Global Drug Development/Immunology

Personalized medicines from the 3D-printer: challenges and opportunities

Marina Fanous, PhD

"Innovations in genomic diagnostics for personalized medicine, quality improvement, teaching and research" conference in Kühtai, Austria
April 15th, 2023

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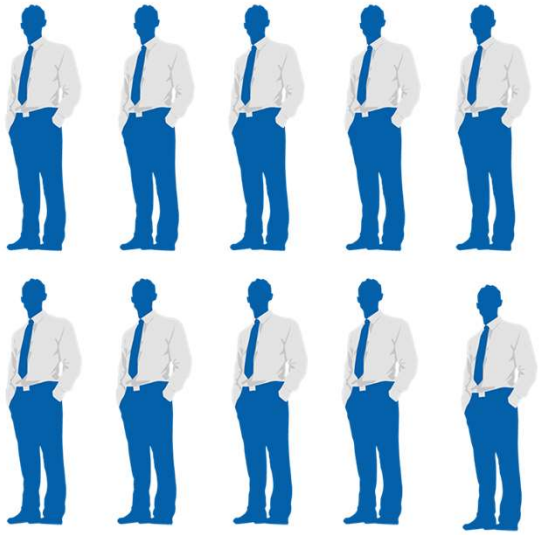
Opinions expressed within the content are solely **my own** and do **not** express **the views** or **opinions** of **my employer**

Agenda

1. Background
2. Introduction to 3D-printing / Fused Deposition Modeling (FDM)
3. Development of Immediate Release (IR) 3D-printed tablets with a **hydrophilic** model compound
4. Development of 3D-printed tablets with a **lipophilic** model compound
   - FDM-printing as a tool to achieve amorphous solid dispersion (ASD) on demand
   - Immediate Release (IR) 3D-printed tablets development with a lipophilic model compound
   - Identification of key morphological parameters responsible for dissolution acceleration
5. Simplification of FDM 3D-Printing Paradigm: **Direct Powder Printing** development
6. Summary
7. Outlook and opportunities

Precision medicine: reimagining dosage forms needed



Large-scale tablet manufacturing: limited number of dosage strengths

Personalized medicines: one person – one product

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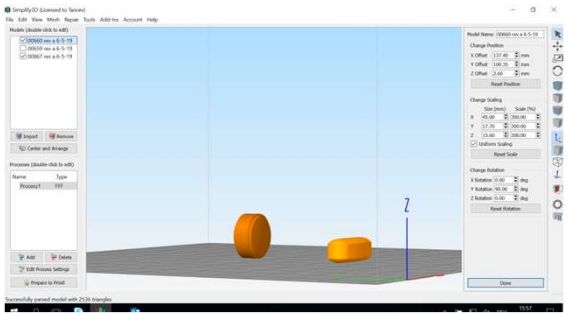
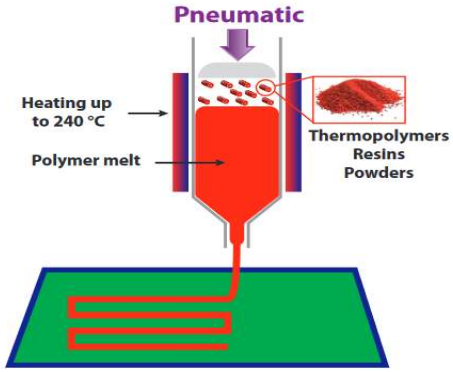
Introduction to 3D-printing technology

Current extemporaneous preparations → **3D-printing** → **Personalized Dosage Forms**





Adapted from M. Fanous et al., IJP, 2020

Pharmaceutical potential:

- **Prototyping** dosage form designs
  - ❖ flexibility and versatility of designs
  - ❖ idea of short-development times from complex **prototype** to **full-scale production** (scale-up by parallelization)
- **Combination products** (multiple API's in one dosage form), including tailored release profiles per inividual API
- **Personalized medicine** in conjunction with **decentralized** printing step
  - – Extemporaneous preparation of **clinical trial** medication personalized to individual patients
  - – **Commercial** drug products personalized to individual patients

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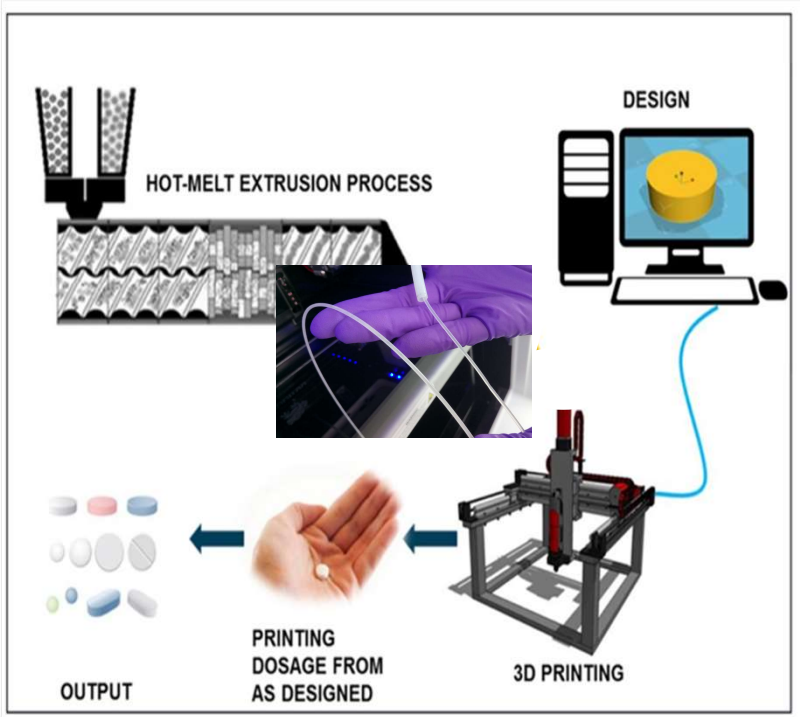
Fused Deposition Modeling (FDM) 3D-printing for pharmaceuticals

- Advantage: easy to manufacture on-clinical-site, no post-processing required
- Challenge: suitable mechanical properties, **slow** and incomplete drug release, thermal degradation
- Need: majority of DFs are immediate release (IR; 70% of total oral tablet market share[1])
- **Goal: 3D-printable IR formulations**



