A toolkit for the rational formulation development of 3D printed FDM pharmaceutical solid dosage forms

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INNOVATIVE MULTICOMPONENT DRUG DESIGN

What could have changed in 2 years?

86% expect their 3D printing use to more than double over the next few years (65% in 2017).

Driver: Individualisation & Saving

79% believe they will more than double their 3D printing use for production parts over the next few years (56% in 2017).

What prevent industry using 3D printing?

- 56% say **materials** issues (cost or availability of materials needed) are number one.
- 44% highlight their workforce issues (such the lack of qualified personnel or subject matter **experts**)
- 39% highlight **process** issues (such as design or post-processing issues).
- 94% of survey respondents said that their design and engineering teams frequently choose traditional manufacturing methods over 3D printing due to a lack of **materials**.

Headlines

Too many…

- Much better success in surgical and medical industry than pharmaceutical industry
- What cause the hesitation?
- Does repetitive proof-of-concept studies useful to the development of the field?

Personalised polypills by FDM

Conceptualisation

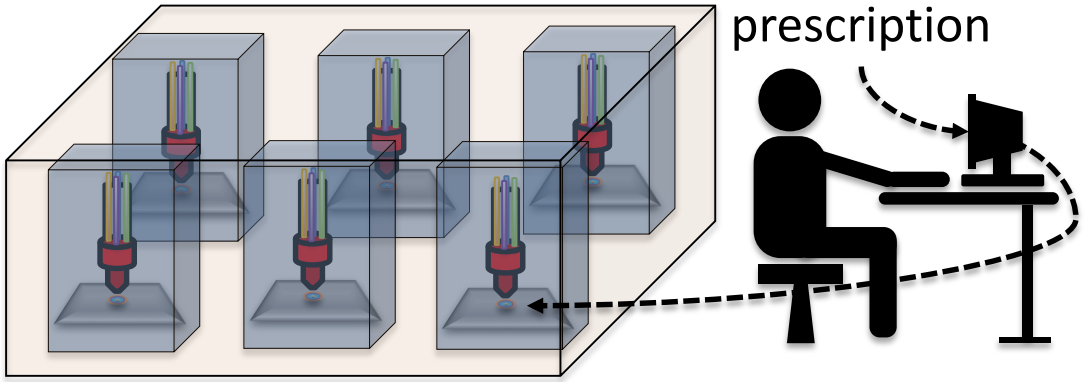
Personalised drug combination & dose

save NHS staff time
↓ misuse of drugs
↑ patient adherence

Point-of-care Polypill Printing

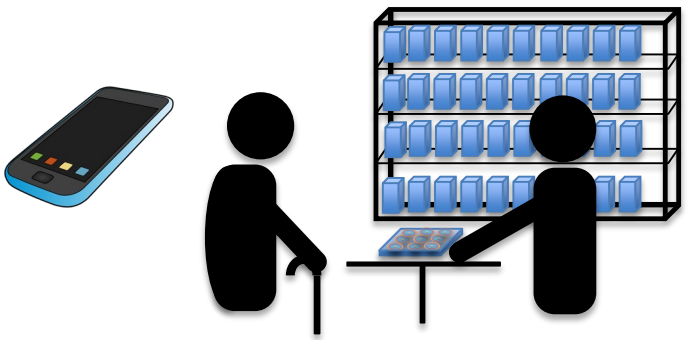
GMP printing units

GP electronic prescription



Polypill Dispensing

Mobile App to alert patient for picking up or posting



Personalised polypills by FDM

Personalised polypills by FDM

Reality

What to feed in?

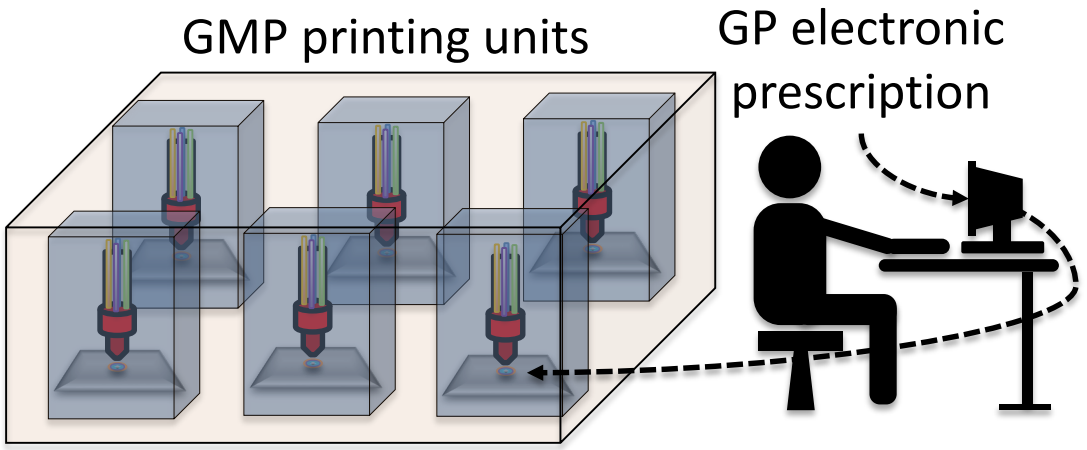
How to QA and QC the end product?

Role and profit change for pharma industry

New costing model

Regulatory barriers

Point-of-care Polypill Printing



Polypill Dispensing

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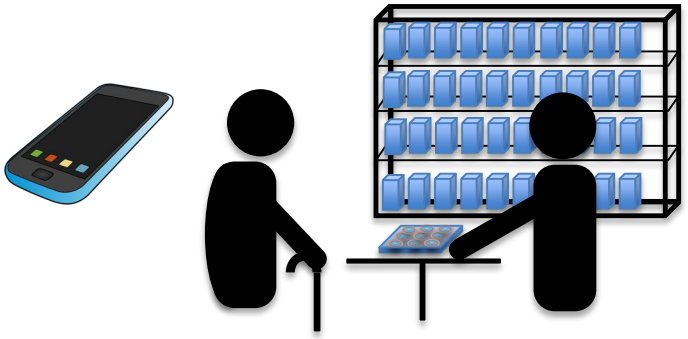
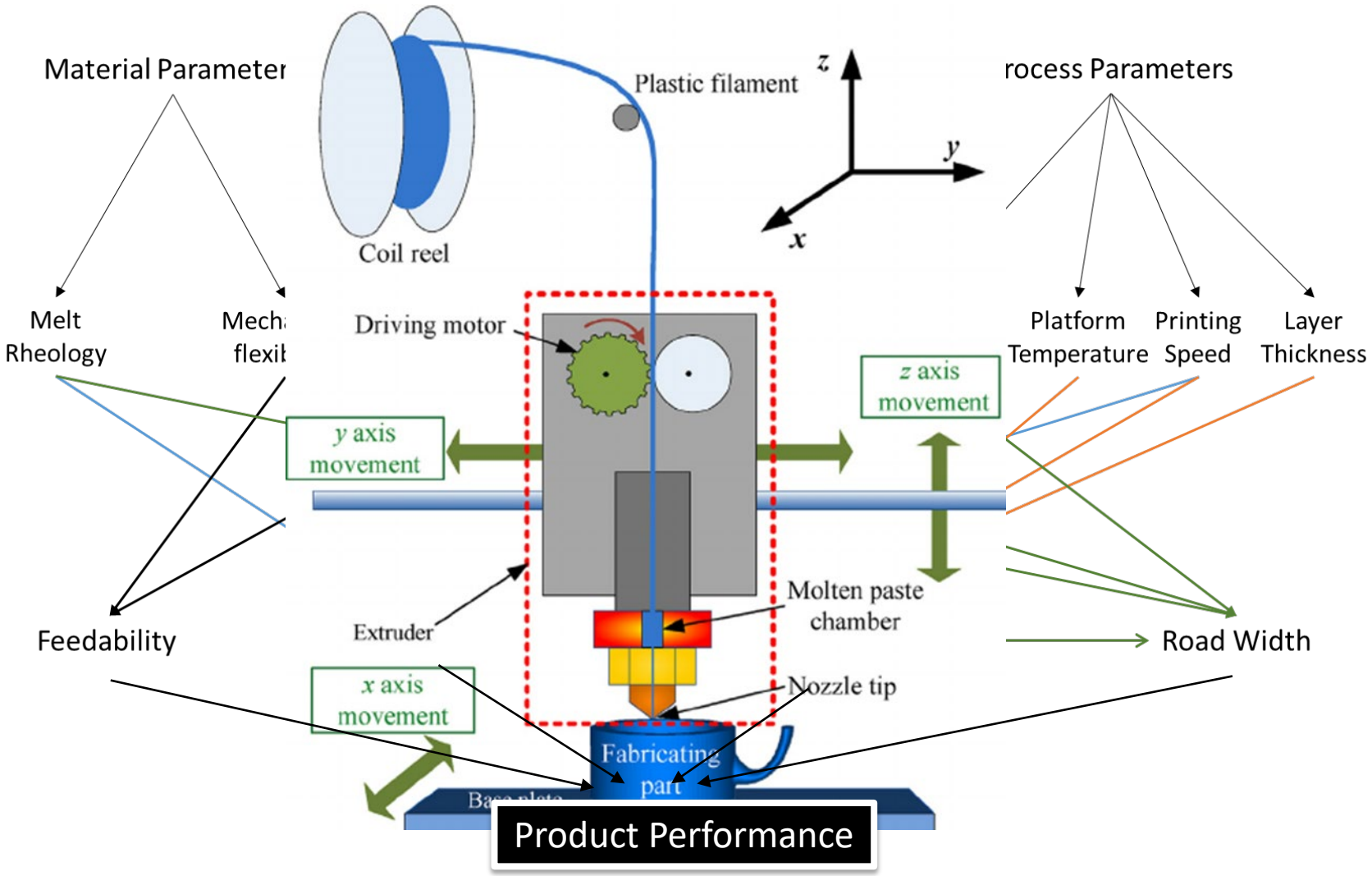


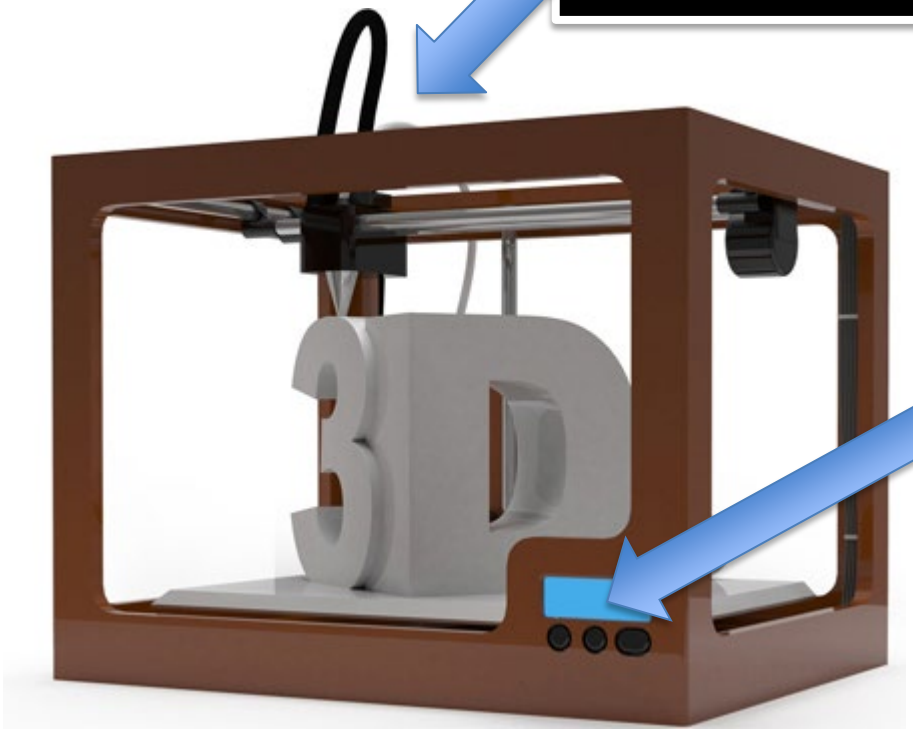
FDM Printing Control



Challenges for Pharma

Custom-engineered materials

- Optimisation of material
- Optimisation of engineering of the printer



Rationalised product development principle

- Identification of critical attributes
- Optimisation principle of process design

