UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Quality Control of 3D Printed Controlled Release Dosage Forms in Distributed Manufacturing Networks

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by

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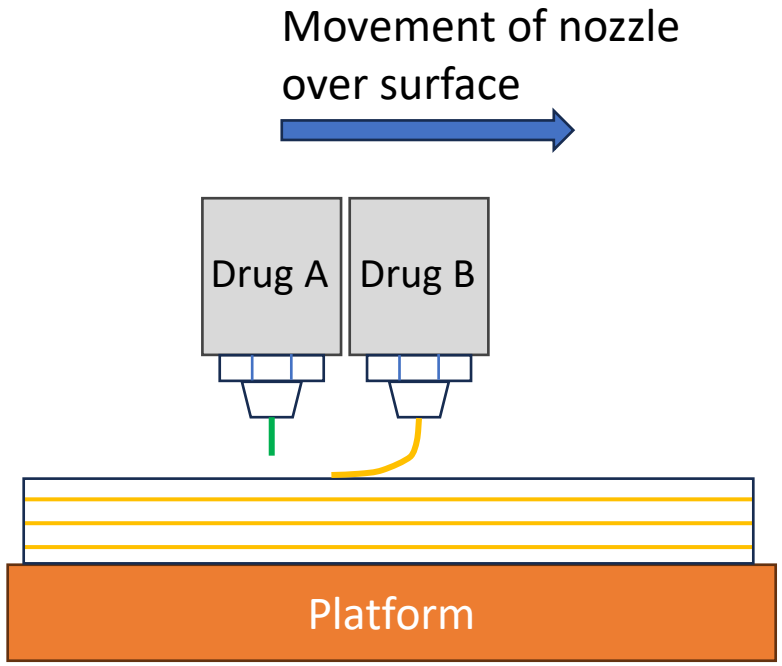
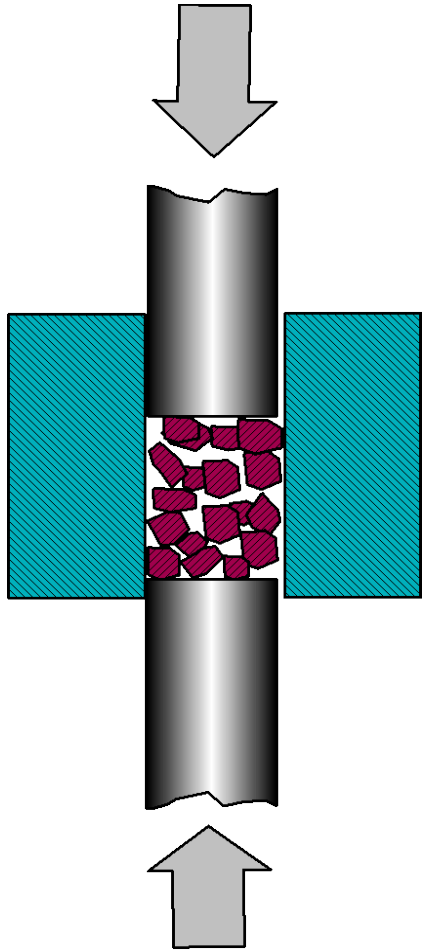
Outline

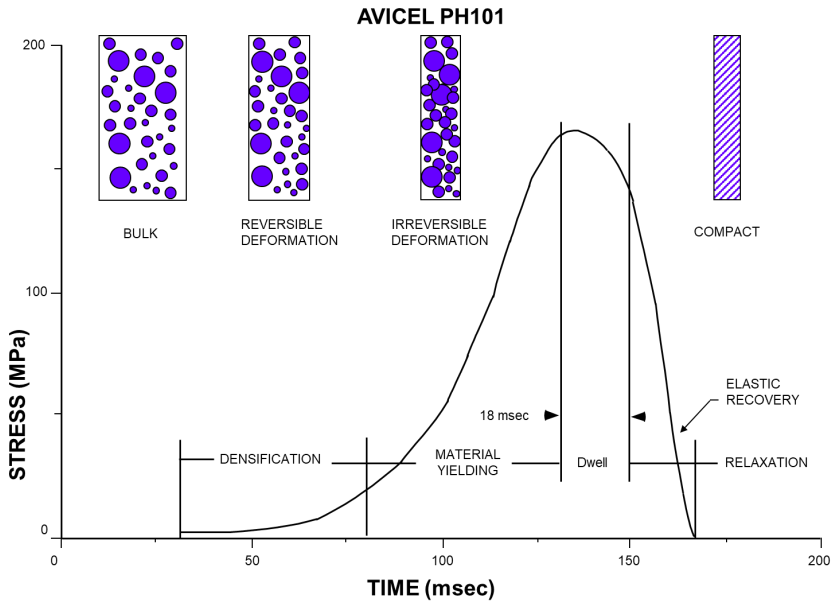
- Introduction to 3D printing
- Use cases for 3D printing
- 3D printing and quality attributes
- Process Analytical Technologies (PAT) for 3D printing QC
- Summary

Additive vs Traditional Manufacturing



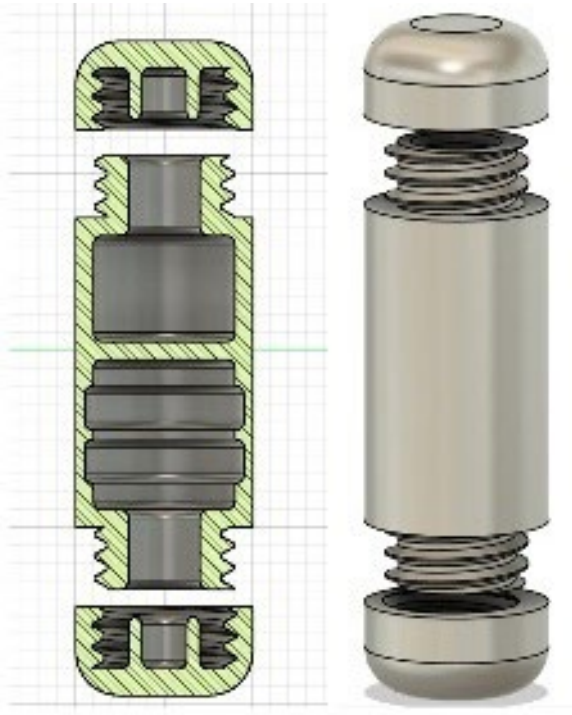
<u>Additive manufacturing</u>
Fabricate three-dimensional objects layer-by-layer





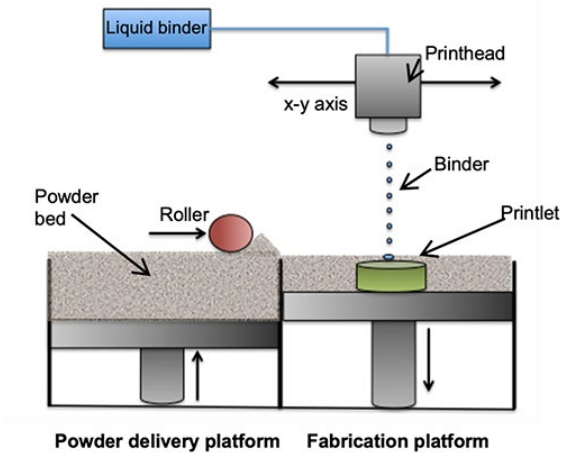
<u>Traditional manufacturing</u>
Tablet press, HME, Spry drying, etc.

