Shelf-Life Prediction Method for Early Stage API Candidates by iChemExplorer

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Solid Stability Evaluation

iChemExplorer

- Solid Stability Assessment is critical to advancement of Early Stage API Candidates
- 40% of all failures in Phase Three Clinical Assessment are due to unstable API's
- Once the molecule is set little can be done in preparation or formulation to enhance stability
- Current assessment methods require grams of material and at least a month in testing before an answer is available
- The Stability Assessment presented here consumes less than a gram of API with an answer in 48 hours = GAME CHANGER for pharma development!!!

Solid State Drug Degradation

iChemExplorer

- Drug degradation can occur by direct reaction in the crystal lattice of the solid ("topochemical degradation") or at the surface of the drug
- Topochemical reactions are readily identified since they either do not occur in the solution state or are much slower in the solution state compared to the solid state
- Most drug substances **do not** degrade in this manner, but rather occur at the surface of the particle
- Furthermore, for the bulk of pharmaceutical materials it is the adsorbtion of a surface layer of water around the drug particle that drives degradation of the solid (the "Leeson-Mattocks" model)

D. Zhou, *Journal of Validation Technology*, 2009, 37.

Leeson-Mattocks Model

iChemExplorer

- The Leeson-Mattocks model proposes a contiguous water layer around the solid in which the material dissolves to saturation
- Degradation occurs only in the solution layer (solvent mediated degradation)
- A constant flux of solid into the solution layer maintains saturation
- A recent analysis by Guerrieri *et.al.* has shown that the rate of solid degradation is given by equation (**1**)

$$k_{(s)}=k_{(aq,pH)}CW \quad (1)$$

k=first order rate constant for solid degradation
$k_{(aq,pH)}$=first order rate constant for aqueous solution degradation at saturation pH
C=Mass fraction aqueous solubility
W=water content in solid (as a mass fraction)

P. Guerrieri *et.al., J. Pharm. Sci.*, **2010**, *99*, 3719.

Obtaining the Required Data

iChemExplorer

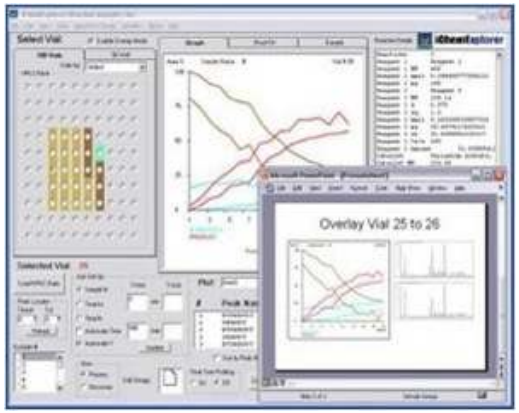
From non-isothermal degradation experiment

From DVS measurement

$$k_{(s)}=k_{(aq,pH)}CW$$

From solubility measurement

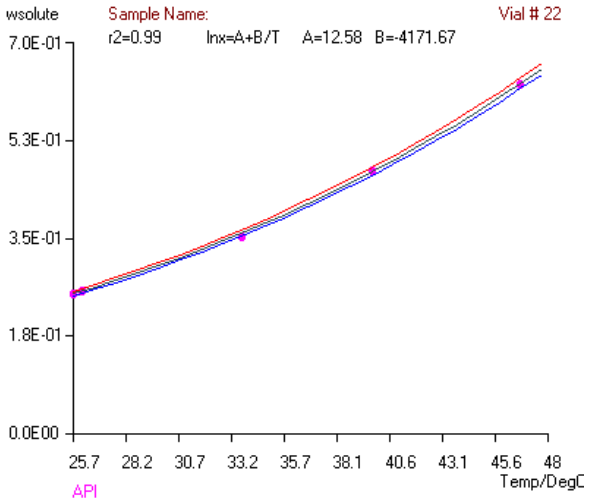
iChemExplorer – A powerful tool for your HPLC!



- Integrates cooling/heating (0 to 150˚C) and stirring (up to 1200 RPM) into an Agilent HPLC auto-sampler
- Typical reaction scale 250µl to 1ml
- Perform up to 54 reactions right on the auto-sampler deck
- Real-time profiling of chromatographic data
- Robust hardware and intuitive software
- Sample-quench and direct inject modes of operation

