Elucidation of Tablet Dissolution and Functional Excipient Behavior with In Situ Exposure Imaging

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CRS 2025 ANNUAL MEETING & EXPOSITION
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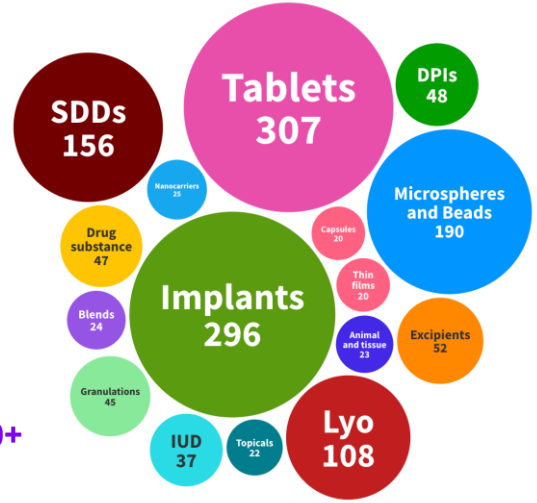
NEXT-GENERATION DELIVERY INNOVATIONS

Product Development Solutions
Guided by Microstructure Science

Built in Boston

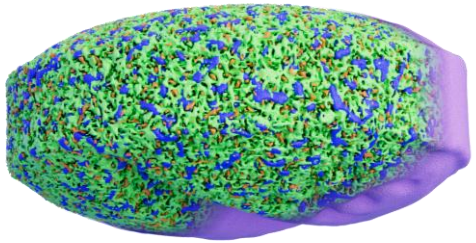
Advanced Microscopy → **Drug Product CQAs** → **Image-based Dissolution and Digital Design**



2,400+ products studied across 300+ programs

Workflows for all dosage forms, with solutions across development lifecycle

Accelerated decision making and wholistic vision of drug product



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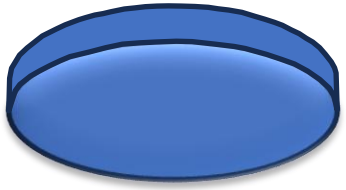
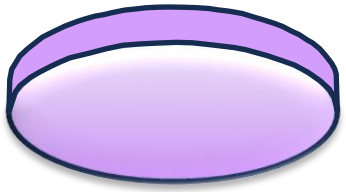
- Image analytics, data management, and simulation tools for pharmaceutical microscopy data
- Cleared security and used by FDA and big pharma companies

From Image to Simulation

Understanding root cause dissolution variability in oral tablets can significantly expedite product development

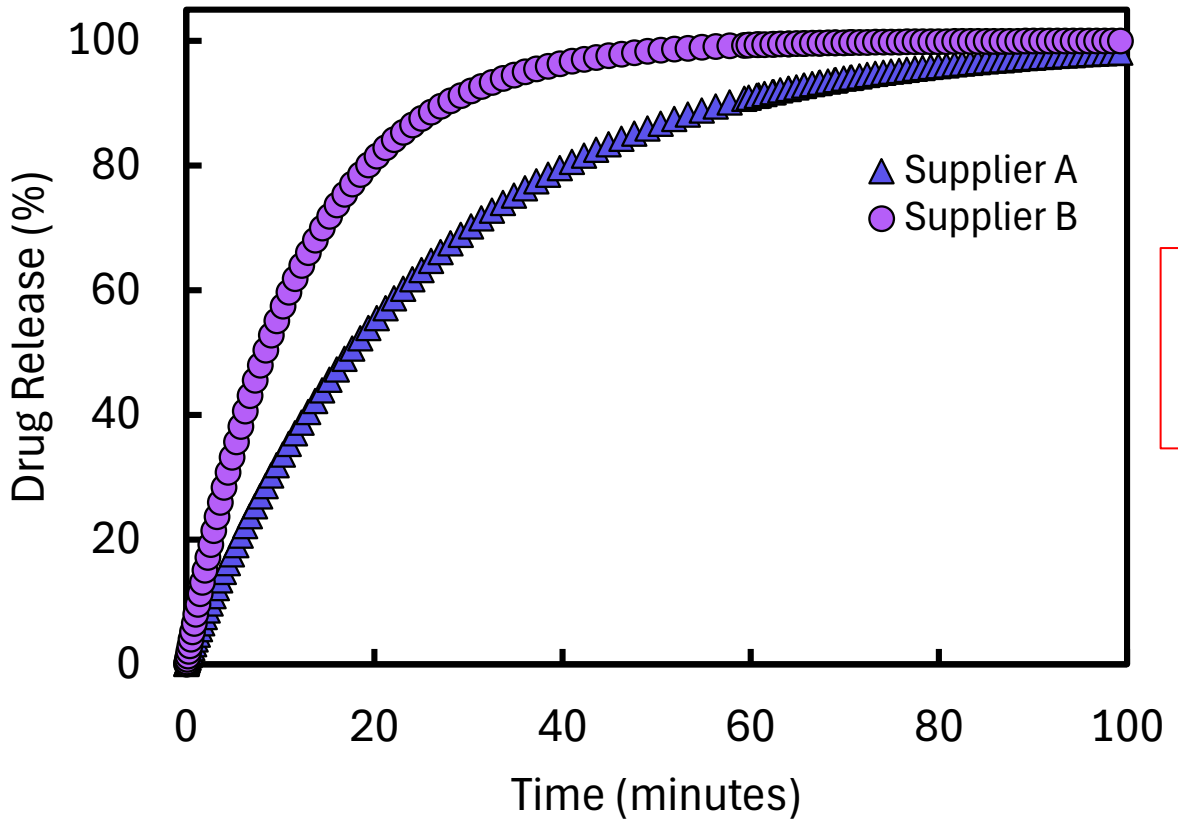
Excipient 3 from Supplier A





Excipient 3 from Supplier B

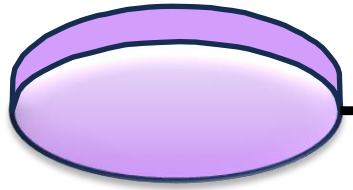
Formulation
API – 50%
Excipient 1 – 20%
Excipient 2 – 20%
Excipient 3 – 10%



How can we mechanistically understand the variability to produce targeted performance changes??

