Formulation for 3D Printing

A project funded by EPSRC
Supported by GSK, PPG, Syngenta, Unilever and Malvern Panalytical

Phill, we asked a 100 companies what was holding AM back …

Tim, are materials on there?

The UK National Strategy for Additive Manufacturing revealed that lack of materials was the #1 concern for adoption of AM/3DP

http://www.amnationalstrategy.uk/

The vision

Vision: We will remove the barriers to the uptake of 3D printing through the adoption of high throughput formulation, establishing sector specific material libraries and creating a “plug and play” approach to materials selection, thereby securing the UK at the forefront of the 3D printing revolution

Formulation for 3D printing:
Creating a plug and play platform for a disruptive UK industry

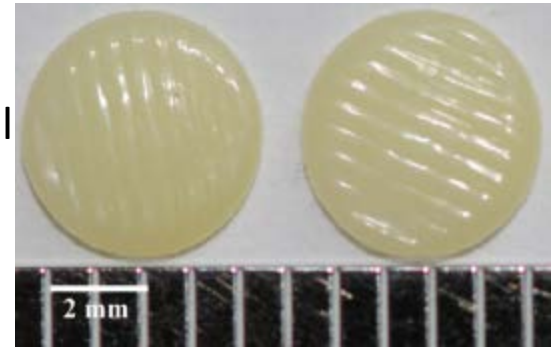
- EPSRC – £3.53M grant, 4 Years, started 1 Oct 2016
- Project partners:

- Academic partners

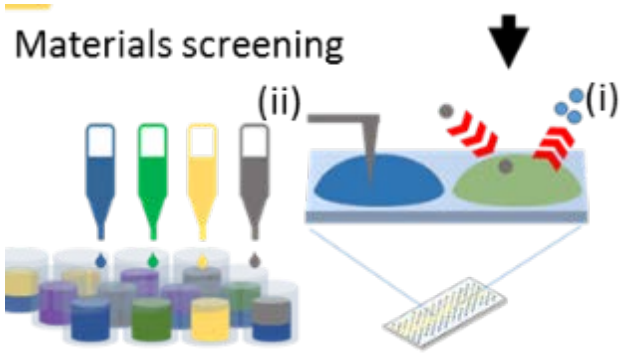
- Industrial partners

Additive Manufacturing has shown that it has many levers that allow us to formulate to need

We can systematically reformulate the material



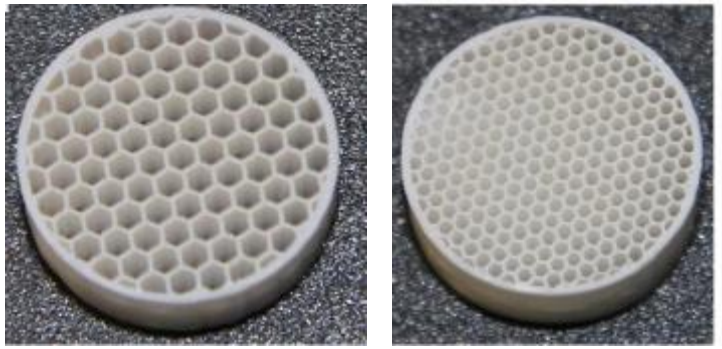
Additive Manufacturing has shown that it has many levers that allow us to formulate to need



We can find new materials via screening

Additive Manufacturing has shown that it has many levers that allow us to formulate to need

We can we change the shape and geometry



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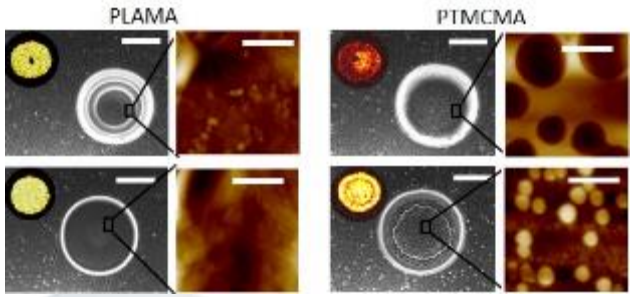
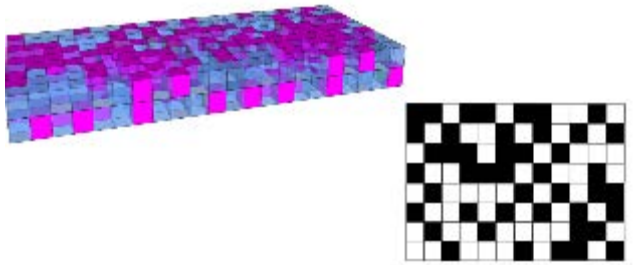


We can manipulate the microstructure

Additive Manufacturing has shown that it has many levers that allow us to formulate to need

We can vary the composition



An example API formulation problem

- Find materials that enable ink jet printing of both poorly soluble and highly soluble drugs

Ropinirole HCl (Requip™)

For treatment of Parkinson's

Highly soluble in water

Carvedilol (Coreg™)

For treatment of hypertension

Poorly soluble in water

Clark et al. '3D Printing of Tablets using Inkjet with UV photoinitiation' International Journal of Pharmaceutics, 529 2017 523-530

Clark et al. 'Making tablets for delivery of poorly soluble drugs using photoinitiated 3D inkjet printing' International Journal of Pharmaceutics, 578 2020 118805

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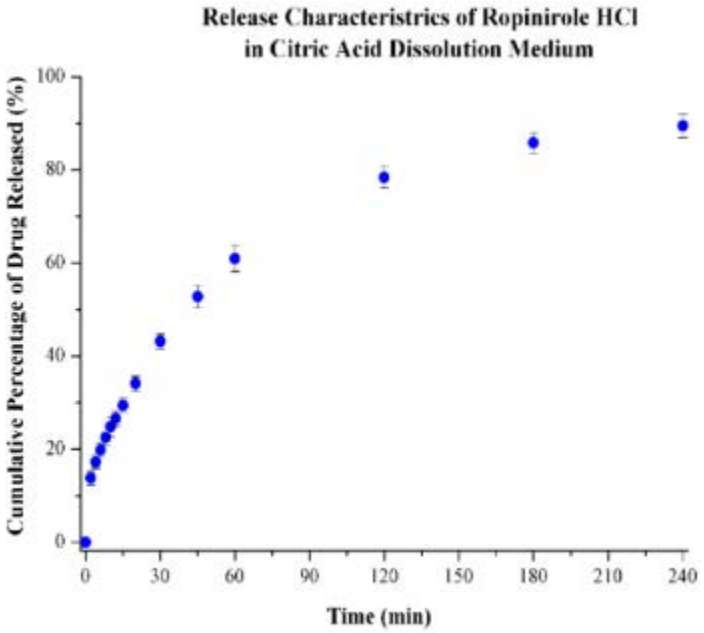
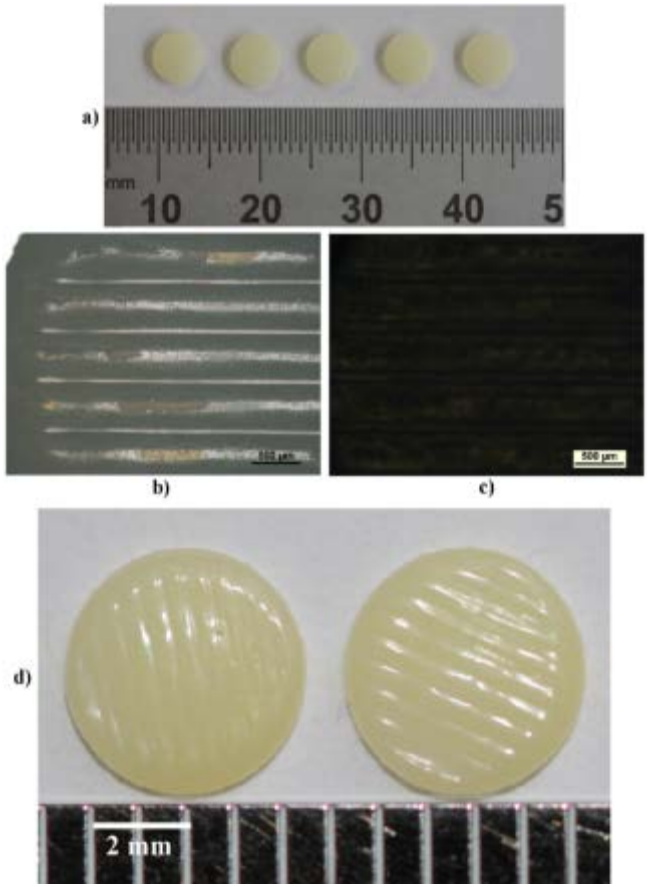
UV curable materials for solid dosage forms: soluble

Material	wt %
PEGDA	30
Irgacure 2959	0.5
ropinirole	2
Water	67.5

Formulation:

- Printable
- API stable
- API elutes within prescribed limits





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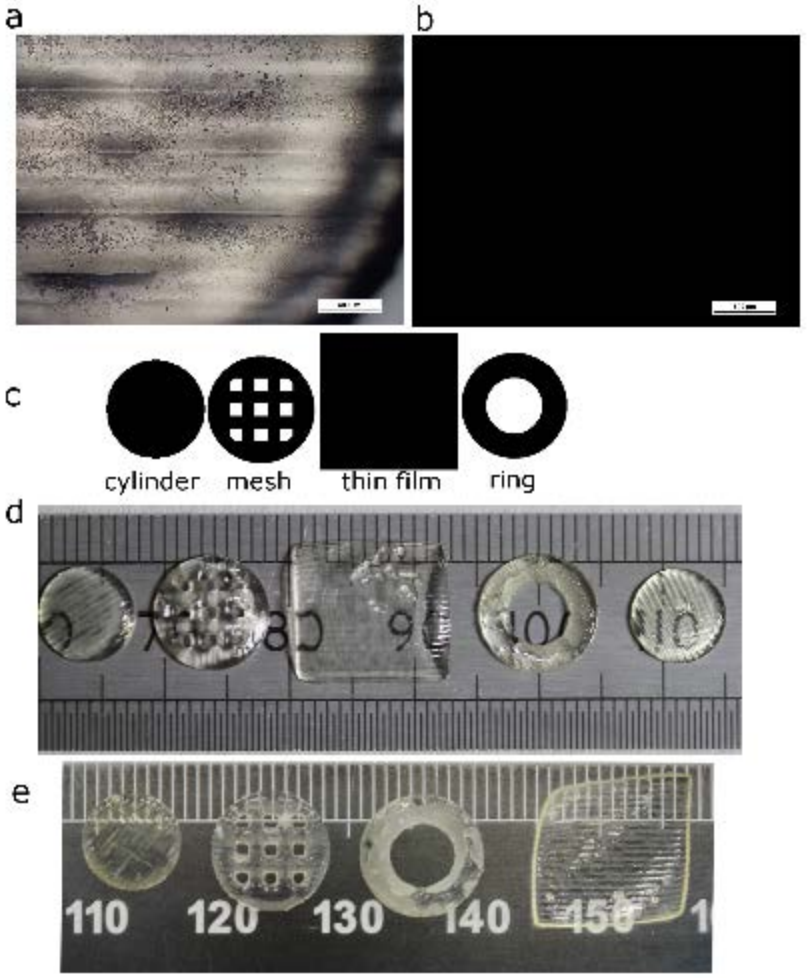
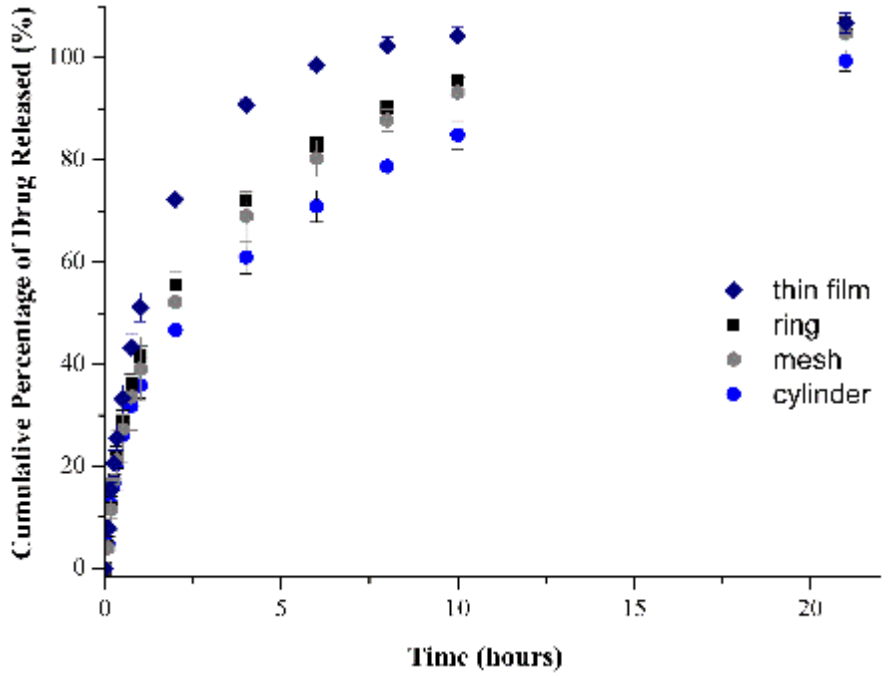
UV curable materials for solid dosage forms: poorly soluble



Irgacure 2959	0.50 wt%
Carvedilol	10.00 wt%
N-vinyl 2-pyrrolidone (NVP)	73.06 wt%
PEGDA (M_n= 250 g/mol, Sigma-Aldrich)	16.44 wt%



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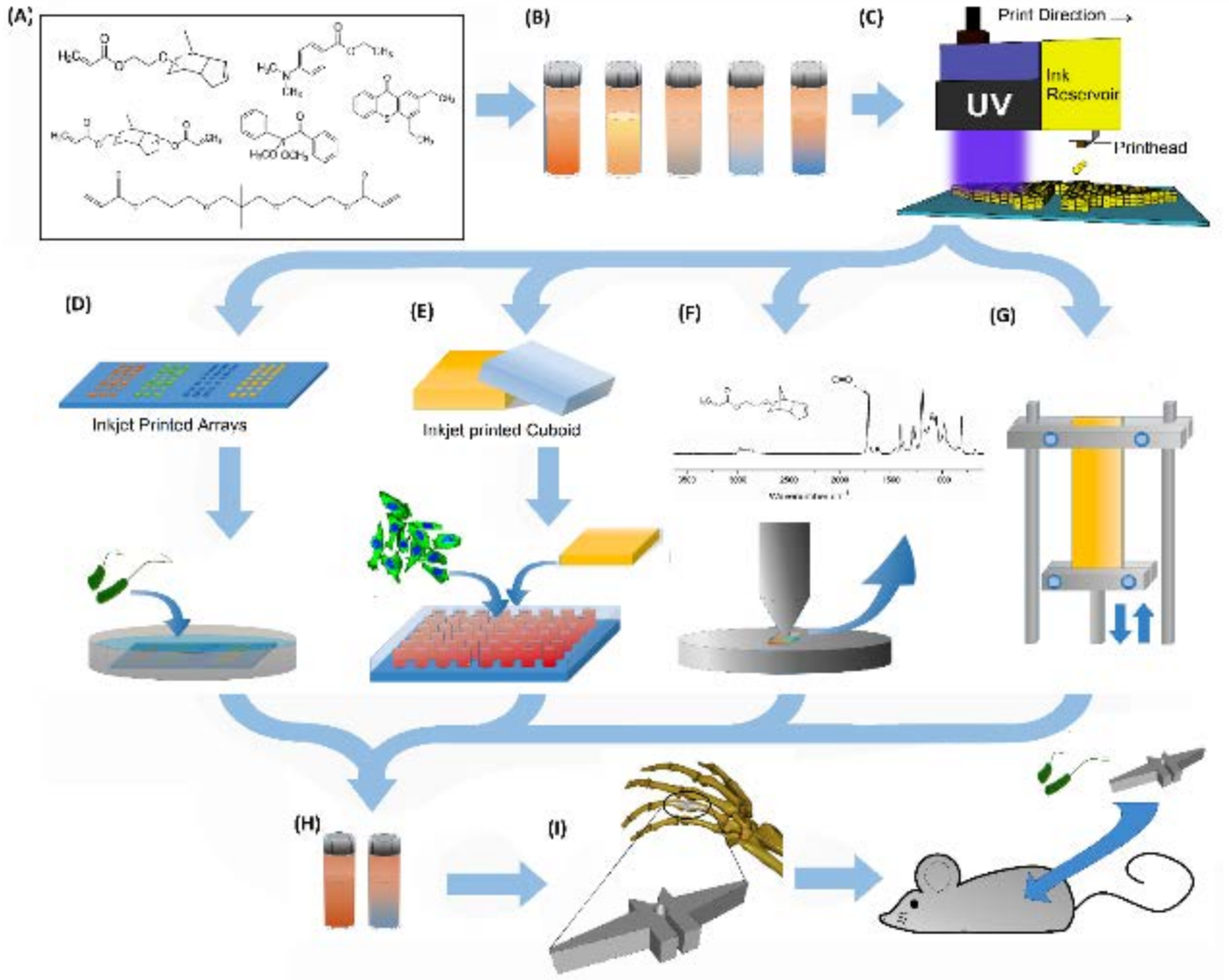
When we don’t quite know what will work: screening