Step 1: Measure Solubility

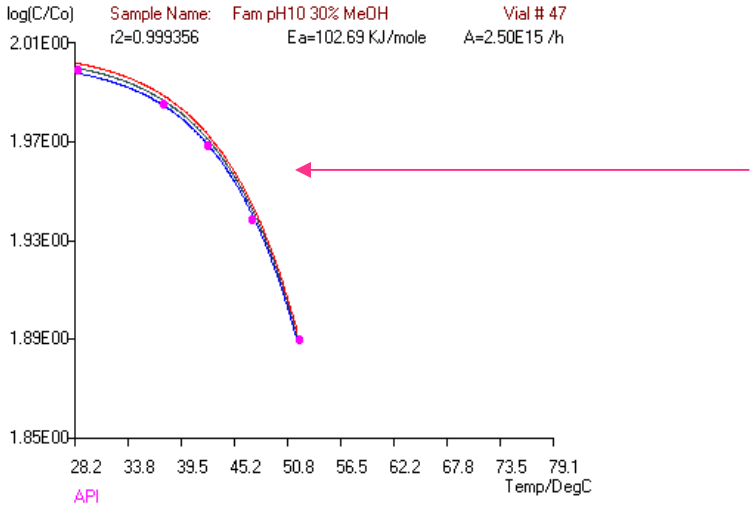
- This can be done by any acceptable method – typically a shake flask approach is adopted.
- In our studies a micro-scale shake flask approach was employed using HPLC vials - typically with < 500mg material
- iChemExplorer may be used to simply the process using filter vial technology to readily construct solubility curves with fitting to the Van't Hoff Equation



- pH of the saturated solution is measured with a pH meter

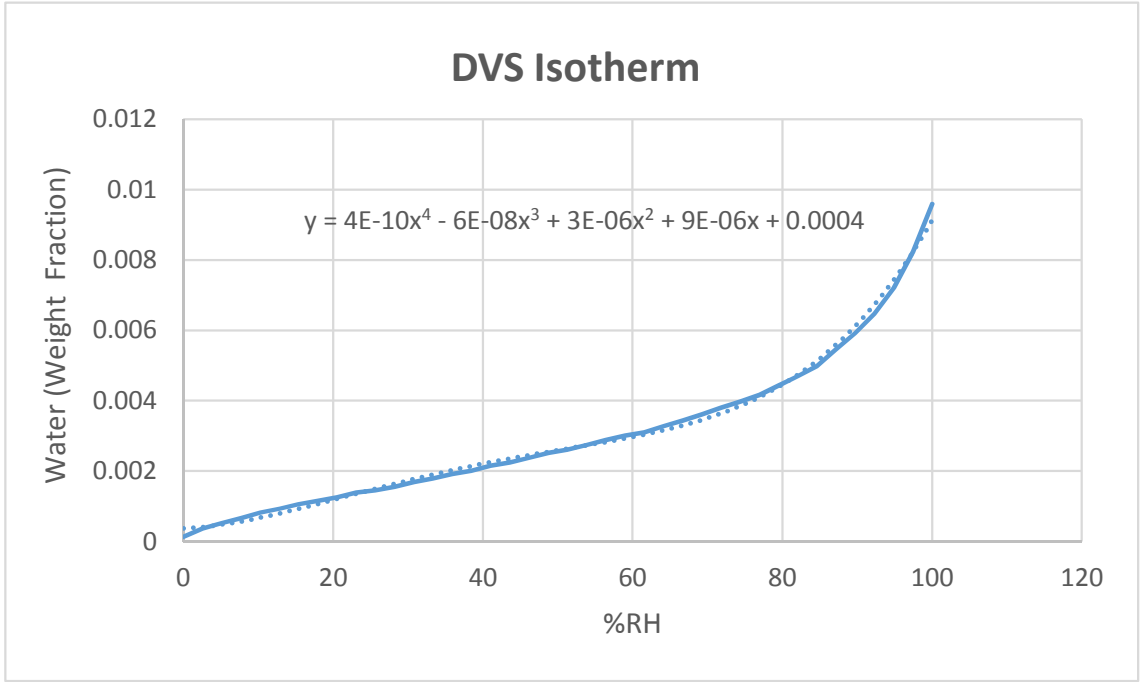
Step 2: Measure Degradation at Saturation pH

- Prepare 0.5-1 mg/ml solution of API in aqueous buffer at pH of saturated solution. A small amount of water miscible co-solvent may be added if required to ensure dissolution.
- Use iChemExplorer to measure degradation using a linear non-isothermal ramp from 25ºC to 80ºC over 19h.
- Rate constants are fitted automatically using iChemExplorer



Degradation kinetics fitted using iChemExplorer. Correlation and model confidence intervals are used to interactively exclude outliers.

