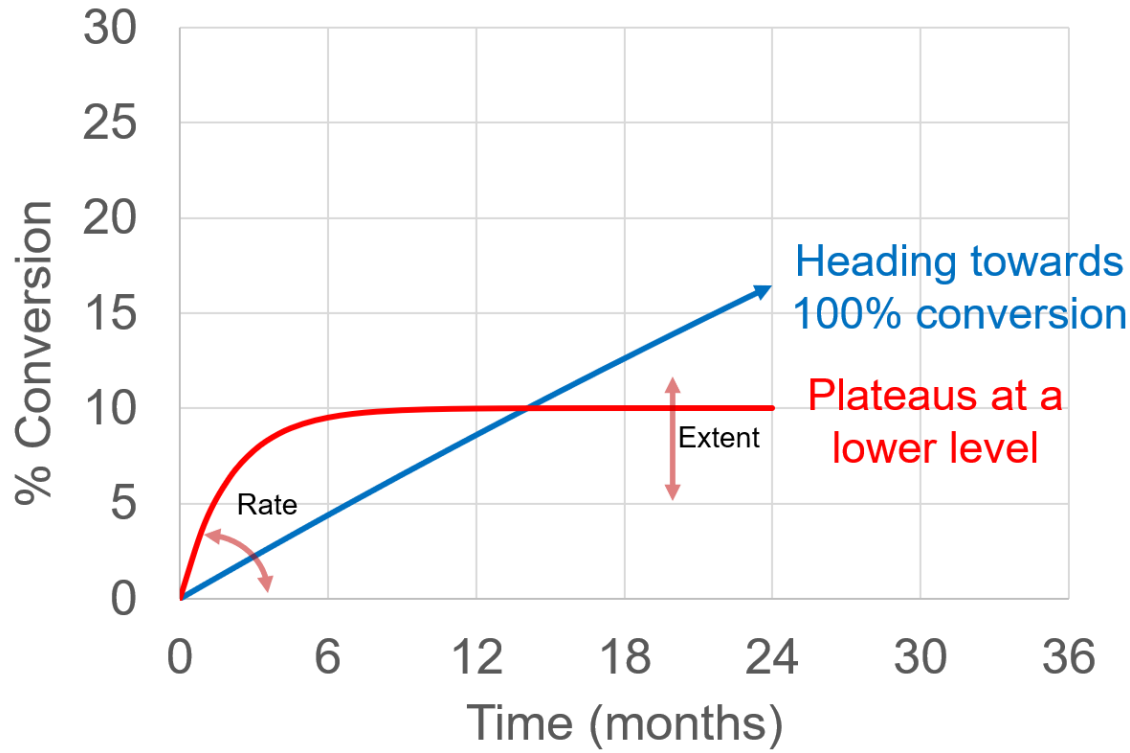
E.g. Nitrites present as trace impurities in excipients

- LC-MS-MS is needed to provide the necessary sensitivity and selectivity
- The data may be subject to noise as compared to other degradation products

Same Objective: Predict degradation levels as a function of formulation, storage conditions and time

Curve Shape

What factors affect the rate and extent of nitrosation?