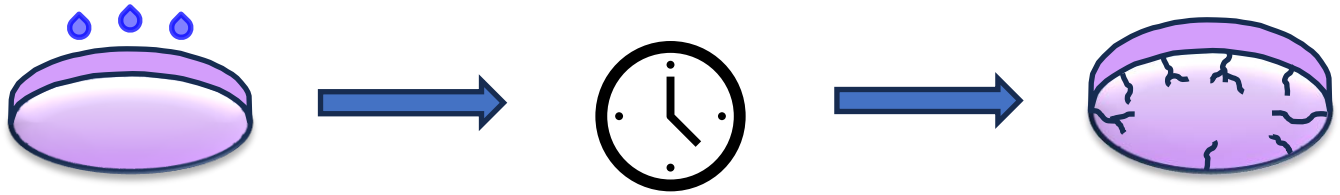
The formulation and manufacturing between the two tablets are the exact same, yet there's significant variability between the two dissolution profiles.

Dynamic structural characterization to assess and understand the exact impact of excipient/structural variation on disso



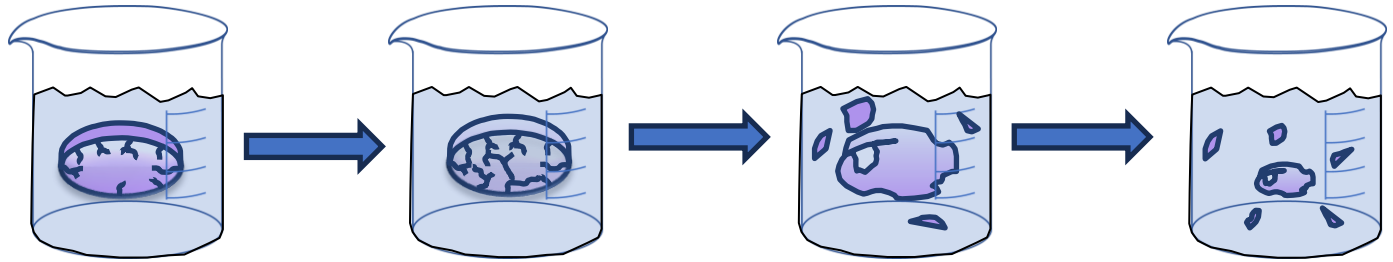
Dry tablet as received (t_0) is imaged to establish the base structure

Targeted perturbation



- Simple experimental design, can be done in any lab with any media
- Analysis is forensic in nature: perturbation produces structural changes and the exact mechanism is not directly observed.