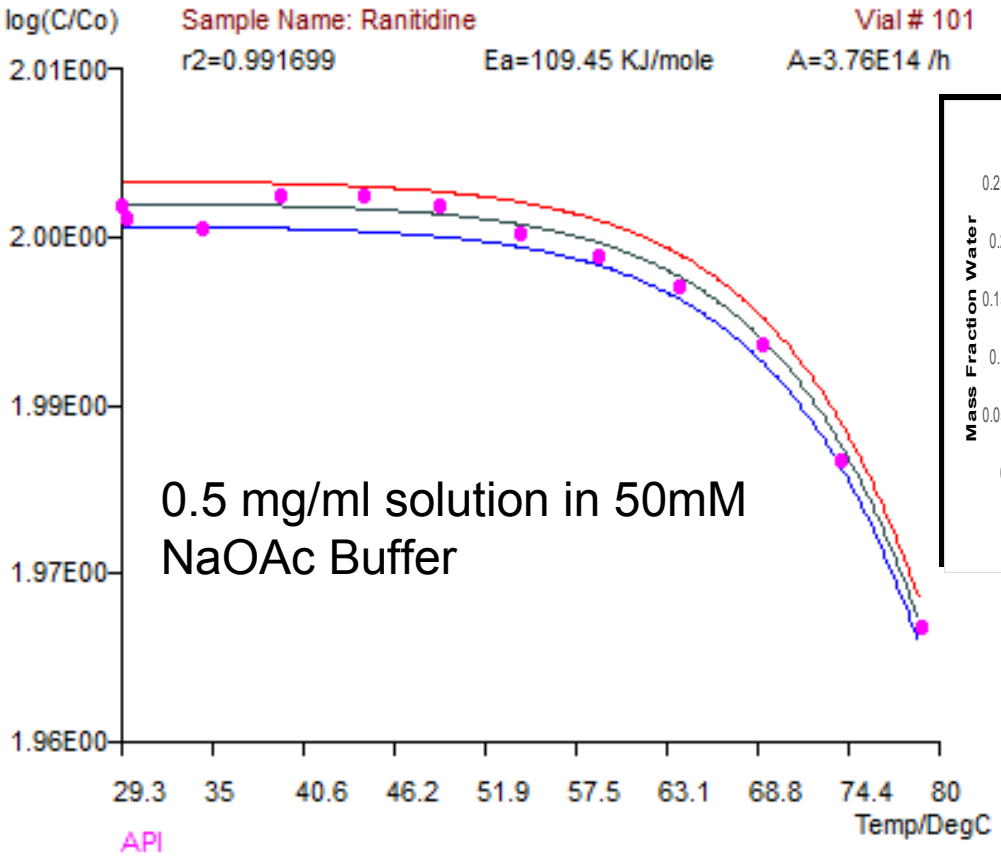
Step 3: Measure DVS Isotherm

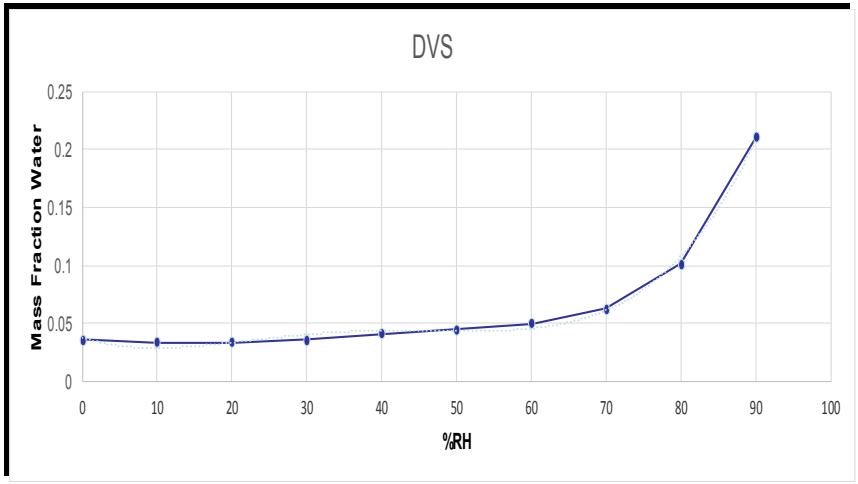


- DVS is measured at 45ºC and fitted isotherm imported into iChemExplorer
- Solid Stability Contour Plots with shelf life predictions can now be generated using iChemExplorer software
- Will be exemplified with 3 compounds