A scheme for identifying printable, resistant to bacterial attachment materials



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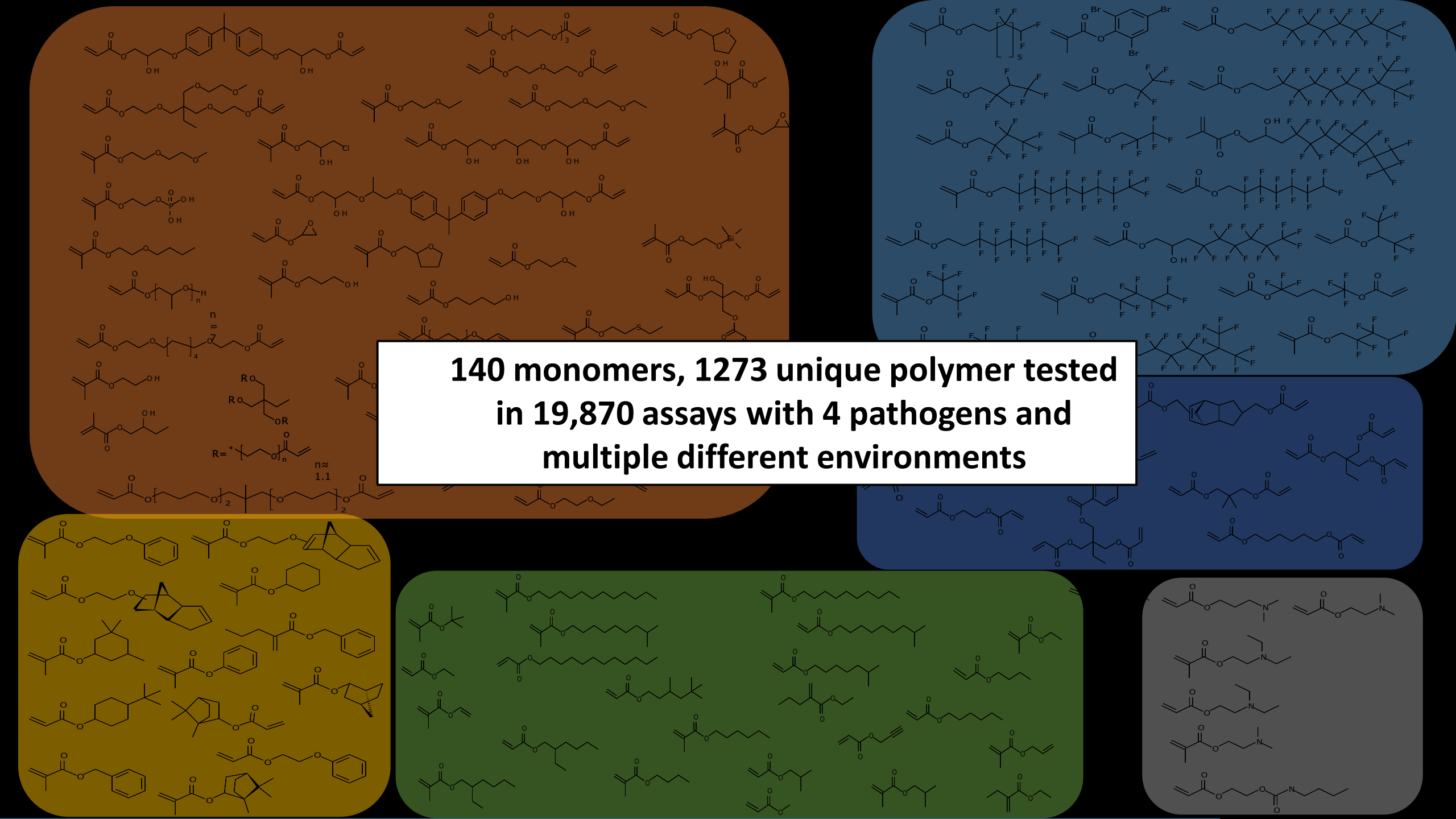
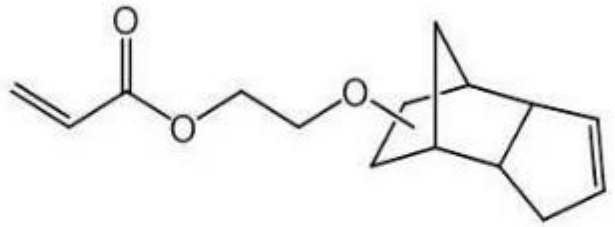
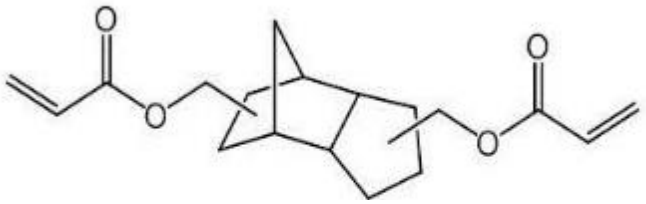

140 monomers, 1273 unique polymer tested
in 19,870 assays with 4 pathogens and
multiple different environments

Borrowing materials shown to have microbial resistance



Ethylene glycol dicyclopentenyl ether acrylate



Tricyclo[5.2.1.0.2,6] decanedimethanol diacrylate

Begines et al ‘Development, printability and post-curing studies of formulations of materials resistant to microbial attachment for use in inkjet based 3D printing’, Rapid Prototyping Journal, 22, 2016 835-841

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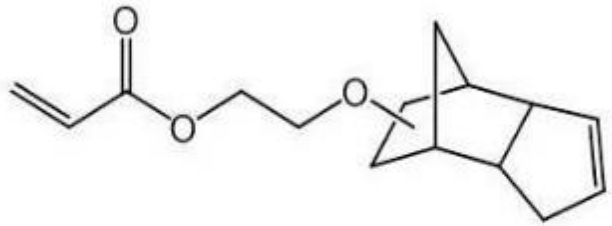

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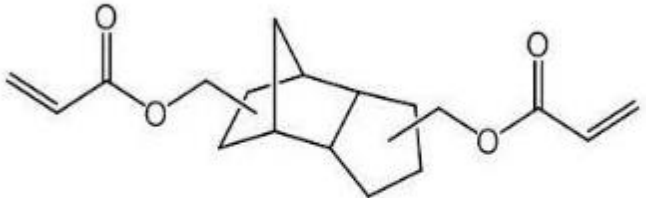

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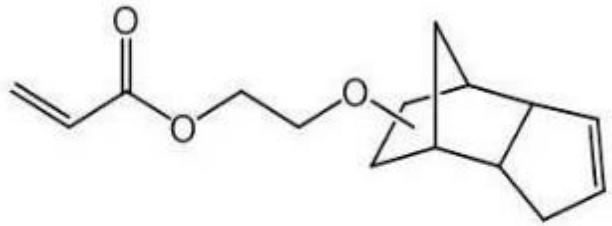

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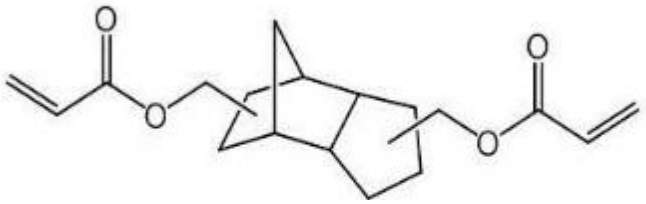

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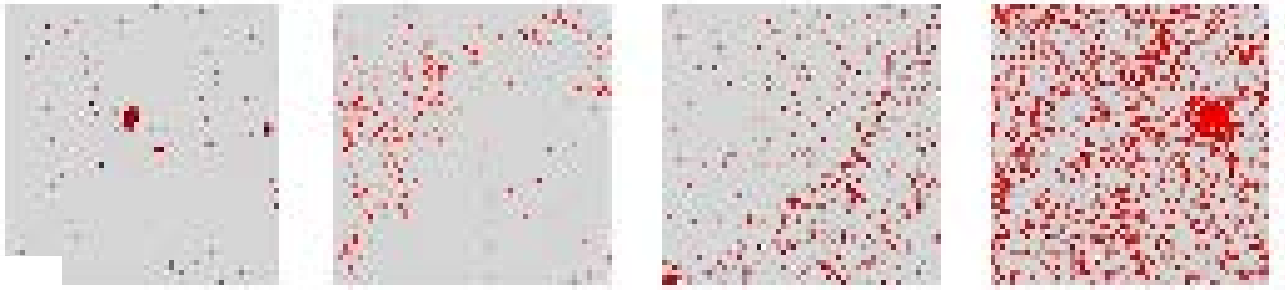

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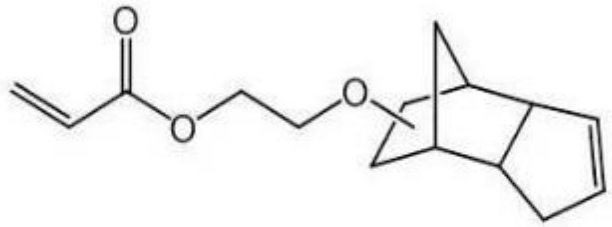

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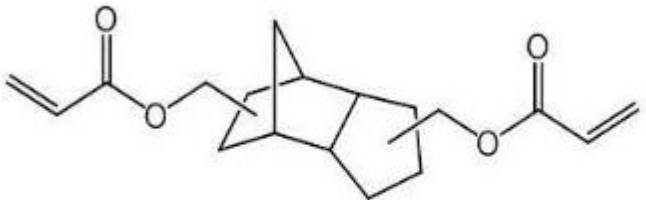

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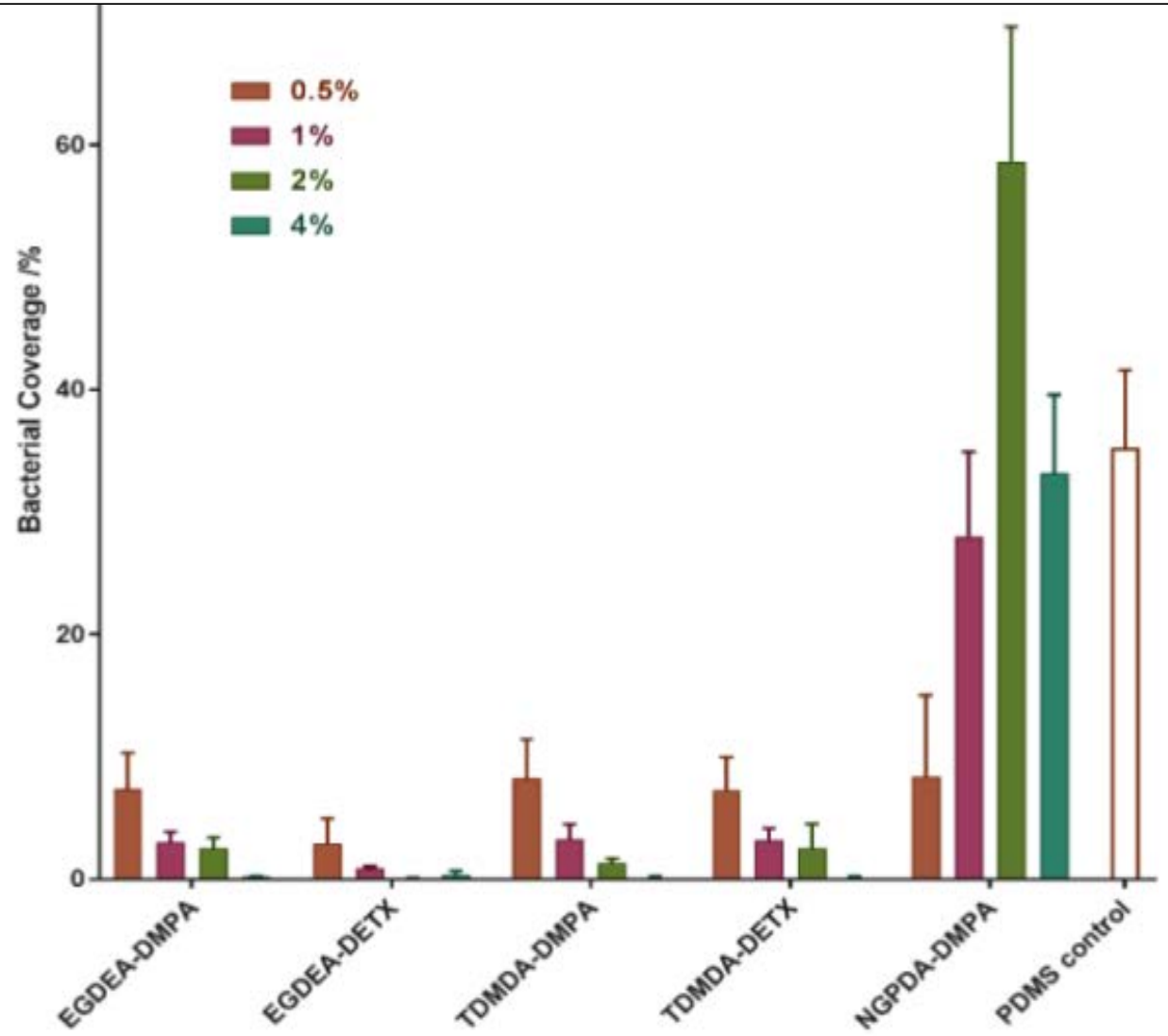

