Building an Enhanced Analytical Toolbox for In-vivo Predictive Dissolution

Justin Pennington, Sanjay Patel, Jesse Kuiper, Amanda Mann, Andre Hermans

PSCS-Analytical Sciences

MERCK Be well 125 YEARS

Outline

- Determination of Dissolution Mechanism
- 1x Bio-Relevant Dissolution
- Transfer Model for Weakly Basic APIs
- Future of Dissolution Methodology (Time Permitting)

MERCK
Be well

Outline

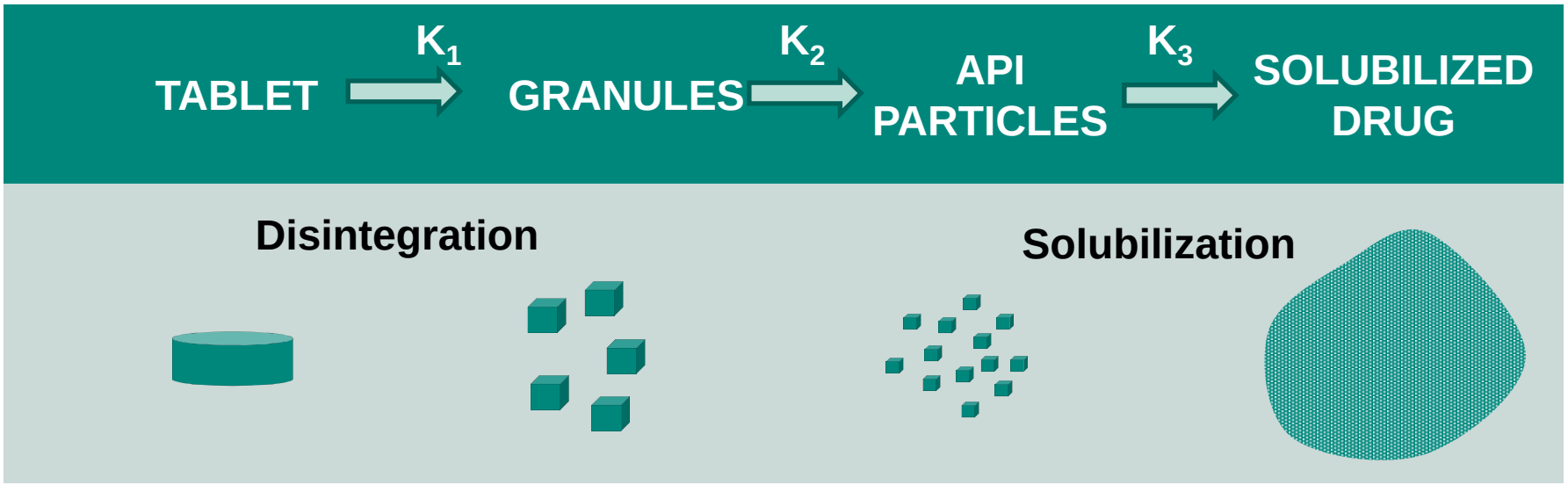
- Determination of Dissolution Mechanism
- 1x Bio-Relevant Dissolution
- Transfer Model for Weakly Basic APIs
- Future of Dissolution Methodology (Time Permitting)

MERCK
Be well

The Power of the Dissolution Test

Dissolution is the only product test that truly measures the effect of formulation and API physical properties on the rate of drug solubilization

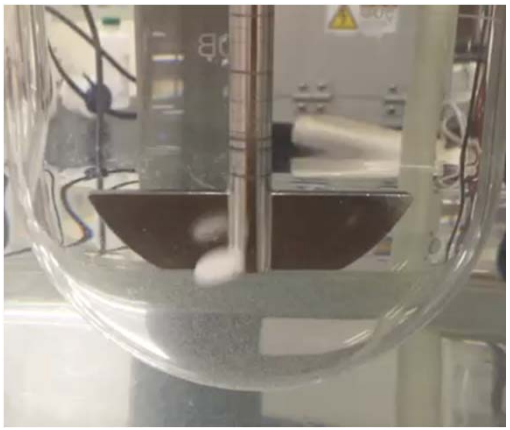
Dissolution = disintegration + intrinsic dissolution

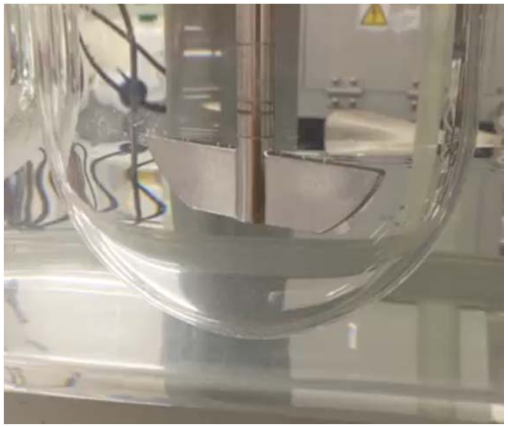


MERCK
Be well

Determination of Dissolution Mechanisms

- The determination of dissolution mechanism is mainly accomplished through visual observations.
- **Erosion Based:**
  - An observable “dry core” throughout the dissolution experiment.
  - May swell to some degree and granules may flake off
  - Measured Dissolution rate is relatively unaffected by granule properties
- **Granule Based:**
  - Rapid release of granules into the bulk solution
  - Granules will typically be large and will decrease in size over time
  - Tend to disintegrate rapidly and are highly affect by changes to granulation properties

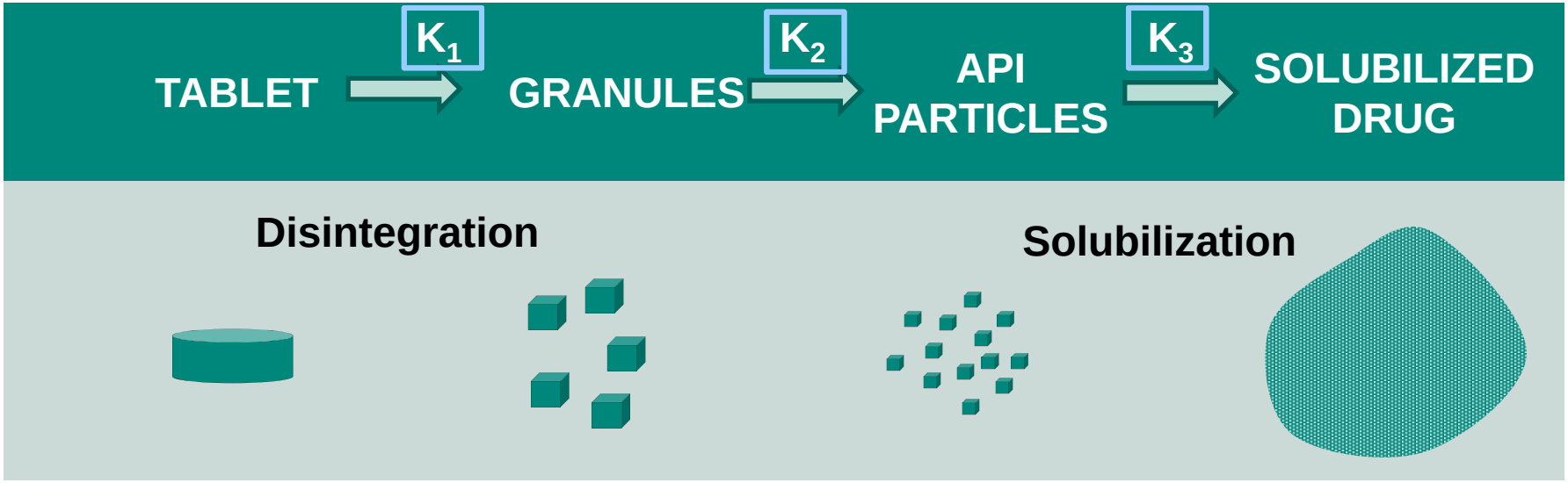




MERCK
Be well

Dissolution Mechanism Summary

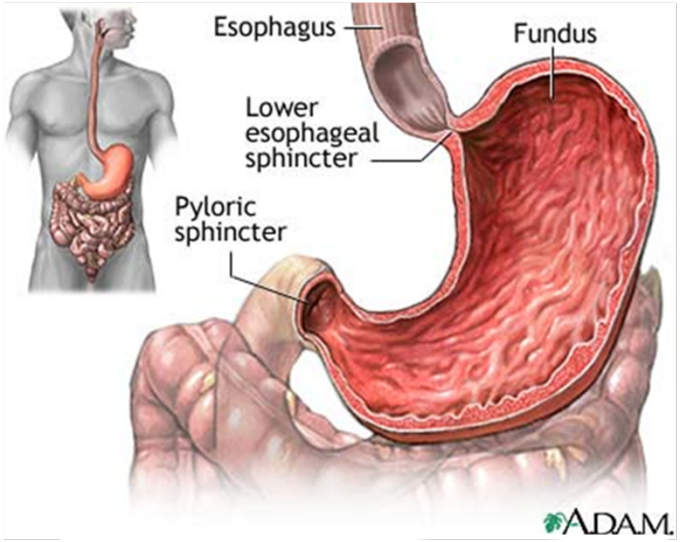
- The extent and location of dissolution of a pharmaceutical product is critical to ensure proper drug delivery to the patient and can greatly affect the observed pharmacokinetics for a drug candidate.
- While there are many factors at play to consider when evaluating dissolution, the general manner in which a dosage form dissolves can be generalized in the following matter.