Ranitidine HCl

iChemExplorer





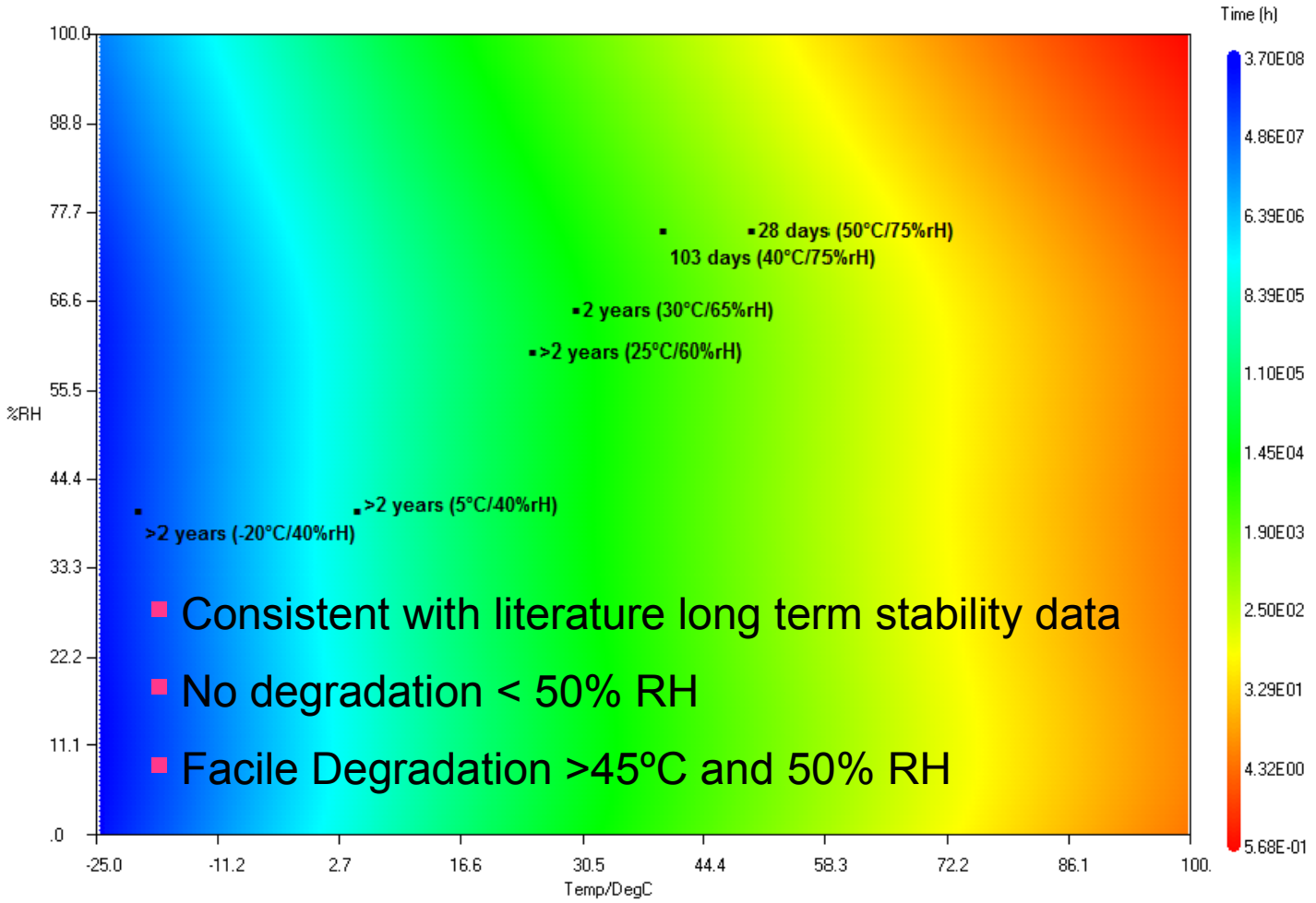
- **Solubility**: 880 mg/ml at 25ºC
- **ln(W)** = -0.76
- **Saturation pH**: 4.83