Heading towards 100% conversion

Often seen in Solutions

Plateaus at a lower level

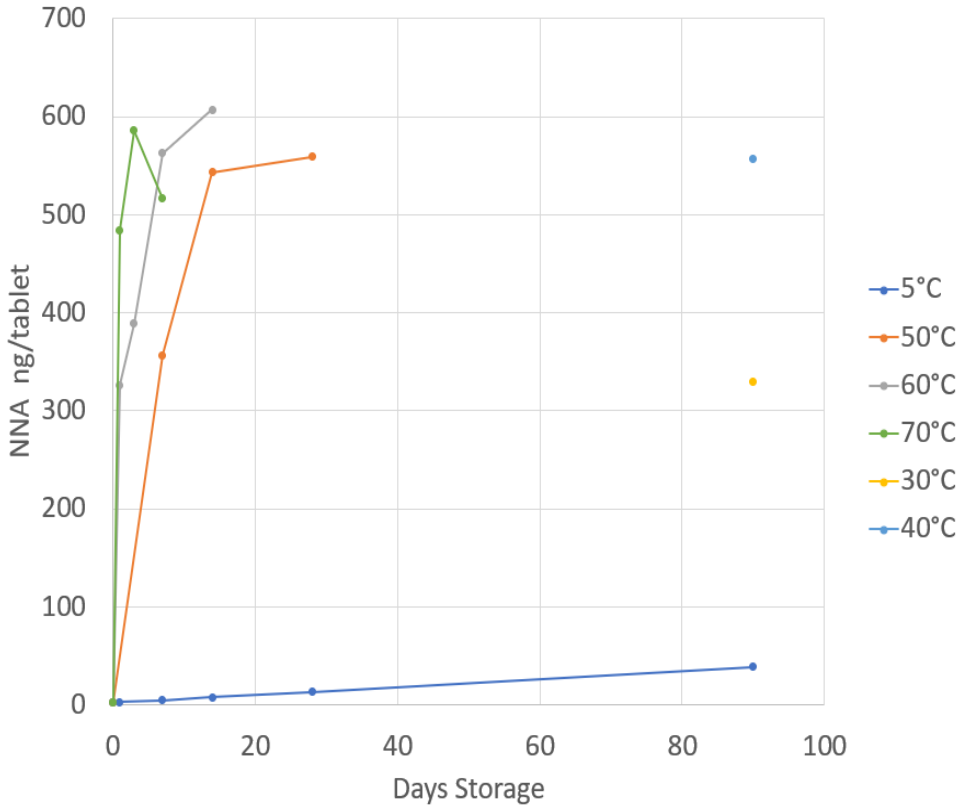
Sometimes seen in solids

Model experiments appear to have plateauing behaviour

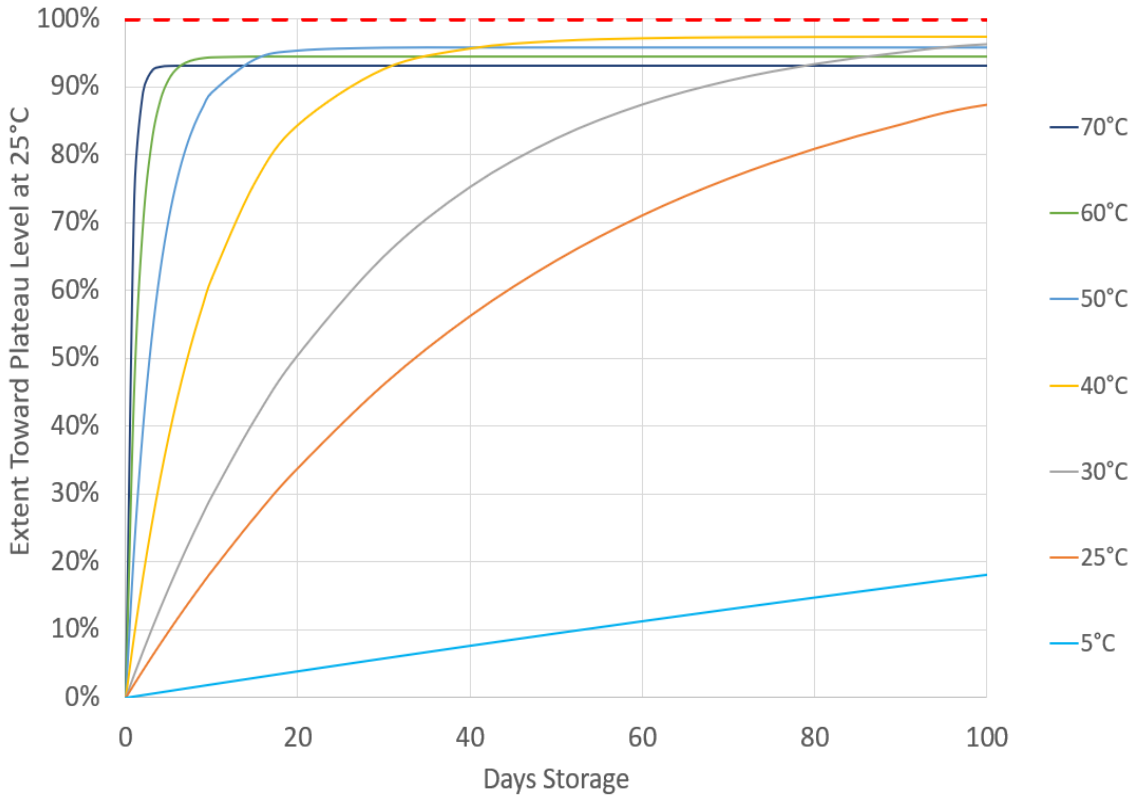
Solutions:	**Factors affecting 'rate' are important**
Solids:	**Factors affecting 'extent' are arguably more important**

Curve Shape and Effect of Temperature: Product G

Example **measured** data from a batch of tablets with a 0.5% drug load



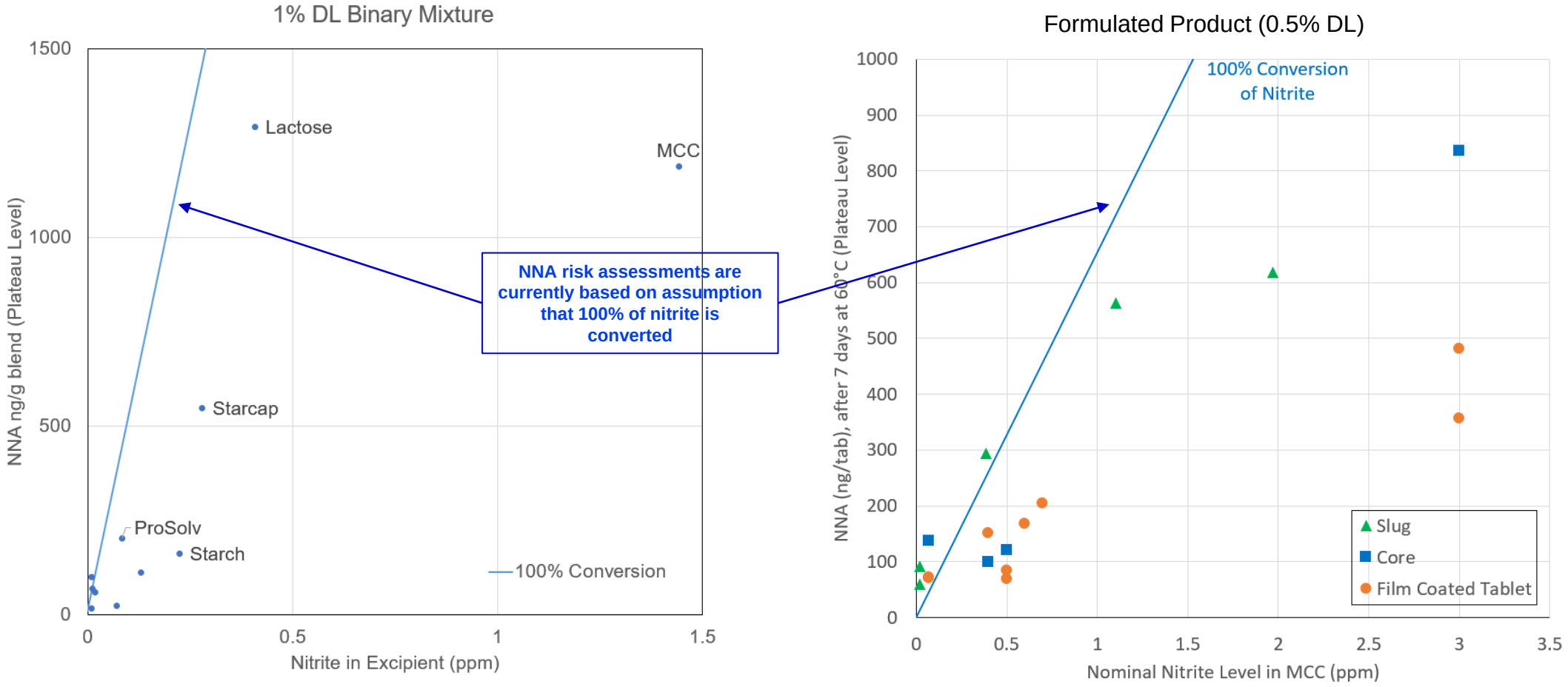
Model of effect of temperature across multiple batches



