# Understanding and Managing the Risk of Physical Instability During Drug Product Design

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Science of Stability - 'It's all about the science'
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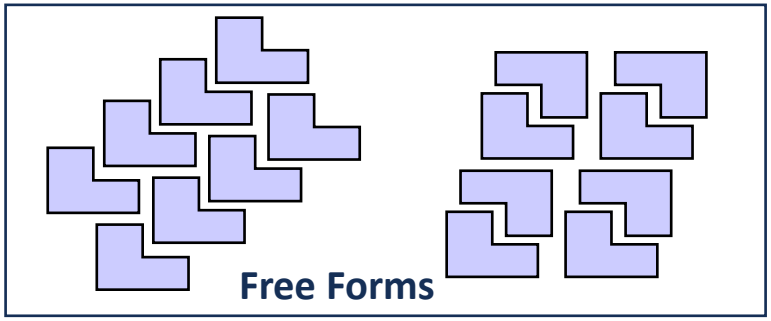
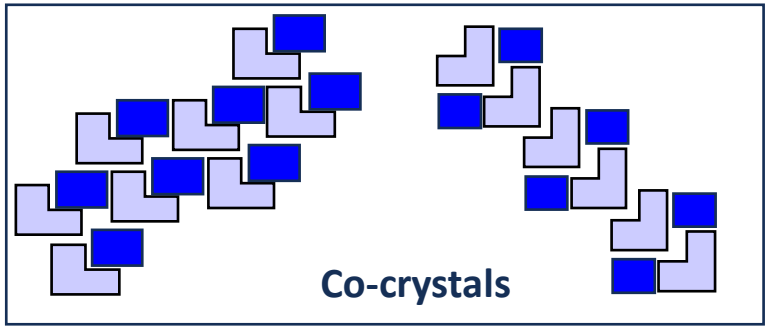
# The physical forms: opportunities and risks

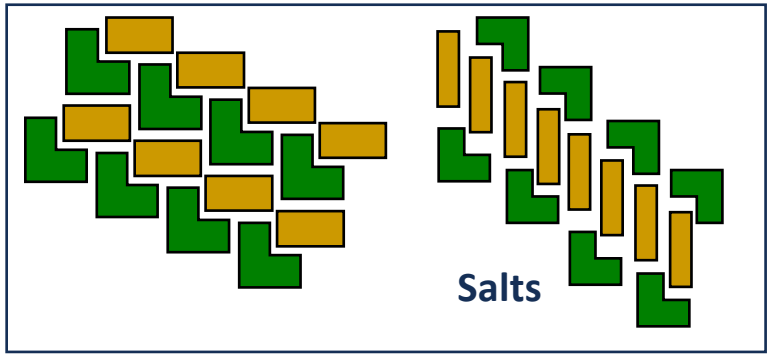
- Selecting the physical form of the API presents an **opportunity** to optimise the isolation, formulation development, biopharmaceutics and stability.
- Key **risk** factors in relation to the physical form in the process of managing and understanding the drug product are:
  - polymorphs (e.g. kinetics of nucleation and growth),
  - solvation/hydration (e.g. wet granulation, isolation)
  - salt disproportionation
  - generation of disorder (e.g. size reduction, compression).
- The Materials Science discipline evaluates the opportunities and risks associated with the solid state landscape of a molecule and selects the most suitable solid form for drug product development.
- We want to build upon the experiences within the community and move the use of these tools from trouble-shooting to an integral part of design

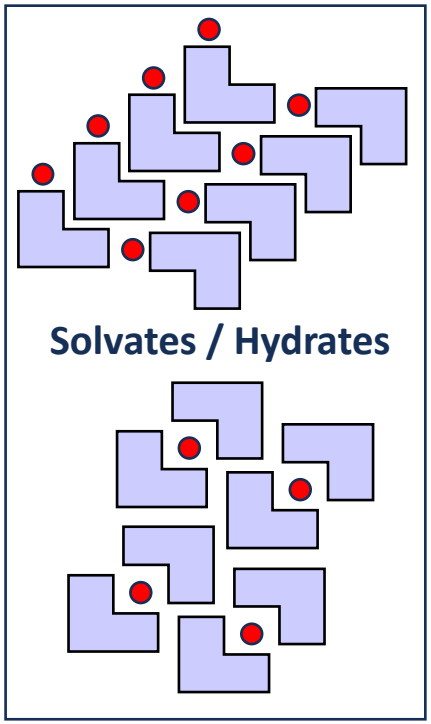
# Polymorphism of different crystalline forms

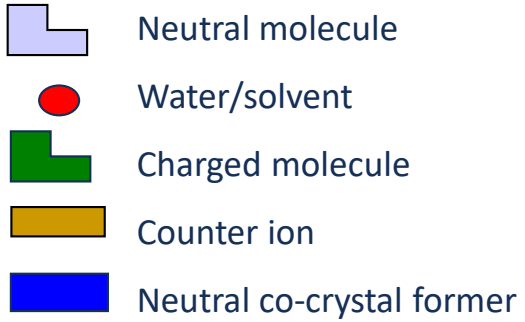
Polymorphism is the ability of a molecule to pack in distinct 3-D arrangements