- Total material requirement: 900mg
- Time Requirement: 3 days

Ranitidine HCl Solid Stability Contour

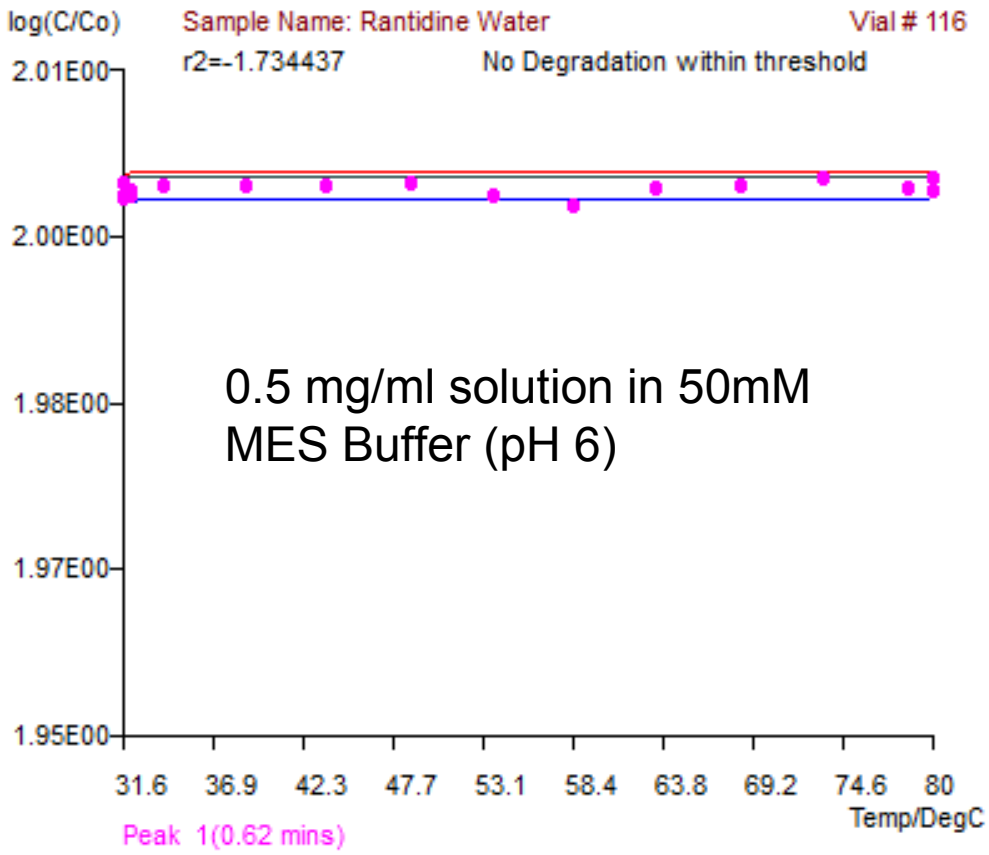
iChemExplorer

- 2% Isoconversion Contour Plot



Y. Matsuda *et.al., J. Pharm. Sci.*, **1993**, *82*, 601.

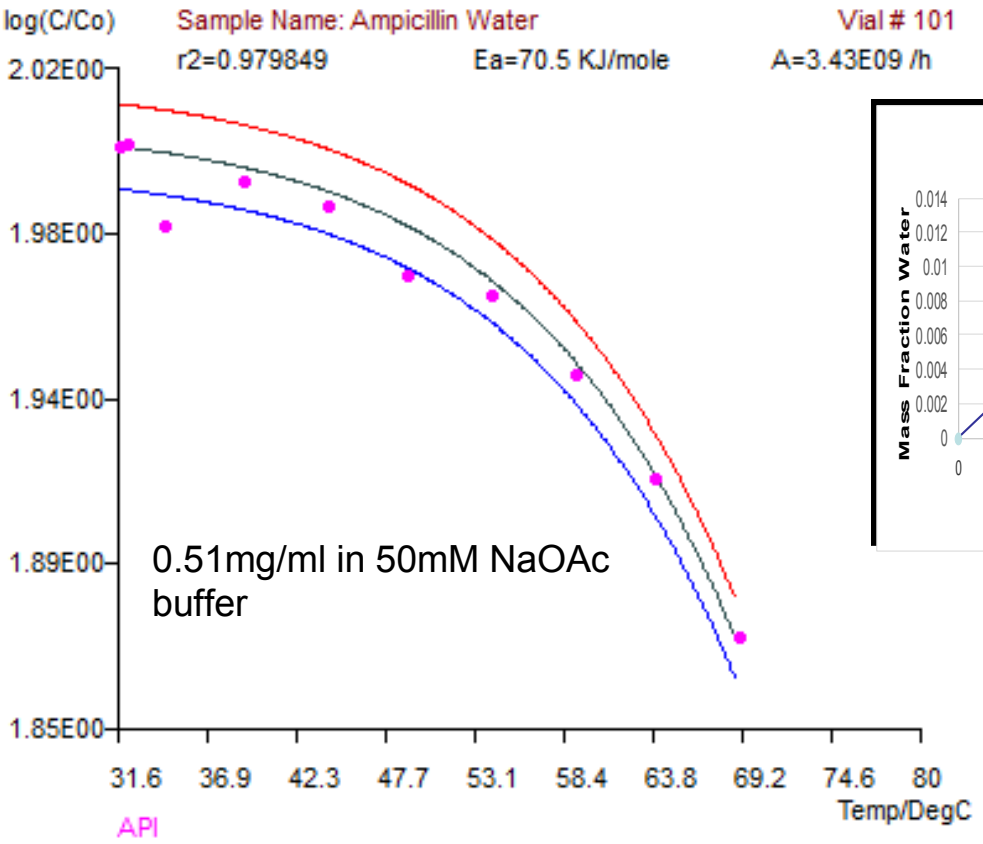
Importance of Saturation pH Measurement

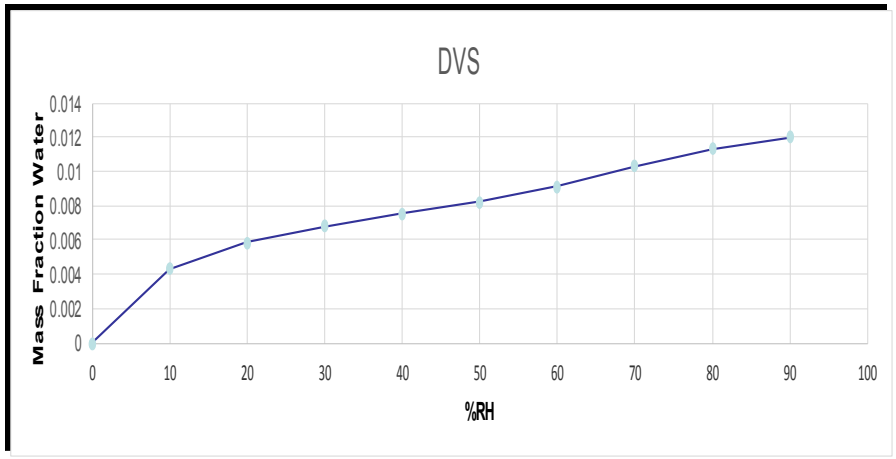


- No solution degradation at pH6 (*cf* pH 4.8 of saturated solution)
- Highlights importance performing degradation run close to pH of saturated solution

