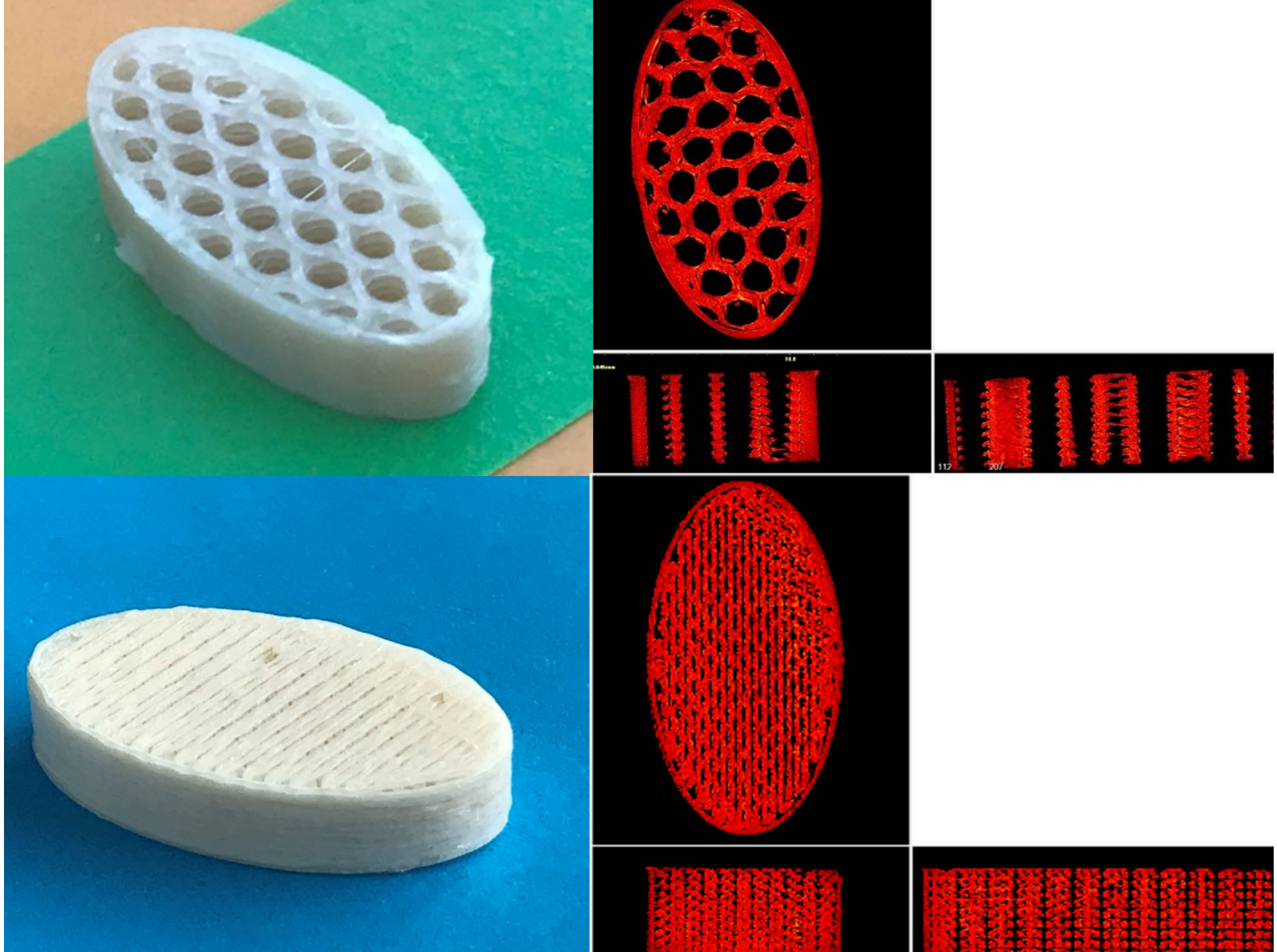


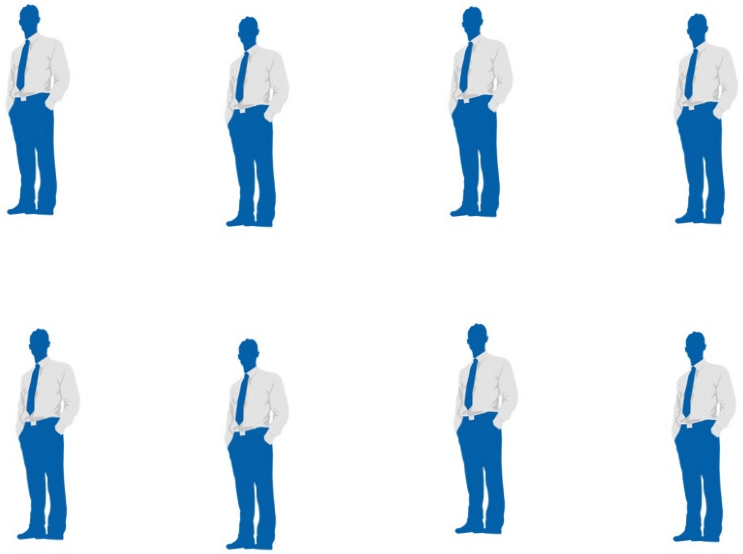
Additive manufacturing of pharmaceutical tablets –

Possibilities, technical challenges, future promises

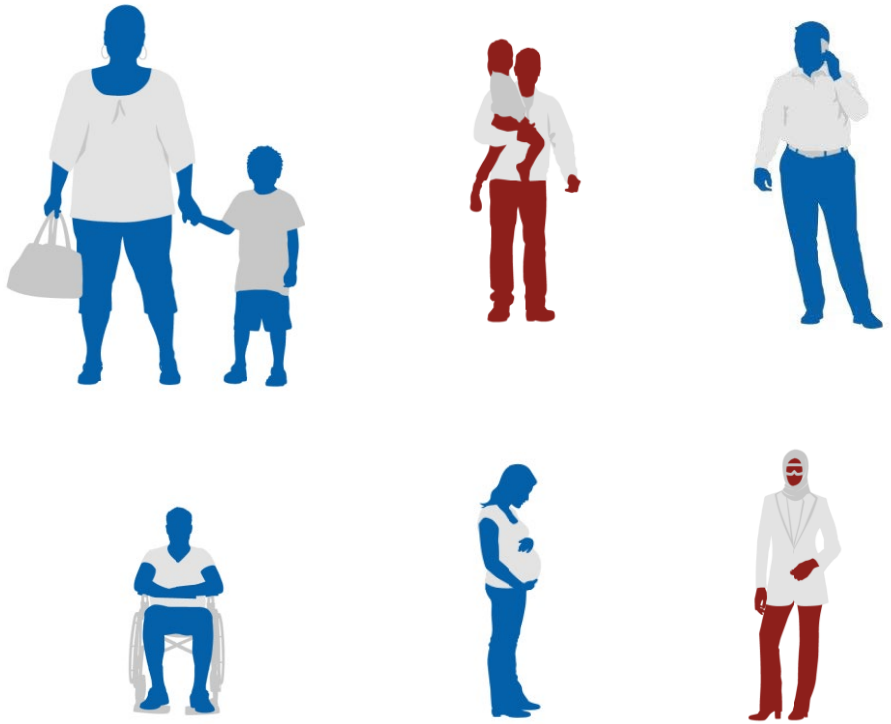
School of Life Sciences – University of Applied Sciences NW Switzerland

In part from the PhD thesis of Marina Fanous-Gurina in collaboration with Novartis Pharma AG