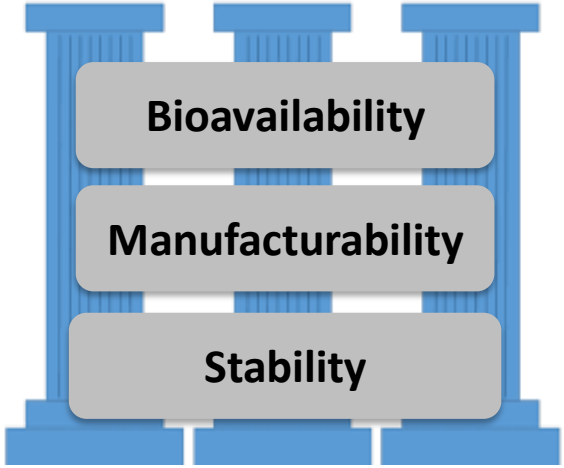


# Thermodynamics and Kinetics of Solid Phases

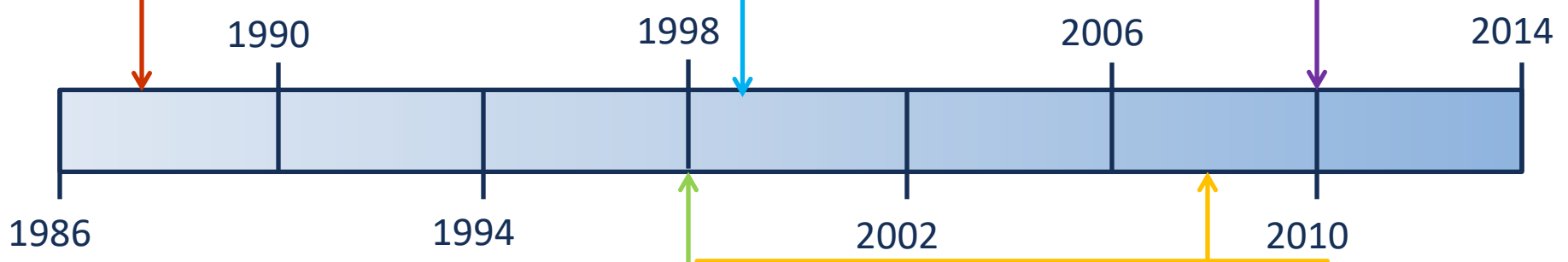
- Stability of solid phase is described with Gibbs' free energy.
- The most thermodynamically stable form has lowest free energy.
- Stability of solid phases is dependent on environmental conditions:
  - temperature
  - humidity/water activity
  - pH
- Thermodynamically most stable form is typically preferred but sometimes meta-stable forms are developed
  - kinetics of conversion become the key factor in drug product design

# Crystal Form Risks and Impact – 25 year summary

1988: Tegretol (Carbamazepine)
Clinical failure of CBZ tablets, possibly due to form conversion of anhydrate to dihydrate.

1999: Vermox (Form C)
Raw material contained an inactive/less efficacious polymorph. An analytical test was required by regulatory bodies.

2010: Coumadin (Warfarin)
Recall of 1.5m tablets amidst concerns over varying levels of propylene glycol, affecting the crystallinity of the API (solvate).




1998: Norvir (Ritonavir)
Product withdrawal due to capsules failing dissolution – attributed to appearance of a more thermodynamically stable form.

2008: Neupro (Rotigotine - transdermal)
Batch recall due to crystallisation of a new polymorph.

2010: Avalide: (Hydrochlorothiazide/Irbesartan)
60m tablets recalled due to variable levels of a less soluble polymorph of Irbesartan, and the effect on disso rates.

# Control of hydrate formation

Effect of drug product storage conditions on hydrate formation

# Background

- Compound X has rich polymorphic landscape containing multiple solvates and hydrates and one anhydrous form (Form A).
- Increasing the $A_w$ during isolation can lead to the nucleation of a hydrate (Form B).
- Thermodynamic slurries have defined relative stabilities of Form A and Form B over a range of temperatures and $A_w$.
- Form B is a variable channel hydrate, which is difficult to nucleate and isolate.
- Form A is physically stable as API when stored at relevant conditions and it is easy to isolate and process. Form A is the preferred commercial form.
- Some limited conversion of Form A to Form B has been observed in the drug product at extreme accelerated conditions (70°C/75%RH) within 2 weeks.
- No conversion was detected at relevant ICH conditions over the same time period.

# Problem statement

## Objective

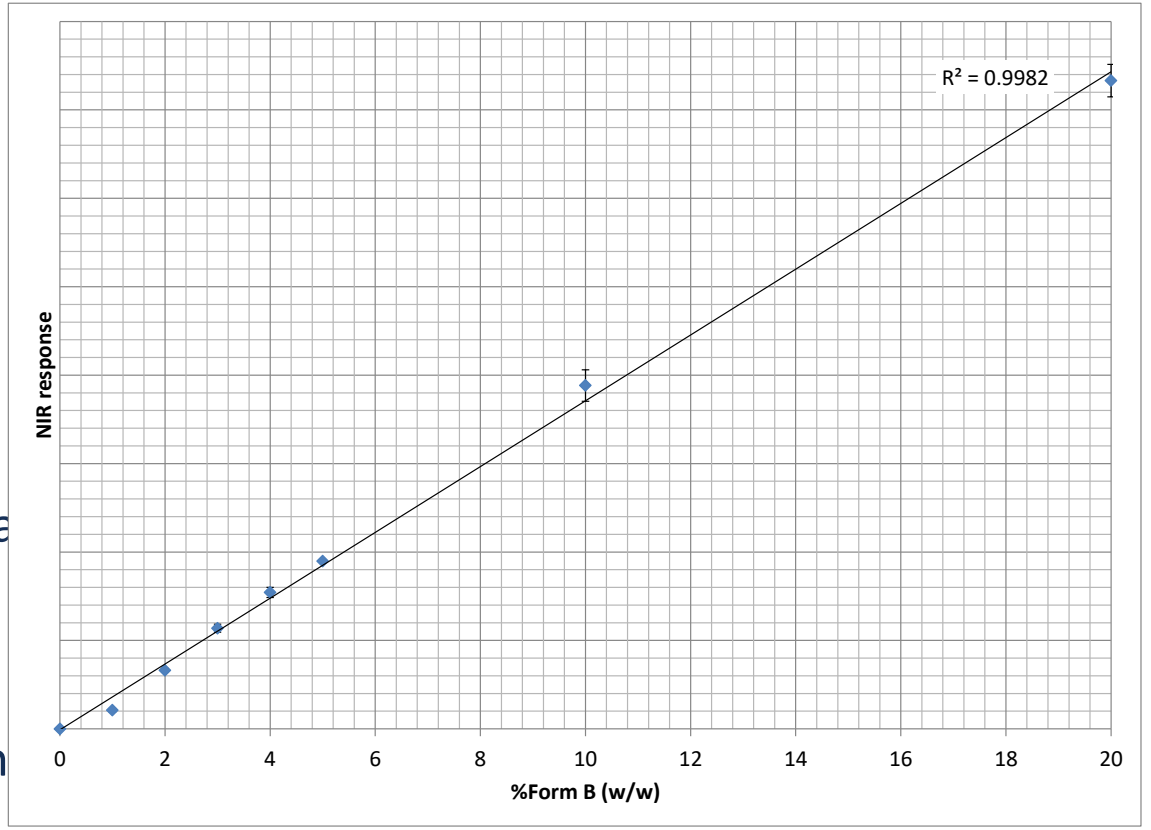
- Need to understand the risk of conversion from Form A to Form B in the drug product at relevant conditions

## Challenges

- The team faced the challenge of understanding the risks surrounding the presence of Form B within an accelerated time frame.
- Form A has very good kinetic stability where Form B is more thermodynamically stable
  - Kinetics of conversion are slow even with spiked slurries.
  - In solid-state the kinetics are very slow – spiked API has never seen to change
- To overcome the challenges associated with slow kinetics, we have used:
  - Spiked tablet samples (~5% Form B)
  - Extreme/accelerated storage conditions to drive changes (70°C/75%RH)
  - Open-dish storage