Use Cases for 3D Printing

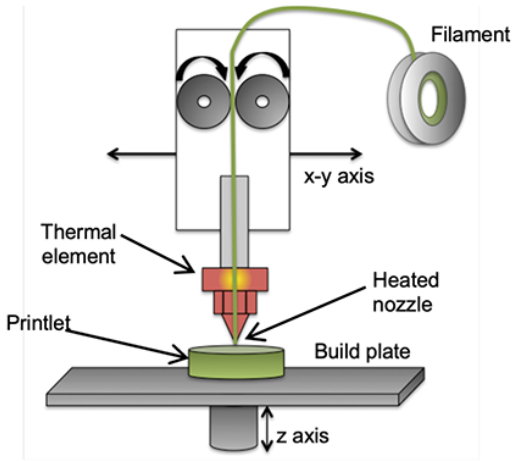


- Commercial production
  - Spritam (levetiracetam) ODT
  - Aprecia's ZipDose
- Rapid production of clinical supplies
  - Some propose “bucket” to put drug in
    - Equivalent to powder in a capsule – with control over release rate
  - BCS II and IV may need excipients for dissolution and bioavailability
- Specialized Geometries/spatial material combinations
  - Device drug combinations
    - E.g., orthopedic implants with drug coatings, growth factors, anti-inflammatory, etc.
  - Long-acting implants
    - Combine multiple materials for long term release
      - Hormones, testosterone and estrogen
      - Drug addiction, buprenorphine
      - Infectious diseases
- Hospital and compounding pharmacy
  - Personalized medicine – Customization of dose and drug ratio on fixed dose combinations
    - Pediatrics (especially neonates)
    - Geriatrics
  - Manufacturers supply “3D printing inks” pharmacist can print for individual patient

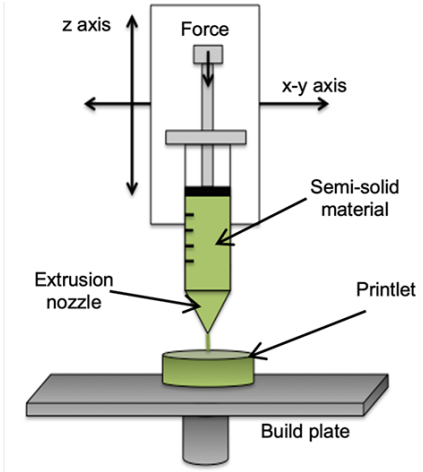
Principle Types of 3D Printers



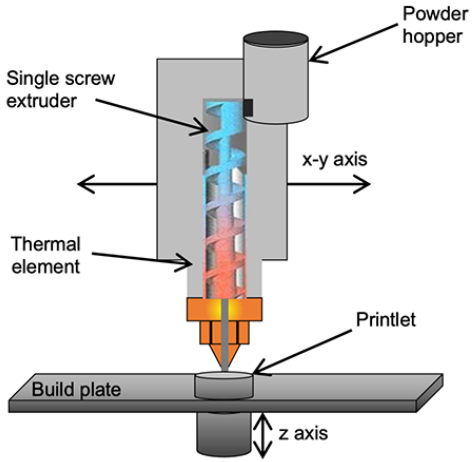
Binder jetting (BJ)



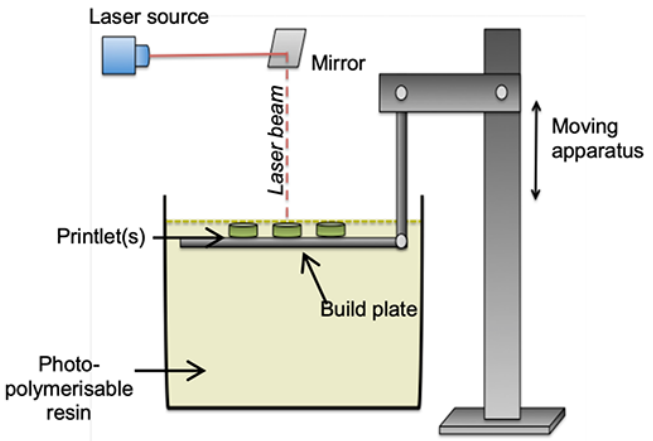
Fused deposition modeling (FDM)



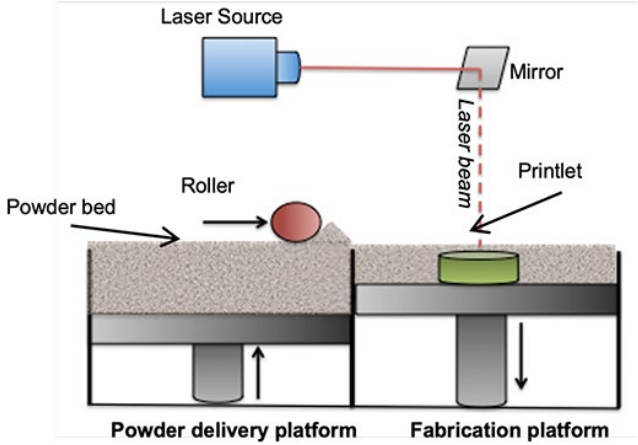
Semi-solid extrusion (SSE)



Direct powder extrusion (DP)



Stereolithography (SLA)



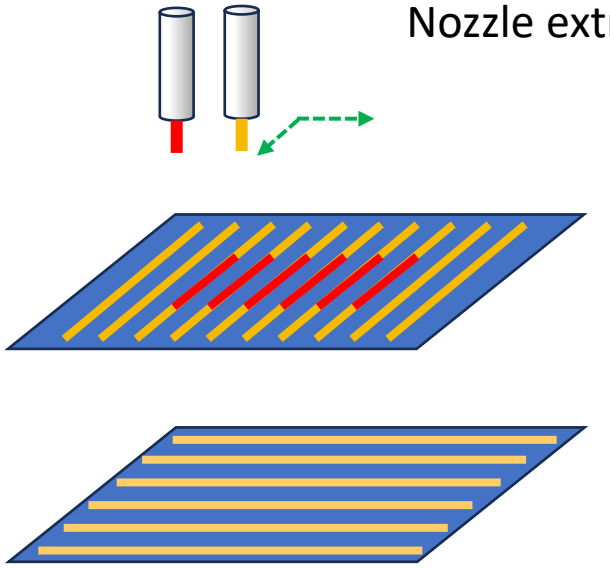
Selective laser sintering (SLS)

Image Source: https://pharmaceutical-journal.com/article/research/3d-printing-of-pharmaceuticals-and-the-role-of-pharmacy

Classification of 3D Printers

Nozzle Systems (2D grid)

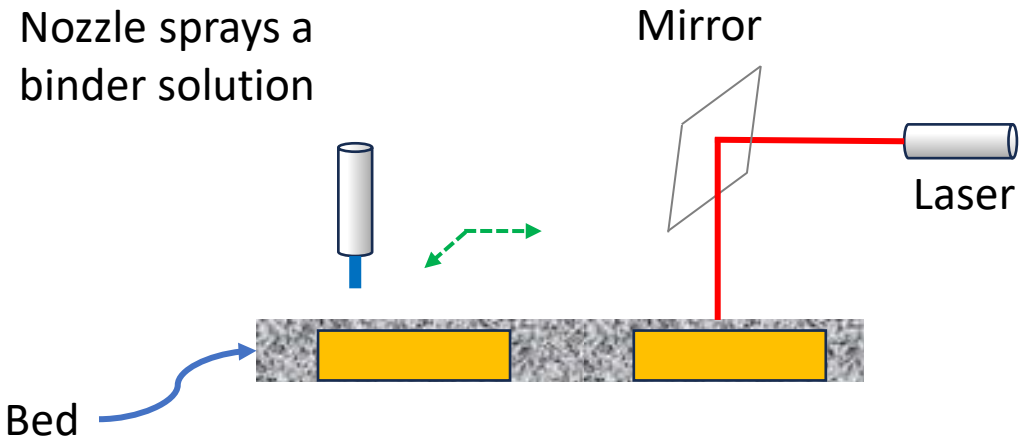
- Fused deposition modeling (FDM)
- Semi-solid extrusion (SSE)
- Direct powder extrusion (DP)



