aaps PharmSci 360

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Pharmaceutical Experiments for Microgravity

October 19, 2022

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Session Description and Objectives

- Pharmaceutical experiments in microgravity have tremendous advantages over land-based methods. In such an environment, crystal nucleation and growth can be altered, whether the goal is to crystallize the most stable form, create a purely amorphous sample, or find new forms. With the launch scheduled for 2023, current research is focused on designing and testing hardware that will provide antisolvent crystallization, evaporation, and melt/quench capabilities using model compounds such as L-histidine, indomethacin, or ritonavir.

Learning objectives:

- Understand how crystallization behaves differently in microgravity compared to terrestrial environment.
- Understand the requirements in hardware designs for conducting crystallization experiments in spaces.
- Evaluate current crystallization challenges to see if microgravity provides a path forward.

Biography and Contact Information

Improved Pharma is a research and information company dedicated to improving pharmaceutical methods, formulations, and processes. Services include solid-state form studies, formulation design, synchrotron techniques, analytical testing, and expert consulting for the development and defense of intellectual property matters.

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Microgravity Enables Improved Pharmaceuticals

Elimination of buoyancy, natural convection, sedimentation, phase separation drives significant differences in transport-driven phenomena.

Microgravity Results
Controllable, uniform crystal size
Isolation of stable forms
More ordered crystals
Larger or smaller crystals
Novel crystal structures or morphologies

Range of Formulation Benefits
Enable new routes of administration
Improved bioavailability and solubility
Reduced side effects and toxicology
Extended shelf life
Novel form discovery

Free Energy Barrier for Nucleation

Barrier for nucleation of the stable form may be difficult to overcome

It is necessary to find conditions that provide sufficient driving force

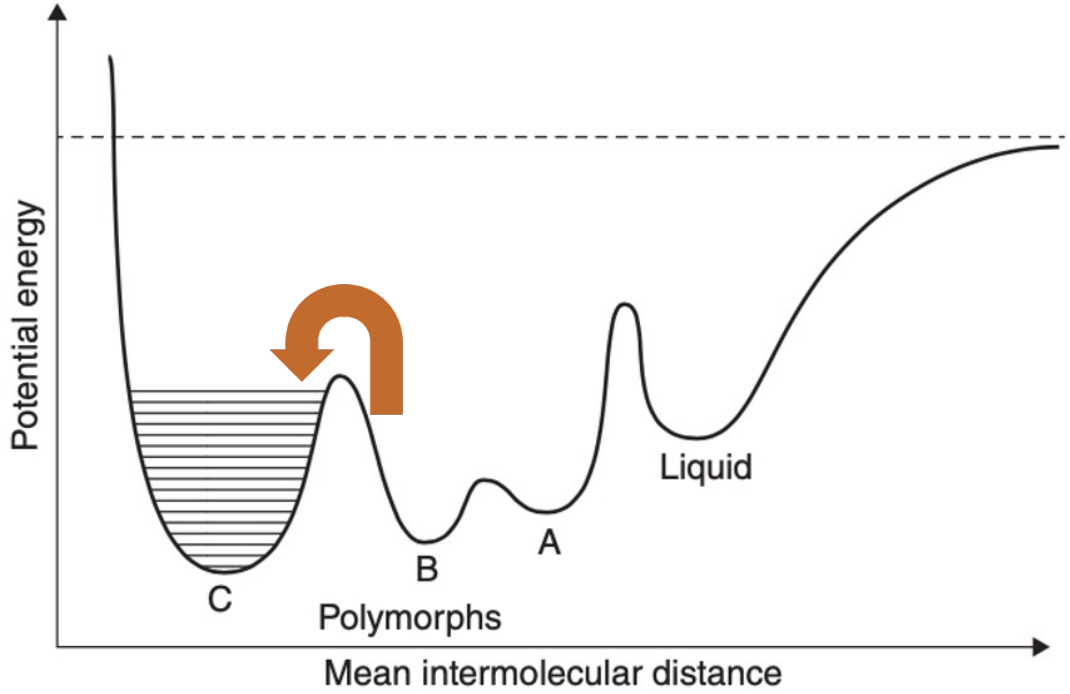


Figure 1. Comparison of potential energy of various solid forms.