Toolkit for printable materials

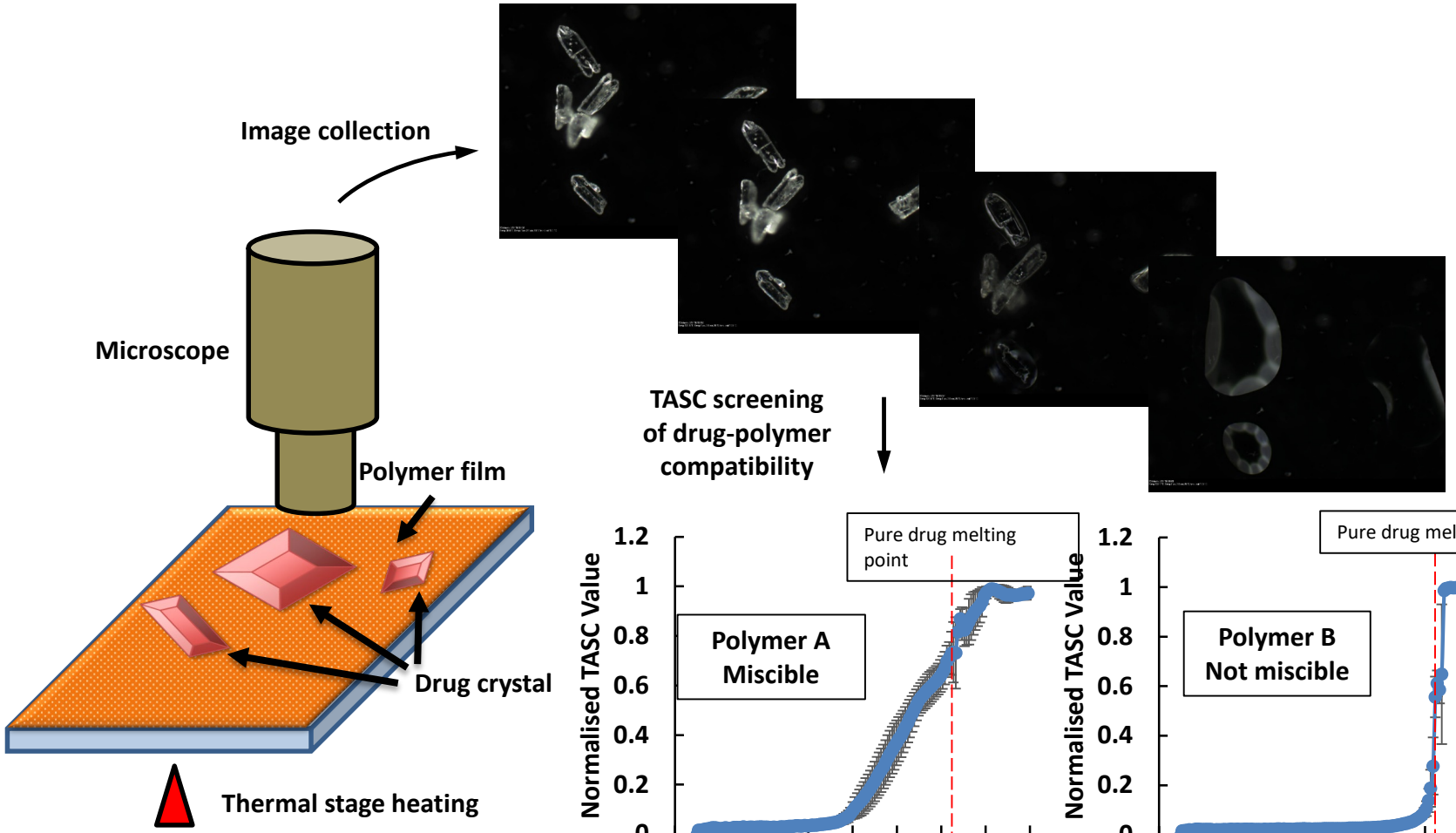
- Polymer-drug compatibility (solubility)
- Processability of conventional filament printing

Current approaches

Method	Drawbacks
Solubility parameter (δ) and Flory-Huggins theory	Lengthy calculation Relying on theoretical prediction
Melting point depression	Time consuming Heating rate dependent
Real-time experimental measurements	Time consuming Labour intensive

TASC Working Principle

Thermal Analysis by Structural Characterisation (TASC)



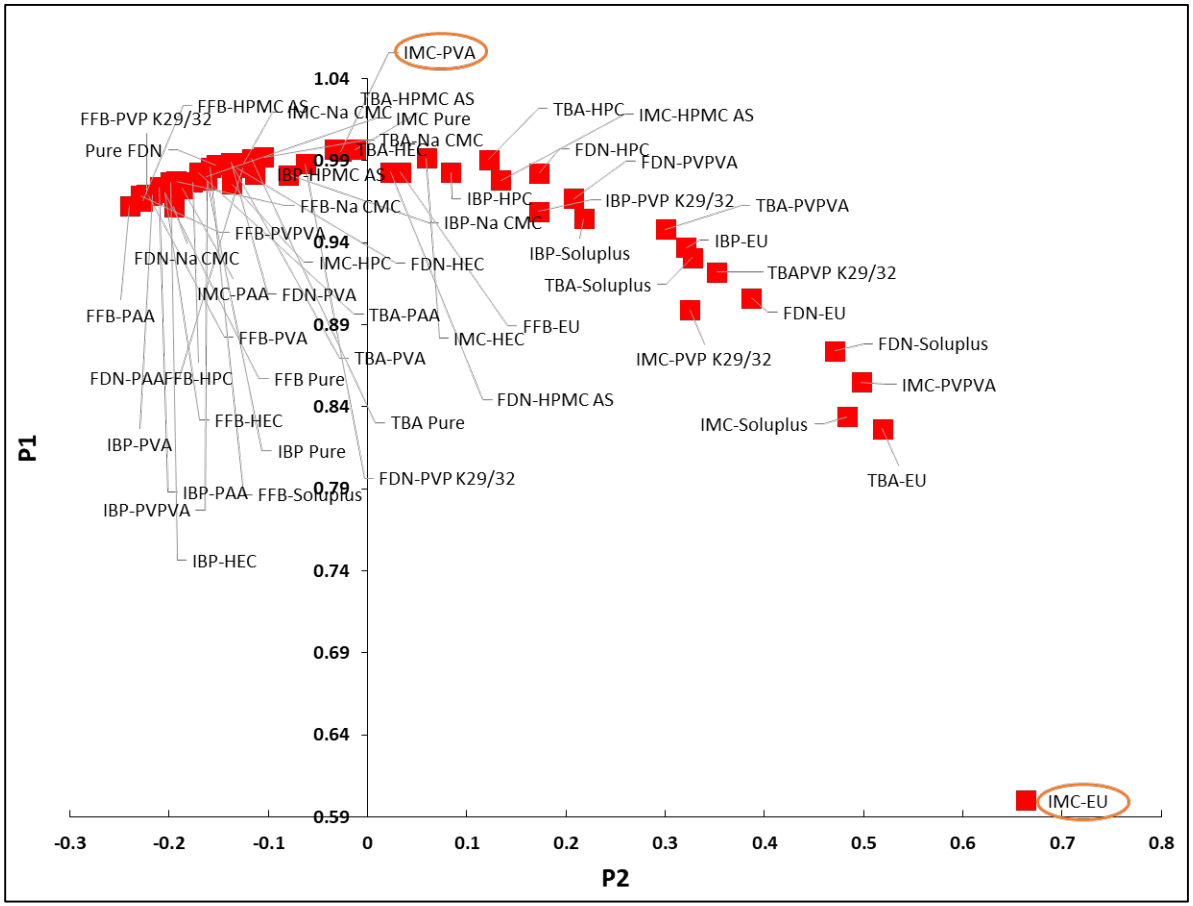
Ref: Alhijjaj, M., et al., 2015, Analytical Chemistry. 87, 21, p. 10848–10855; 2018, Molecular Pharmaceutics. 15, 12: 5625–5636; 2017, Pharmaceutical Research. 34, 5, p. 971–989

TASC Screening Capability

TASC method:
8 minutes per pair
7.5 hours in total

Conventional DSC method:
Average 160 minutes per pair
16 days (working hour lab time)

Quantity of sample:
TASC needs 1/1000th of the weight of DSC sample



LIMITATION: a thermodynamic method, does not taking into account any kinetic factors influencing the stability

Ref: : Alhijjaj, M., et al. 2019, submitted

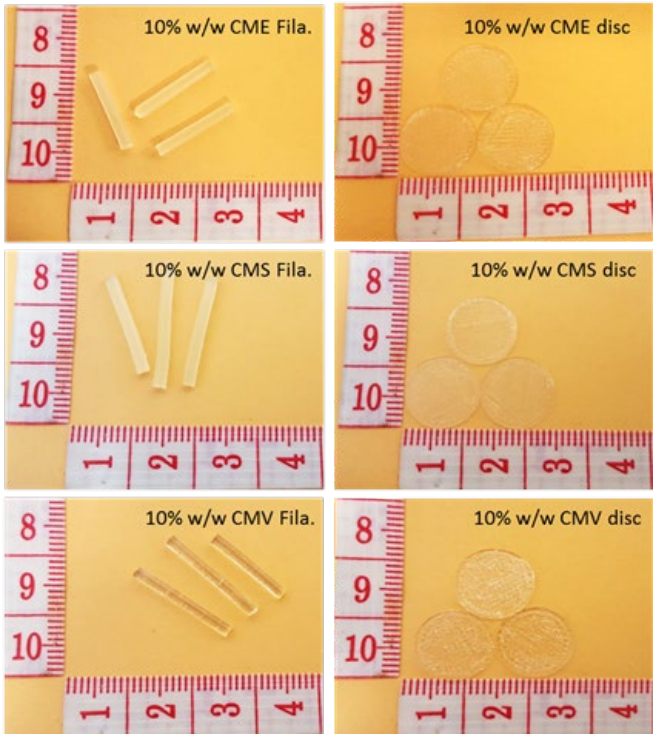
Key message

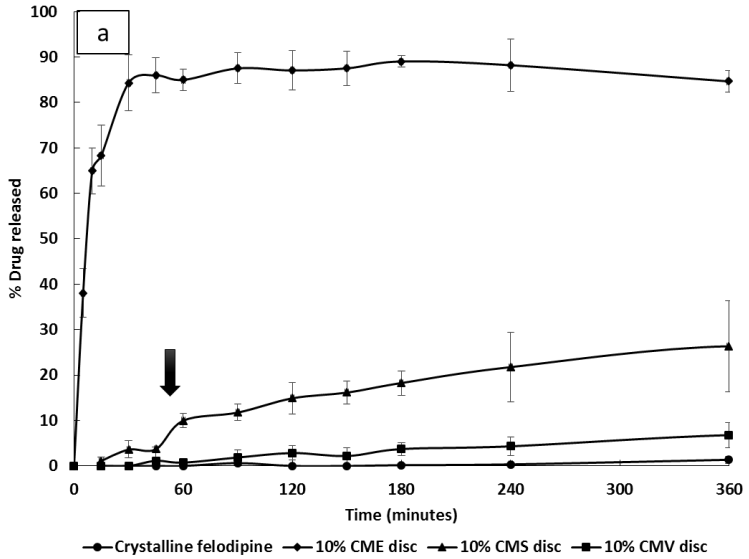
Any thermodynamic measuring method for solubility does not take into account kinetic factors (i.e. storage temperature and relative humidity).