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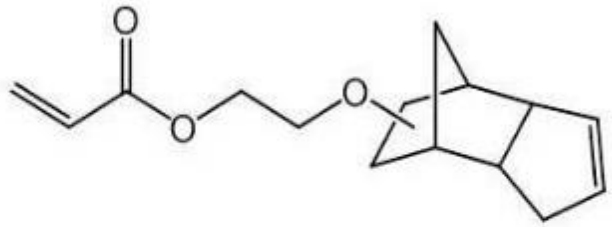

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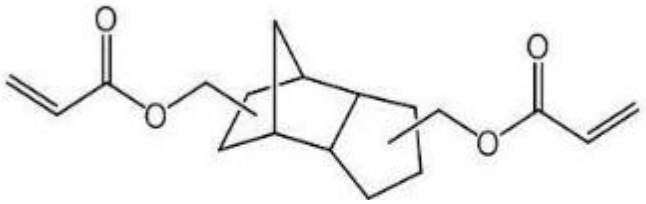

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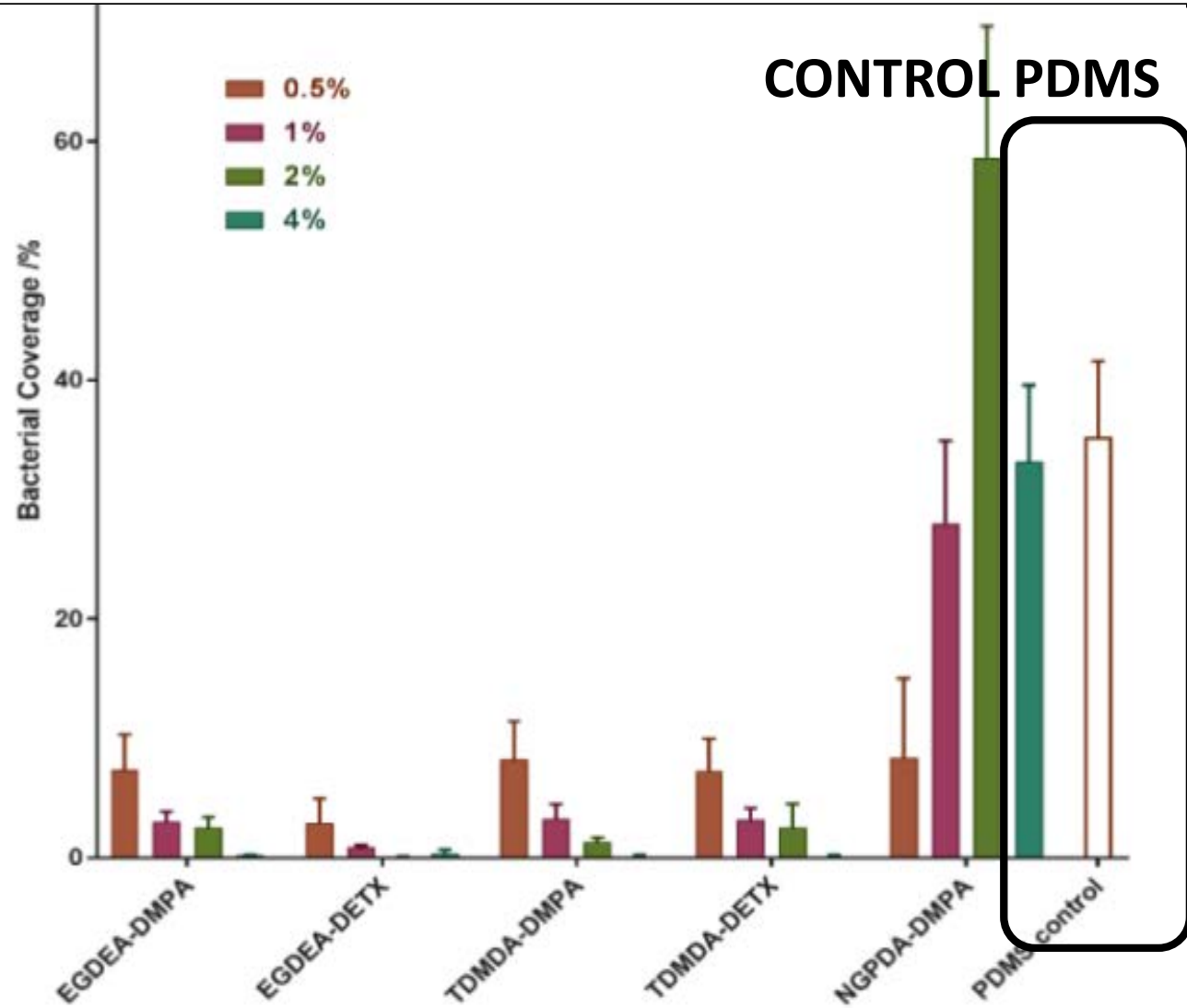

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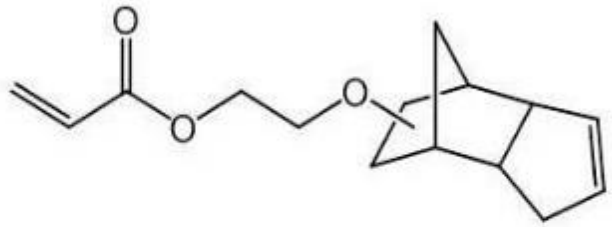

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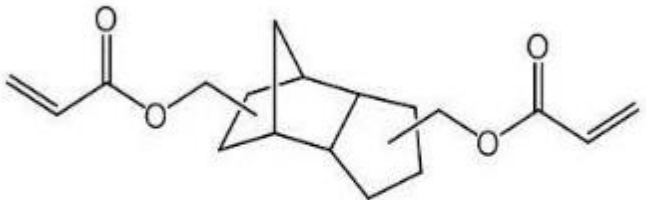

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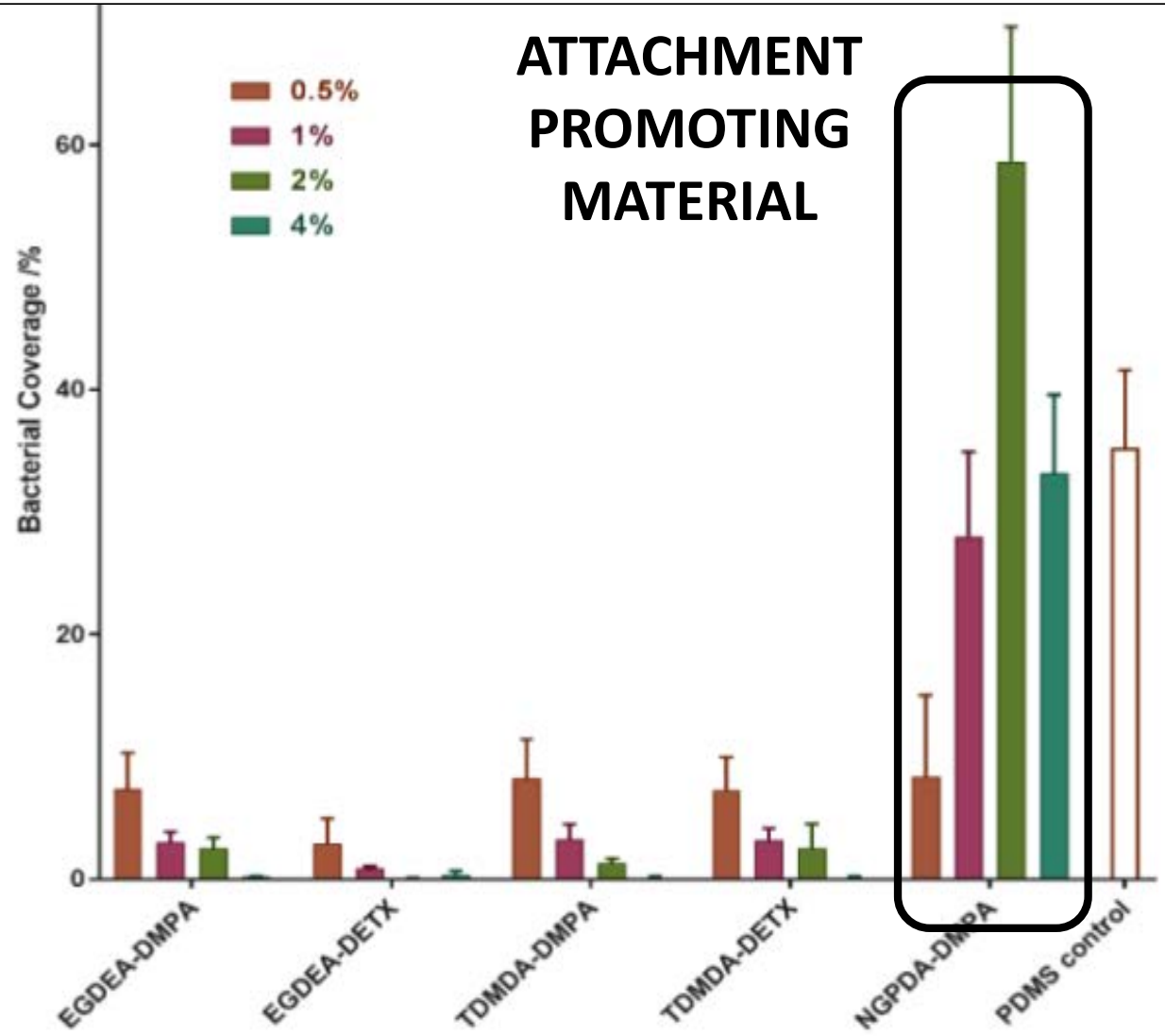