Nozzle extrudes print material

Layering Systems (Pint on powder bed)

- Binder jetting (BJ)
- Stereolithography (SLA)
- Selective laser sintering (SLS)



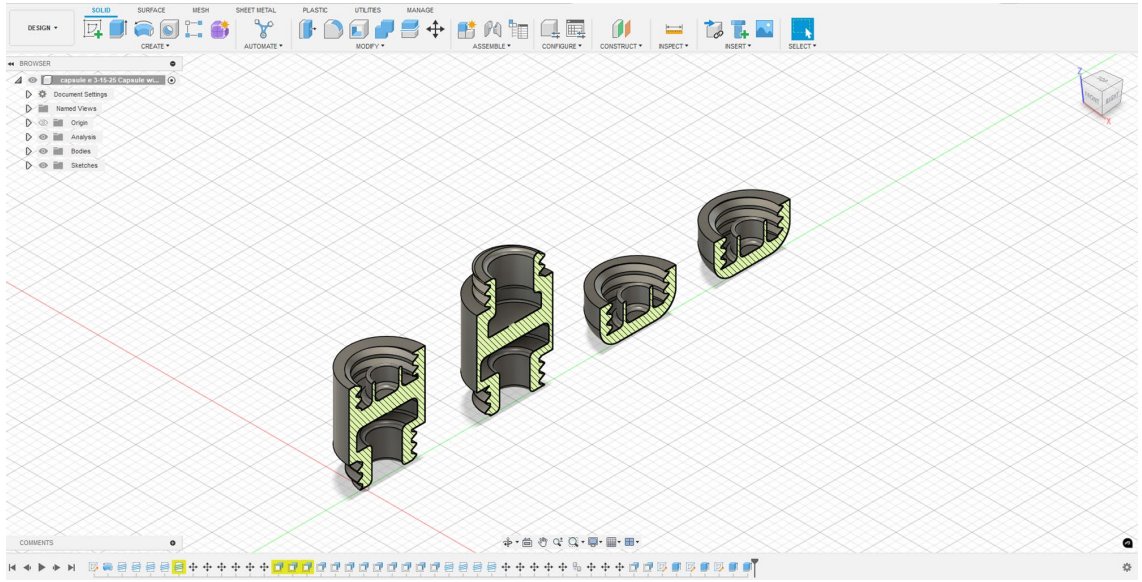
SLA – UV-vis laser to induce photochemical reactions to cross link system

SLS – Uses laser to heat and fuse particles together

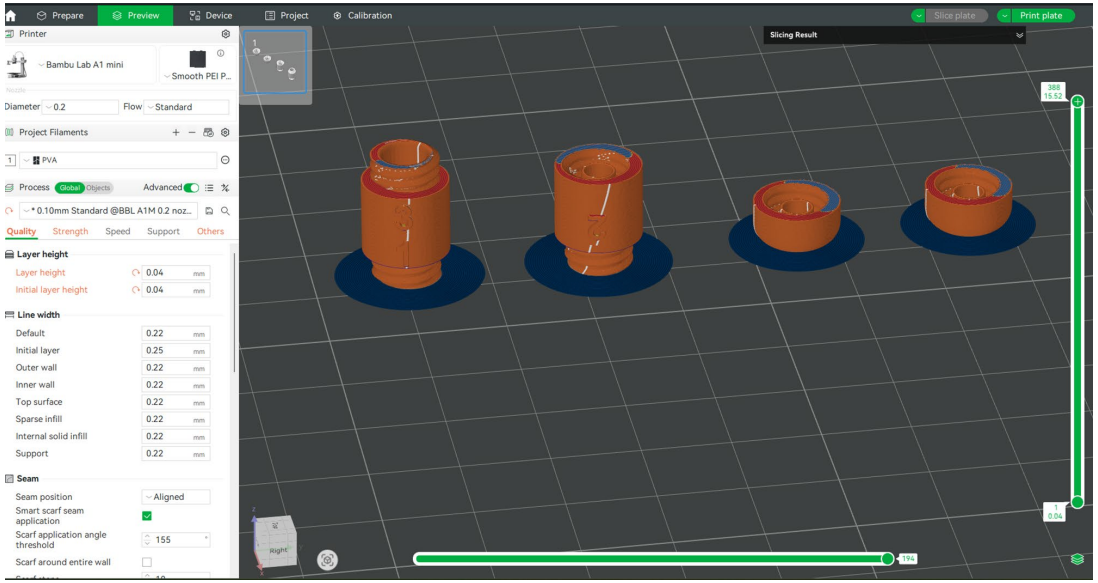
The research questions depend upon printing mechanism