Precision pharmaceuticals – Because one size does not fit all



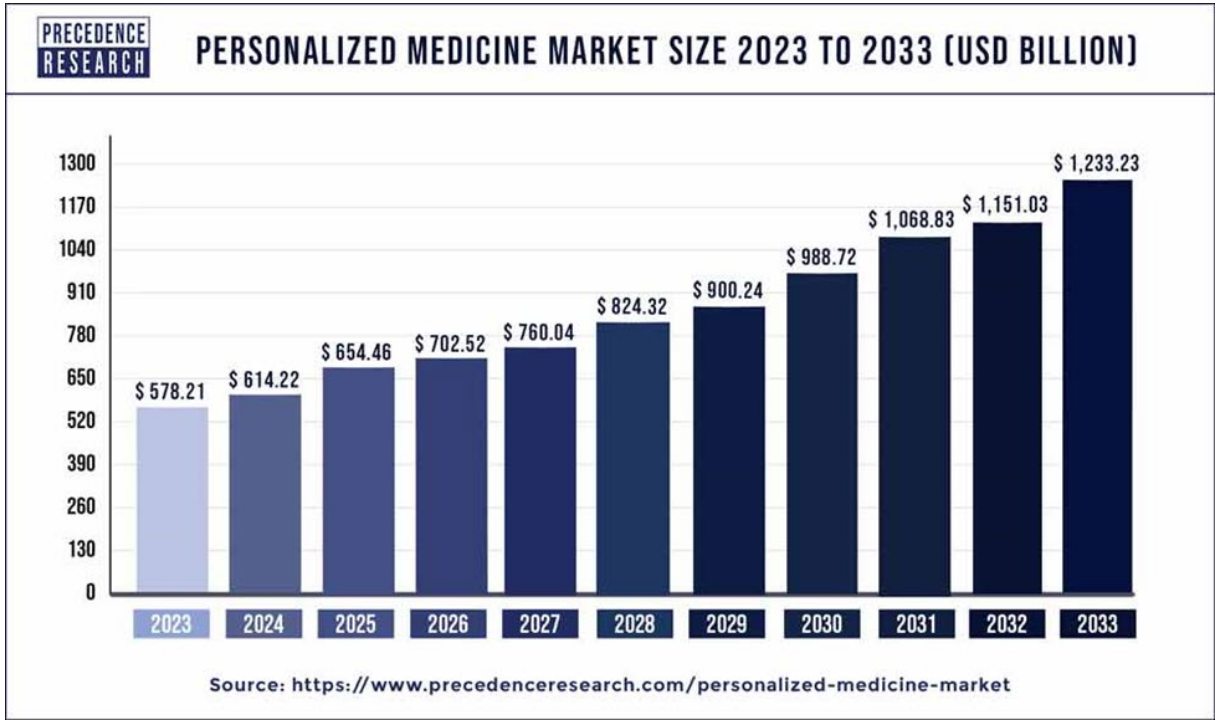
Current: Large scale manufacture for the average individual



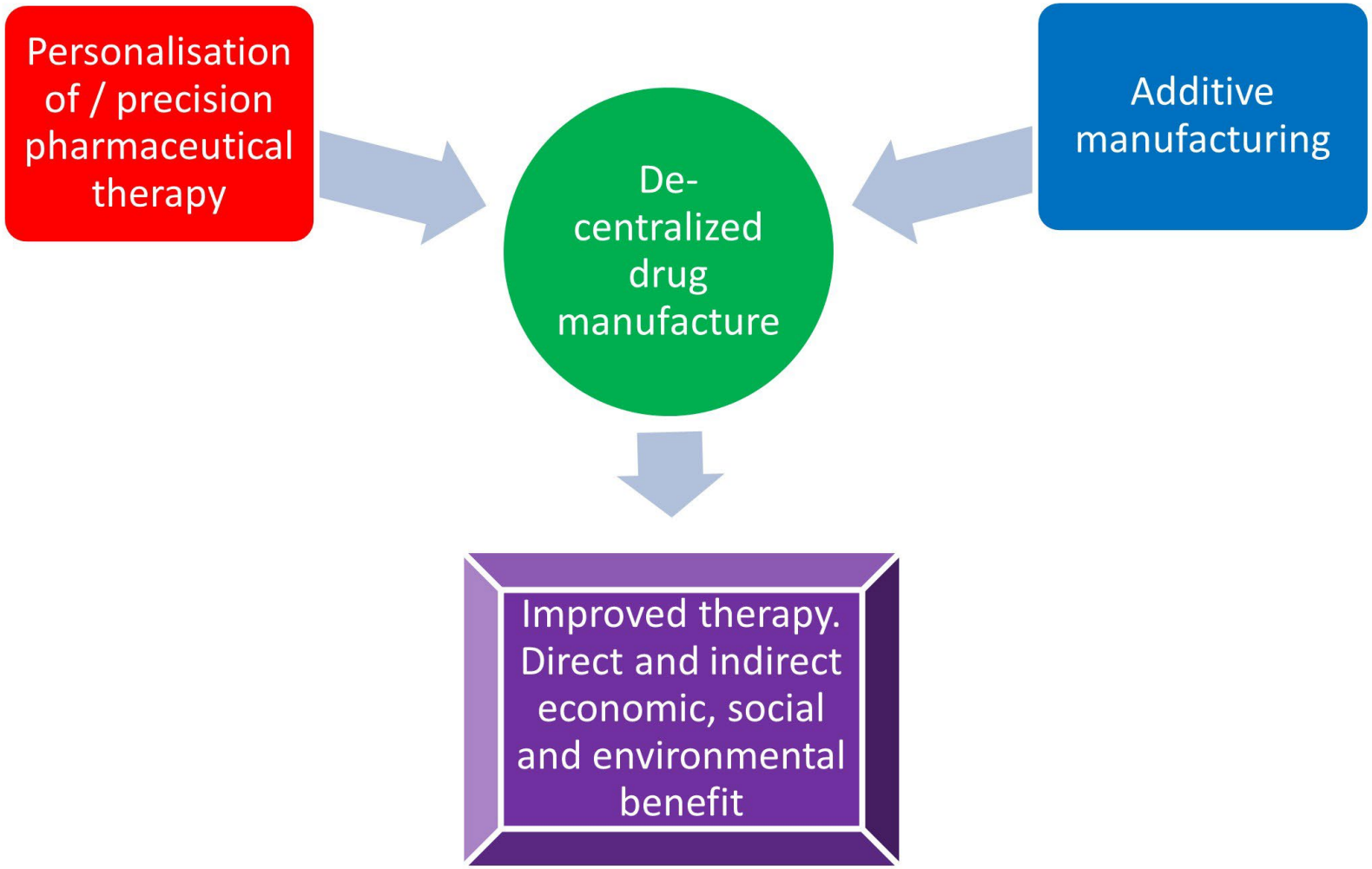
Upcoming: Personalized medicines, one person – one product

Estimated volume of personalized pharmaceuticals and decentralized manufacturing p.a.		
	Units / Doses	Monetary value
World (total)		$578 \cdot 10^9$ $US (2023) – $5.39 \cdot 10^{12}$ $US (2022) CAGR 8.1% (2024-2033)
World – Compounding community pharmacies		$8.12 \cdot 10^9$ $US (2021) – $13.5 \cdot 10^9$ $US (2025) CAGR 6.2% (2022-2031)
Switzerland (10 most common products and active ingredients in pediatrics)	150,000 doses	
Typical University hospital – Pharmacy In- and out-patients	3,500 units * (packages)	215,000 CHF (based on official remuneration tariffs) 500,000 – 700,000 CHF (full-cost accounting)
Four University hospitals and 46 other public institutions in Switzerland		$12 \cdot 10^6$ CHF (full-cost accounting)
Typical University hospital – Savings by personalized compounding due to reduced waste compared to current practice		200,000 CHF **
Compounding typical community pharmacy	14,000 units (packages)	400,000 CHF
Decentralized manufacturing for compensation of drug shortages	500 products 30% increase 2021-2022 (USA)	Priceless since lack of medication has resulted in documented deaths of patients
Investment for 3D-printer (for cost / benefit comparison)		≈ 100,000 CHF
Remarks: *Solid and liquid dosage forms ** CHF 13,000 per ward; CHF 1 – 1.4 million for the whole of Switzerland.		

