TEXAS A&M UNIVERSITY
Irma Lerma Rangel
College of Pharmacy

# 3D Printing and Bioprinting: Examples, mechanism, Quality Control and Impact in Pharmaceutics

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# Outline

- 3D printing and bioprinting – scope of the presentation today
- Historical development
- 3D printer technologies – and mechanisms
- SLS and Research in our lab at Texas A&M University
- Some regulatory considerations – Quality control and impact

# 3D printing

- 3D printing describes various methods of construction objects in a layer-by-layer fashion (also called additive manufacturing).
- Early concept from MIT involved printing a liquid binder onto a thin powder
- Now there are many other types with wide mechanisms and applications
- In almost all cases, the object to be printed is created using computer added design (CAD) software package, which is then exported to a file to be printed.
- The exported file splits the 3D object into a series of layers. The object is then printed layer-by-layer. You can imagine multiple possibilities . E.g. combination products.
- Basic componts; hardware (3D printer), software (CAD), and materials used.

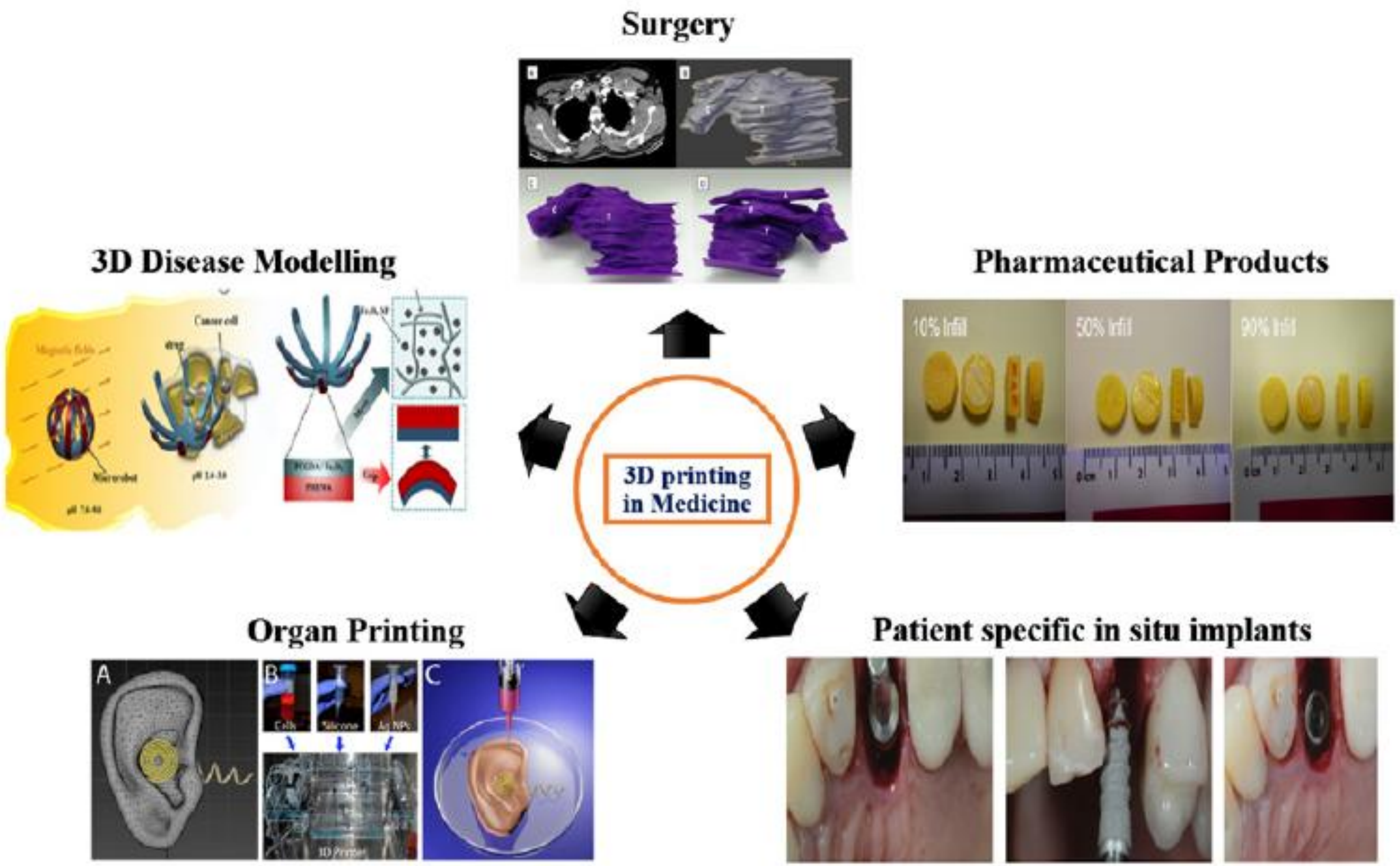
# Bioprinting

- Now 3D printing has advanced. It utilizes biocompatible materials and even viable cells into complicated 3D functional tissue constructs.

- Bioprinting has potential to develop desired tissues and organs that are suitable for many biomedical applications – such as organ transplantation or cancer drug screening

- Printing of 3D printed patient specific models, devices, implants or organs require high resolution images or scans of body parts. Technologies such as computer aided tomography (CT scans for hard bone structures), and magnetic resonance imaging (MRI for soft tissues) are already in widespread use. Post processing of acquired images,0.25 to 2 mm slices of these images are stacked together to give detailed 3D information pathology of the tissue.

- Next step is reconstruction of 3D tissue models using acquired CT or MRI scans. For that CAD software are utilized  to analyze and process every 2D scan (eg Solid works, MIMICS, 3Matic). This step provides complete information on patients' organ geometry. The final model is converted into steriolithography (STL) format for printing.


Surgery
3D Disease Modelling
Pharmaceutical Products
10% Infill
50% Infill
90% Infill
3D printing
in Medicine
Organ Printing
A
B
C
Patient specific in situ implants

# History

- 1980 – Hideo Kodama, Municipal Industrial Research Institute – 3D plastic models with photo hardening thermoset polymers; patent for XYZ plotter
- 1984 – Charles Hull (SLA technology, used CAD file to make computer-aided object), 3D systems Company
- 1987- Carl Deckard (SLS), University of Texas; laser sinitered the powder in specific areas based on digital data from a CAD file
- 1989 – Scott and lisa Crump, Stratasys Inc (FDM)
- 1993 - Ely Sachs and Mike Cima (Binder jetting)

# Challenges in Pediatric Dose Selection

- Heterogeneous Population
- Several dose calculation approaches
  - Age, body size (mg/kg), body surface area etc.
- Some PK considerations
  - Variable Gastric emptying time
  - Variable Gastric pH
  - SA of the absorptive sites
  - GI permeability
  - Biliary functions
  - Body water and adipose tissue
  - Transporter expression

# Pediatric/Geriatric Product: Special Considerations

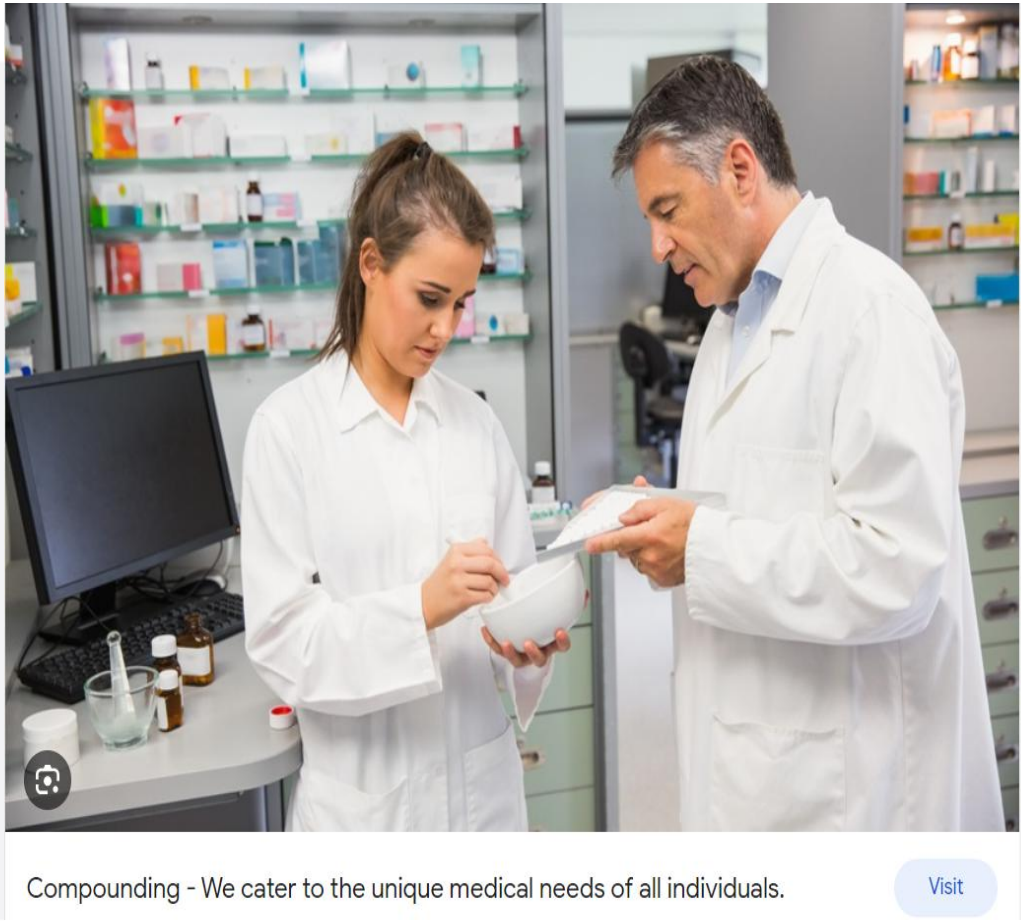
- Minimal/safe excipients
- Stability under high heat/humidity
  - Physical, chemical, and microbiological
- Palatable
  - Flavor selection based on cultural preferences
- Easy-to-swallow or dissolvable dosage form
- Ability to titrate dose
- Adequate bioavailability
- Avoidance of extemporaneous compounding
- Commercially available

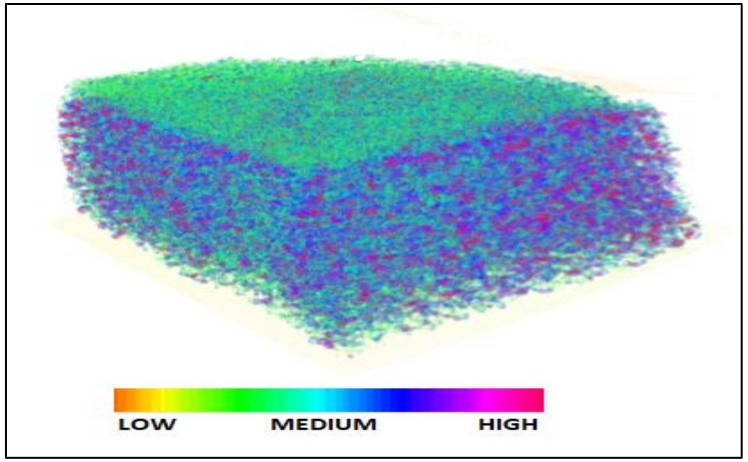
Anne Zajicek, NIH

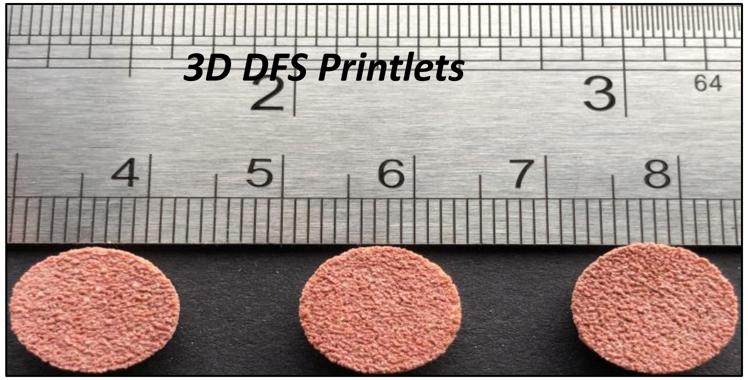
# Issues With Compounded Medications

- Palatability
- Dose accuracy
- Quality –
  - Failed in basic potency and content uniformity - potency range 59-89%
  - Over the period 2008–2010, the Texas State Board of Pharmacy found an overall potency failure rate of 23 % for compounded drugs
- Stability
- Bioavailability issue
- Adverse events use of compounded drugs

# Pediatric drug challenges – Dose flexibility is required






*SEM Images of DFS printlets*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CrossMark

*Review Article*
*Theme: Precision Medicine: Implications for the Pharmaceutical Sciences*
*Guest Editors: Marilyn N. Martinez and Adel Karara*

## Additive Manufacturing with 3D Printing: Progress from Bench to Bedside

**Ziyaur Rahman,[1,4] Sogra F. Barakh Ali,[1] Tanil Ozkan,[2] Naseem A. Charoo,[3] Indra K. Reddy,[1] and Mansoor A. Khan[1]**

*Received 30 October 2017; accepted 5 April 2018; published online 12 September 2018*

***Abstract.*** Three-dimensional (3D) printing was discovered in the 1980s, and many industries have embraced it, but the pharmaceutical industry is slow or reluctant to adopt it. Spiritam® is the first and only 3D-printed drug product approved by FDA in 2015. Since then, the FDA has not approved any 3D-printed drug product due to technical and regulatory issues. The 3D printing process cannot compete with well-established and understood conventional processes for making solid dosage forms. However, pharmaceutical companies can utilize it where mass production is not required; rather, consistency, precision, and accuracy in quality are paramount. There are many 3D printing technologies available, and not all of them are amenable to pharmaceutical manufacturing. Each 3D technology has certain prerequisites in terms of material that it can handle. Some of the pertinent technical and regulatory issues are as follows: Current Good Manufacturing Practice, in-process tests and process control, and cleaning validation. Other promising area of 3D printing use is printing medications for patients with special needs in a hospital and/or pharmacy setting with minimum regulatory oversight. This technology provides a novel opportunity for in-hospital compounding of necessary medicines to support patient-specific medications. However, aspects of the manufacturing challenges and quality control considerations associated with the varying formulation and processing methods need to be fully understood before 3D printing can emerge as a therapeutic tool. With these points in mind, this review paper focuses on 3D technologies amenable for pharmaceutical manufacturing, excipient requirement, process understanding, and technical and regulatory challenges.