FabRx M3dimaker 2

CAD Software



Slicer Software



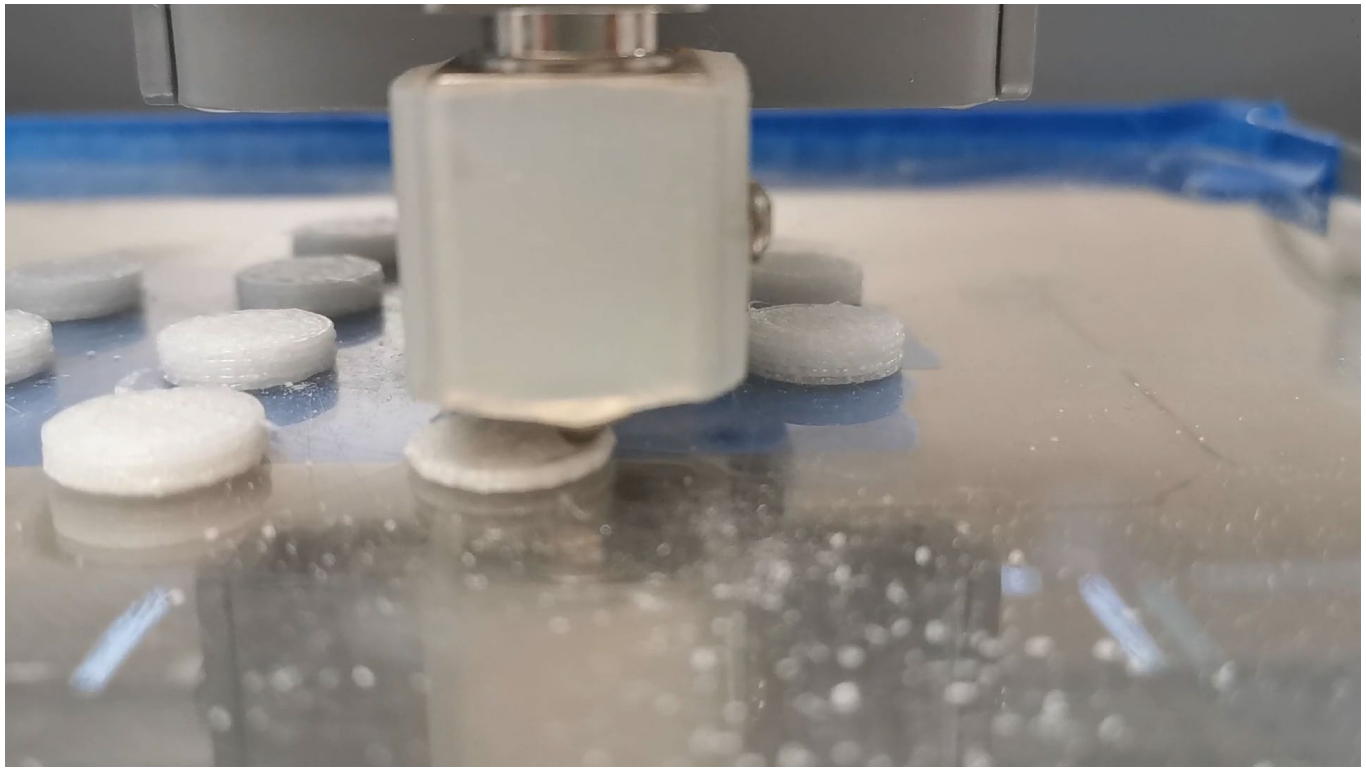
G-Code File

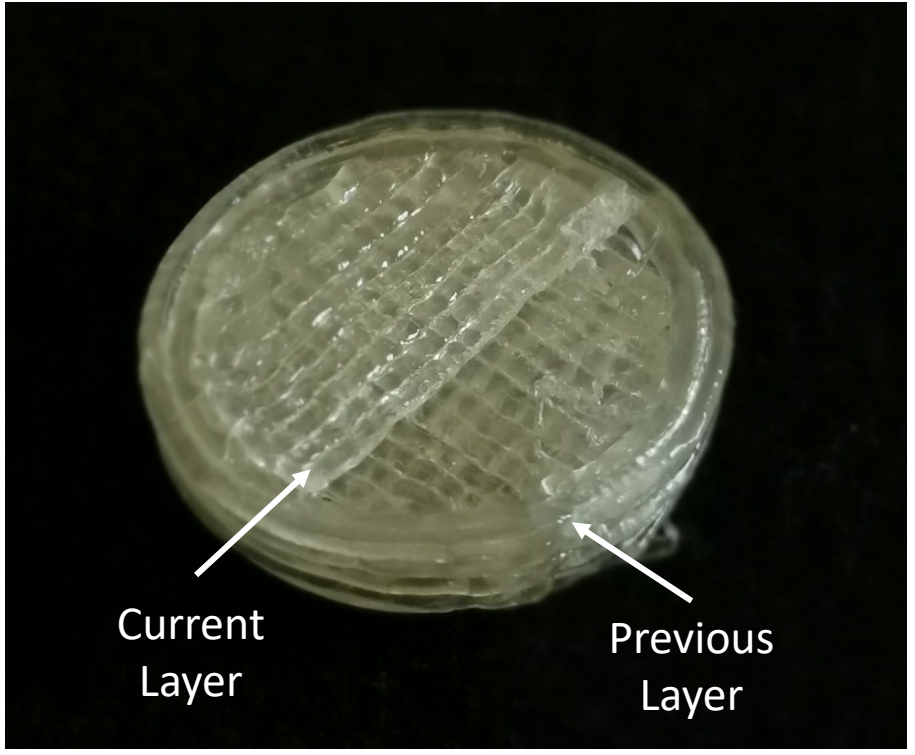
End gcode routine

```
; fabrx_end
G91
G1 Z+40 E-20 X-20 Y-20 F3300
G90
M106
M104 T1 S180 ; set temperature after print
; M140 S0 ; set bed temperature after print
M104 T1 S180 ; set temperature after print
; M140 S0 ; set bed temperature after print
M104 T1 S180 ; set temperature after print
```

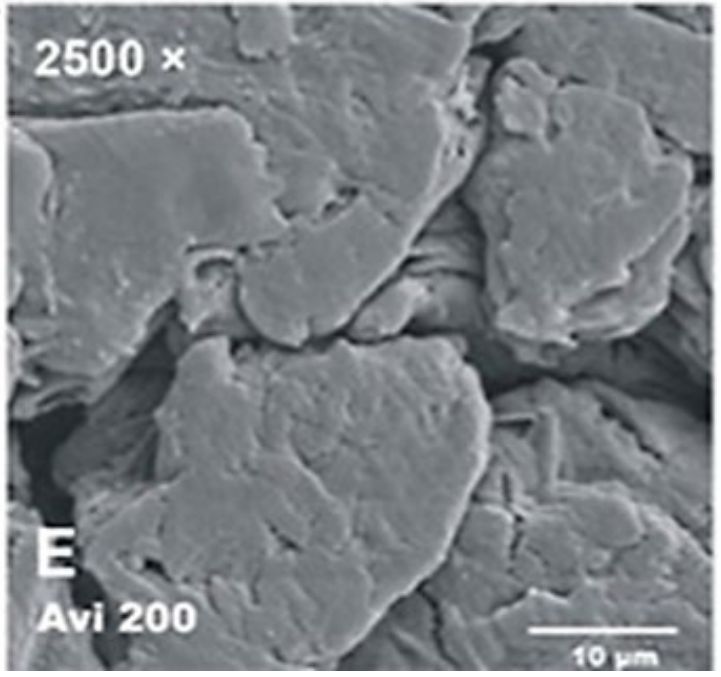
3D Print

3D Printing Process





SEM of MCC Tablet



3D vs traditional Tablets have very different Internal structures

- Internal structure dictates drug release & mechanical properties
  - Internal structure created by compression
  - Internal structure created nozzle extrusion

Key Quality Questions

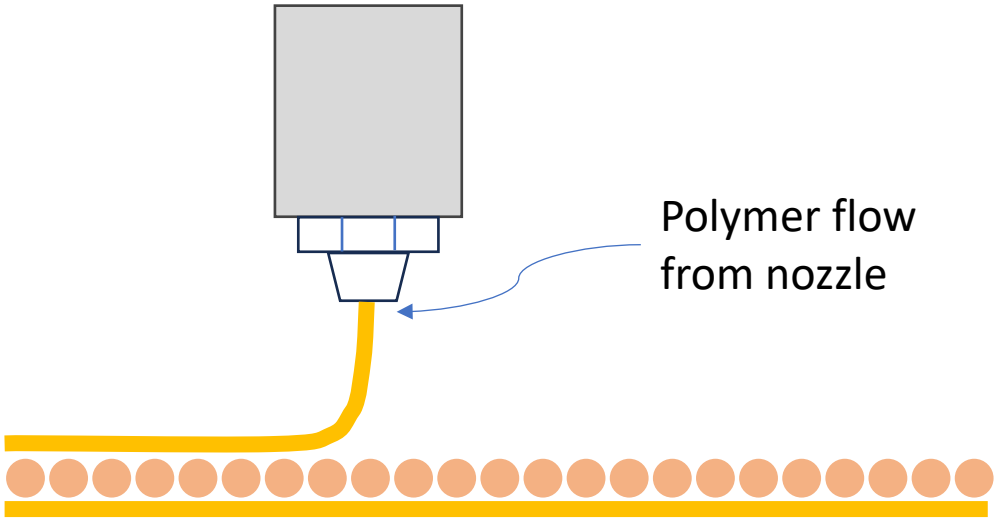
- With any new technology, how do we ensure efficacy and safety?