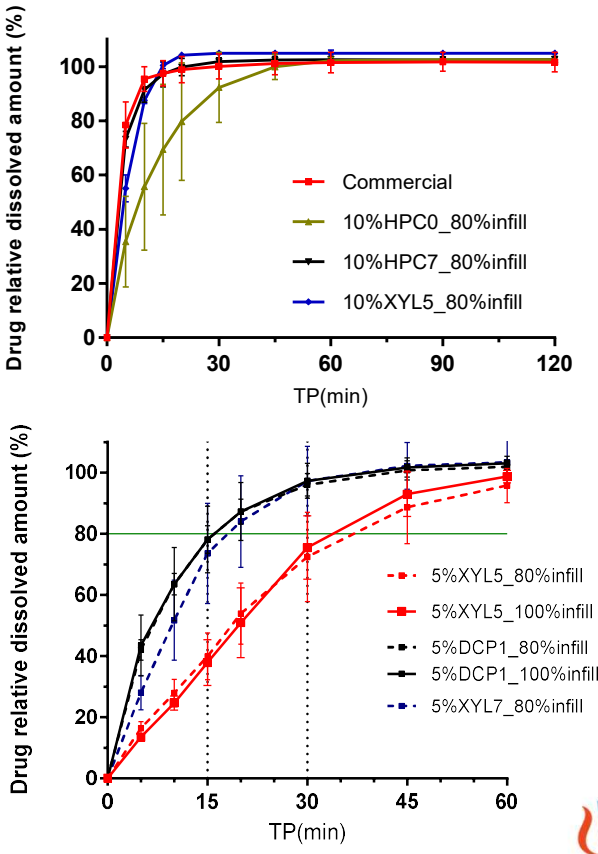
Adapted from J. Zhang et al, 2017

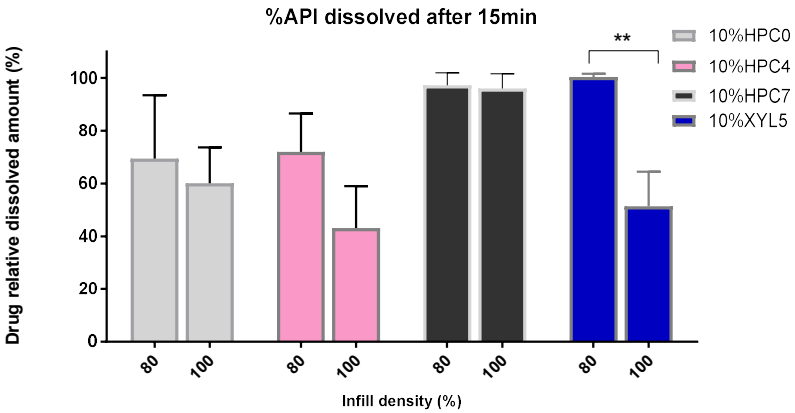
1. GBIResearch, 2012; Marketsandmarkets, 2013

Development of IR 3D-printed tablets with a hydrophilic model compound

Formulation strategy- toolbox approach

- Primary matrix formers (HPC/HPMC)
- Rapidly dissolving hydrophilic polymers (Kollidon VA64, Kollicoat IR, PVA)
- Hydrophilic plasticizers (Xylitol, PEG4000)
- Dissolution accelerators (DCP,Maltodextrin)





Dissolution profiles of FDM **caffeine** 3D-printed tablets with 80% or 100% infill density (pH=2, USP II paddle 50 rpm)

M. Fanous et al., EJPS, 2020

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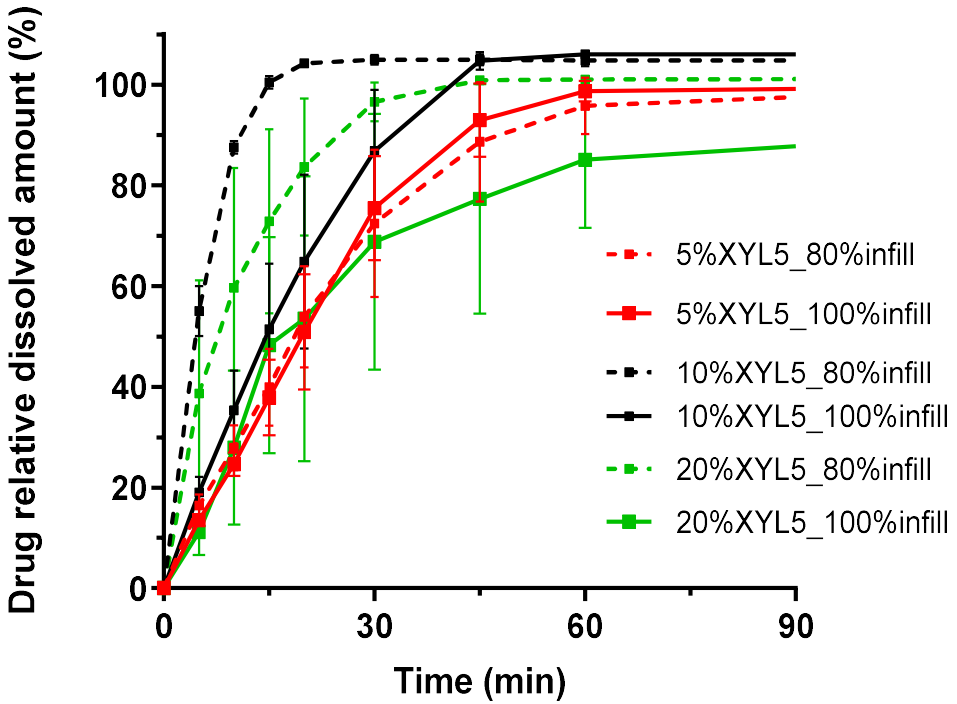
IR 3D-printed tablets with a hydrophilic model compound

- Drug load affected drug release profile depending on formulation
- No degradation products detected, assay correlated well with the weight of 3D-printed tablets, however weight uniformity appears to be variable due to filament diameter variability and incomplete printing process
- Main technical constraint is mechanical properties of the intermediate product (filament) – feasible drug load up to 20%
- Main risk is thermal degradation during hot-melt extrusion – to be checked with a thermally labile compound



Dissolution profiles of FDM 5-20% **caffeine** 3D-printed tablets with 80% or 100% infill density (pH=2, USP II paddle 50 rpm)

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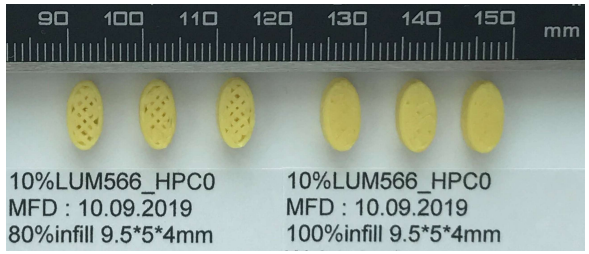
Development of 3D-printed tablets with a lipophilic model compound



- BCS Class IV compound, thermolabile, **amorphous solid dispersion (ASD)** is critical for desired bioavailability
- Tablets with size suitable for children above 6 years were sucessfully printed, with improved weight uniformity and external apperance
- No additional degradation during 3D-printing for HPC-based formulation, but additional degradation of about 10% for Kollicoat® IR-based formulation
- Previously developed formulation knowledge did not result in achieving IR: need in a different main matrix former
- Filaments contained crystallinity traces already 2 months after manufacturing

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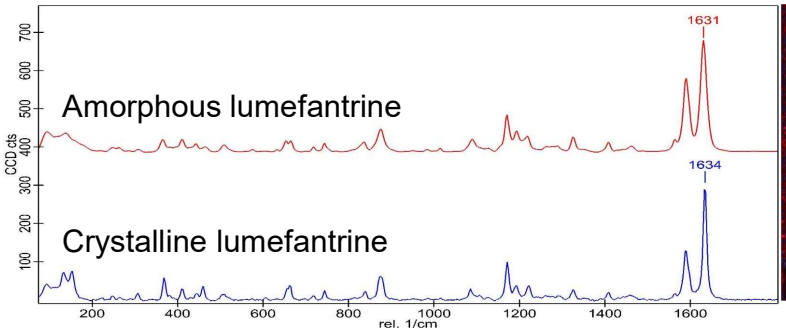
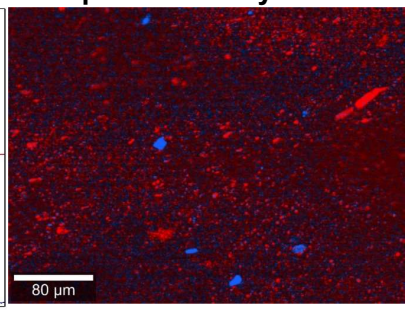
Overcoming recrystallization in filaments: FDM 3D-printing as a tool to achieve ASD on demand