# Solid-state analytics – drug substance

- Near-infrared spectroscopy has been applied to develop a platform method for the API
- The technique shows good discrimination between Form A and Form B
- The integrated area of the peak 1490 nm can be used to create a linear calibration



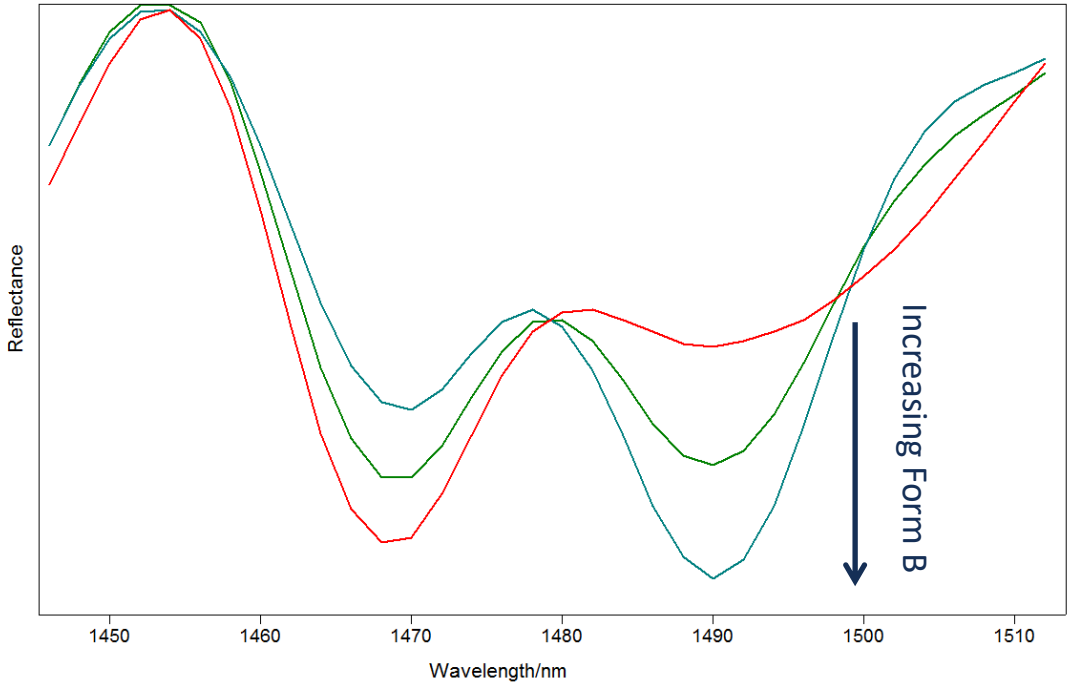

- NIR provides rapid and represen for drug product applications

Caveat:

- Need to ensure that the method is still sensitive to the form changes in drug product

# Monitoring Form B in drug product

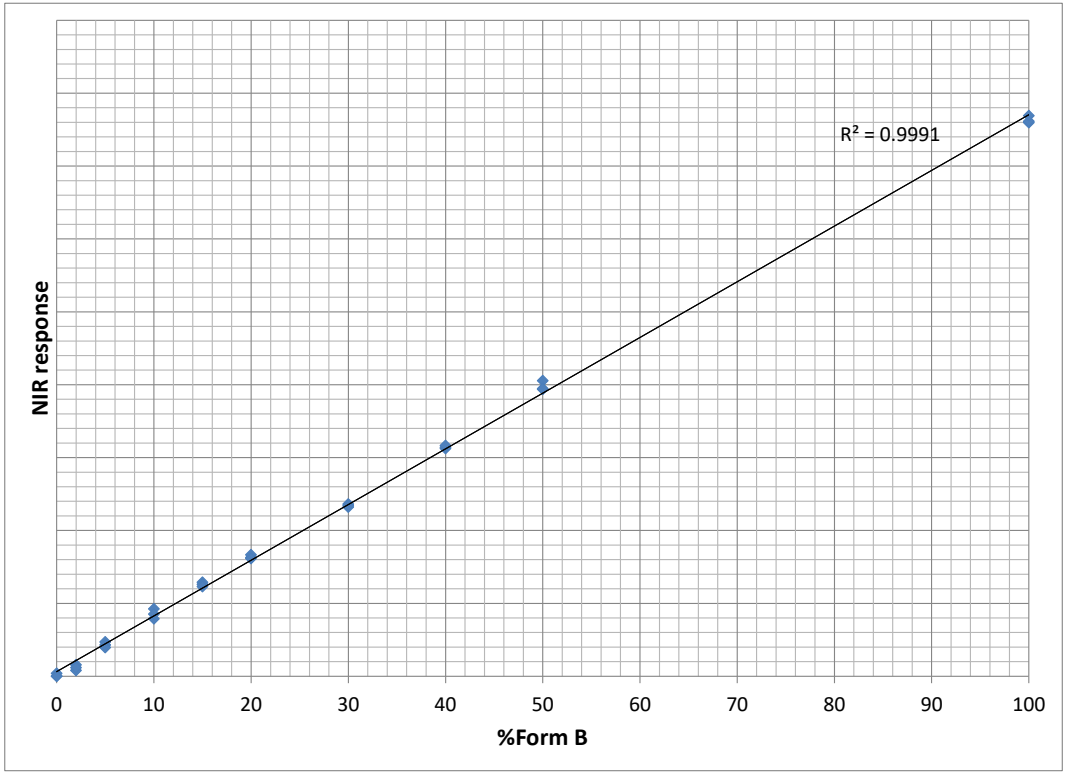
- ‘Spiked’ prototype tablets stored at extreme conditions for two weeks
- NIR spectroscopy capable of detecting and monitoring growth of Form B in the drug product
- Band at 1490 nm selected over 1434 nm because of interference from excipients.
- Qualitative assessment suggests limit of detection in drug product is between 5 and 10%