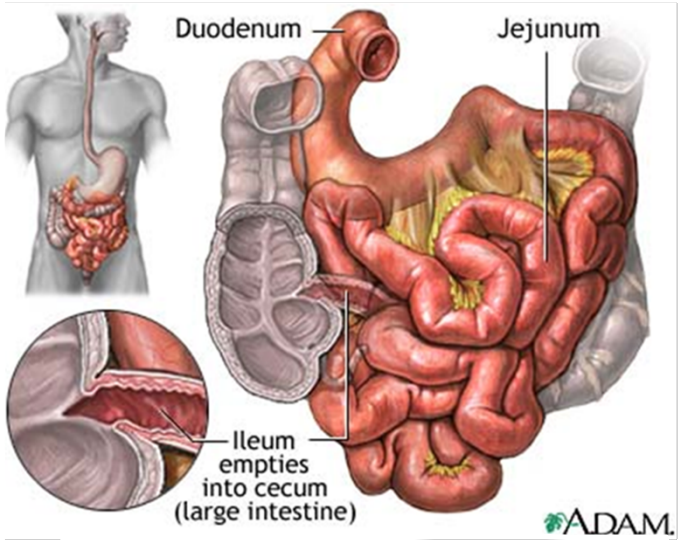


Note: Any factors (k) can be either rate limiting or potentially negligible.

MERCK
Be well

Bioavailability Depends on Dissolution





- Dissolution is the best surrogate for bio-performance if IVIVC can be established.
- It enables selection/ rank ordering of formulation candidates in early development without the need to perform actual in vivo (animal or human) studies significantly accelerating development

MERCK
Be well

Outline

- Determination of Dissolution Mechanism
- 1x Bio-Relevant Dissolution
- Transfer Model for Weakly Basic APIs
- Future of Dissolution Methodology (Time Permitting)

MERCK
Be well

Selection of Dissolution Conditions

Biorelevant dissolution can be conducted under different sink conditions depending on the purpose of the study.

Dose Relevant

- Biorelevant dissolution may be conducted at dose relevant concentration which often exceeds the solubility limit of the most stable API phase in that medium.
- This is used to assess the behavior of a metastable API phase under supersaturated condition and the formulation impact on the kinetics of supersaturation

1x Solubility Limit

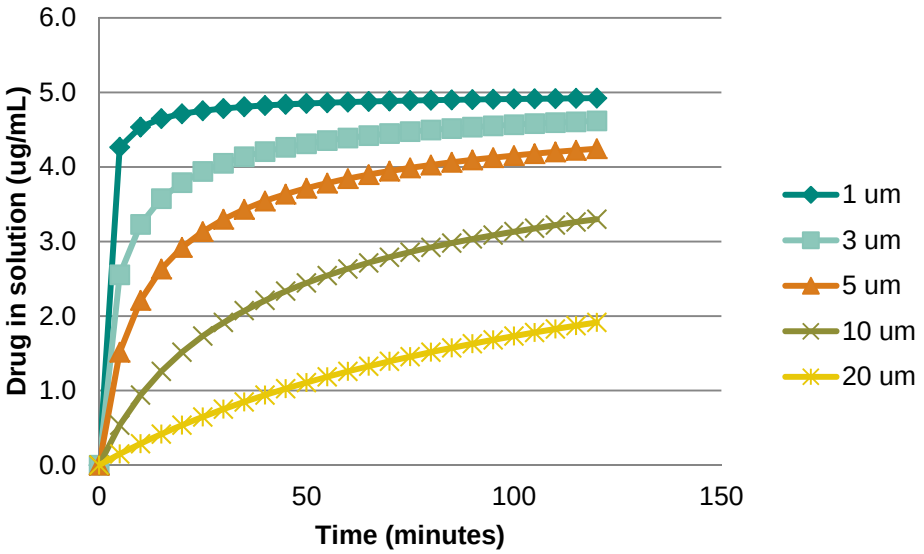
- **Standard Biorelevant test**
- Intended to probe the response of drug dissolution rate to API particle size distribution, wettability and dispersibility.
- May be conducted on all parts of the drug product from API and dispersion/extrudate through granules and tablets

MERCK
Be well

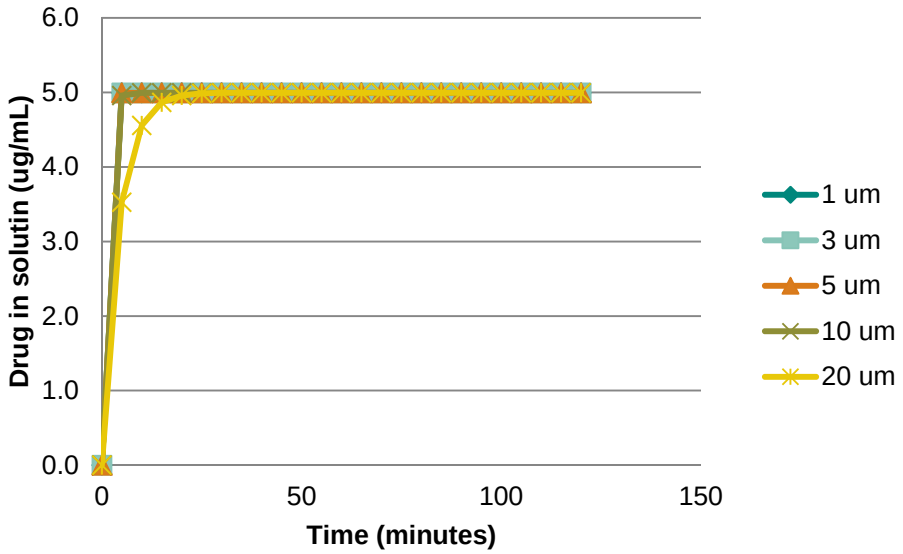
Dissolution at 1X versus Dose Relevant Concentrations

- 1X Solubility Approach Allows Quantitative Comparisons Across Formulation Types

Calculated Dissolution at 1X - 5 ug/mL Drug Solubility, Varying PSD



Calculated Dissolution at Dose Relevant (40X) - 5 ug/mL Drug Solubility, Varying PSD



MERCK
Be well

Practically, What Working at “1X” Means

- Using the 5 μg/mL solubility in FaSSIF example, and the 100 mg dose

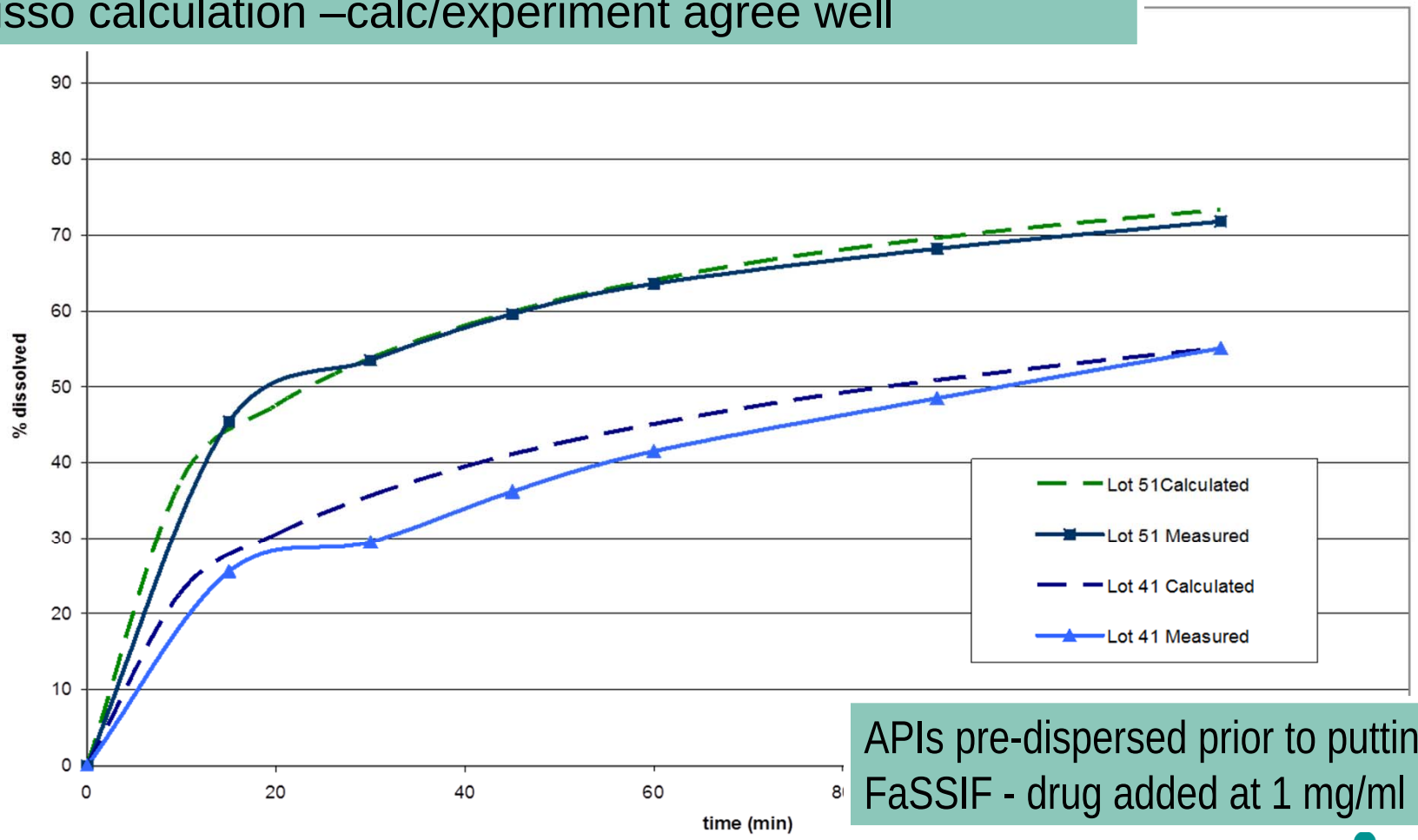
That’s a lot of FaSSIF!