Microgravity influences fluid motion

Fluid motion can influence nucleation

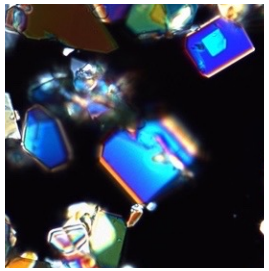
L-Histidine

Only mixtures of stable/metastable or metastable form precipitate from aqueous mixtures

50% Stable

+

50% Metastable



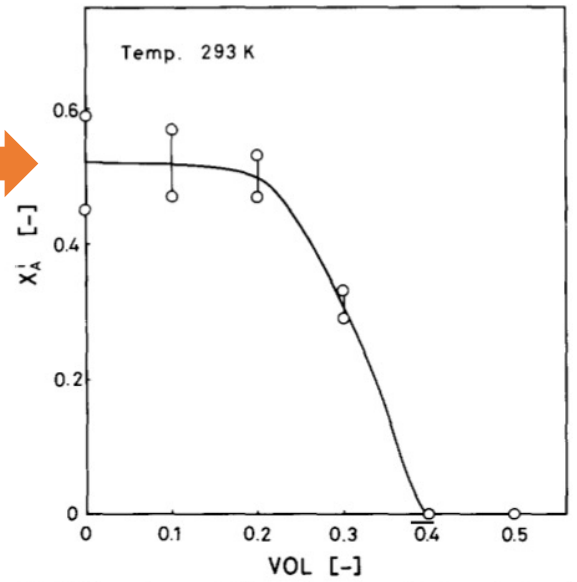
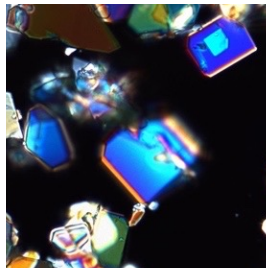


Fig. 1. Dependence of X_A^i on the volume fraction of ethanol (VOL).



100% Metastable

Solvent effect of ethanol on crystallization and growth process of L-histidine polymorphs
Mitsutaka Kitamura, H. Furukawa, M. Asaeda
Journal of Crystal Growth **1994** *141*, 193-199
DOI: 10.1016/0022-0248(94)90112-0

L-Histidine

Change fluid motion to orderly flow

Nucleation of stable form becomes favored

-regardless of antisolvent ratio

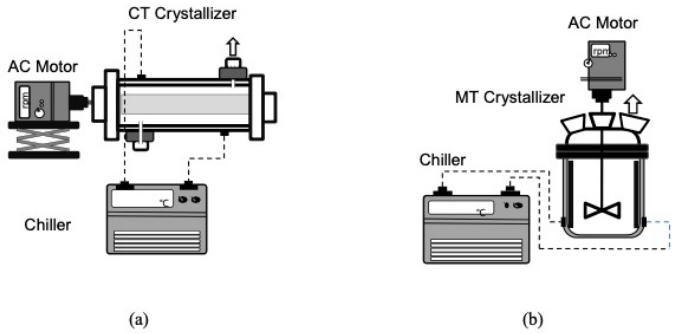
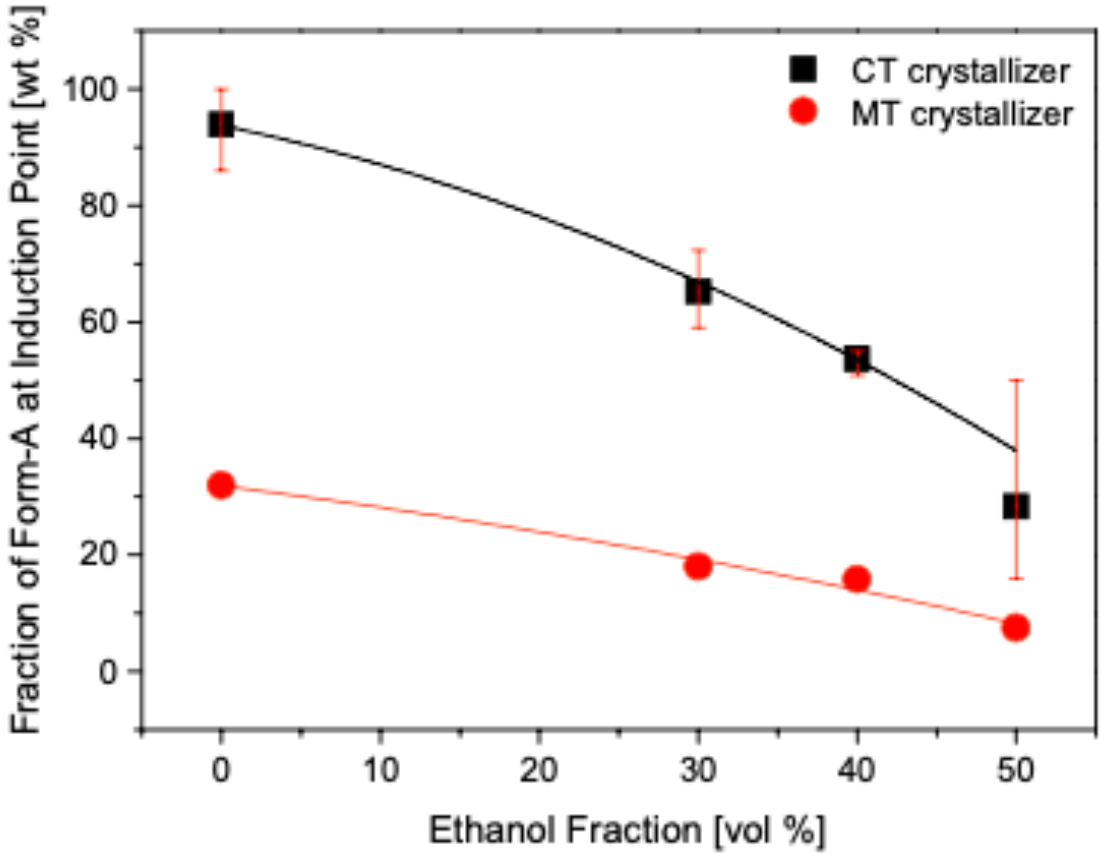