- Drug product platform method required to enable quantitative assessment

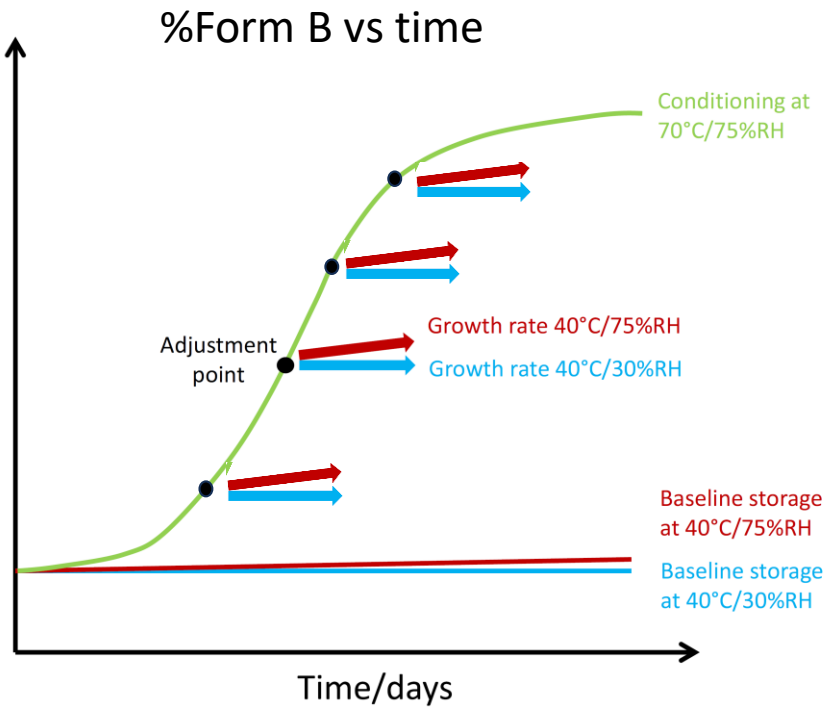
# Solid-state analytics – drug product

- Prototype tablets were prepared with different ratios of Form A and Form B
- Tablet samples were analysed by NIR spectroscopy
- Calibration was built using simple univariate analysis
- Excellent linearity ($R^2$>0.999)
- Very reproducible based on n=3



# Exploring the effect of initial levels of Form B on the kinetics of form conversion

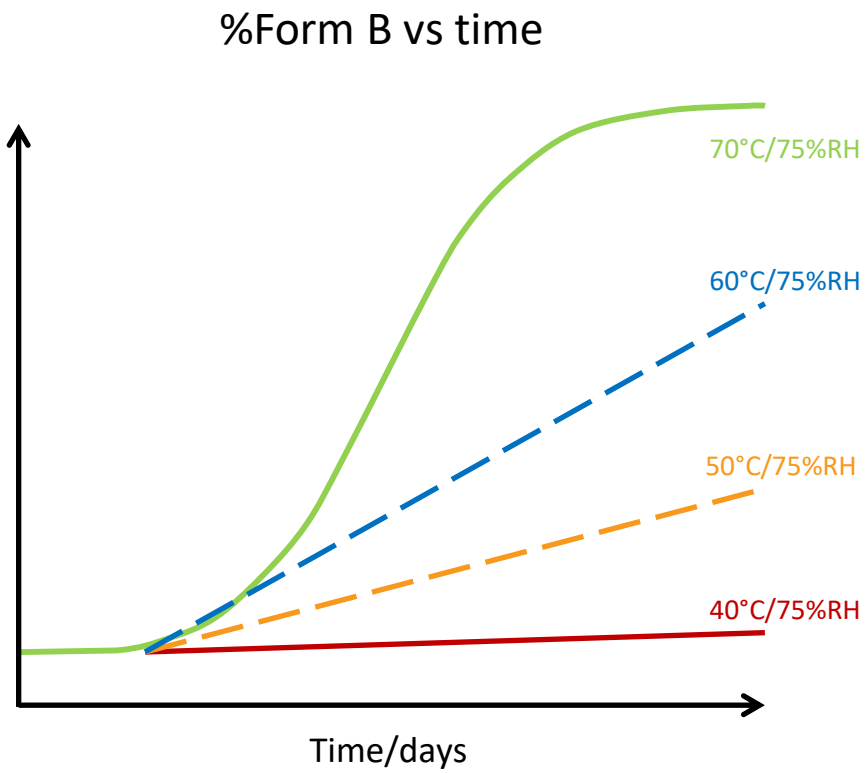
- Tablets were prepared containing API spiked with ~5% Form B.
- Storage at 70°C/75%RH was used to 'condition' the samples, promoting the growth of Form B.
- At specified adjustment point selected tablets were transferred to storage at 40°C/75%RH or 40°C/30%RH.
- NIR was used to monitor the levels of Form B in the samples.




- Demonstrated initial levels of phase impurity have no impact on kinetics in this case.
- Enabled team to underwrite proposed packaging strategy

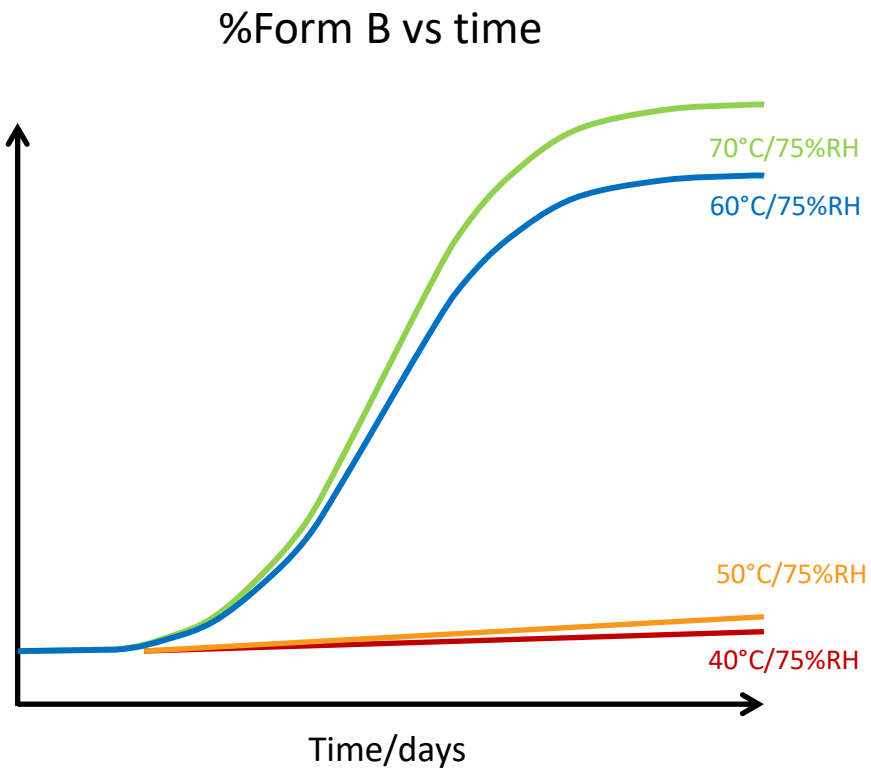
# Exploring the effect of temperature on the kinetics of form conversion

- Spiked tablets were stored at 75%RH over a range of temperatures to assess the effect of temperature on the kinetics of form conversion
- Data could then potentially be used to model the kinetics and predict shelf-life