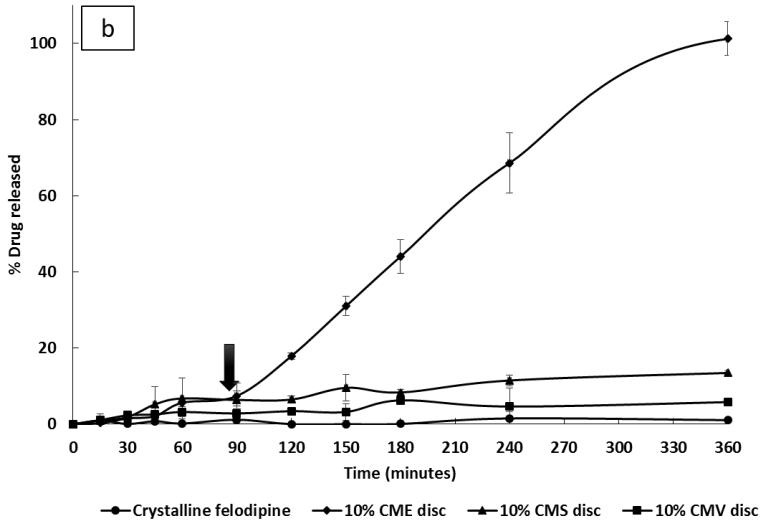
Therefore rapid prediction needs to be validated by real-time stability data. But the screening method can help to rapidly reduce the number of highly promising candidates.

Learn from the past lesson

Minimal 5 excipients and 2 different plasticisers



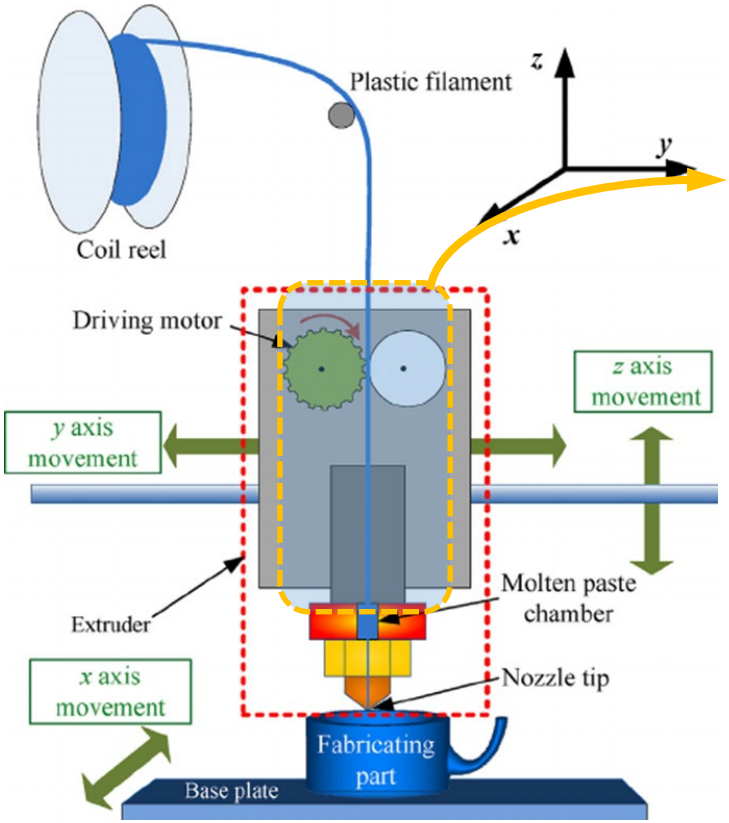


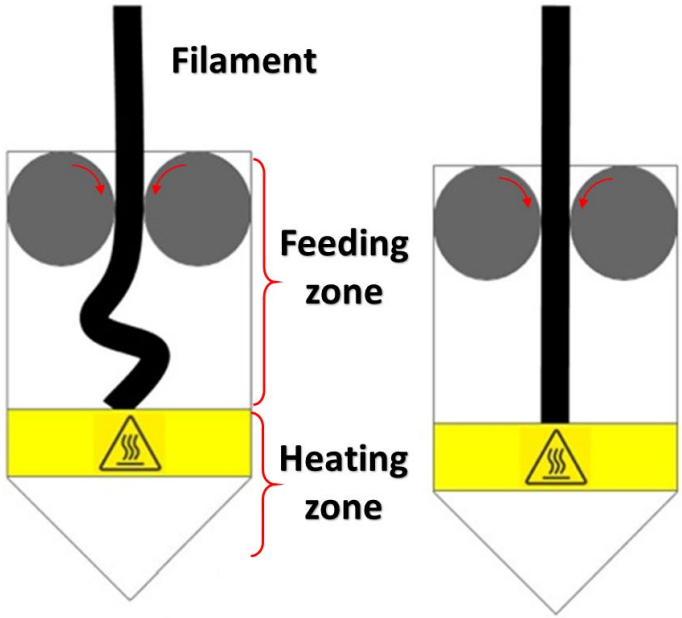


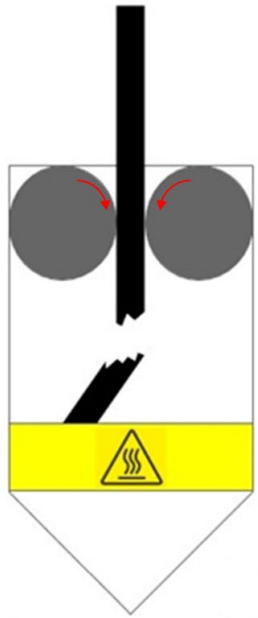
Common issue: most of pharmaceutical polymers are not 'FDM printable'---~~trial and error approach~~

Ref: Alhijjaj, M., et al, 2016, Eur J Pharm Biopharm. 108, p. 111–125.

No Feeding, No Printing

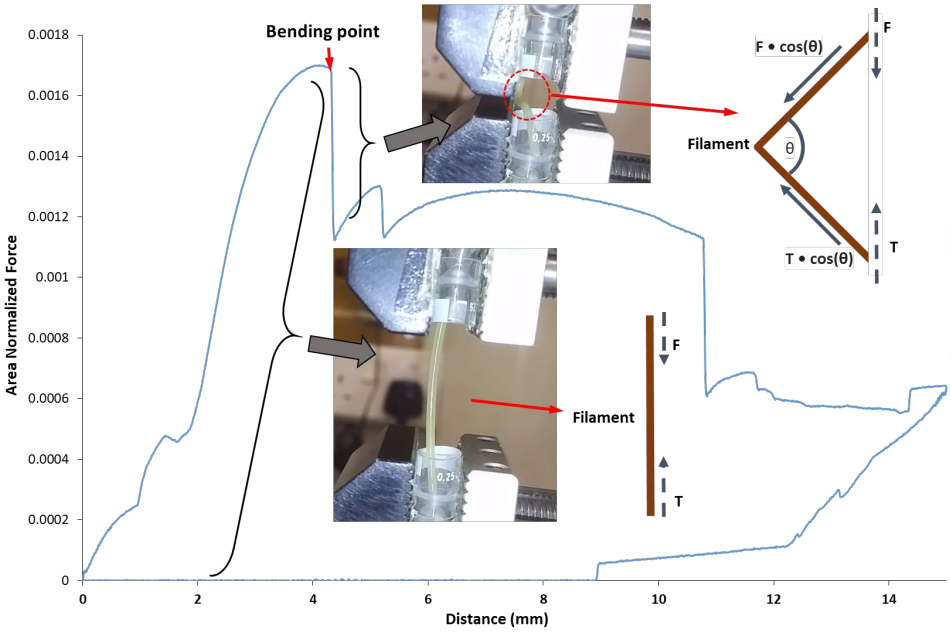




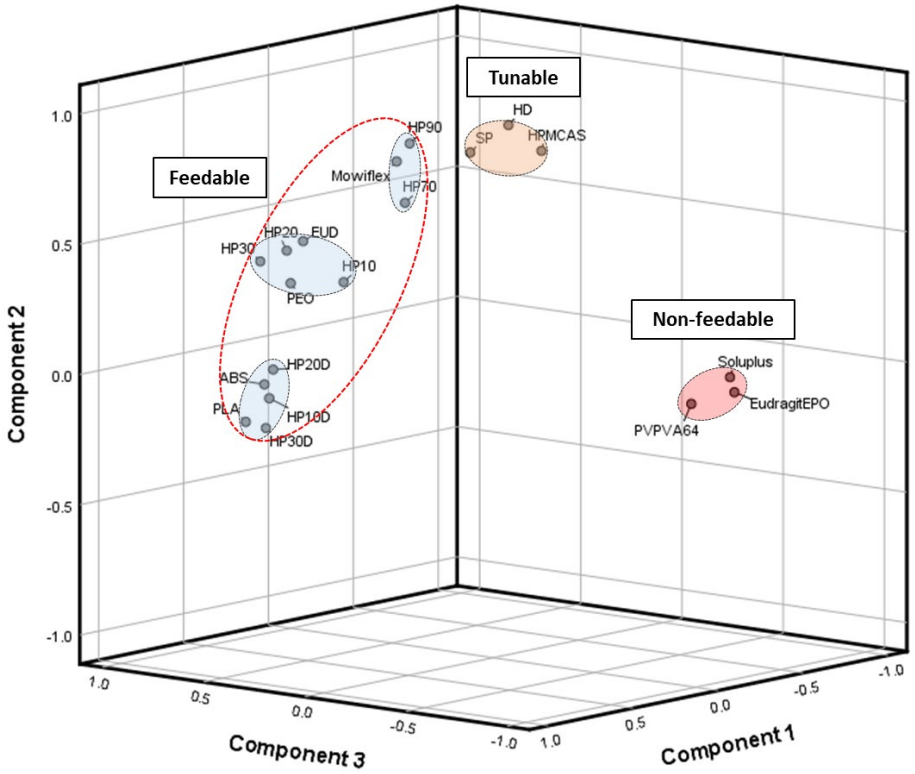


Ref: Nasereddin, J. M., et al. 2018, Pharmaceutical Research. 35, 8, 151.