Figure 1. Experimental systems for polymorphic crystallization of L-histidine in (a) Couette-Taylor crystallizer and (b) mixing tank crystallizer.

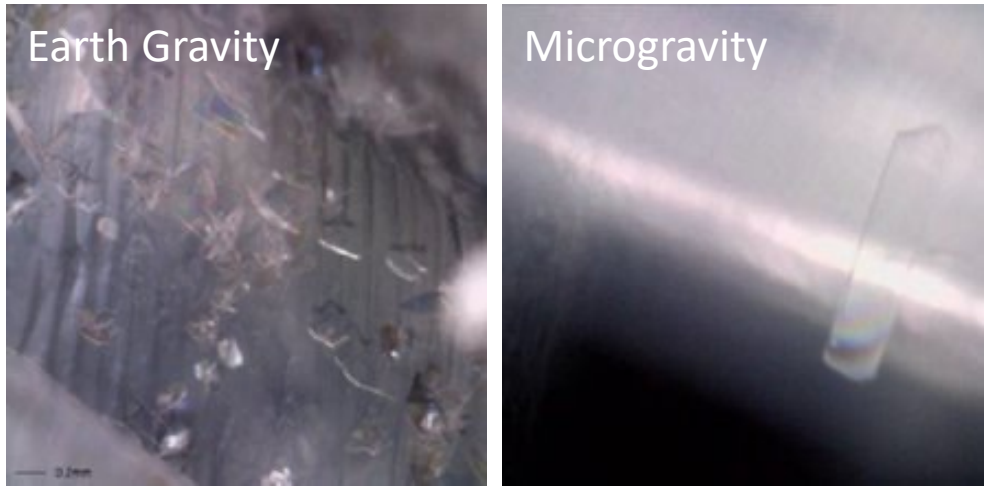


Influence of Fluid Motions on Polymorphic Crystallization of L-Histidine: Taylor Vortex Flow and Turbulent Eddy Flow
Suna Park, Woo-Sik Kim
Cryst. Growth Des., **2017**
DOI: 10.1021/acs.cgd.7b01067