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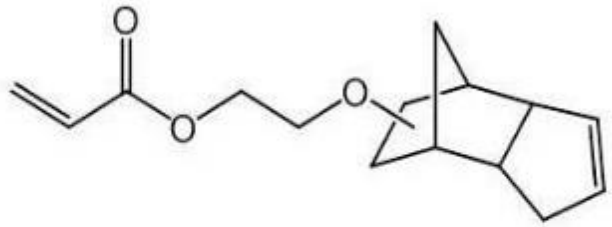

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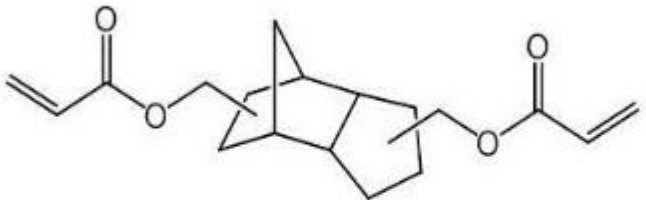

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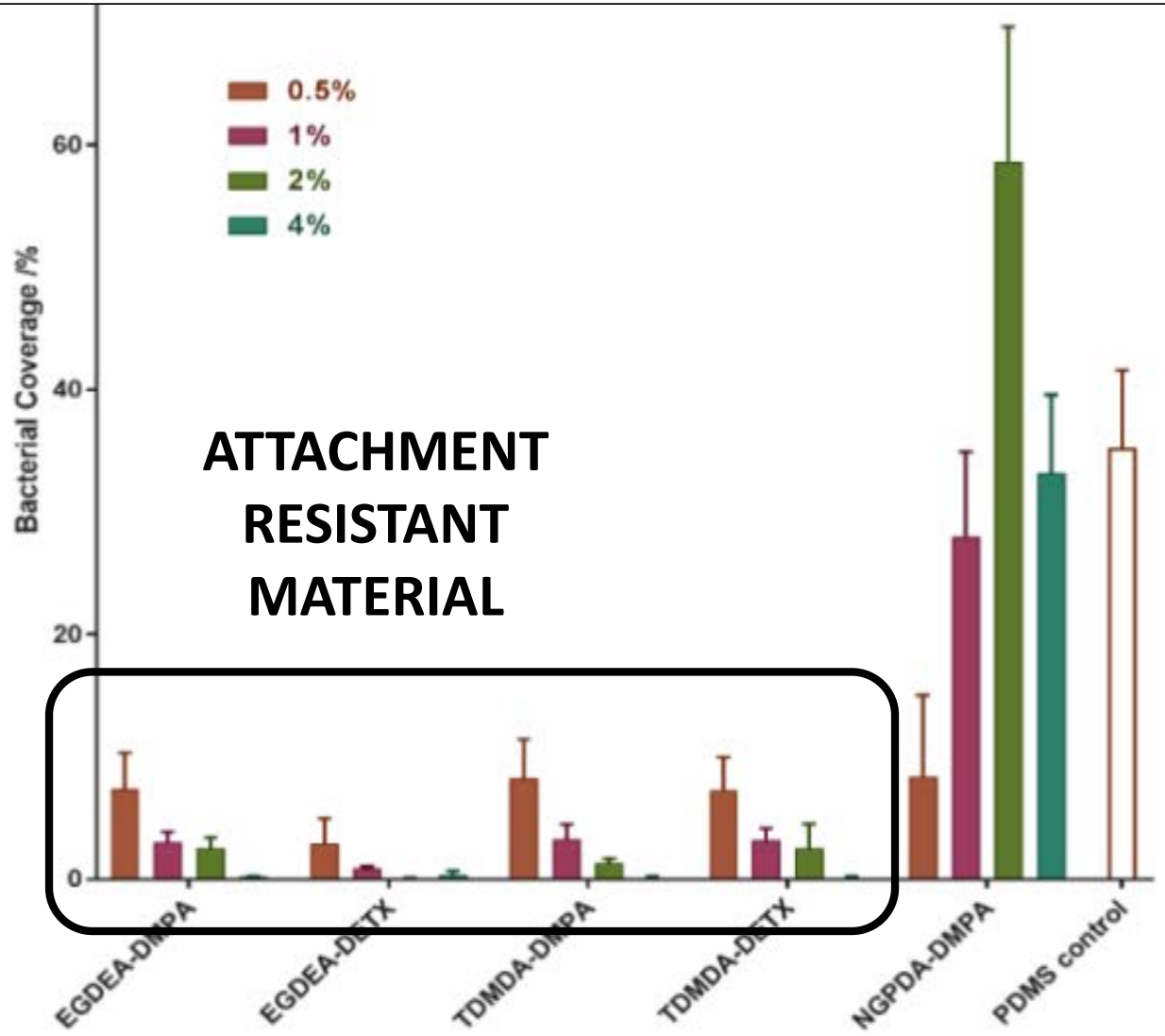

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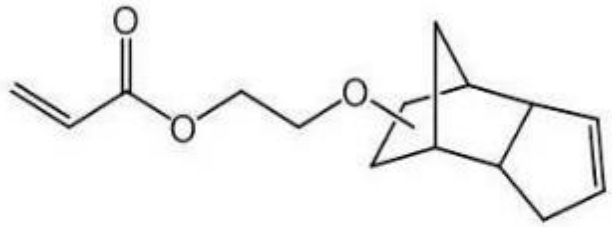
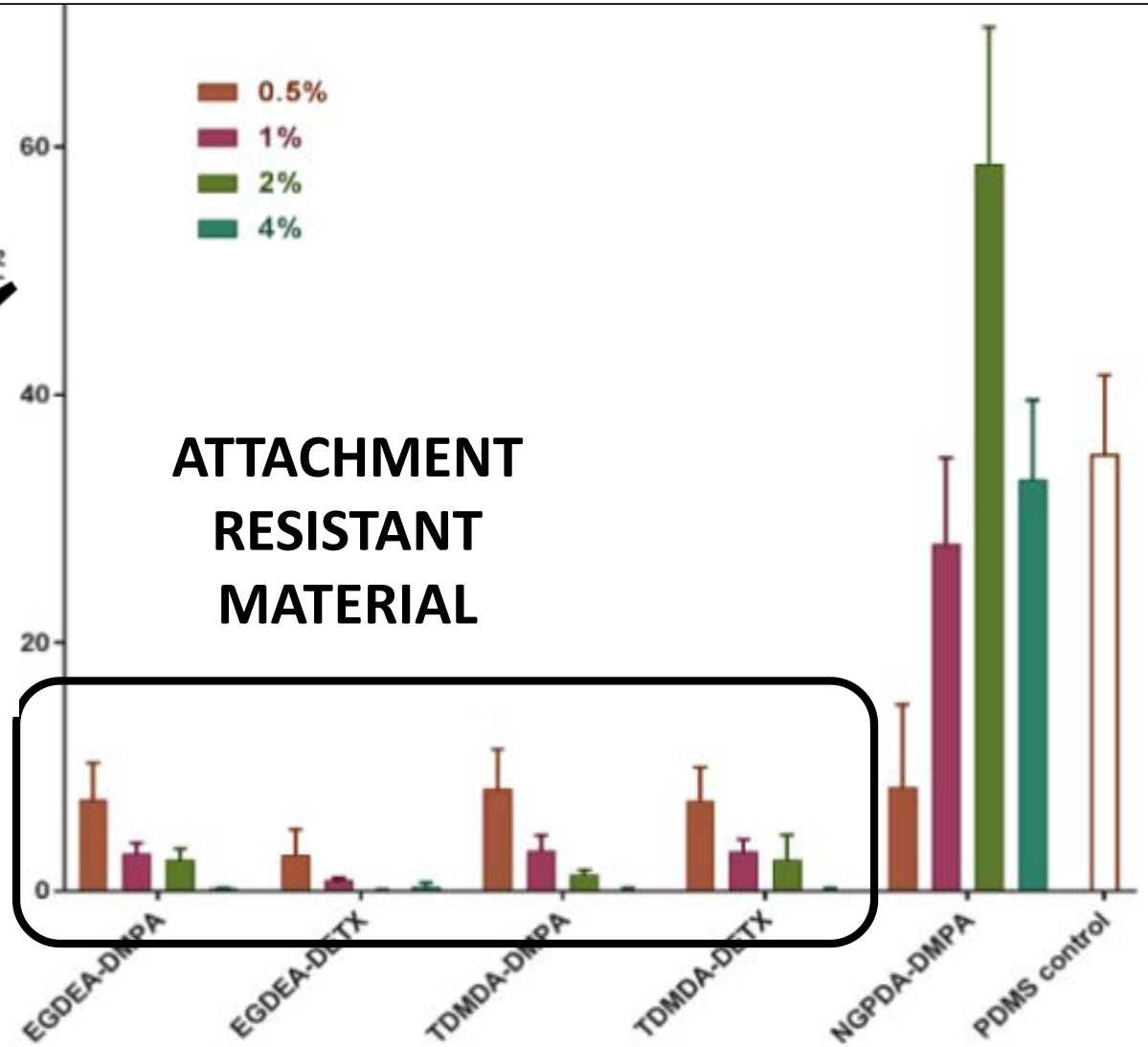