Forecasted growth



Concept


Personalisation of / precision pharmaceutical therapy
Additive manufacturing
De-centralized drug manufacture
Improved therapy. Direct and indirect economic, social and environmental benefit

Emerging technology to meet existing need

So far…

<u>3D-printing – Potential</u>

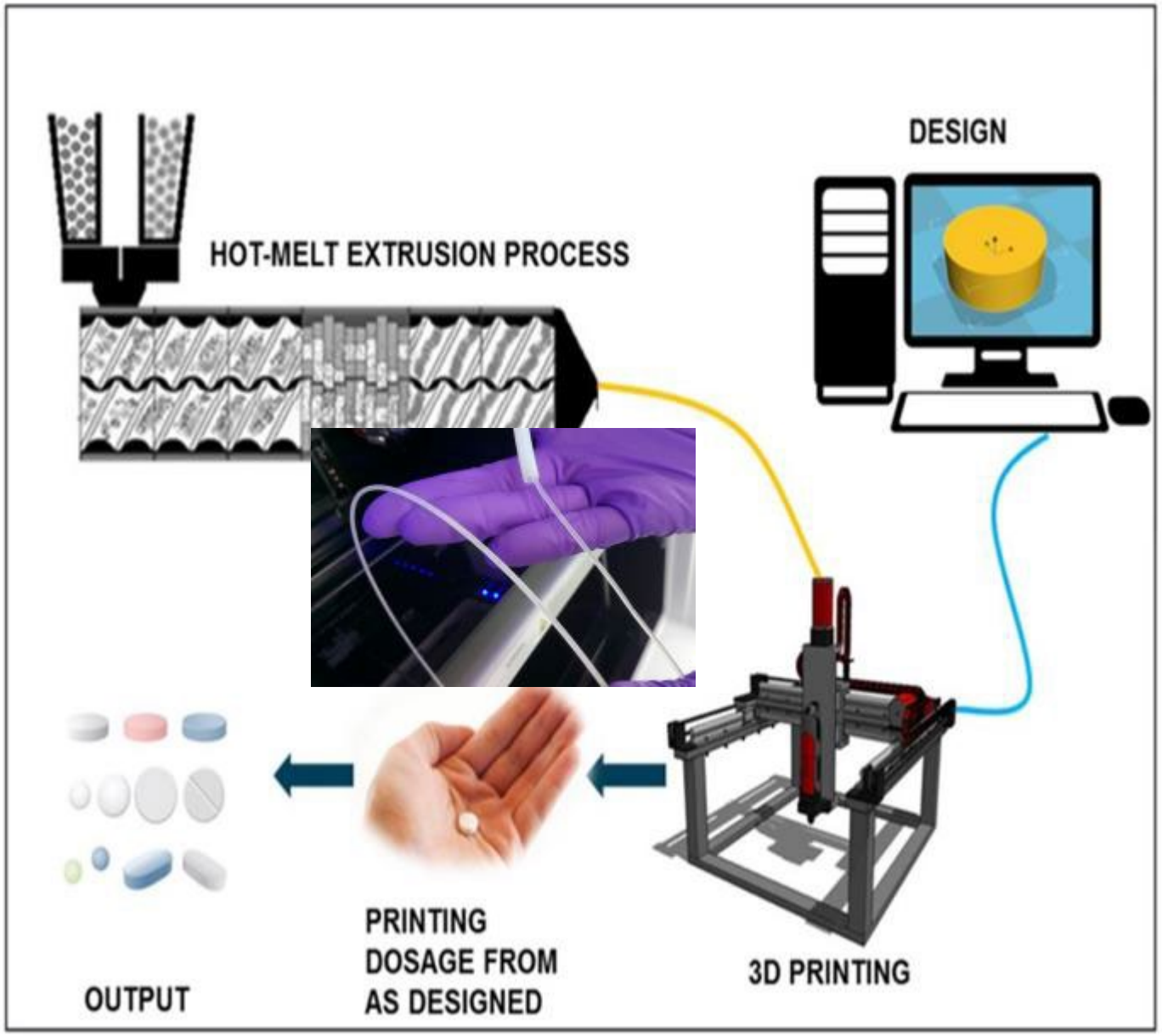
- Combination of personalization with decentralized / on-site manufacture
- Tailored dosing
- Pediatrics, geriatrics, multi-morbidity
- Tailored release profile
- Short(er) development path
- No production scale-up
- No shipment, no storage
- Reduced waste
- From clinical trial to patient treatment
- Flexibility & versatility of dosage form design
- Prototyping

