# A 3D-Printed Polymer–Lipid-Hybrid Tablet towards the Development of Bespoke SMEDDS Formulations

Bryce W. Barber, Camille Dumont, Philippe Caisse, George P. Simon and Ben J. Boyd

*MDPI – Pharmaceutics, 2021*

MONASH University
Institute of Pharmaceutical Sciences

GATTEFOSSÉ

# Unmet needs for bespoke oral dosage forms

"One size fits all"
Generic oral dosage forms

Polypharmacy
Poor adherence

Δ Age
Δ Disease state
Δ Genetic factors

↑↑↑Adverse Drug Reactions

2019, Patient Harm - 40$ USD Billion

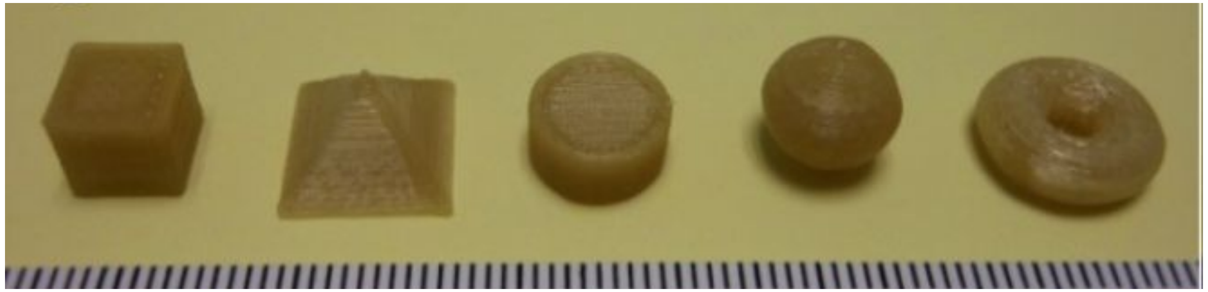
# Unmet needs for bespoke oral dosage forms

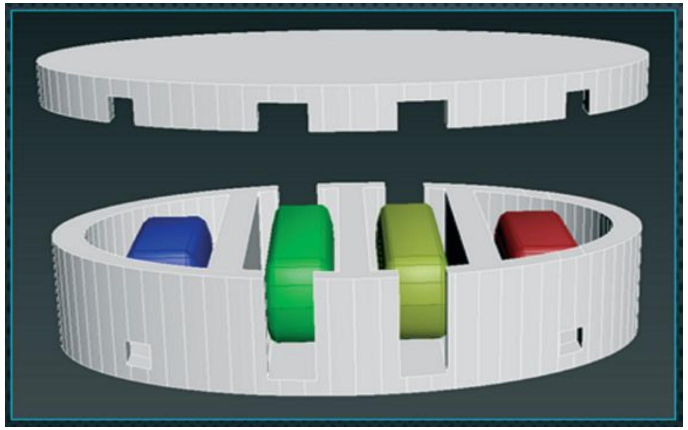
Solution:
3D Printed Oral Dosage Forms

→

↓ Adverse Drug Reactions

# Features of 3D printed oral dosage forms





{Tabriz, 2021; Robles-Martinez, 2019; Pereira, 2020}

Enabling bespoke design:

Tuneable Dose and Pharmacokinetics

Research dominated by:

Polymer Formulations

Hydrophilic Drugs

# 3D printed solid lipid formulations

Advantages of lipid based systems

- Increased bioavailability of poorly water soluble drugs
- Circumvent heat related degradation of drugs

## Novel 3D printed tablet to evaluate:

- Lack of understanding for SA:V
- Multi drug release from multiple types of lipid formulations

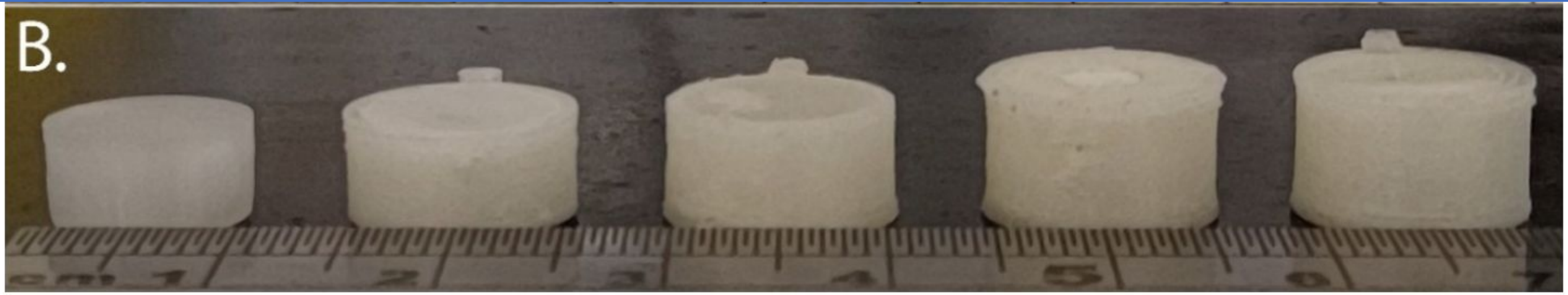
→ Improved understanding of personalized solid lipid-based formulations

## Generation of partially 3DP polymer lipid hybrid tablets

# Single compartment tablets

Non-dissolvable
PLA filament

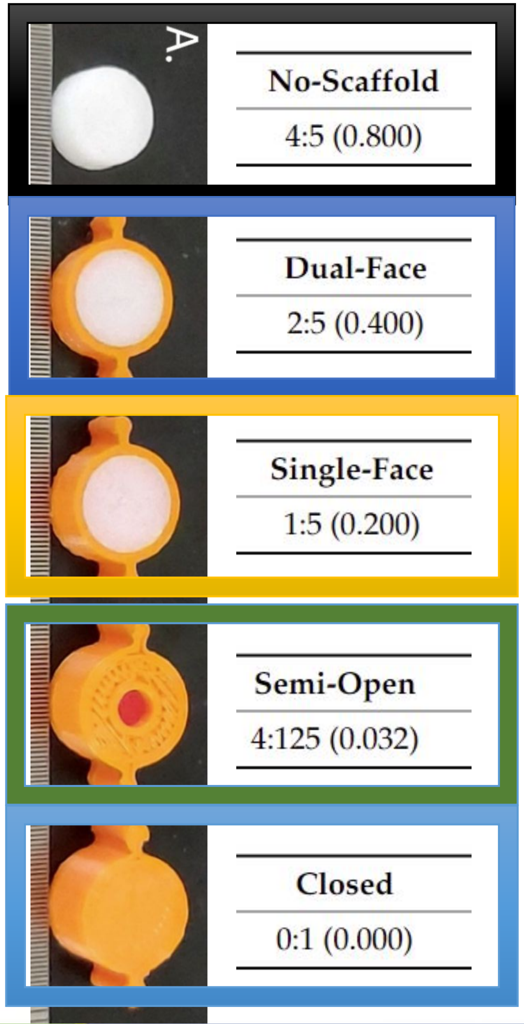

Dissolvable
PVOH filament

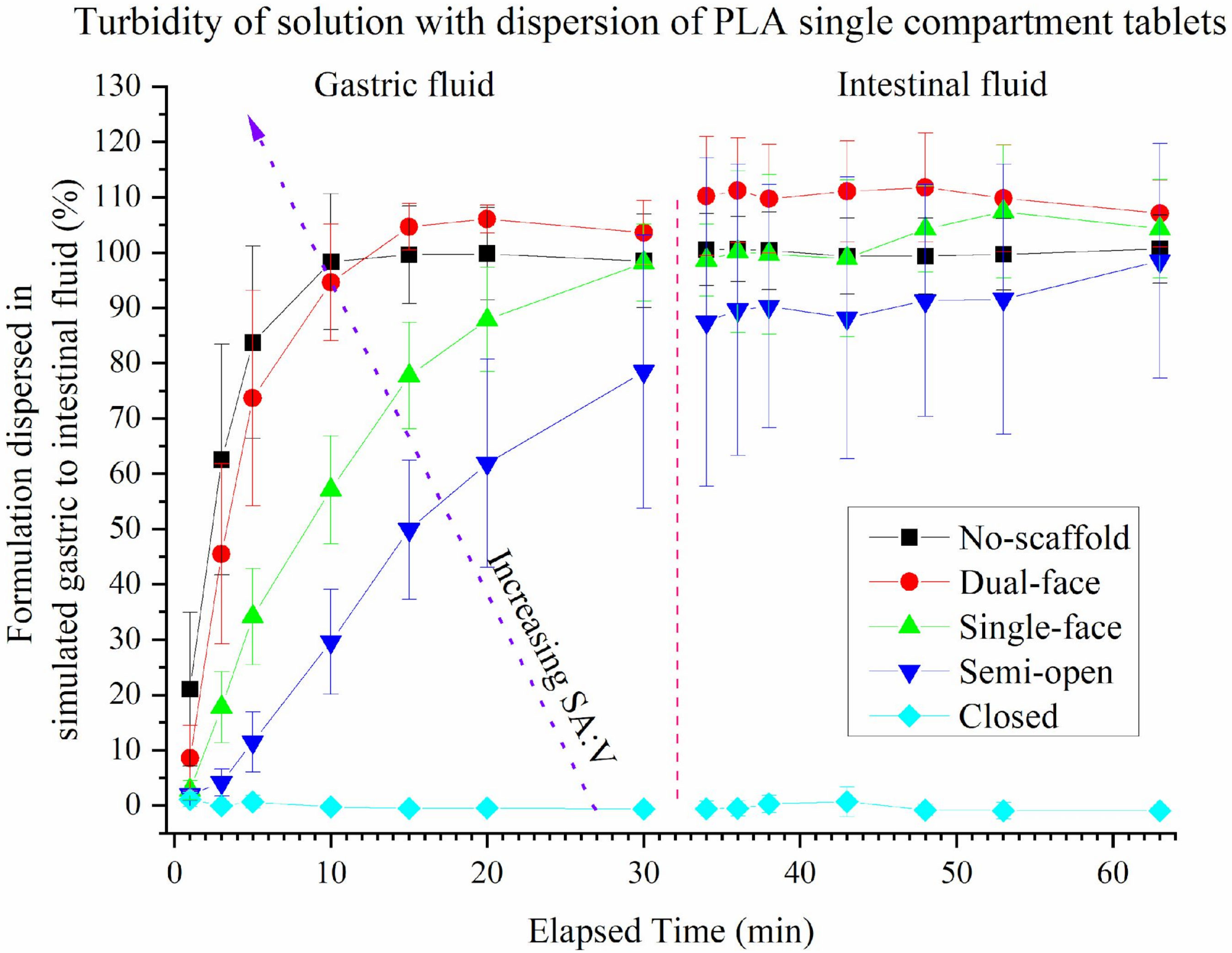



| Tablet Type | No-Scaffold | Dual-Face | Single-Face | Semi-Open | Closed |
|---|---|---|---|---|---|
| SA:V ratio ($mm^2 \times \mu L^{-1}$) | 4:5 (0.800) | 2:5 (0.400) | 1:5 (0.200) | 4:125 (0.032) | 0:1 (0.000) |

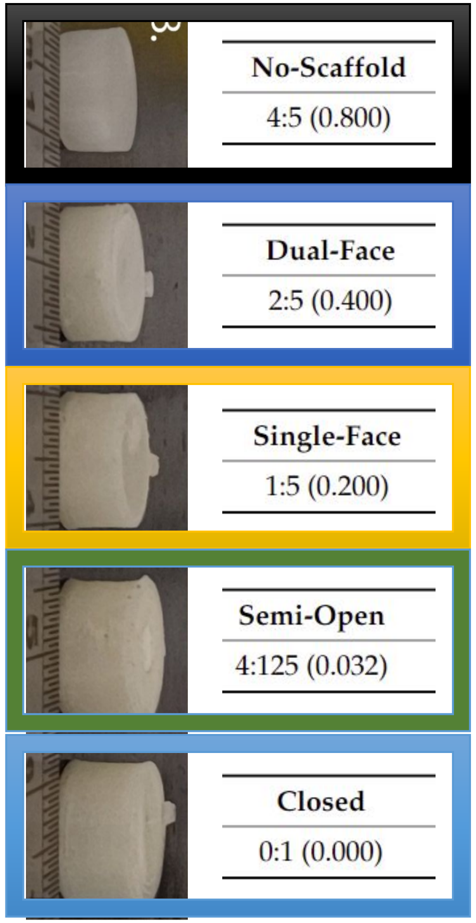
| Single Compartment Systems | |
|---|---|
| SMEDDS A | Component (% $w/w$) |
| Drug | FEN |
| Drug content | 7.0 |
| Gelucire® 44/14 | 46.5 |
| Gelucire® 48/16 | 23.3 |
| Kolliphor P 188 | 23.2 |

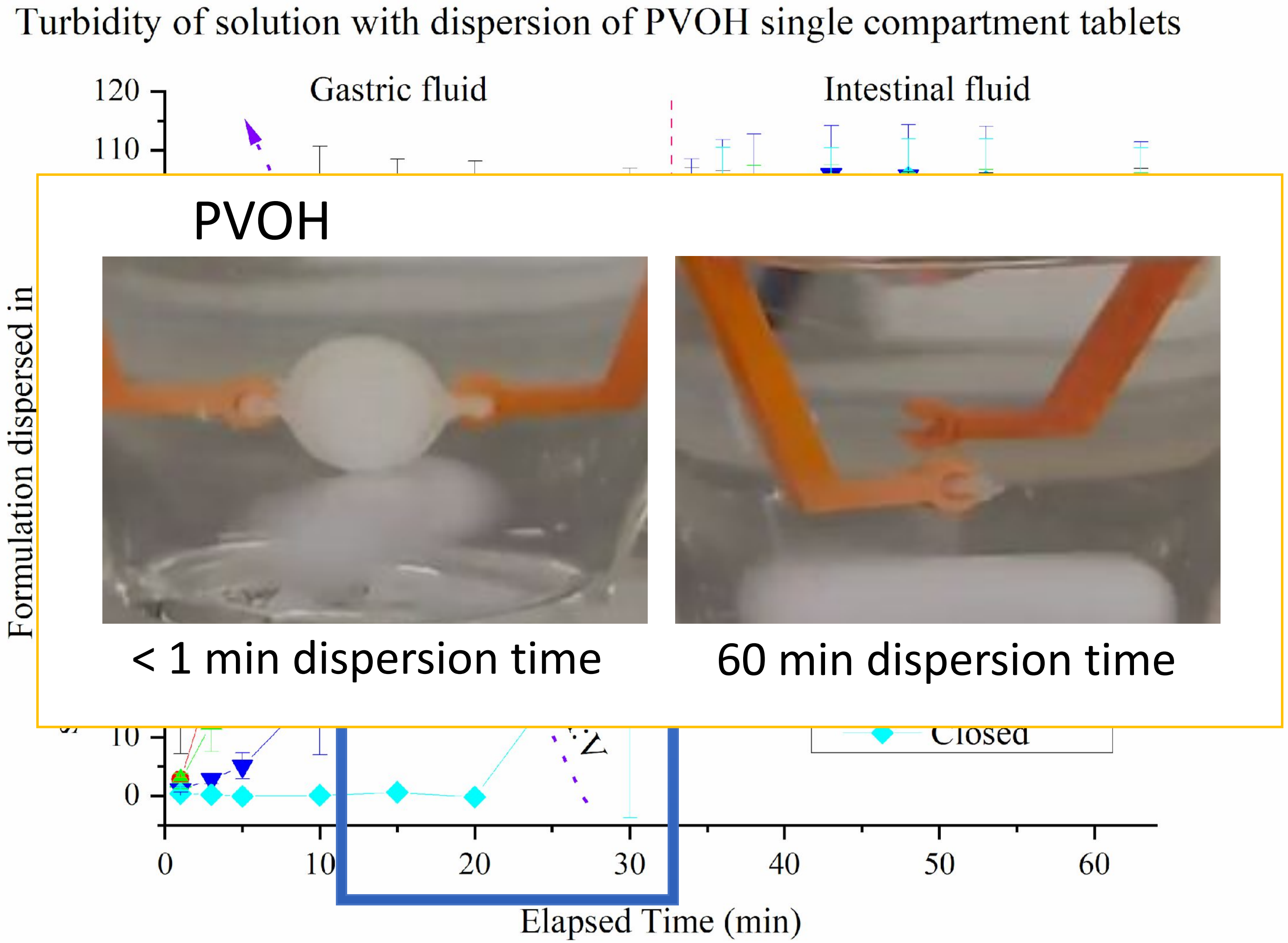
# Results: Blank lipid dispersion from non-dissolvable PLA scaffolds