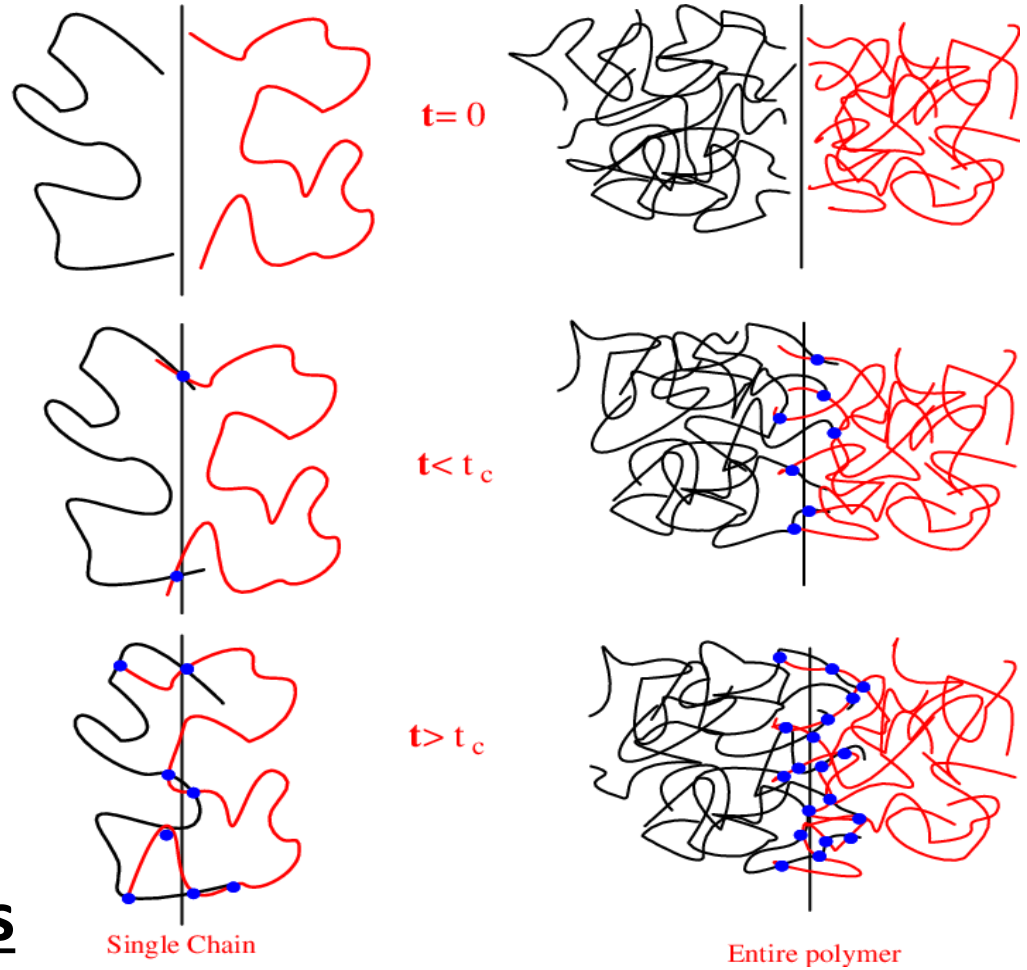
- Key questions are (for this discussion):
  - How does one control the 3D printing process to ensure product quality
    - Does the 3D printing process produce toxic materials
  - How does the 3D printing process affect dissolution, bioavailability and bioequivalence
    - Does the 3D printing process affect how dissolution, bioavailability (BA) & bioequivalence (BE) should be measured

Factors Affecting Quality

- Material properties
  - Viscoelastic flow of materials in the rubbery state above Tg
  - Powder bed density
  - Cohesiveness and adhesiveness of layers
- Dosage form geometry created by CAD software
  - Matrix vs reservoir or combination
  - Wall thickness
- Slicer → G-code generation
  - Dosage form porosity – infill density
  - Layer height
- Printing
  - Printer speed
  - Nozzle size
  - Polymer flow rate
- Error detectability
  - Can process analytical technologies (PAT) sensors detect faults?

Material Properties





Flow and Adhesion / Cohesion Factors

1. Polymer Tg
2. Formulation viscosity (η)
3. Interfacial polymer diffusion

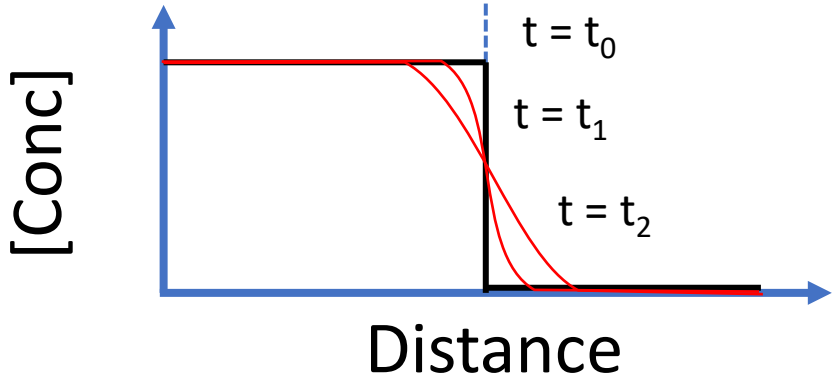


Image Source: DOI:10.1007/s00397-012-0629-7

3D Printing Materials – Safety Concerns

Thermal Methods

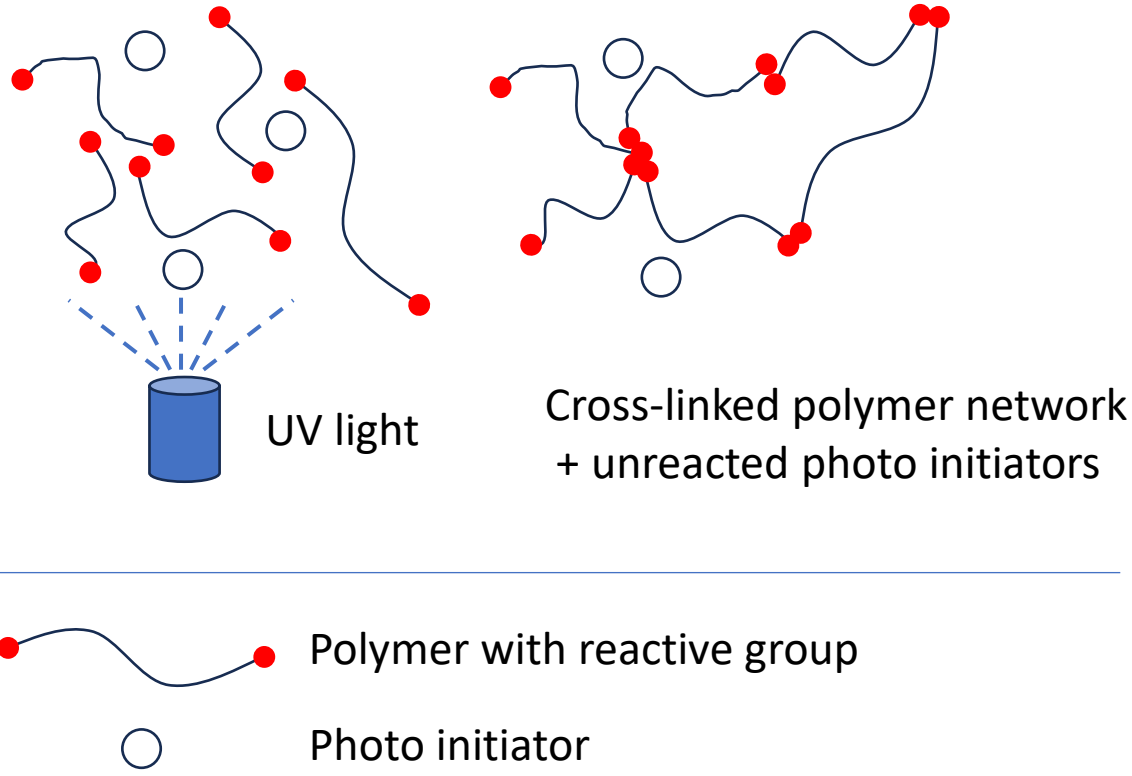
- Polymers are fused by heating
- Current research uses well known GRAS status polymers