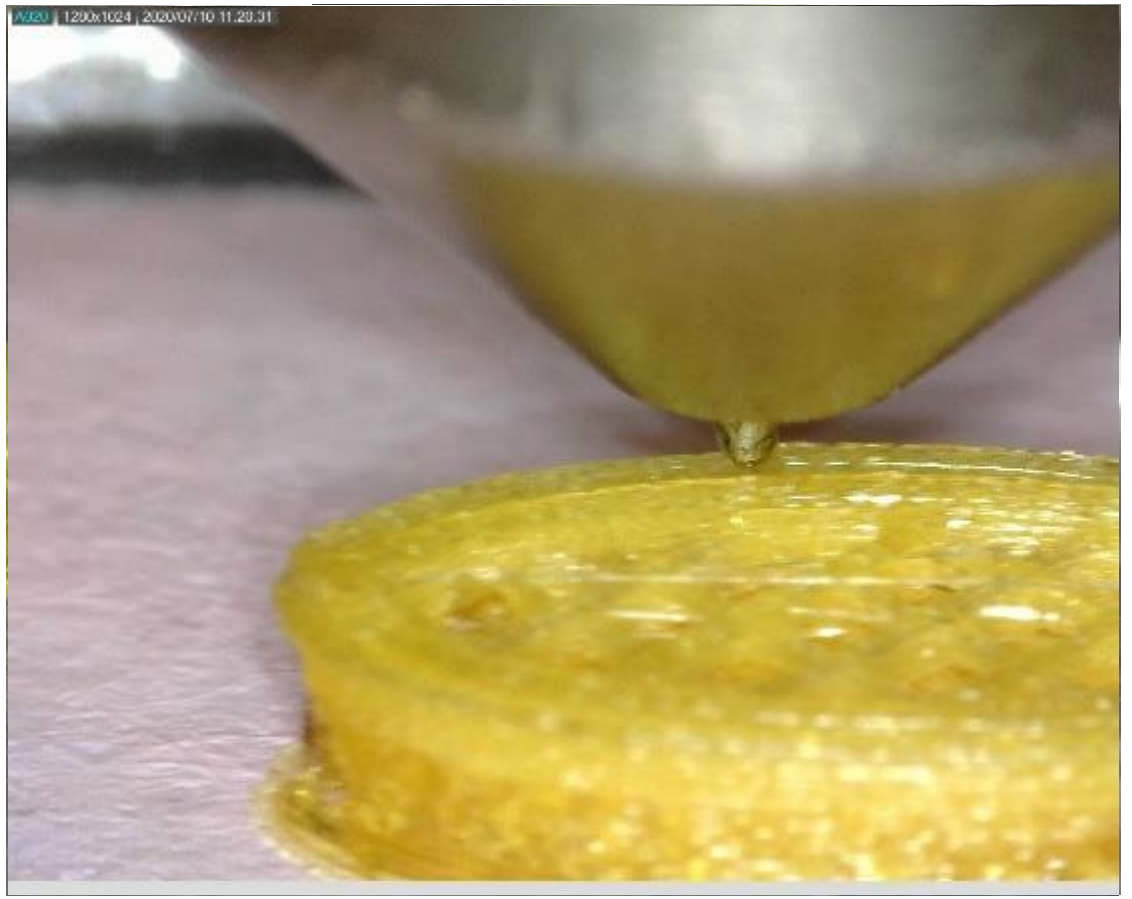
3D-printed tablets	Hard gelatine capsules	Liquid suspensions
Automation / digitalization	Manual operation	Manual operation
Possibility for full cGMP compliance	Only partially possible due to lack of process standardization	Only partially possible due to lack of process standardization
Standardization and good accuracy and reproducibility possible due to automation	Operator dependent	Operator dependent
Attainability of current industry standards feasible	Limited possibility due to, in part, antiquated methodology	Limited possibility due to, in part, antiquated methodology
Process validation and integrated documentation (batch record) possible due to computer control	Validation practically impossible and documentation can be performed only by hand	Validation practically impossible and documentation can be performed only by hand
Orally dispersible tablets (ODT) assure improved storage stability		Challenging and often limited physical stability of suspension Limited chemical stability of active ingredient in liquid form
ODTs provide easy and accurate administration		Liquid administration to babies and infants problematic Reading mistakes of the scale unit cause dosing failures Sedimentation compromises uniformity
Immediate release (IR) tablets based on structured infill and designed accessible surface area in combination with adequate formulation	Powder-filled capsules provide limited possibility to control or modify release especially of poorly water-soluble drug substances	
Ease of adjusting the dose by changing the size of the printed tablet using the same formulation and the same hardware (3D-printer)	Change of capsule size, filling machine and amount of bulking agent of the formulation required to adjust dose	
Content uniformity can be achieved based on the homogeneity of the printed semi-solid formulation	Content uniformity extremely difficult to realize at low dose and low drug load due to cohesiveness and segregation of powder mixtures	
No need for a capsule	Use of gelatine poses problems due to water sensitivity	

Profitability calculation

	Current	Future
Typical batch size	25 to 100	500
Mode	Manual	Automatic
Variation within batch	Not possible	Programmable
Labor cost per batch (wages only)	CHF 95 (1 hour)	CHF 190 (4 hours)
Labor cost for annual production	CHF 1,672,000 (batch of 25) to 418,000 (batch of 100)	CHF 160,000
Sales price based on ALT tariff for processing and finishing of capsules (annual)	CHF 915,000 (batch of 25) to CHF 400,000 (batch of 100)	CHF 400,000 (?)
One-time investment for equipment (3D-printer)	n/a	≈ CHF 100,000
Annual production = 440,000 doses		

Fused deposition modeling (FDM) 3D-printing



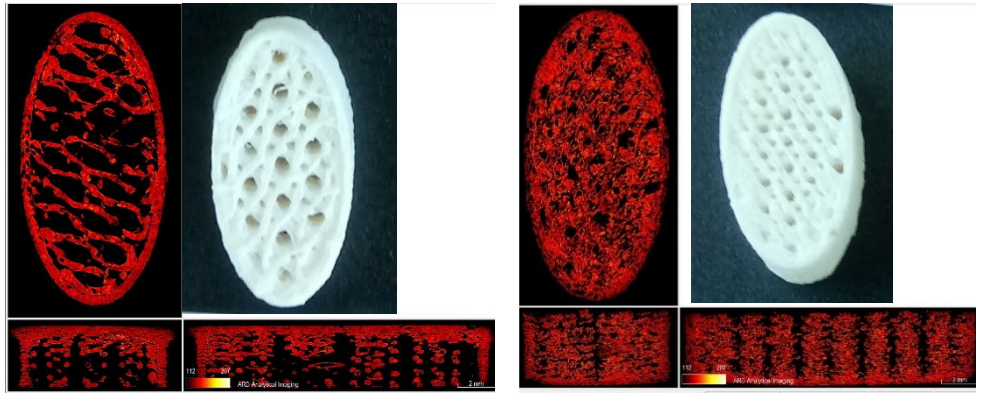


Caffeine formulations for immediate release (IR) tablets

<u>Components</u>
HPC SSL
Kollidon VA64
Kollicoat IR
PEG 4000
Maltodextrin
Xylitol