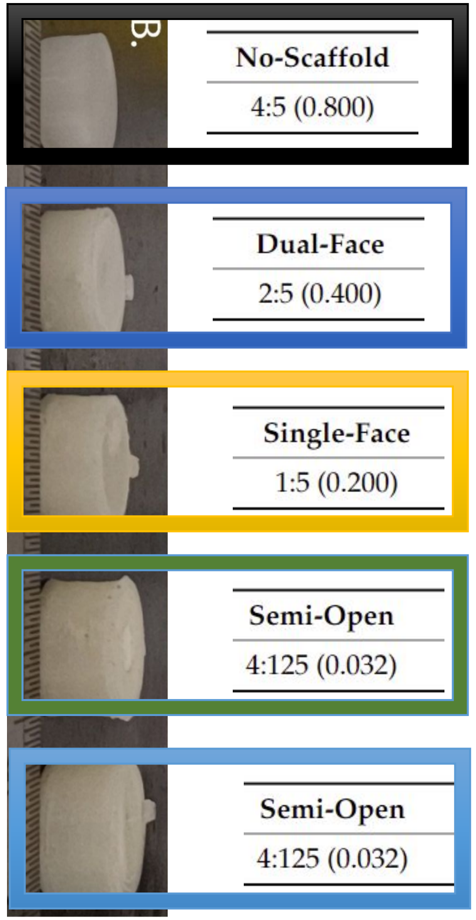



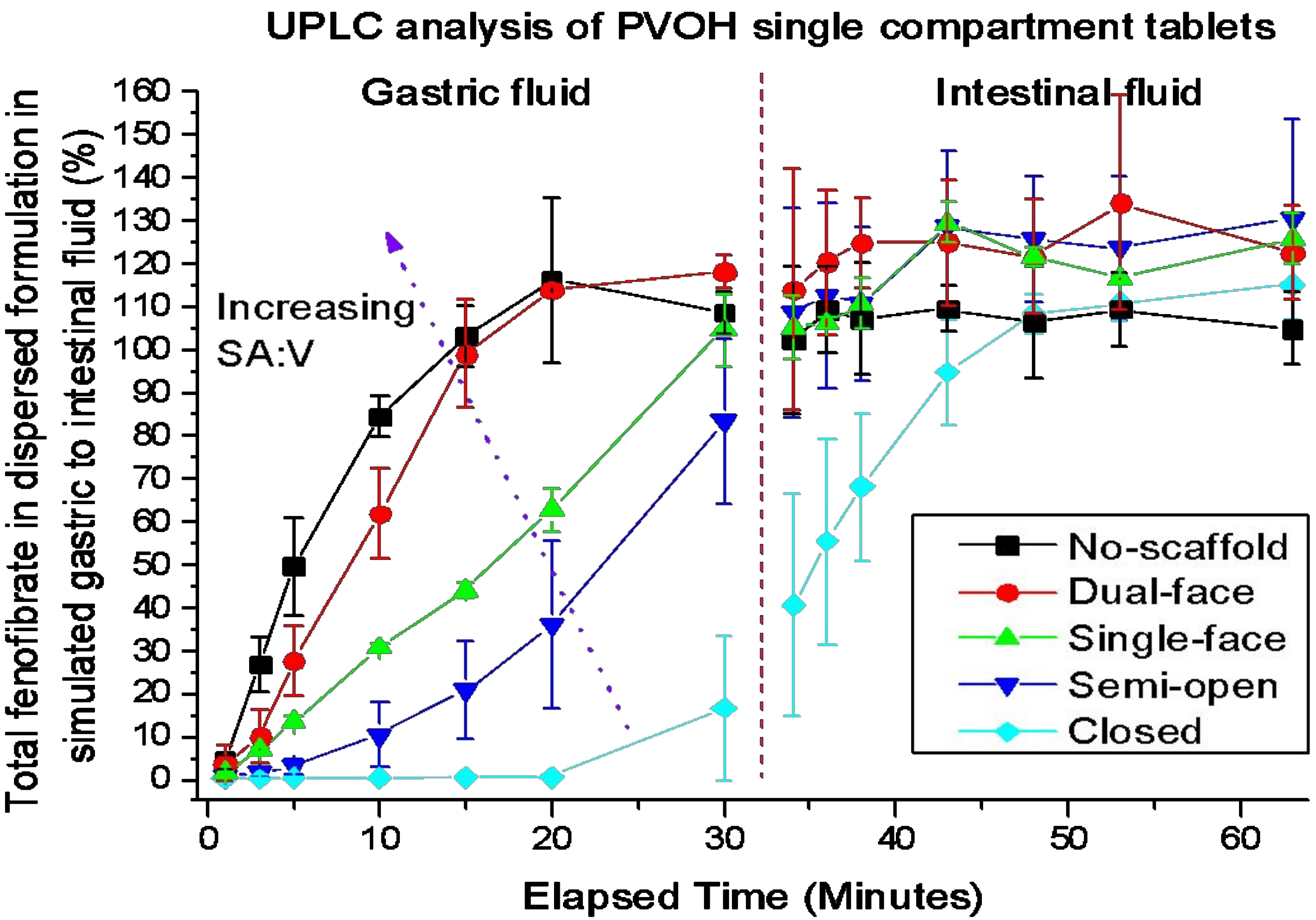
# Results: Blank lipid dispersion from dissolvable PVOH scaffolds



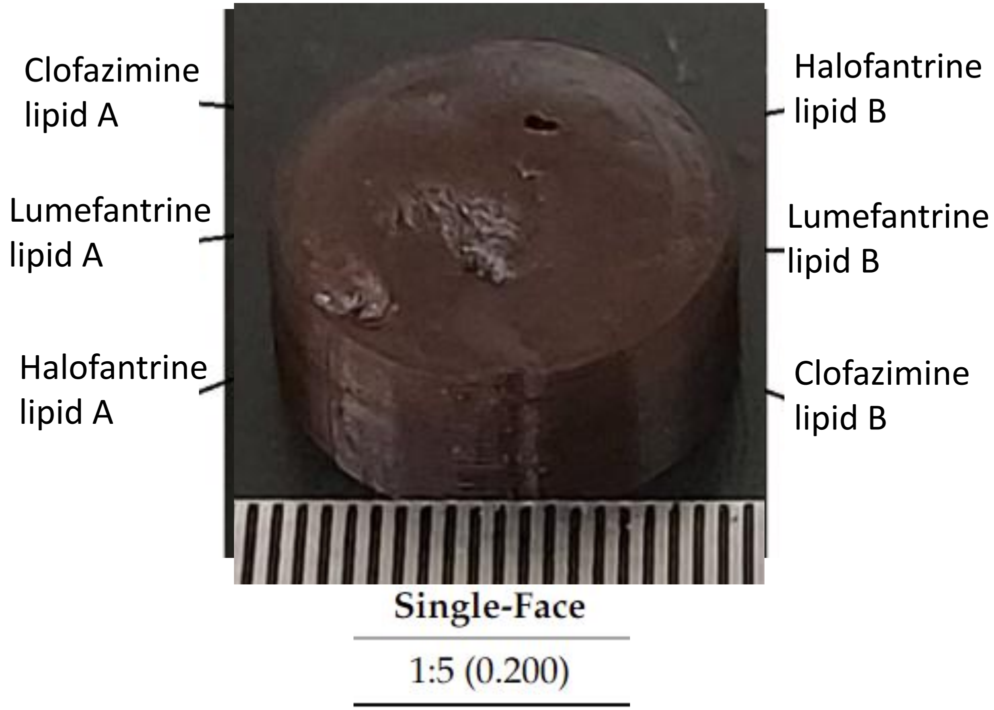



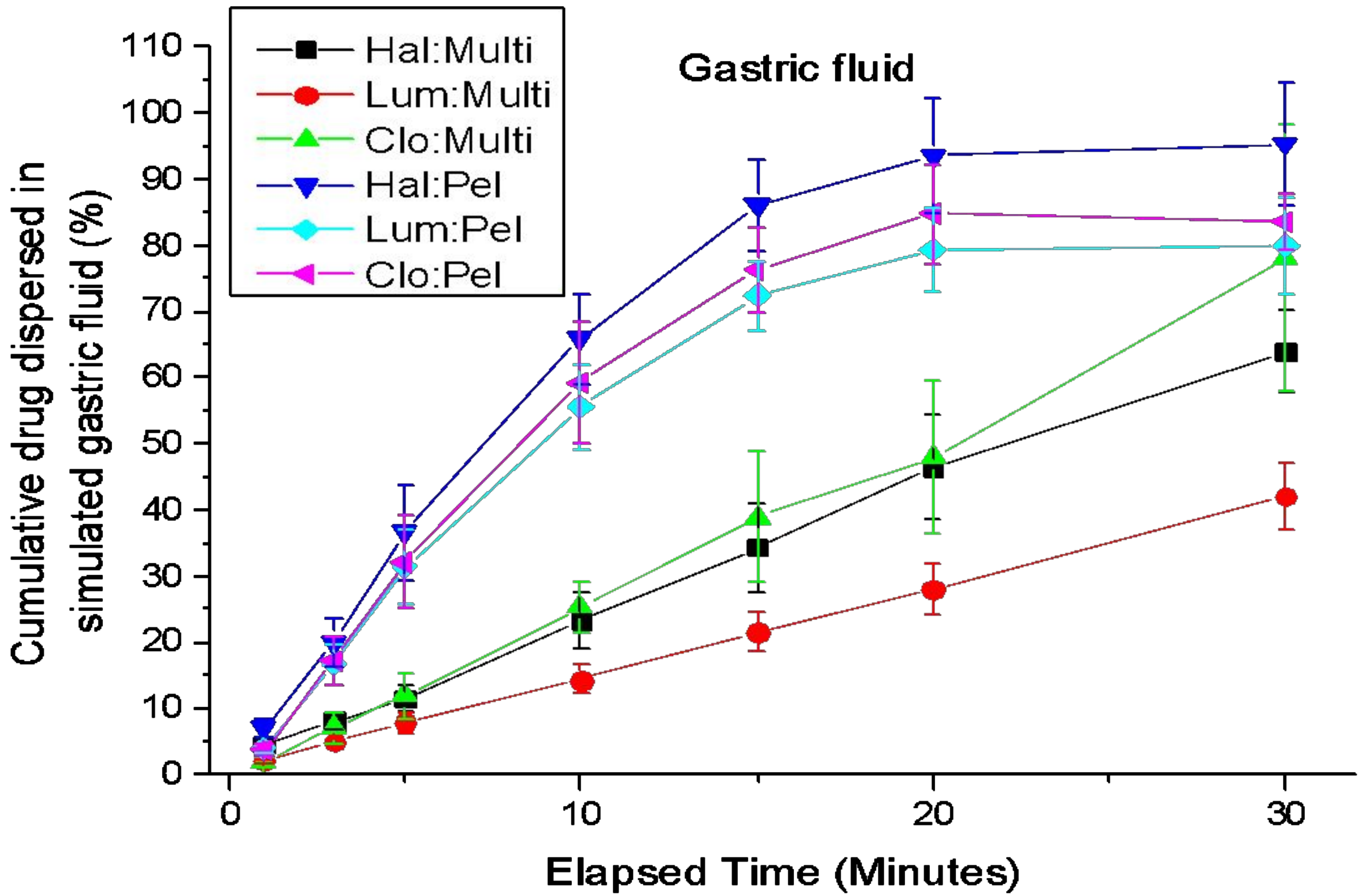
# Results: Fenofibrate release from lipid with dissolvable scaffolds



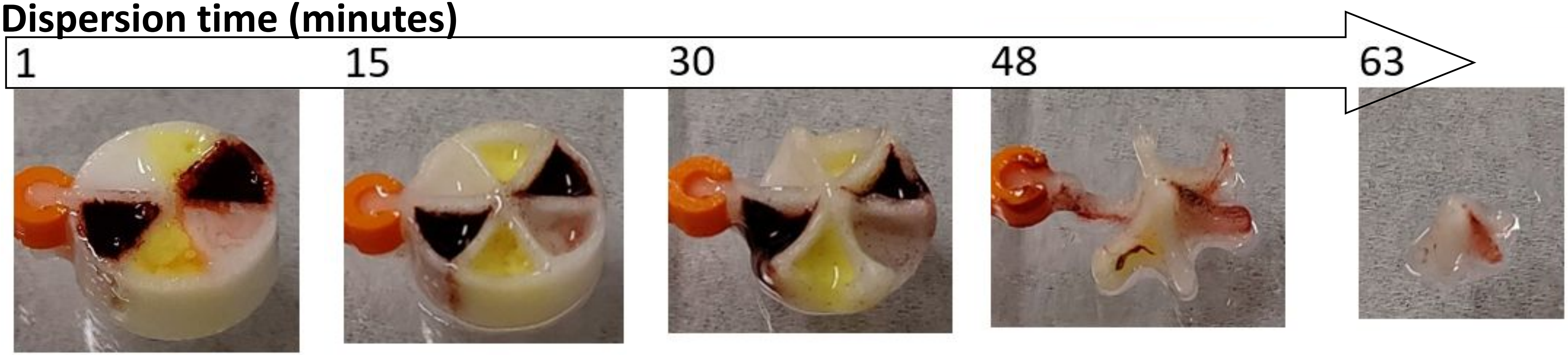
# Results: multi-drug release from multi-compartment tablets



# Multicompartment tablet - scaffold erosion

**Dispersion time (minutes)**




- Erosion behaviour ~> linear release
- Multicompartment design enables SA:V controlled complex release kinetics
  - Tuneable, zero-order, asynchronous drug release

# Findings and potential benefits

3DP Scaffold driven dispersion rate of solid lipid-based formulations.