Polymers Used in 3D Printing
HPC(LF)/Klucel
Kollicoat Protect / Polyvinyl alcohol-polyethylene glycol graft copolymer
Kollidon VA 64 / Copovidone
Polyvinyl alcohol (PVA)

- To date there are few additional safety concerns

Photo Activation Methods

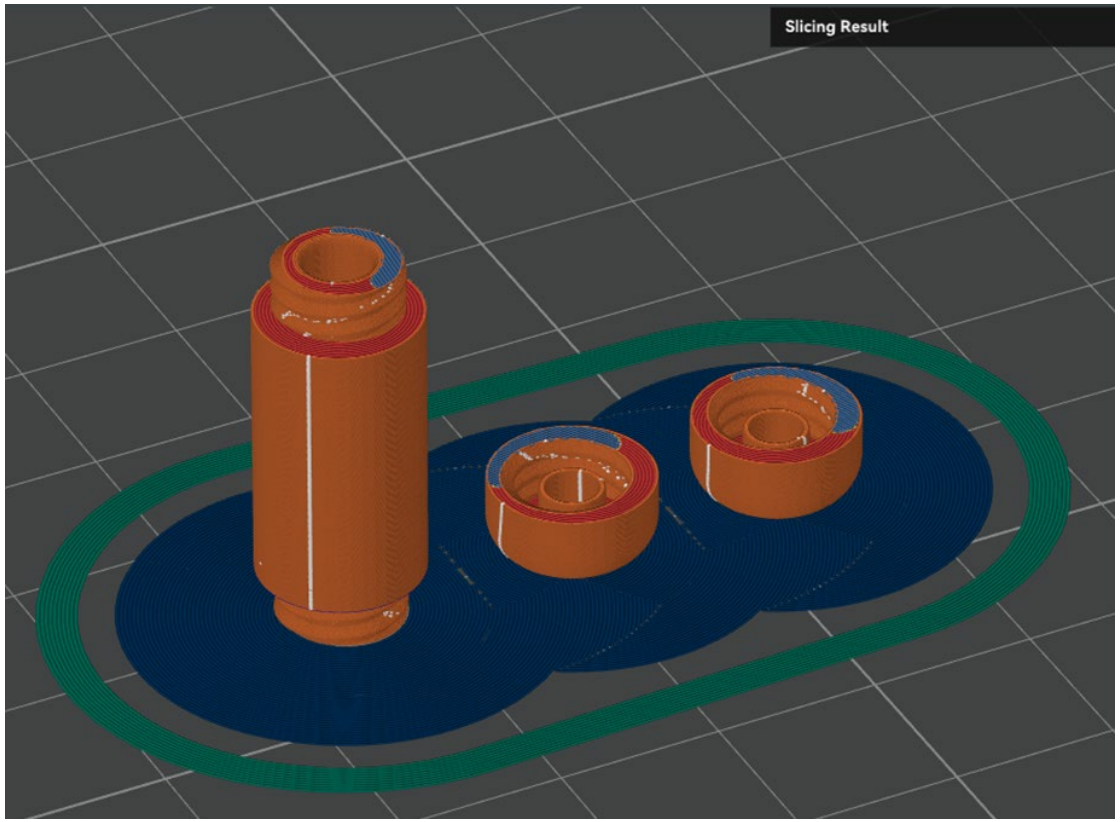
- Have a polymer with reactive group and photo initiator

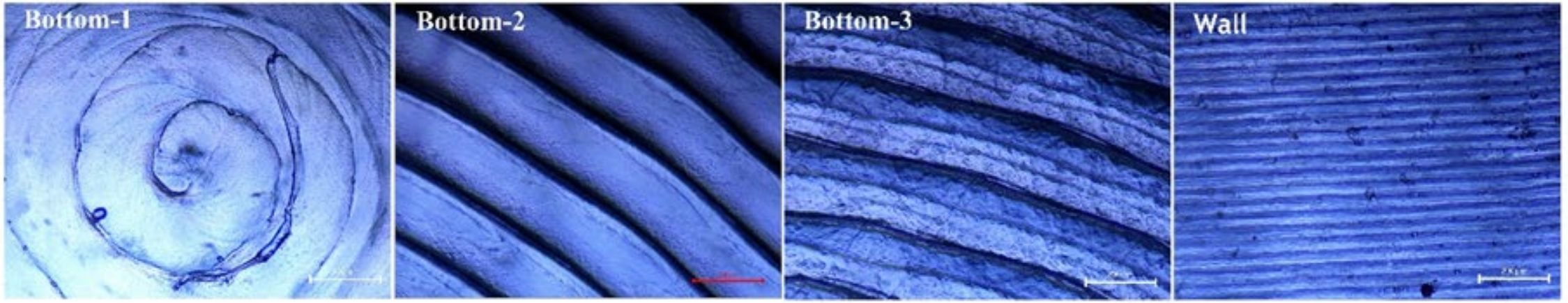


Slicer → g-code Settings

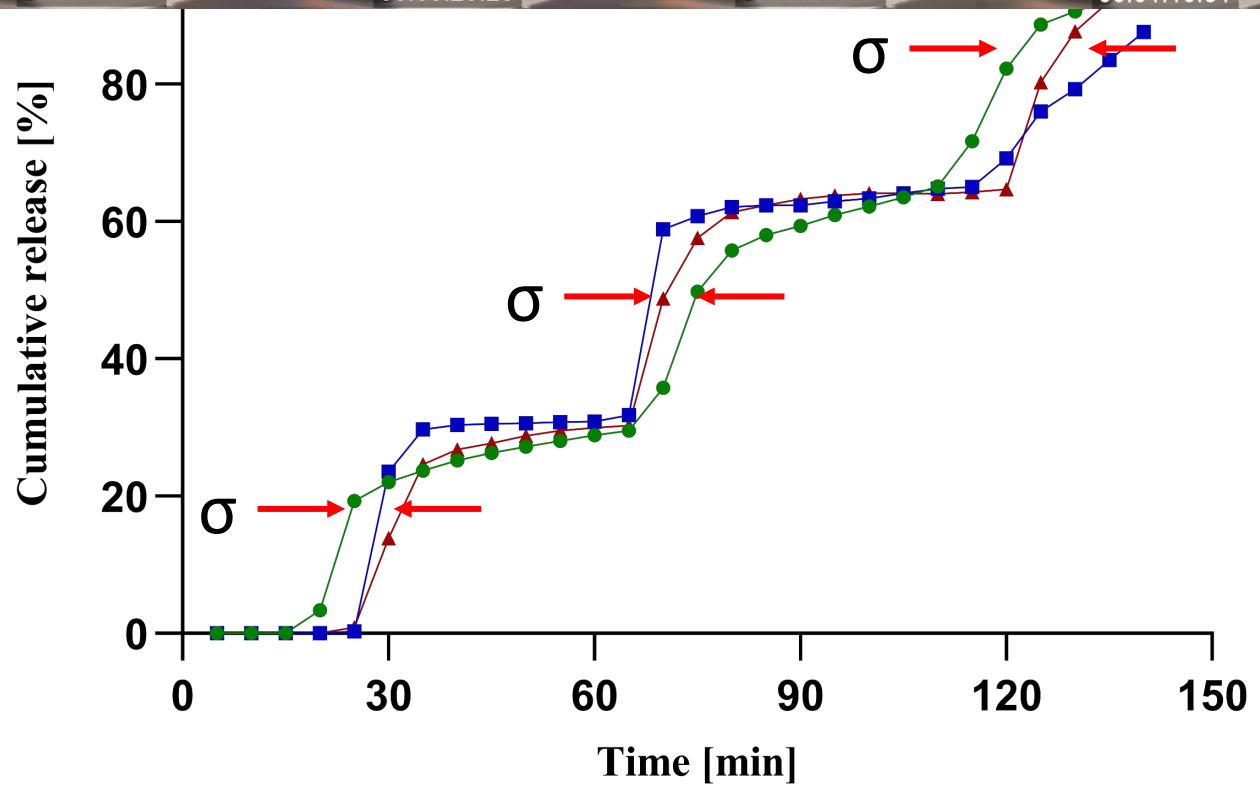
- Layer height
- Print speed
- Etc.