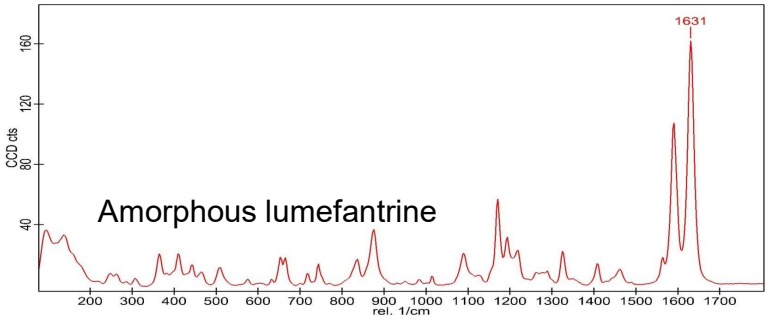
10% LUM566 HPC0, **filament**, 3M, RT



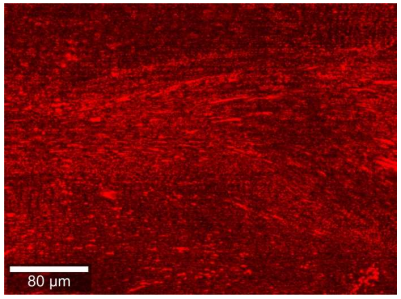
Cross section: A mixture of **amorphous and crystalline API**



10% LUM566 HPC0, **FDM-tablet**,1M,RT



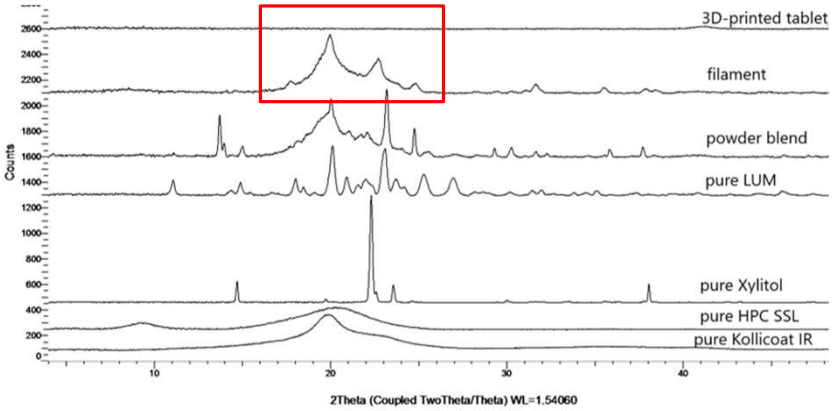
Cross section: **Amorphous API**



M.Fanous et al., 2021, EJPB, under review

- Amorphous state of lumefantrine is critical for the desired bioavailability
- Potential to overcome ASD physical stability hurdles via decentralized 3D-printing
- **It was possible to achieve full ASD independently on the solid state of the intermediate product**

10% LUM566 XYL5, XRPD overlay



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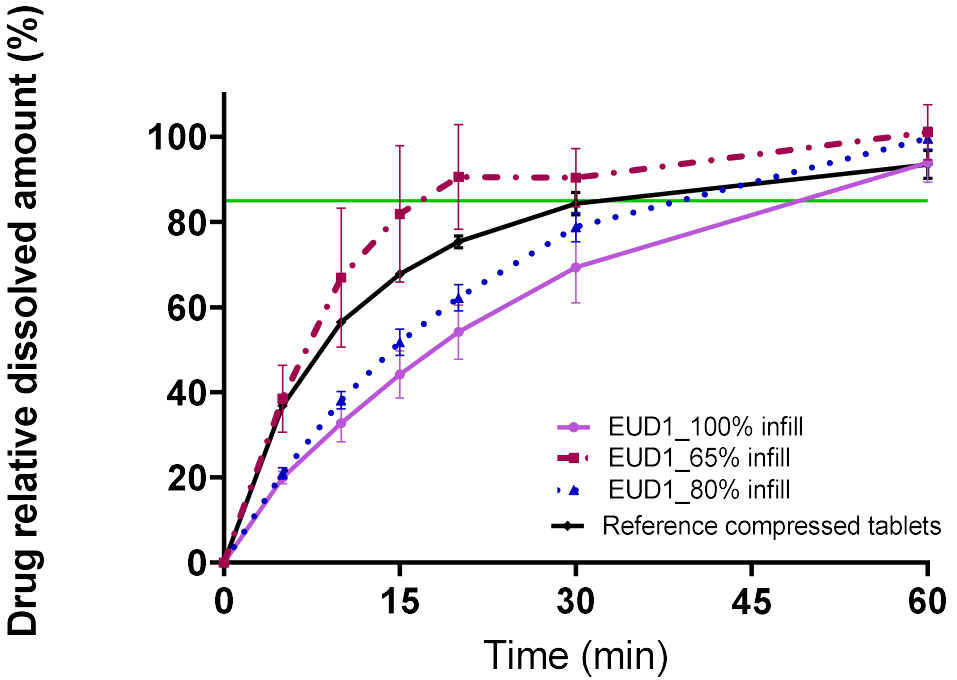
Immediate Release (IR) 3D-printed tablets development with a lipophilic model compound

- Different main matrix former was explored
- IR 3D-printed LUM tablets developed via combining Eudragit® EPO-based formulation approach with design modifications
- 80% infill density was not sufficient, 65% infill density was required
- To bridge between printed morphology and dissolution performance, actual morphology should be studied

M. Fanous et al., Int J Pharm, 2021



Dissolution profiles of 3D-printed tablets (5% lumefantrine, 72% Eudragit E PO, 13.5% xylitol, 9.5% maltodextrin) with 100%, 65% and 80% infill density; and of reference compressed 120 mg lumefantrine tablets

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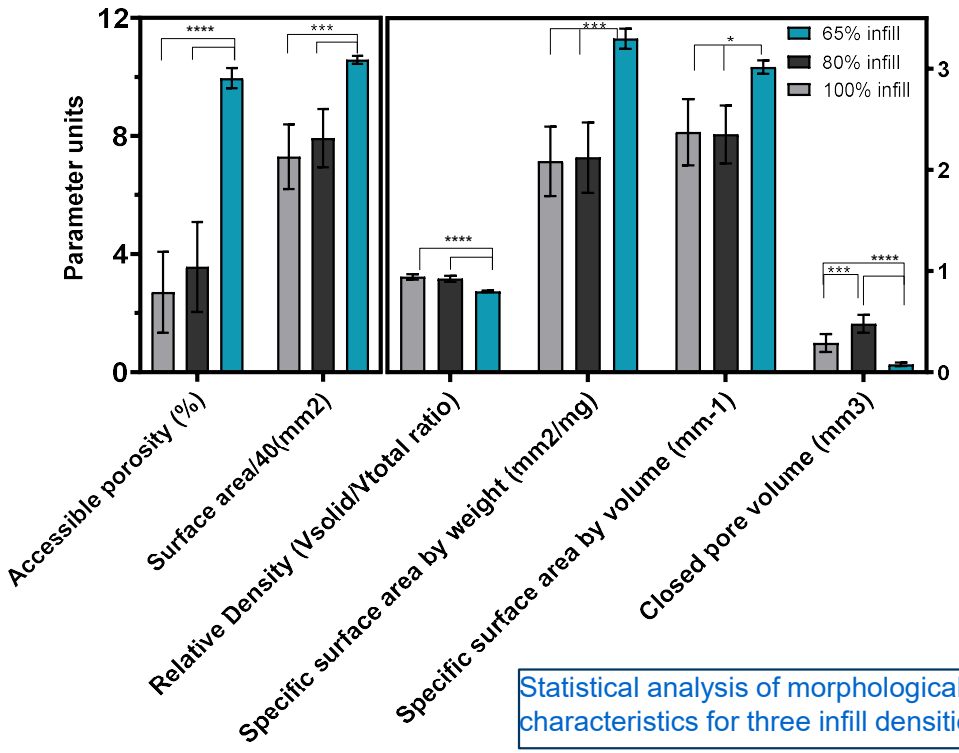
Immediate Release (IR) 3D-printed tablets development with a lipophilic model compound