Designed infill density

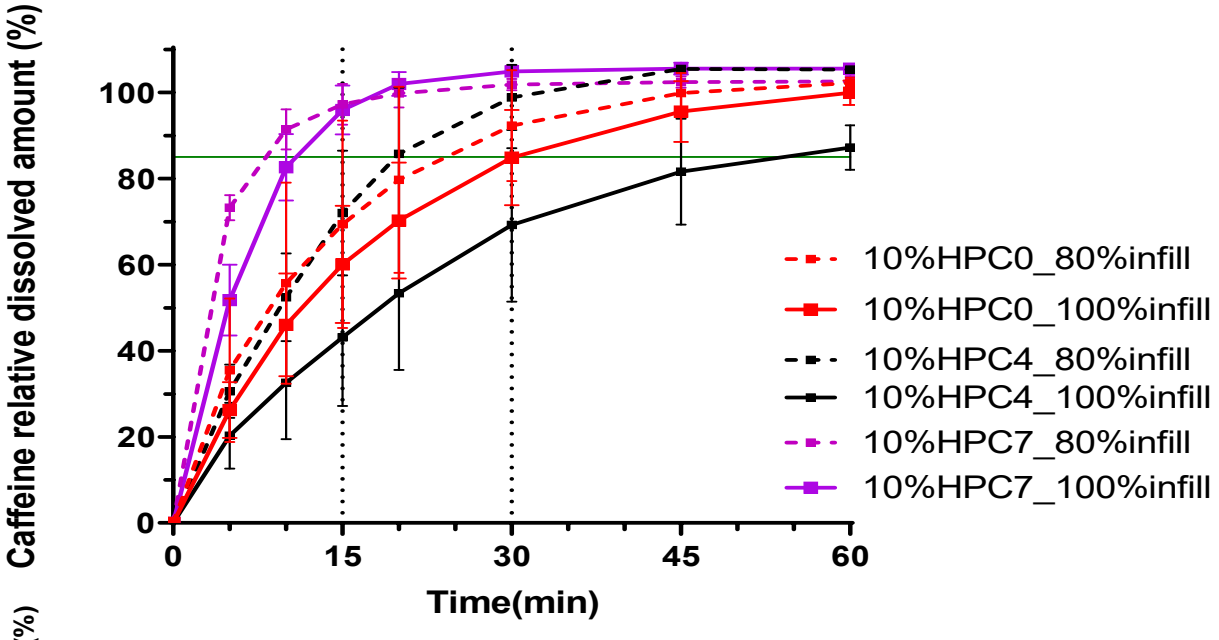
80% 100%

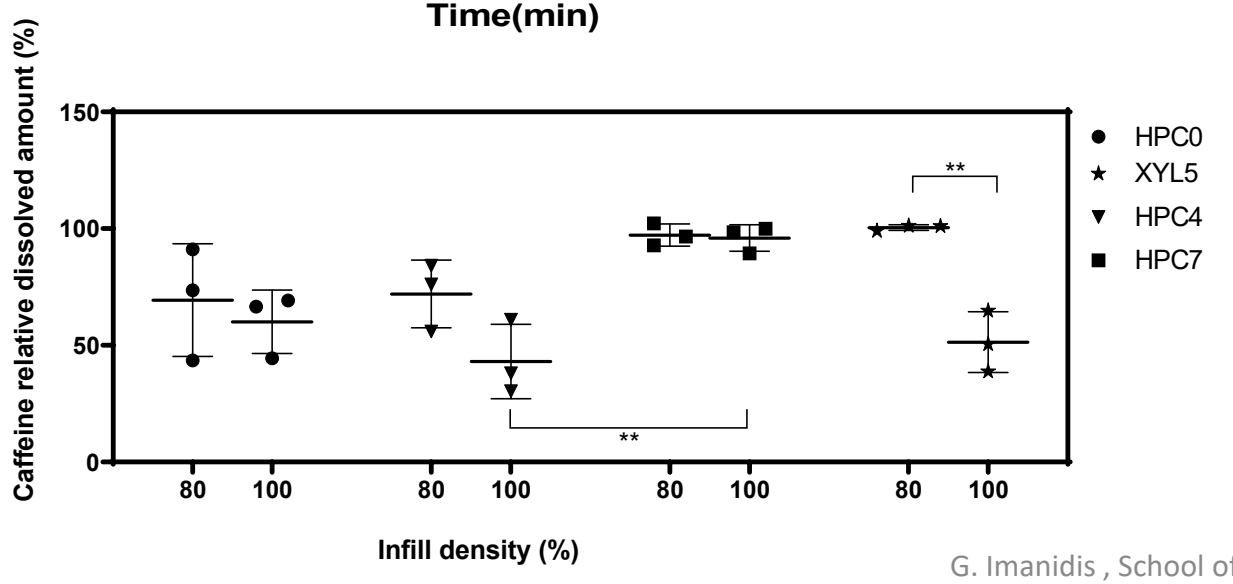


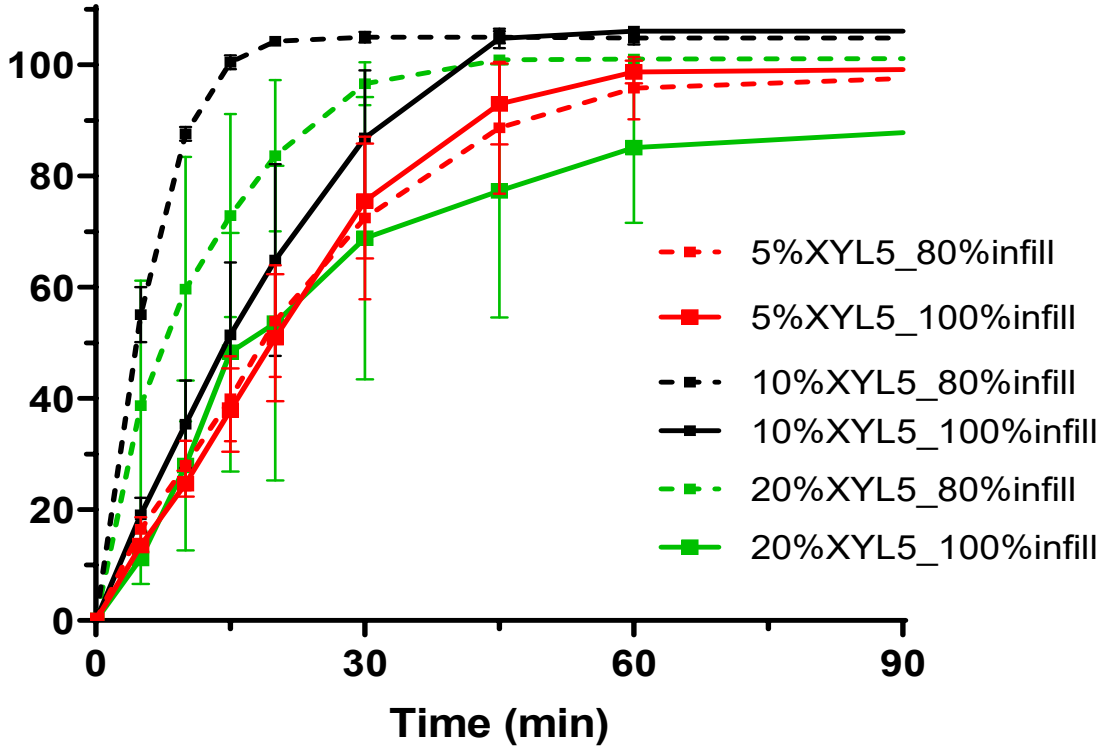
Dependence of tablet weight on formulation, drug load and infill density

Nominal drug load (%)	Formulation code	Programmed infill density (%)	Average weight (mg) ± std (%)	Assay (%) ± std (%)
10	HPC0	80	201±15.9	87.4±0.4
10	HPC0	100	222.7±11.1	
10	HPC4	80	201.6±15.4	96.5±4.9
10	HPC4	100	254.7±18.6	
10	HPC7	80	190±15.9	98.4±1.0
10	HPC7	100	203.25±6.4	
5	XYL5	80	273.4±8.6	104.7±1.7
5	XYL5	100	307.1±4.0	
10	XYL5	80	269.8±5.9	96.0±0.9
10	XYL5	100	254.7±18.6	
20	XYL5	80	237.1±1.7	96.8±2.3
20	XYL5	100	291.8±6.0	
5	XYL7	80	266.5±9.8	100±0.8
5	DCP1	80	312.5±6.3	98.3±0.8
5	DCP1	100	306.9±7.7	

Influence of formulation, drug load and infill density on drug release





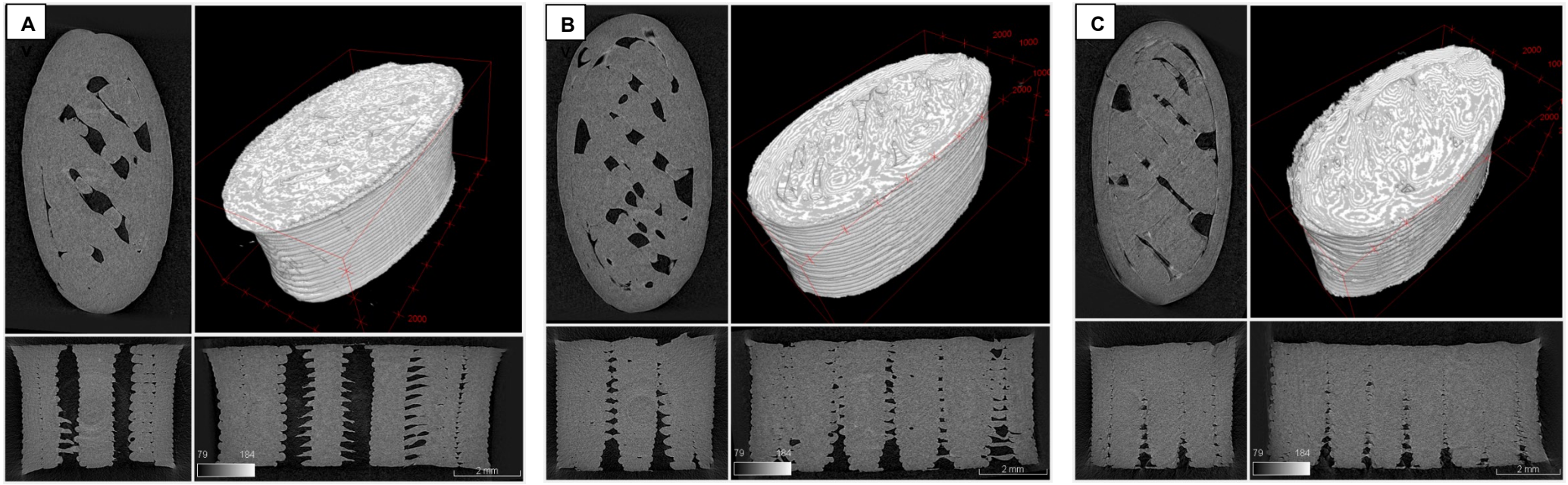


Formulation of lumefantrine (BCS class IV API) for IR tablets

Components: Eudragit EPO, maltodextrin, xylitol. Drug load: 5%

Designed infill density

65% 80% 100%



Morphological characteristics of tablets with different programmed infill density