In situ monitoring

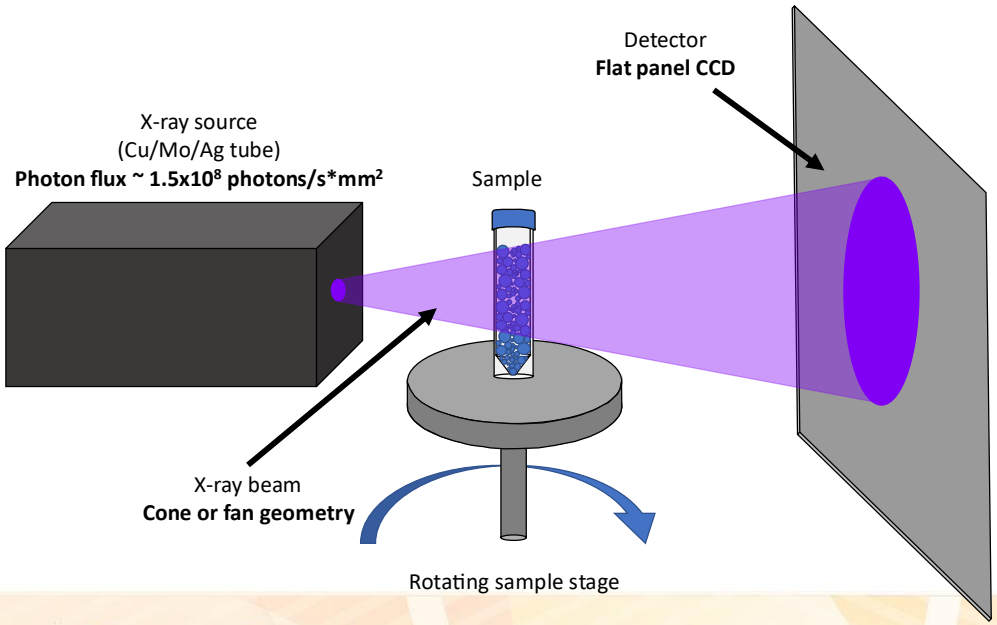


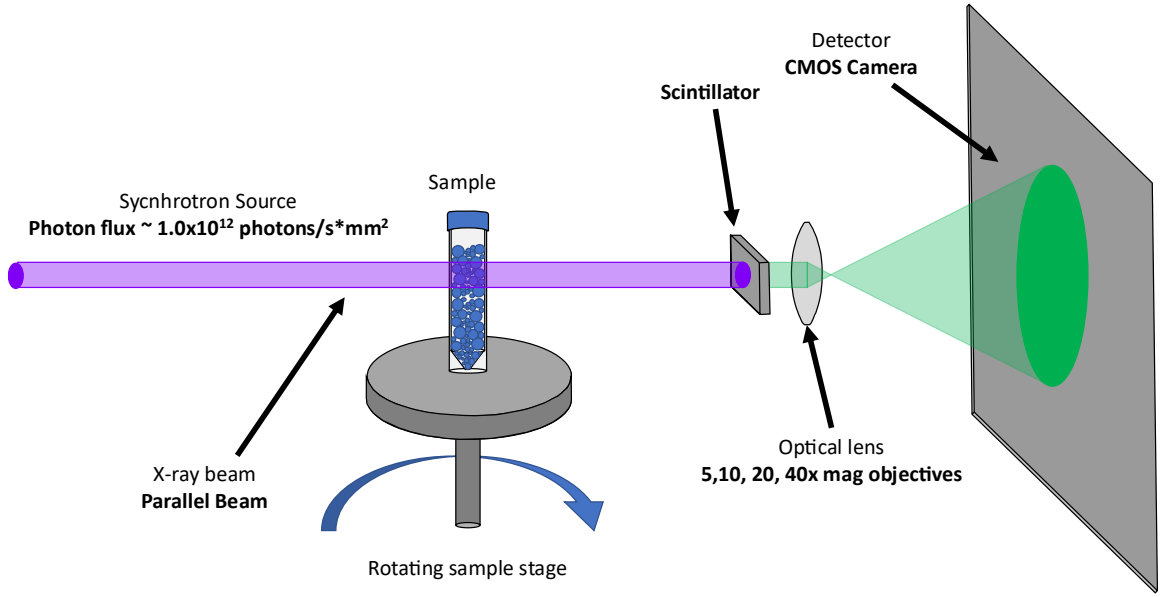
- Live time structural changes at multiple timepoints allowing for 4D characterization
- Requires fast data acquisition to capture the dynamics appropriately

Micro computed tomography (μCT) methods are powerful non-invasive tools for structural characterizations

Lab-based microCT

- Average image acquisition time → 2-6 hours
- X-ray beam geometry limits total sample size
- Generally, only one imaging mode (absorption contrast imaging)
- Polychromatic X-ray induced imaging artifacts

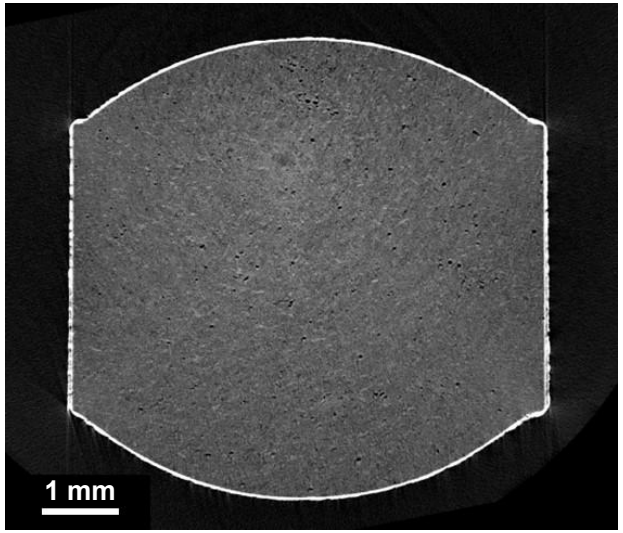




Synchrotron CT

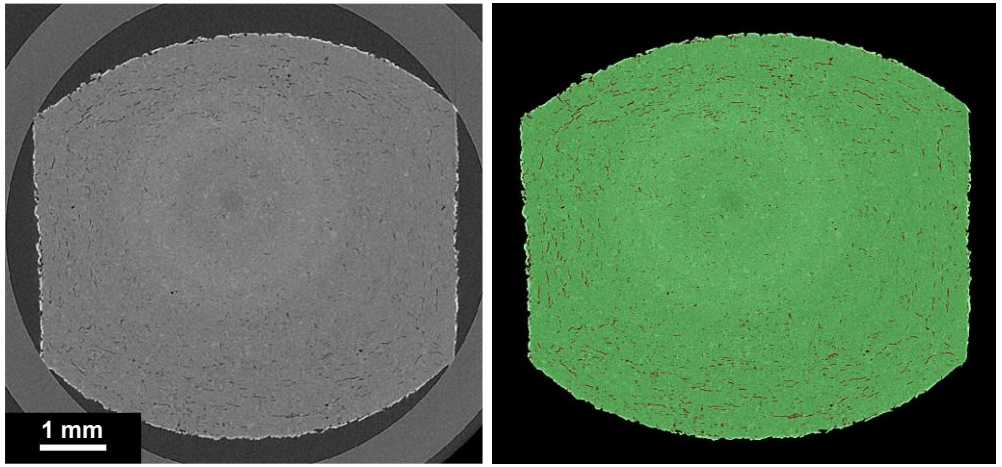
- Average image acquisition time → 0.5-15 minutes
- Parallel beam geometry allows for larger samples
- Multiple imaging modes possible (absorption, phase, diffraction contrast imaging)
- Monochromatic X-rays minimize imaging artifacts

Perturbation investigation reveals pH-dependent porosity evolution attributed to excipient pH behavior