- Key structural parameters for the dissolution were detected using non-destructive accurate morphological analysis based on µCT
- Accessible porosity and specific surface appeared to critically impact the model drug dissolution rate
- Maximal drug load of 5% was feasible due to the filaments' **brittleness**



Statistical analysis of morphological characteristics for three infill densities

M. Fanous et al., Int J Pharm, 2021

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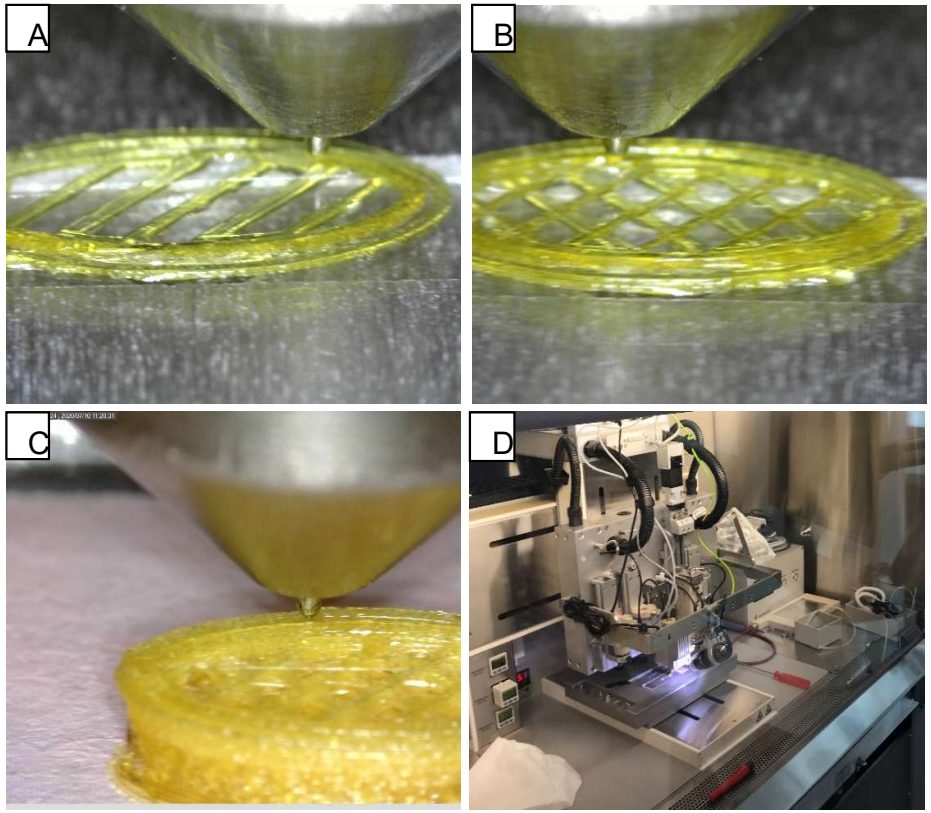
Simplification of FDM 3D-Printing Paradigm: Direct Powder Printing development

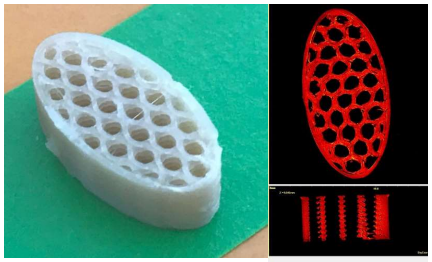
- **Direct Powder Printing (DPP) concept (powder blend---tablet) was developed**
  - To reduce number of process steps
  - to allow 3D-printing independently of mechanical properties of a filament and potentially prolonging product shelf life
- **DPP with high drug load**
  - High resolution (0.2 mm nozzle) 3D-printed tablets were successfully printed using with 15-30% lumefantrine Eudragit EPO-based formulations
  - The printable formulations had a clinically relevant drug load - 15% and 30%, when for FDM only 5% drug load was printable
  - Full amorphous solid dispersion confirmed 3 months after manufacturing (Current drug product is limited to 17%)

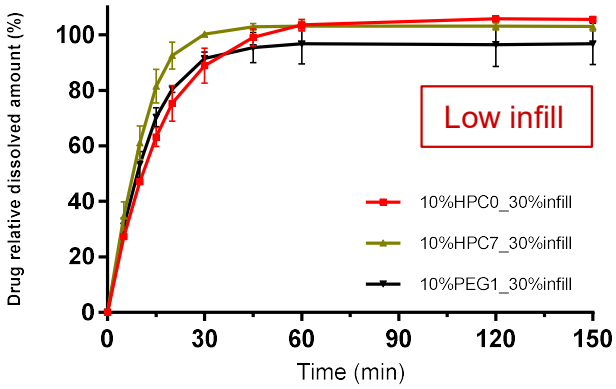


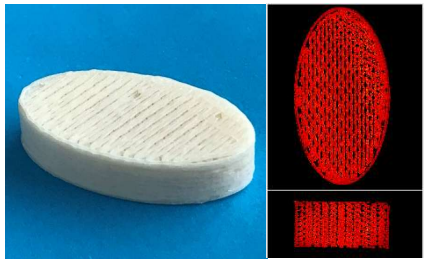
Representative example of 15% lumefantrine Direct powder printing with 50% grid infill density (A-C) with RegenHU Bioprinter set up (D)

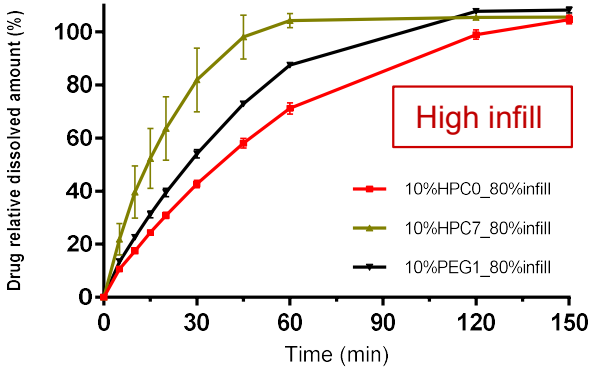
Direct powder printing of IR tablets

- High resolution tablets loaded with a hydrophilic drug model were sucessfully directly printed from powder
- Infill density affected drug release profile similarly to FDM 3D-printed tablets
- Developed formulations demonstrated acceptable weight and content uniformity, and rapid dissolution of the drug
- A customized printhead with a controlled heating zone to reduce the melt residence time, and an alternative for a compressed air are still to be developed