L-Histidine

Experimentally Demonstrated Microgravity Effects

Micro-Scale



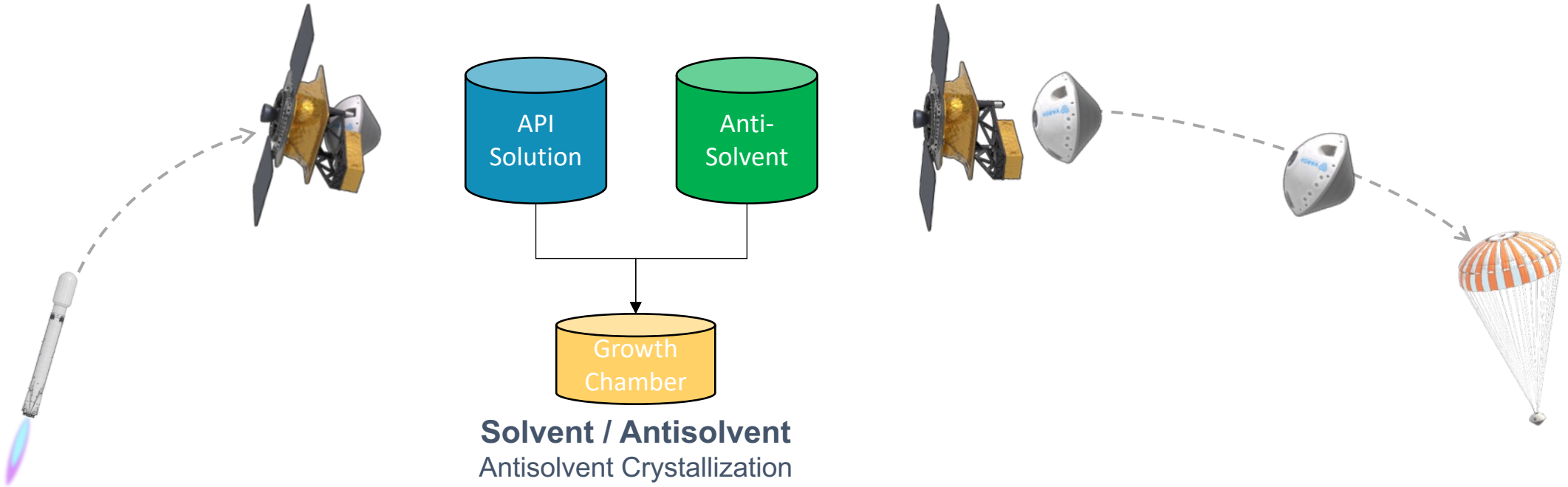
Different polymorphs of L-histidine are produced in microgravity than by the same process on Earth.

Antisolvent Crystallization of L-histidine in Micro-Channel Reactor under Microgravity
Yan Zhang, J Cheng, Y Glick, G Samburski, J Chen, C Yang
Microgravity Science and Technology, **2020** *32*, 27-33
DOI: 10.1007/s12217-019-09728-4

Microgravity Effects with Solvent/Antisolvent Hardware

Process capabilities will leverage difference in fluid motion found in microgravity

Can perform multiple milligram- to gram-scale experiments (not micro-scale)



Solvent / Antisolvent

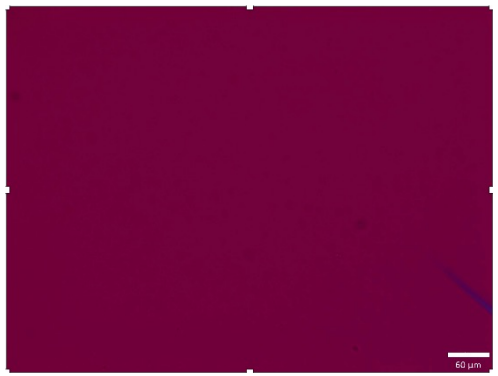
Antisolvent Crystallization
Slurry Crystallization
Cooling Crystallization
Evaporative Crystallization

Microgravity Effects in Melt/Cool Hardware w/ Ritonavir

For most, crystallization from melt should follow Ostwald's progression

- Formation of crystal not determined by stability
- Structure closest in energy/arrangement to molecules in parent phase