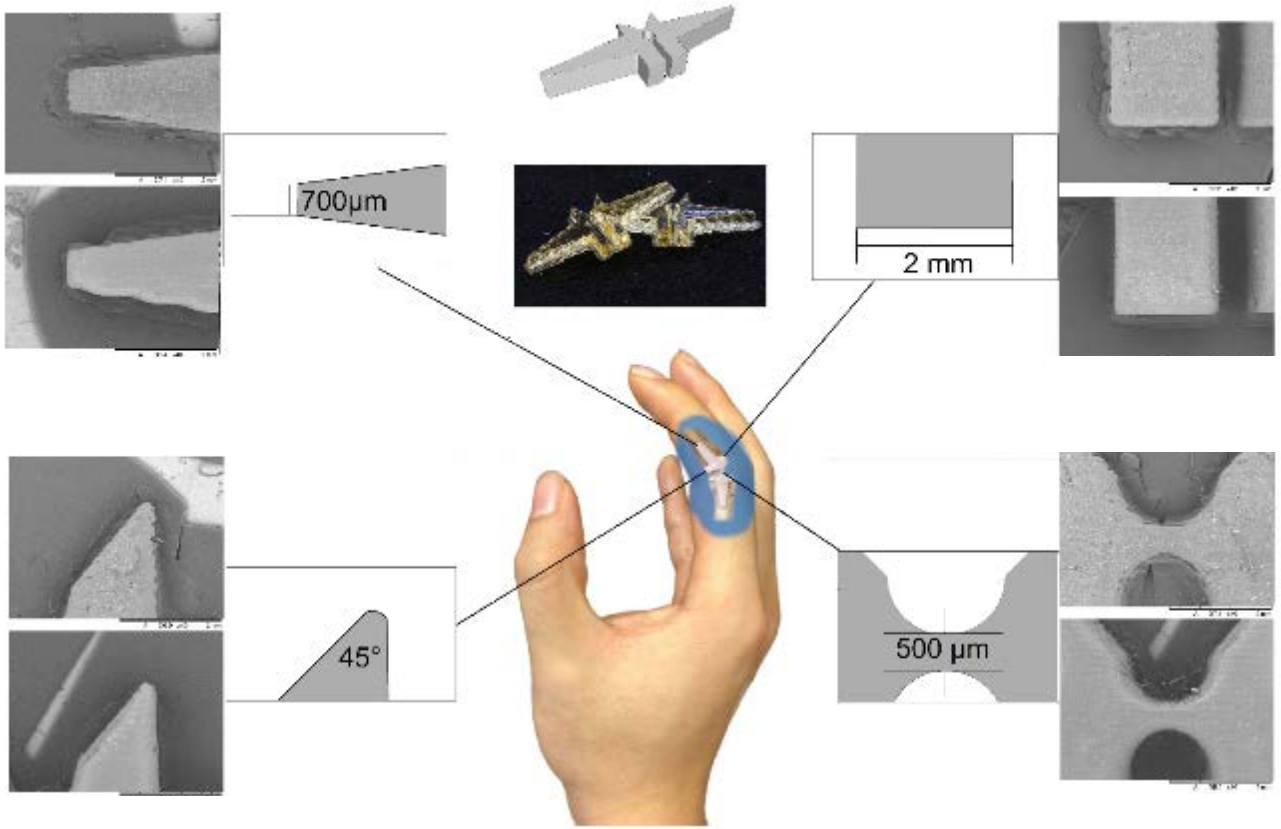
Scaled up materials RETAIN functionality

Tricyclo[5.2.1.0.2,6] decanedimethanol diacrylate



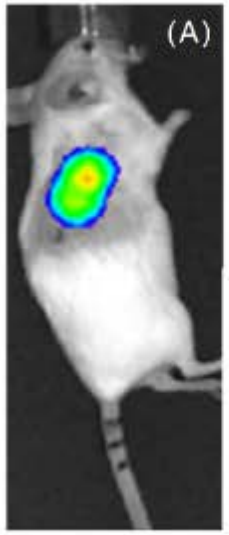
ATTACHMENT RESISTANT MATERIAL

Begines et al 'Development, printability and post-curing studies of formulations of materials resistant to microbial attachment for use in inkjet based 3D printing', Rapid Prototyping Journal, 22, 2016 835-841

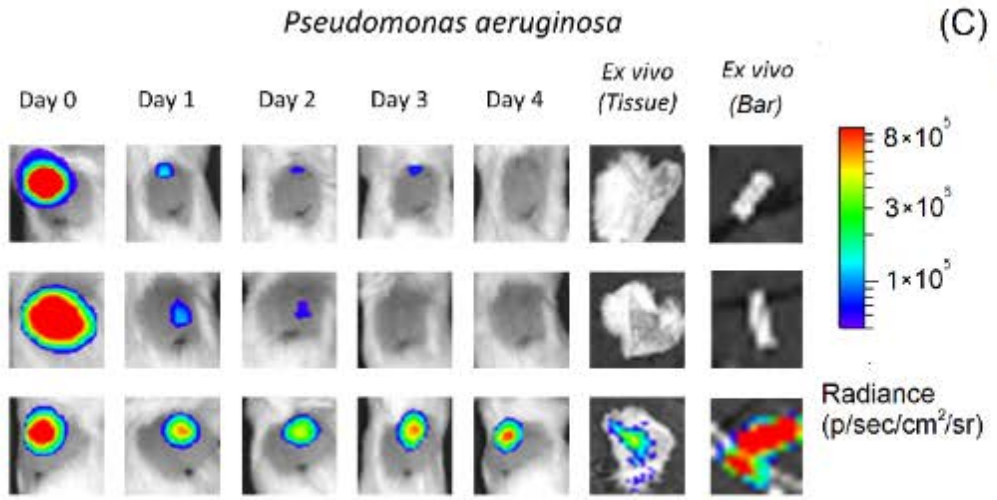


Design and manufacturing a bacterial resistant implant ✓

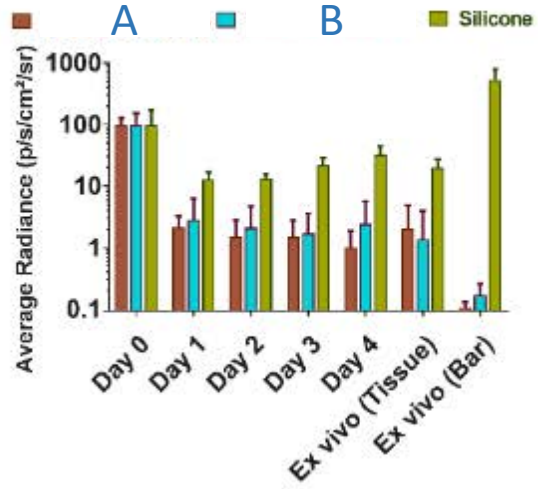
Assess efficacy using an in vivo mouse model ✓



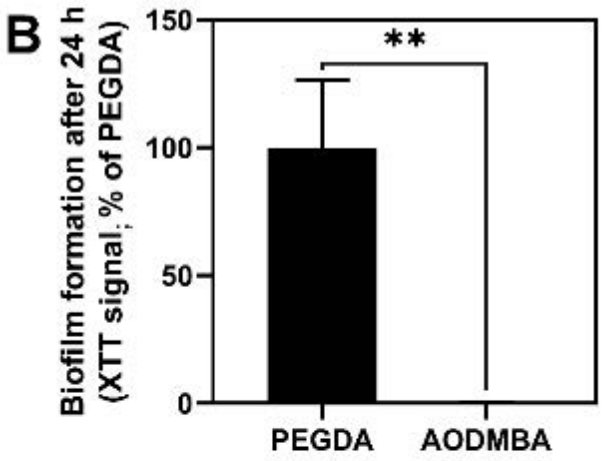
(B)

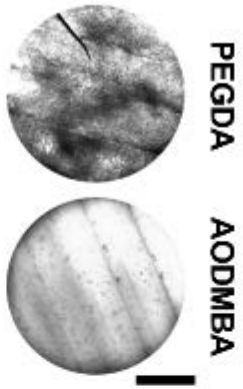


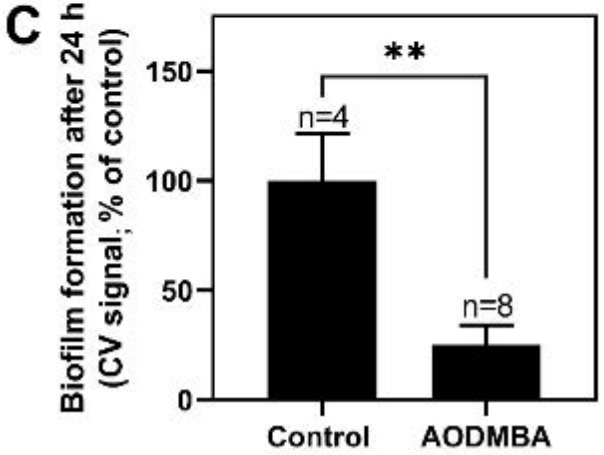
(C)