Drug dissolution profiles of Directly printed 10% caffeine tablets with low(left) and high (right) infill density. M.Fanous et al, IJP, 2020

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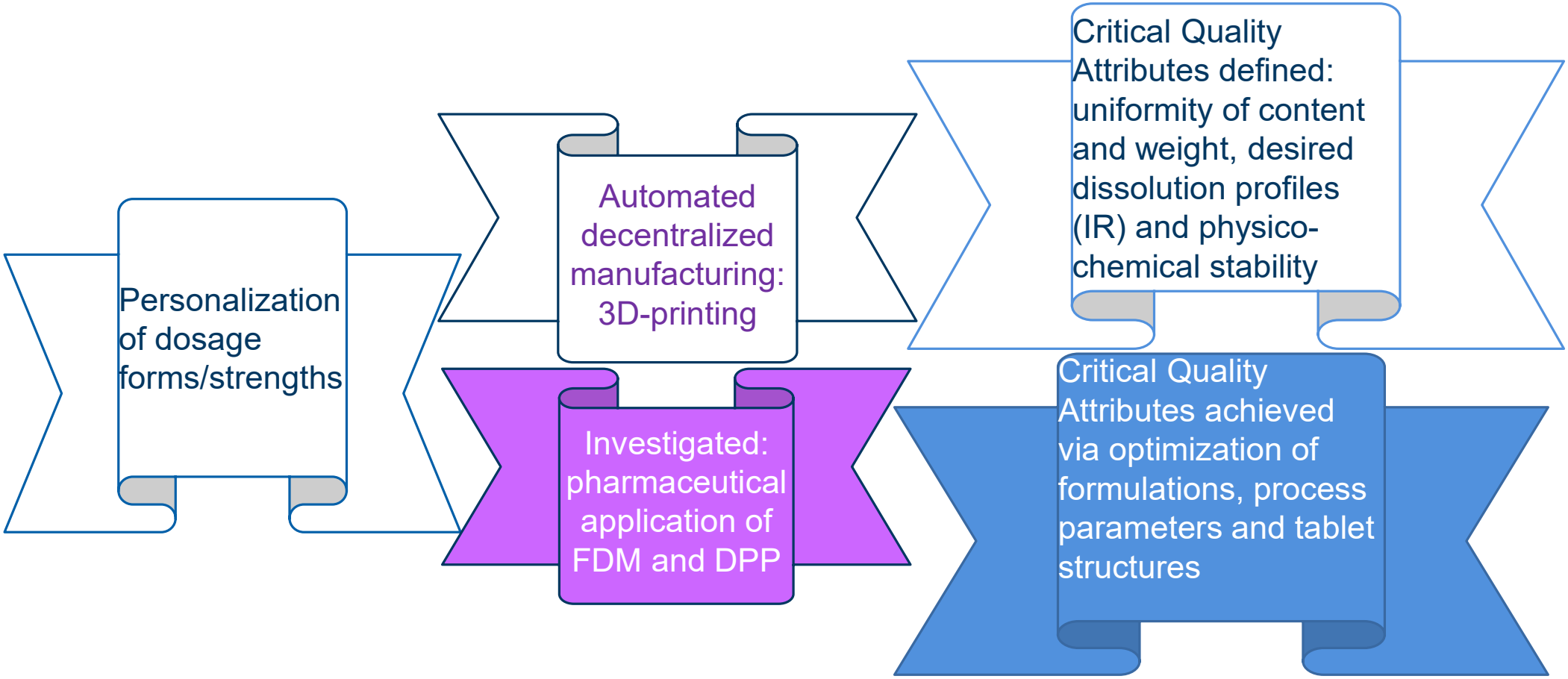
Summary



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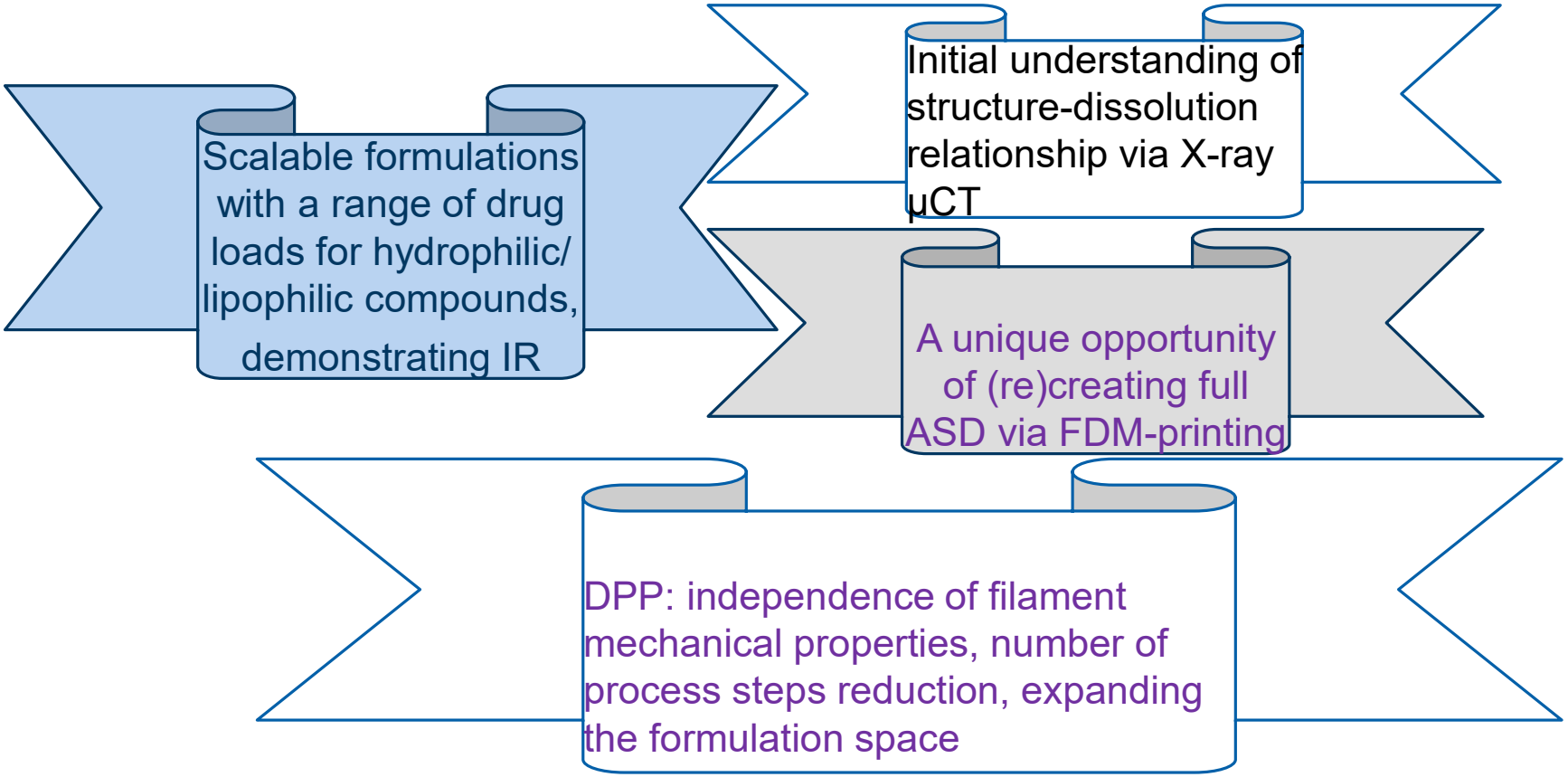
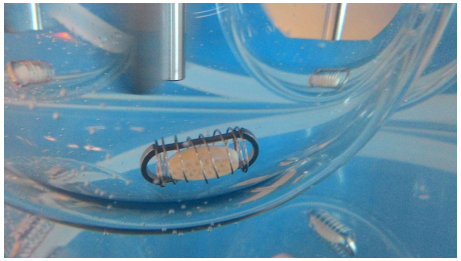
Summary