3DP biodegradable PLH tablet, using poly-vinyl alcohol and lipid formulation (SMEDDS), may be modified to deliver bespoke and combined therapies in a single multi-compartment tablet.

Potential to circumvent challenges with adherence and polypharmacy.

# Future opportunities for 3DP lipid formulations

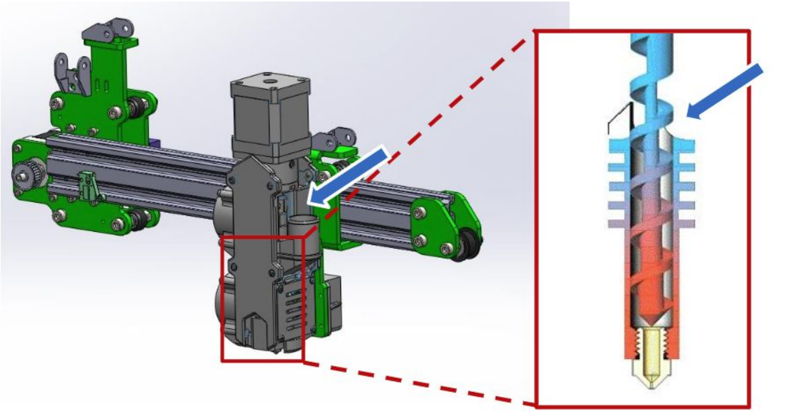
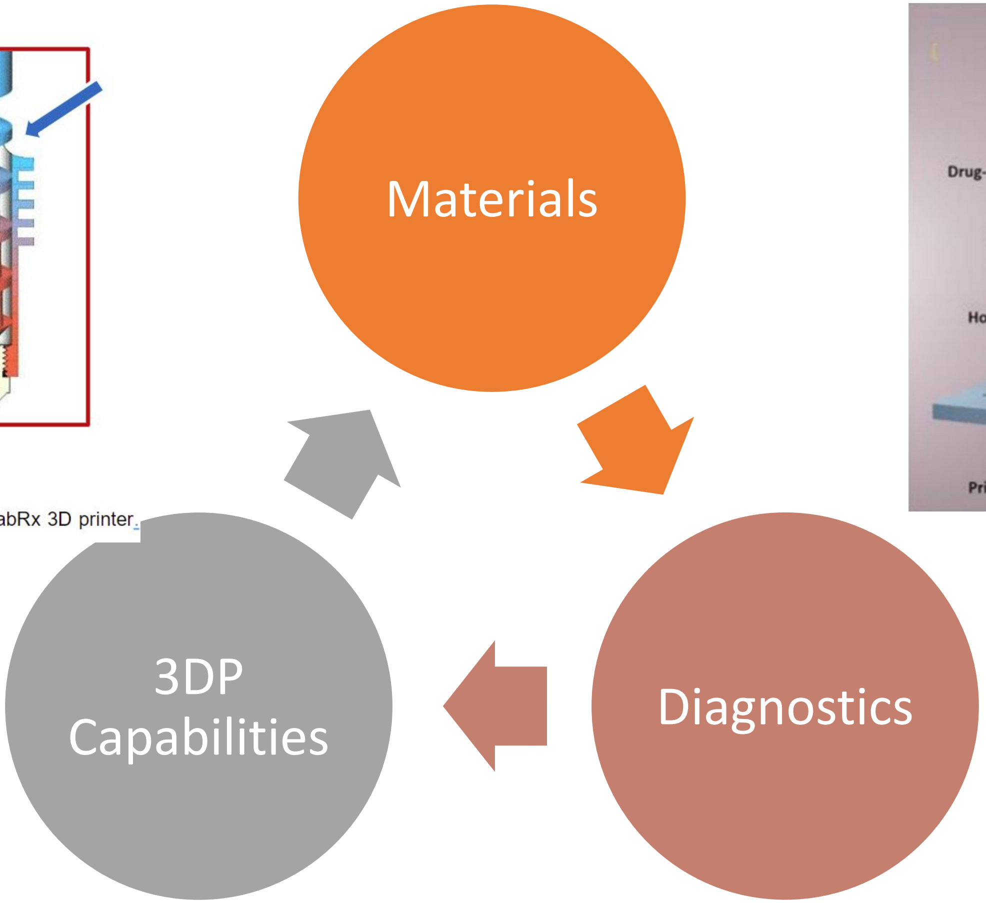
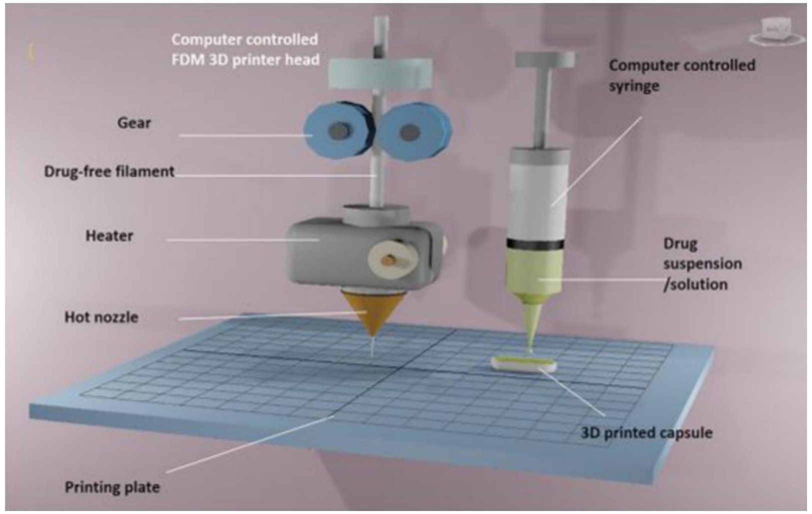


Figure 1. Design of the nozzle of the direct single-screw powder extruder FabRx 3D printer.
{Goyanes, 2019}




Schematic of dual headed 3DP printing a liquid capsule {Vithani, 2019}

# Thankyou for listening!

Contact me..

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# A 3D-Printed Polymer–Lipid-Hybrid Tablet towards the Development of Bespoke SMEDDS Formulations

MDPI
pharmaceutics

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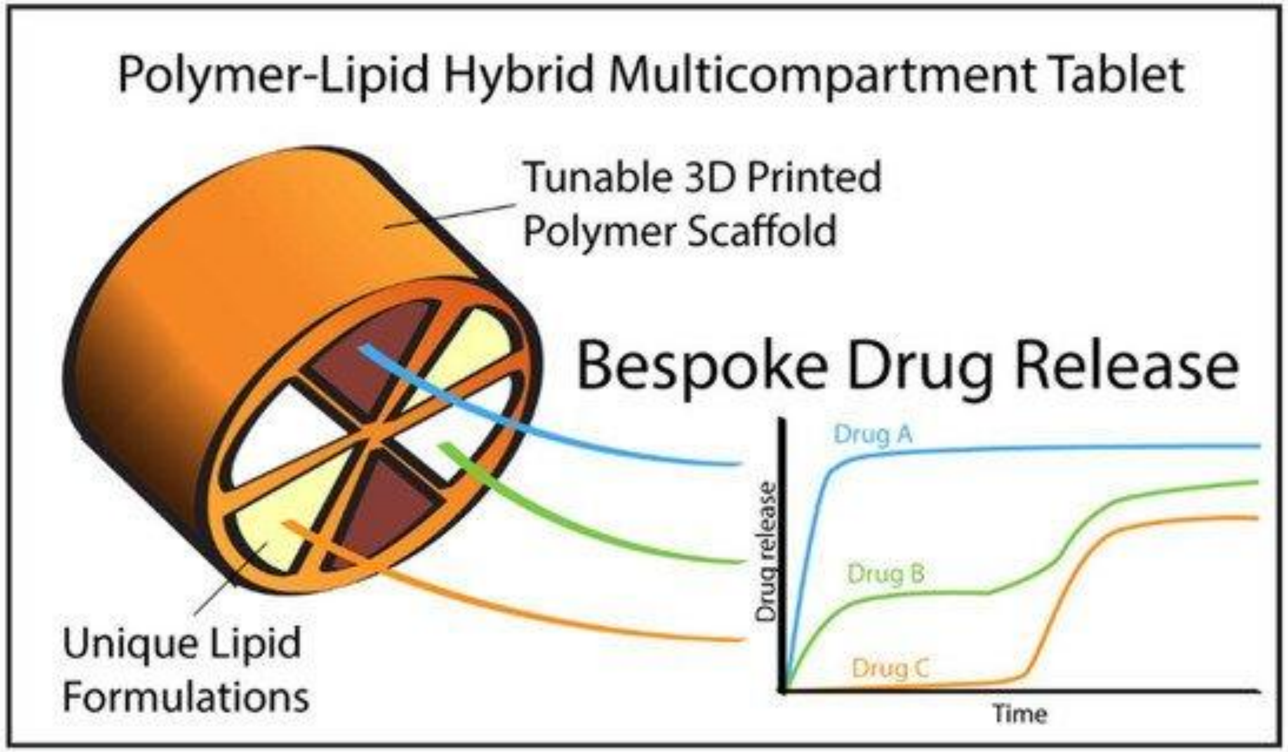
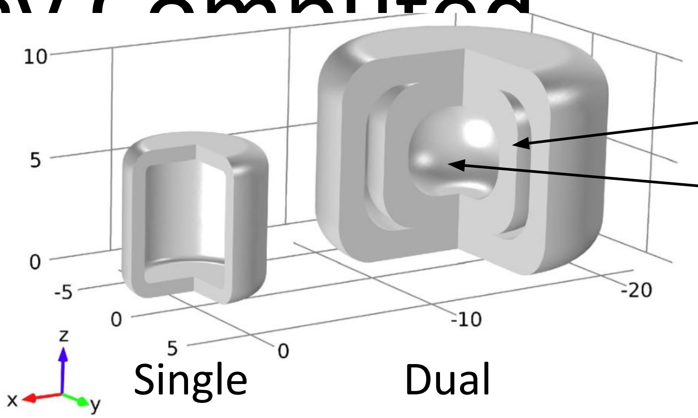



*Graphical abstract (https://www.mdpi.com/1999-4923/13/12/2107)*

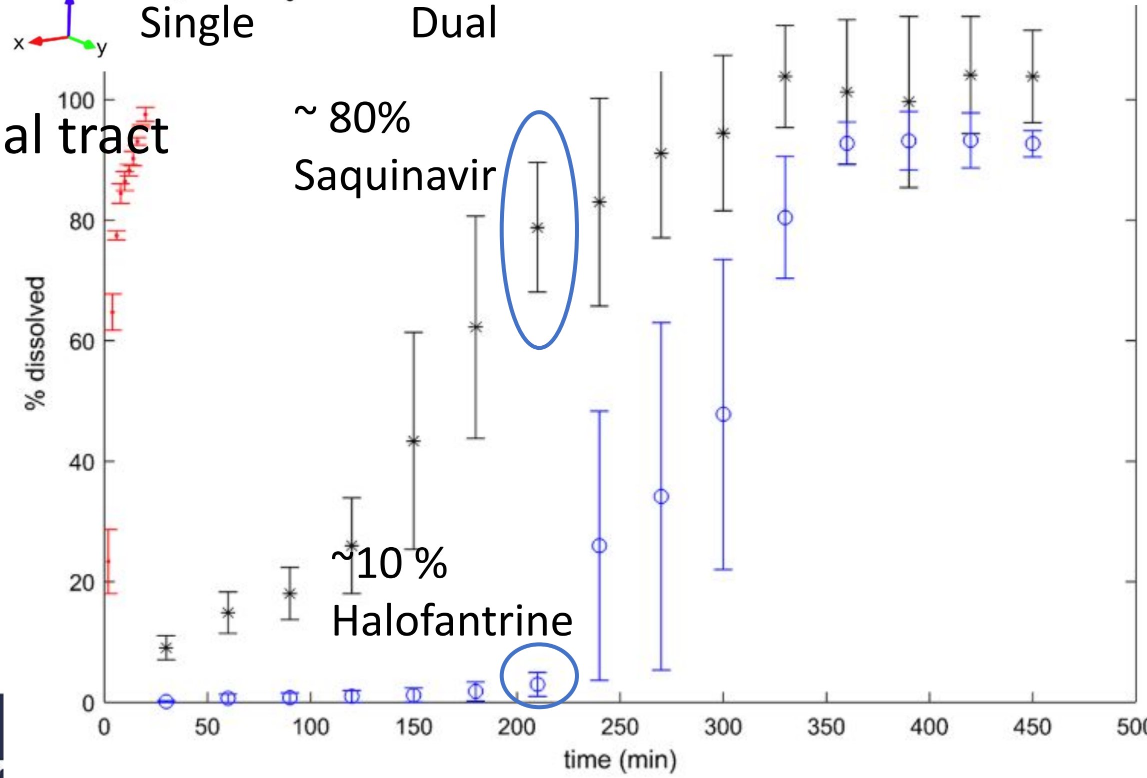


{Markl, 2017}

# Analysis of 3D Prints by X-ra[y Computed] Microtomography and Tera[hertz Ima]ging



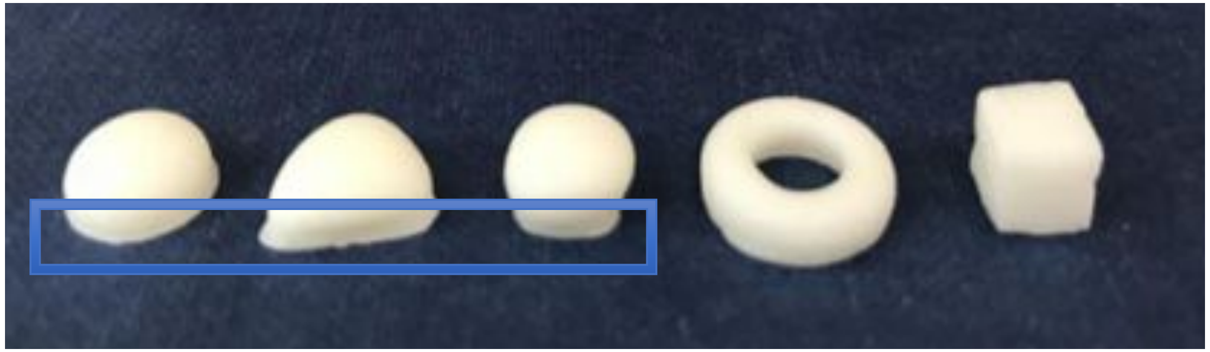

- Core shell design:
  - PLA – not-biodegradable
  - PVOH – biodegradable
  - Target different parts of the gastro-intestinal tract
- Filling (manually)
  - Liquid lipid formulation (SNEDDS)
- Dual compartment at 210 min
- Drawbacks of liquid Lipids
  - Messy manufacturing/storage
  - Poor drug stability (in solution)