Feedability Screening

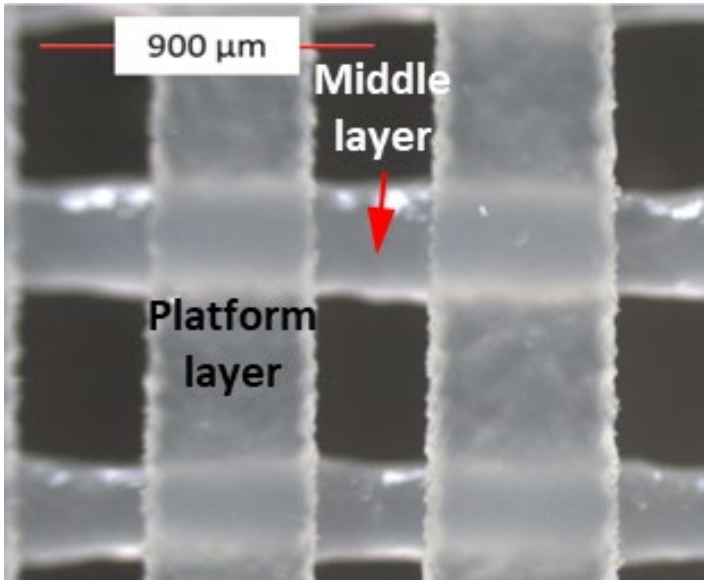


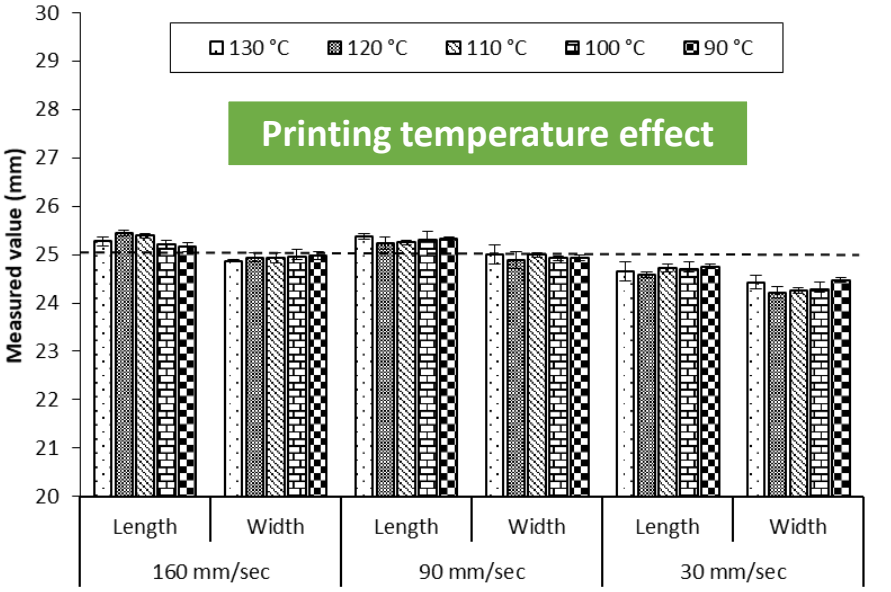
Principle component analysis

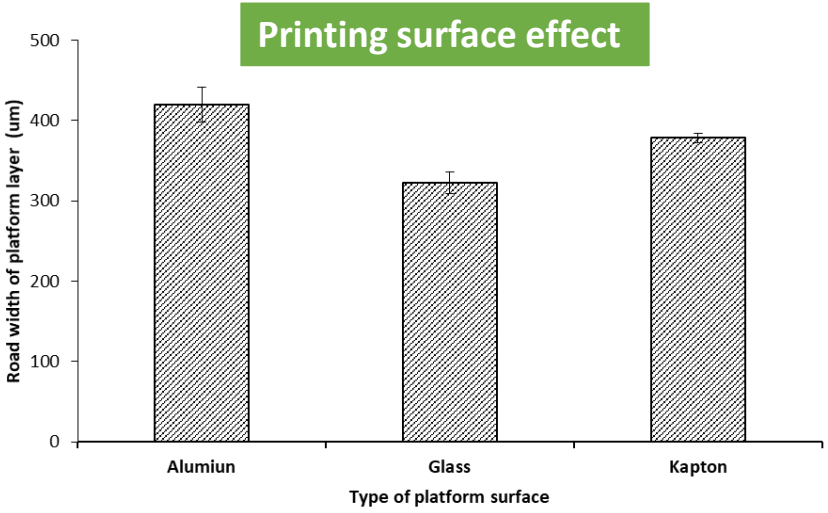


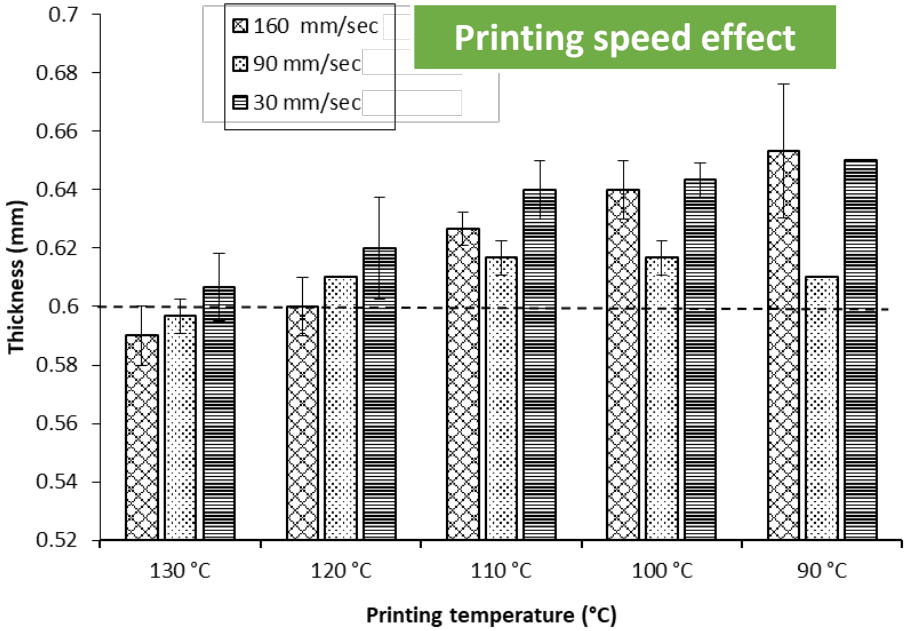
Ref: Nasereddin, J. M., et al. 2018, Pharmaceutical Research. 35, 8, 151.