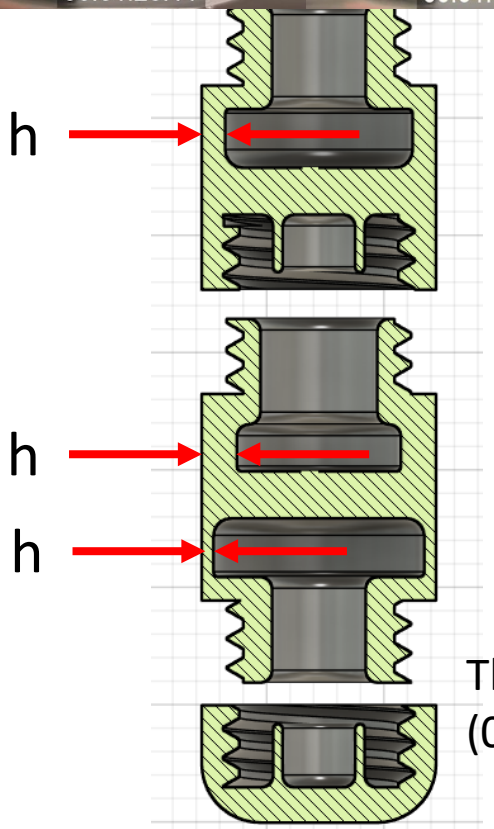
- Nozzle size & temperature
- Cooling rate



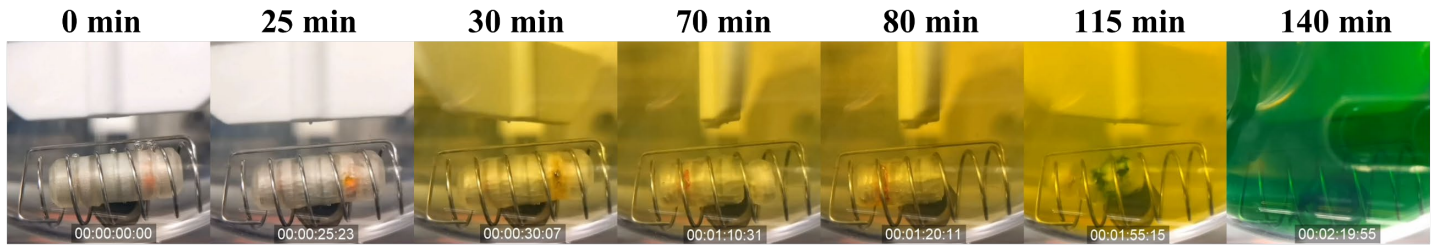


- All of these factors can affect product quality especially for MR products





Three-compartment Capsule
(0.5/ 1.0/ 1.5 mm)

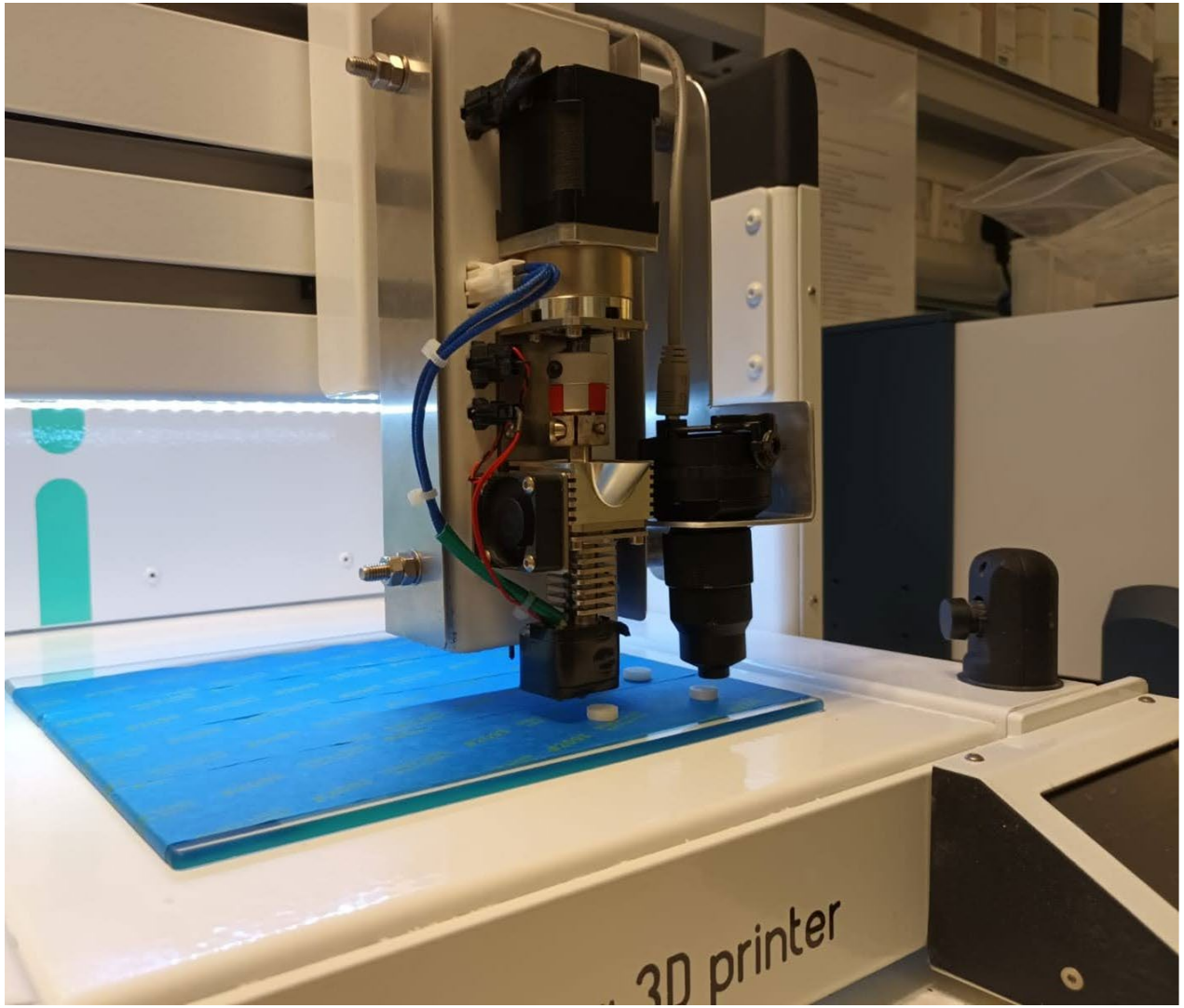


Bioequivalence, Bioavailability and Dissolution

- Generic drug products
  - To date there are no generic 3D printed products approved
    - Little research has been done on establishing BE for MR 3D printed products
  - Much research is needed