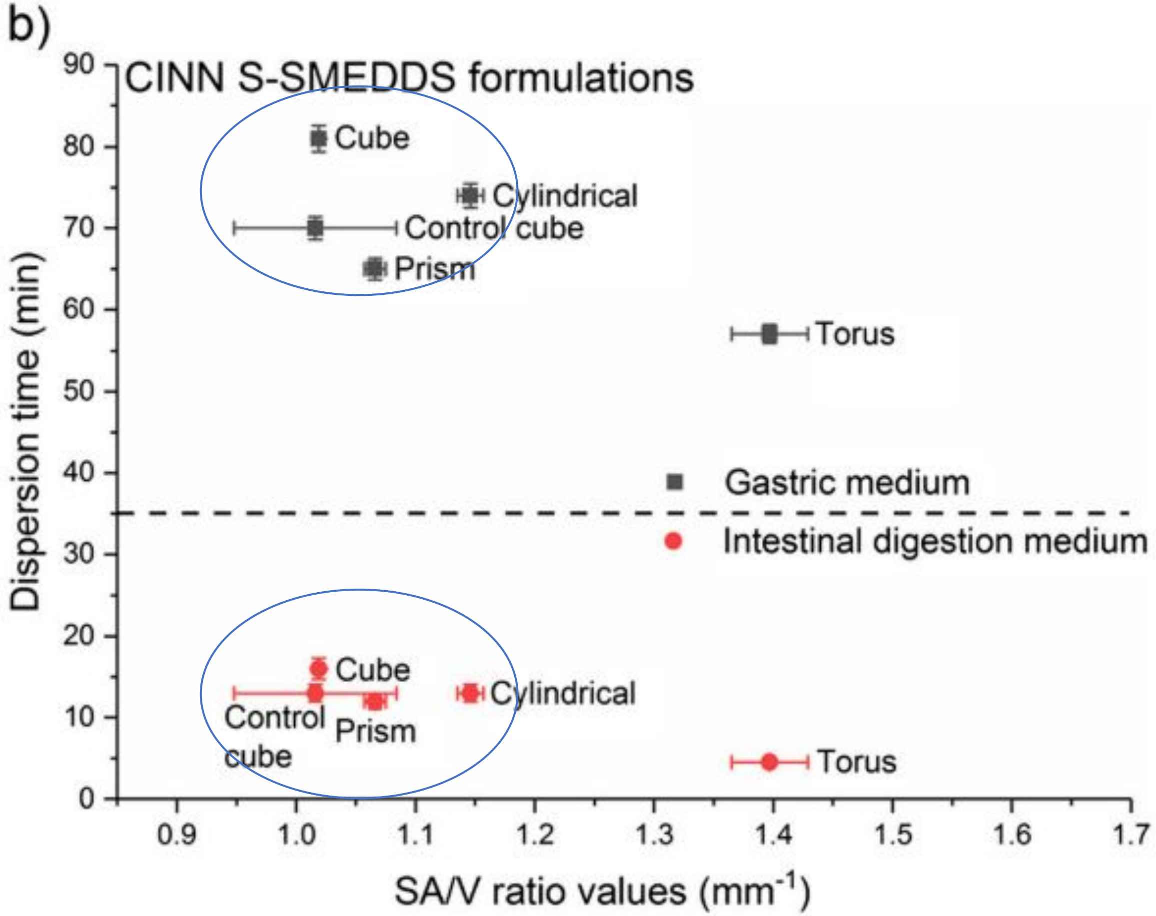


{Vithani, 2019}

# "A Proof of Concept for 3D Printing of Solid Lipid-based Form[ulations]"

- SSE 3D printing of solid lipid SNEDDS
  - 7% drug loading
- Low temperature 65 C – solvent free
- Poor control over tablet fidelity/resolution
- Further investigation into SA:V vs dispersion

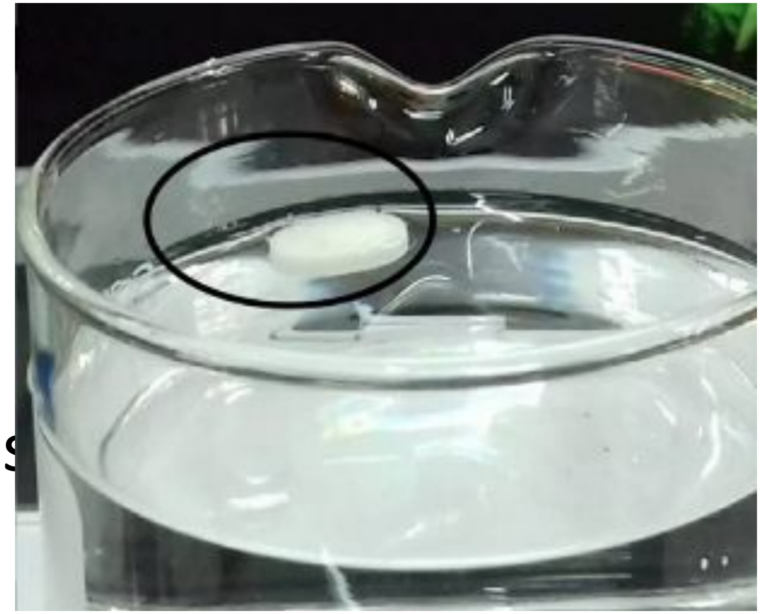


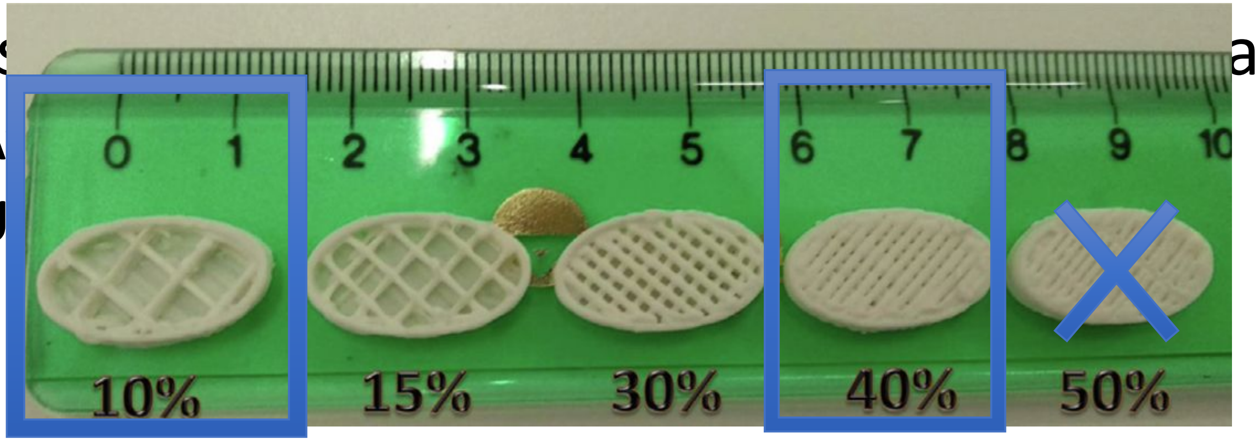


{Real, 2020}

# ".. An innovative solvent-free alternative method for 3D printing.."

- Dispersion of gastro-retentive/floating tablets
  - Up to 25% drug loading
  - Ricobendazole (RBZ) + Gelucire 50/13 (lipid)
  - Low temperature 49 C – Solvent free
- Dens... as
  - A
  - U






2 hours Dispersion

~ 80 % RBZ dispersed

~ 60 % RBZ dispersed

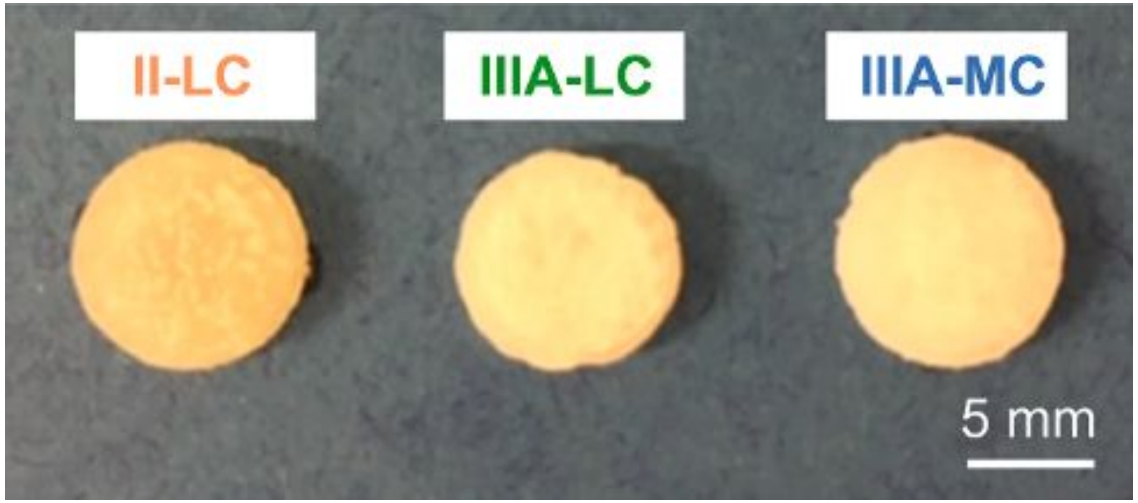
{Johannesson, 2021}

# 3D-printing of solid lipid tablets from emulsion gels

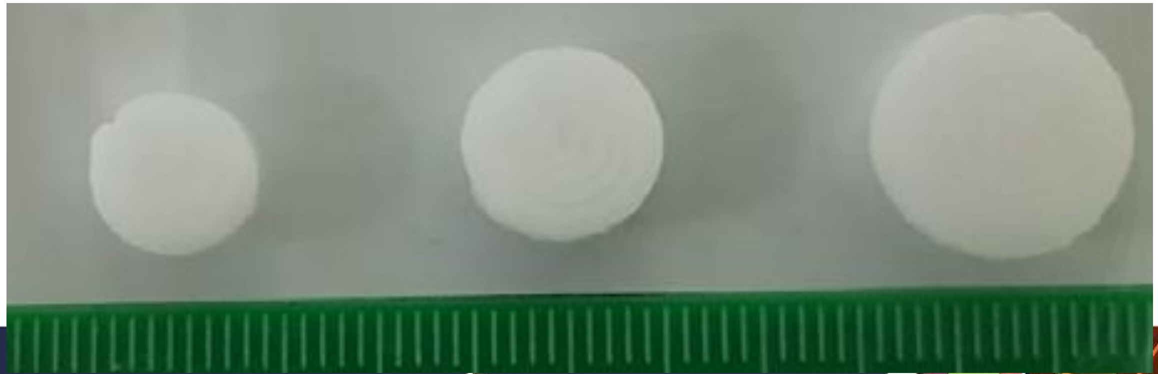
- SSE of Oil in Water emulsion
  - Gel = Drug + water + lipid, sonication
  - Room temperature
  - Requires drying step + porous
- Rapid dispersion time < 15 minutes
- Lipid dependent digestion time
- Similar study; Non-digestible lipids

- Drawbacks
  - Poor fidelity/resolution
  - Single drug delivery

type II long-chain, type IIIA long-chain, medium-chain




Increasing rate of digestion



{Algahtani, 2021}

# Generation of partially 3D printed polymer-lipid hybrid tablets: Scaffold

.STL

↓

.Gcode

↓

Print!

Scaffold printing (~12 mm diam.):

Computer Aided Drawing (CAD) of models:

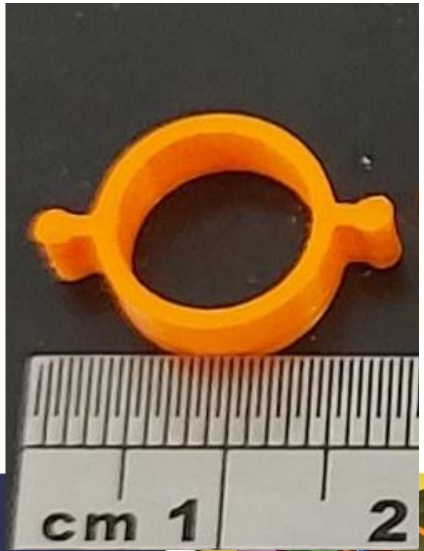
- Sketchup-Free

CAD model processing/slicing:

- Ultimaker Cura
- High resolution + minimal artefacts
  - Forum sourced suggestions

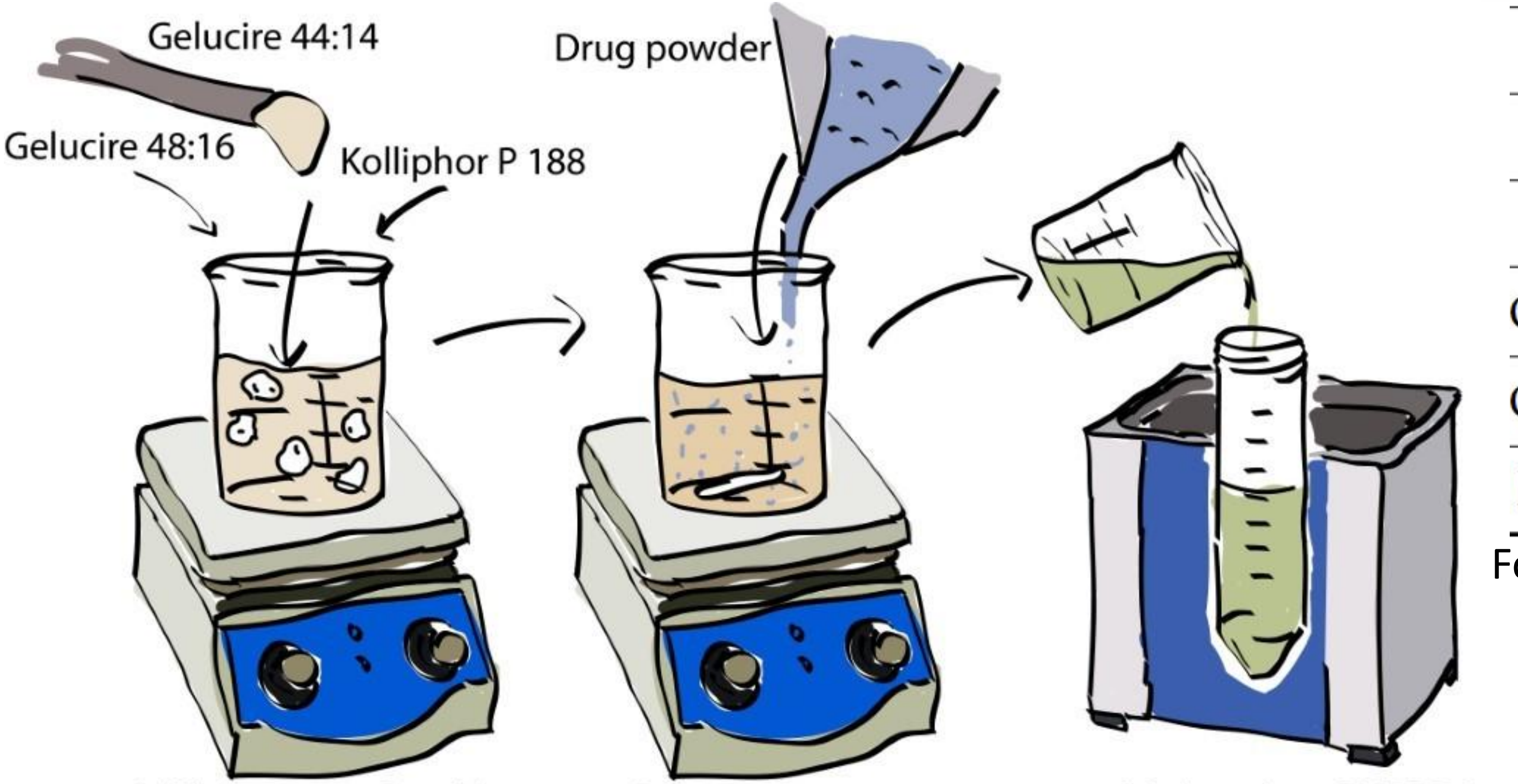
Ultimaker 2 Printing

- Poly-lactic acid (PLA) of poly-vinyl alcohol (PVOH)
  - Nozzle diameter 0.6 mm
  - Print layer height: 0.1 mm per layer
  - Extrusion speed: 40 mm/sec
- 2.5 – 5 minutes per scafold