Printing Quality Optimisation









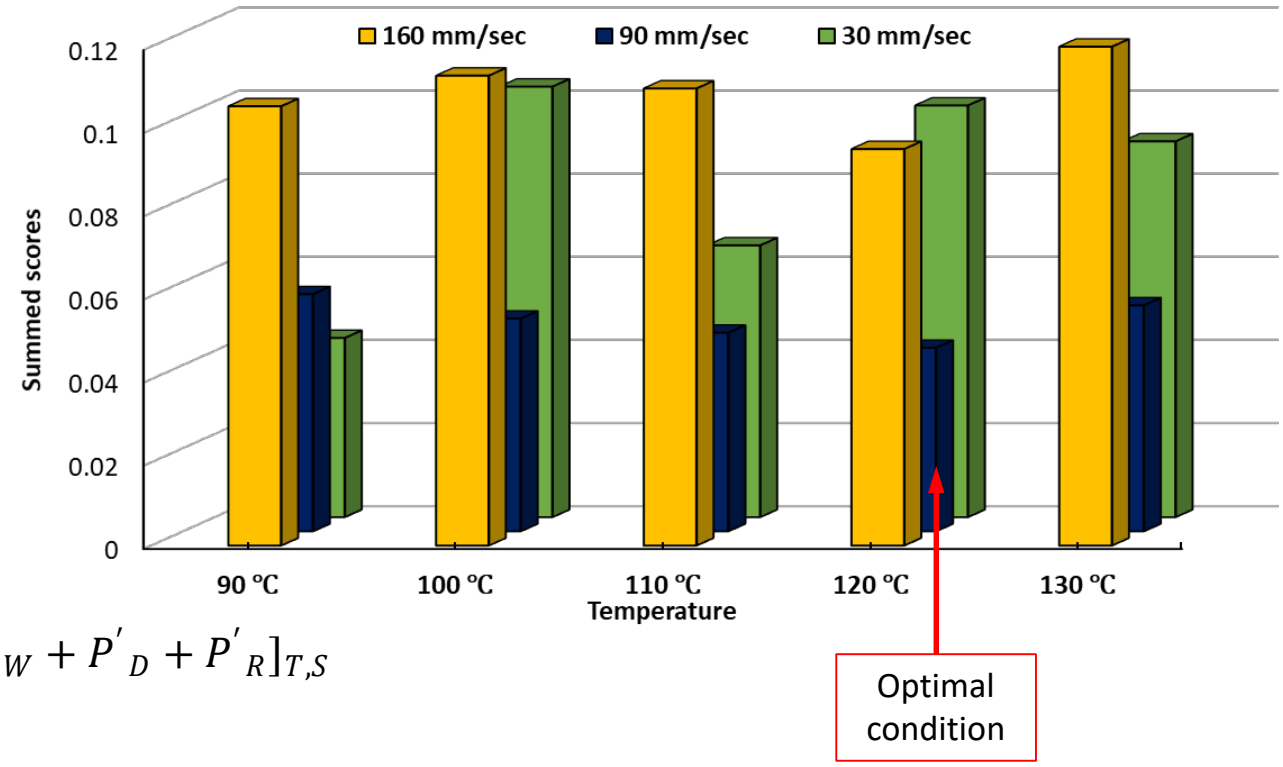
Printability Scoring

Summed Standard Deviation (SSD) score

$$P_i^{'} = \left(\frac{\sigma_i^p}{P_i}\right)_{T,S}$$

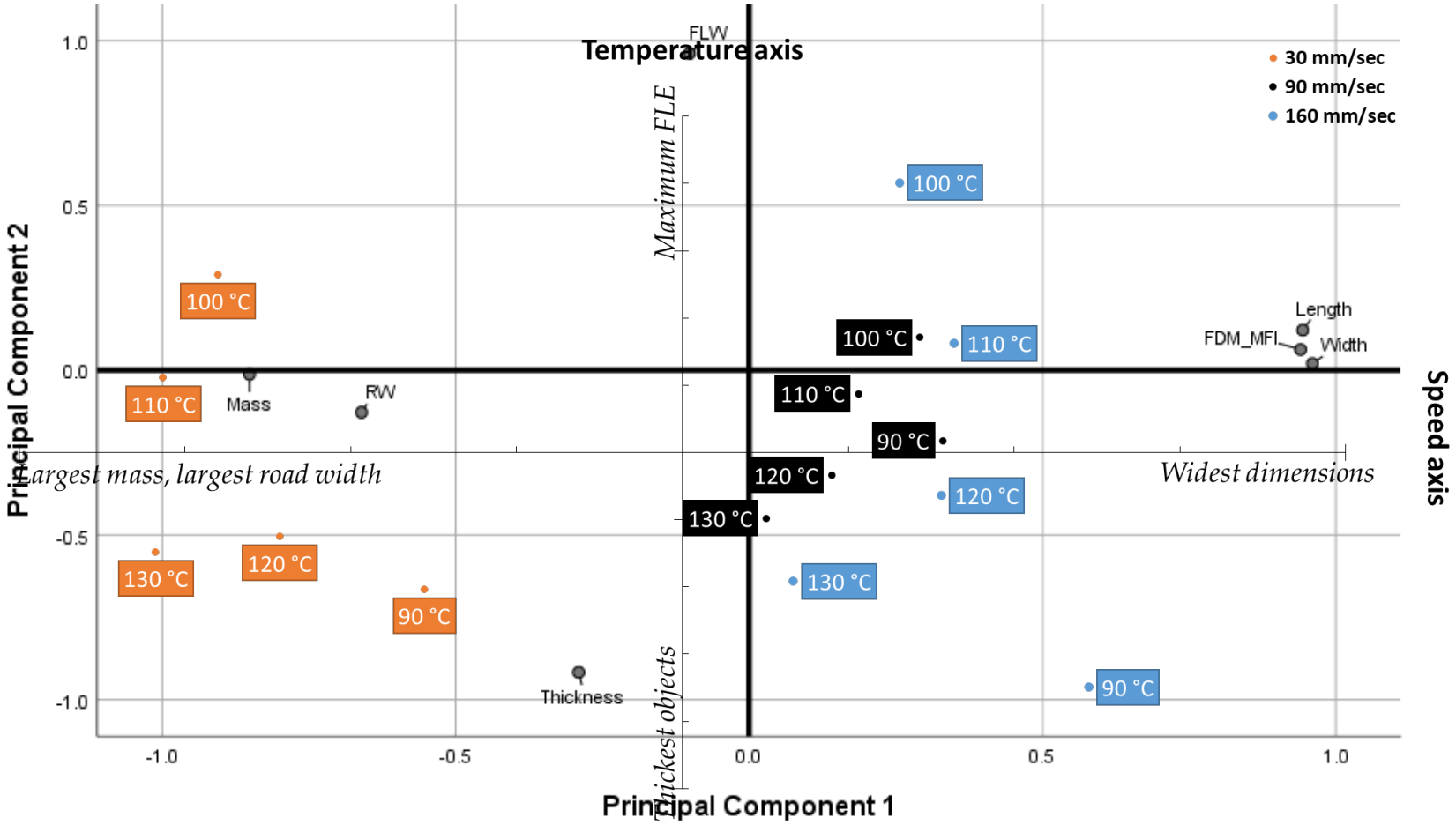
$$SSD = \sum_{\substack{T=0 \\ S=0}}^{\substack{T=n \\ S=n}} [P^{'}{}_M + P^{'}{}_L + P^{'}{}_W + P^{'}{}_D + P^{'}{}_R]_{T,S}$$

SSD scores of printability of all tested conditions



Ref: J. M. Nasereddin et al., 2019, submitted & under review

Rationalisation (attempt)



Key Message

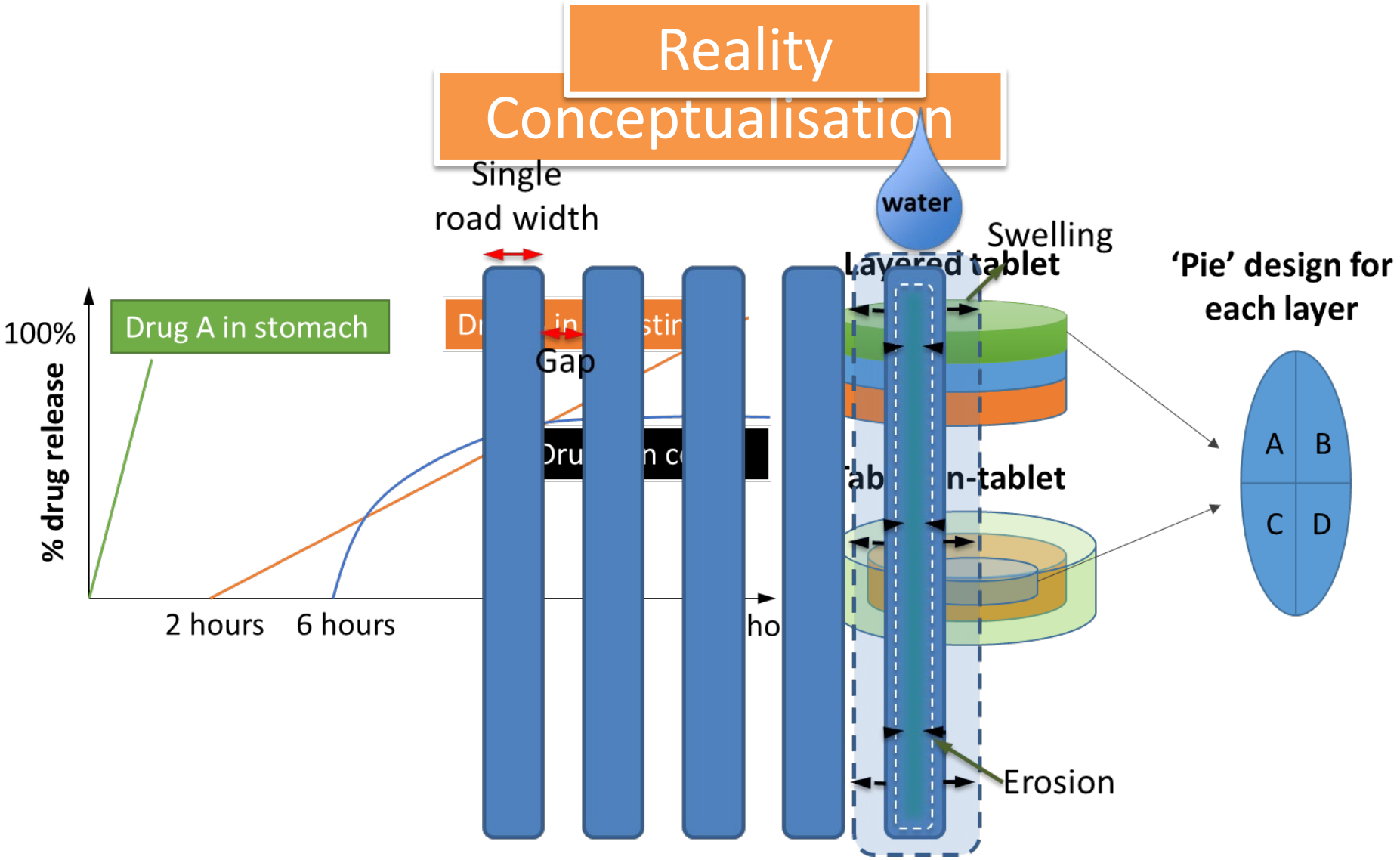
Once the engineered material is printable, the printing speed has a higher level of influence on the printing reproducibility of the object than the printing temperature.

Improvement in the feeding step motor and printing head movement control could potentially help improve this issue.

Critical Attributes to Aid 3D Design

- Process-functionality relationship
- Design-functionality relationship

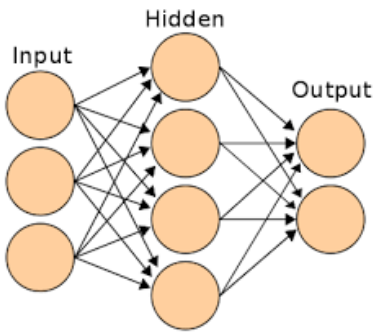
‘Bottom-up’ Design Development



Single Road Behaviour

Polymer (pH 6.8)	Swell (Y/N)	Swell max (%)	Swell rate (%/min)	Hydration rate (%/min)	Erosion rate (%/min)	Solubility (mg/ml)	Drug MW (g/mol)	Polymer MW (g/mol)	log P	pKa	t50 (min)	t80 (min)	t80-t50	R2	D X 10-6 (cm2/s)	Drug Release time (min)
HPMCAS+PEO+Paracetamol 20%	Y	19	0.0131	0.0154	0.0219	13.6	151.16	2018000	0.46	9.38	26	52	26	0.92	4.7	83
HPMCAS+PEO+Carbamazapine 20%	Y	18	0.0057	0.0067	0.0095	0.0177	236.269	2018000	2.45	13.9	160	348	188	0.84	2.3	480
HPMCAS+soluplus+Paracetamol 20%	N	0	0.0000	0.0030	0.9980	13.6	151.16	133000	0.46	9.38	75	240	165	0.89	8.9	620
HPMCAS+soluplus+Carbamazapine20 %	N	0	0.0000	0.0160	0.0025	0.0177	236.269	133000	2.45	13.9	13	34	21	0.79	9.4	60
HPMCAS+Lidocaine 10%	N	0	0.0000	0.0080	0.0280	4.1	234.34	18000	2.44	8	18	39	21	0.97	6.5	120
HPMCAS+Lidocaine 30%	N	0	0.0000	0.0280	0.0310	4.1	234.34	18000	2.44	8	5	7	2	0.98	3.4	30
HPMCAS+Ibuprofen 10%	Y	5.9	0.0197	0.0038	0.0038	0.021	206.29	18000	3.97	5.3	36	64	28	0.99	4.5	120
HPMCAS+Ibuprofen 30%	Y	4.6	0.0053	0.0079	0.0079	0.021	206.29	18000	3.97	5.3	17	31	14	0.97	7.8	90
HPMCAS+Paracetamol 10%	N	0	0.0000	0.0067	0.0312	13.6	151.16	18000	0.46	9.38	25	48	23	0.98	1.2	132
HPMCAS+Paracetamol 30%	N	0	0.0000	0.0073	0.0298	13.6	151.16	18000	0.46	9.38	14	21	7	0.98	3.3	95
Zein+Lidocaine 10%	Y	97	0.0003	0.0006	0.0000	4.1	234.34	22500	2.44	8	740	1600	860	0.99	4.5	2880
Zein+Lidocaine 30%	Y	125	0.0026	0.0005	0.0000	4.1	234.34	22500	2.44	8	370	1750	1380	0.97	1.2	3000
Zein+Ibuprofen 10%	Y	37	0.0001	0.0002	0.0000	0.021	206.29	22500	3.97	5.3	14	23	9	0.77	3.2	120
Zein+Ibuprofen 30%	Y	25	0.0009	0.0001	0.0000	0.021	206.29	22500	3.97	5.3	900	2100	1200	0.95	2.4	2880
Zein+Paracetamol 10%	Y	85	0.0060	0.0008	0.0000	13.6	151.16	22500	0.46	9.38	509	1940	1431	0.98	5.1	2780
Zein+Paracetamol 30%	Y	117	0.0057	0.0006	0.0000	13.6	151.16	22500	0.46	9.38	432	1480	1048	0.97	8.7	3000
PEO+Lidocaine 10%	Y	291	0.0323	0.0513	0.0048	4.1	234.34	2000000	2.44	8	50	95	45	0.99	5.3	120
PEO+Lidocaine 30%	Y	302	0.0562	0.0360	0.0028	4.1	234.34	2000000	2.44	8	23	52	29	0.97	6.8	190
PEO+Ibuprofen 10%	Y	49	0.0492	0.0160	0.0578	0.021	206.29	2000000	3.97	5.3	32	66	34	0.98	9.4	90
PEO+Ibuprofen 30%	Y	28	0.0467	0.1010	0.0542	0.021	206.29	2000000	3.97	5.3	21	34	13	0.95	8.9	60
PEO+Paracetamol 10%	Y	257	0.342	0.0478	0.0036	13.6	151.16	2000000	0.46	9.38	28	88	60	0.97	10	140
PEO+Paracetamol 30%	Y	298	0.334	0.0323	0.0028	13.6	151.16	2000000	0.46	9.38	16	68	52	0.98	9.3	90