It is more important to understand the plateau level than the rate constant

Factors that Affect Plateau Level: Nitrite in Excipient

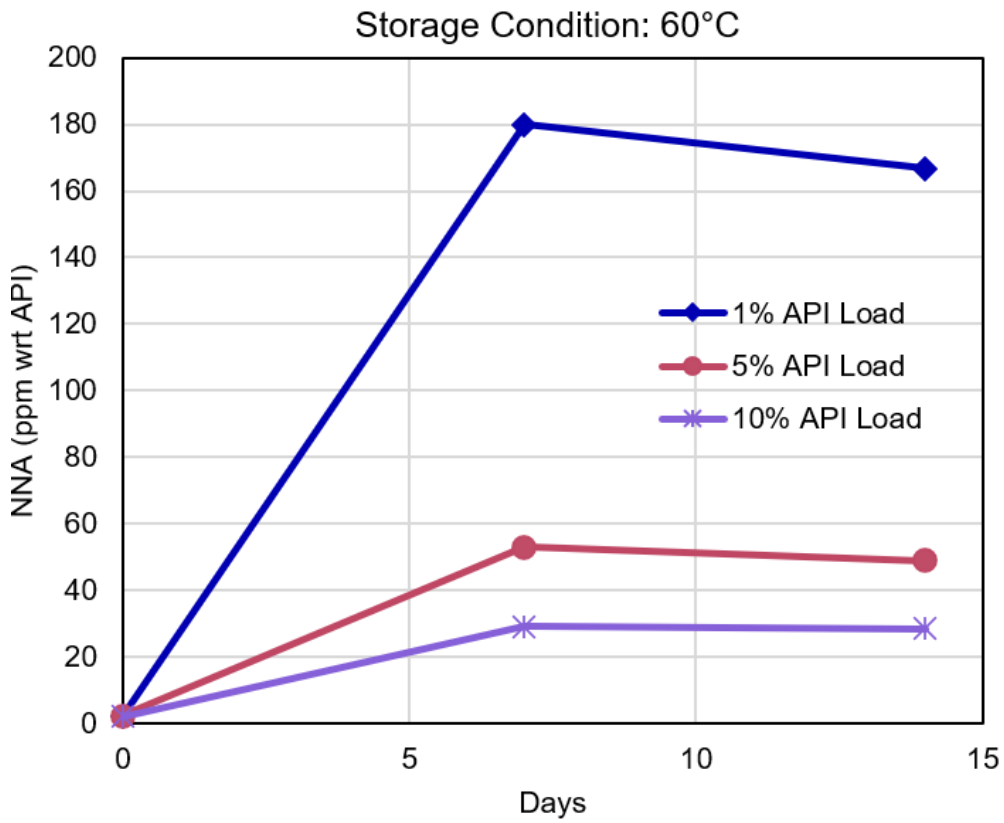
Product G

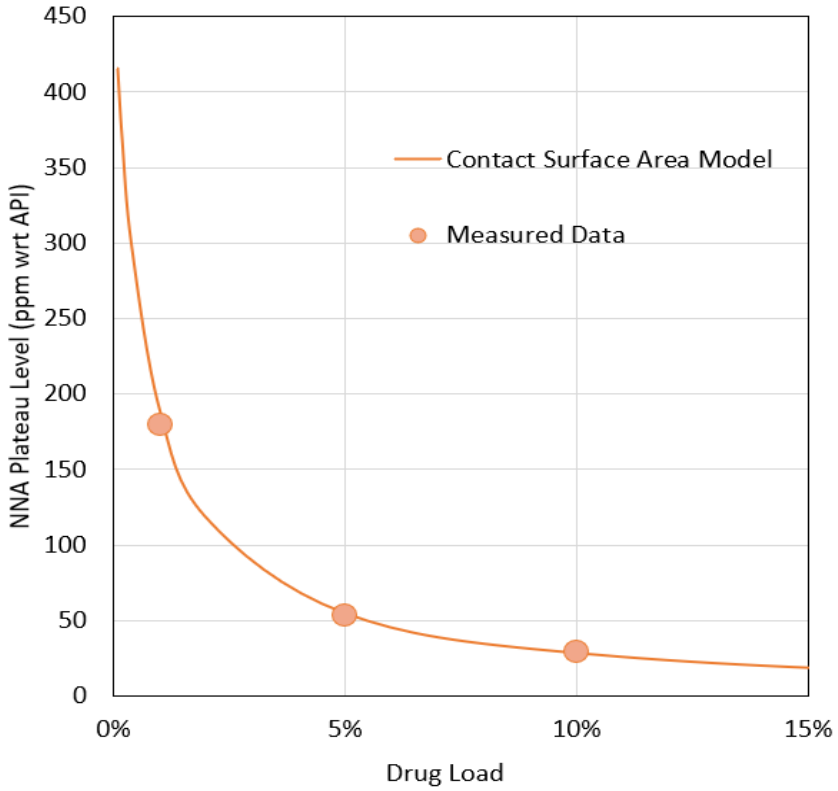


- Note: Trace Methods - Consider the error bars in both the horizontal and vertical axes
- Nitrite is generally <100% converted into NNA
- Nitrite levels may account for ~70% of variation in NNA levels