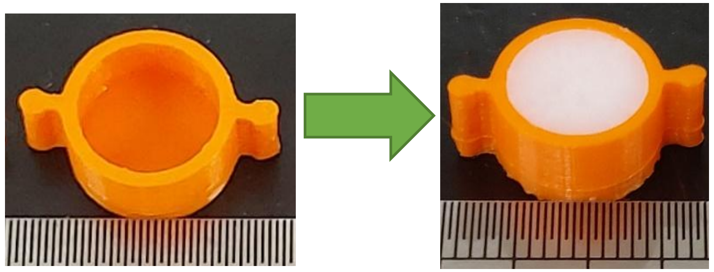

PLA printed Scaffold

# Generation of partially 3D printed polymer-lipid hybrid tablets: Filling scaffolds



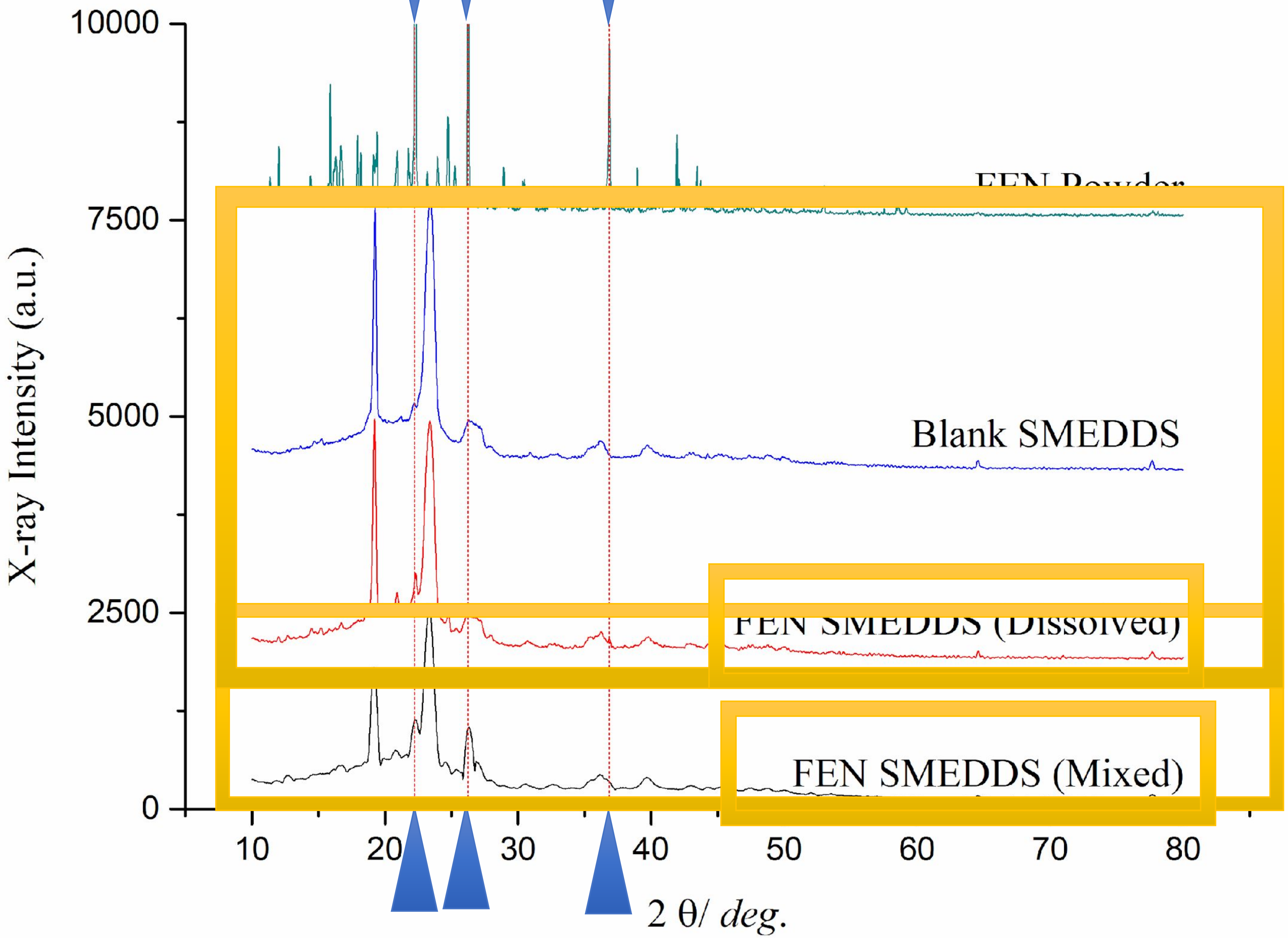

| Single Compartment Systems | |
|---|---|
| SMEDDS A | Component (% $w/w$) |
| Drug | FEN |
| Drug content | 7.0 |
| Gelucire® 44/14 | 46.5 |
| Gelucire® 48/16 | 23.3 |
| Kolliphor P 188 | 23.2 |

Formulation and method based on {Vithani, 2019}



Manual filling (autopipette)
- 392.6 µL/~400 mg

# X-Ray Diffractometry: Solid state characterisation



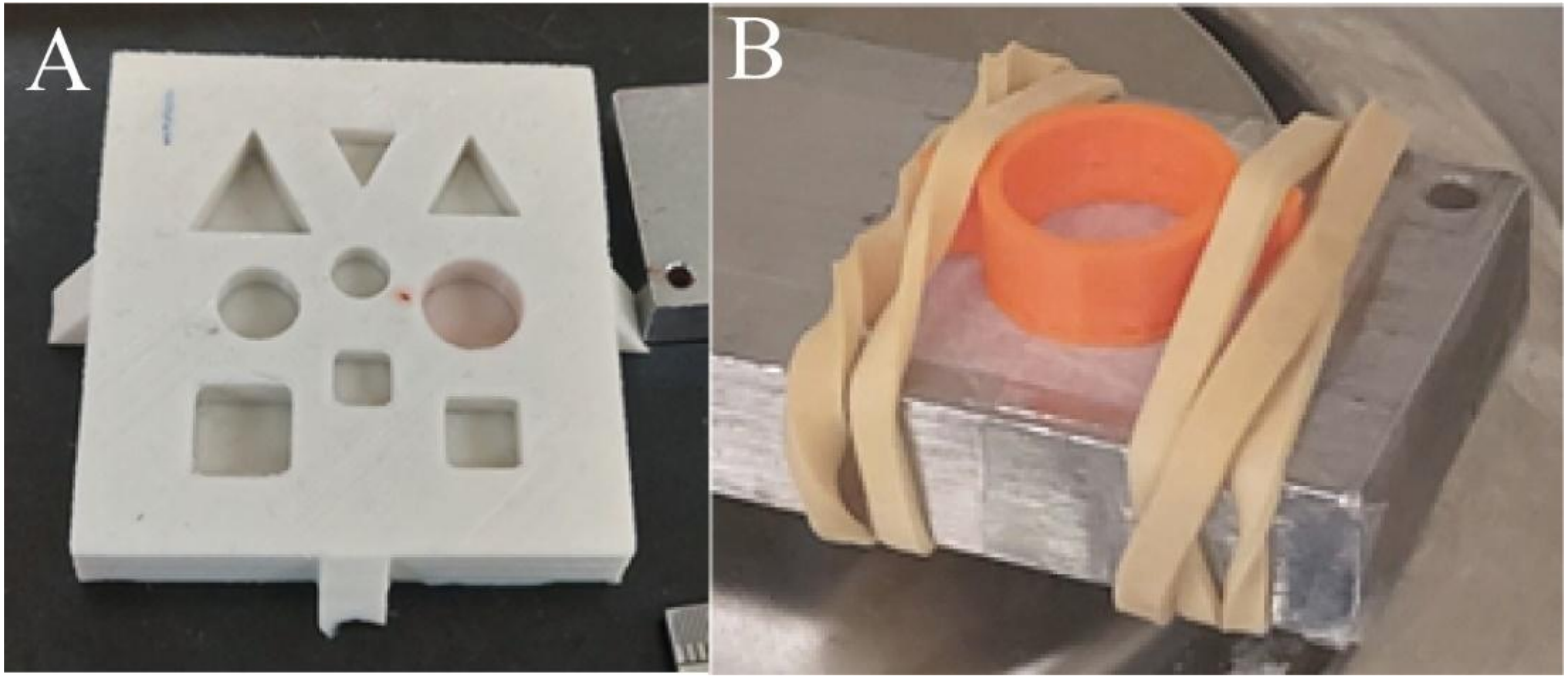



**Figure S1**[M1] **. (A)** Silicon mould used in generating ‘no-scaffold’ type systems **(B)** PLA scaffold attached to a steel plate via rubber band used for filling ‘dual-face’ type systems.

# X Ray CT structural analy

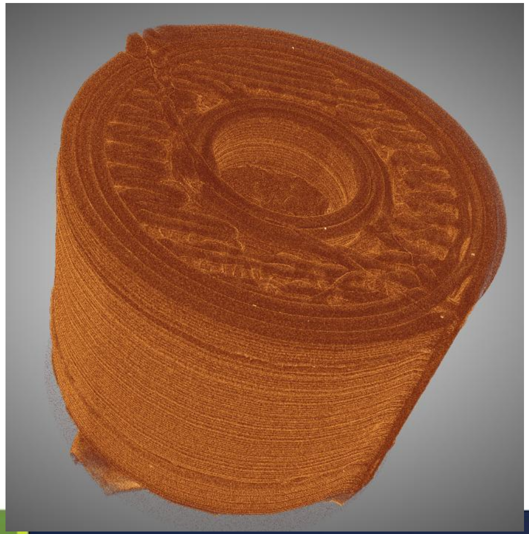
- X Ray Computed Tomography (CT)
  - Non-destructive imaging
  - Generates 3D image from 2D "slices"
- Features associated with differences i
  - Cracks, porosity, changes in physical mo
- Dragonfly software is used to process


*Photograph of the Zeiss Xradia 520 Versa, available at the department of Civil Engineering (Monash Clayton campus).*

https://www.zeiss.com/content/dam/Microscopy/us/download/pdf/Products/xradia520versa/xradia-520-versa-product-information.pdf
https://issuu.com/tonyhuynh3/docs/xrayct-monash-engineering