Outlook and opportunities



- The presented approaches of hydrophilic polymeric matrices combined with designed CAD structures for 3D-printing could be applied in future personalized pharmaceutical development
- For the clinical implementation of the technology, development of equipment, Quality Control and real-time-release-testing (RTRT) strategy is required
- The healthcare ecosystem needs be modified accordingly, including a coordinated effort between pharma companies
- In the future, drugs might be printed decentrally based on the approaches developed in this work, following personalization of the dose based on the patient's biomarkers, questionnaires or interactive artificial intelligence (AI) interface

What's next?

- Powder-based 3D-printing technology: first pharmaceutical Spritam® (levetiracetam) was **approved** by the FDA in **2015**
- Extrusion/melt-based technology: IND clearance from FDA for pharmaceutical T19 (for Rheumatoid Arthritis) in **2021** and T20 (cardiovascular and coagulation disorders) in **2022**
- New: T21 (for Ulcerative Colitis) developed in partnership between Triastek, Inc and Eli Lilly received IND clearance from FDA in **November 2022**
- **Future: which drugs/indications in your opinion require personalization?**

Source: Clinical trials authorised for 3D-printed ulcerative colitis drug (europeanpharmaceuticalreview.com), accessed 21-Mar-2023

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Manan Vora
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Mohamed Raoui
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Patricia Seiler
Renate Pflugi
Silvain Mueller
Séverine Serreau
Swiss 3D-printing Network
Toni Widmer
3D-printing Network@Novartis

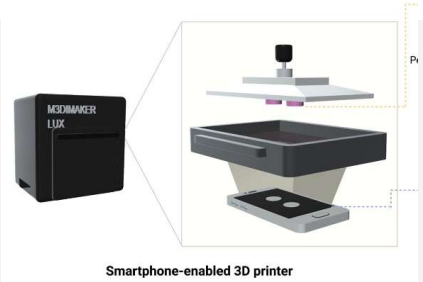
Back up

Opportunities - Medimaker

FabRx

M3DIMAKER

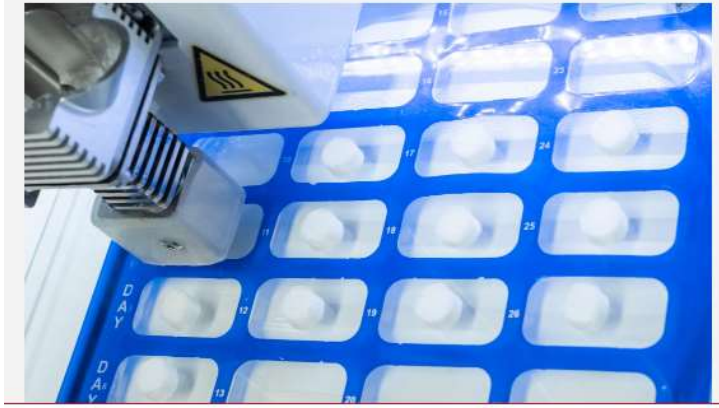
The world's first pharmaceutical 3D printer for personalised medicines.



Smartphone-enabled 3D printer

October 25, 2021 | Featured

Smartphone-enabled 3D printing of medicines



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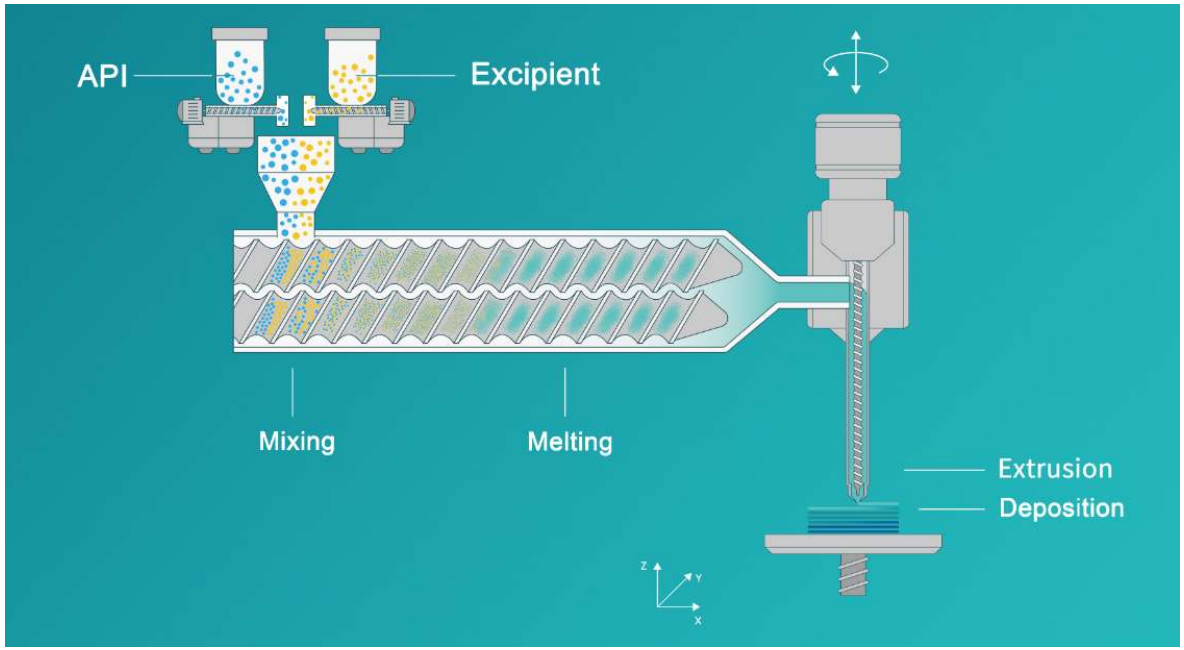
Opportunities – Melt Extrusion Deposition (MED®)



Triastek, Inc

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Pharmacogenomics already routinely used for drug therapy decisions incl. dose personalisation

- Established in the Netherlands:
  - Medication guidelines from pharmacist association KNMP: actionable recommendations on interactions and dose adaptations based on genetic information, with links to comprehensive monographs

KNMP PGx guidelines

- Being studied Europe-wide in European Community funded large U-PGx program:
  - Prepare-Study: 8100 patients in 7 centers in Europe for treatment with 42 drugs - either as per standard label or applying KNMP guidelines using the patient's pharmacogenetic data to select the right drug or dose.
    => Effect on clinical outcomes?

U-PGx - Design & ategy, ClinPharmTh

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THE STARTUPS DISRUPTING THE PHARMACY SECTOR IN 2020

Which companies are gaining traction and where?

Virtual Pharmacy

Digital Therapeutics

Chronic Disease Management

Pharmacogenomics

Home Lab Testing & Monitoring

Direct-to-Consumer Prescription Services

Expand Pharmacist Services & Workflow

2020 EXITS & ACQUISITIONS

Who went public or got bought?