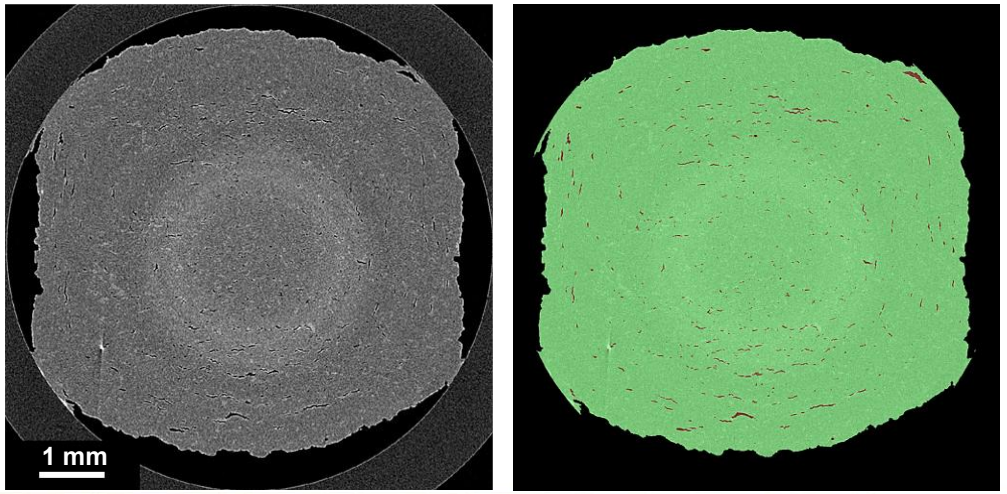


Ranolazine ER
Exposure imaging
Lab Source

HCl exposed



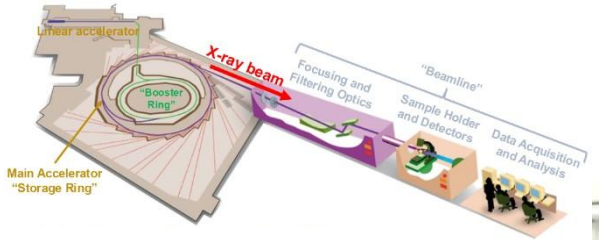
PBS exposed

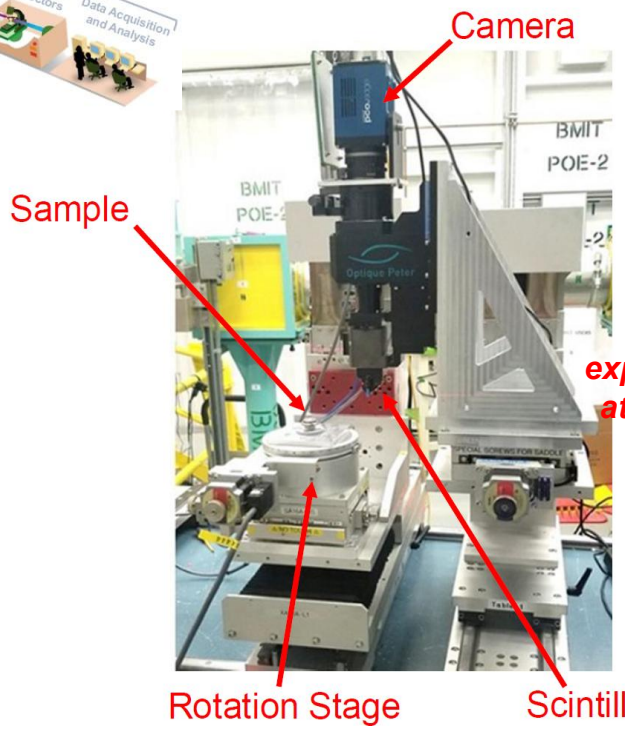


Phase Fraction (%)	T_0	HCl Exposed (pH = 2)	PBS Exposed (pH = 7.4)
Solid	94.6	96.2	98.4
Pores	5.4	3.8	1.6

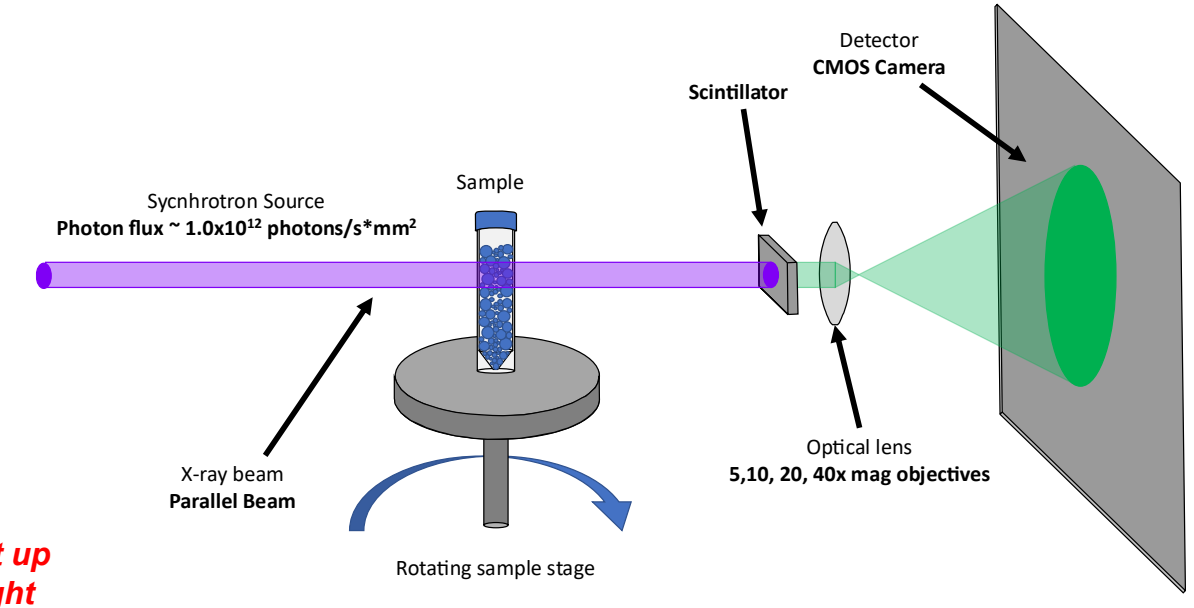
- The porosity decreases in both PBS and HCl indicating tablet swelling during media exposure due to excipients.
- The coating is removed faster in the PBS media suggesting further pH impact on media ingress from the coating
- **The dynamic swelling process and coating behavior therefore are key features in table disso**