**KEY WORDS:** 3D printing; QbD; excipients; process; regulatory.

**Age-appropriate flexible pediatric drug delivery systems**
**2 NIH R01s and one R56 – 7 millions.. (with Collaborations from COE, SVM, Life Sciences, HCRF, Driscoll Childrens.. Two more grants are scored..**

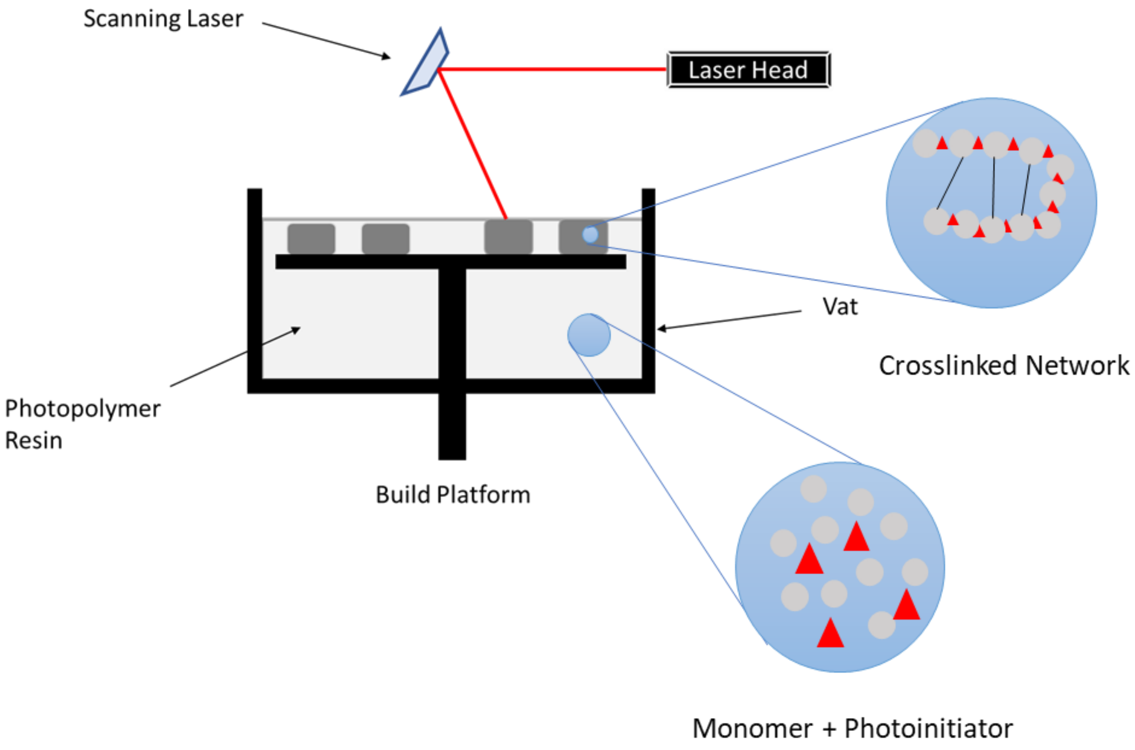
# 3D Printing Techniques For Pharmaceuticals

- Fused deposition modeling
- Stereolithography
- Selective laser sintering
- Binder jetting

# Main 3D printing Technologies

| 3D Printing Categories | Technologies | Materials Used | Working mechanism |
|---|---|---|---|
| **Binder Jetting** | **Powder Bed inkjet**, S-printing, M-printing | Plaster, metal, sand, polymer | Liquid binder is deposited selectively on powder bed |
| **Vat Polymerization (polymer in tanks cured by UV)** | **Stereolithography (SLA)** Digital light projection (DLP) | Photopolymer (Liquid) | Vat filled with photopolymer is cured by precise application of light. |
| **Powder Bed Fusion** | **Selective Laser Sintering (SLS)**, Direct metal laser sintering, electron beam melting | Metal, plastic and polymer powders | Laser or electron beam fuses selected areas on powder bed |
| **Material Extrusion** | **Fused Deposition Modelling (FDM)** Gel/paste Extrusion | Filaments of thermoplastic polymers | Melted viscous material is deposited on a surface |
| Material Jetting | Ink-jet printing, Polyjet | Wax-Like materials, photopolymers. | Droplets of materials are deposited |
| Directed Energy Deposition | Electron beam direct manufacturing direct metal tooling (DMT) | Metal wires, powder | Focused laser or electron beam melts powders/wire as its being deposited |
| Sheet Lamination | Laminated object manufacturing | Sheets | Sheets are bonded to form objects |

# Stereolithography (SLA)




SLA Printed Dentures
Photo Credit: dentca.com

SLA Printed Hearing Aids
Photo Credit: envisionTEC

# Stereolithography (SLA)

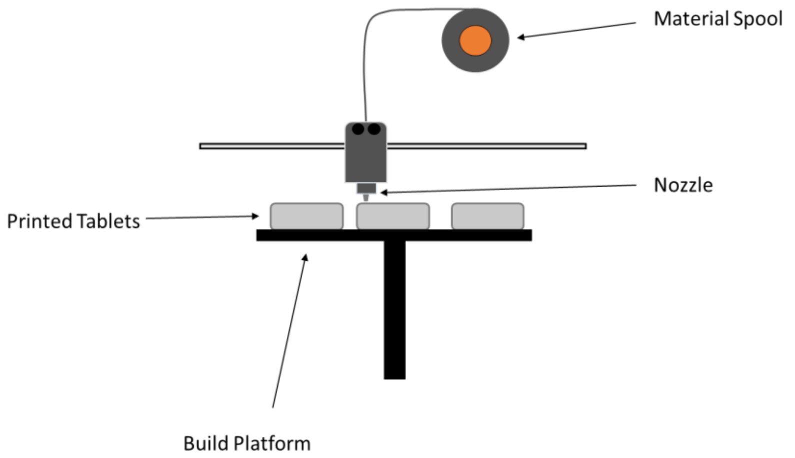
**Advantages**

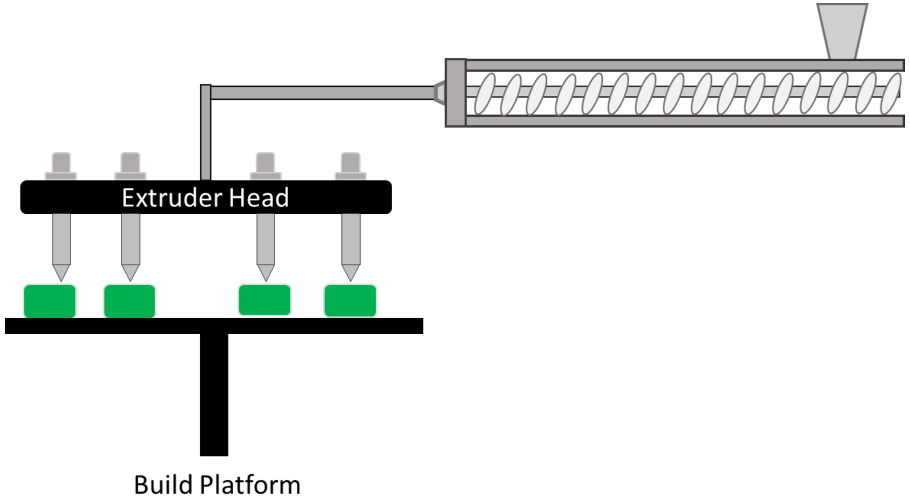
- High resolution printed products.
- Capable of printing complex geometries.
- Used in printing tissue like structures and scaffolds.

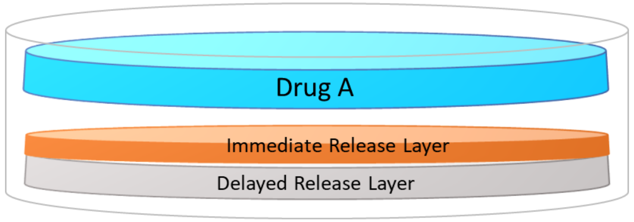
**Disadvantages**

- Biocompatibility and toxicity issues.
- Most photoinitiators and photopolymers have cytotoxic properties.
- Post processing is often necessary.

# Fused Deposition Modelling (FDM)



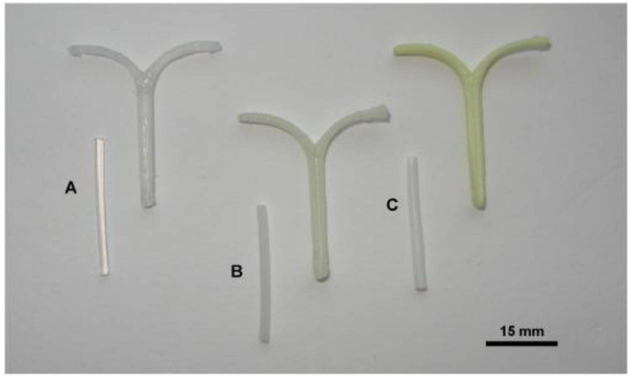




Photo Credit: Genina et al 2016

# Fused Deposition Modelling (FDM)

**Advantages**

- One of the most feasible Additive Manufacturing (AM) methods.
- Low cost, user friendly wide range of available materials.
- No need for post processing
- Allows integration of multiple materials/filaments.

**Disadvantages**

- High temperatures are often needed for printing. Hence, requires careful selection of drugs and polymers.
- Requires manufacturing of drug loaded filament.

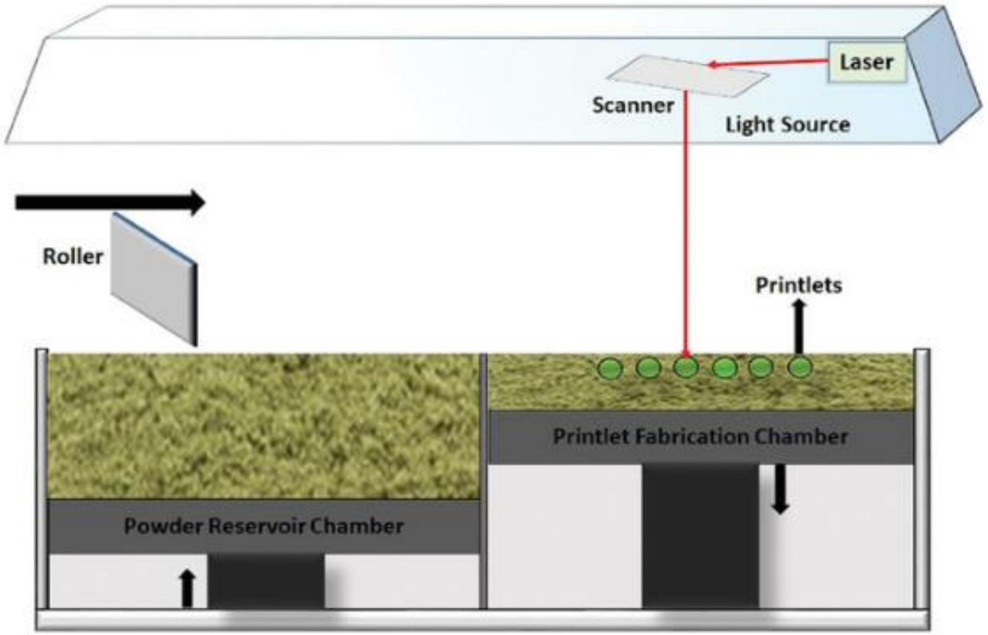
# SELECTIVE LASER SINTERING-

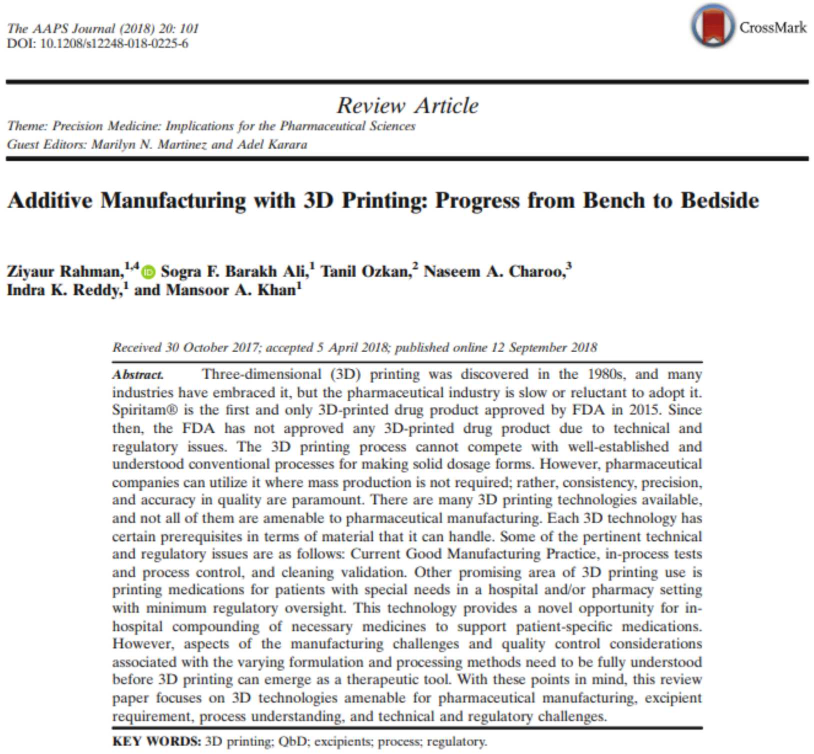
➢ The technologies offers many advantages over other methods of 3DP for pharmaceuticals printing.

- Solvent free, makes it ideal to fabricate water and organic solvent sensitive drug molecules
- Relatively high speed compared to other methods
- No requirement of filament form of raw material, polymerizable monomer/polymer liquid binder, and post processing
- Furthermore, printlets will be immediately available after printing for dispensing and consumption since there is no post processing steps
- Printlets containing multiple drugs with different release and mechanical characteristics can also be fabricated by manipulating process and material attributes

# SELECTIVE LASER SINTERING- How it works?

- ➢SLS forms 3D objects by laser energy to selectively heat powder particles which results in fusion.
- ➢The fused particles subsequently solidify to form a 3D structure. The SLS system comprises of three main components, i.e. a spreading platform, powder bed and a laser system (laser and scanner).