- To work at “1X” with a complete 100 mg tablet then would require a 20,000 mL volume
- We work with granules (example here, 1/40th weight of a tablet in 500 mL faSSIF) or portions of tablets – or pre-disintegrated in SGF

MERCK
Be well

1X Dissolution is Readily Modeled

If API is dispersed properly and that PSD put into the disso calculation –calc/experiment agree well



APIs pre-dispersed prior to putting in FaSSIF - drug added at 1 mg/ml

MERCK
Be well

This Approach Allows Quantitative Comparisons Across Formulation Types

Formulation Attribute	1x Dissolution Response
API Dispersion in dose	Formulations that do this better will have faster rates of dissolution than those that do this poorly
Granulation of API	Granulation can help with dispersion of particles in dissolution – also over granulation can add additional dissolution rate slowing (increase in ρ term (particle density)
Addition of Surfactants	Helping wet the particles may improve dissolution rate

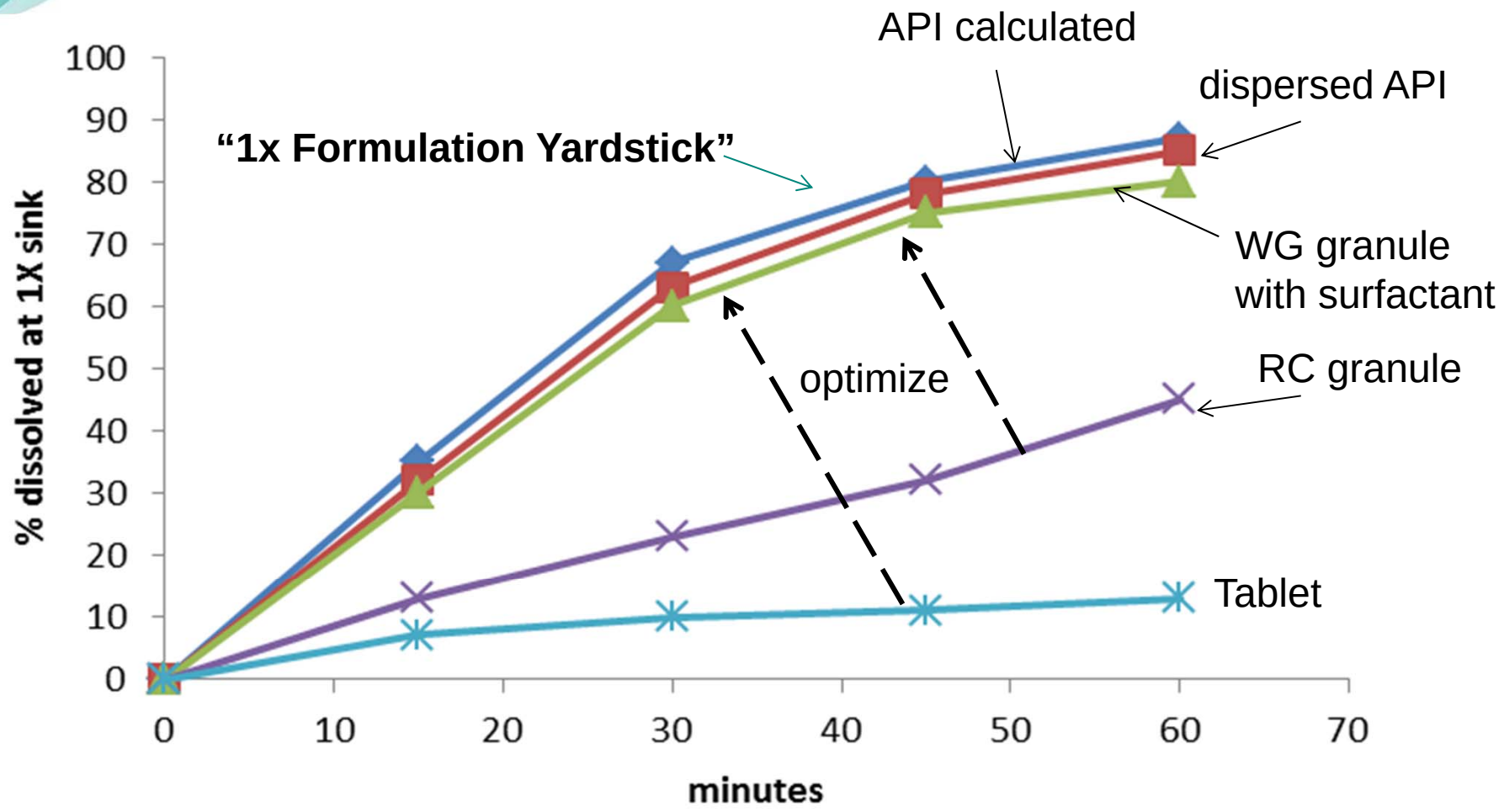
MERCK
Be well

This Approach Allows Quantitative Comparisons Across Formulation Types

Understanding the dissolution rate of well dispersed API particles is the first step in evaluating dissolution performance – as a very well dispersed formulation with very fast granule dissolution will approach dispersed API dissolution rate.

MERCK
Be well

Representative 1X Data Comparing Formulation Components



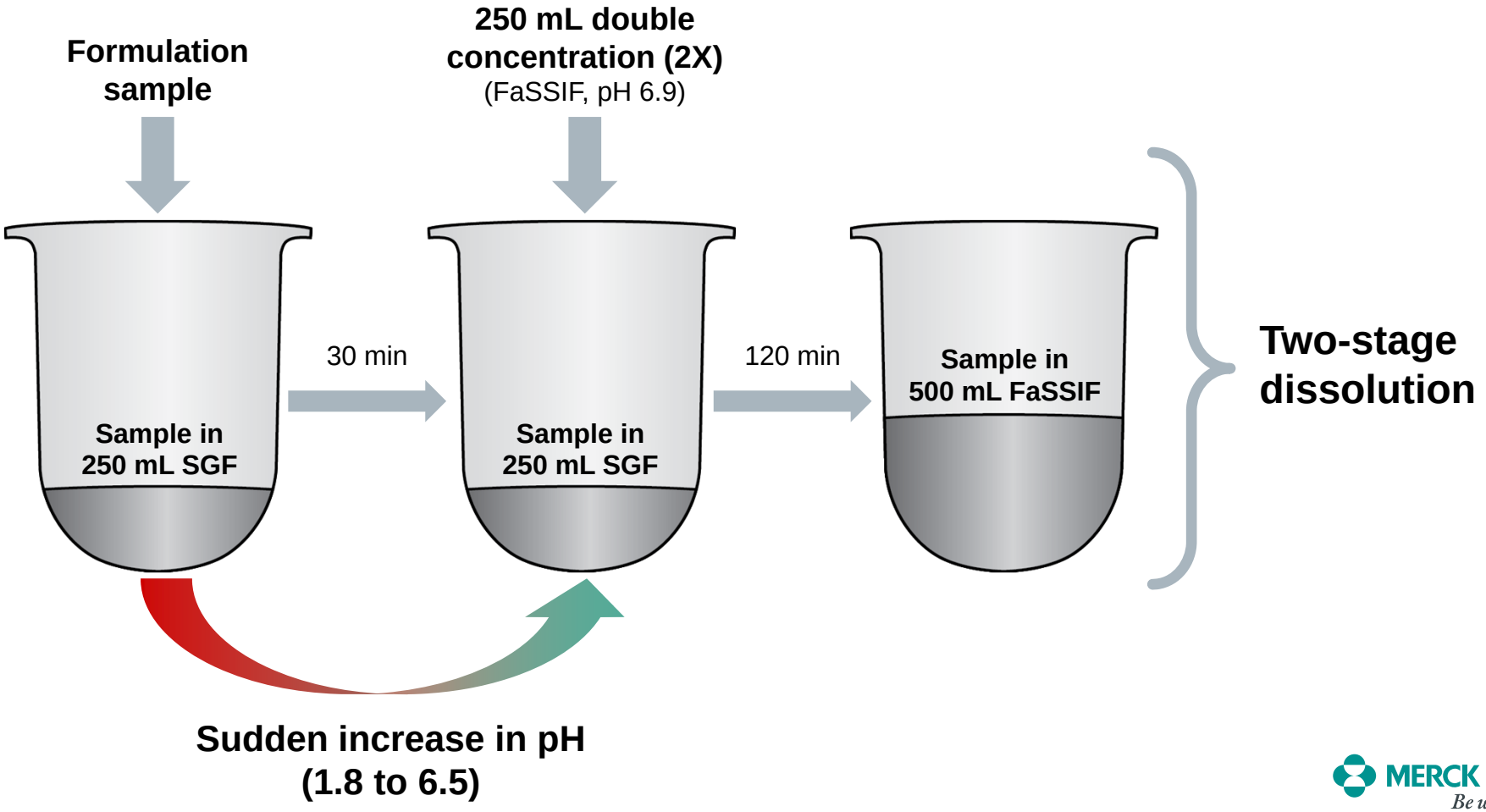
Outline

- Determination of Dissolution Mechanism
- 1x Bio-Relevant Dissolution
- Transfer Model for Weakly Basic APIs
- Future of Dissolution Methodology (Time Permitting)