- Point of Care (POC)
  - Bioavailability needs to be established
  - Animal studies have been done establishing in vitro-in vivo correlation (IVIVC) in rodents
  - To the best of the author's knowledge there are no publicly available studies
  - Much research is needed especially for MR products

PAT QC Methods

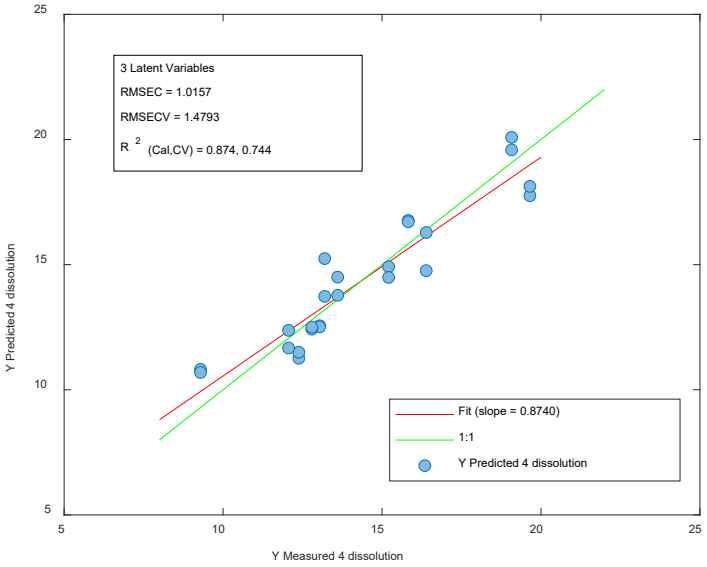


Viavi Micro NIR Spectrometer

PAT Techniques Point of Care (POC) QC

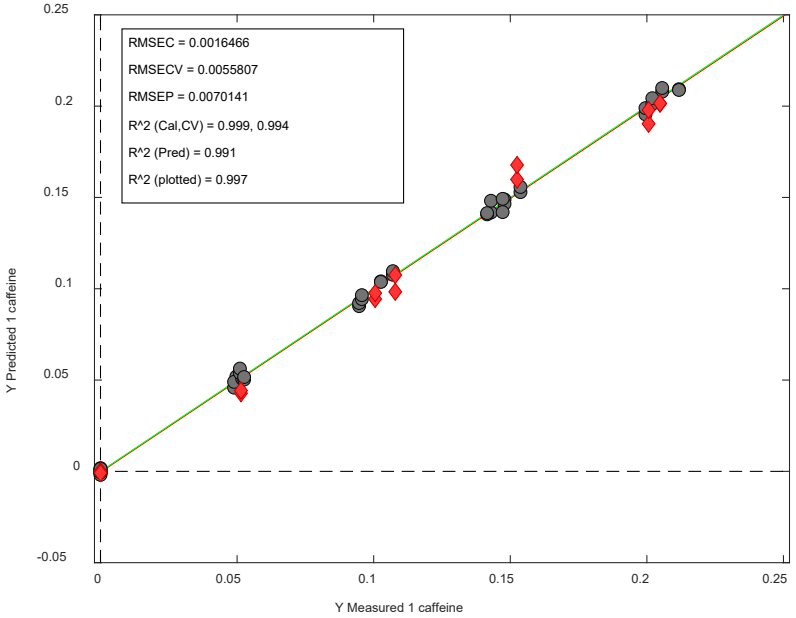
- Research done in our lab, shows that micro NIR spectrometers and machine learning(ML) algorithms can be used to predict:
  - Content/ assay, content uniformity and dissolution rate

Dissolution Model Prediction

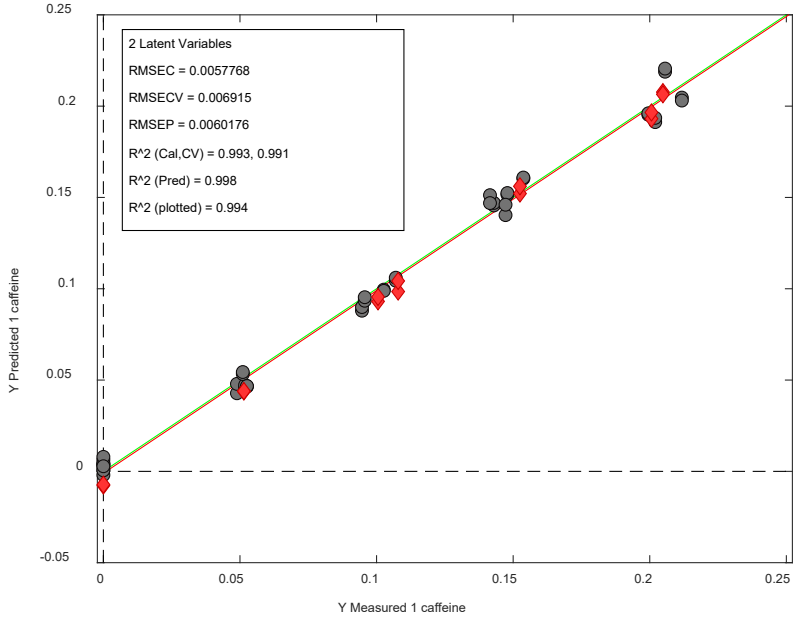


Assay Prediction using ANN, PLS and SVM ML algorithms

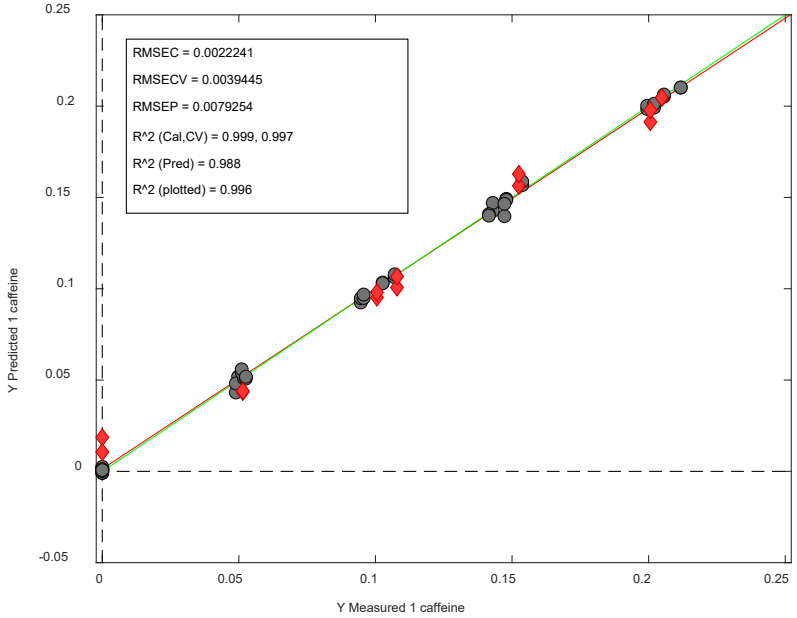
ANN



PLS



SVM



Summary – Key Research Needs

- Excipient Material Science
  - Melt polymer rheology
    - Extrusion speed and filament uniformity
  - Polymer interfacial diffusion
    - Strength and release rate
- Product design
  - Products dimensions and construction materials influence release rate
  - Printer settings greatly influence product quality
- BA/ BE and dissolution testing
  - Little research has been done, and much research is needed
- PAT
  - Assessment of best practices for validation of PAT methods for QC analysis of products for POC personalized medicine