A metastable form is expected to crystallize preferentially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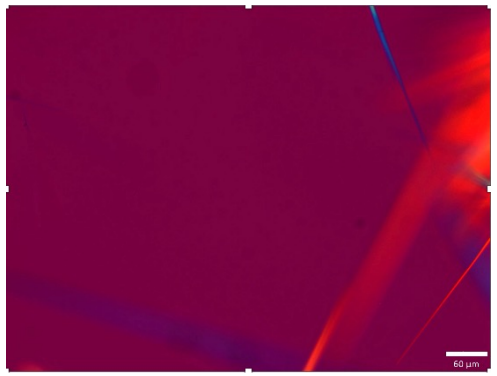
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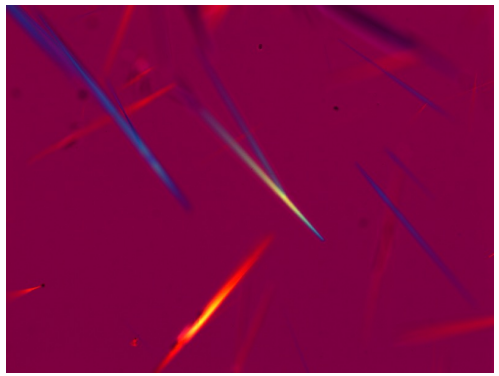
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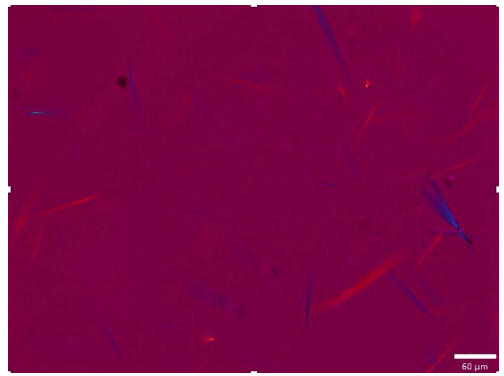
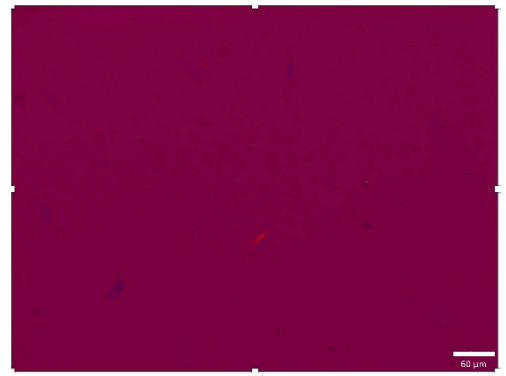

5hr 75 C


5hr 70 C

Microgravity Effects in Melt/Cool Hardware w/ Ritonavir

- Showed ability to isolate and grow “Form III” Ritonavir on flight hardware

Ritonavir Form III: Lighting strikes twice at the same time, 137 miles apart

Stephan D. Parent[1], Pamela A. Smith[1], Dale K. Purcell[1], Daniel T. Smith[1], Susan J. Bogdanowich-Knipp[1], Ami S. Bhavsar[2], Larry R. Chan[2], Jordan M. Croom[2], Haley C. Bauser[2], Andrew McCalip[2], Stephen R. Byrn[1], Adrian Radocea[2]