Factors that Affect Plateau Level: Drug Load

Product G

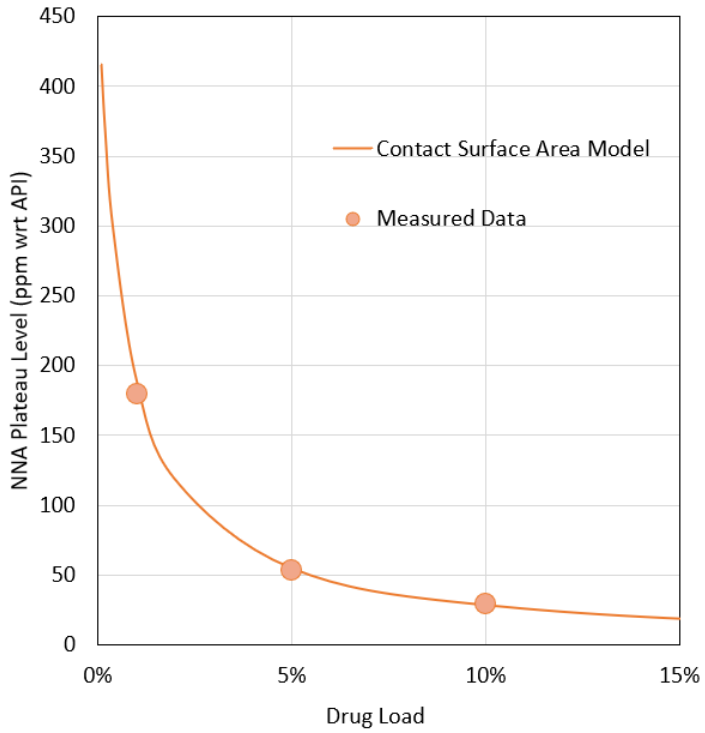


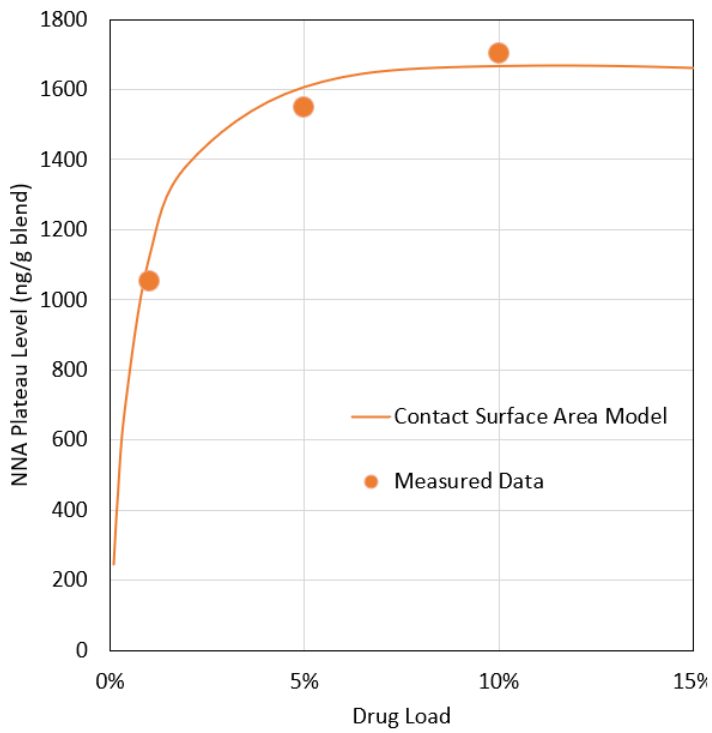


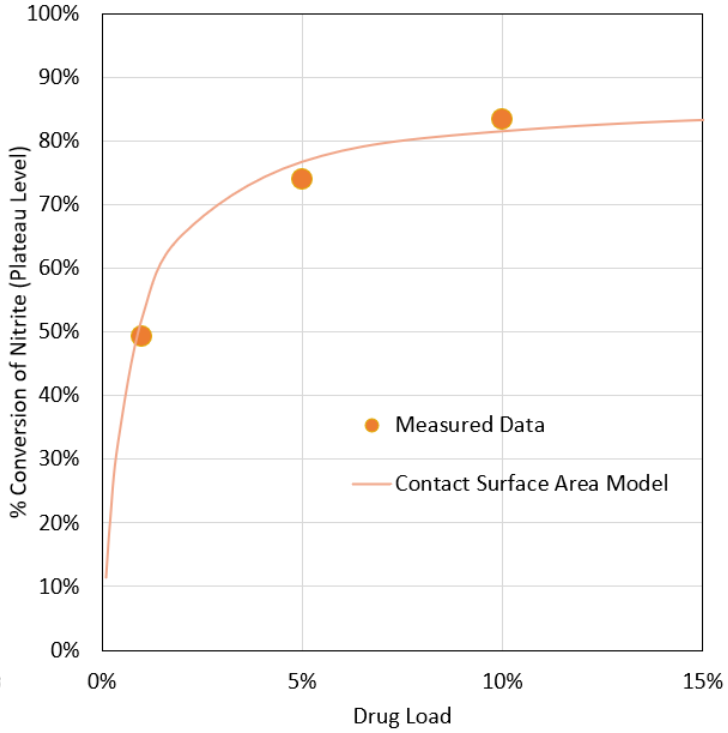
Factors that Affect Plateau Level: Drug Load

Product G

Same data presented three different ways:



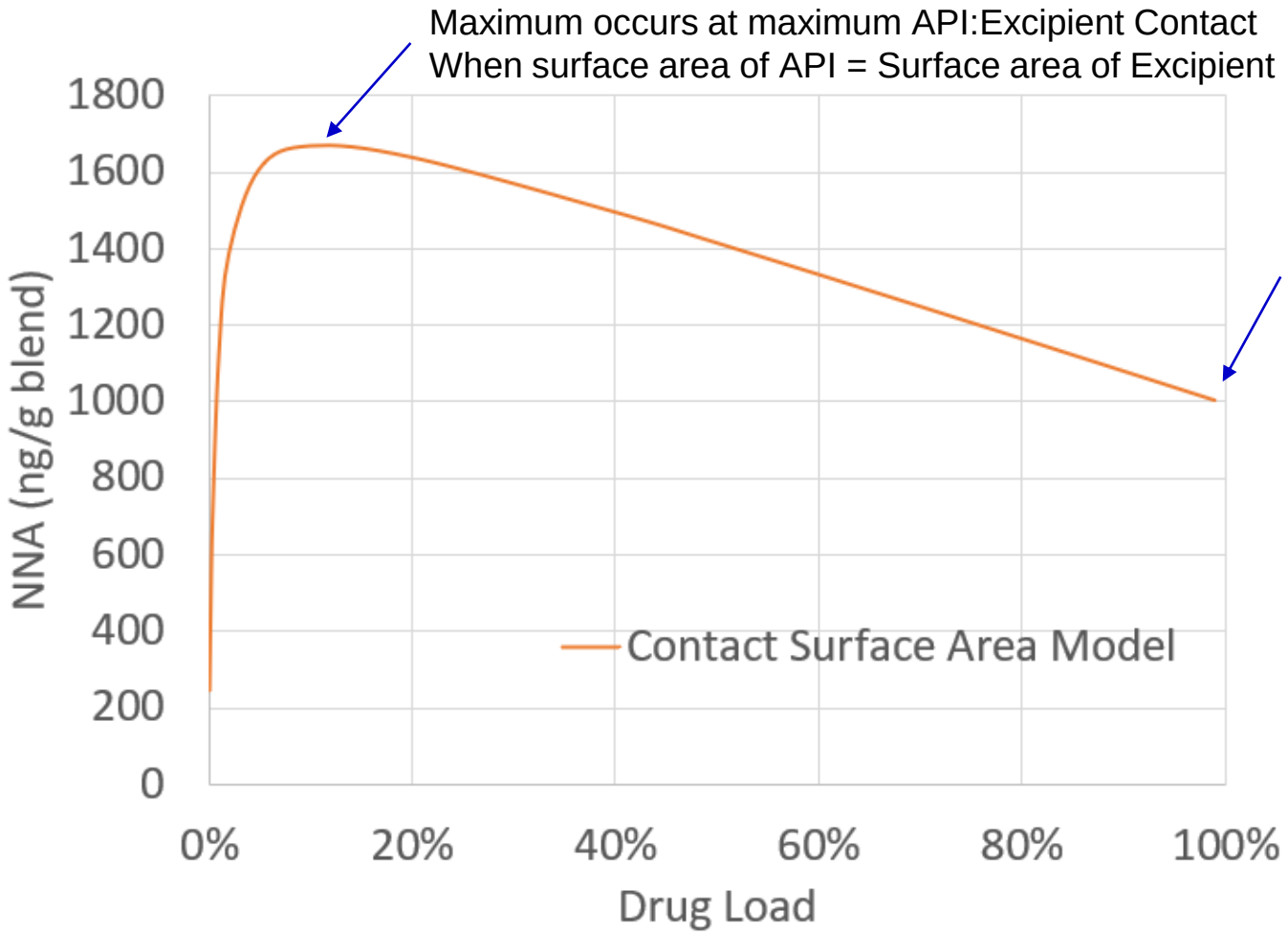




- If contact surface area model is applicable, then this provides a means of predicting NNA levels for excipients with different particles sizes (surface areas) **[“Assuming All Other Factors Remain the Same”]**.
- Variability in excipient particle size may account for some causes of the imperfect correlation between NNA level and nitrite levels.

Factors that Affect Plateau Level: Drug Load (Aside)

Product G



Pure API:
API itself contains ~1 ppm NNA

Maximum occurs when

$$L = \frac{1}{\sqrt{R} + 1}$$

Where

$$R = \frac{ASA_{API}}{ASA_{Excipient}}$$

ASA = "Available Surface Area"

Predicting NNA Levels for Different Formulation Compositions

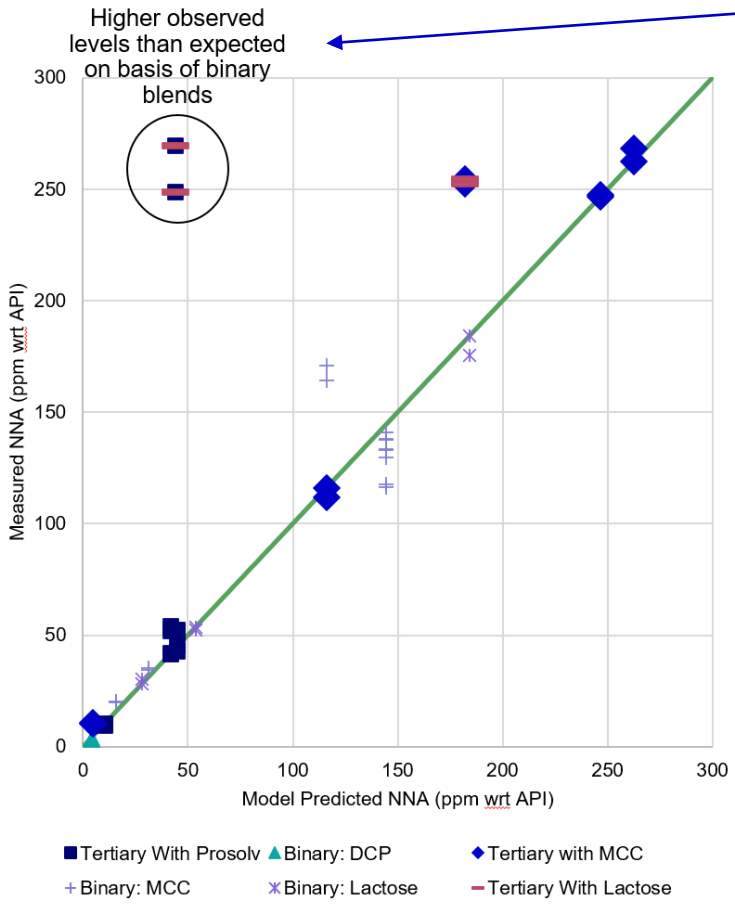
Product G

Can the model account for the levels observed in binary and ternary blends at different drug loads?