ANN (Artificial Neural Network)



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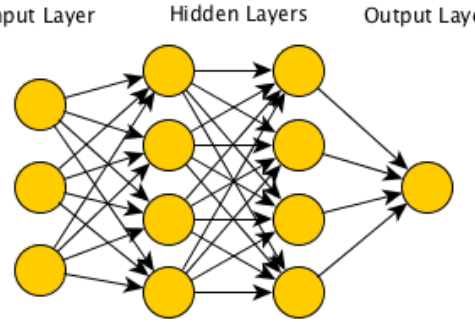
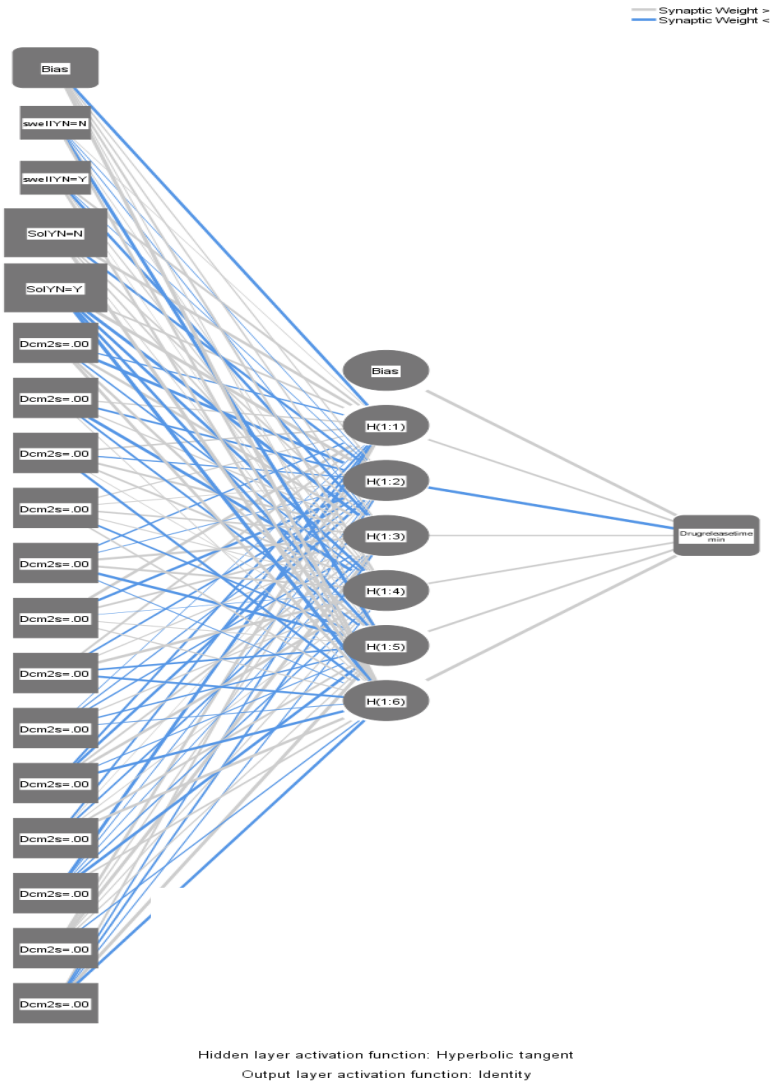
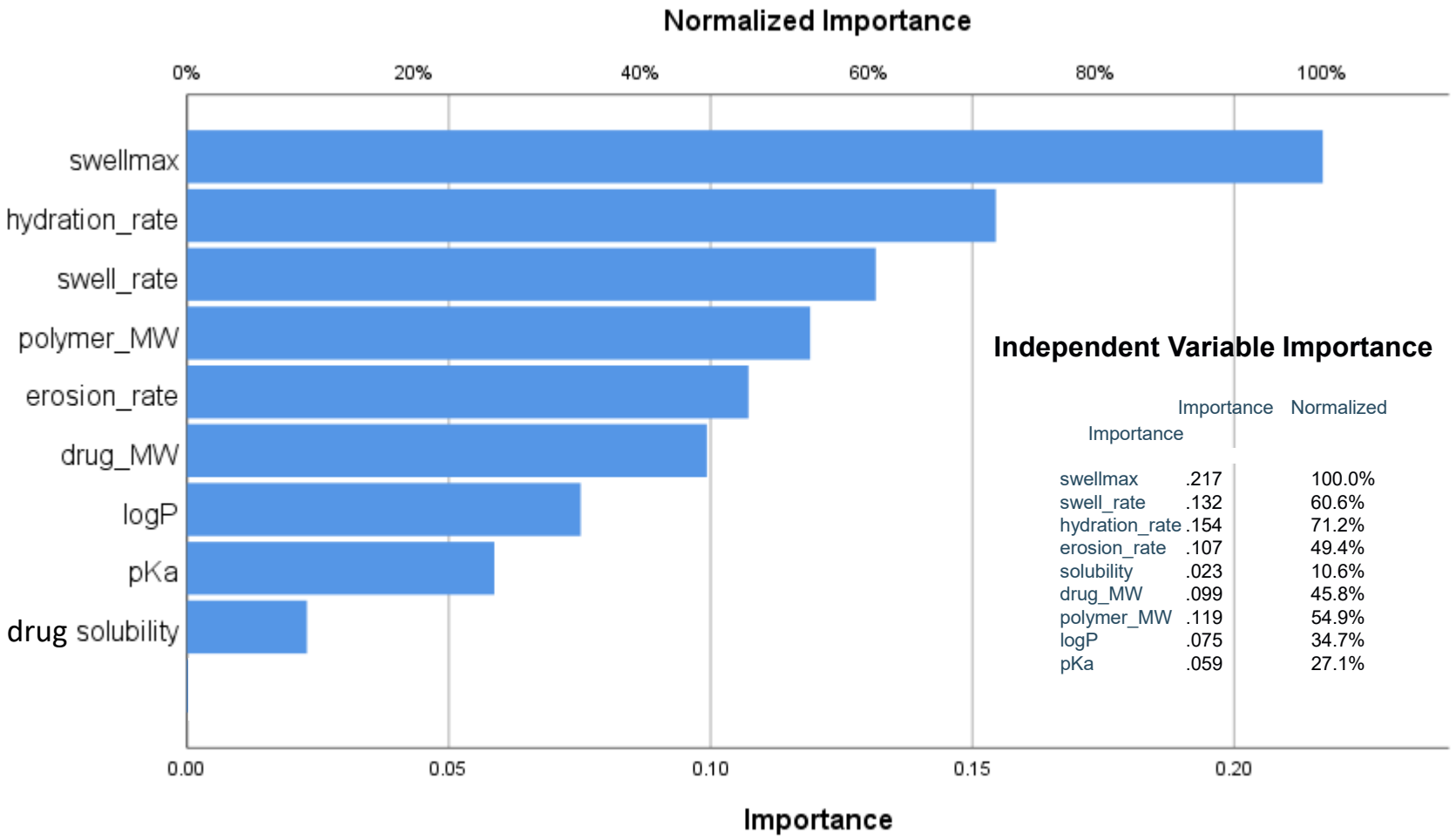


INPUT
Maximum Swelling
Swelling Rate
Hydration Rate
Erosion Rate
Solubility
Drug MW
Polymer MW
Lop
Diffusion Coefficient
pKa

OUTPUT
Drug Release Time



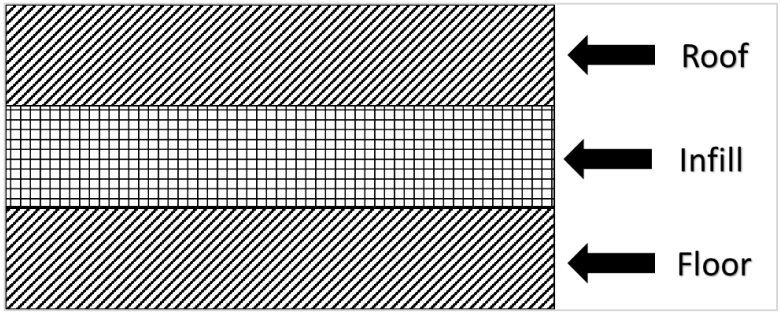
Variables Ranking Analysis

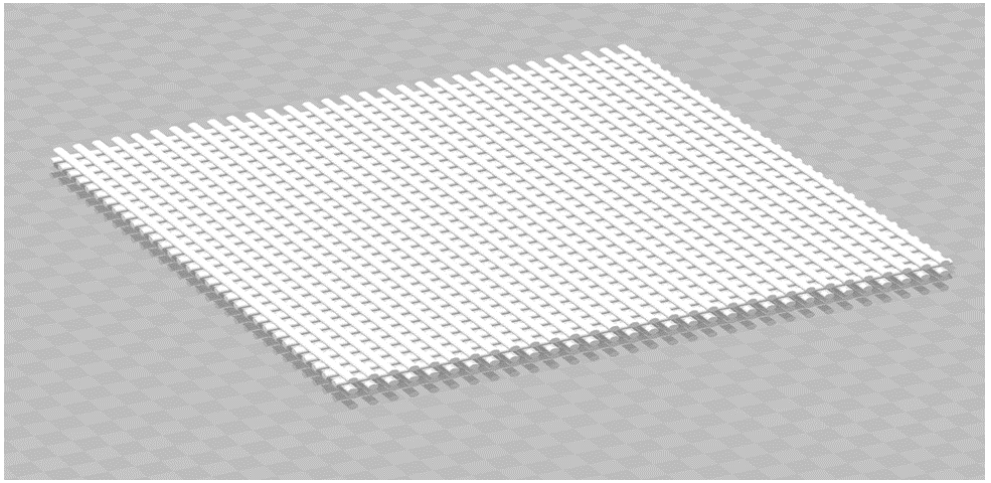


Independent Variable Importance

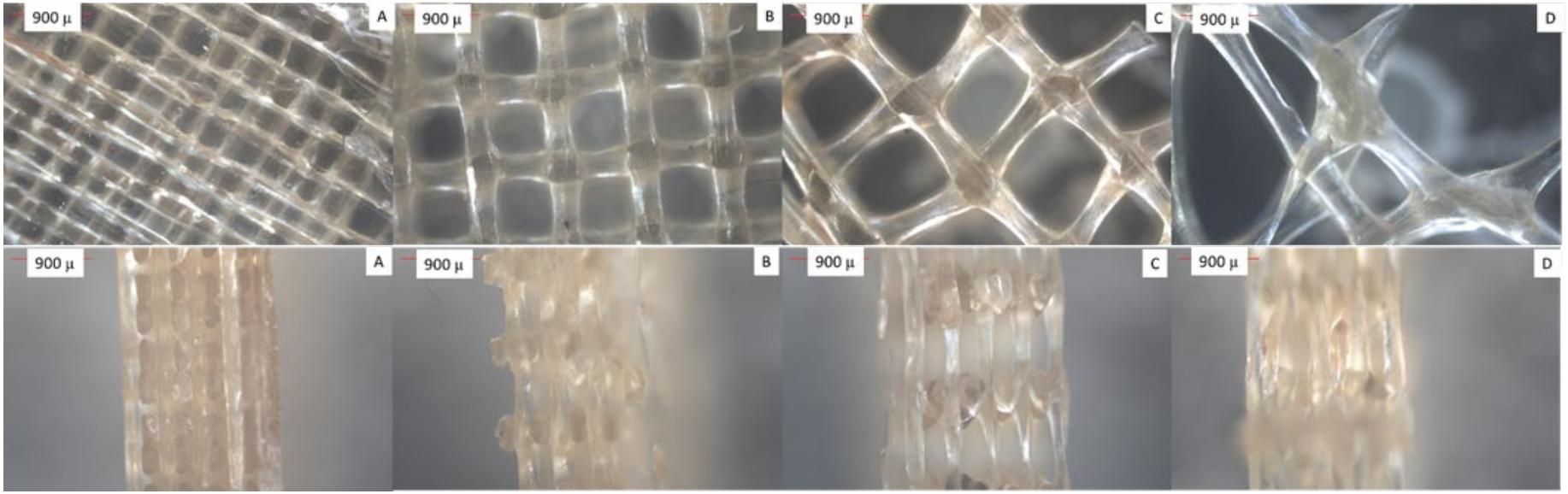
	Importance	Normalized Importance
swellmax	.217	100.0%
swell_rate	.132	60.6%
hydration_rate	.154	71.2%
erosion_rate	.107	49.4%
solubility	.023	10.6%
drug_MW	.099	45.8%
polymer_MW	.119	54.9%
logP	.075	34.7%
pKa	.059	27.1%