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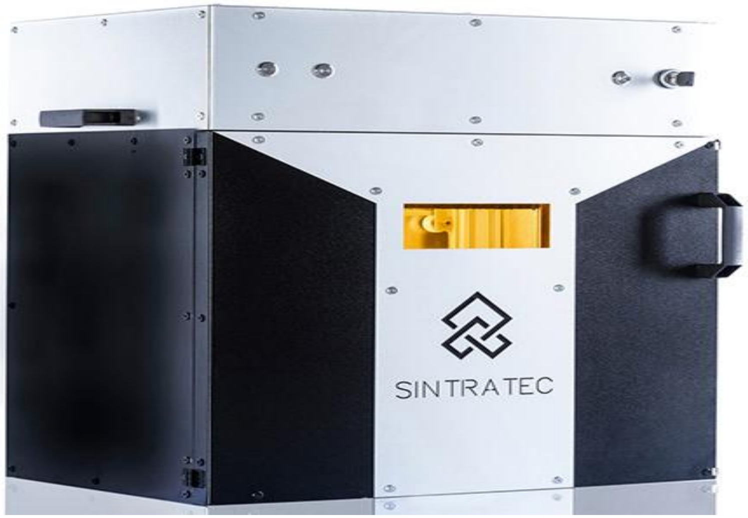



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Review Article

**Selective laser sintering 3D printing – an overview of the technology and pharmaceutical applications**

Naseem A. Charoo, Sogra F. Barakh Ali, Eman M. Mohamed, Mathew A. Kuttolamadom, Tanil Ozkan, Mansoor A. Khan & ...show all

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**Abstract**

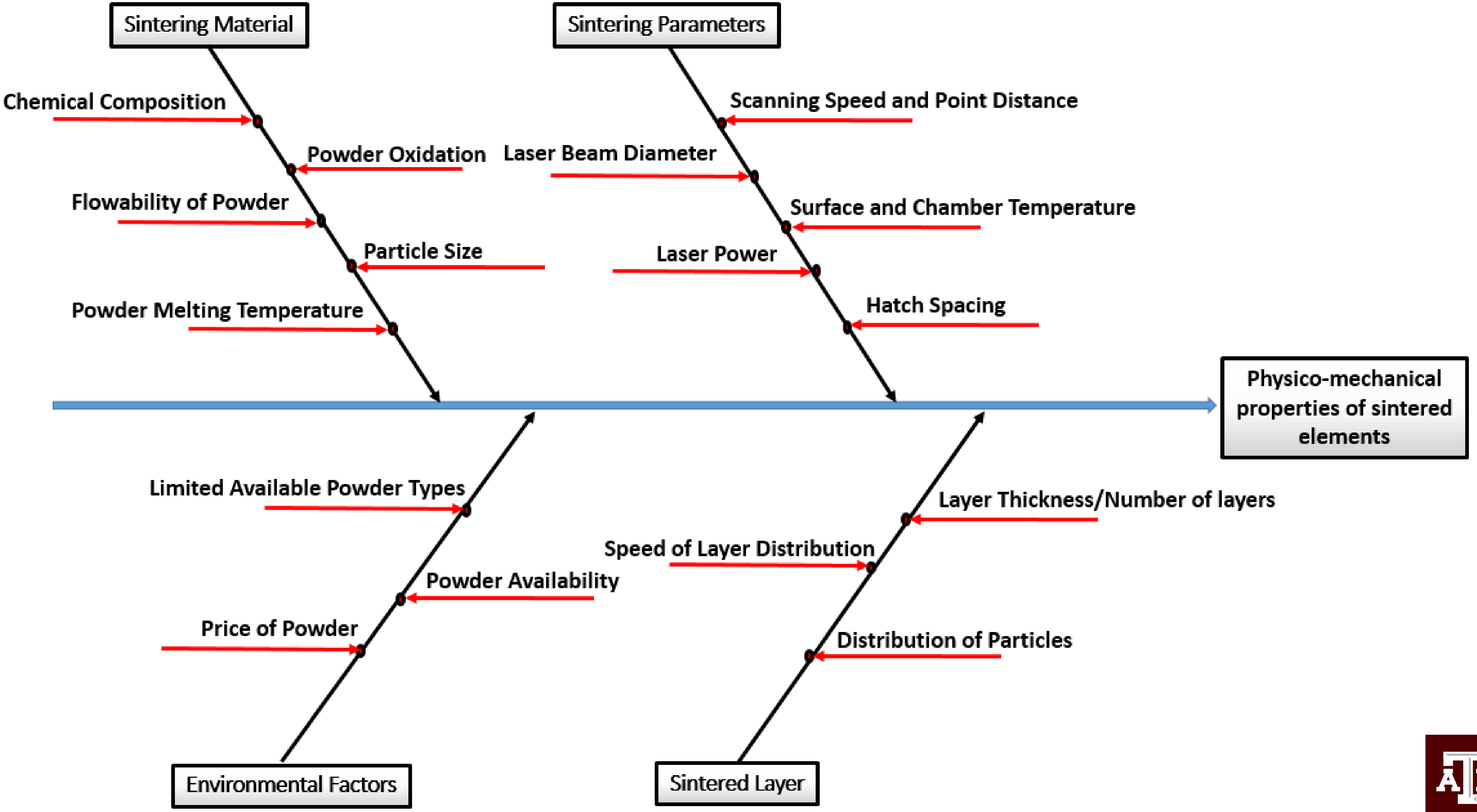
Food and Drug Administration (FDA) has approved a drug product (Spritam®) and many medical devices manufactured by three-dimensional printing (3DP) processes for human use. There is immense potential to print personalized medicines using 3DP. Many 3DP methods have been reported in the literature for pharmaceutical applications. However, selective laser sintering (SLS) printing has remained least explored for pharmaceutical applications. There are many advantages and challenges in adopting a SLS method for fabrication of personalized medicines. Solvent-free nature, availability of FDA approved thermoplastic polymer/excipients (currently used in hot melt-extrusion process), minimal/no post-processing step, etc. are some of the advantages of the SLS printing process. Major challenges of the technology are requirement of at least one thermoplastic component in the formulation and thermal stability of drug and excipients. This review provides an overview of the SLS printing method, excipient requirements, process monitoring, quality defects, regulatory aspects, and potential pharmaceutical applications.

Keywords: 3D printing, selective laser sintering, pharmaceuticals, in-process monitoring, quality defects, personalized medication

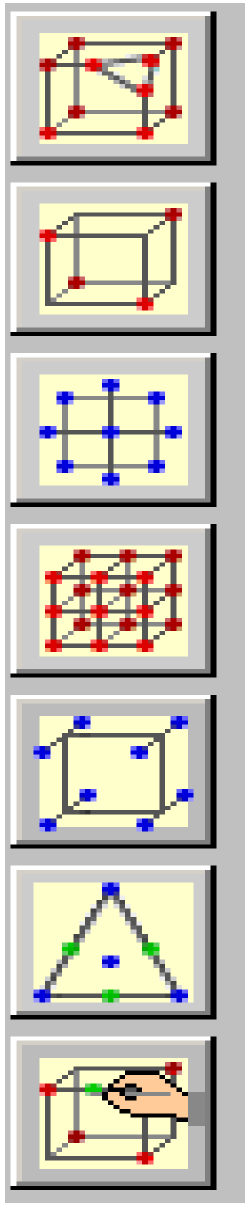
## SELECTIVE LASER SINTERING- Process Parameters

- It is important to understand the interplay of process parameters such as powder bed temperature, laser scanning speed, laser power, etc., and formulation factors such as particle size, density, melting point, etc. on the critical quality attributes (CQAs) of printed dosage forms.
- The pharmaceutical Quality by Design (QbD) is a systematic approach to development that commences with predefined objectives and emphasizes product and process understanding.

# SELECTIVE LASER SINTERING- Fish bone diagram



# DESIGN OF EXPERIMENTS (DOE)



**Custom Design**

**Screening Design**

**Response Surface Design**

**Full Factorial Design**

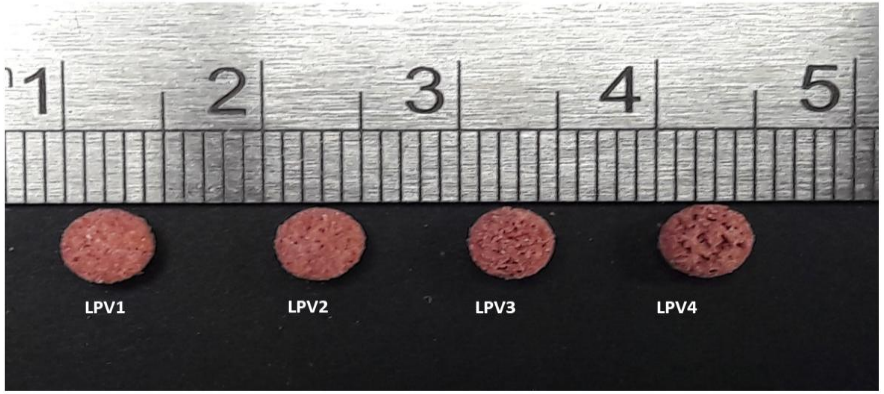
**Taguchi Arrays**

**Mixture Design**

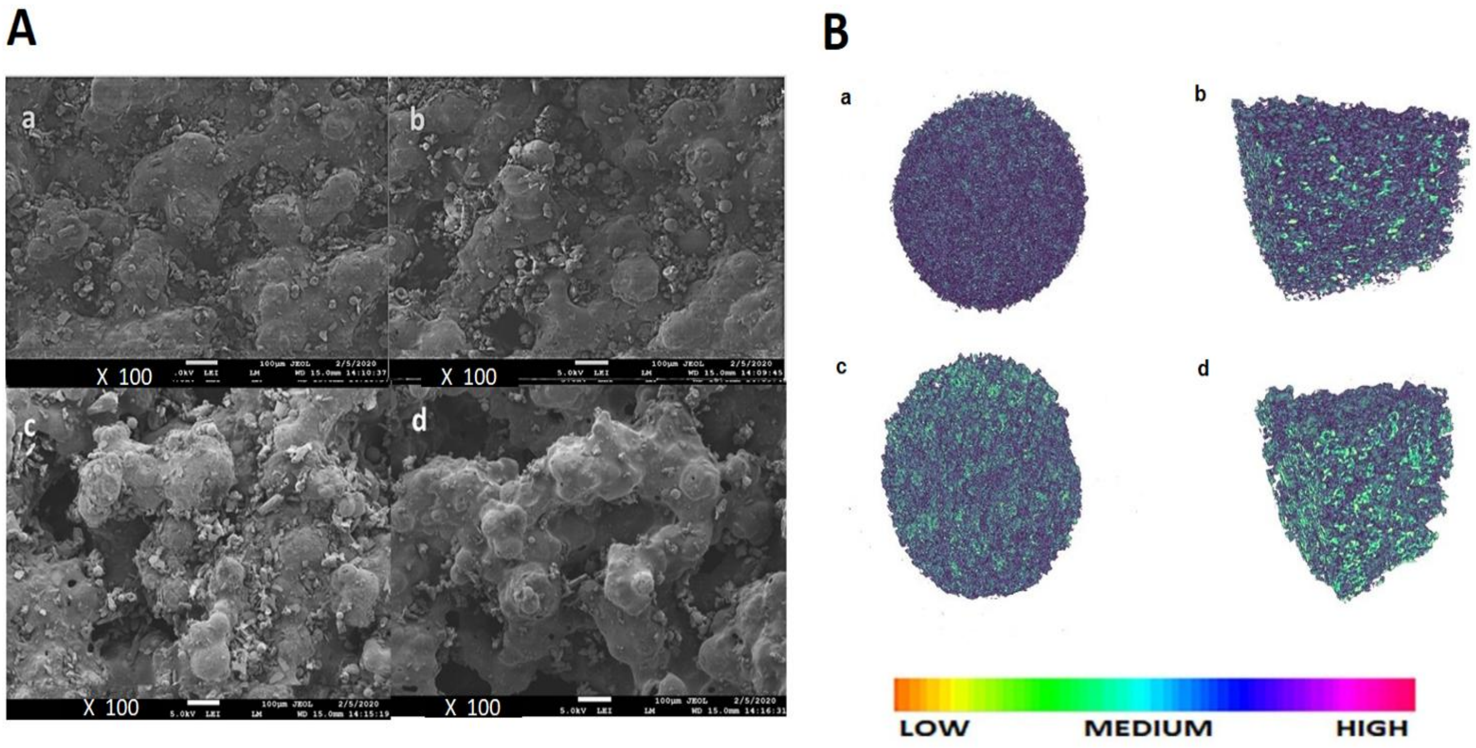
**Augmented Design**

# SELECTIVE LASER SINTERING- Amorphous Solid Dispersion (Lopinavir)

| Miniprintlets | LPV (%) | Kollicoat® IR (%) | LMH (%) | Talc (%) | Candurin® NXT Ruby red (%) | Chamber temperature (°C) | Surface temperature (°C) | Laser scanning speed (mm/s) |
|---|---|---|---|---|---|---|---|---|
| LPV1 | 25.0 | 60.5 | 10.0 | 1.5 | 3.0 | 70 | 90 | 75 |
| LPV2 | 37.5 | 48.0 | 10.0 | 1.5 | 3.0 | 70 | 90 | 75 |
| LPV3 | 50.0 | 35.5 | 10.0 | 1.5 | 3.0 | 70 | 90 | 75 |
| LPV4 | 50.0 | 35.5 | 10.0 | 1.5 | 3.0 | 70 | 90 | 100 |

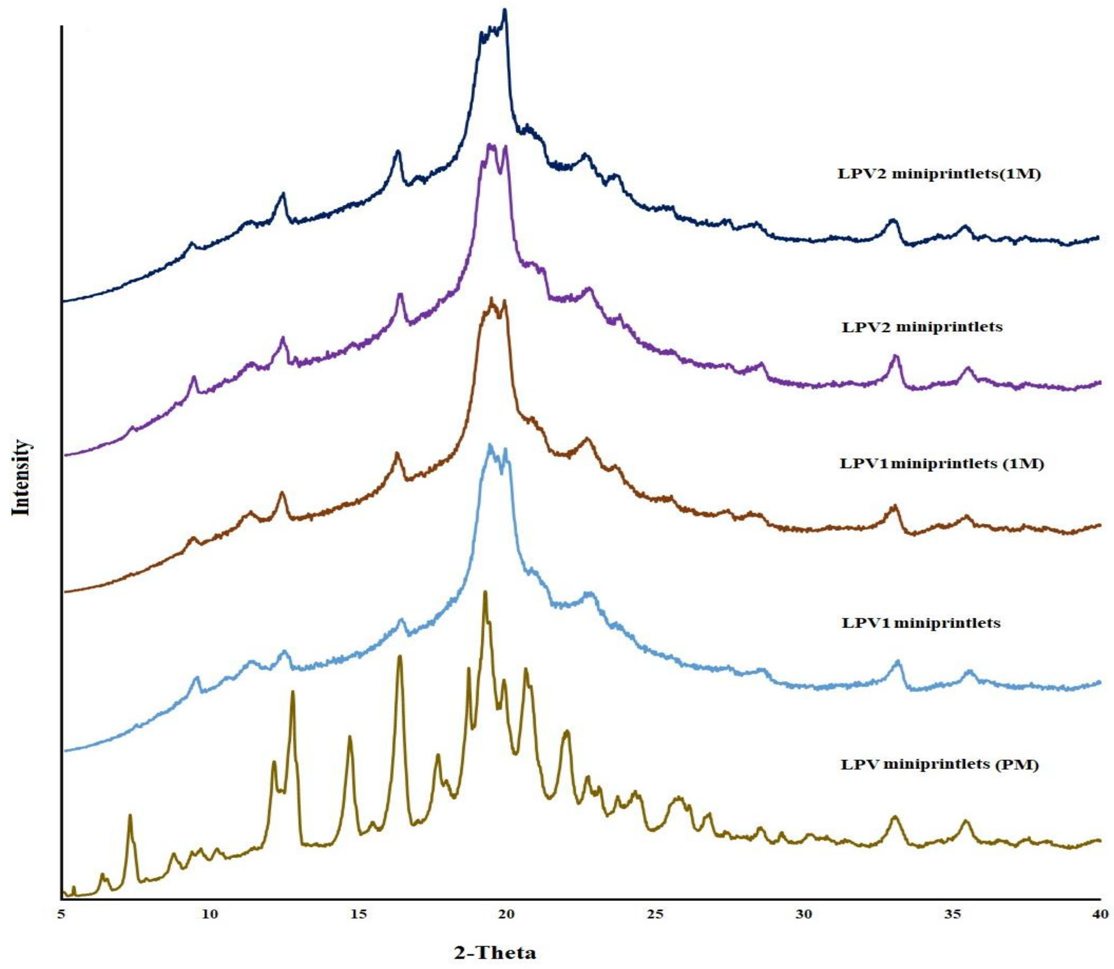


# SELECTIVE LASER SINTERING- Amorphous Solid Dispersion




(A) SEM images of (a) LPV1, (b) LPV2, (c) LPV3, and (d) LPV4 printlets at 100X and (B) X-ray micro-CT images of (a, b) LPV1 and (c, d) LPV3 printlets. The color scale bar represents the density in LPV1 and LPV3 printlets.