Example Data Input to Model

Composition Information

API	MCC	Prosolv	DCP	Lactose	Kollidon	Pruv	Hyqual	sum	NNA ng / g blend
10	90							100	1170
5	95							100	1020
1	99							100	814
1	99							100	794
1	99							100	768
1	99							100	685
1.71	132.2		66.1					200.01	283
1.71	132.2			66.1				200.01	1094
1.7	132.2							133.9	1168
1.7	132.2				6			139.9	782
1.7	132.2					4		137.9	2402
1.7	132.2						2	135.9	1762
1		99						100	148
1.7		132.2	66.1					200	717
1.7		132.2		66.1				200	1754
1.7		132.2						133.9	764
1.7		132.2			6			139.9	1340
1.7		132.2				4		137.9	865
1.7		132.2					2	135.9	1921
1			99					100	21
10				90				100	1703
5				95				100	1550
1				99				100	1053
100								100	994



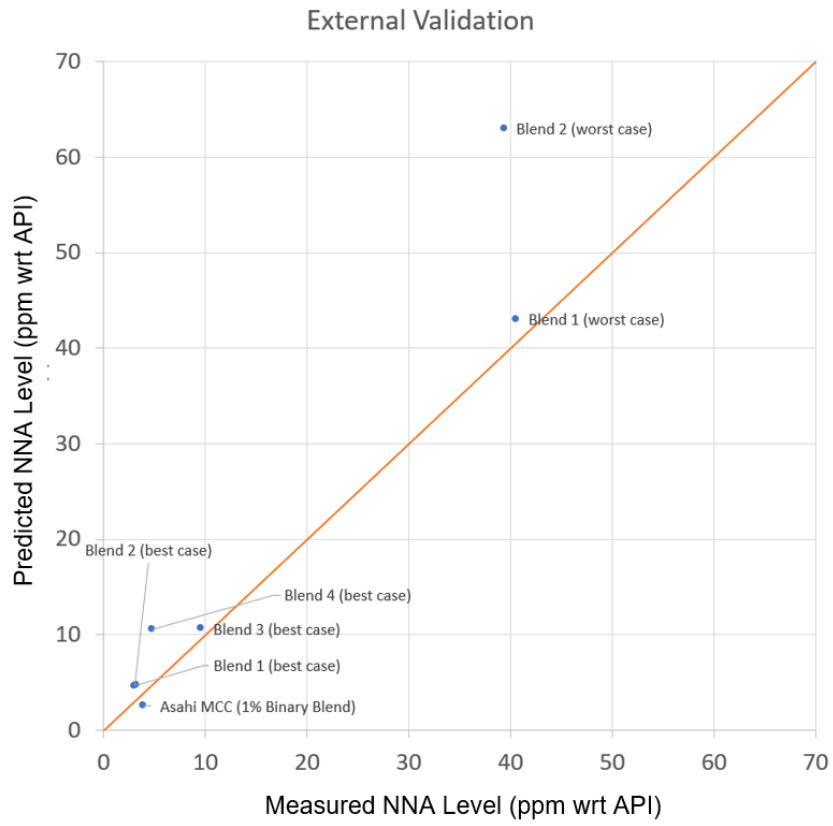
Possibility that in certain excipient combinations, one excipient (e.g. an acidic excipient?) might ‘activate’ the nitrite present in another excipient?

Predicting NNA Levels for Different Formulation Compositions

Product G

Later multicomposite blends were made comprising 5 excipients. By way of external validation, the model was used to predict their NNA levels:

	mg Per unit								
	API	MCC	E2	DCP	Lactose	E5	E6	E7	Sum
Alt Supplier MCC (1% Binary Blend	1	99							100
Blend 1 (worst case)	5		60.7		30.2	3.01		1	99.91
Blend 2 (worst case)	5.02	60.7			30.3	2.99		1	100.01
Blend 1 (best case)	5.01	60.7		30.3		2.99		1	100
Blend 2 (best case)	5.01	60		30		2.99	2		100
Blend 3 (best case)	5.01		60.7	30.29		3		1	100
Blend 4 (best case)	5		60	30		3	2		100



Predicting NNA Levels for Different Formulation Compositions

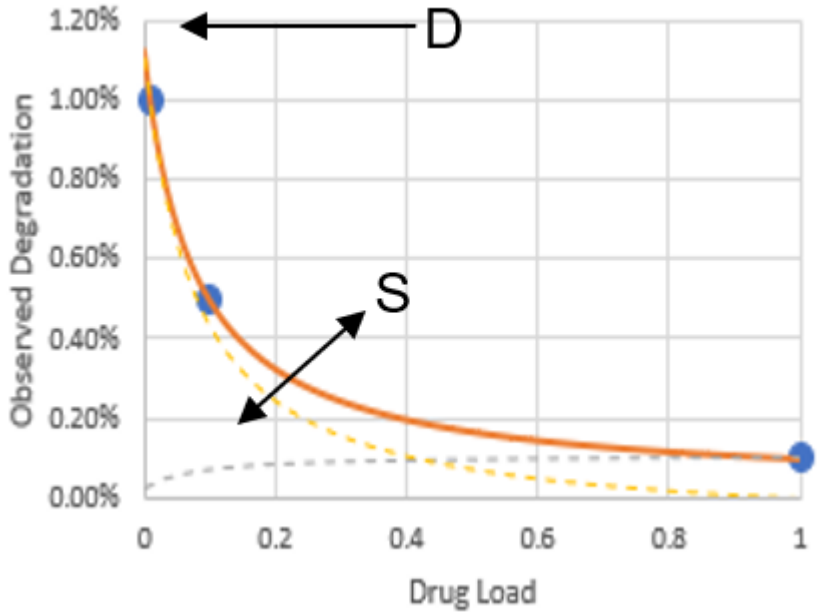
Product G

Recap of Contact Surface Area Model:

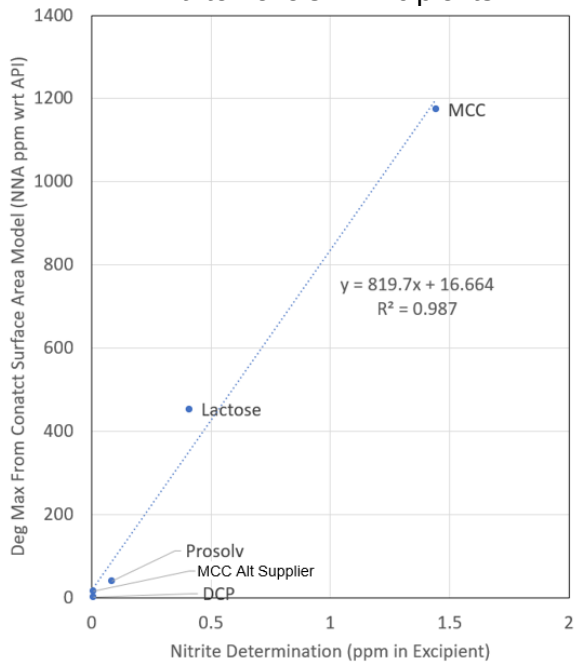
Each excipient requires 2 fitted parameters “S” and “D”

“S” : loosely based on reactive / available **S**urface area. Also likely to be dependent on strength of interaction between excipient and the API.

“D” : based on the **D**egradation extent. This is the degradation extent at maximum dilution of the API in the excipient:



Correlation between ‘D’ Parameter and Nitrite Levels in Excipients



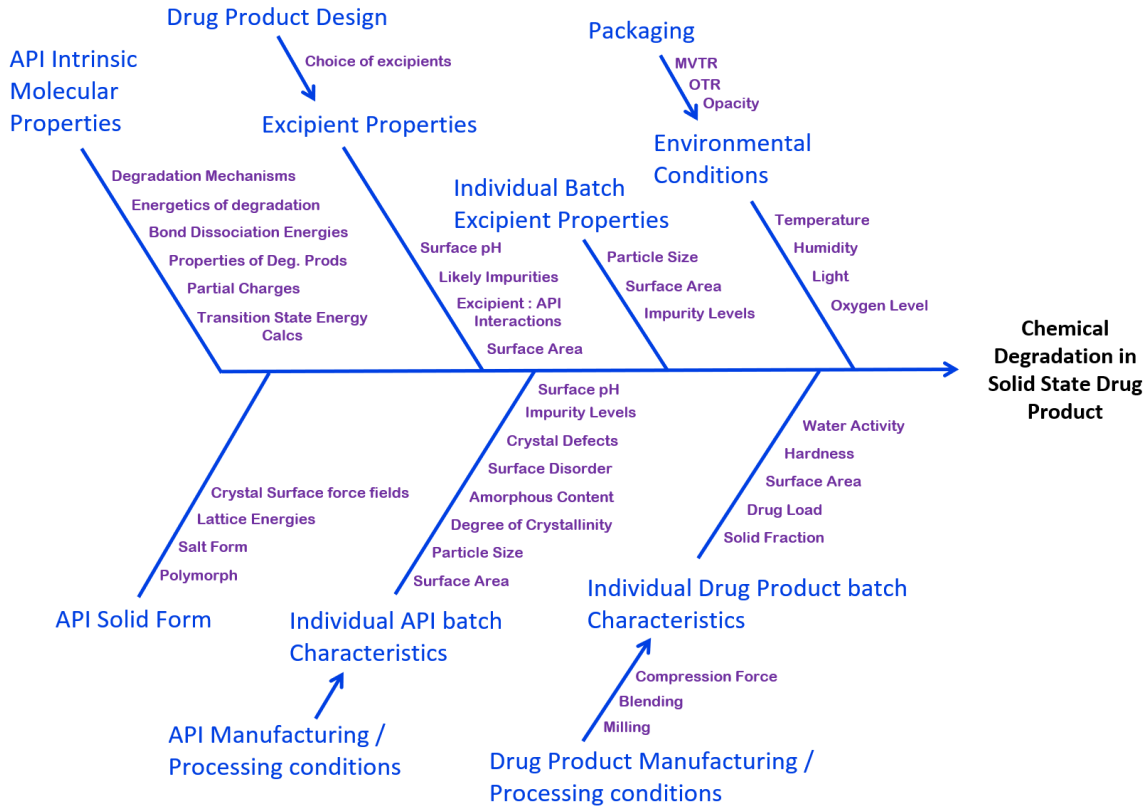
Summary

Contact surface area model

- Is the simplest model for predicting the stability of different formulations
- It has been found to be applicable to a broad range of products
- It can predict the effects of API particle size, excipient particle size, drug load and formulation composition

  “Assume All Other Factors Remain the Same”
- It has been extended to predict different solid fractions and capsule sizes
- It can be used in combination with ASAP models for T and RH, to provide a comprehensive drug product stability model
- Exceptions to the model may occur. Further investigations into these may identify inter-particle interactions, e.g. ‘activation’ of nitrite in excipients