# Exploring the effect of temperature on the kinetics of form conversion

- Spiked tablets were stored at 75%RH over a range of temperatures to assess the effect of temperature on the kinetics of form conversion
- Data could then potentially be used to model the kinetics and predict shelf-life
- Significant step change in rate constant observed between 50°C/75%RH and 60°C/75%RH



# Exploring the effect of initial levels of Form B on the kinetics of form conversion

## Summary

- A novel experimental design was used to investigate the kinetics of form conversion
- Monitoring the cessation of form conversion instead of growth to investigate physical stability of API in drug product
  - Comparing accelerated storage with simulated packaging conditions
  - Demonstrated initials levels of phase impurity have no impact on kinetics in this case.
  - Enabled team to underwrite proposed packaging strategy
- The experimental design enabled data to be generated rapidly to support decision making within an accelerated programme.
- The kinetics of the conversion have been investigated with respect to temperature
- A significant step change in the rate constant is observed between 50°C and 60°C at 75%RH

# Securing control over potentially high risk manufacturing process

Securing control over potentially high risk manufacturing process

# Background

- Compound Y exists as two polymorphic forms: anhydrous Form A and hydrate Form B
- Critical water activity between Form A and Form B has been determined to be $A_w$ = 0.3 - 0.4
- Both Form A and Form B API have very good kinetic stability at wide %RH range
- Since Form A is a physically stable anhydrous API and it is easy to isolate and process it was selected as a preferred commercial form
- The drug product manufacturing process for this compound was wet granulation due to the requirement for a high drug loading
- Significant difference in solubility between forms

# Problem statement

## Objective

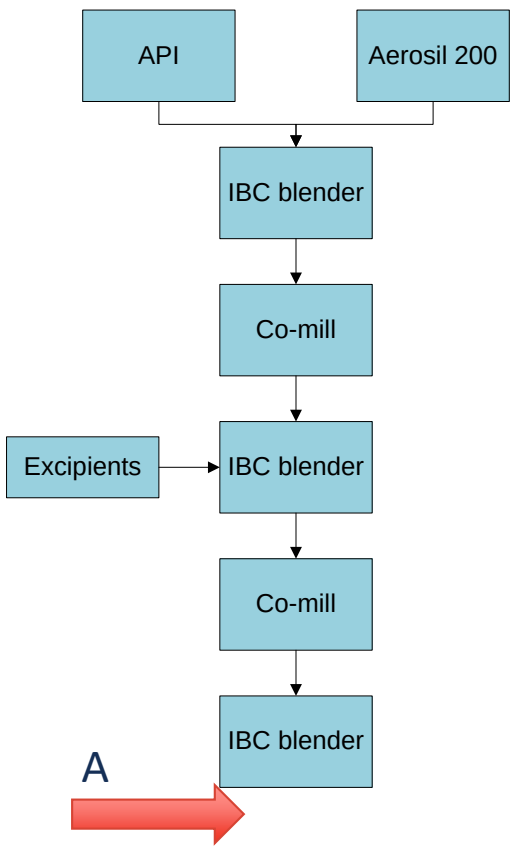
- Need to understand the risk of conversion from Form A to Form B during the drug product processing, and on subsequent storage

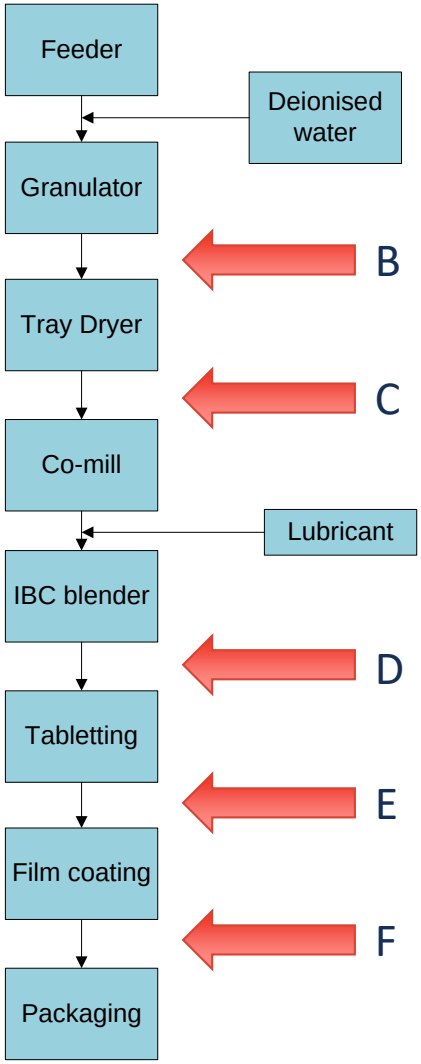
## Challenges

- Method required to detect/monitor hydrate at low-levels, and needs to be transferrable to continuous manufacturing framework.
- Form A has excellent solid-state stability (even at $A_w$ = 0.9), conversion to hydrate only observed in solution.
- To overcome the challenges associated with slow kinetics, we have used:
  - Spiked API (10% Form B)
  - Accelerated storage conditions to drive changes (40°C/75%RH)
  - Open-dish storage
  - 'Wet' and 'Dried' material

# Testing procedure

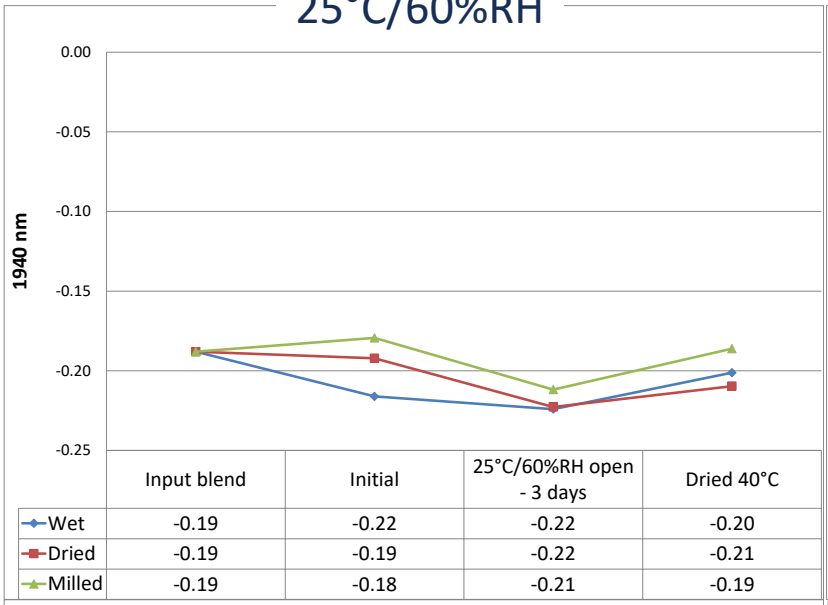
- Off-line analysis by NIR spectroscopy and ssNMR
- Assessment at each stage of form in drug product
- Material can potentially remain in the system for several days; need to demonstrate robustness with respect to form over this period.
- Samples then stored open dish (25°C/60%RH and 40°C/75%RH) for 7 days as part of a hold-time study