In situ structural characterization requires synchrotron CT to capture the fast dynamics of dissolution





Actual experimental set up at Canadian Light Source BMIT beamline



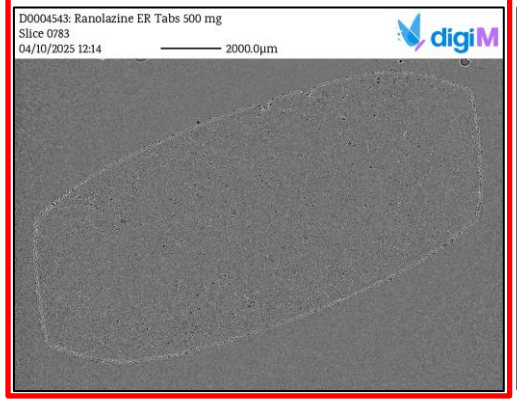
Synchrotron CT

- **Average image acquisition time → 0.5-15 minutes**
- **Parallel beam geometry allows for larger samples**
- **Multiple imaging modes possible (absorption, phase, diffraction contrast imaging)**
- **Monochromatic X-rays minimize imaging artifacts**

Simple sample holder compatible with both basic dissolution and CT imaging

Extended release tablet behavior observed over initial 10 minutes of media exposure to assess immediate structural changes

1.5 min



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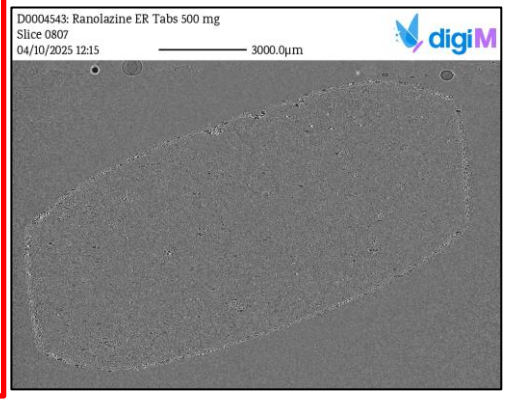
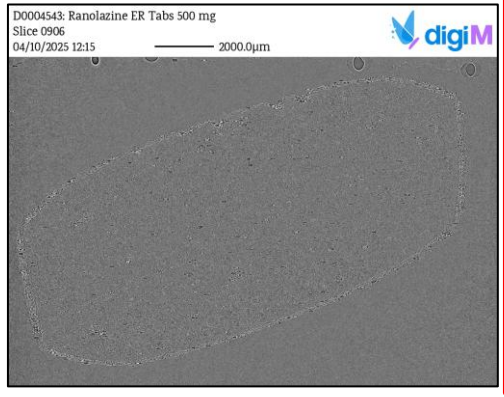
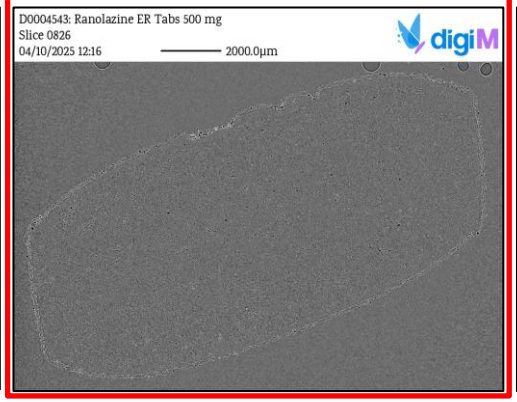


3.5 min



4.5 min



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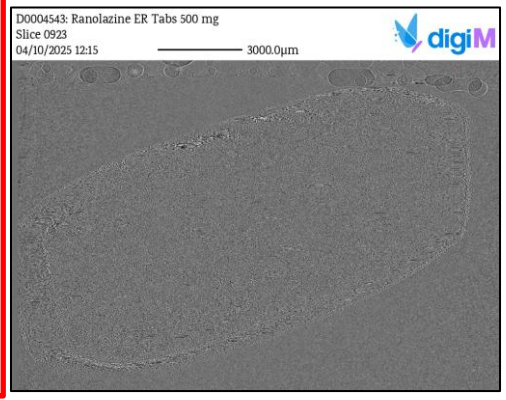
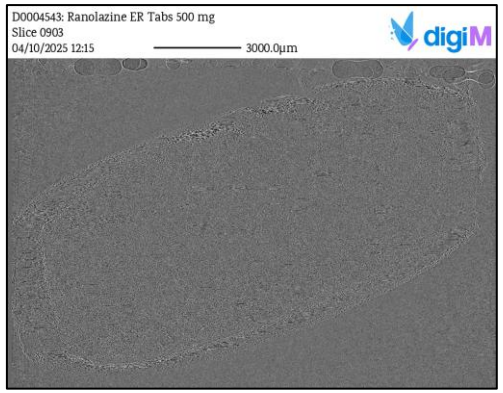