Infill

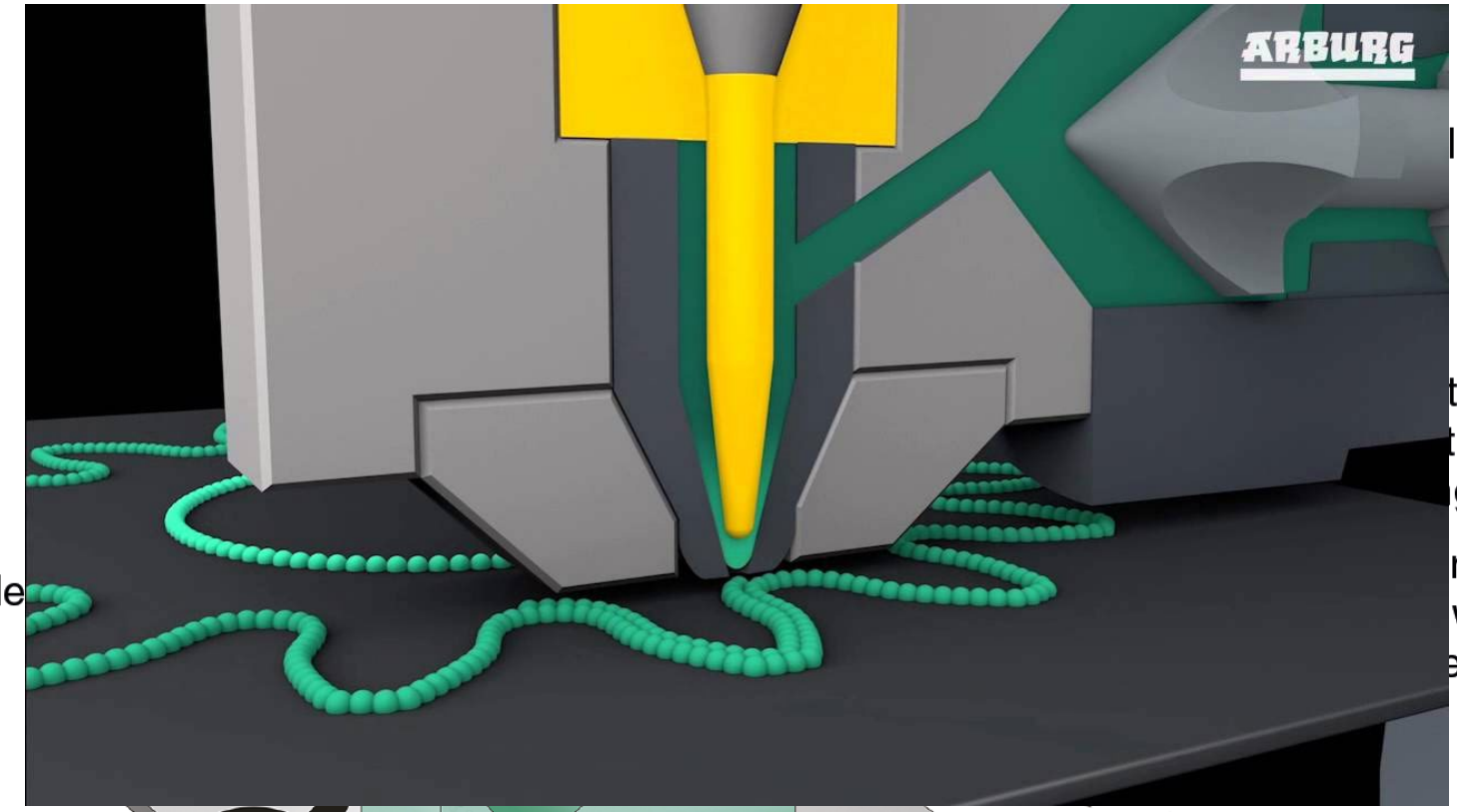




100% infill **75% infill** **50% infill** **25% infill**



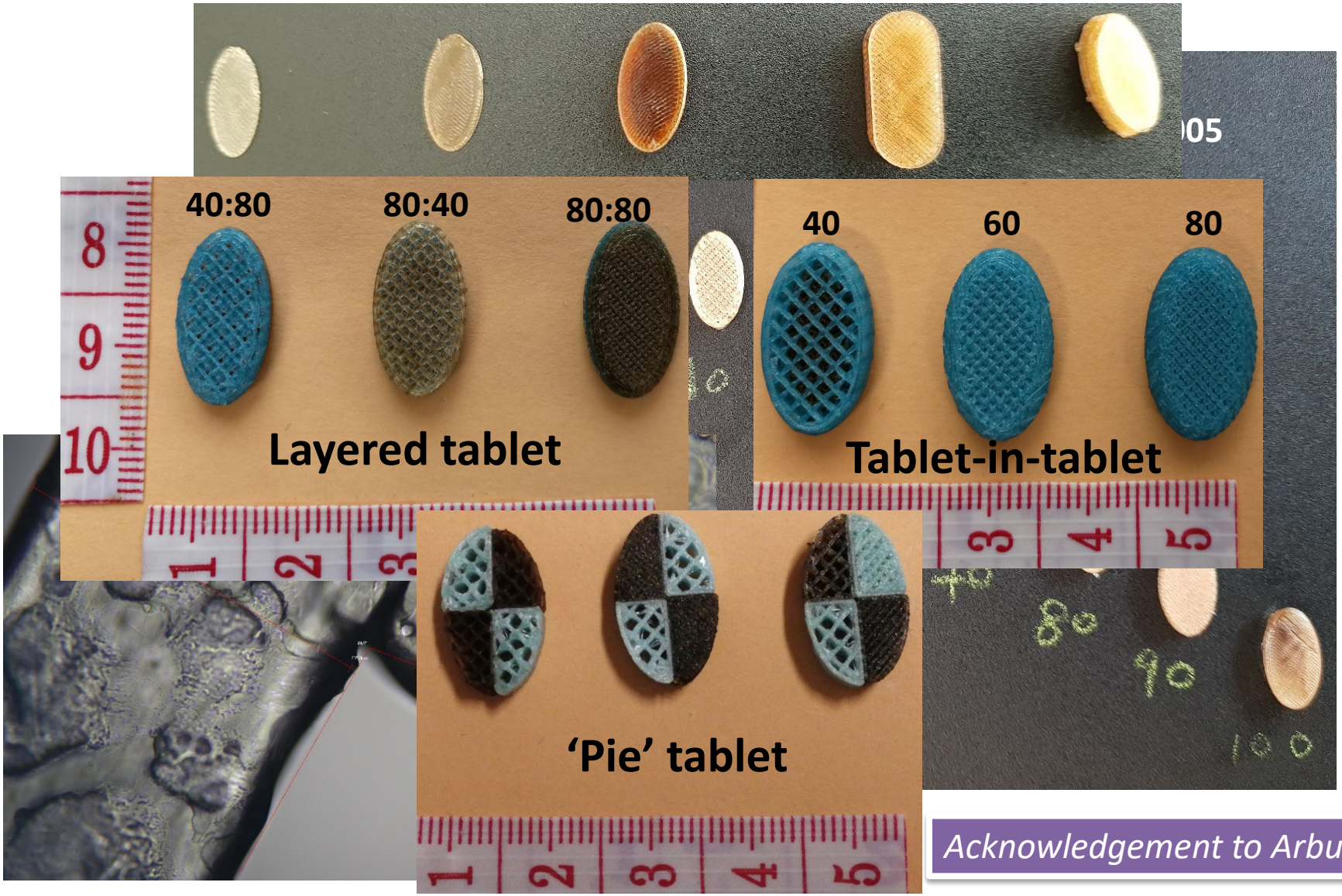
Filament v.s. Pellets
Extrusion v.s. injection