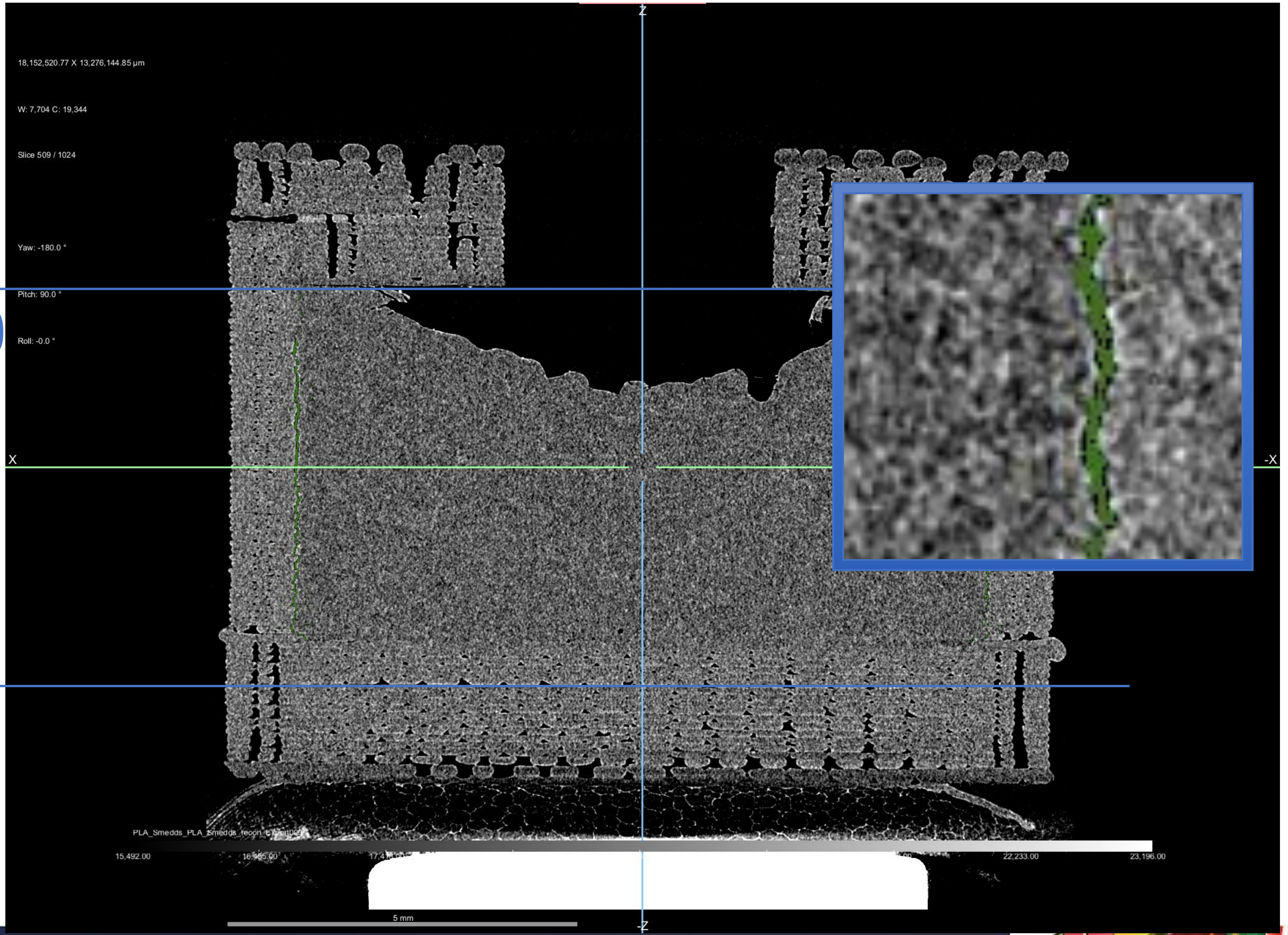
# Preliminary X-Ray CT imaging

Original semi-open tablet



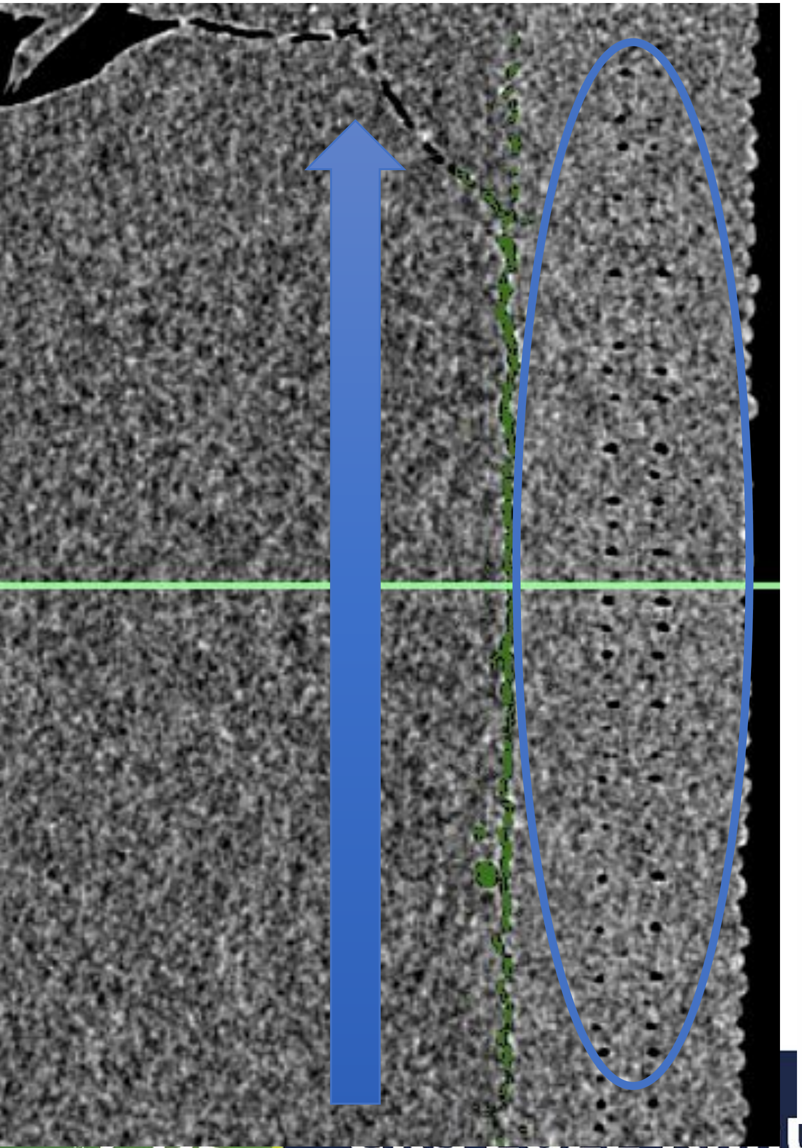
Slice ~7500

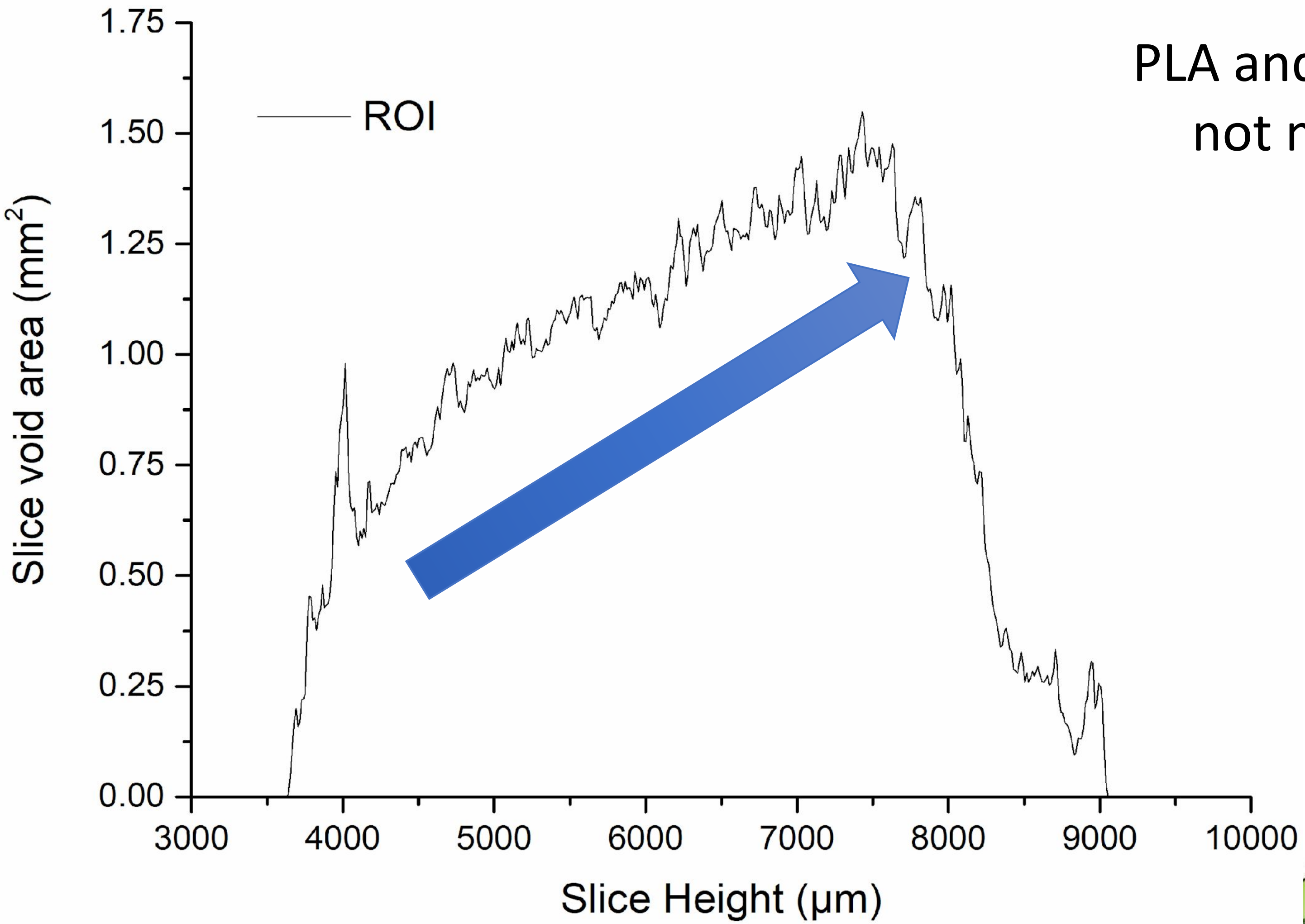
Slice ~3500




Pixel size (µm) = 12.51

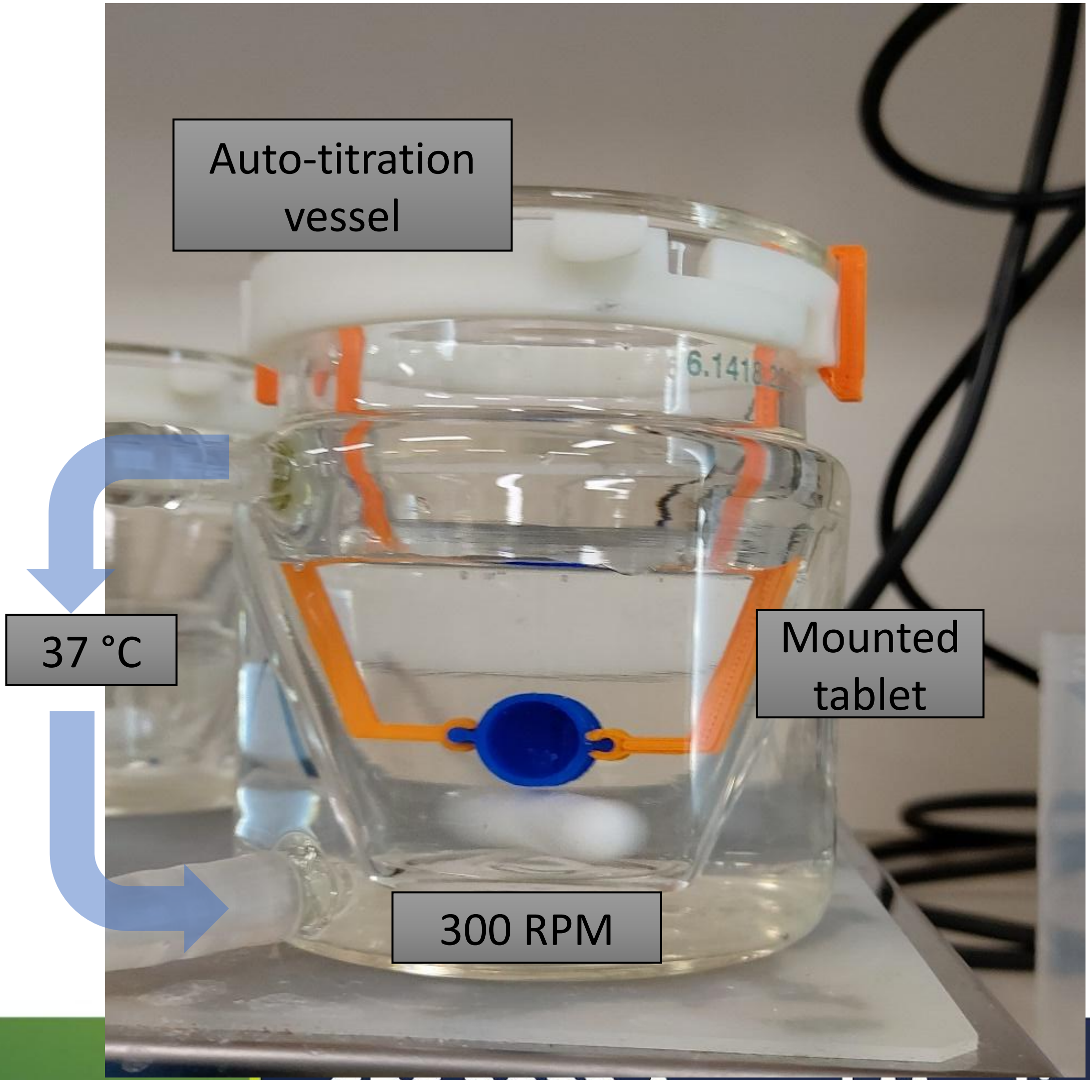
# Analysis of PLA-SMEDDS interfacial void volume






PLA and SMEDDS not miscible

# Invitro dispersion of PLH tablets




- Non-USP, reproducible method
- Tablet mounted within vessel

Simulated physiological conditions

| Gastric phase | → | Intestinal phase |
|---|---|---|
| 0.1 M HCL | | FaSSIF |
| pH 1.2 | | pH 6.5 |
| 0 - 30 min | | 30 - 60 min |

Sample Analysis:

- Tubidity > Nephelometry
- Drug concentration > HPLC

https://www.biocompare.com/20799-Nephelometer-Microplate-Nephelometers/2759712-NEPHELOstarPlus/

# Dispersion sample analysis: measurement of turbidity

- Turbidity analysis via nephelometry (NepheloStar)
  - Samples loaded into 96 well plate
  - Detects light scattered
    - More particulate/turbulent samples will scatter more