6.5 min



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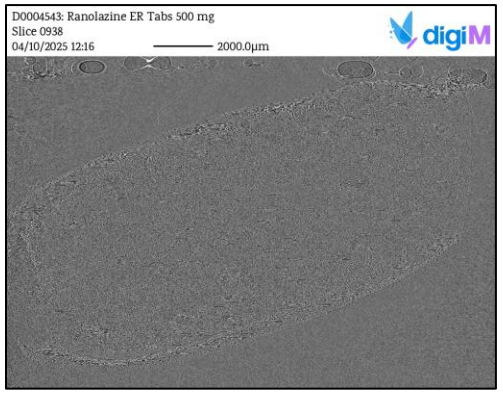
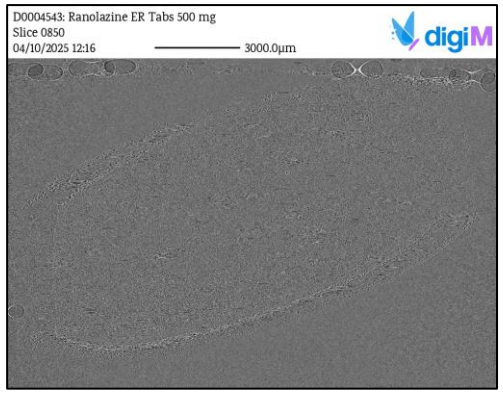
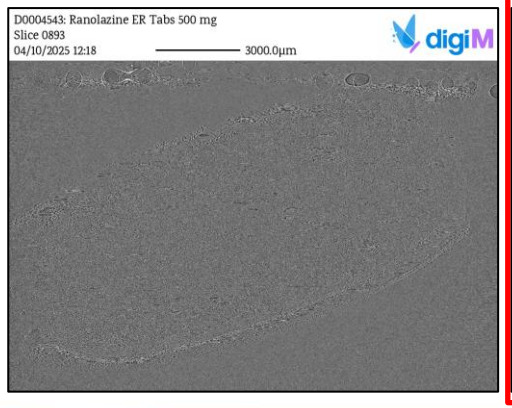


8.5 min



9.5 min



10.5 min

The coating dissolution and advancement of porosity observed in the initial media exposure