# SELECTIVE LASER SINTERING- Amorphous Solid Dispersion

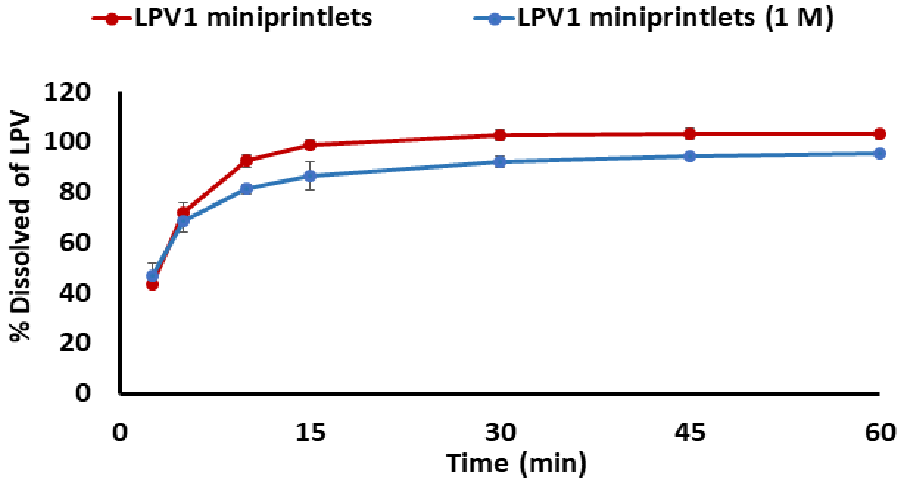


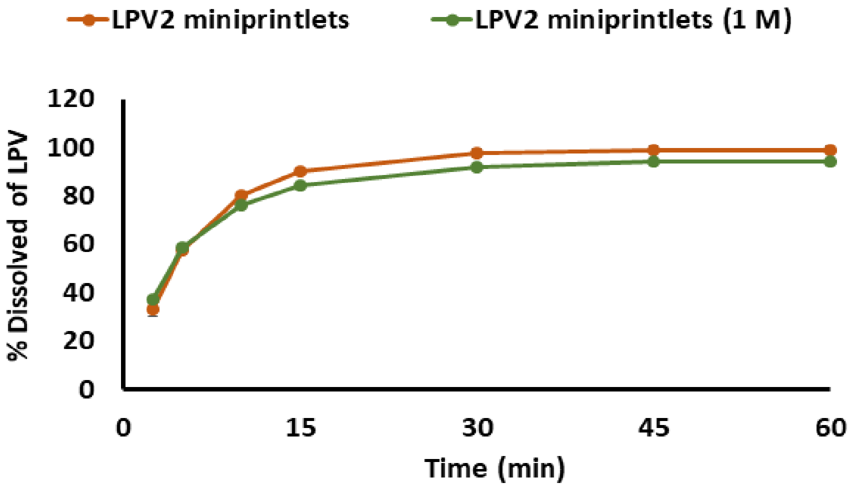

| Sample | Actual | | Predicted | |
|---|---|---|---|---|
| | Crystalline LPV (%) | Amorphous LPV (%) | Crystalline LPV (%) | Amorphous LPV (%) |
| TS1 | 15 | 85 | 17.1±0.4 | 82.9±0.4 |
| TS2 | 25 | 75 | 26.3±0.6 | 73.7±0.6 |
| TS3 | 7.5 | 92.5 | 9.5±0.1 | 90.5±0.1 |
| TS4 | 15 | 85 | 15.5±0.1 | 84.5±0.1 |
| LPV1 miniprintlets | - | - | 7.2±0.3 | 92.8±0.3 |
| LPV3 miniprintlets | - | - | 4.6±0.4 | 95.4±0.4 |
| LPV4 miniprintlets | - | - | 11.5±0.6 | 88.5±0.6 |
| LPV1 miniprintlets (1 M) | - | - | 11.3±0.7 | 88.7±0.7 |
| LPV3 miniprintlets (1 M) | - | - | 5.9±0.4 | 94.1±0.4 |
| LPV4 miniprintlets (1 M) | - | - | 12.7±0.8 | 87.3±0.8 |

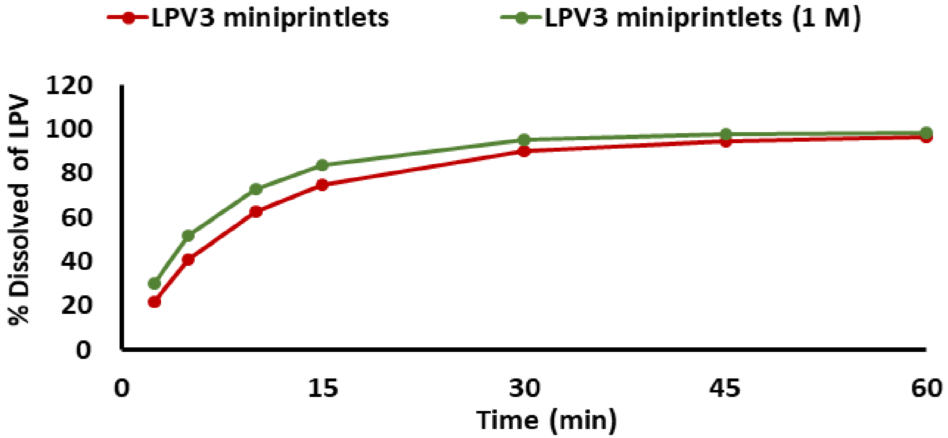
***Stable after 1 month exposure to 40 $^{o}$C/75% RH***

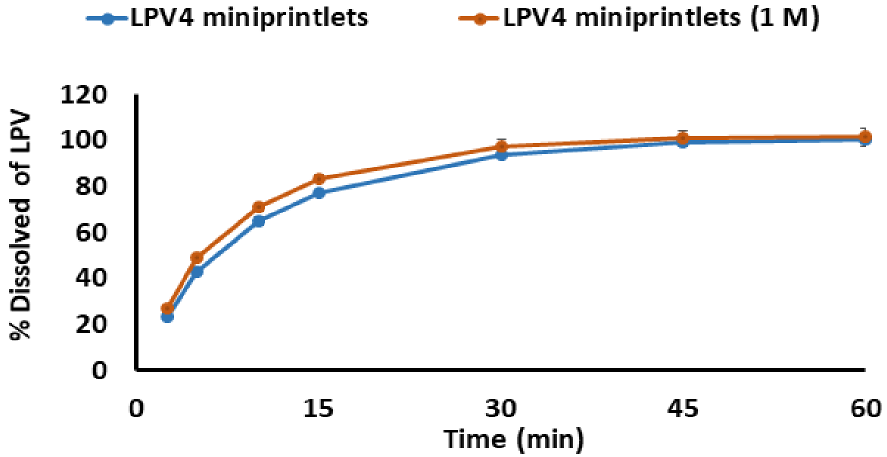
XRPD patterns of (A) LPV crystalline, LPV amorphous, Kollicoat® IR, and LMH, (B) PM (before printing), LPV1 printlets, LPV1 printlets (1 M), LPV2 printlets, and LPV2 printlets (1 M), and (C) LPV3 printlets, LPV3 printlets (1 M), LPV4 printlets, and LPV4 printlets (1 M).