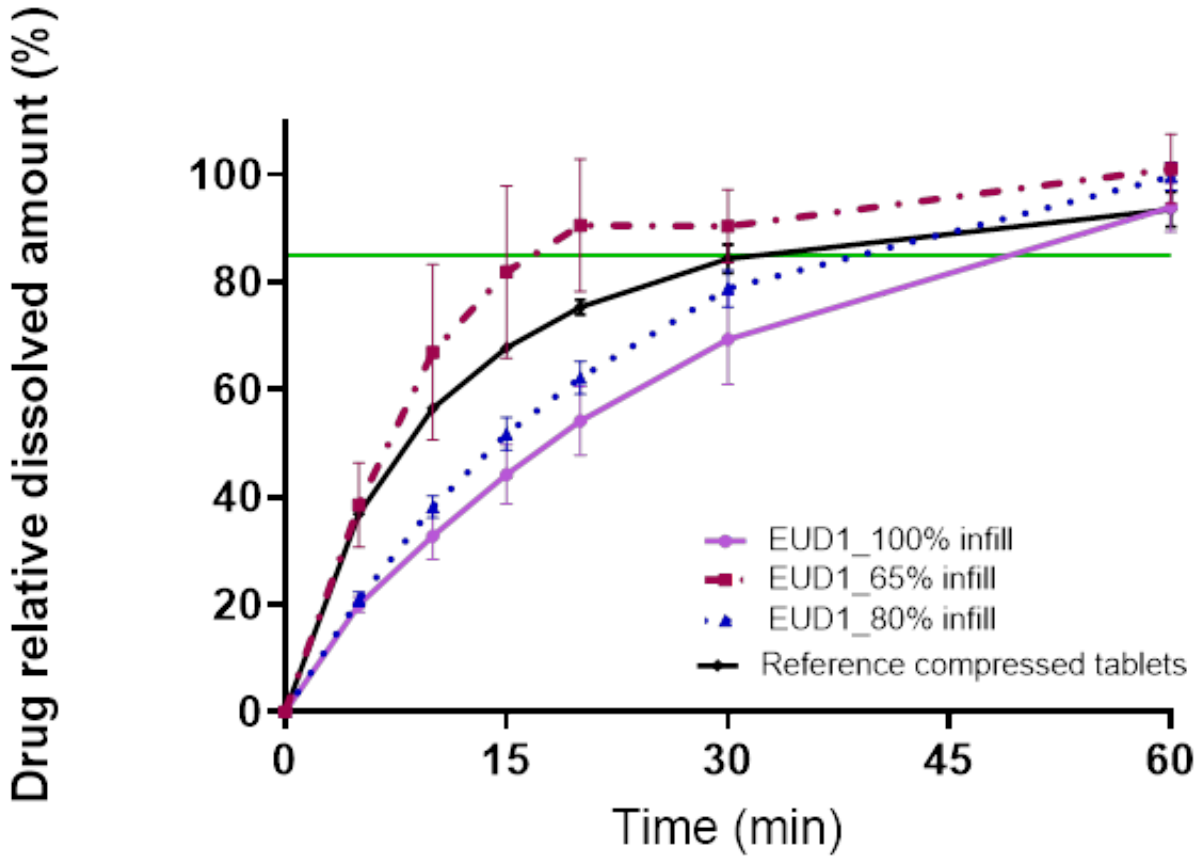
Programm-ed infill density	Weight (mg)	x dimension (mm)	y dimension (mm)	z dimension (mm)	Surface area (mm^2)	Closed pore volume (mm^3)	Open pore volume(mm^3)	Measured relative density
65%	108±2***	9.2±0.3	4.9±0.1	3.9±0.05	422.9±5.4***	0.08±0.02	13.96±0.40***	0.8±0.007***
80%	142±1	8.9±0.2	4.5±0.1	4.0±0.01	316.9±39.5	0.48±0.09	4.80±2.06	0.925±0.031
100%	139±1	9.2±0.3	4.9±0.1	3.9±0.05	291.8±43.8	0.29±0.09	3.33±1.72	0.943±0.028

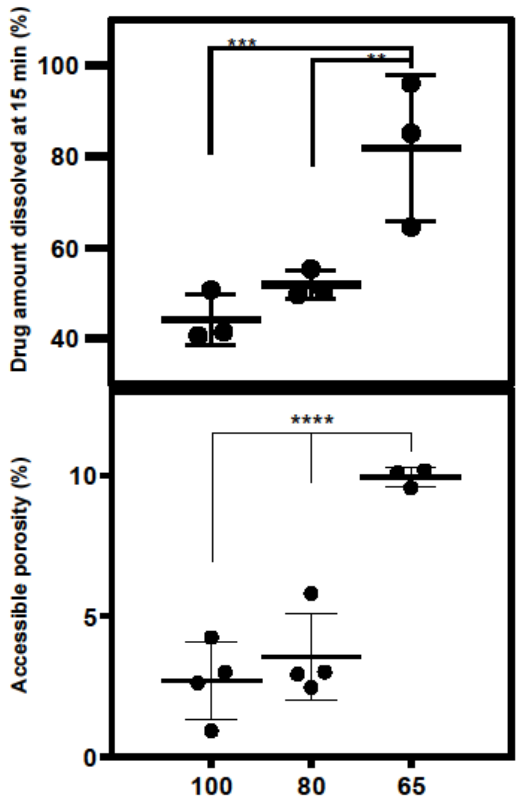
Depending on the quantitative composition, the response to the CAD parameters is different

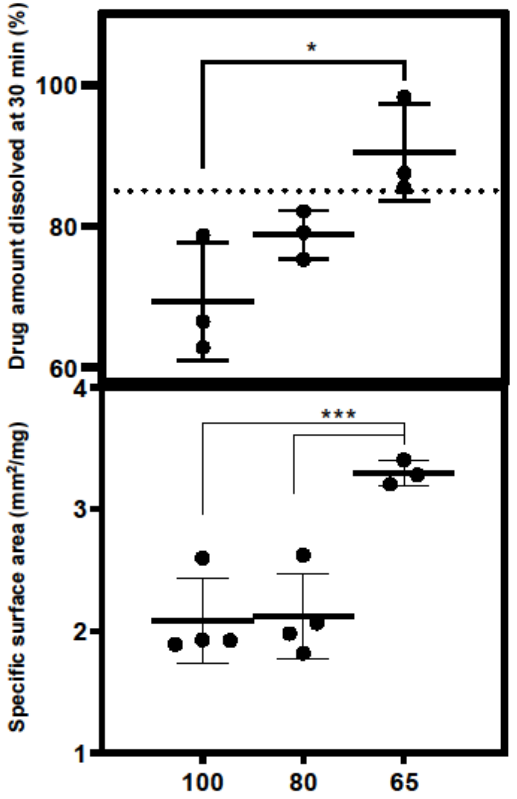
Components: HPC SSL, Kollicoat IR, maltodextrin, xylitol. Drug load: 10%