MERCK
Be well

Two-Stage Dissolution

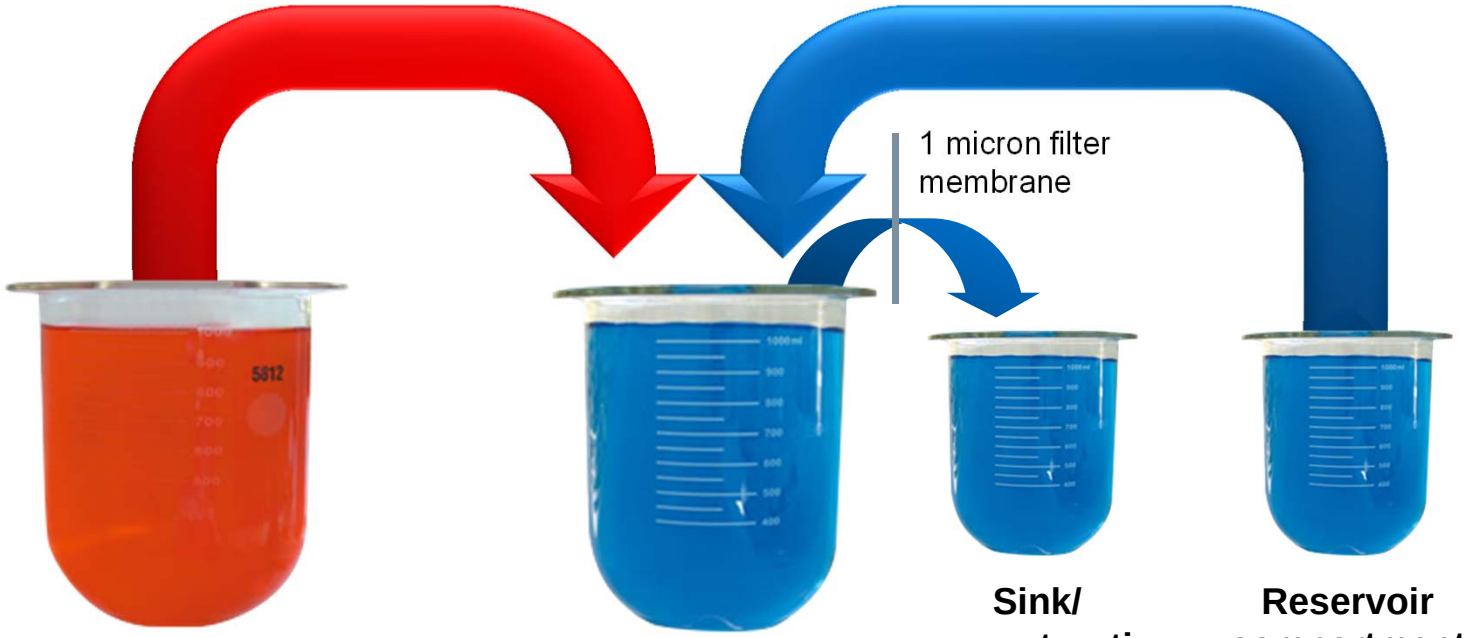
During the typical two-stage dissolution, 1X addition of FaSSIF creates sudden pH change for the 2nd stage. This may be especially problematic for weak bases, which may undergo precipitation in the 2nd stage.



MERCK
Be well

Multicompartment Transfer Model to Predict Dissolution/Precipitation of Weakly Basic Drug

Flow rate 5 mL/min



Gastric compartment
(SGF, 250 mL, 100 rpm)

Intestinal compartment
(FaSSIF, 250 mL, 50 rpm)

Sink/ supersaturation

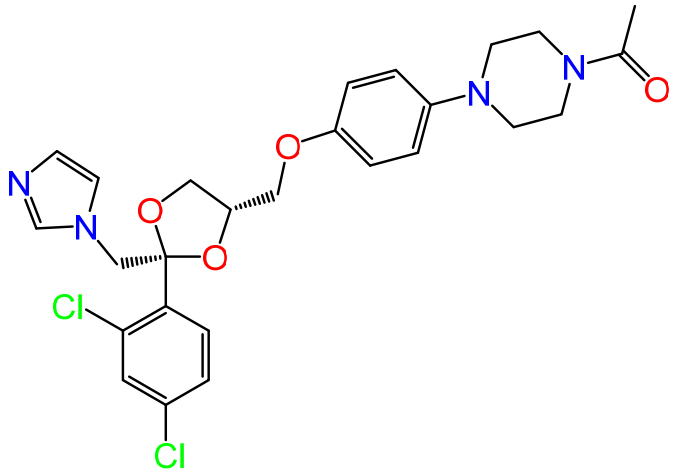
Reservoir compartment
(FaSSIF, pH 7.0)

MERCK
Be well

MERCK
Be well

Case Study: Ketoconazole

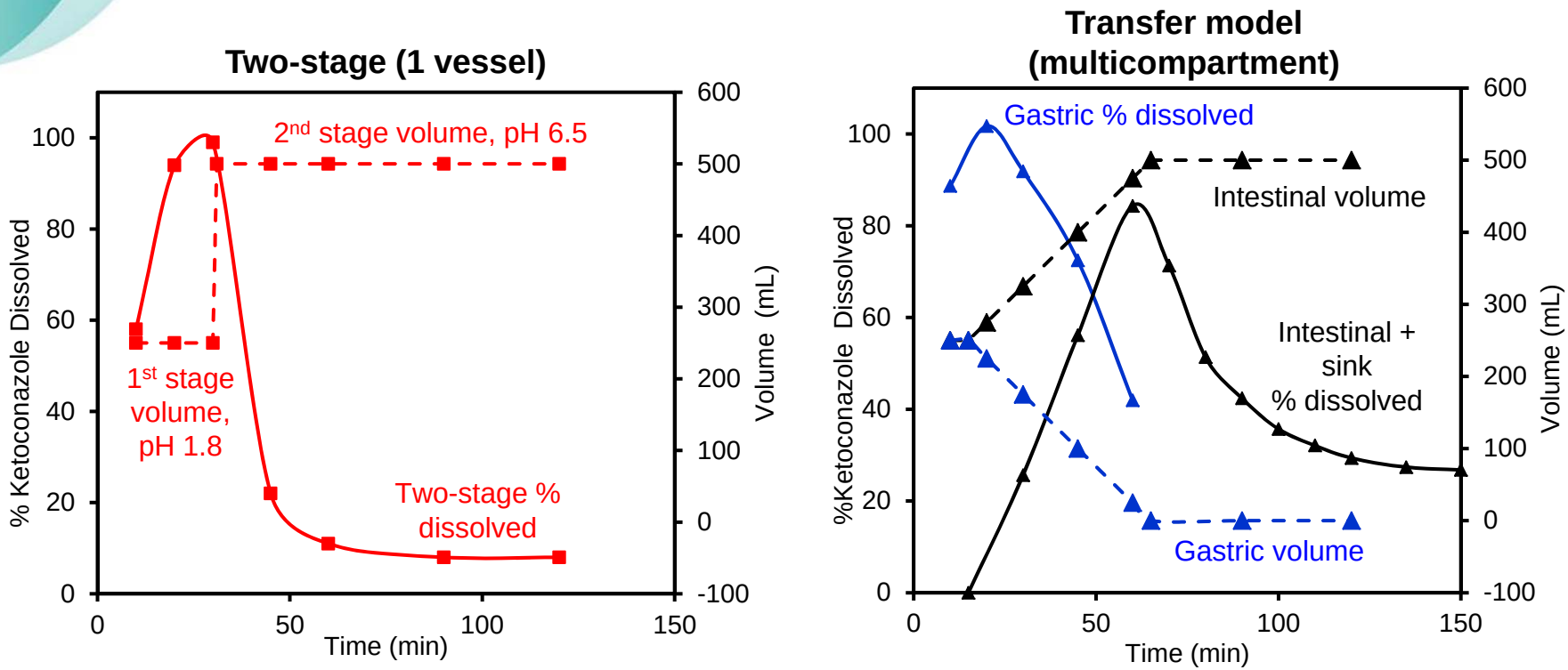
- Ketoconazole: Weak dibasic antifungal agent
- pKa: 2.94, 6.51
- BCS II
- Permeability:
  Caco-2 Peff=53x10^{-6} cm/sec
- Solubility:
  - Virtually insoluble at pH 5 or higher
  - Detailed solubility profile (right)
- Administration:
  - Exposure was well known as being affected by elevated stomach pH
  - Recommended to codose w/acidic cola drink



pH	Solubility (mg/mL)
1.6 (FaSSGF)	9
3 (buffer)	1.8
3.5 (buffer)	0.7
4.5 (buffer)	0.25
5 (buffer)	0.1
6.5 (buffer)	0.007
SGF	6
FaSSIF	0.02537

MERCK
Be well

Ketoconazole Tablets: Transfer vs Two-Stage

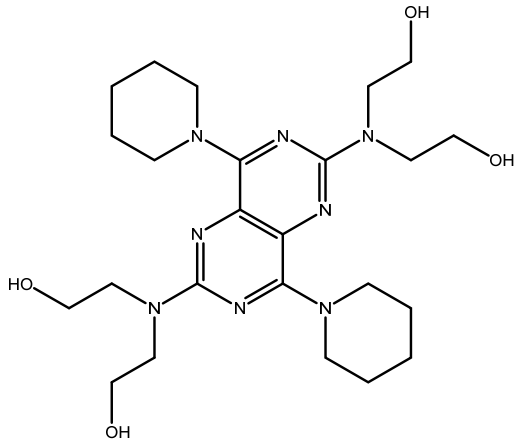


- Some precipitation observed in the transfer model; significant precipitation in two-stage dissolution
- A ***small amount of precipitation*** was observed in fasted adult study (Psachoulias D, et al. *Pharm Res.* 2011;28(12):3145-3158. doi: 10.1007/s11095-011-0506-6)