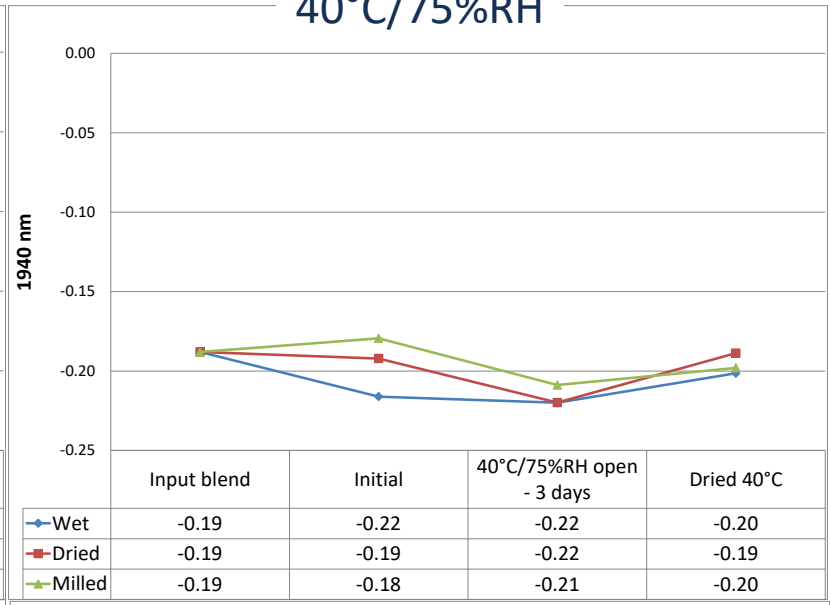
# Results

## 25°C/60%RH

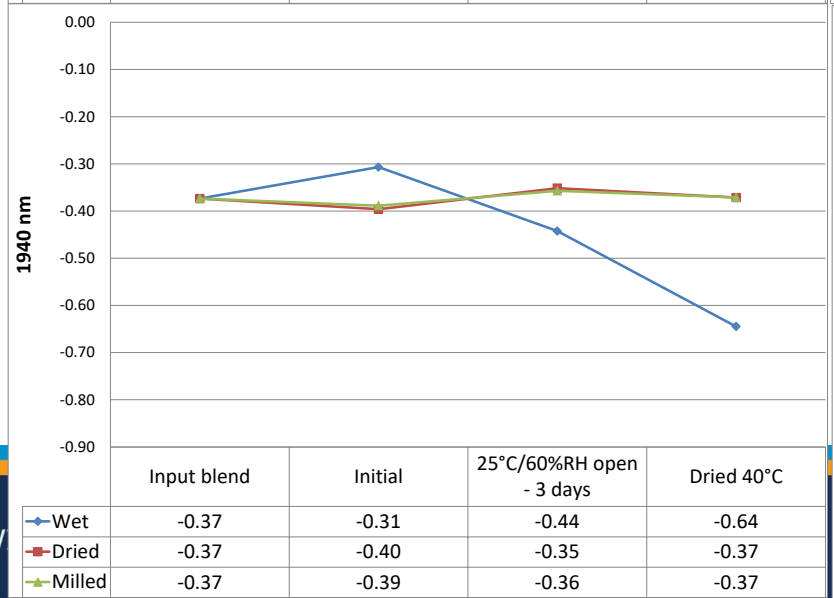


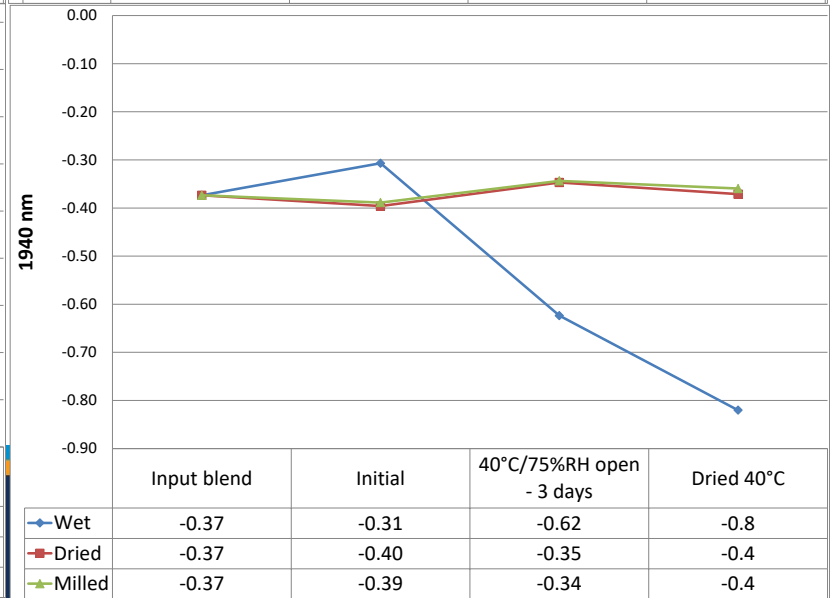

| | Input blend | Initial | 25°C/60%RH open - 3 days | Dried 40°C |
|---|---|---|---|---|
| Pure Form A | | | | |
| Wet | -0.19 | -0.22 | -0.22 | -0.20 |
| Dried | -0.19 | -0.19 | -0.22 | -0.21 |
| Milled | -0.19 | -0.18 | -0.21 | -0.19 |
| 10% Form B | | | | |
| Wet | -0.37 | -0.31 | -0.44 | -0.64 |
| Dried | -0.37 | -0.40 | -0.35 | -0.37 |
| Milled | -0.37 | -0.39 | -0.36 | -0.37 |

## 40°C/75%RH




| | Input blend | Initial | 40°C/75%RH open - 3 days | Dried 40°C |
|---|---|---|---|---|
| Pure Form A | | | | |
| Wet | -0.19 | -0.22 | -0.22 | -0.20 |
| Dried | -0.19 | -0.19 | -0.22 | -0.19 |
| Milled | -0.19 | -0.18 | -0.21 | -0.20 |
| 10% Form B | | | | |
| Wet | -0.37 | -0.31 | -0.62 | -0.8 |
| Dried | -0.37 | -0.40 | -0.35 | -0.4 |
| Milled | -0.37 | -0.39 | -0.34 | -0.4 |



# Summary

- A series of experiments has been performed to understand the risk within a potentially challenging product manufacture
- The risk has been monitored throughout the process using off-line NIR analyses (with a view to transitioning to in-line)
- The manufacturing process and the drug product have been shown to be robust
  - Form change is only observed in wet spiked samples that are stored in humid conditions for a number of days.