# SELECTIVE LASER SINTERING- Amorphous Solid Dispersion

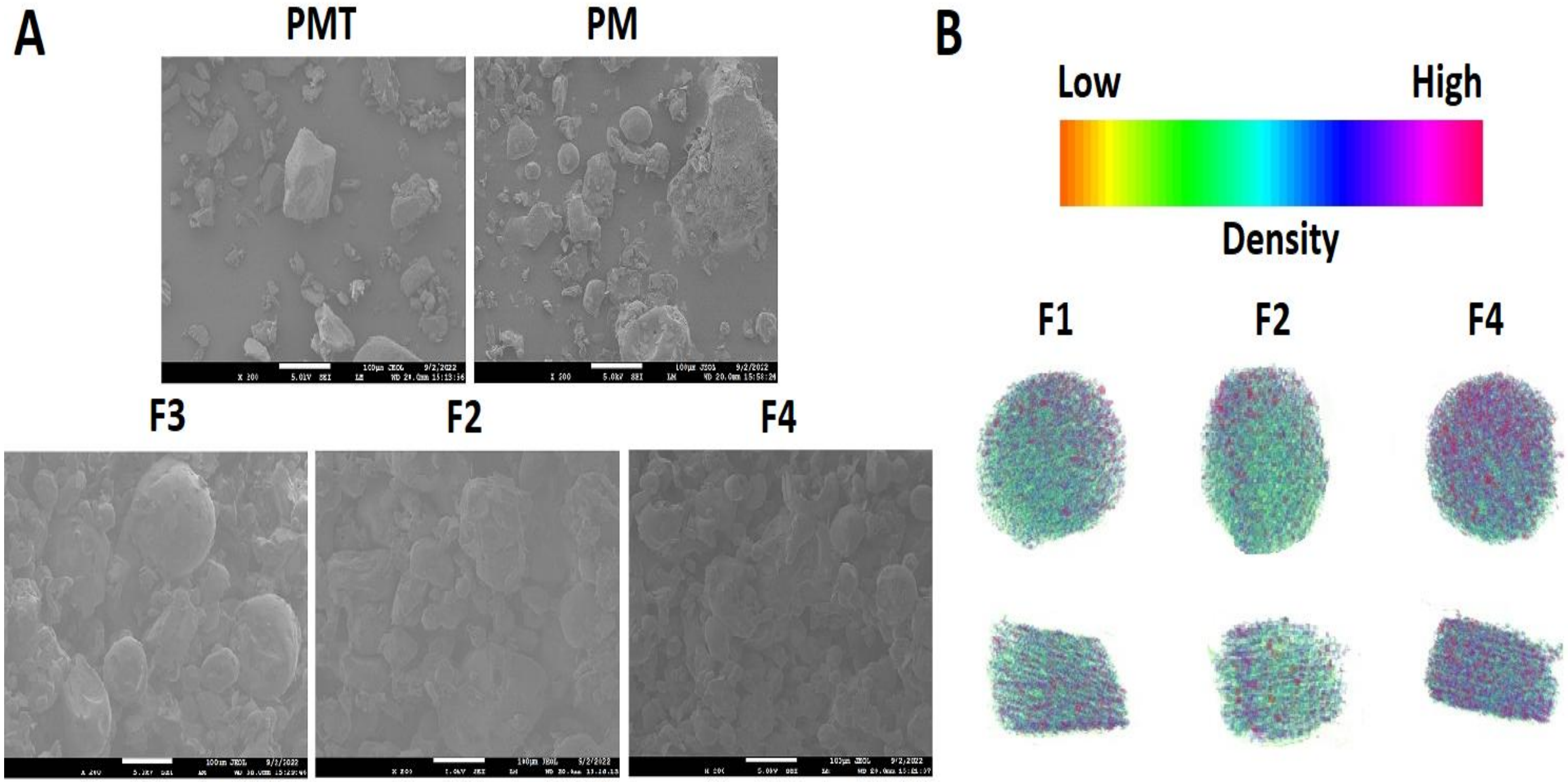


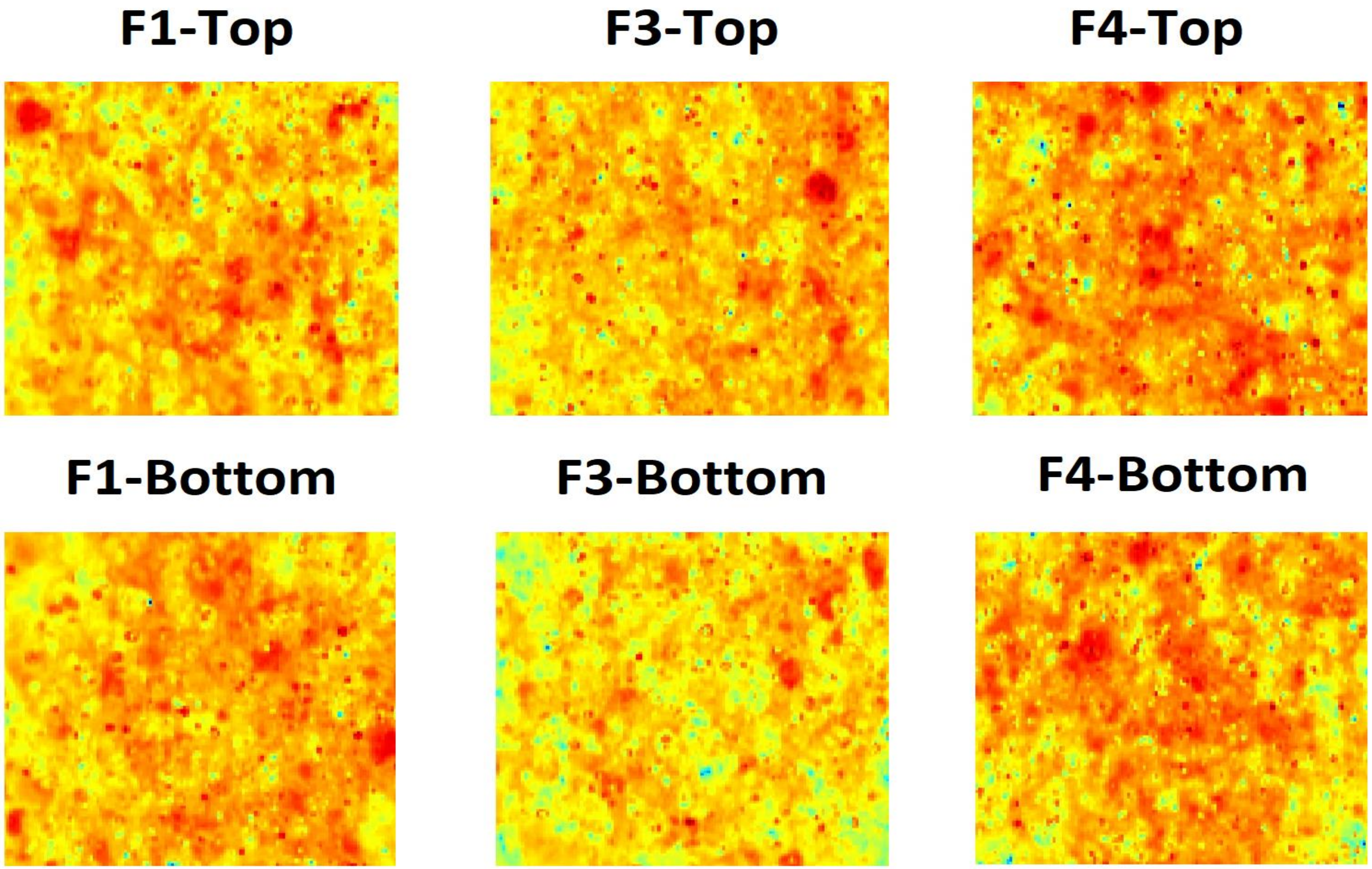



# SELECTIVE LASER SINTERING- Pyrimethamine printlets



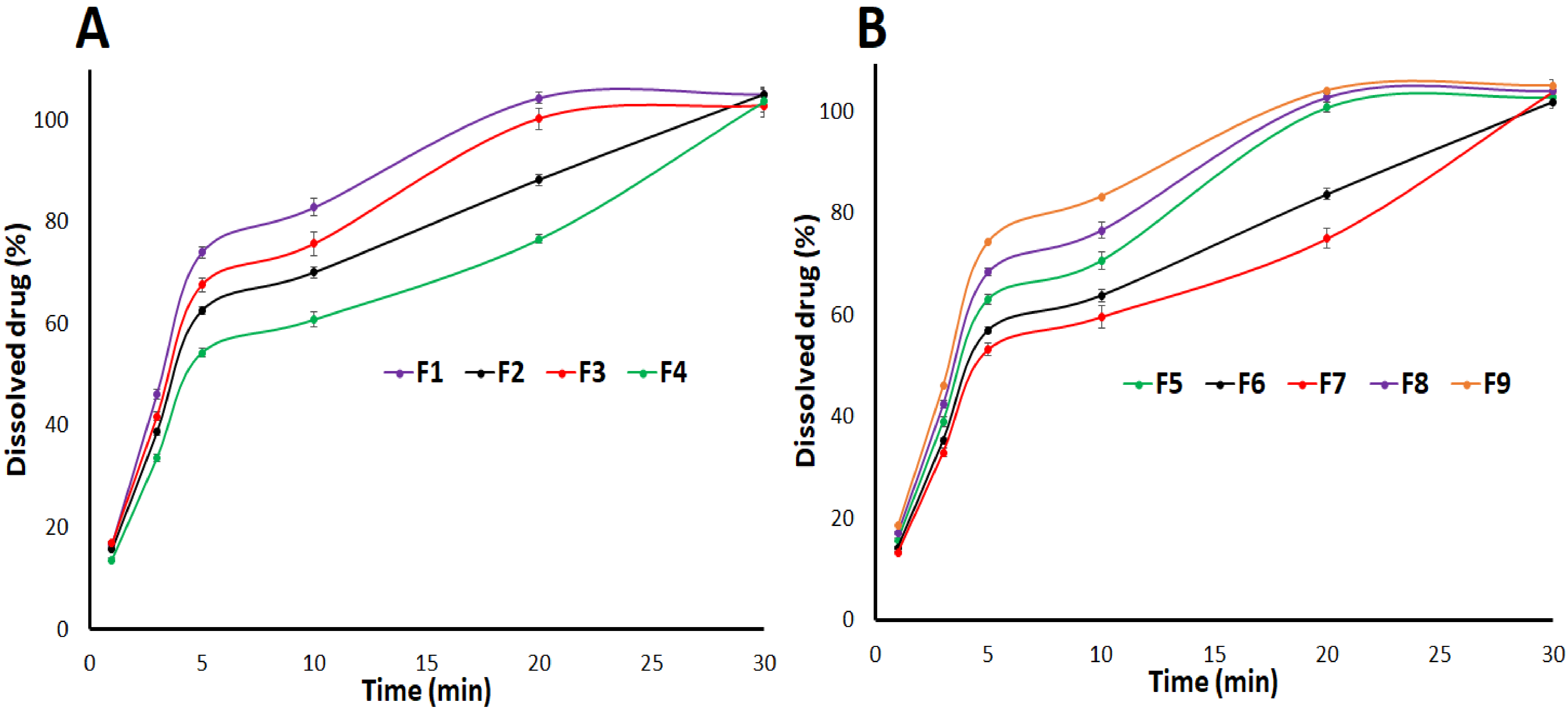

A) Microphotographs and B) micro-CT images of the printlets.

# SELECTIVE LASER SINTERING- Pyrimethamine printlets




Pyrimethamine drug distribution

# SELECTIVE LASER SINTERING- Pyrimethamine printlets



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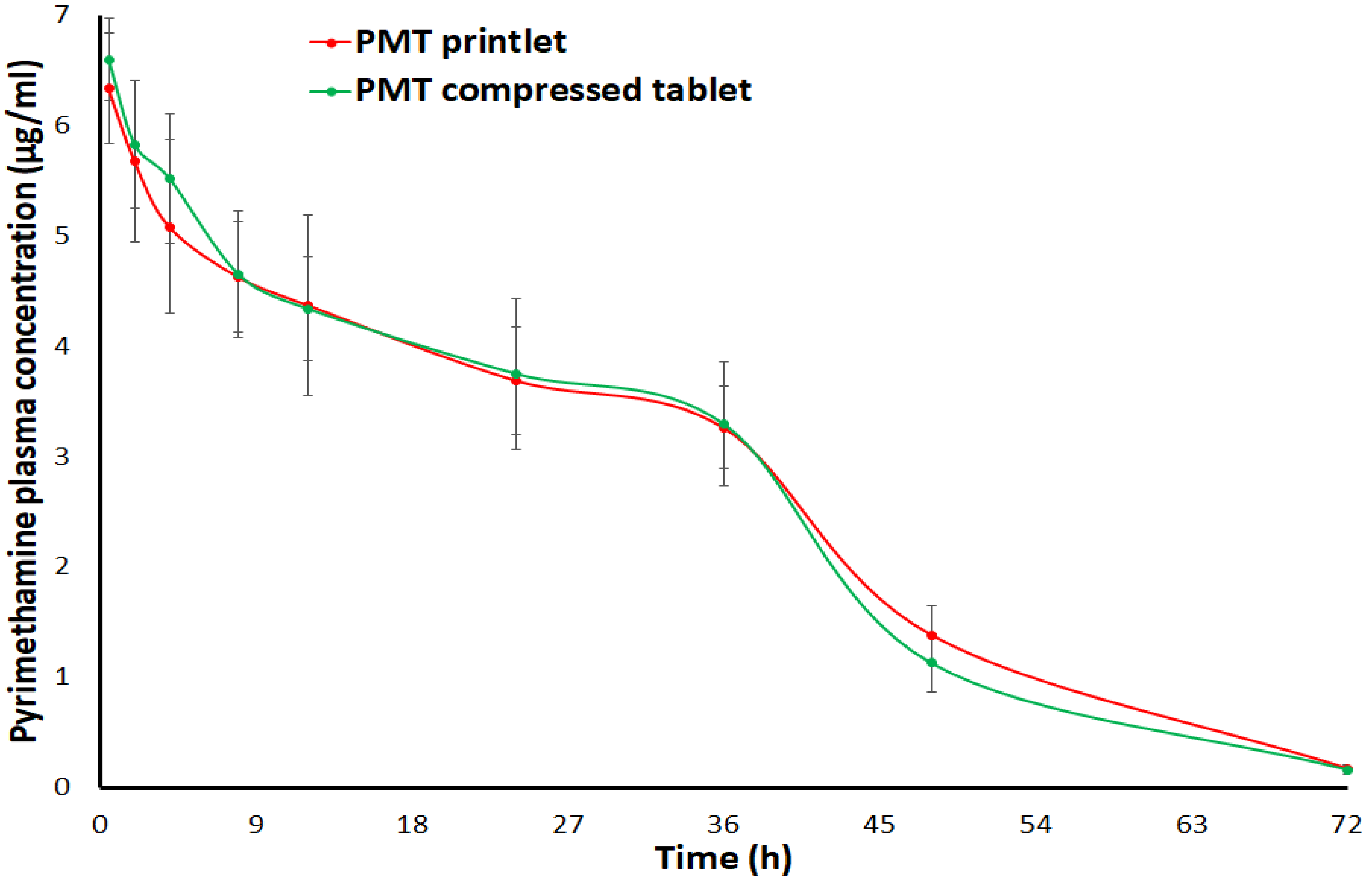
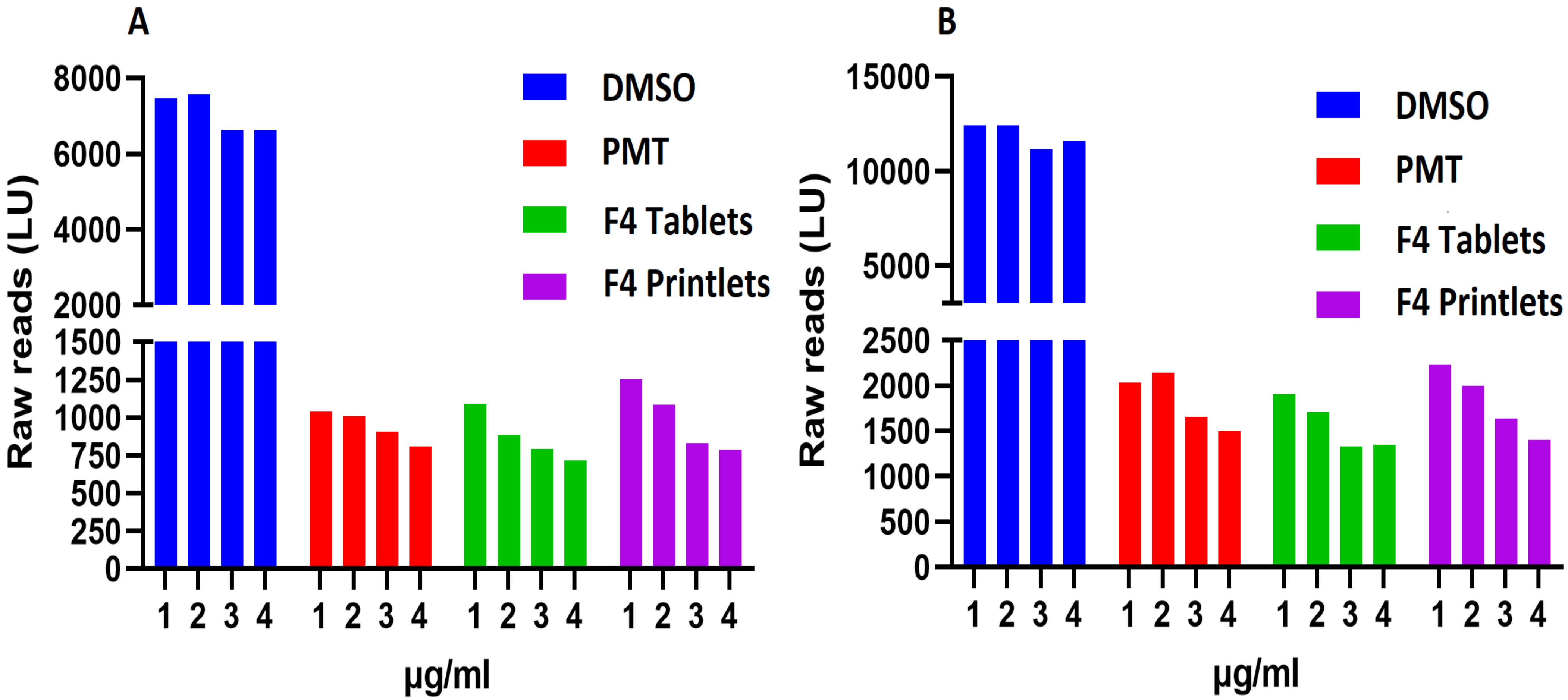


# SELECTIVE LASER SINTERING- Pyrimethamine printlets

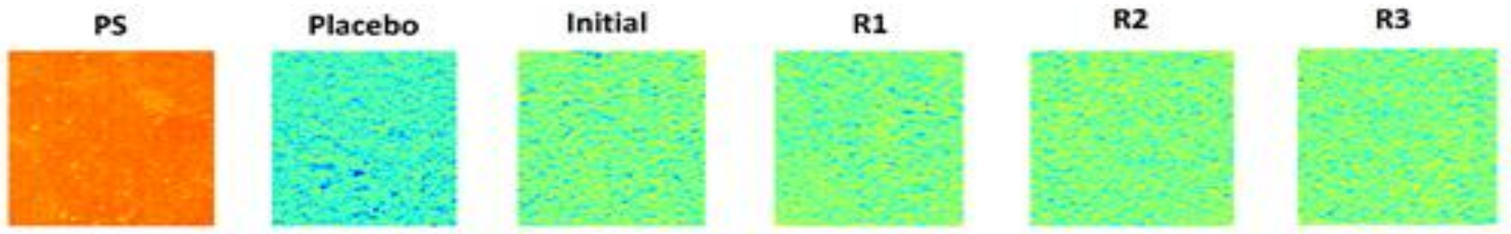


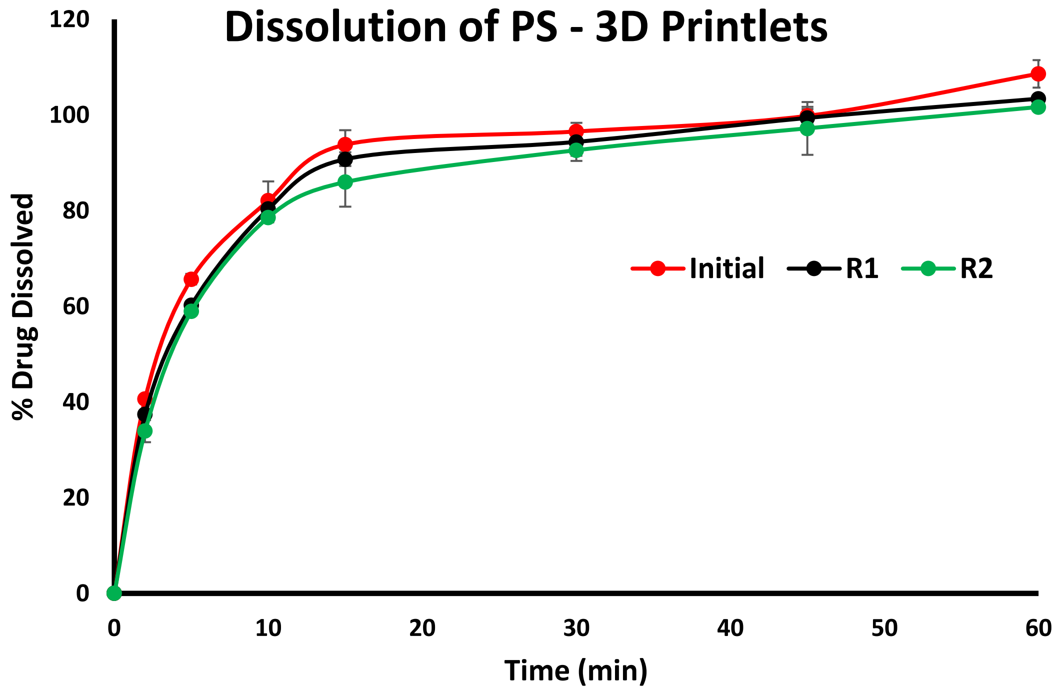

Comparative anti-toxoplasma activity of printlets and compressed tablets against positive (pyrimethamine) and negative (DMSO) control at A) multiplicity of infection 1 and B) multiplicity of infection 2.