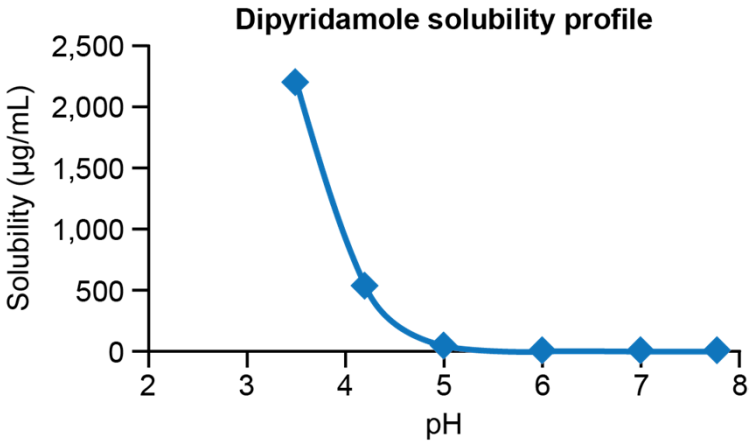
MERCK
Be well

Case Study: Dipyridamole

- Inhibits thrombus formation (antiplatelet)
- Free base with pKa of 6.4
- BCS Class II
- Permeability: Estimated human Peff 1.5 (cm/sec x 10^{-4})
- Tablets: 25 mg, 50 mg, 75 mg
- Recommended dose: 75-100 mg 4 times daily
- **Significantly decreased exposure with famotidine-treated healthy elderly patients**
- **The absolute bioavailability is 27 +/- 5.5% (range 11% – 44%)**



Molecular Weight: 504.6, pKa = 6.4

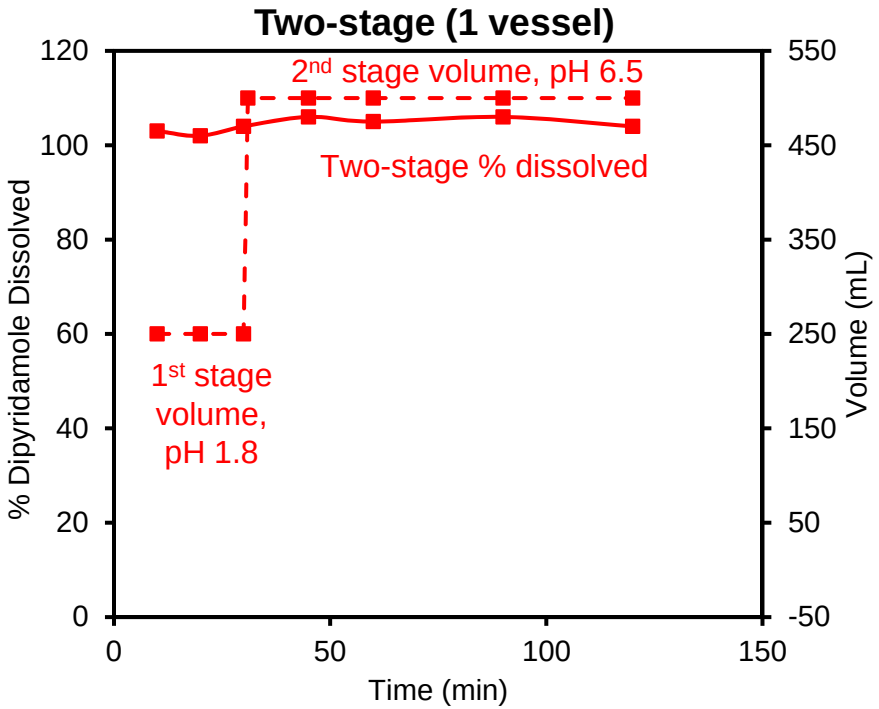


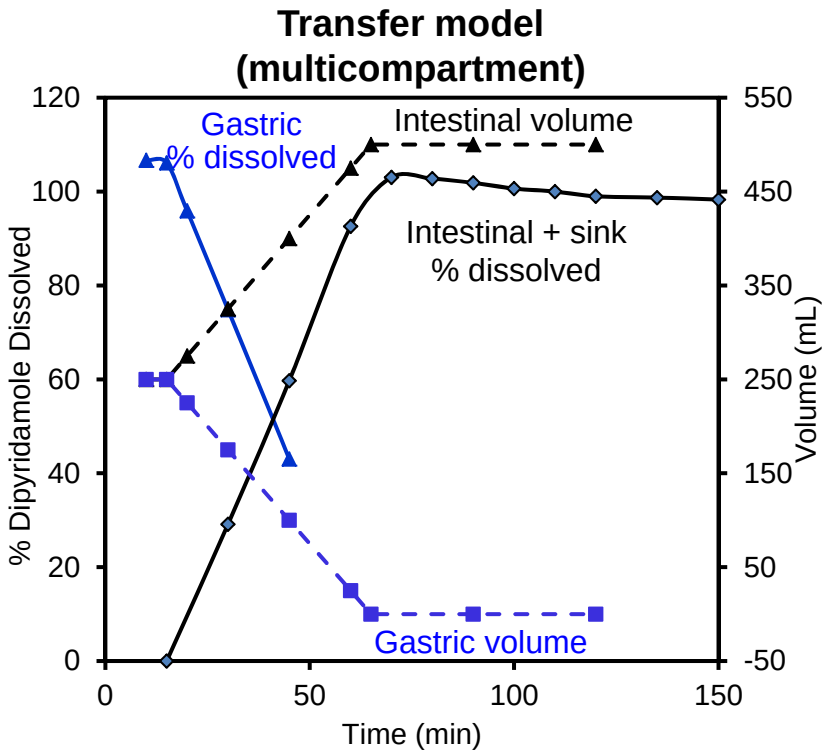
pH	Solubility (mg/mL)
3.5	2.2
4.2	0.5
5	0.0054
6	0.0010
7	0.0005
7.8	0.0006
SGF	8
FaSSIF	0.01148

Terhaag B, et al. *Int J Clin Pharmacol Ther Toxicol*. 1986;24(6):298-302.
Glomme A, et al. *J Pharm Sci.* 2005;94(1):1-16.

MERCK
Be well

Dipyridamole Tablets: Transfer vs Two-Stage





- Both models indicate dipyridamole does not undergo rapid precipitation
- Absorption modeling studies also indicate a prolonged in vivo precipitation
- Dipyridamole precipitation is concentration dependent
  (Box K, et al. Approaches for measuring intestinal precipitation rates of oral drugs [abstract])

MERCK
Be well

Transfer Model Summary

- A multicompartment transfer system was established to investigate the in vivo behavior of weak basic compounds
- Preliminary data showed promising results to support transfer model as an alternative way to estimate in vivo precipitation in intestinal compartment for weak basic compounds
- Opportunities:
  - In silico model – Develop full mathematical model to describe simultaneous transfer/precipitation process
  - Nanoparticle formers/enabling formulation

MERCK
Be well

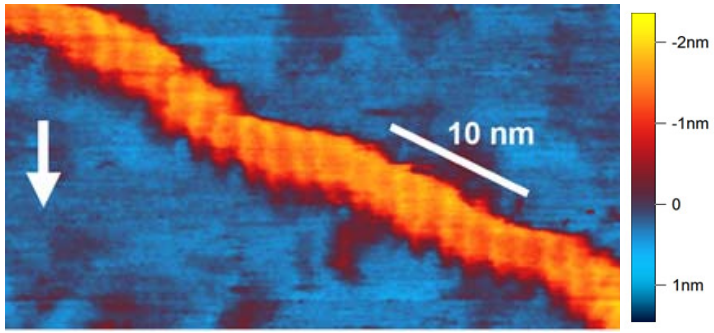
Outline

- Determination of Dissolution Mechanism
- 1x Bio-Relevant Dissolution
- Transfer Model for Weakly Basic APIs
- Future of Dissolution Methodology (Time Permitting)

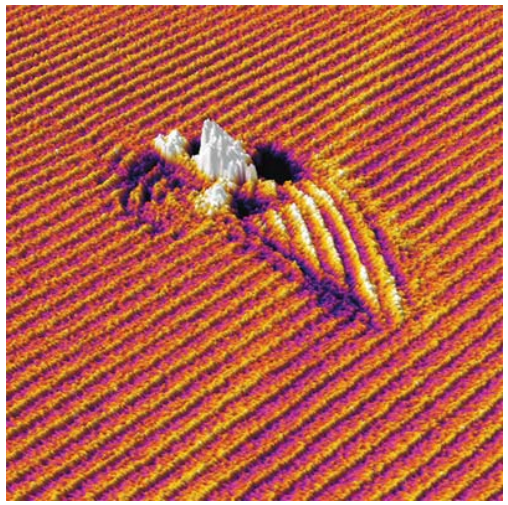
MERCK
Be well

Atomic Force Microscopy

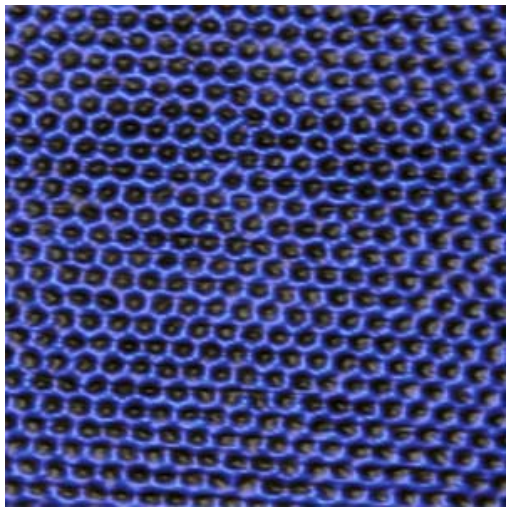
Atomic force microscopy (AFM) has been utilized to map topographical features, mechanical, electrical, and magnetic properties for nanoparticles, films, and biological materials with sub-nanometer resolution.