# Linking chemical and physical stability: Salt disproportionation

Understanding risk of disproportionation

# Salt disproportionation

- Salt disproportionation is the conversion of a salt to its free acid/base and the corresponding counter ion.

$$pH_{max} = pK_a + log\frac{[B]_s}{\sqrt{K_{sp}}}$$

- The propensity for a salt to disproportionate is governed by the $pH_{max}$ and is also influenced by factors such as pH microenvironment, temperature, and humidity

# Background

- Compound Z is a weak free base with $pK_a$ of 5.1. The preferred form for commercialisation is a tosylate salt, which shows good physical stability as drug substance
- Risk of disproportionation since $pH_{max}$ of tosylate salt (4.01) is below the pH microenvironment for many commonly used excipients.
- The salt appears to degrade in the presence of excipients on stability, although free base not directly observed.
- The degradation is accompanied by a colour change.

| Excipient | pH |
|---|---|
| Microcrystalline cellulose (Avicel PH102) | 4.03 |
| Lactose monohydrate (Fast Flo) | 4.24 |
| Mannitol | 4.7 |
| Sodium starch glycolate (Explotab) | 4.77 |
| Dibasic calcium phosphate anhydrous (A-TAB) | 5.1 |
| Sodium croscarmellose | 5 - 7 |
| Magnesium stearate | 7.1 |

# Problem statement

## Objective

- Managing the disproportionation risk in the drug product is key for ensuring adequate shelf-life for the product.
- Understanding the degradation pathways is important for application in drug product design

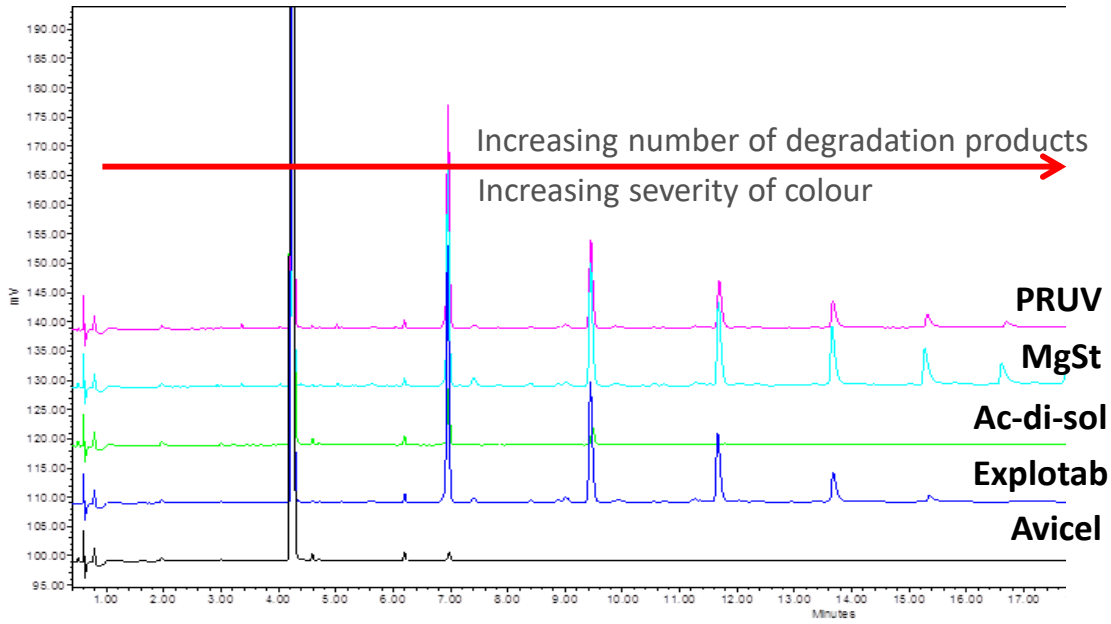
## Challenges

- Establishing the occurrence of a disproportion event is not straightforward since the free base is not directly observed
- Free base is non-crystalline, which can present challenges with respect to ease of detection.
- Understanding mechanism/pathway of degradation to allow team to design a solution

# Physical and chemical stability

- Binary phase mixtures, Tosylate/Excipient (1:1)
- Samples analysed by Raman and ssNMR for form change
  - Loss of crystallinity
  - Change in form of API
  - Not consistent with free base, or other references – cannot confirm identity of form in drug product
- Chemical stability reveals a consistent excipient compatibility profile
  - Increasing number of degradants corresponds to increased discolouration

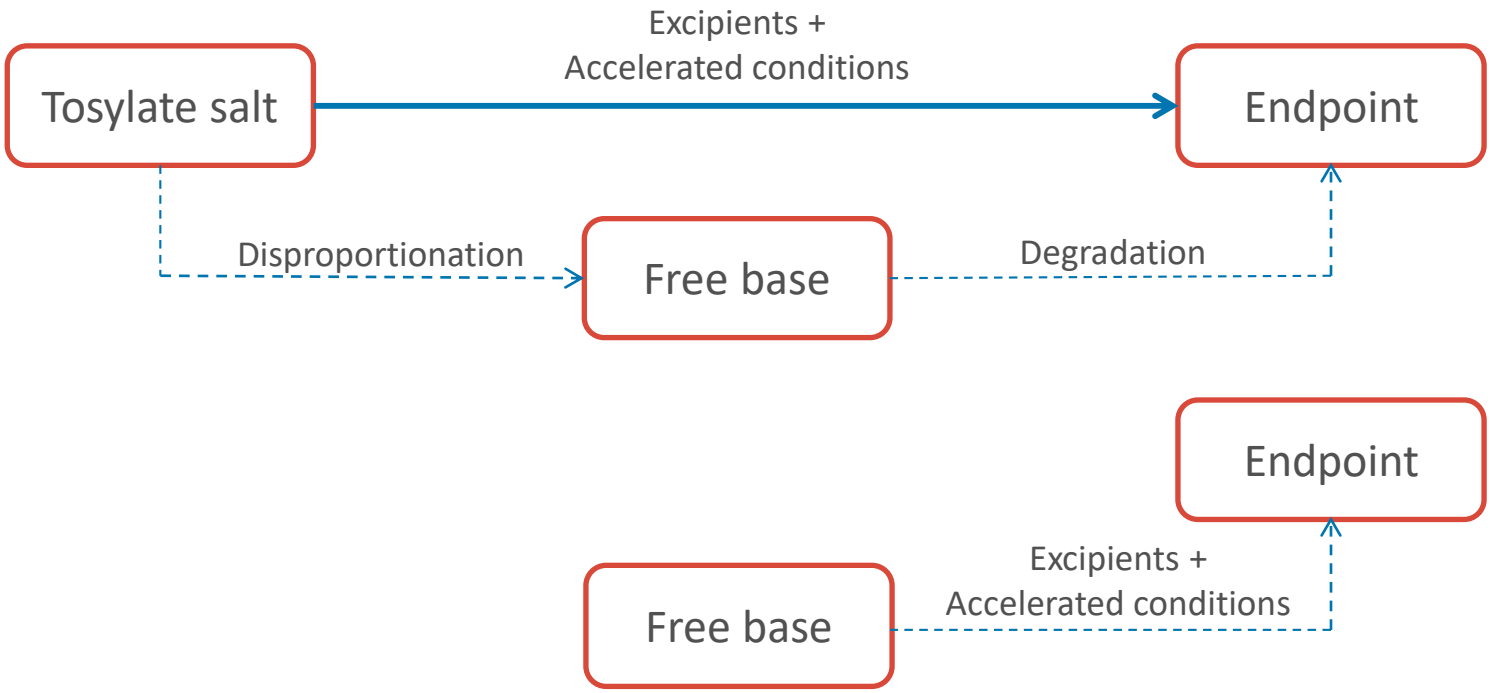
| Fillers | Disintegrants | Lubricants |
|---|---|---|
| Microcrystalline cellulose (Avicel) | Sodium starch glycollate (Explotab) | Magnesium stearate |
| Lactose monohydrate (FastFlo) | Croscarmellose sodium (AcDiSol) | Sodium stearyl fumarate (PRUV) |
| Dicalcium phosphate (A-TAB) | | |