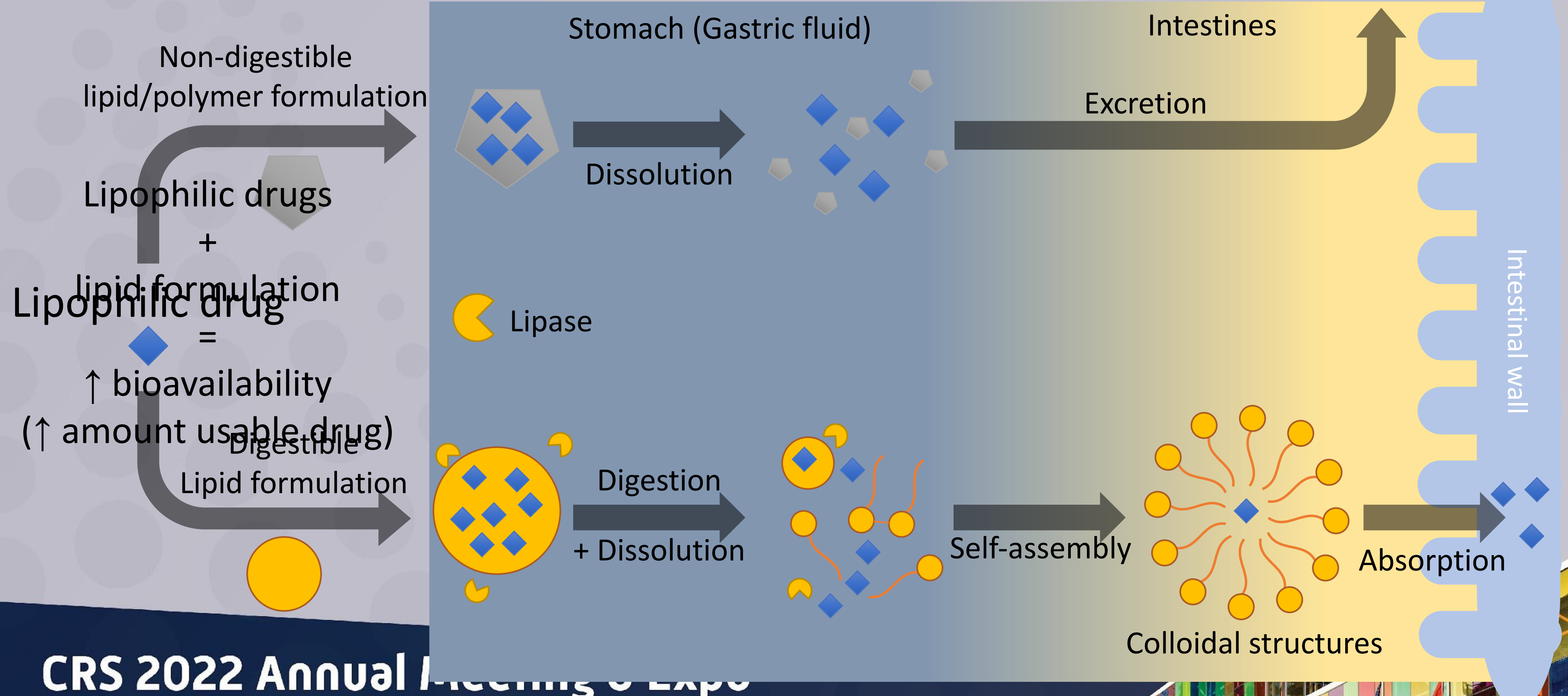



https://shimadzu.com.au/prominence-hplc

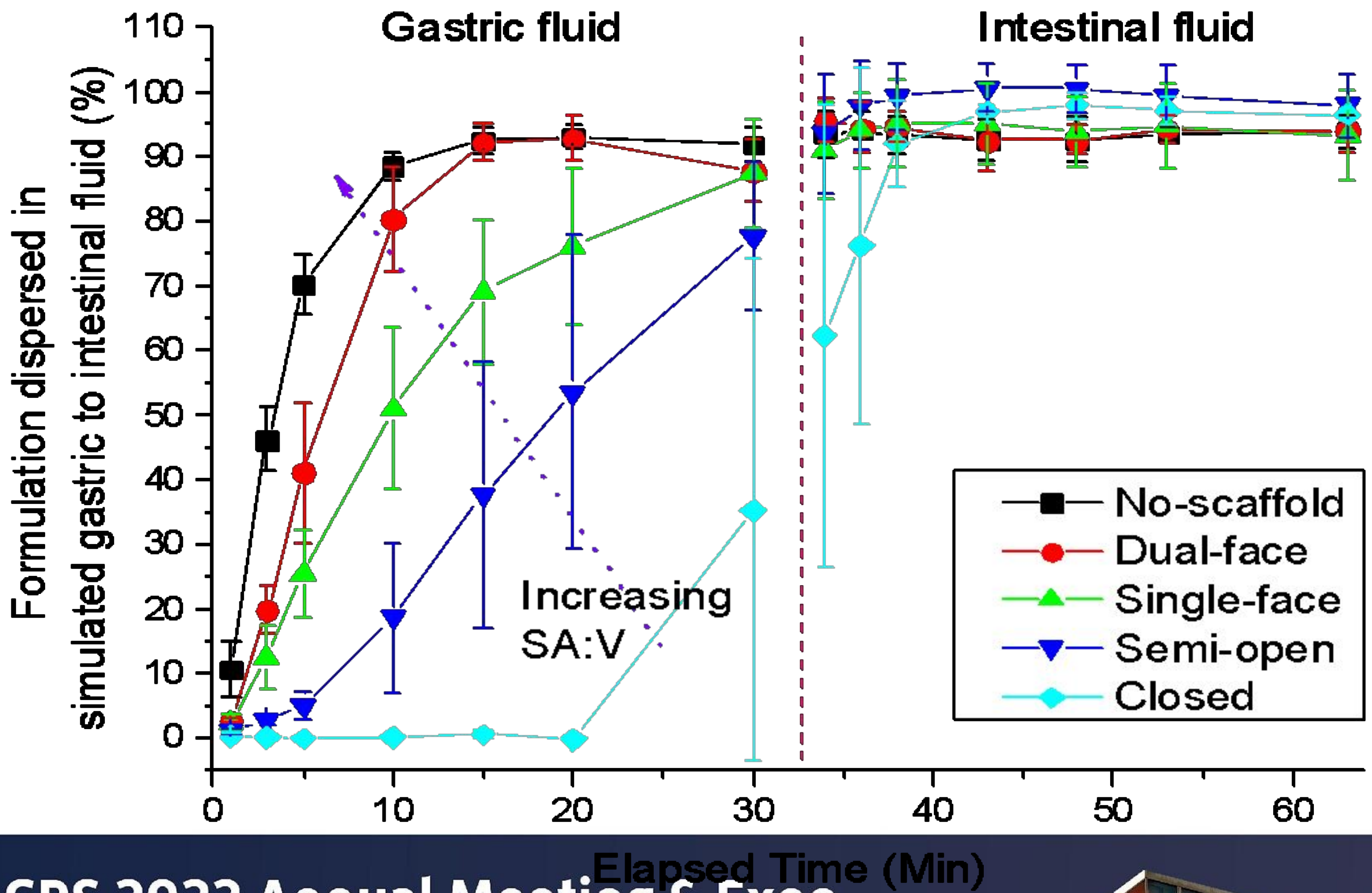
# Dispersion sample analysis: measurement of drug concentration

- Drug concentration analysis via HPLC (Shimadzu)
  - Multiple methods to separate and quantify concentration of drug in solution
    - Fenofibrate
    - Halofantrine and lumefantrine
    - Clofazimine
  - Detect absorption of light at different wavelengths
    - Higher drug content in samples will lead to higher intensity

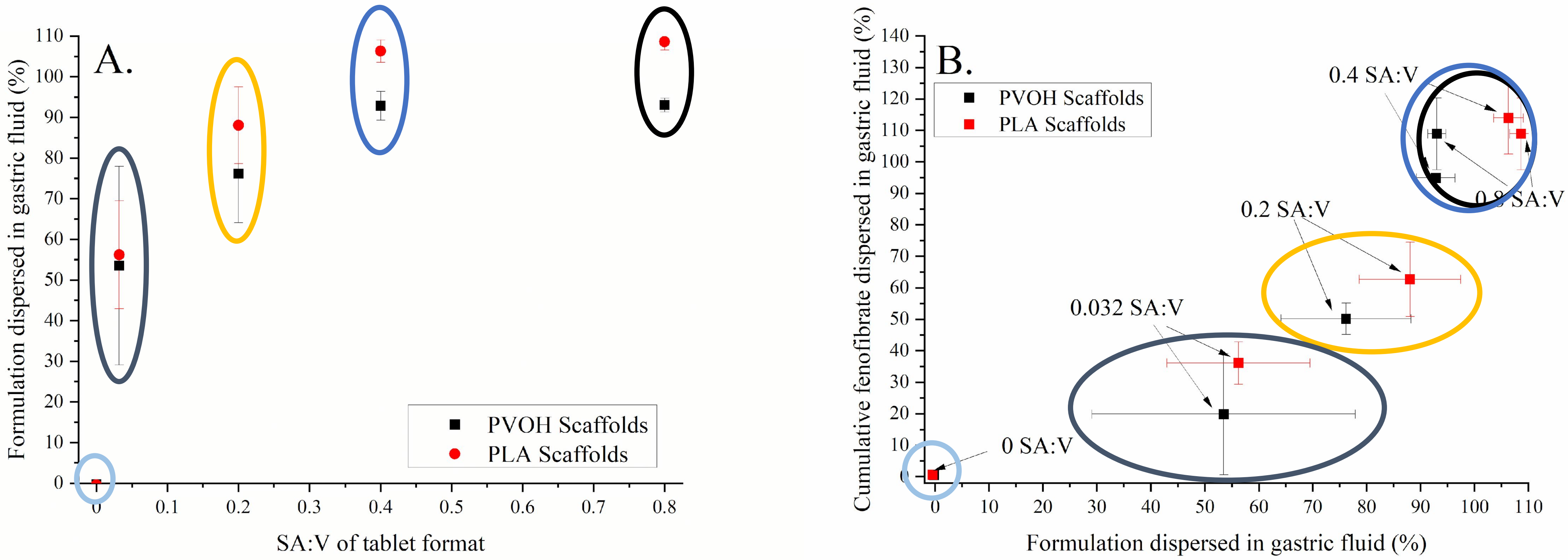
# bioavailability of lipophilic drug



## Turbidity analysis of PVOH single compartment tablets



# Dispersion + drug release (20 min snapshot)




| Tablet Type | No-Scaffold | Dual-Face | Single-Face | Semi-Open | Closed |
|---|---|---|---|---|---|
| SA:V ratio ($mm^2 \times \mu L^{-1}$) | 4:5 (0.800) | 2:5 (0.400) | 1:5 (0.200) | 4:125 (0.032) | 0:1 (0.000) |

| Scaffold Composition | Scaffold Type | Formulation Mass (AVG ± %RSD, mg) | Scaffold Mass (AVG ± %RSD, mg) | Total Mass (AVG ± %RSD, mg) | Scaffold % Total Mass |
|---|---|---|---|---|---|
| | No scaffold (NS, n = 3) | 399.2 ± 0.3% | - | 399.2 ± 0.3% | - |
| PVOH | | | | | |
| | Single face (1F, n = 4) | 401.0 ± 0.2% | 151.8 ± 0.5% | 552.9 ± 0.2% | 27.4 % |
| | Double faced (2F, n = 4) | 401.5 ± 0.3% | 221.2 ± 1.5% | 622.8 ± 0.7% | 35.5 % |
| | Semi-open (SO, n = 4) | 401.2 ± 0.2% | 319.3 ± 2.8% | 717.1 ± 1.1% | 44.5 % |
| | Closed (CL, n = 3) | 399.8 ± 0.2% | 321.6 ± 0.9% | 720.3 ± 0.2% | 44.6 % |
| PLA | | | | | |
| | Single face (1F, n = 4) | 399.4 ± 0.3% | 243.7 ± 4.6% | 643.1 ± 1.8% | 37.8% |
| | Double faced (2F, n = 3) | 400.8 ± 0.4% | 502.3 ± 0.1% | 903.1 ± 0.9% | 55.6% |
| | Semi-open (SO, n = 4) | 399.0 ± 0.3% | 768.1 ± 4.3% | 1167.1 ± 2.9% | 65.8% |
| | Closed (CL, n = 3) | 398.6 ± 0.1% | 801.9 ± 2.5% | 1200 ± 1.7% | 66.7% |

# Masses of drug and lipid in each compartment of multicompartment systems.

| Multicompartment PLH | | | | | | | |
|---|---|---|---|---|---|---|---|
| Compartment | A | B | C | D | E | F | Total |
| Drug (X%) | Clofazimine (7%) | Lumefantrine (7%) | Halofantrine (3.5%) | Clofazimine (7%) | Lumefantrine (7%) | Halofantrine (3.5%) | - |
| Base formulation | SMEDDS | SMEDDS | SMEDDS | Gelucire 48/16 | Gelucire 48/16 | Gelucire 48/16 | - |
| Mass.Average ± %RSD (n = 4, mg) | 60.9 ± 1.4% | 62.3 ± 2.1% | 63.1 ± 0.7% | 61.2 ± 0.8% | 64.3 ± 2.4% | 61.7 ± 1.2% | 373.7 ± 0.7% |

***Clofazimine, halofantrine and lumefantrine each possess high logP values of 5.2, 7.6, 8.6 and 8.6, respectively (Pubchem)

**In a clinical setting, all three are anti-infective drugs, with clofazimine being used for leprosy [43], and lumefantrine and halofantrine to treat malaria [44,45]

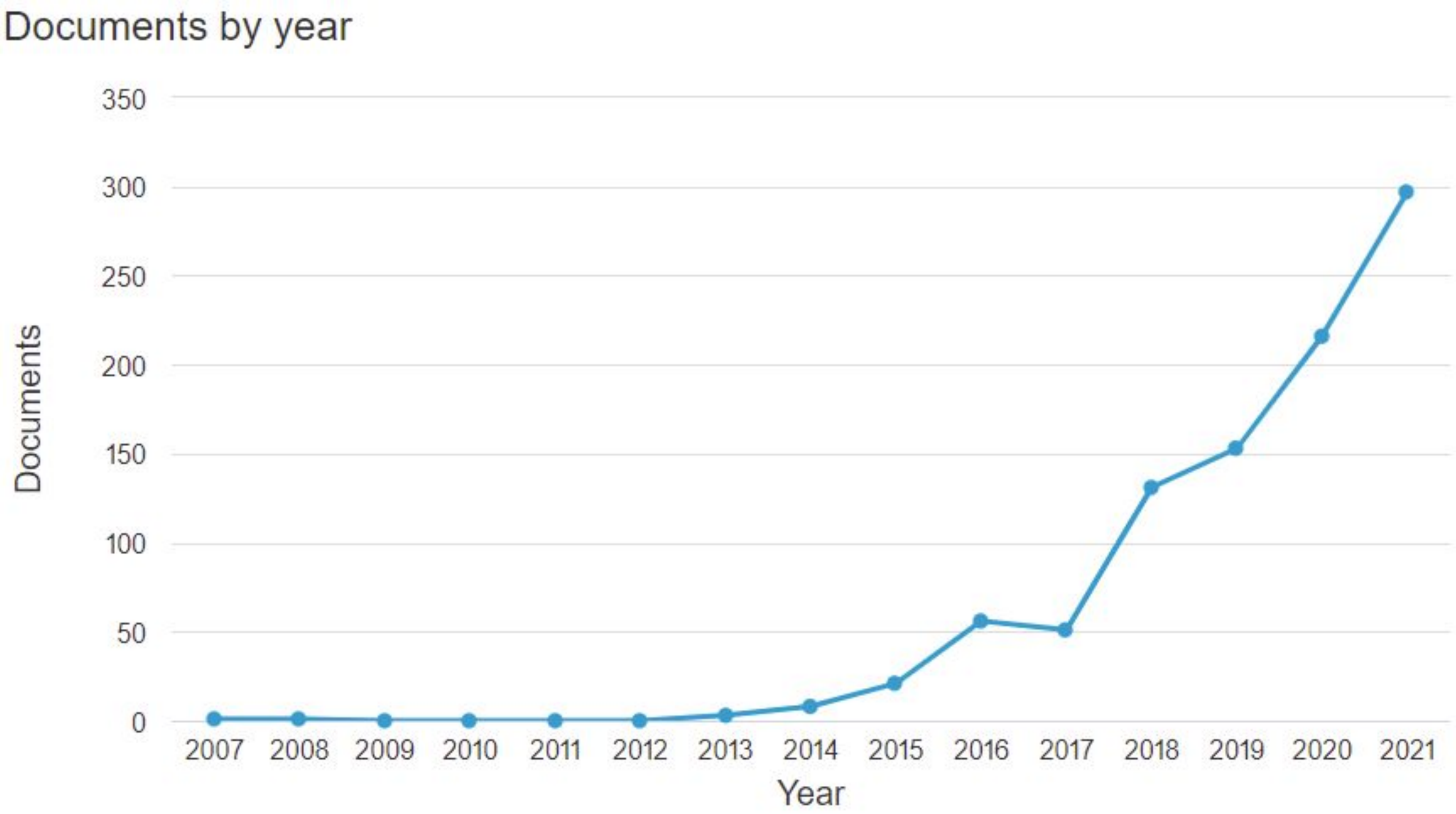
# Growing interest for 3D printing in pharma

Analysed search results at Scopus

Keyword search:
‘*3D printing*’

Filtered by subject area:
‘*Pharmacology, Toxicology and Pharmaceutics*’

53 Published so far this year




https://www-scopus-com.ezproxy.lib.monash.edu.au/term/analyzer.uri?sid=cf3f36147cd5e917f58194034d234044&origin=resultslist&src=s&s=KEY%283D+printing%29&sort=plf-f&sdt=cl&sot=b&sl=16&count=991&analyzeResults=Analyze+results&cluster=scosubjabbr%2c%22PHAR%22%2ct&txGid=3a5ea9699acb06cc68d88c428e145de8