Single DNA Strand
https://www.asylumresearch.com/Gallery/Cypher/Cypher34.shtml



CTAB on Defect (graphite)
https://www.asylumresearch.com/Gallery/Materials/SelfAssem/Self5.shtml

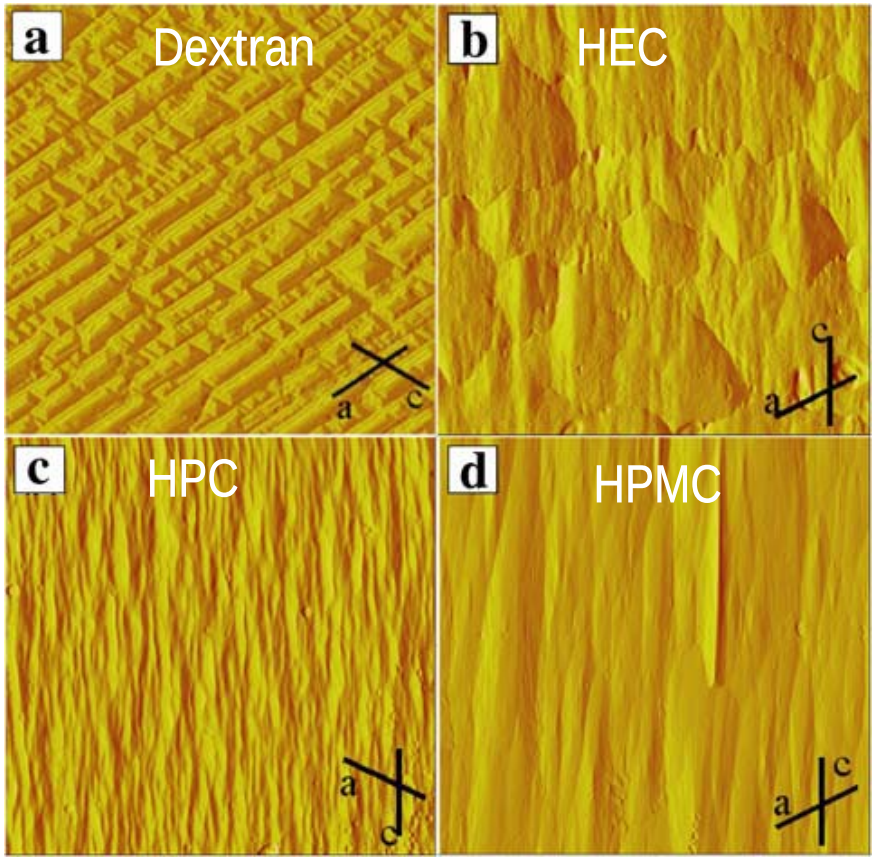


Graphite (5nm x 5 nm) (STM)
https://www.asylumresearch.com/Gallery/Cypher/Cypher1.shtml

MERCK
Be well

Previous AFM Dissolution Experiments

AFM has been utilized to monitor the dissolution of acetaminophen crystals. Due to the challenge of collecting AFM images in liquids, these samples are exposed to the dissolution medium, dried, and then imaged.



Correlate AFM images to the intrinsic dissolution rate and changes in etching patterns to interaction between the polymer and acetaminophen.

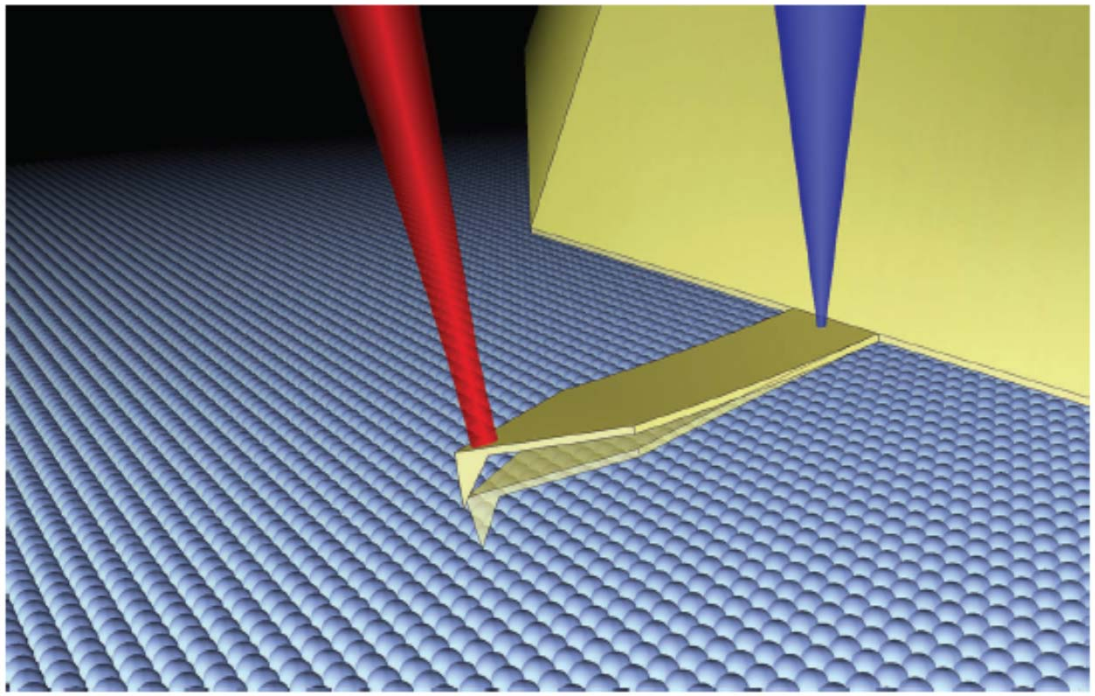
Wen, H., Morris, K.R. & Park, K. Pharm Res (2008) 25: 349.

MERCK
Be well

Asylum AFM

Detection

Drives the cantilever

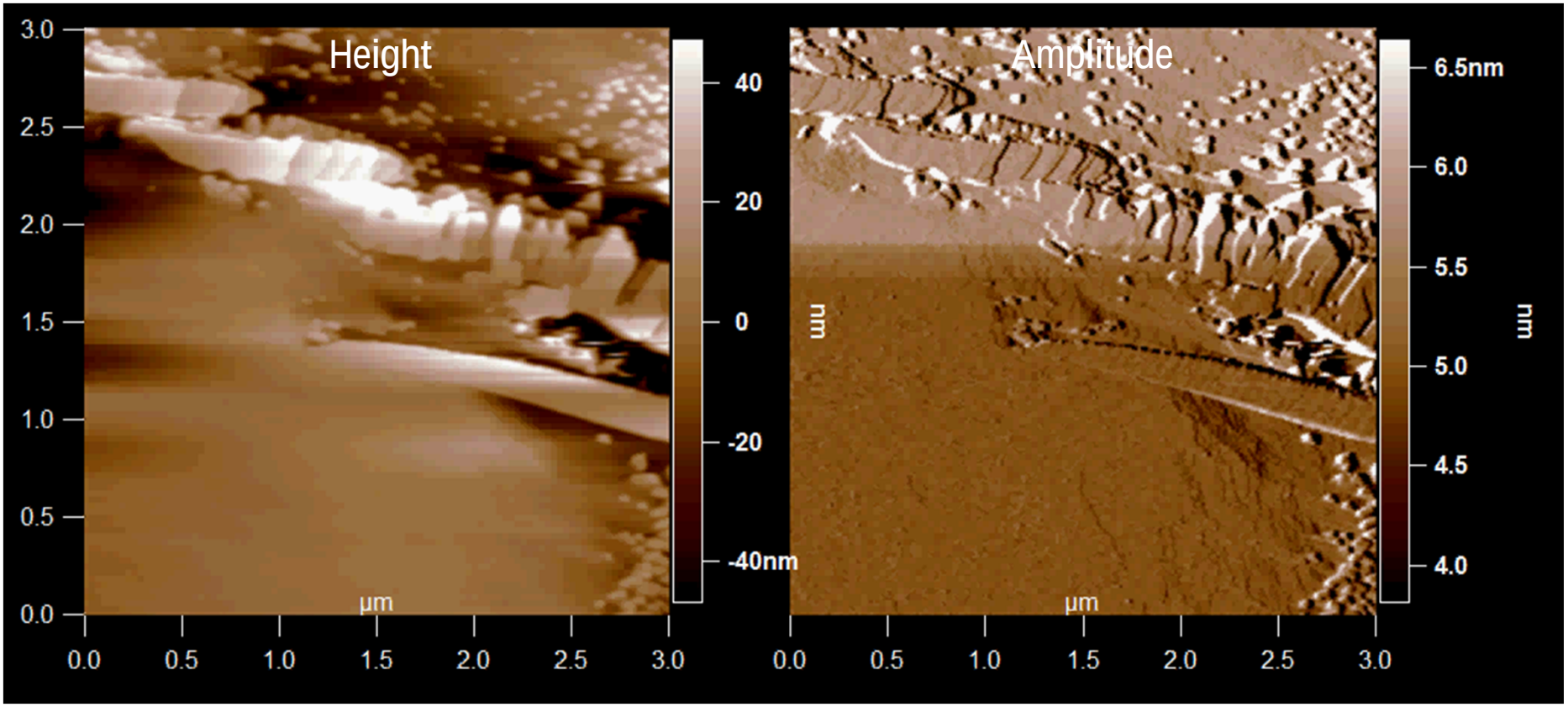


Cypher ES blueDrive (Asylum Research)

Typically, piezoacoustic excitation is used to drive the cantilever oscillation. blueDrive excites the cantilever photothermally.