GoodRx
Went public launching their IPO in November 2020.

MedAvail
Acquired MYOS RENS Technology and became listed in November 2020.

divvyDOSE
UnitedHealth acquired divvyDose in September 2020 for around $300M

Livongo
Teladoc acquired Livongo for $18.5B in October 2020.

zipdrug
Anthems' new PBM (IngenioRx) acquires ZipDrug for an unknown amount in July 2020.

2021 PREDICTIONS

What happens post-COVID19?

FOCUS ON VACCINATIONS
With a likely need to use pharmacists to boost the vaccination needs of the public, there will be a focus on companies expanding their platforms to leverage or champion these services which may be a short term service.

MORE DELIVERIES
Post-pandemic will see patients more inclined to stop going into the pharmacy and see more mail order, meaning also pivoting other pharmacy products (eg. OTC).

REMOTE CARE
Pharmacy businesses will see a push for using remote care via RPM or DTx to add further clinical services - medication management and mental health are large areas.

IN PHARMACY SERVICES
Brick and mortar pharmacies will seek to expand services to draw customers back in, such as testing or a push for expanded clinical services only face-to-face can accomplish.

MOBILE ENGAGEMENT
No matter what, post-covid will see consumers of health expect mobile first then in-person if not feasible. Companies will stregthen mobile platforms and clinical services.

TheDigitalApothecary.com

Ver. 3.2 | Last updated December 15, 2020

Created by
TIMOTHY AUNGST, PHARMD

Real-Time-Release-Testing (RTRT)

- **RTRT:** a system of release that gives assurance that the product is of intended quality, based on information collected during the manufacturing process (based on product knowledge and process understanding & control)
- Platform: quality risk management principles & application of an appropriate pharmaceutical quality system

Batch-wise Quality Control and release

+

Validated, controlled printing process; documented

RTRT – omitting end-product testing

- Filament diameter
- Content uniformity
- Mechanical properties

- Nozzle/bed temperature
- Melt viscosity
- Structure and weight monitoring

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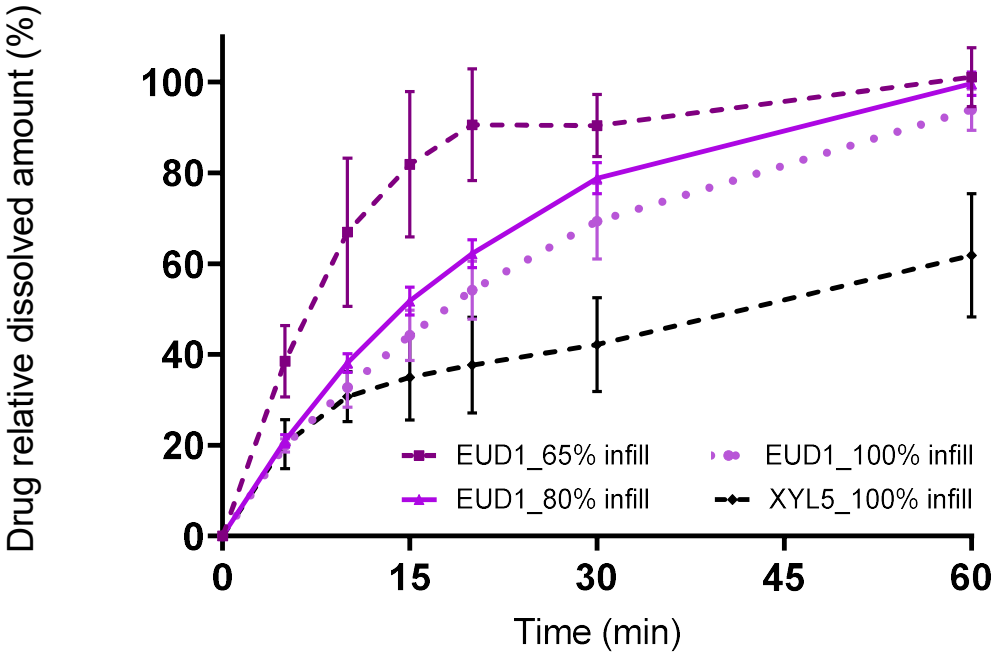
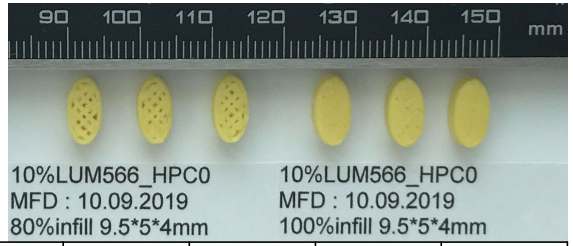
Improving dissolution rate via printing design

- Lumefantrine: BCS class IV compound, solubility in water 0.01 mg/L
- Immediate Release is possible to achieve via formulation and design combination





Formulation component (% w/w)	EUD1	EUD1	EUD1	HPC0	HPC0	XYL5	XYL5
LUM566	5	5	5	10	10	10	10
HPC SSL				90	90	22.5	22.5
Kollicoat IR						45	45
Eudragit E PO	71.3	71.3	71.3				
Maltodextrin	9.5	9.5	9.5			9.5	9.5
Xylitol	14.3	14.3	14.3			14.3	14.3
3D-printed tablets							
infill density (%)	80	100	65	80	100	80	100
Average weight (mg)	142	139	100	128	152	142	163
Std (mg)	10.6	13.4	1.4	9.1	2.3	5.9	2.3
std (%)	7.5	9.7	1.4	7.1	1.5	4.2	1.4

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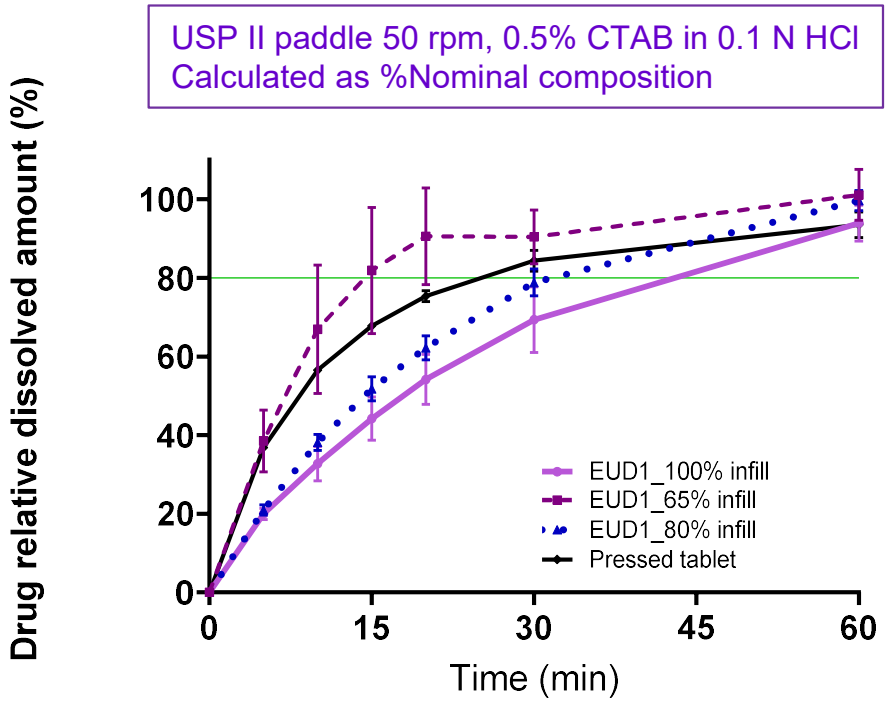
Conclusions and possible next steps