Ampicillin Trihydrate

iChemExplorer





- **Solubility**: 50 mg/ml at 25ºC
- **ln(W)** = -3.04
- **Saturation pH**: 6.85

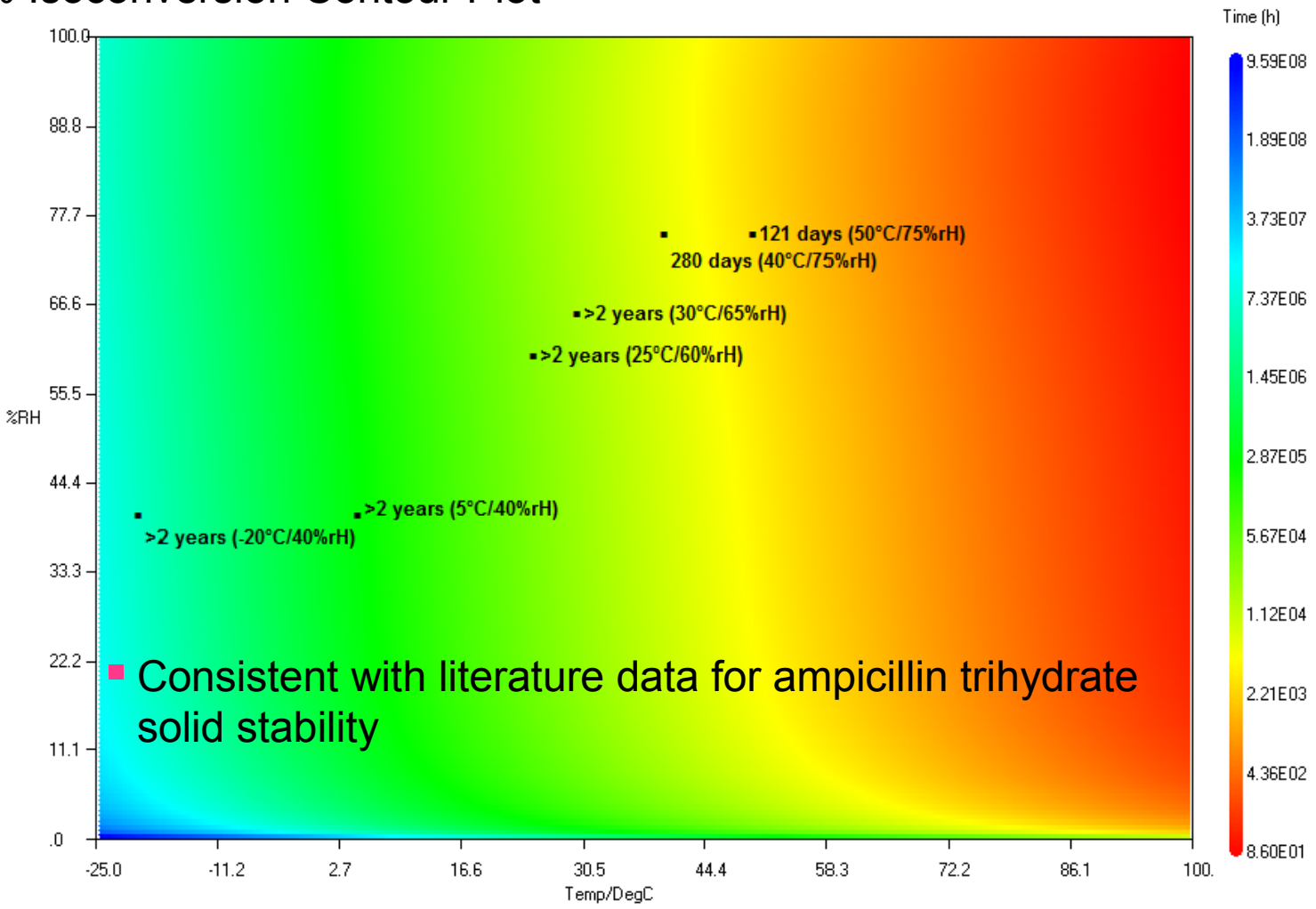
Mean Error (%): -8.43E-05
Standard Dev. (%): 2.80E-01