MERCK
Be well

Compound A Phosphate Buffer

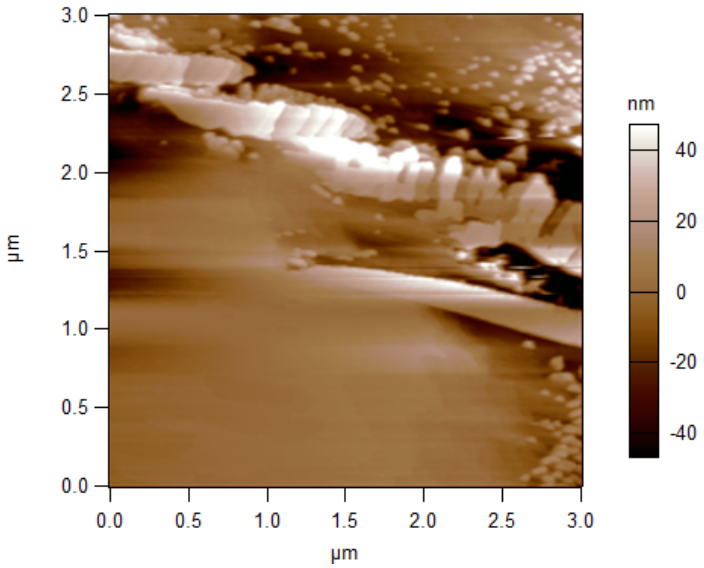


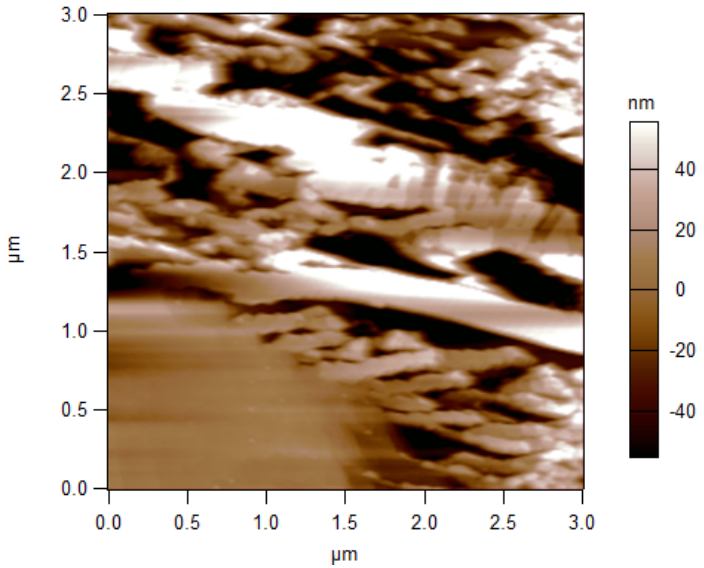
Dissolution is slowed down by dissolving Compound A into the solution prior to addition to the AFM.

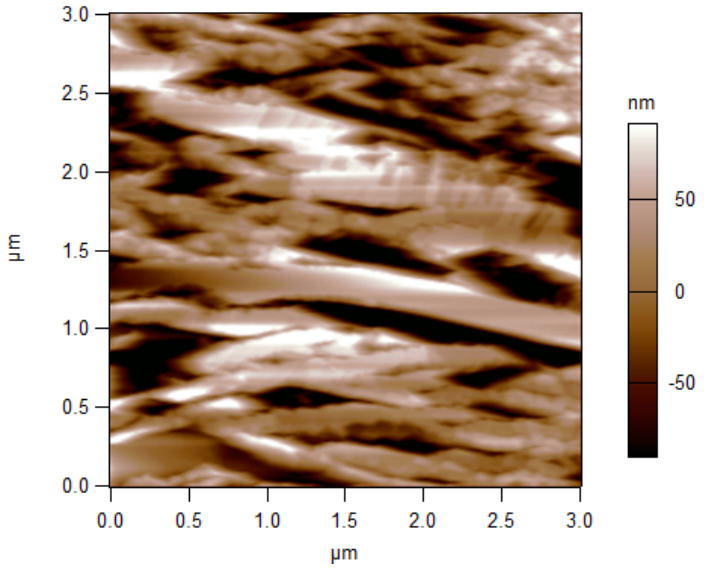
Phosphate buffer (pH 6.5)

MERCK
Be well

Compound A Phosphate Buffer



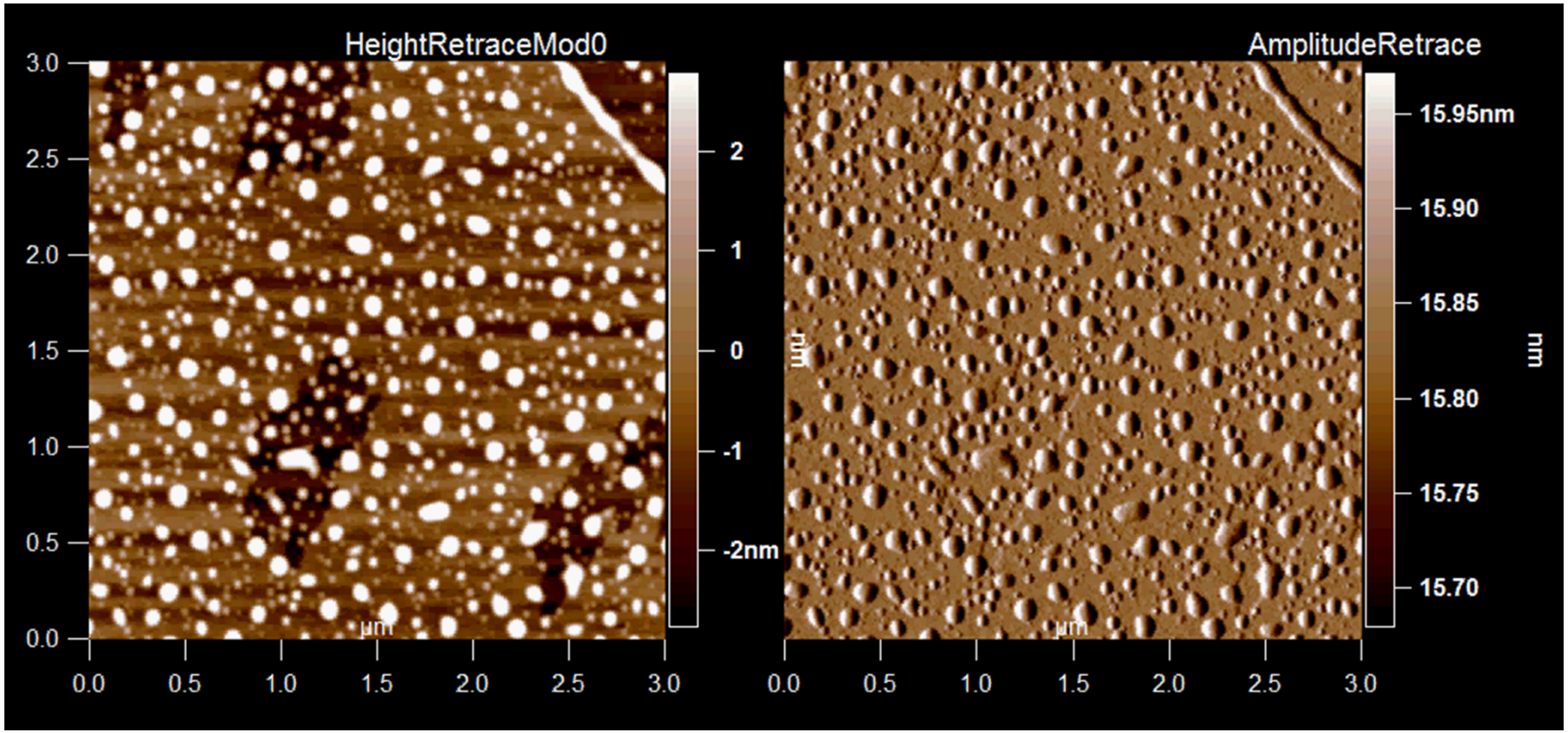




The surface appears to form pits on the surface
Certain surface features are maintained throughout the experiment
The etching starts near a defect and moves across the surface

MERCK
Be well

Compound A FaSSIF

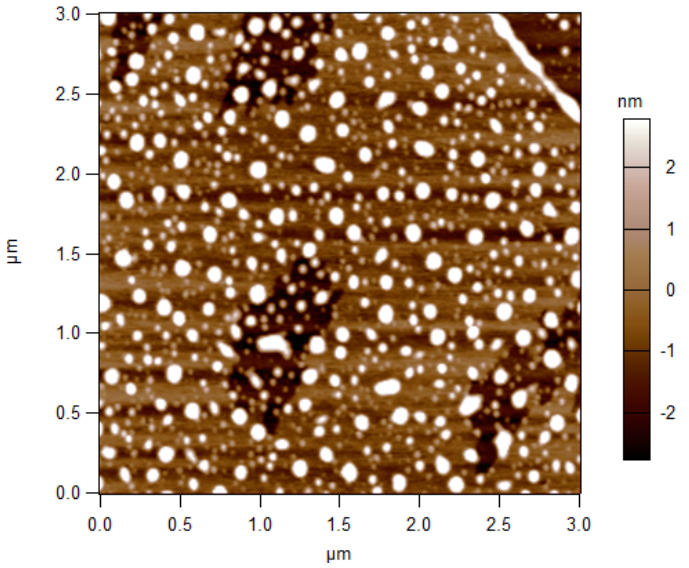


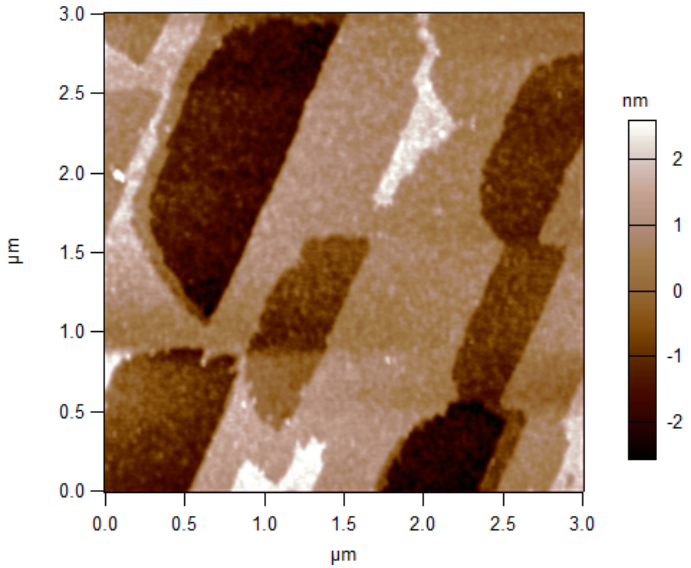
Dissolution is slowed down by dissolving Compound A into the solution prior to addition to the AFM.