1. Improved Pharma LLC, West Lafayette, IN 47906
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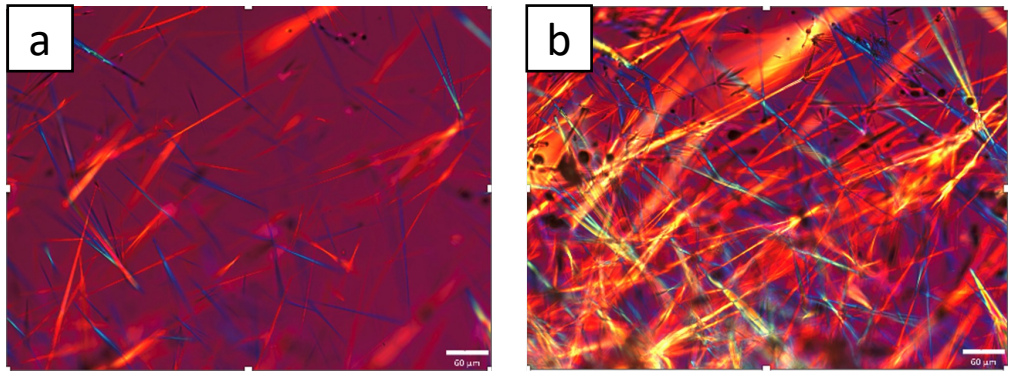
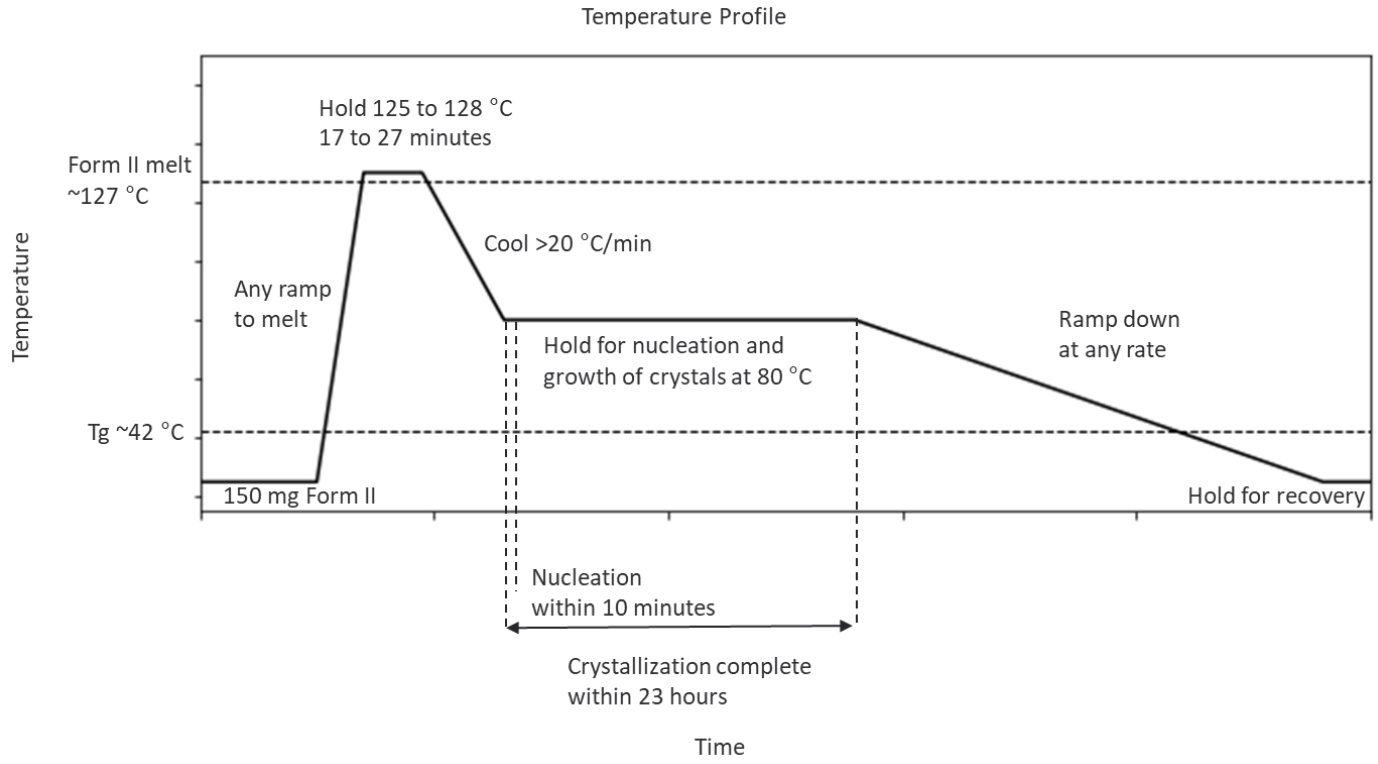


Hot stage microscopy during growth at a) 5 hours and b) 8 hours

Microgravity Effects in Melt/Cool Hardware w/ Ritonavir

- Microgravity will likely affect the expected progression
- Extending results to microgravity with first flight in early 2023



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- Park, S.; Kim, W.-S. Influence of Fluid Motions on Polymorphic Crystallization of L-Histidine: Taylor Vortex Flow and Turbulent Eddy Flow. *Crystal Growth & Design* **2018**, *18* (2), 710–722. https://doi.org/10.1021/acs.cgd.7b01067.
- Kitamura, M.; Furukawa, H.; Asaeda, M. Solvent Effect of Ethanol on Crystallization and Growth Process of L-Histidine Polymorphs. *Journal of Crystal Growth* **1994**, *141* (1-2), 193–199. https://doi.org/10.1016/0022-0248(94)90112-0.
- Zhang, Y.; Cheng, J.; Glick, Y.; Samburski, G.; Chen, J.; Yang, C. Antisolvent Crystallization of L-Histidine in Micro-Channel Reactor under Microgravity. *Microgravity Science and Technology* **2019**, *32*(1), 27–33. https://doi.org/10.1007/s12217-019-09728-4.
- Parent S, Smith P, Purcell D, Smith D, Bogdanowich-Knipp S, Bhavsar A, et al. Ritonavir Form III: Lightning strikes twice at the same time, 137 miles apart. ChemRxiv. Cambridge: Cambridge Open Engage; 2022; This content is a preprint and has not been peer-reviewed.

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