- Total material requirement: 40 mg
- Time Requirement: 3 days

Ampicillin Trihydrate Solid Stability Contour

iChemExplorer

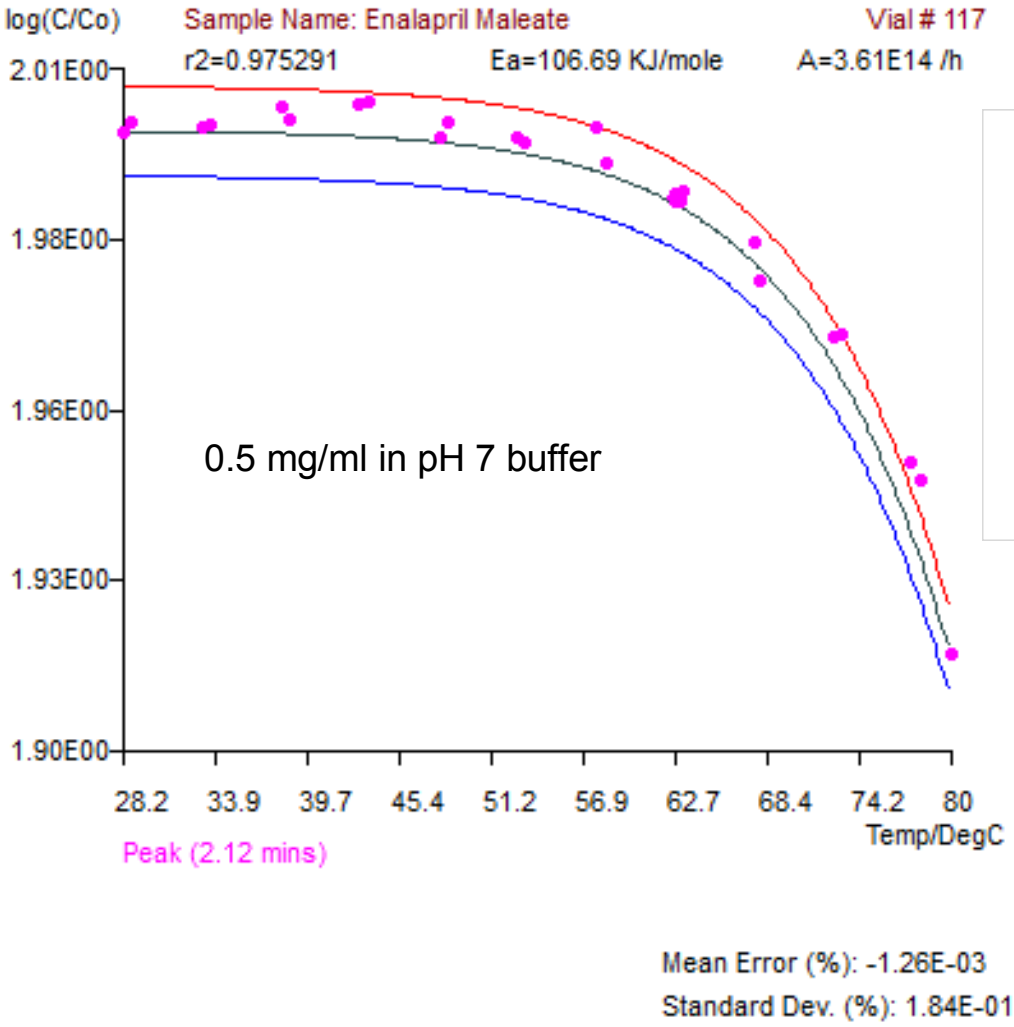
- 2% Isoconversion Contour Plot

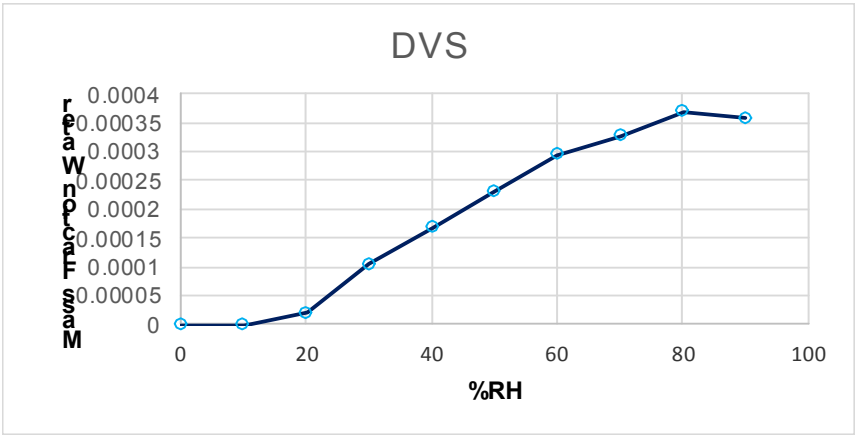


- Consistent with literature data for ampicillin trihydrate solid stability

K. Florey (ed.) *Analytical Profile of Drug Substances.*, **1973**, *2*, 1-61 ; WHO publication WHO/PHARM/86.529

Enalapril Maleate





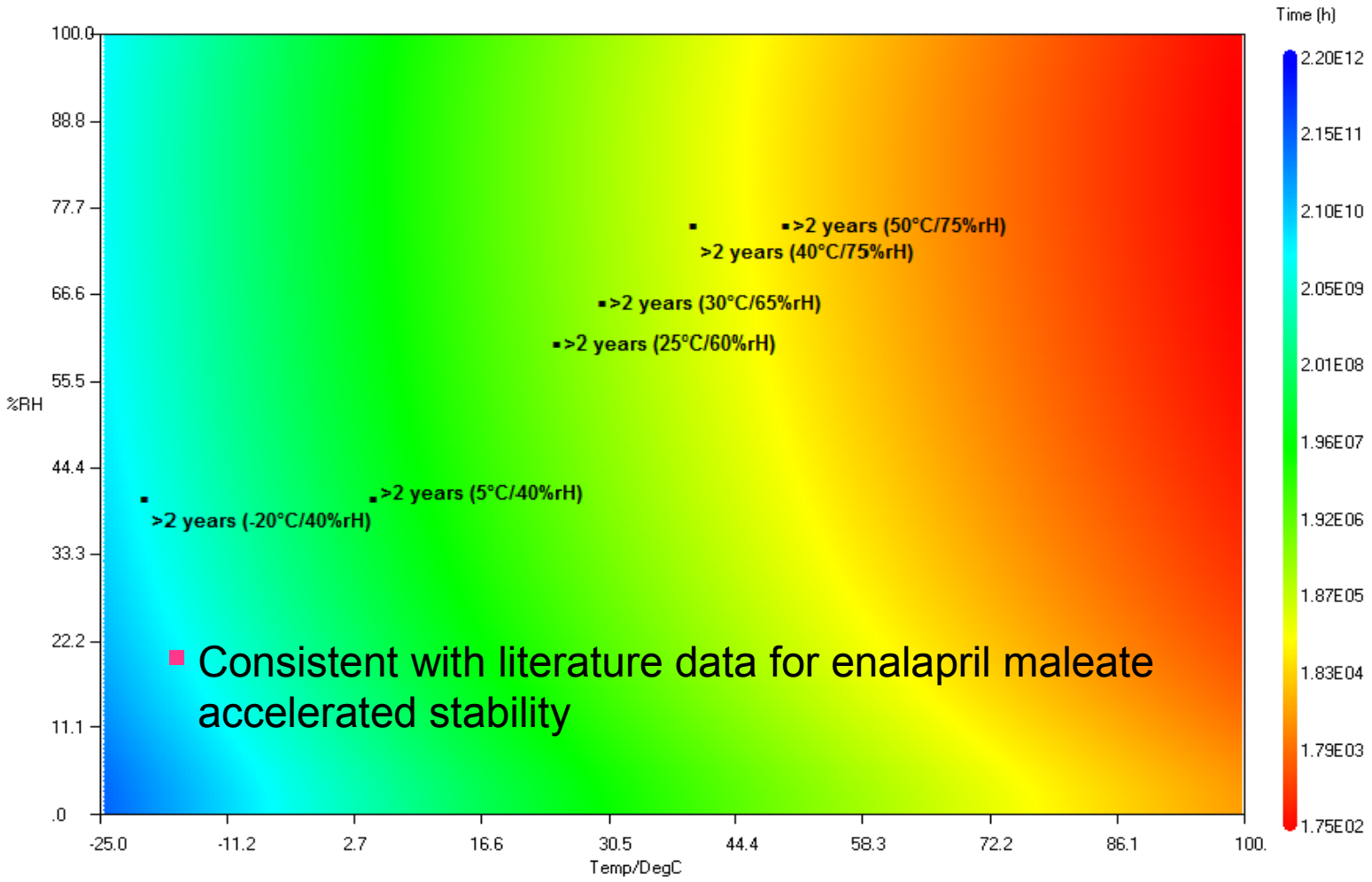
- **Solubility**: 16.4 g/ml at 25ºC
- **ln(W)** = -0.06
- **Saturation pH**: 7.16

- Total material requirement: 40 mg
- Time Requirement: 3 days

Enalapril Maleate Solid Stability Contour

iChemExplorer

- 2% Isoconversion Contour Plot



- Consistent with literature data for enalapril maleate accelerated stability

M. de Diego *et al., Quim. Nova.*, **2011**, *34*, 450

Conclusion

- A rapid and bulk sparing method for early assessment of API solid stability has been developed
- Typically takes less than 3 days and requires < 1g API
- Have demonstrated good correlation to literature data for commercial compounds and accelerated stability data for proprietary compounds
- Intrinsically simple to perform using iChemExplorer platform
- Does not require use of a multi experiment design space as is typical for humidity corrected isoconversional methodology
- Assessment of further compounds is in progress in preparation for publication