# SELECTIVE LASER SINTERING- Recycling of Powder

- One of the major challenge is recycling/reuse of unprinted raw material after the printing process.
- It is not feasible to reuse certain materials such as polymers owing to adverse impact on their quality and purity.
- Additionally, the byproducts of SLS process may adversely impact the chemical quality of powders making them unsuitable for further use.
- Some particles may fuse without getting attached to the part, affecting size distribution of the material causing inconsistencies if reused.
- Recycling can also impact the mechanical properties of materials, thus affecting their usability for further use.
- The impact of recycling on thermal stability of drug and other formulation components, and CQAs need to be evaluated if reused

# SELECTIVE LASER SINTERING- Recycling

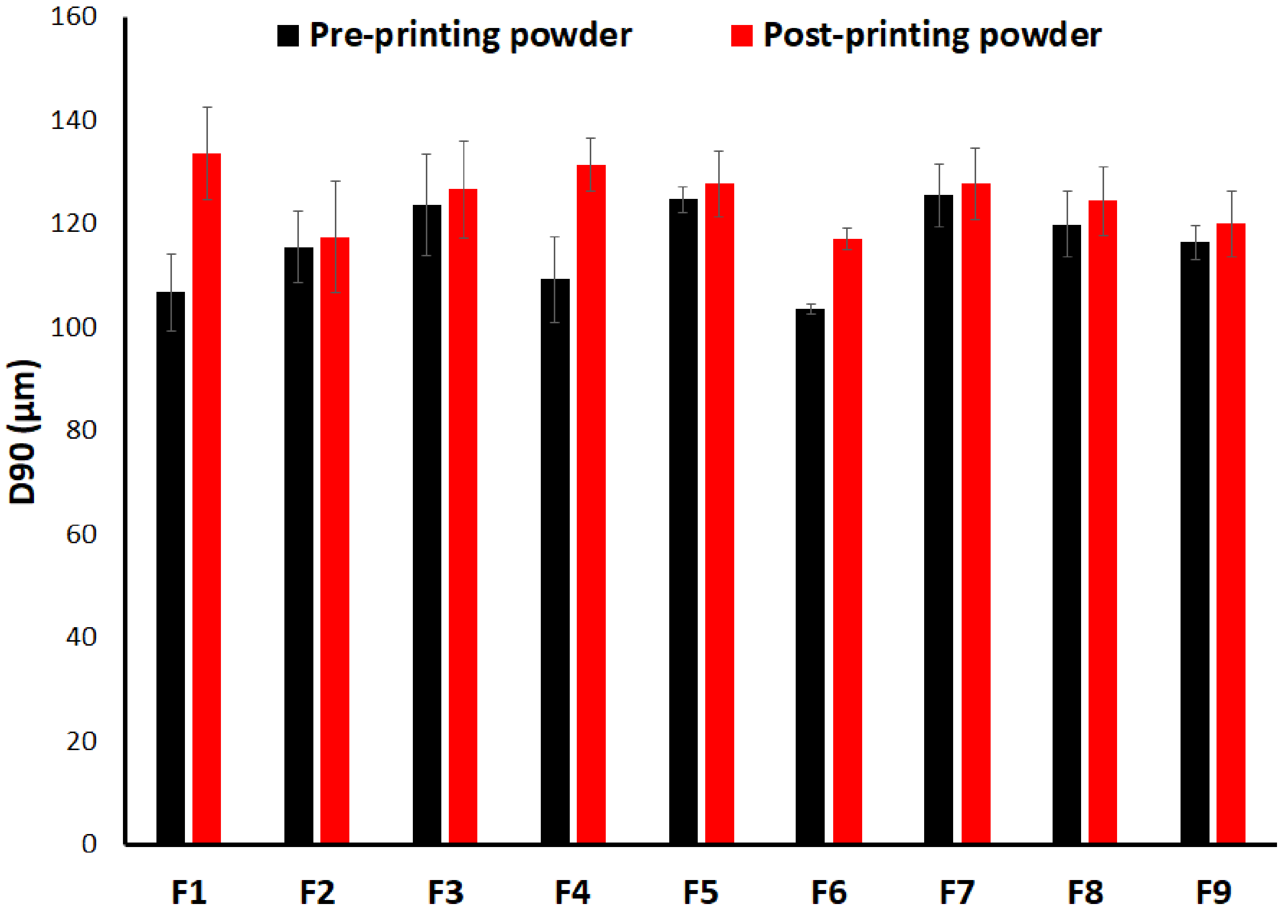


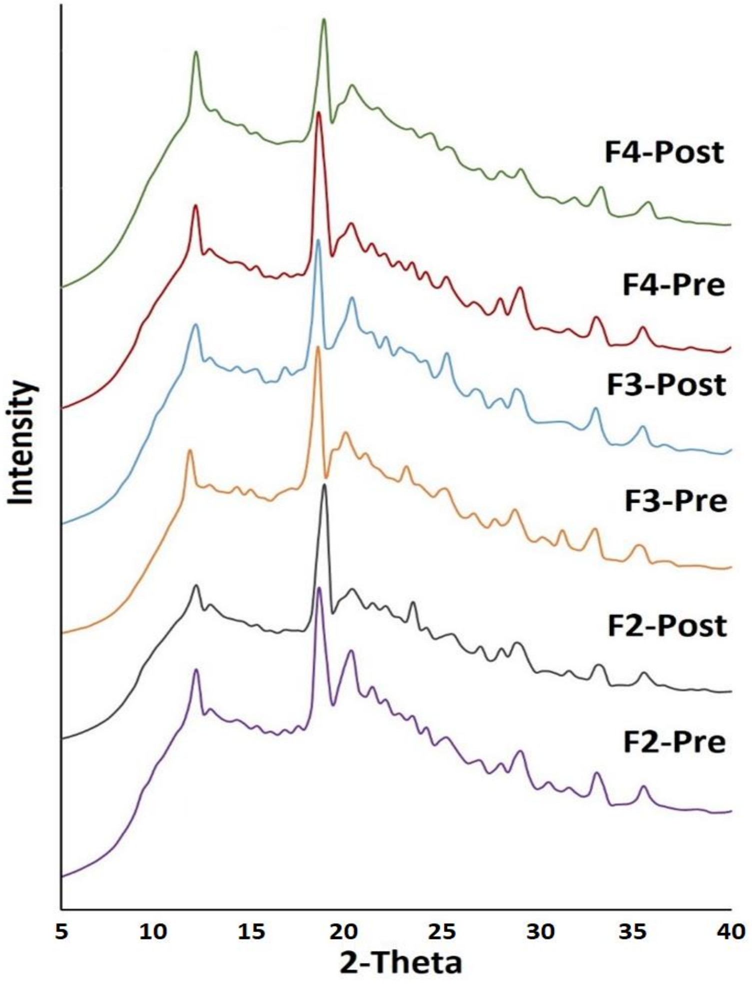




| Assay of powder (%) | | | |
|---|---|---|---|
| Initial | Recycle | | |
| | R1 | R2 | R3 |
| 100.6±0.7 | 100.1±0.6 | 99.8±0. 4 | 99.4±1.1 |

Insignificant change in dissolution and assay (phenytoin sodium) after printing

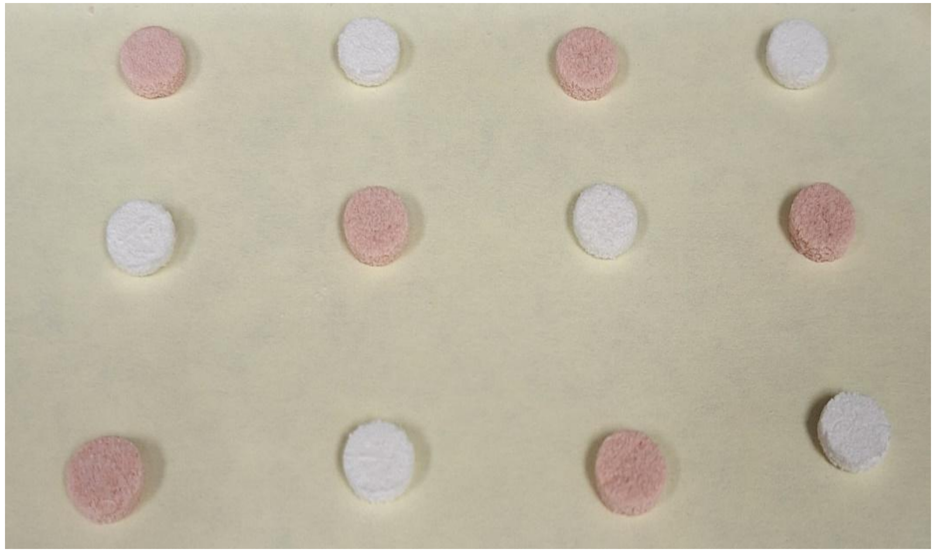
# SELECTIVE LASER SINTERING- Recycling




Insignificant change in particle size distribution and crystallinity of pyrimethamine after printing

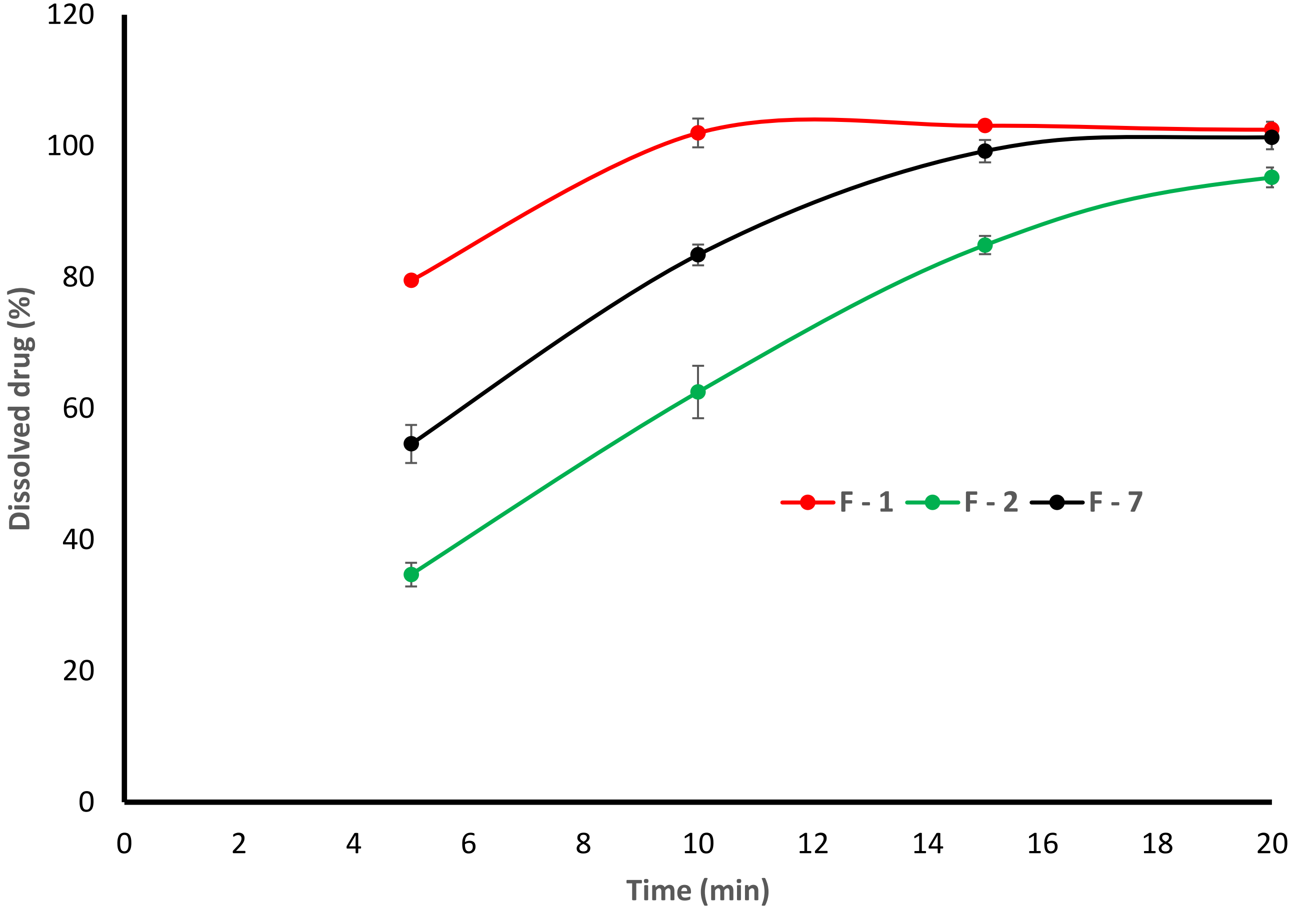
# Binder jetting

# Lamivudine – 3D printing using Binder jet

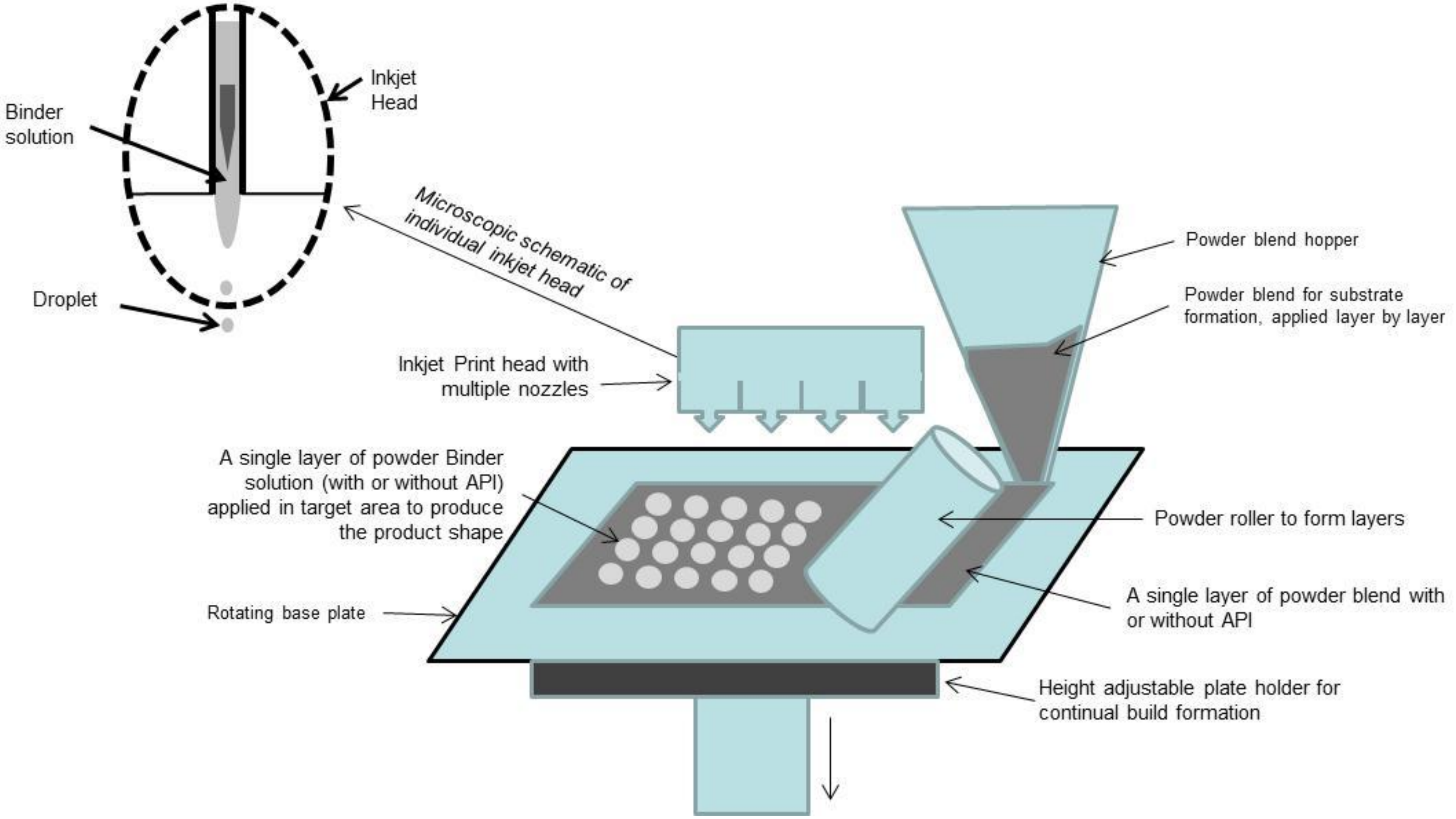
## DOE (Design of Experiment) – Screen Designing

| | Pattern | sprays (nu... | thickness (mm) | Delay time (sec) | Drying temp (degree C) | HPMC (%) |
|---|---|---|---|---|---|---|
| 1 | −−++− | 2 | 0.32 | 10 | 60 | 10 |
| 2 | +−−++ | 4 | 0.32 | 0 | 60 | 30 |
| 3 | −+−+− | 2 | 0.4 | 0 | 60 | 10 |
| 4 | −++−+ | 2 | 0.4 | 10 | 40 | 30 |
| 5 | −−−−+ | 2 | 0.32 | 0 | 40 | 30 |
| 6 | ++−−− | 4 | 0.4 | 0 | 40 | 10 |
| 7 | 00000 | 3 | 0.36 | 5 | 50 | 20 |
| 8 | +++++ | 4 | 0.4 | 10 | 60 | 30 |
| 9 | +−+−− | 4 | 0.32 | 10 | 40 | 10 |