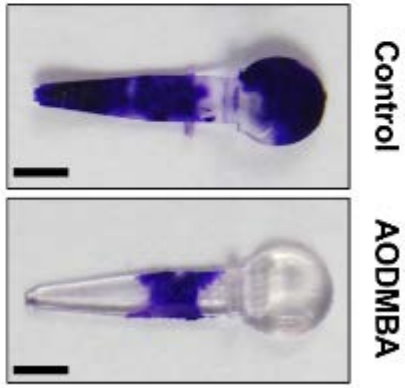


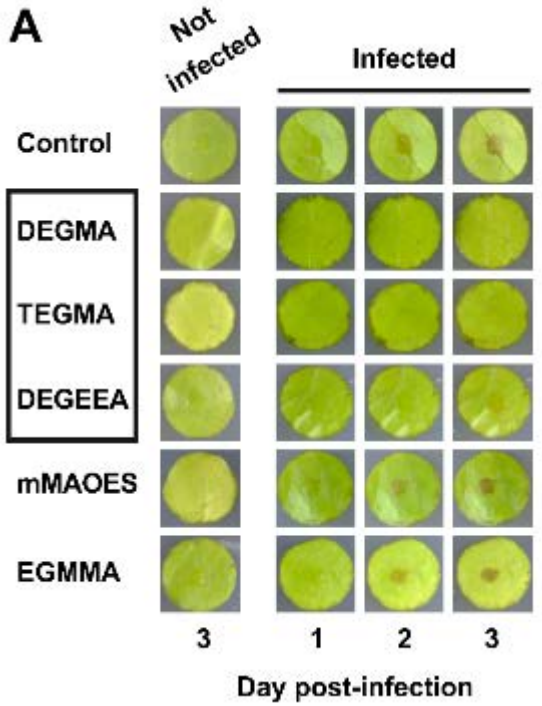
Or will can look at other functionality: fungal attachment

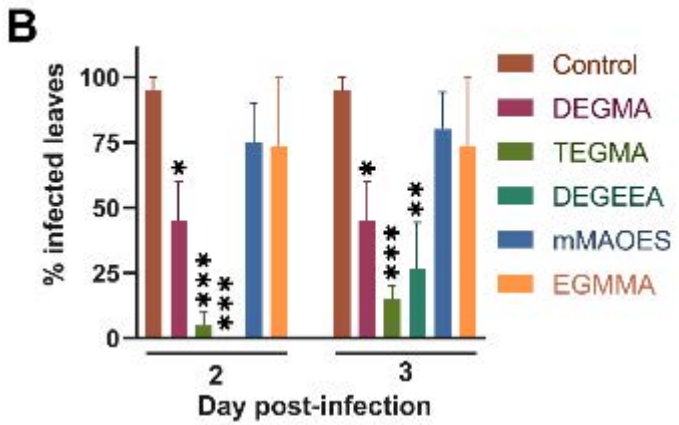


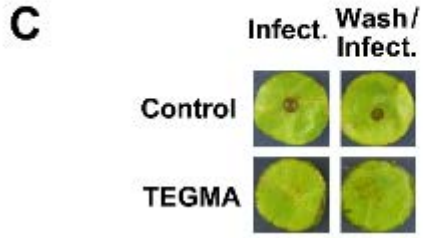


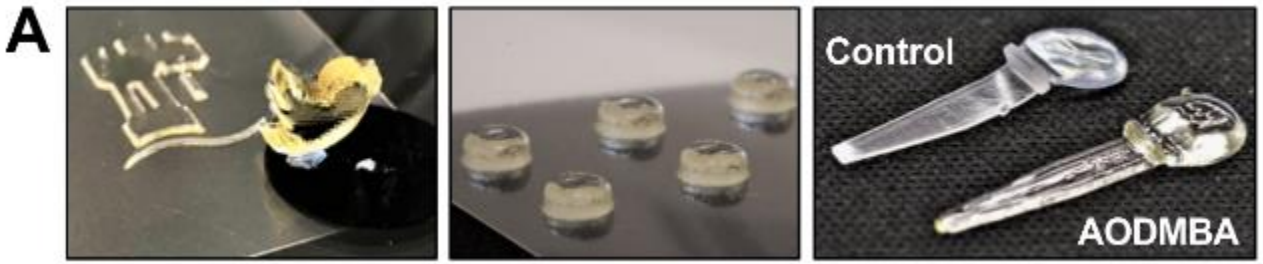












Vallieres et al, Science Advances
10.1126/sciadv.aba6574

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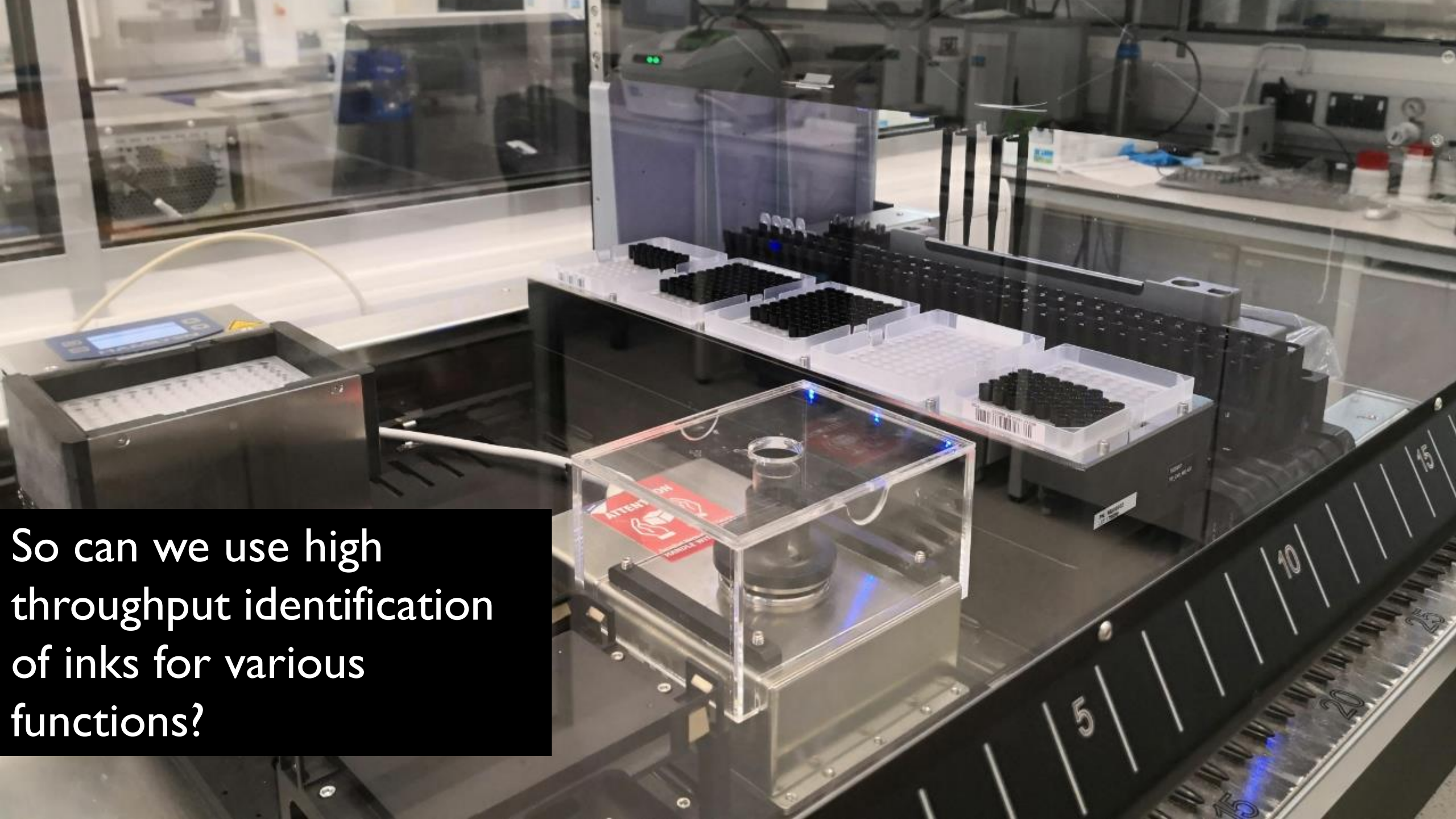
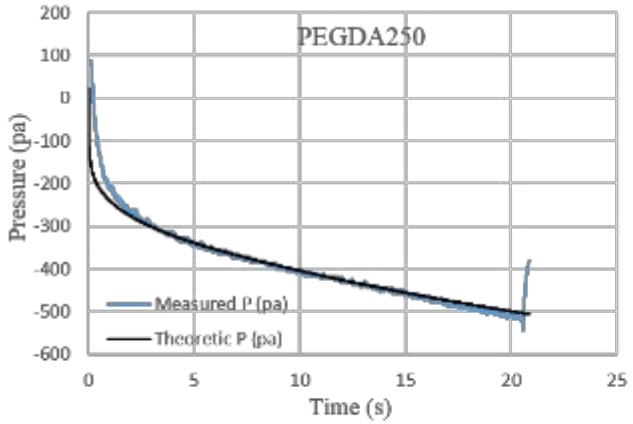
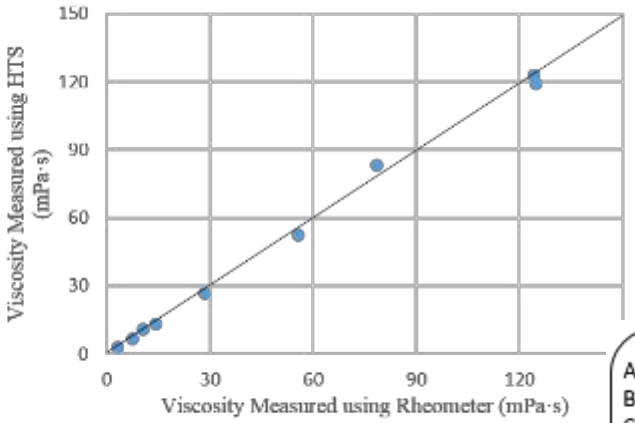


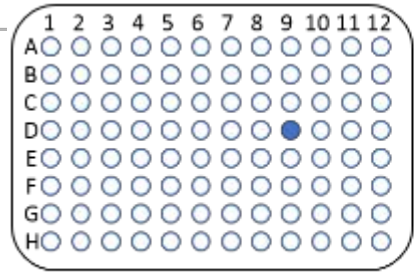
So can we use high throughput identification of inks for various functions?