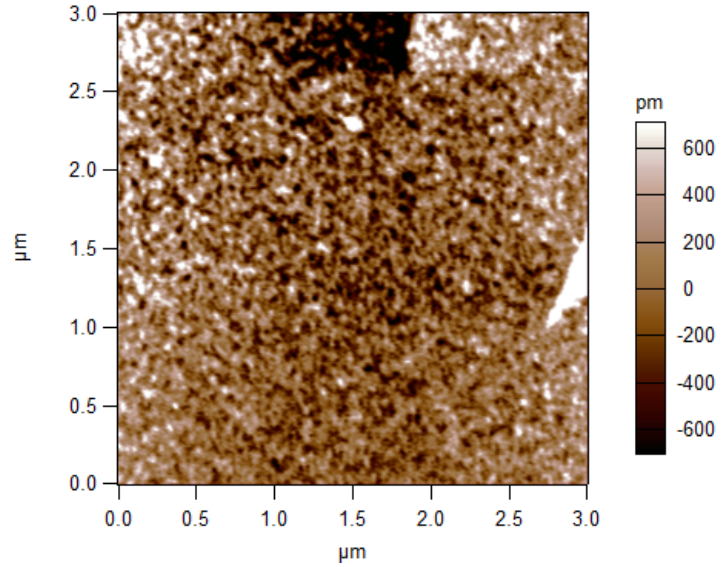
FaSSIF: Phosphate buffer + lecithin + sodium taurocholate (pH 6.5)

MERCK
Be well

Compound A FaSSIF







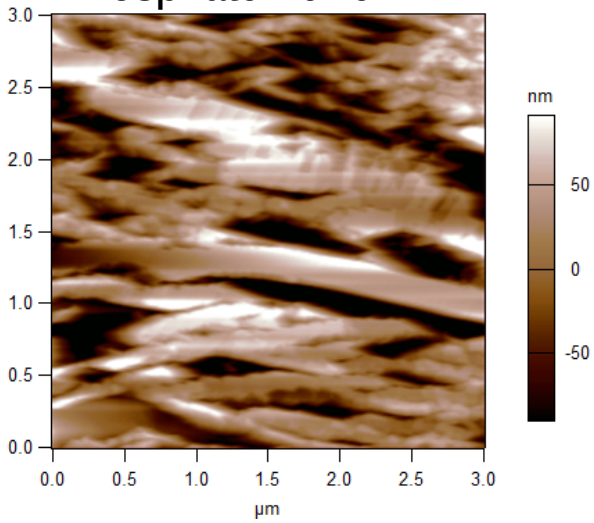
The surface has features that are <5 nm
Dissolution occurs in patches initially
The final surface is very flat (1400pm)
Dissolution is very different than that observed in phosphate

MERCK
Be well

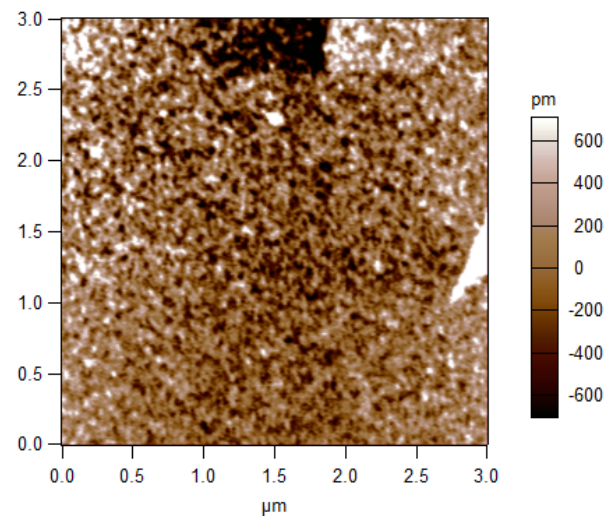
Challenges

- Not all crystals are appropriate for AFM
- In order to track the surface, the solution must have the API added to slow down the dissolution → not as relevant to a dissolution experiment
- No chemical identification of sample
- Quantification is difficult outside of topography/phase
- More replicates needed, different facets show some differences in dissolution

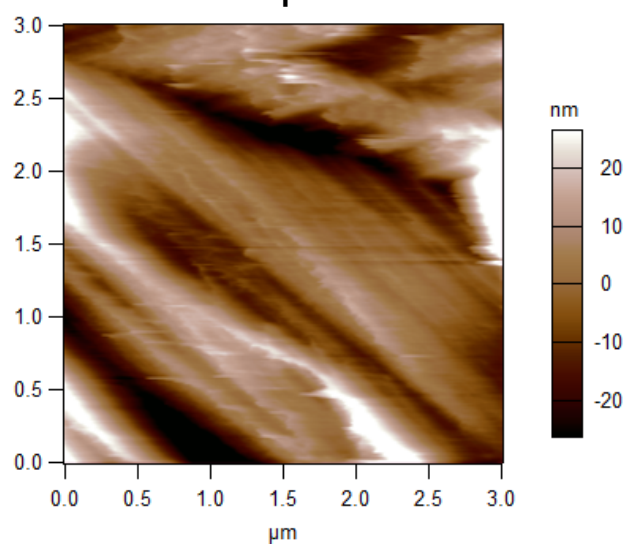
Phosphate Buffer



FaSSIF



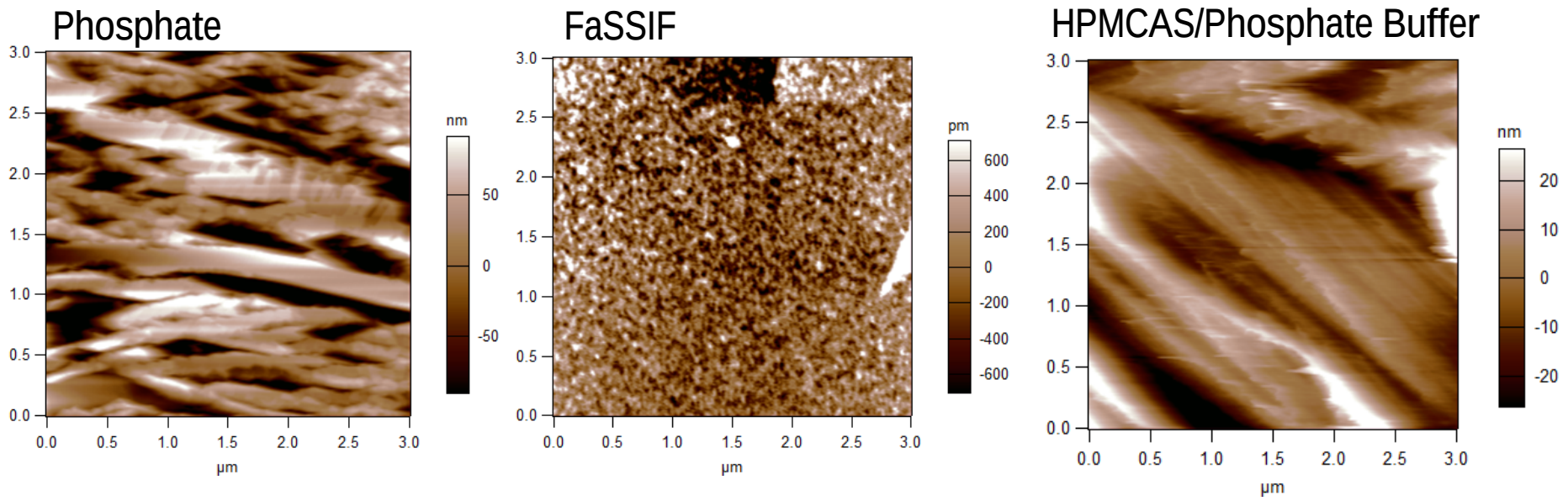
HPMCAS/Phosphate Buffer



MERCK
Be well

AFM Summary

- It is possible to monitor the dissolution of Compound A in *situ* in biologically relevant media (FaSSIF) via liquid AFM imaging
- The components in the media affect how the surface dissolves
- Interpretation is a challenge, but it can compliment traditional dissolution and characterization techniques



MERCK
Be well

Conclusions

- It is vital to understand and determine the fundamental dissolution mechanism early in development to guide formulation and dissolution method development
- 1x Bio-relevant Dissolution provides a straightforward approach to formulation optimization through the “yardstick” approach
- Transfer Models provide an option to gain insight into more predictive dissolution rates for weakly basic compounds
- Future dissolution methodology such as AFM may provide a mechanism to understand dissolution at the nano-scale.

MERCK
Be well

Acknowledgements

- 1x: Paul Harmon, Jesse Kuiper, Mike Socki, and Adam Socia
- Transfer Studies: Sanjay Patel, Wei Zhu and Binfeng Xia
- AFM: Amanda Mann, Matt Lamm, Andre Hermans
- PSCS-Analytical Sciences

MERCK
Be well