Formulation code	Programm-ed infill density (%)	Measured relative density (%) (mean±std)	Finished printed tablet weight (mg) (mean±std)	Accesible porosity (%) (mean±std)	Closed pores volume* (mm^3) (mean±std)	Specific surface area by volume (mm^{-1}) (mean±std)	Specific surface area by weight (mm^2/g) (mean±std)
H0	80	73.9±9.1	128±9.1	13.2±4.4	1.2±0.8	4.8±0.8	5.8±0.8
H0	100	83.9±12.4	152±2.3	7.9±6.4	1.9±1.1	4.2±2.2	4.6±3.0
X5	80	82.9±2.2	142±5.9	8.6±1.1	0.9±0.1	4.7±0.4	4.6±0.4
X5	100	95.6±1.0***	163±2.3	2.1±0.7***	1.1±0.2	2.7±0.2*	2.3±0.2*

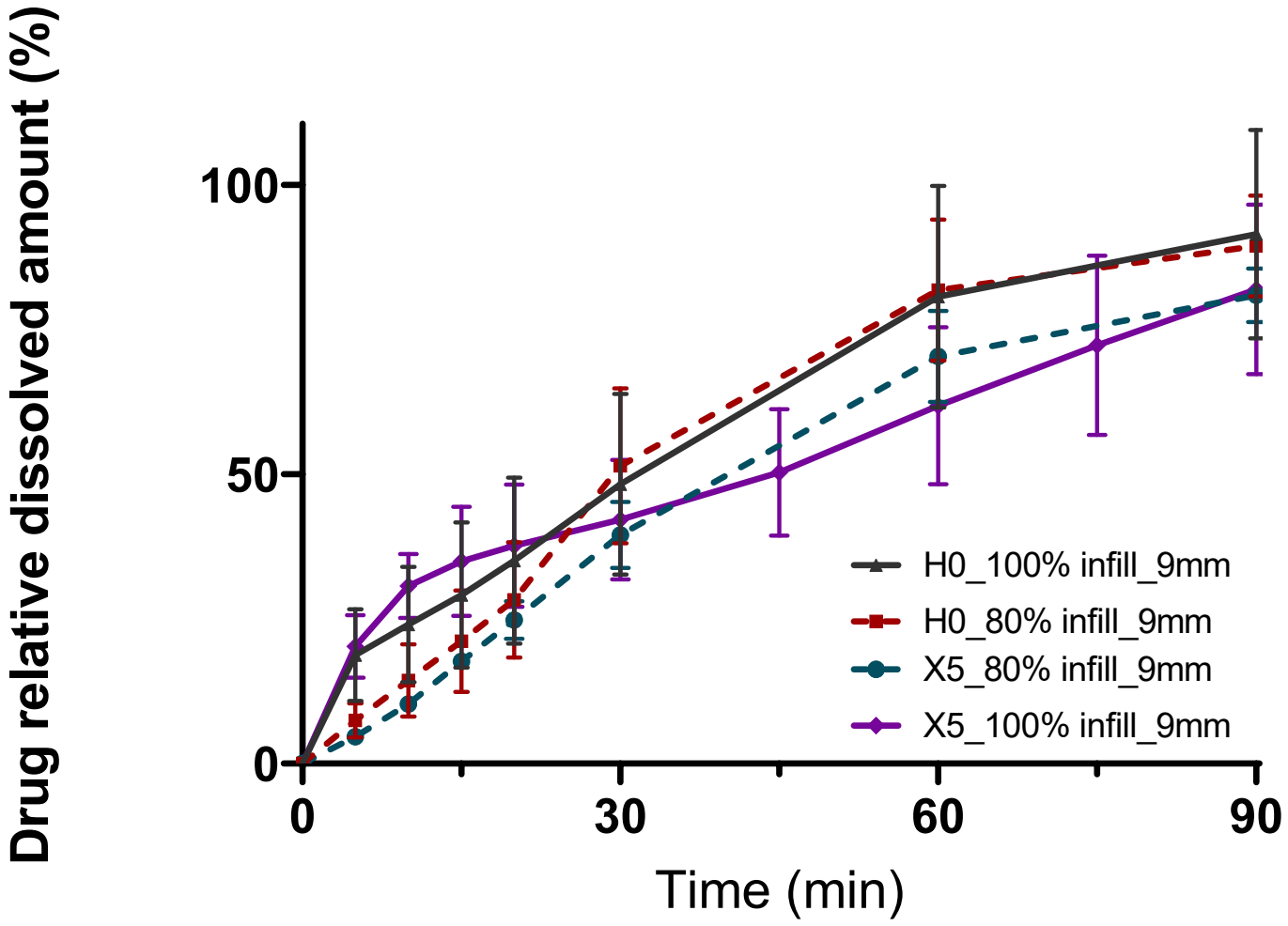
Drug release rate in corroboration with morphological tablet characteristics
IR achieved







At high infill densities, effect of formulation and infill density less obvious…



Confocal Raman microscopy spectral mapping. Lumefantrine formulation H0

Filament cross section

Tablet surface

Tablet cross section

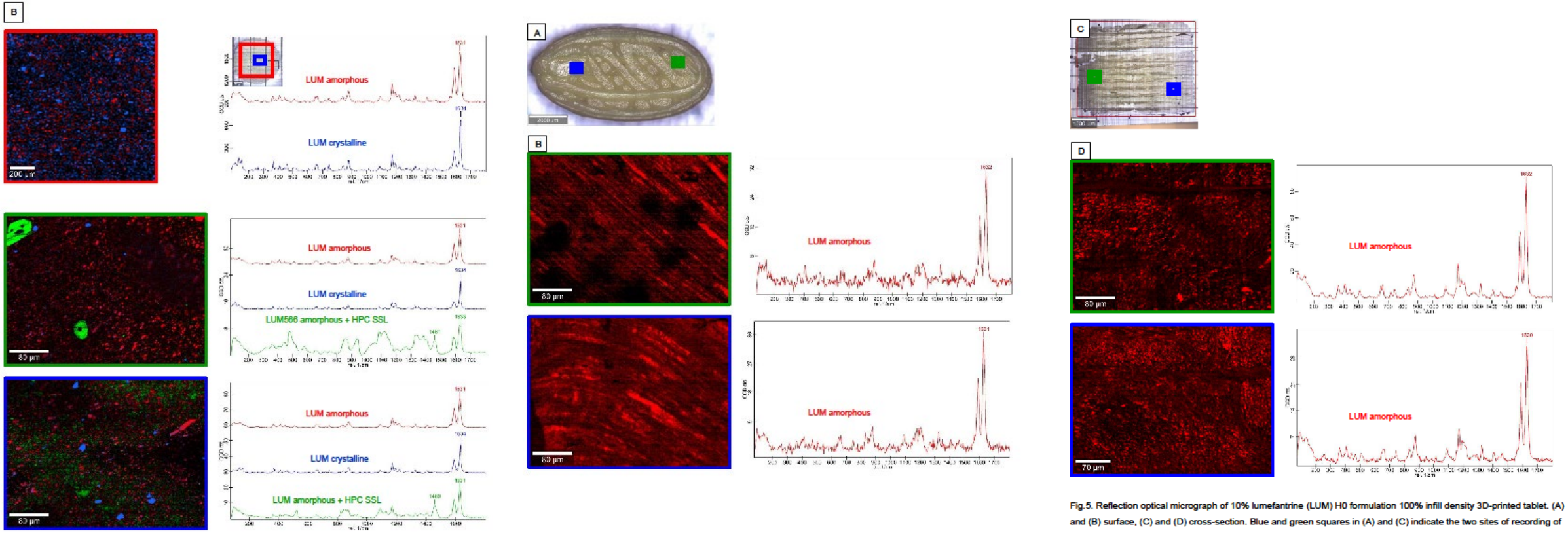


Fig.5. Reflection optical micrograph of 10% lumefantrine (LUM) H0 formulation 100% infill density 3D-printed tablet. (A) and (B) surface, (C) and (D) cross-section. Blue and green squares in (A) and (C) indicate the two sites of recording of Raman spectral maps with corresponding extracted spectra shown in (B) and (D), respectively.