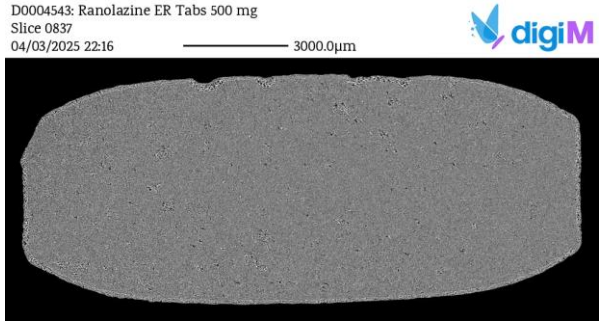
Phase Guide

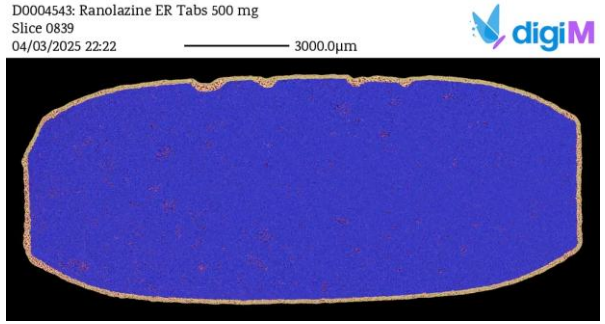
Pores in core

Pores in coating

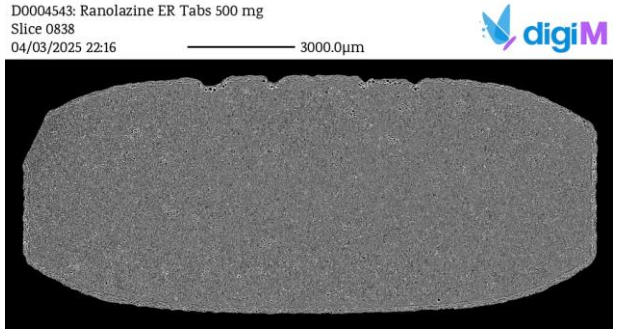
Core Solid

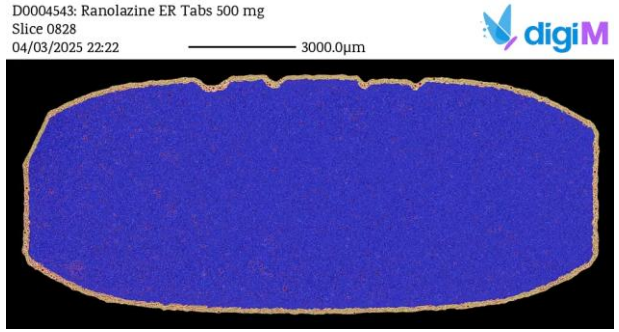
Coating Solid



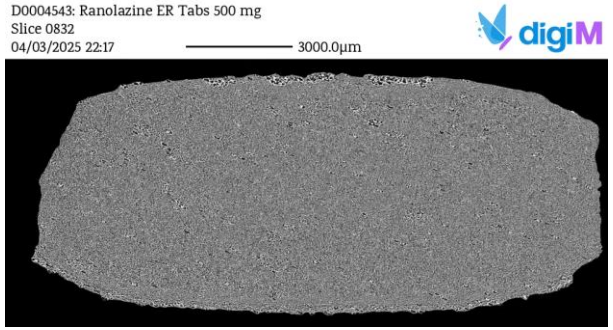


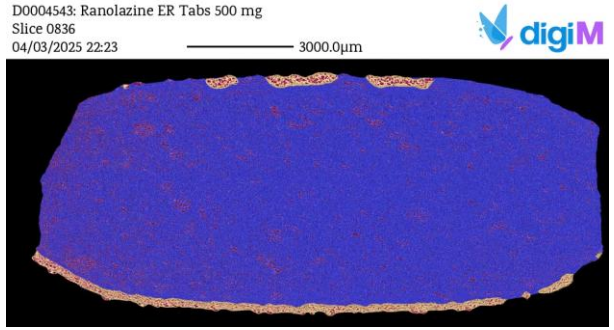
1.5 min

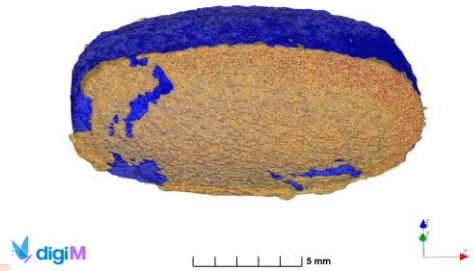




4.5 min



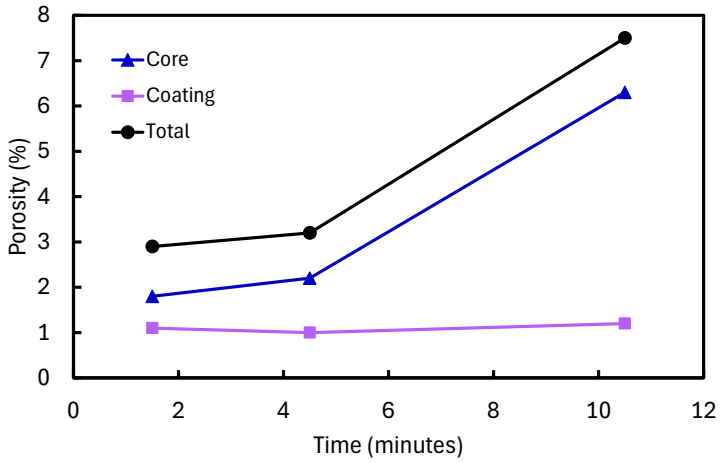


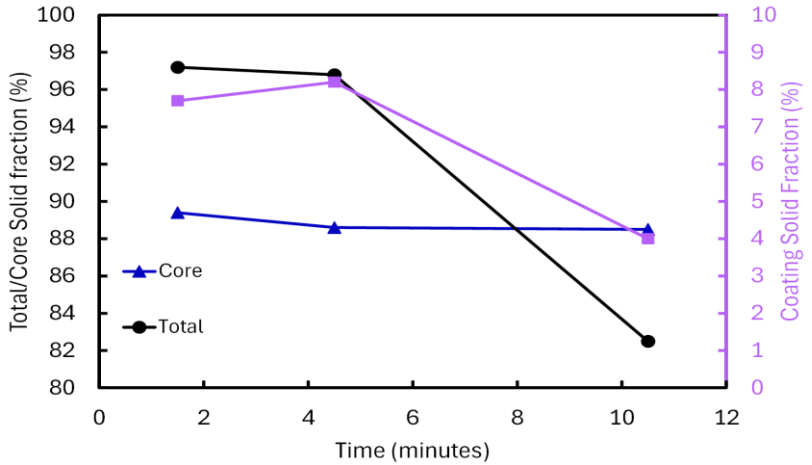


10.5 min

The coating dissolution and advancement of porosity observed in the initial media exposure

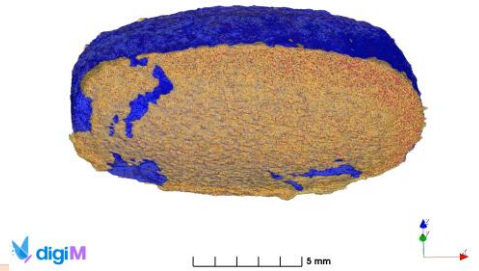
- The porosity in the coating remains relatively constant, even as the coating itself dissolves.
- Porosity within the core spikes after the coating dissolves away suggesting the coating serves as a rate limiting step.
- The coating solid sheds away between minutes 4.5 and 10.5, while the solid domain of the core stays mostly stable, suggesting that the API/excipients are not readily dissolving within the initial 10 minutes which is ideal for an ER tablet.