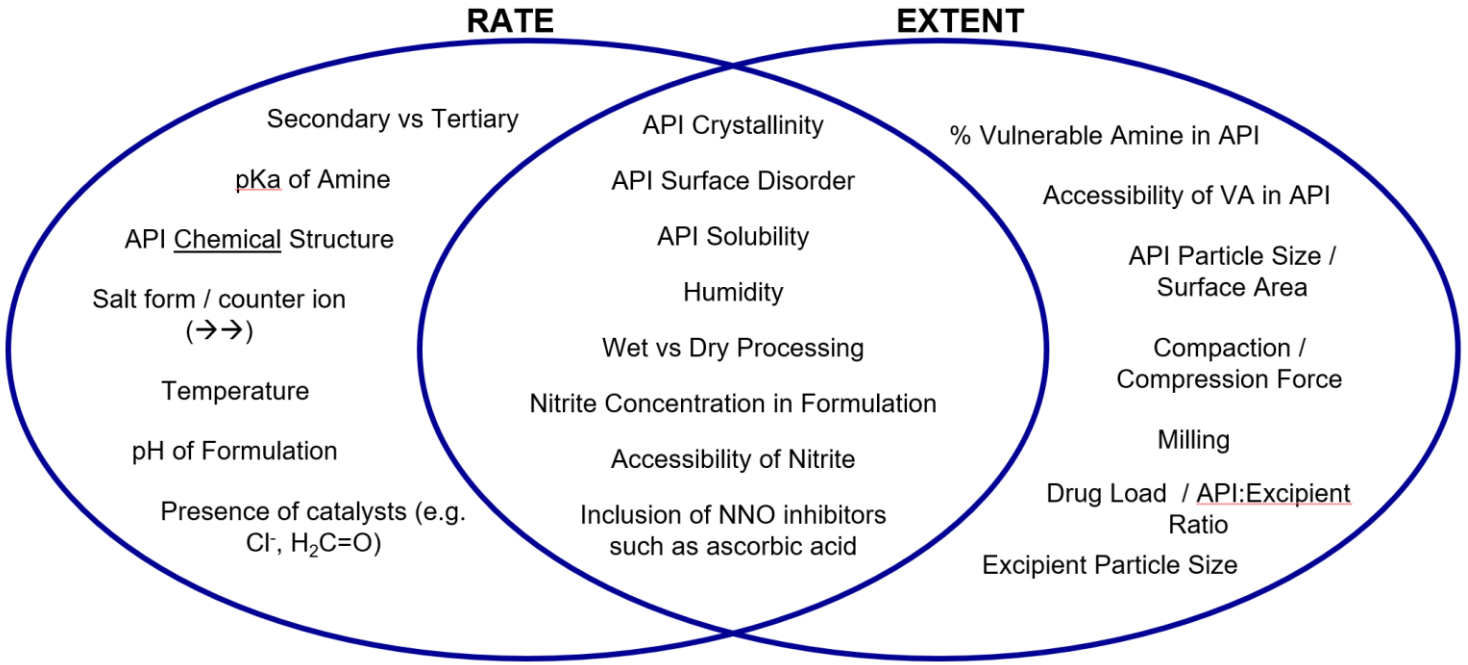
A more quantitative and comprehensive understanding of the factors that affect the rate and extent of chemical degradation in drug products



Summary

Formation of Nitrosamines in Drug Product

- Plateauing has been observed
- Plateau Levels under elevated temperatures are generally in good agreement with plateau levels obtained under long-term storage
- Nitrite levels in excipient may provide a good starting point to estimating nitrosamine level
- <100% conversion of nitrite may be observed
- Correlation requires further refinement: consideration of other factors such as drug load and particle size



Thank You for Your Attention

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Garry O’Connor
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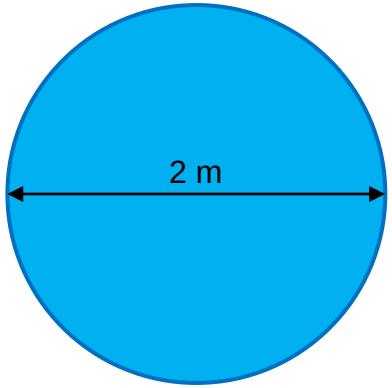
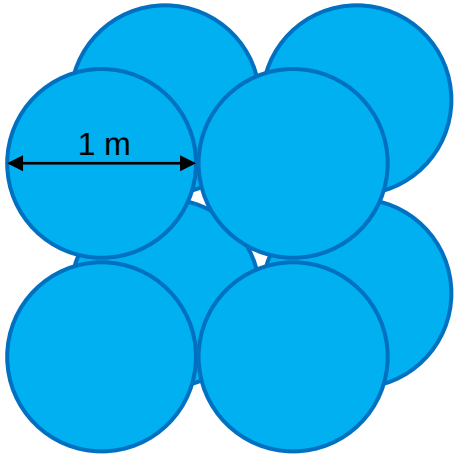
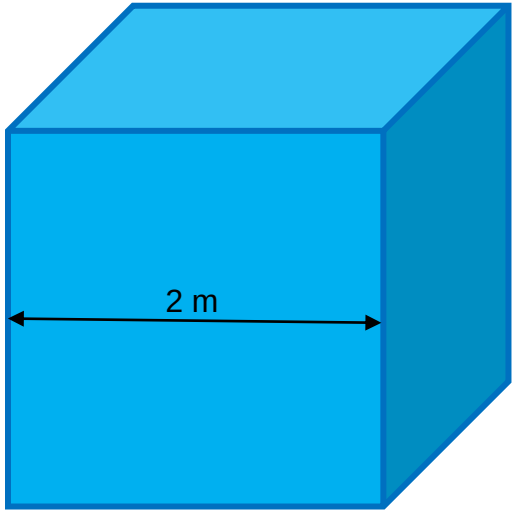


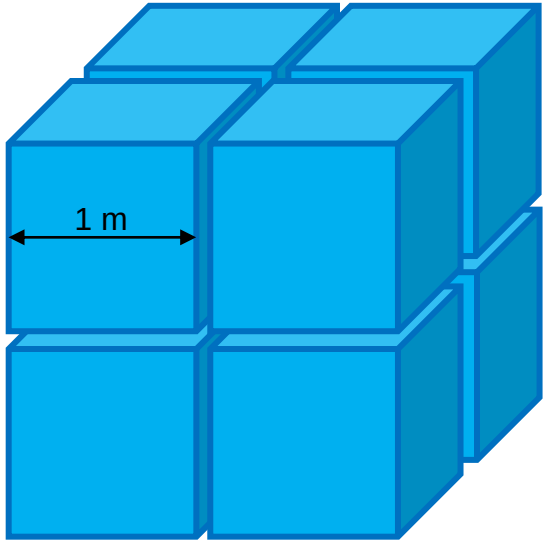
Surface Area
$= 4\pi\ m^2$



Total Surface
Area $= 8\pi\ m^2$



Surface Area
$= 24\ m^2$



Total Surface
Area $= 48\ m^2$