120
100
80
60
40
20
0
Dissolved drug (%)
0
2
4
6
8
10
12
14
16
18
20
Time (min)
F - 1
F - 2
F - 7

# Some Regulatory Considerations



# Defects of 3D Printed Tablets-

- Banding: Ripples on a part’s sides caused by vibration in the x-y plane during printing
- Leaning: Off-axis parts caused by drift in the x-y plane during printing
- Warping: Part distortion caused by thermal expansion or contraction
- Stringing: Wisps of filament caused by filament elongation during an extruder’s off phase
- Collapse:  Loss of porosity caused by sagging layers or excessive mass/energy input
- Residuals: Unbound powder or uncrosslinked monomer caused by incomplete printing

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# A new chapter in pharmaceutical manufacturing: 3D-printed drug products☆,☆☆

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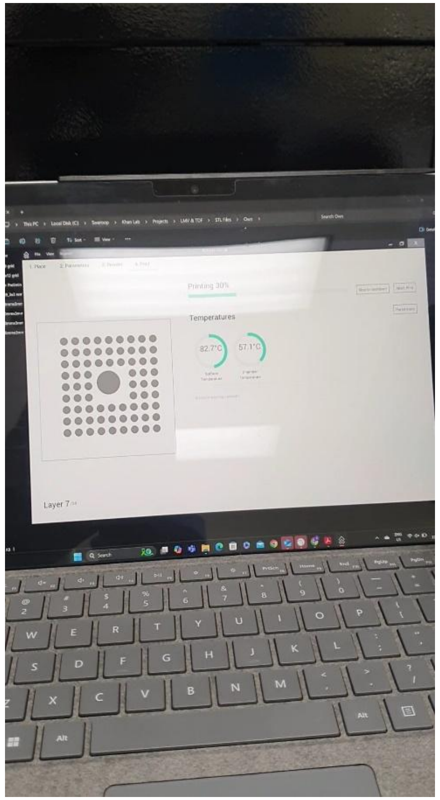
ABSTRACT

FDA recently approved a 3D-printed drug product in August 2015, which is indicative of a new chapter for pharmaceutical manufacturing. This review article summarizes progress with 3D printed drug products and discusses process development for solid oral dosage forms.
3D printing is a layer-by-layer process capable of producing 3D drug products from digital designs. Traditional pharmaceutical processes, such as tablet compression, have been used for decades with established regulatory pathways. These processes are well understood, but antiquated in terms of process capability and manufacturing flexibility. 3D printing, as a platform technology, has competitive advantages for complex products, personalized products, and products made on-demand. These advantages create opportunities for improving the safety, efficacy, and accessibility of medicines.
Although 3D printing differs from traditional manufacturing processes for solid oral dosage forms, risk-based process development is feasible. This review highlights how product and process understanding can facilitate the development of a control strategy for different 3D printing methods.
Overall, the authors believe that the recent approval of a 3D printed drug product will stimulate continual innovation in pharmaceutical manufacturing technology. FDA encourages the development of advanced manufacturing technologies, including 3D-printing, using science- and risk-based approaches.

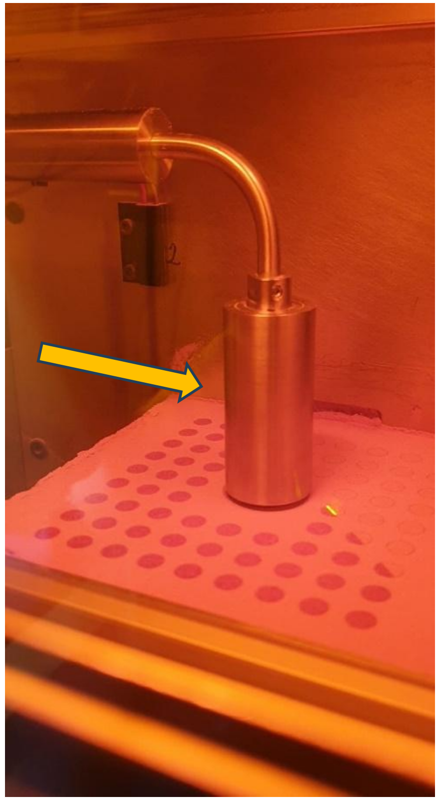
# Lamivudine and tenofovir disoproxil fumarate - Printlets

On-line monitoring of 3D printing process

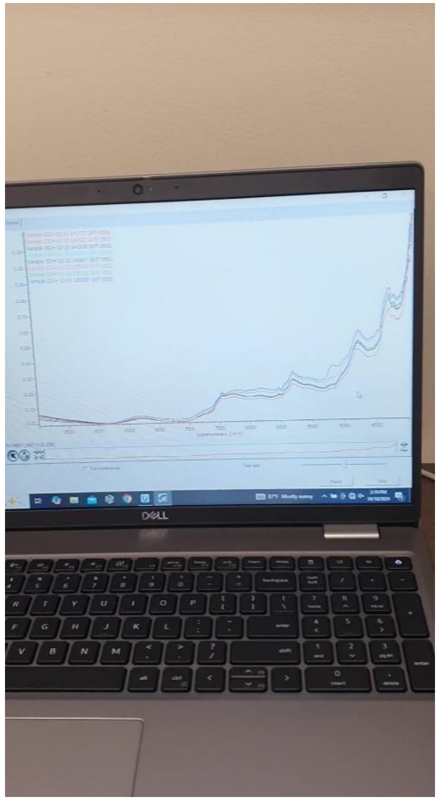


Printing Command on 3D software

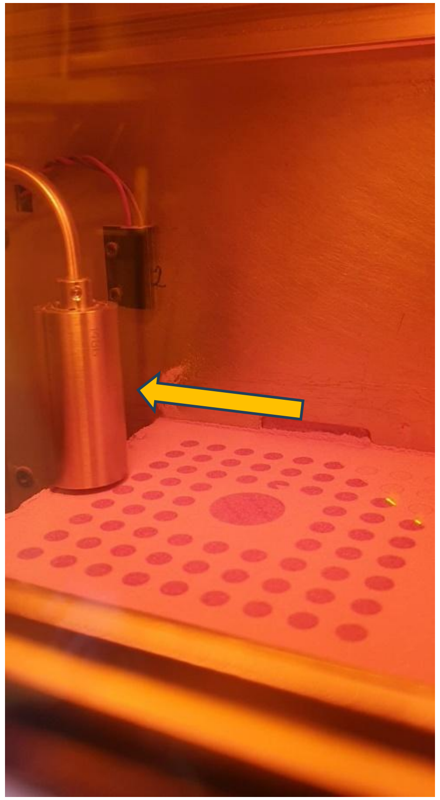
Layer by Layer Printing of the printlets inside the chamber



Real-time NIR probe sent in to collect spectra after every layer



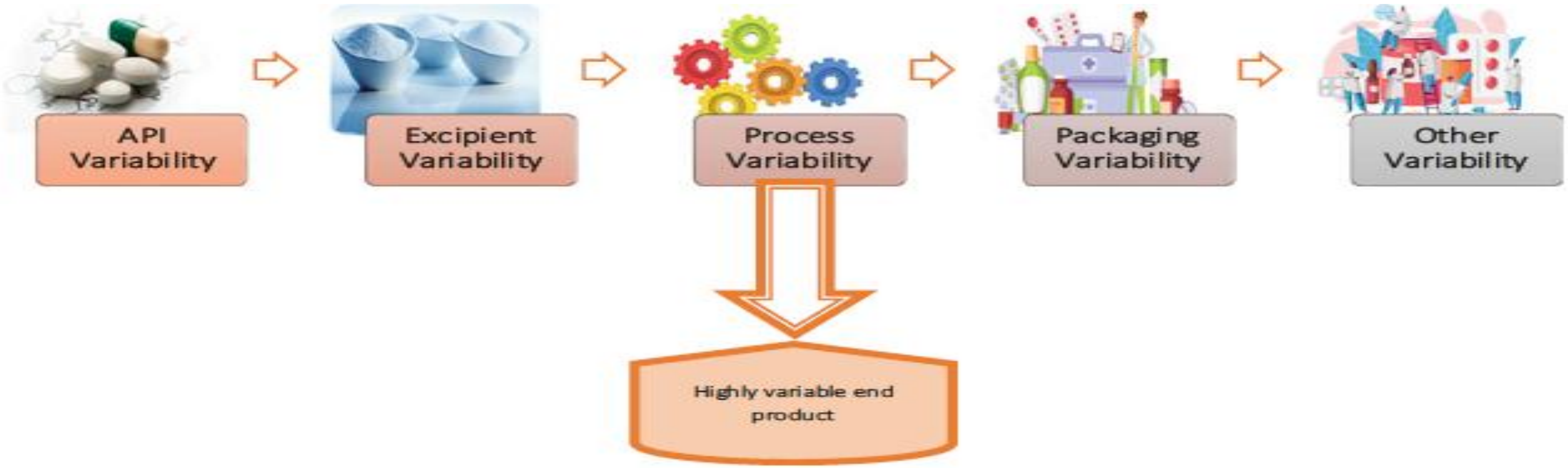
Real-time NIR spectra of the layer getting generated on NIR software



Real-time NIR probe getting retracted

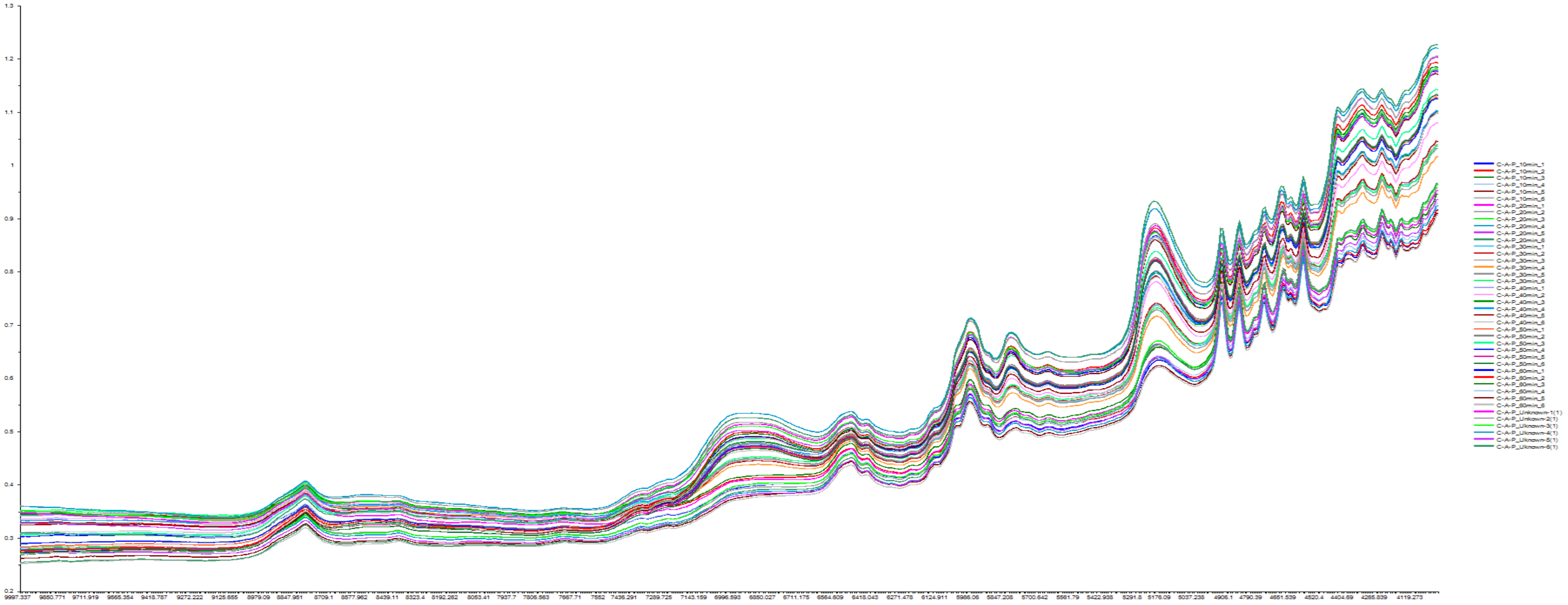
- PAT enables real-time data collection for Quality by Design (QbD), supporting process understanding, scale-up, and data-driven decisions—key to Good Manufacturing Practice.

- PAT enables the real-time measurement and control of critical quality attributes to ensure final product quality.