- Immediate Release 3D-printed tablets were possible to develop via formulation and design combination
- In order to achieve clinically relevant doses, higher drug load is required
- Filaments with higher drug load demonstrated increased brittleness, seems to be not feasible to print via fused deposition modeling (FDM)
- Advantages of Direct Printing: skipping hot-melt extrusion step and application of thermal stress only once, 3D-printing independent of mechanical properties of a filament

Development of IR 3D-printed tablets with a lipophilic model compound

- Combining Eudragit EPO-based formulation approach with design modifications, it was possible to successfully develop IR 3D-printed LUM tablets
- Key structural parameters for the dissolution were detected using non-destructive accurate morphological analysis based on µCT
- Increase in accessible porosity, total surface area, specific surface area by weight and by volume and decrease in relative density appeared to impact the lumefantrine dissolution rate, whereas increase in closed pores volume did not increase the dissolution
- Maximal drug load of 5% was feasible due to the filaments' brittleness

M. Fanous at al, Int J Pharm, 2021



Dissolution profiles of EUD1 (5%EUD1:72% Eudragit E PO: 13.5% Xylitol:9.5% Maltodextrin) with 65%,80% and 100% infill density and commercial LUM tablets 120 mg

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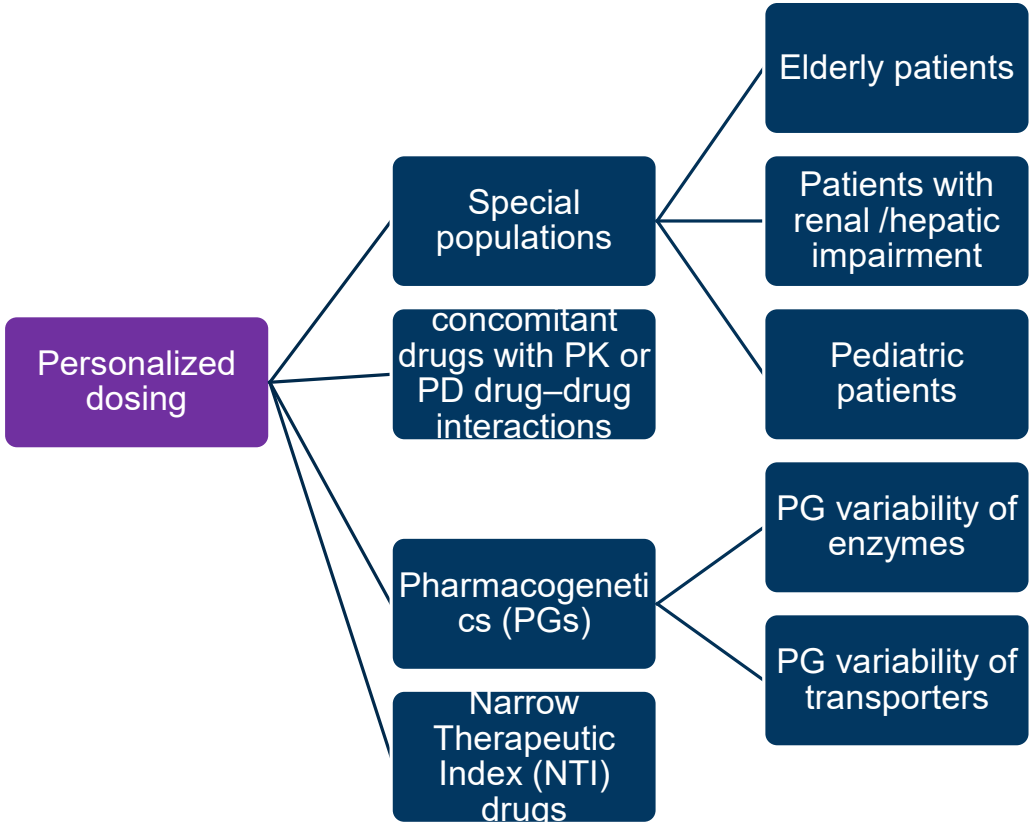
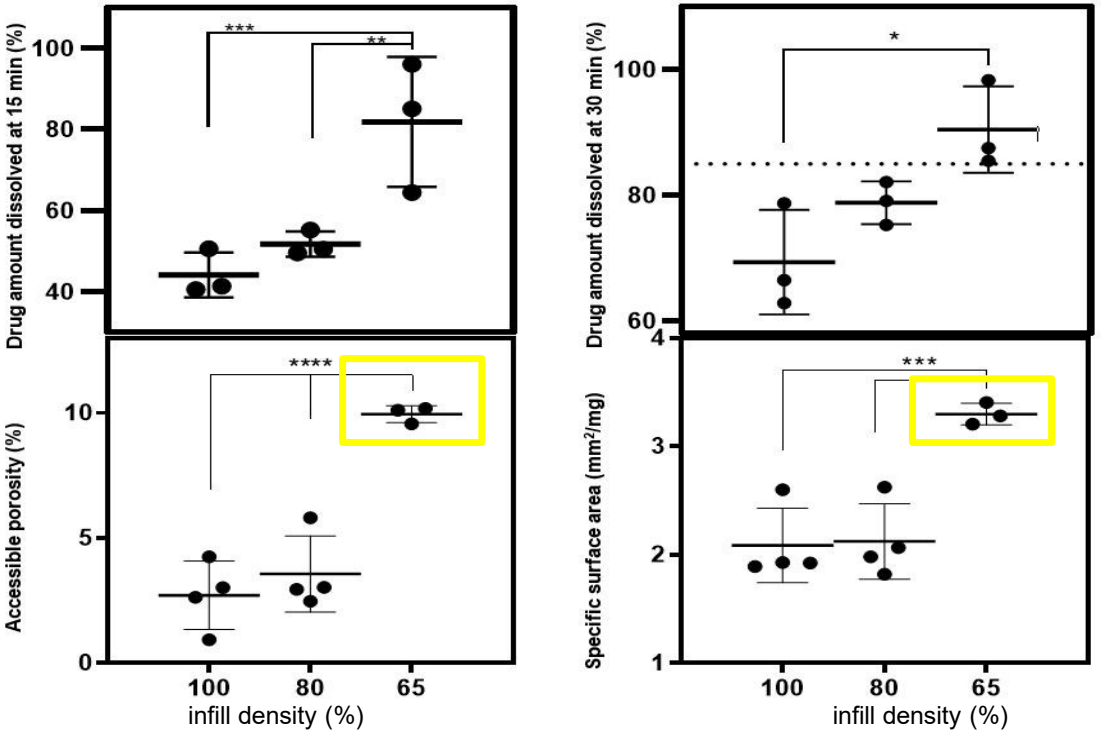
Clinical considerations relevant for the personalized dosing need



Immediate Release (IR) 3D-printed tablets development with a lipophilic model compound

- Key structural parameters for the dissolution were detected using non-destructive accurate morphological analysis based on µCT
- Accessible porosity and specific surface appeared to critically impact the model drug dissolution rate together with decrease in relative density, whereas increase in closed pores volume did not impact the dissolution
- Maximal drug load of 5% was feasible due to the filaments' **brittleness**



Statistical analysis of morphological characteristics and dissolution performance for three infill densities shown in the x-axis, *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001

M. Fanous at al, Int J Pharm, 2021

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