Confocal Raman microscopy spectral mapping. Lumefantrine formulation X5

Filament cross section

Tablet surface

Tablet cross section

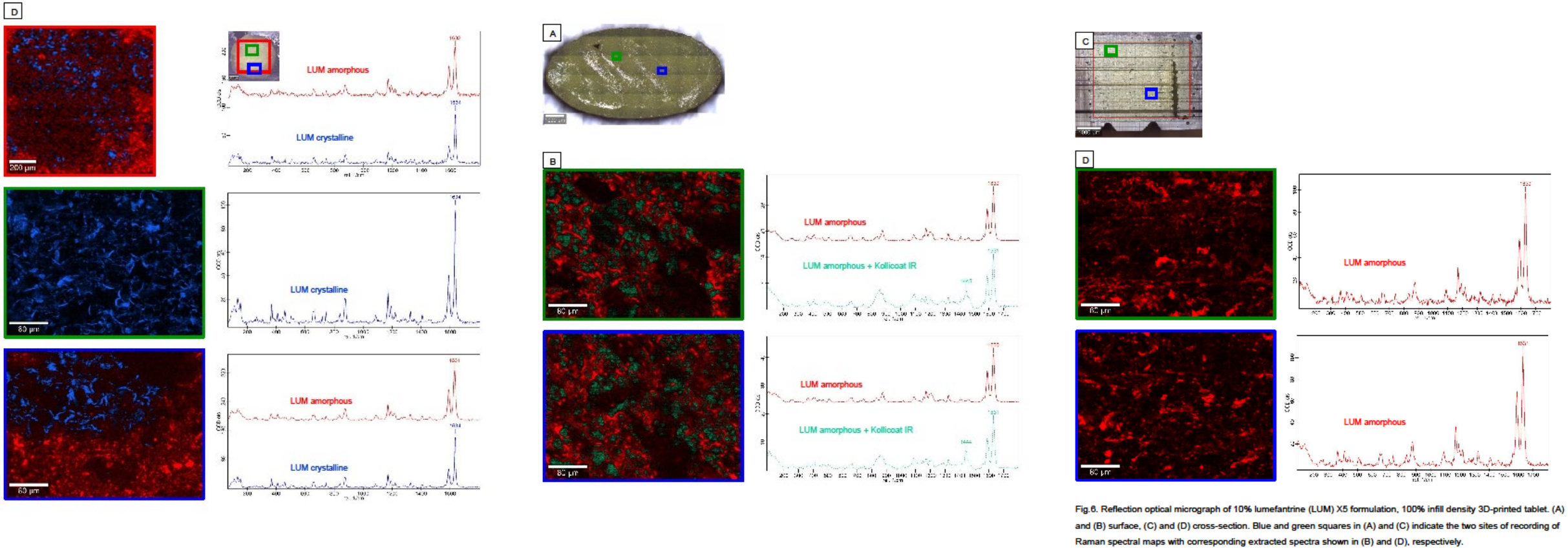


Fig.6. Reflection optical micrograph of 10% lumefantrine (LUM) X5 formulation, 100% infill density 3D-printed tablet. (A) and (B) surface, (C) and (D) cross-section. Blue and green squares in (A) and (C) indicate the two sites of recording of Raman spectral maps with corresponding extracted spectra shown in (B) and (D), respectively.

Conclusions – Future directions

- Structural characteristics of drug product can be influenced by the manufacturing parameters (e.g., infill density)
- IR property is achieved (even) with poorly water-soluble API due to formation of amorphous solid dispersion
- Connection between tablet characteristics and release properties is evident
- Dependencies not linear and dependent on composition
- (Re)creation of amorphous solid dispersion upon on-site / near-patient 3D-printing
- No long-term stability of amorphous state necessary
- New manufacturing paradigm

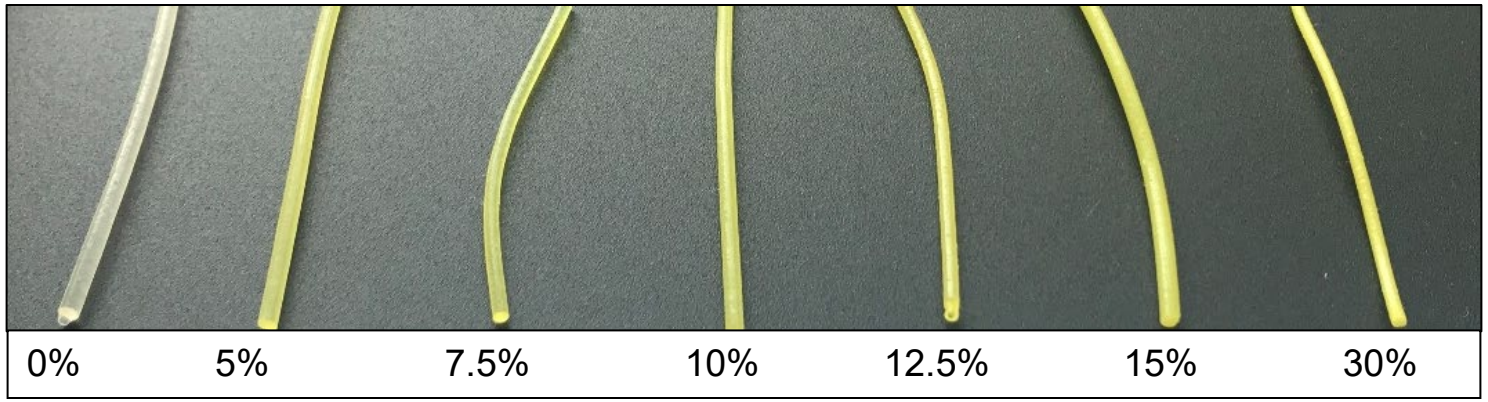
Conclusions – Future directions

❑ For the technology to become viable:

- Better process control and GMP capable equipment required
- Better precision and accuracy required
- Real-time-release testing (parametric release) for decentralized manufacture necessary incl. process monitoring and control by process analytical technologies (PAT)
- Better understanding of material / formulation behavior under 3D-printing conditions required

❑ Implementation in real-life environment

- Preparation of *formula* drug products in the hospital and the community pharmacies
- Pilot project under strictly monitored conditions
- Selected therapeutic areas
- Specific formulations for pediatric application
- Establishment of biopharmaceutical equivalence


0%
5%
7.5%
10%
12.5%
15%
30%

H0 formulation 5% lumefantrine. Infill density 80% (left) & 100% (right)

Infill density 30% (top) & 80% (bottom) by direct powder printing