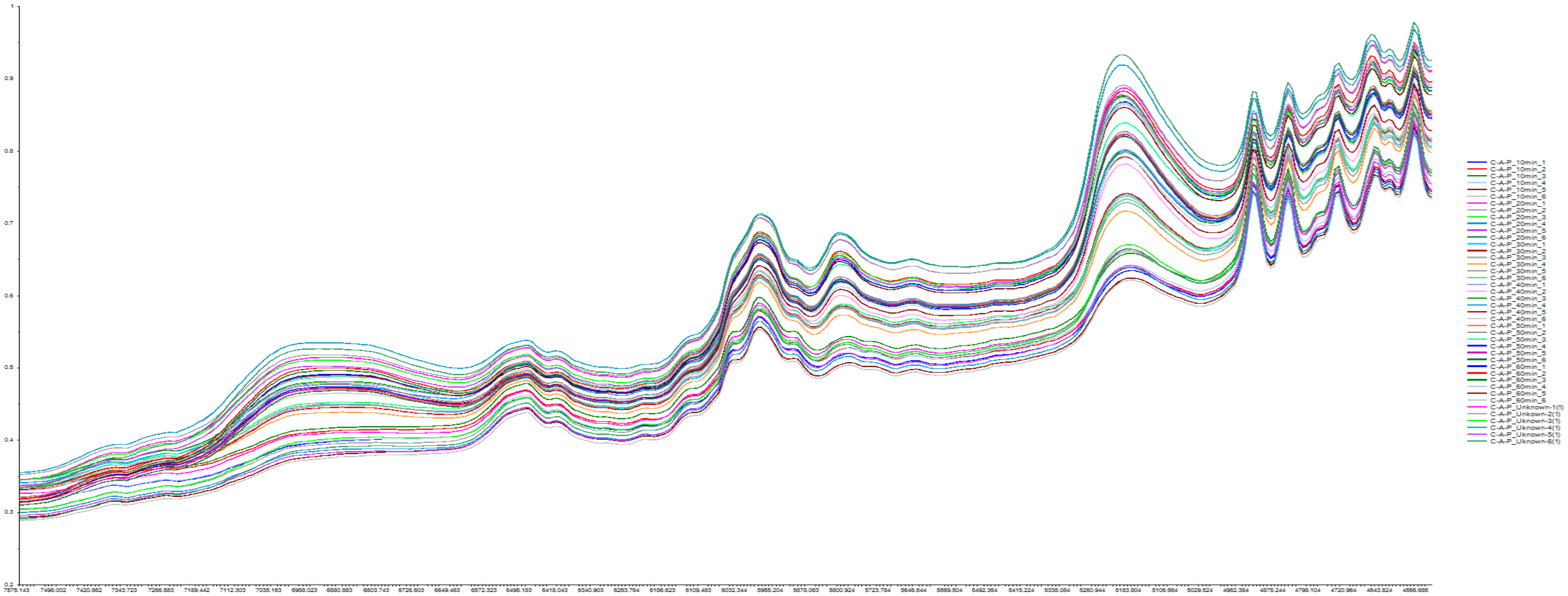



Sources that contribute to quality variation among pharmaceutical products

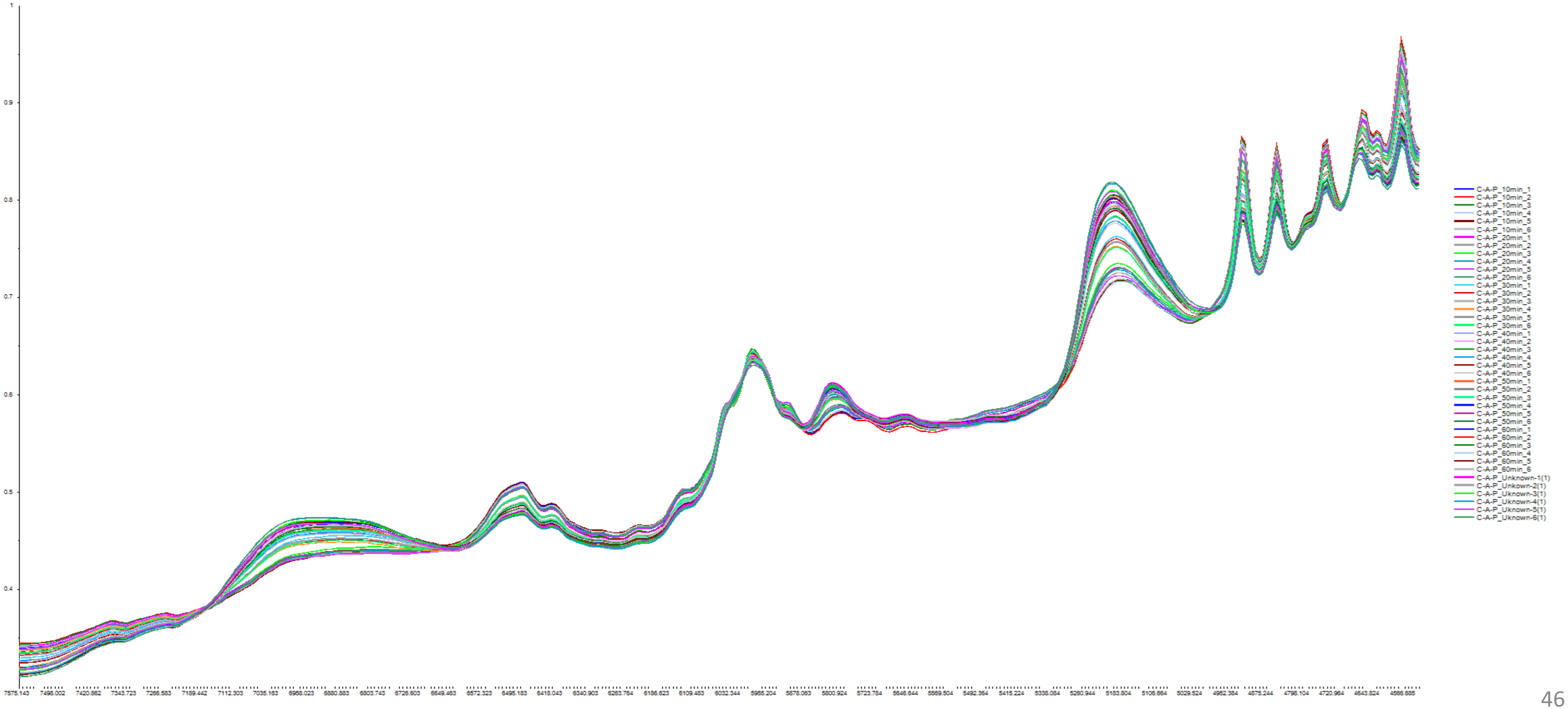
# Raw Data (C-A-P)


1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
9997.337
9850.771
9711.919
9565.354
9418.787
9272.222
9125.655
8979.09
8847.951
8709.1
8577.962
8439.11
8323.4
8192.262
8053.41
7937.7
7806.563
7667.71
7552
7436.291
7289.725
7143.159
6996.593
6850.027
6711.175
6564.609
6418.043
6271.478
6124.911
5986.06
5847.208
5700.642
5561.79
5422.938
5291.8
5176.09
5037.238
4906.1
4790.39
4651.539
4520.4
4404.69
4265.839
4119.273
C-A-P_10min_1
C-A-P_10min_2
C-A-P_10min_3
C-A-P_10min_4
C-A-P_10min_5
C-A-P_10min_6
C-A-P_20min_1
C-A-P_20min_2
C-A-P_20min_3
C-A-P_20min_4
C-A-P_20min_5
C-A-P_20min_6
C-A-P_30min_1
C-A-P_30min_2
C-A-P_30min_3
C-A-P_30min_4
C-A-P_30min_5
C-A-P_30min_6
C-A-P_40min_1
C-A-P_40min_2
C-A-P_40min_3
C-A-P_40min_4
C-A-P_40min_5
C-A-P_40min_6
C-A-P_50min_1
C-A-P_50min_2
C-A-P_50min_3
C-A-P_50min_4
C-A-P_50min_5
C-A-P_50min_6
C-A-P_60min_1
C-A-P_60min_2
C-A-P_60min_3
C-A-P_60min_4
C-A-P_60min_5
C-A-P_60min_6
C-A-P_Unknown-1(1)
C-A-P_Unkown-2(1)
C-A-P_Uknown-3(1)
C-A-P_Uknown-4(1)
C-A-P_Uknown-5(1)
C-A-P_Uknown-6(1)

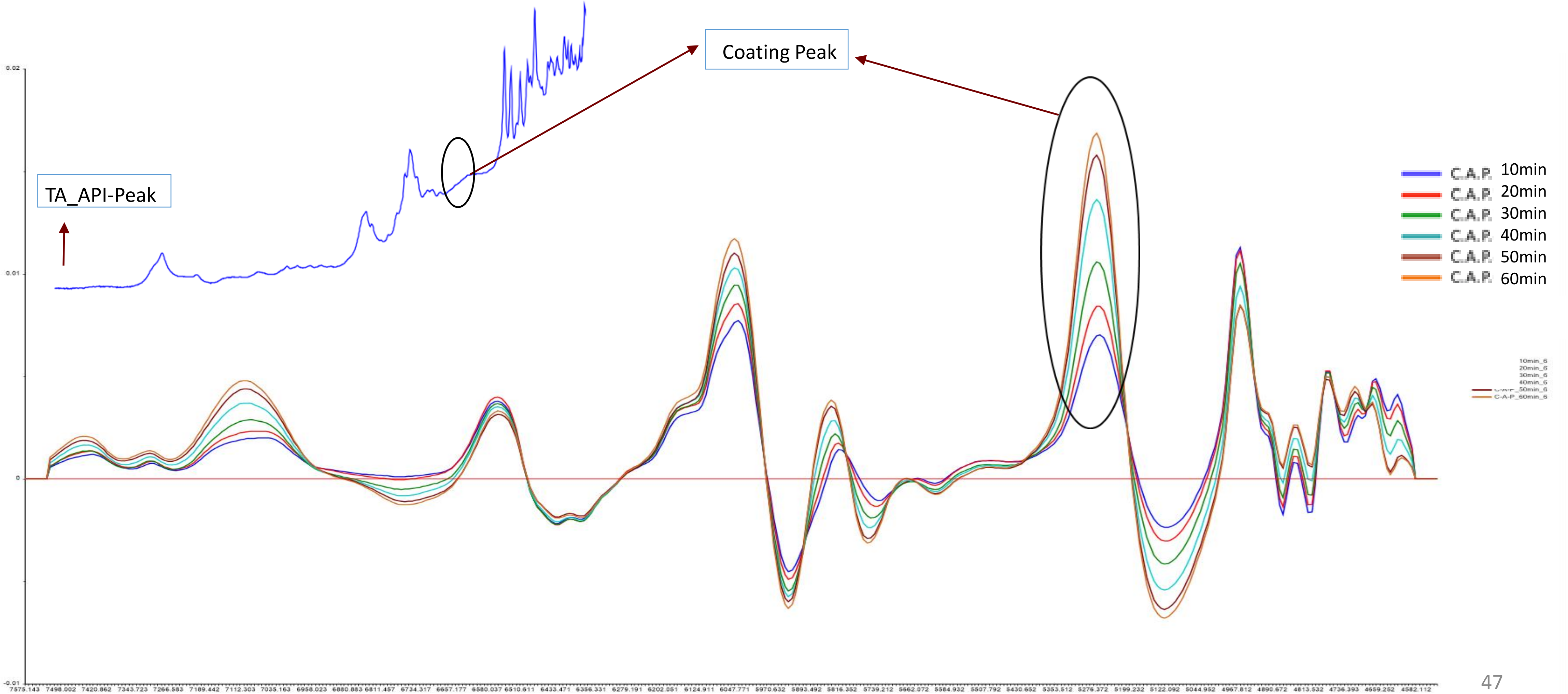
## Truncated Data (C-A-P)



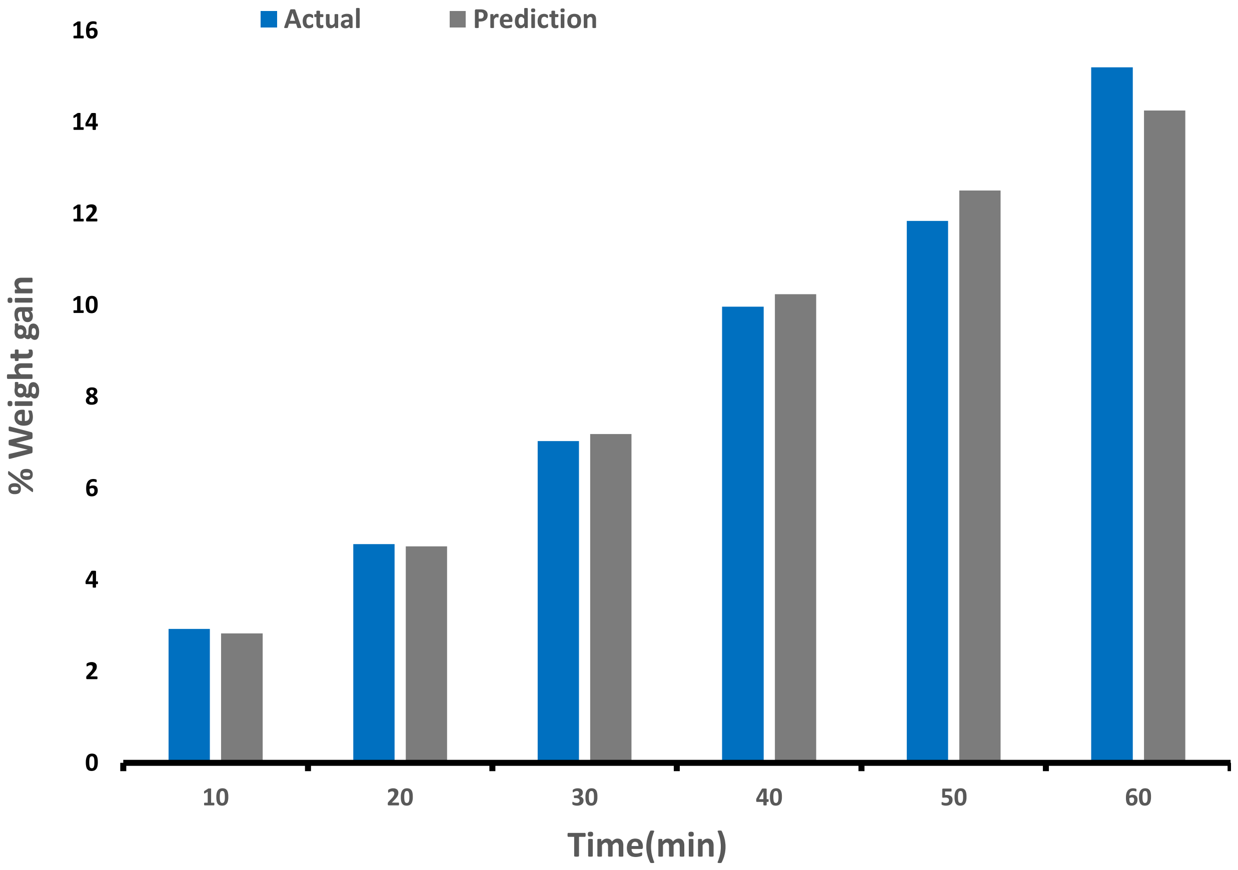
# Multiplicate scattering correction(MSC) Data (C-A-P)



# Savitzky-Golay-1st Derivative (C-A-P)



# Comparison of Actual vs. Predicted % Weight Gain Over Time with Deviation Analysis




| TIME | Actual | Prediction | Deviation |
|---|---|---|---|
| 10 | 2.93 | 2.82 | 0.92 |
| 20 | 4.78 | 4.73 | 0.79 |
| 30 | 7.03 | 7.18 | 0.85 |
| 40 | 9.97 | 10.24 | 0.55 |
| 50 | 11.84 | 12.50 | 0.48 |
| 60 | 15.2 | 14.25 | 0.47 |

# Conclusions

- 3D printing may provide a paradigm shift for certain low volume products
- A case need to be made for marketability and nomenclature
- Possibility of personalized on-demand products
- Enhanced stability of certain products
- Risk based production is feasible
- Technological innovations needed for enhanced yield and control of recycling
- Potential for IR, ER, DR, and other combination products
- Bioprinting is revolutionizing the areas of organ development and transplant in addition to diagnostics and disease modeling.

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