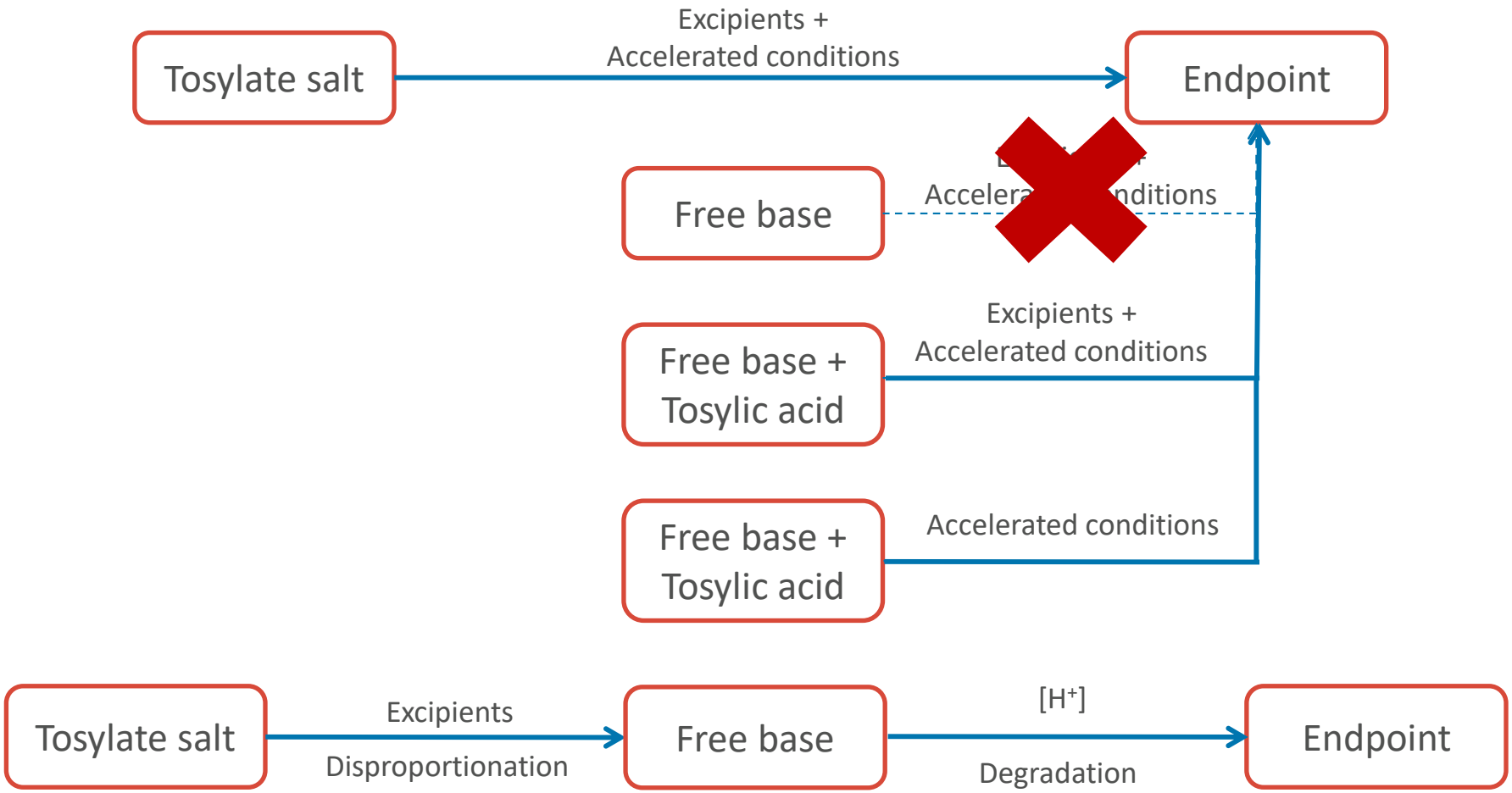
# Establishing a mechanistic understanding

## Hypothesis:

- Disproportionation occurs, but a subsequent chemical reaction is taking place so rapidly that free base is not detected



# Testing the hypothesis



# Summary

- Faced with a complex degradation pathway neither chemical stability data nor physical stability data alone were able to provide a detailed understanding
- Only when both physical and chemical stability information were considered together was the mechanism unravelled
- The degradation has been shown to comprise a two-step process:
  - A disproportionation step governed by the properties of the **excipients**
  - Chemical reaction step is catalysed by the presence of **free acid**

# Final thoughts and outlook

- Work in this area is increasingly important and we need to catalyse further interest at the academic/industry interface
- The translation of rates derived under accelerated/stressed conditions to more conventional conditions remains a gap in our analytical understanding as a community
- The acceleration of the transformation of molecule through to medicine means that this area of work will become more important/pivotal in the product realisation process

# Acknowledgments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