1.5 min

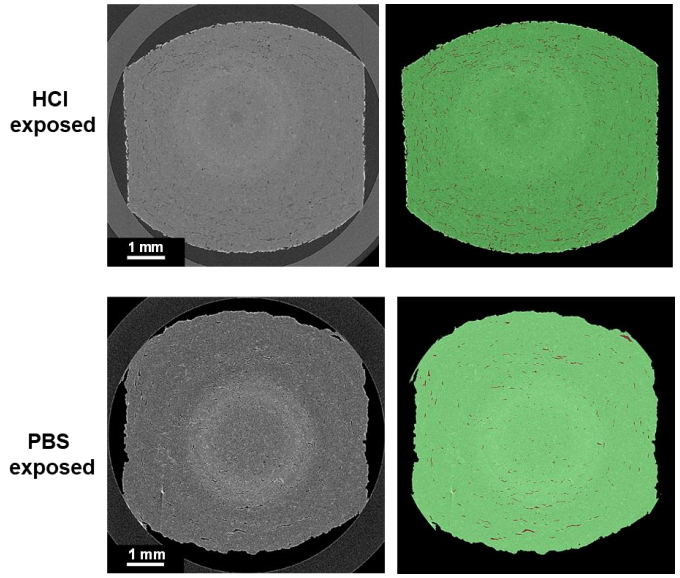
4.5 min



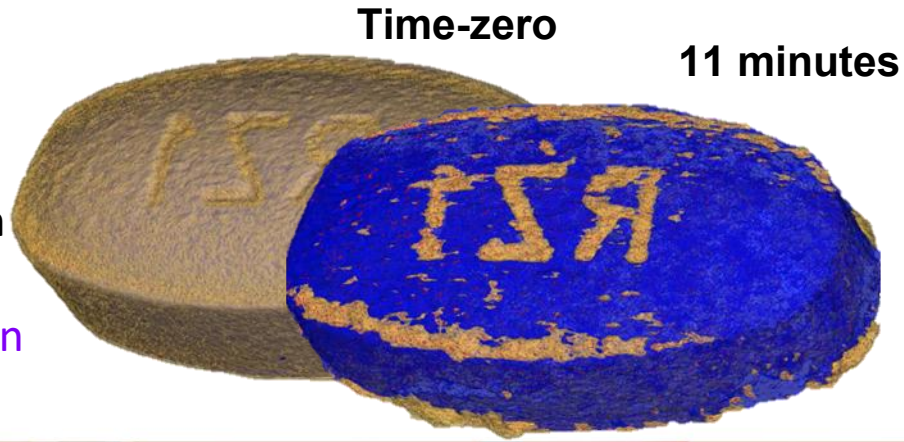
10.5 min

Summary and Conclusions

- Understanding the interplay and evolution of excipients within oral solid tablets can be achieved with dynamic structural charaterizations
- Perturbation imaging of ranolazine ER tablets in different media reveal pronounced pH dependent effects that change the dissolution behavior significantly
- In situ dissolution imaging of ranolazine over the initial 10 minutes of dissolution revealed pronounced structural changes corresponding to the dissolution of the coating and ingress of media driving changes in the excipient matrix
- Dynamic structural imaging offers a powerful path forward for mechanistically understanding tablet behavior empirically and can allow for a truly quality by design approach to excipient selection and tablet development



In situ dissolution imaging
Synchrotron micro-CT



Acknowledgements

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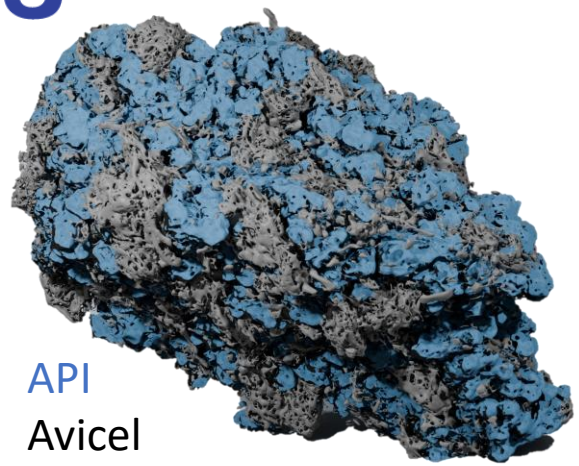
digiM's synchrotron team at Brookhaven National Lab during Long Island's record heat wave!

Wide application areas and solutions for oral solid forms

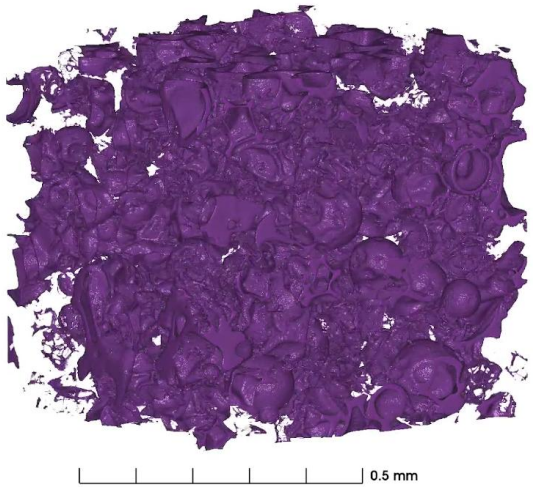
API, SDD, Intermediates, IR, ER, Capsules
Functional Coats, Stability



API
Avicel

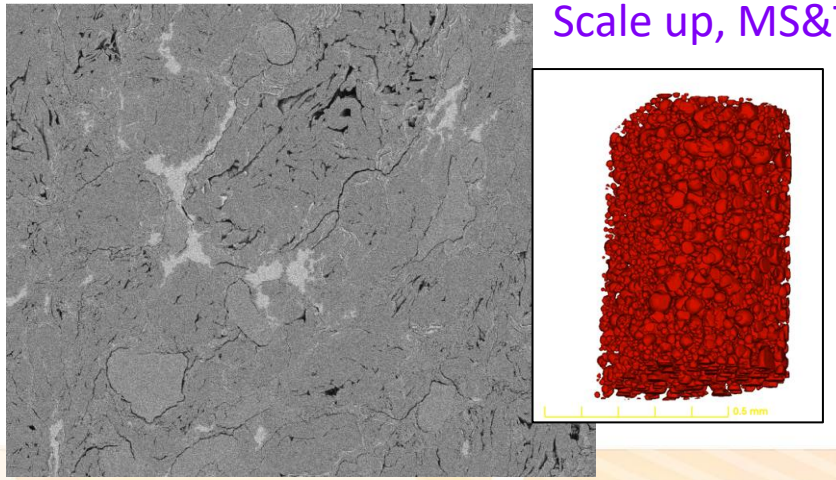
API/Avicel particle attrition and porosity evolution across blend, granulation, tablet
Analysis of critical material attributes and processing

Genentech



Intrinsic dissolution simulation computed directly from images
digiM dissoLab

SDD morphology
Scale up, MS&T



API uniformity and excipient functionality
Mechanistic understanding of formulation properties

Genentech

In situ dissolution imaging
Synchrotron micro-CT

Time-zero **11 minutes**