Nozzle

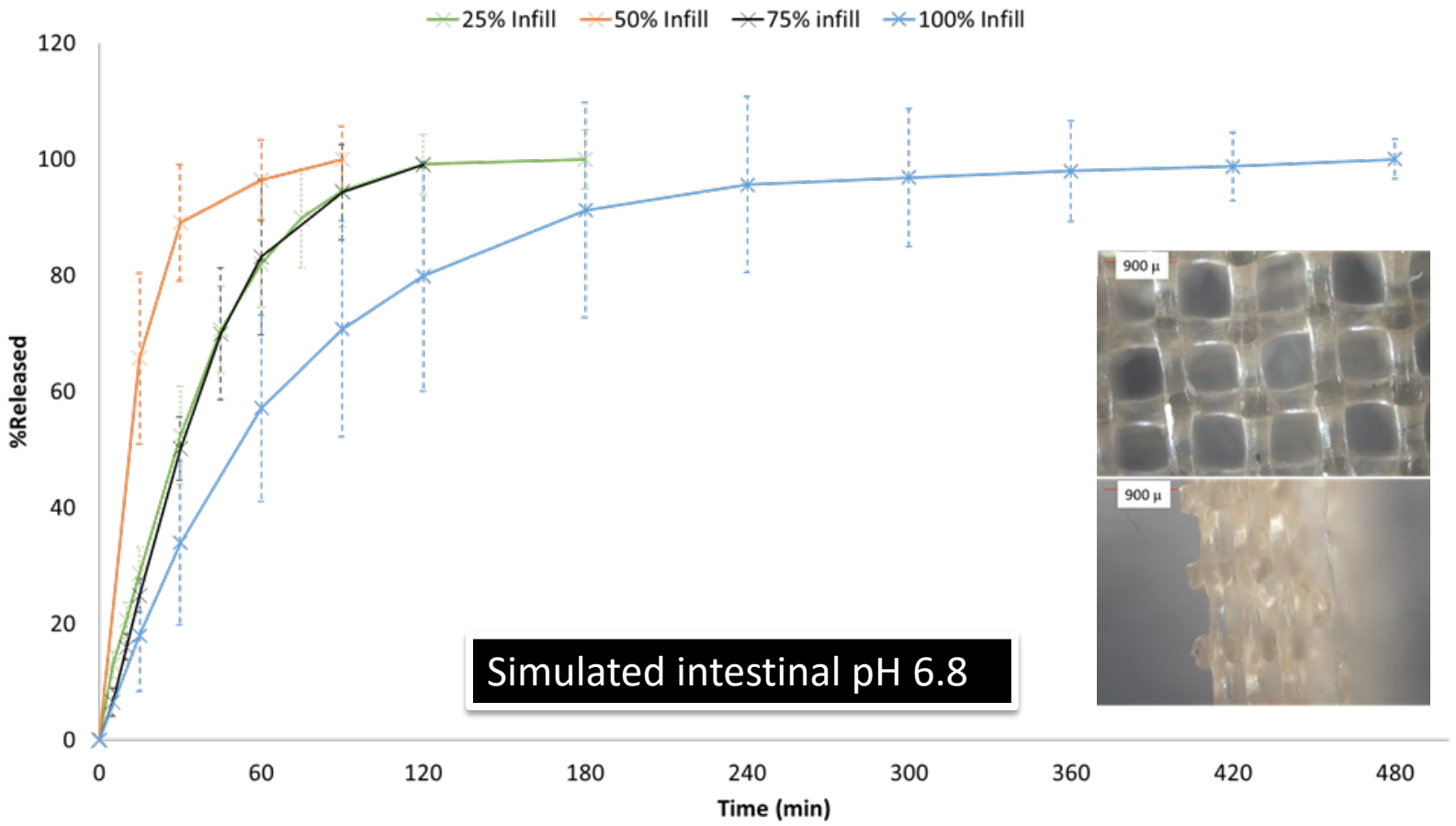
Discharge of individual droplets at the nozzle tip

Density

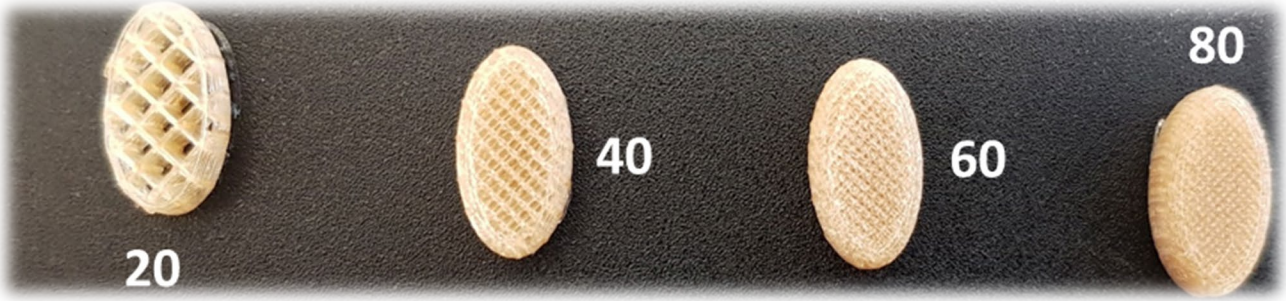


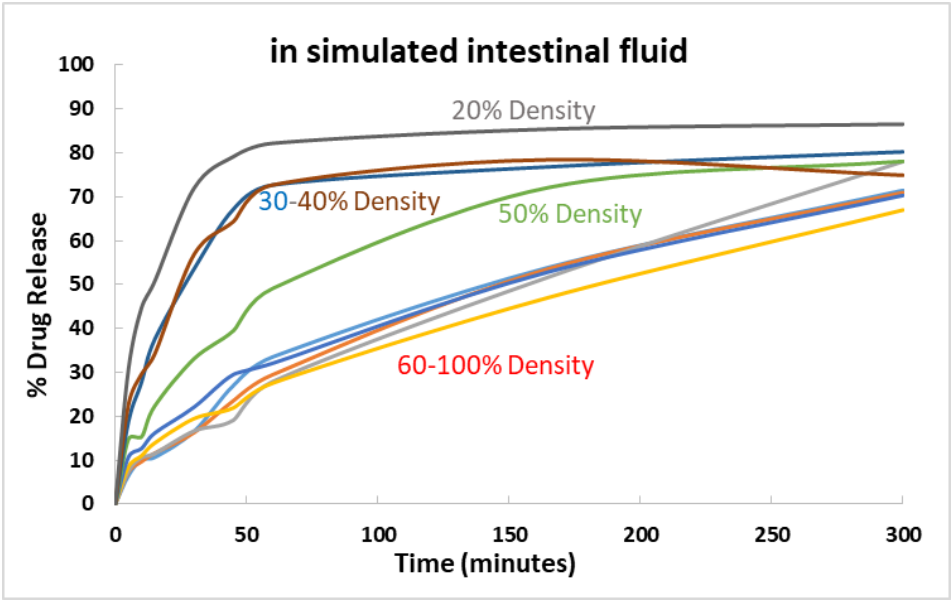
Acknowledgement to Arburg

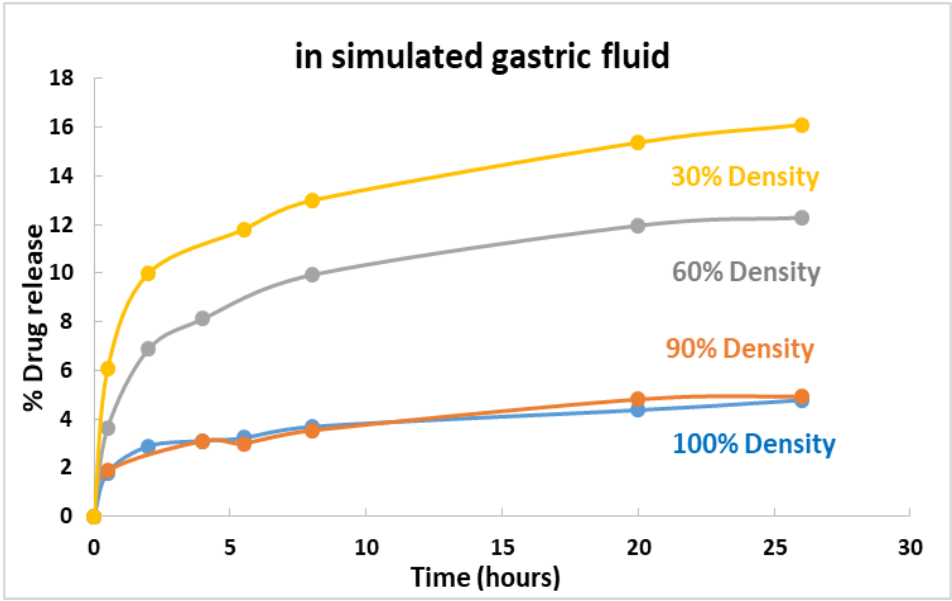
Filament Extrusion Based Printing



Droplet Based Printing



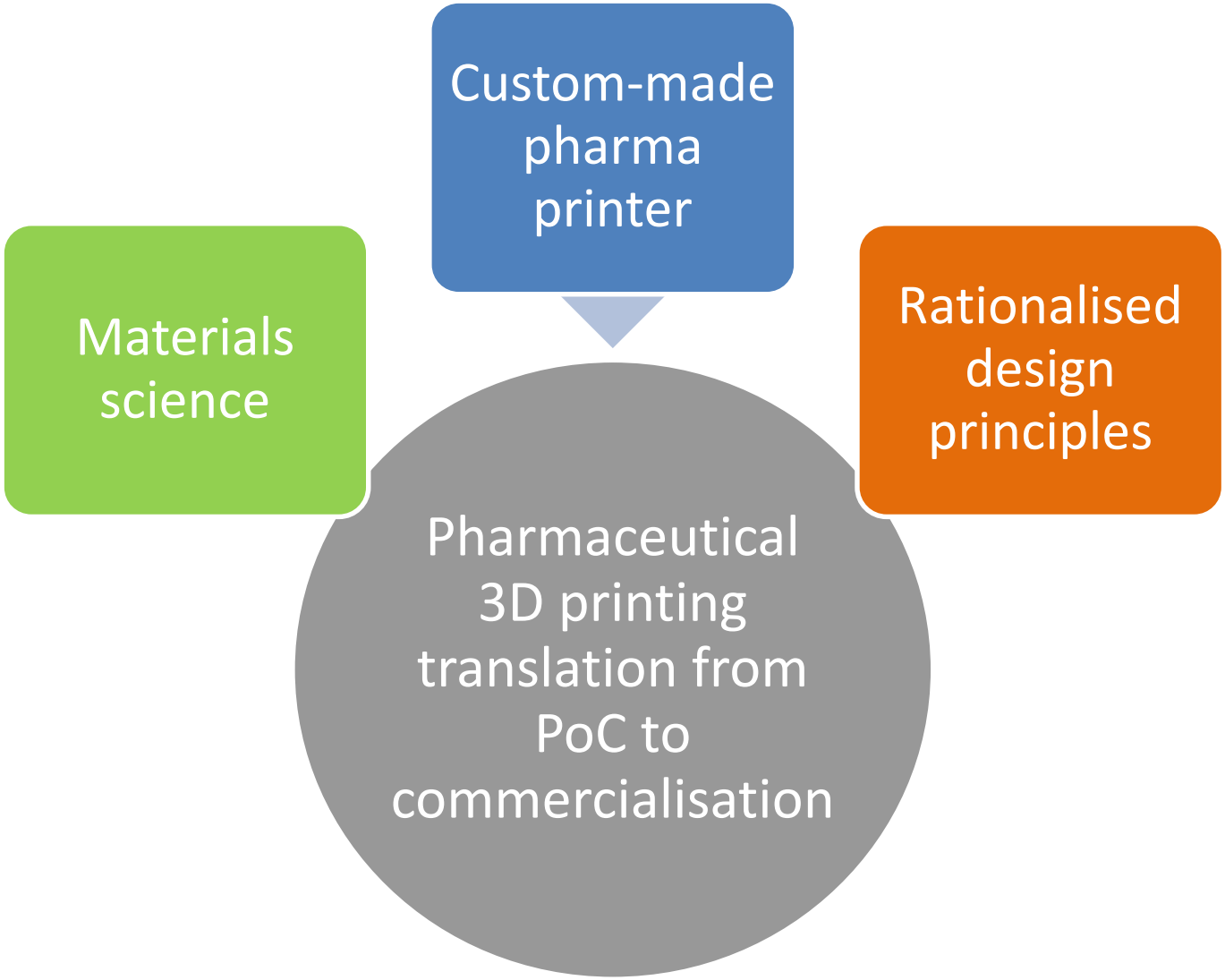




Key Message

Extremely important to understand the swelling/erosion/drug-polymer interaction behaviour of the building block of the 3D object (single road) in order to allow better prediction and guide the design of the 3D dosage form with desired performance.

Summary


Custom-made pharma printer
Materials science
Rationalised design principles
Pharmaceutical 3D printing translation from PoC to commercialisation

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GCRF Global Challenges Research Fund

NHS National Institute for Health Research

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Imode INNOVATIVE MULTICOMPONENT DRUG DESIGN

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