# **General overview of 3D printed oral dosage forms

- 2015, only 3DP oral dosage form on market
  - Leviteracetam, to treat epilepsy, 4+ yo
    - 250/500/750 mg (twice daily)

Spritam®
(levetiracetam)
Tablets for Oral Suspension

https://www.spritam.com

- Majority of 3DP research;
  - Polymer based formulations
  - Hydrophillic drug delivery

| BCS | Candidates | Marketed |
|---|---|---|
| Hydrophillic drugs (high solubility) | 20 % | 60 % |
| Lipophillic drugs (poor solubility) | 80 % | 40 % |

Personalised medicine;

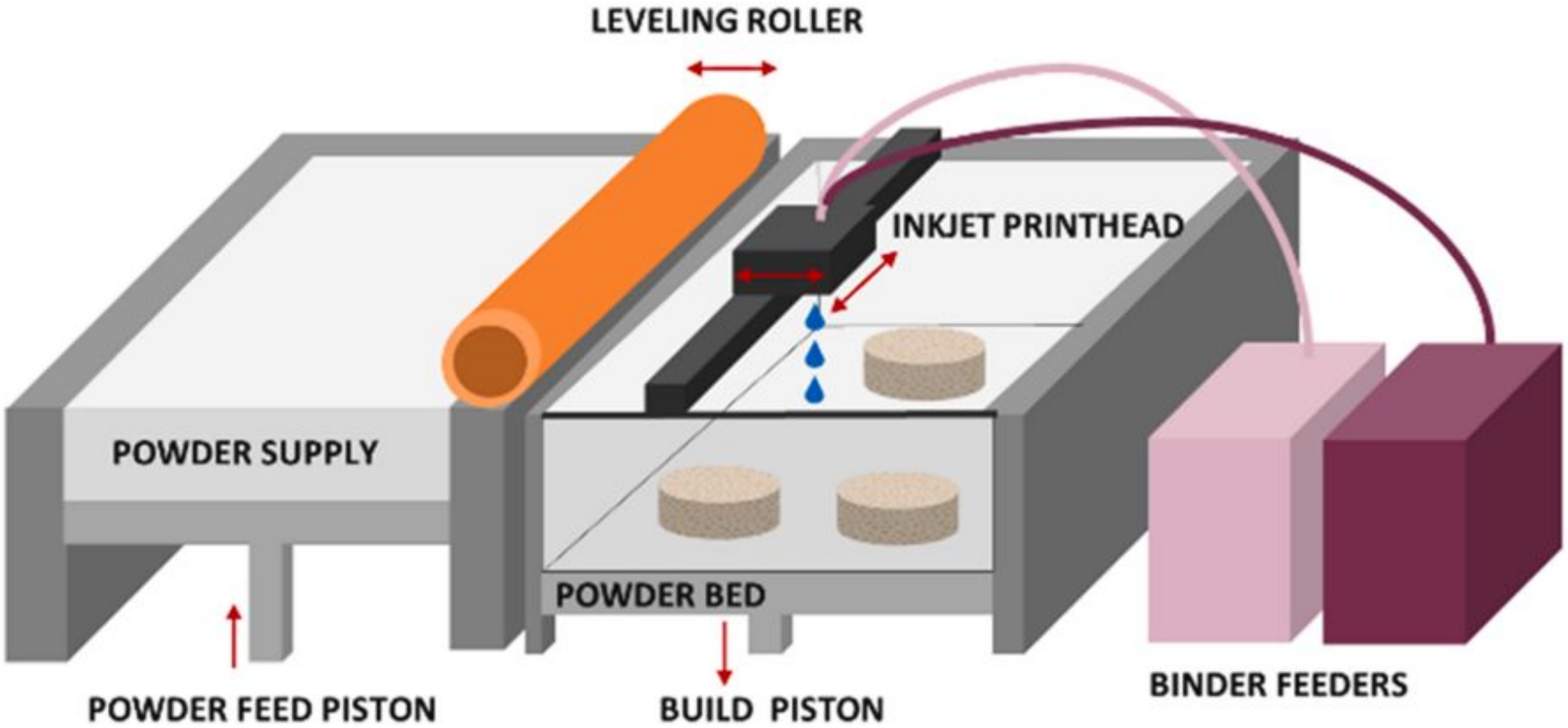
3D printed lipid based formulations



https://www.youtube.com/watch?v=pDAT2PhI1mg

# Common 3DP techniques in pharmaceutical research: powder bed fusion

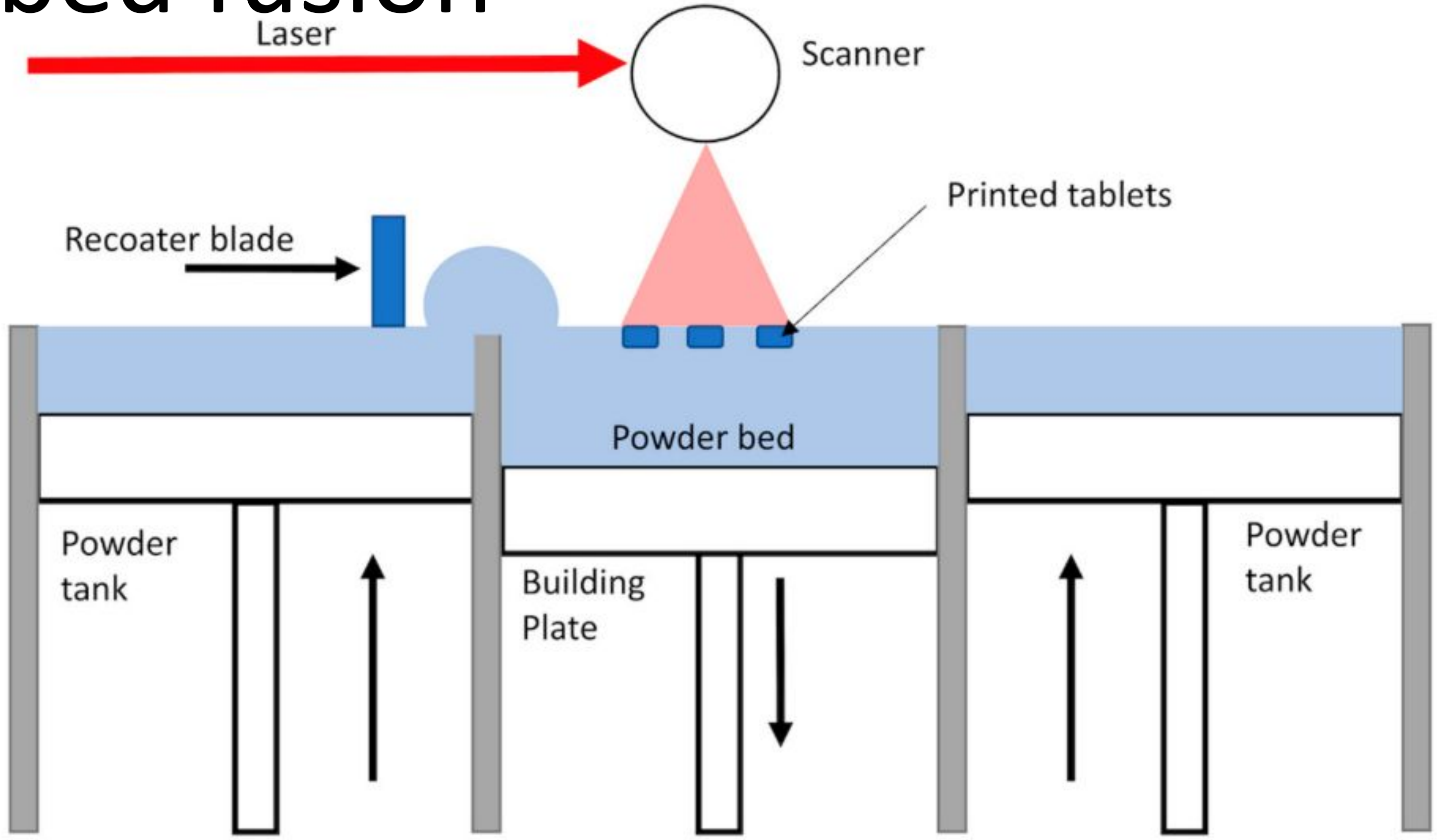
- Binder Jetting
    - Powdered formulation + liqui
    - Additional drying step
        - Porous tablets (Spritam)
- Drawbacks
    - Wastage of materials
    - or soft mate




{Kozakiewicz-Latała, 2022}

# Common 3DP techniques in pharmaceutical research: powder bed fusion

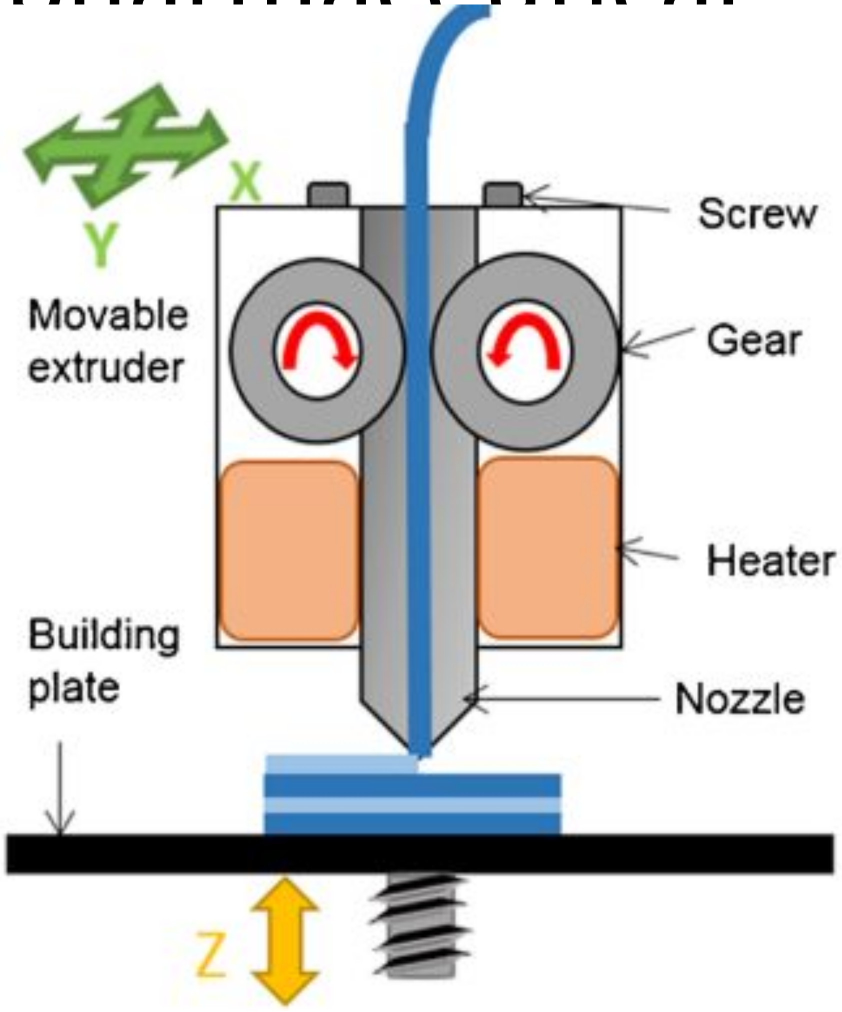
- Selective laser sintering (SLS)
  - Powdered formulation + infrared laser
  - Sintering: Molecular binding =/= melting
    - Porous tablets
  - No drying step
- Drawbacks
  - Wastage of materials
  - Risk of heat related degradation
  - Not appropriate for lipids
    - Oxidative risk




{Gueche, 2021}

# Common 3DP techniques in pharmaceutical research: material extrusion

- Fused Deposition Modelling (FDM)
  - Filament feeding > melting > deposition
  - Continuously produce tablets
  - Pore free/defined surface area
- Drawbacks
  - Risk of heat related degradation
  - Current lipid systems incompatible



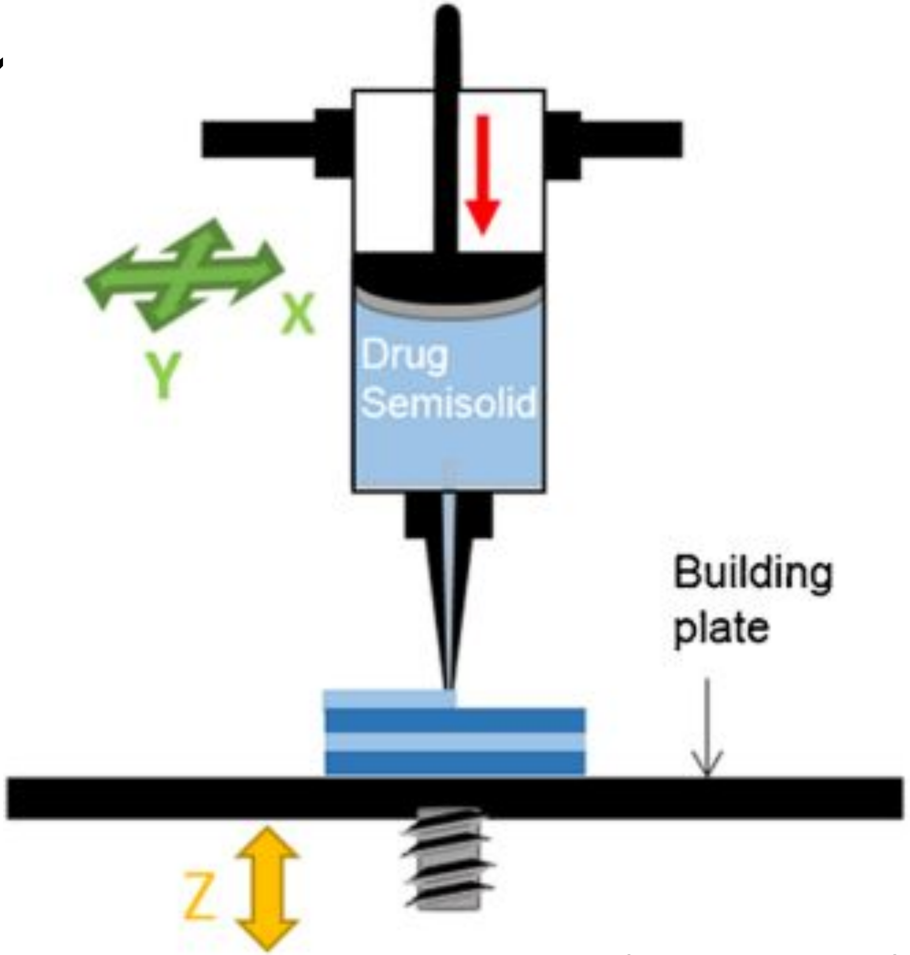

{Alhnan, 2016}

# Common 3DP techniques in pharmaceutical research: material extrusion

- Semi-Solid Extrusion (SSE)
  - Pressure assisted extrusion
  - Low temperatures
  - Non-continuous - cartridge
  - May require solvent drying step

- Appropriate for lipids!
  - Low temperature
  - No drying step

Research strategies for SSE printed lipid based formulations?




{Alhnan, 2016}