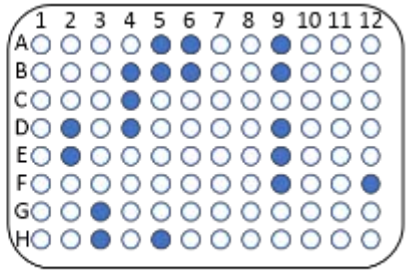
Attempt 2: High-throughput Inkjet Printability Determination

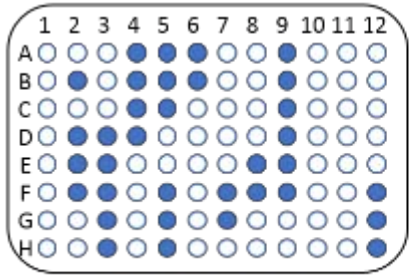


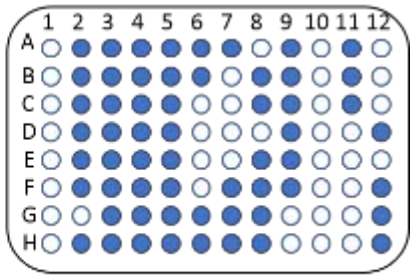


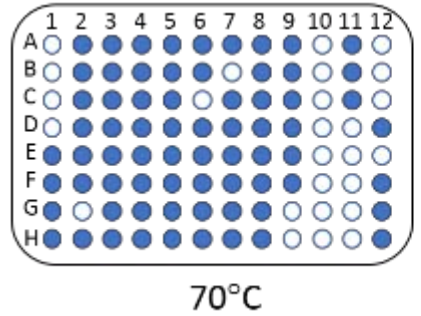
Viscosity (mPa·s) @ 25°C			
	Measured using Rheometer	Measured using HTS	Difference
PEGDA250	10.52	10.87	3.33%
TCDDDA	124.08	122.82	1.02%
S3	3.26	2.85	12.58%
S6	7.37	6.76	8.28%
N10	14.26	13.24	7.15%
S20	28.39	26.59	6.34%
N35	55.70	52.21	6.27%
N75	124.80	119.13	4.54%









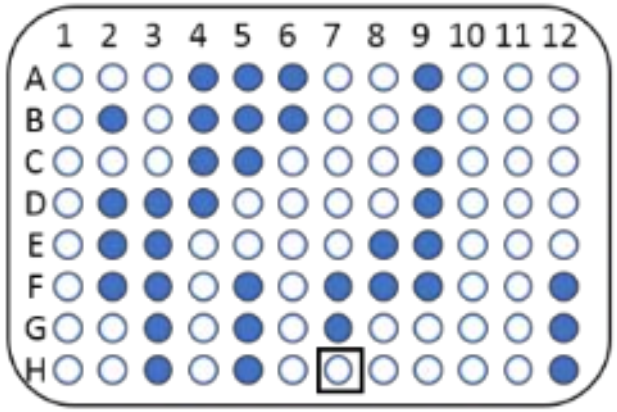


$$P_{gas} = \int_0^H \frac{8\mu Q}{\pi\left(\frac{R_t + R_{(t-0.01)}}{2}\right)^4} dH - \rho g(0.02 - H_t) - \frac{2\gamma\cos\theta}{R_t}$$

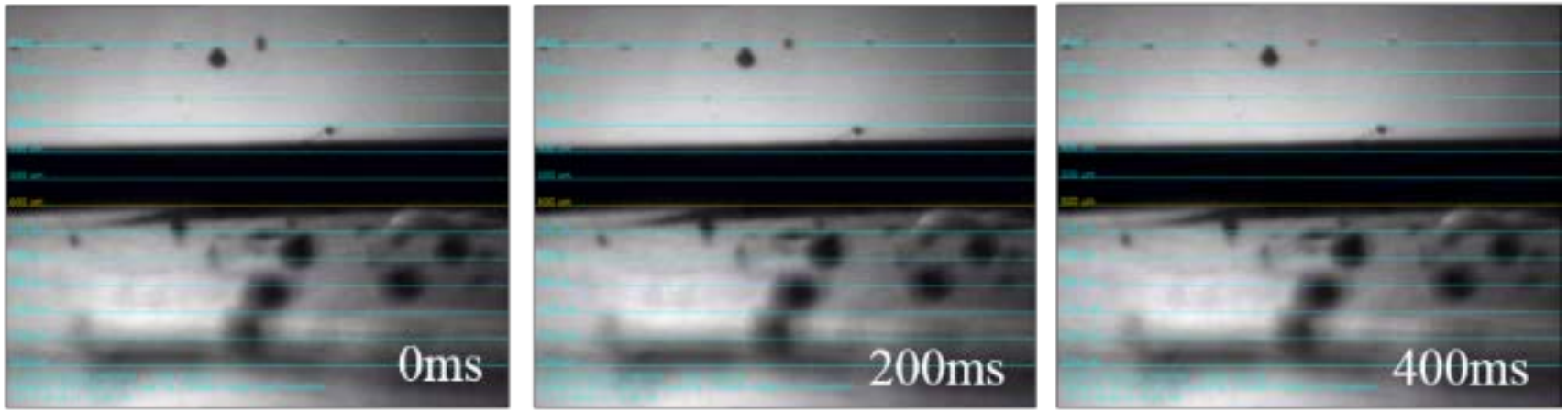
Variation in printability with temperature

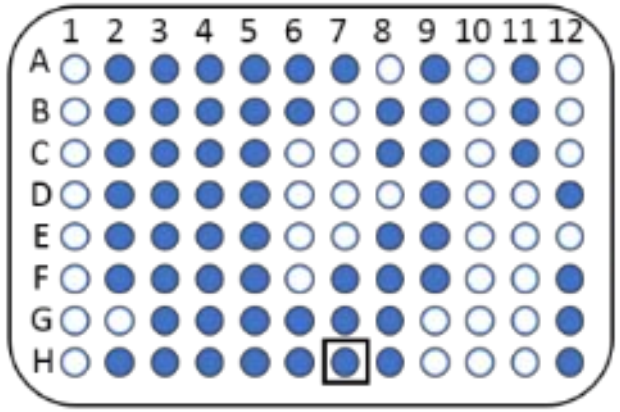
High-throughput characterization of fluid properties to predict droplet ejection for three-dimensional inkjet printing formulations
Zhou et al Additive Manufacturing 29, 100792 2019

Validation of results: demonstration of printability

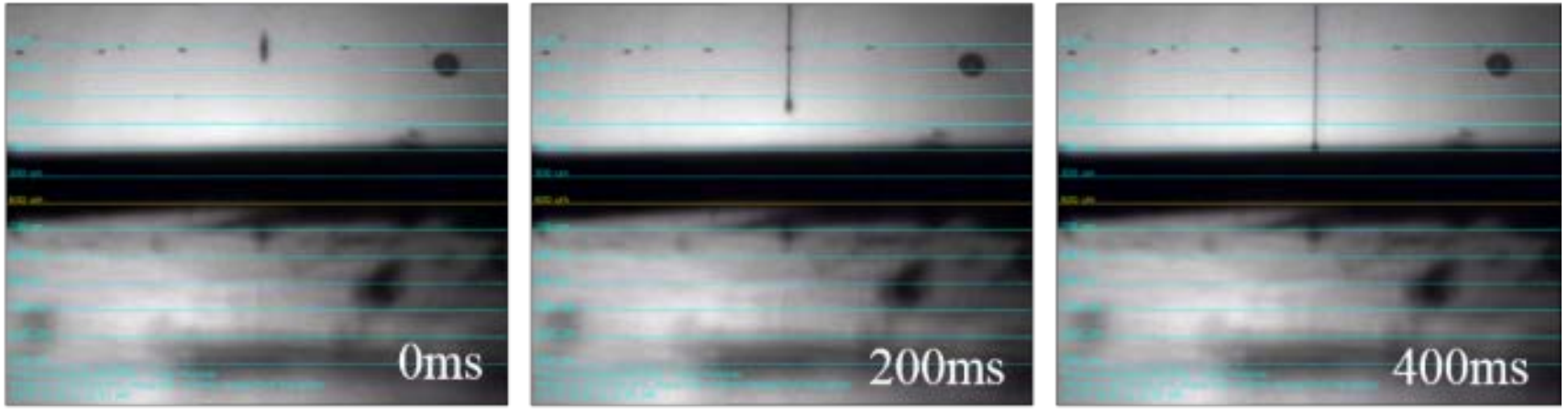


50°C





60°C



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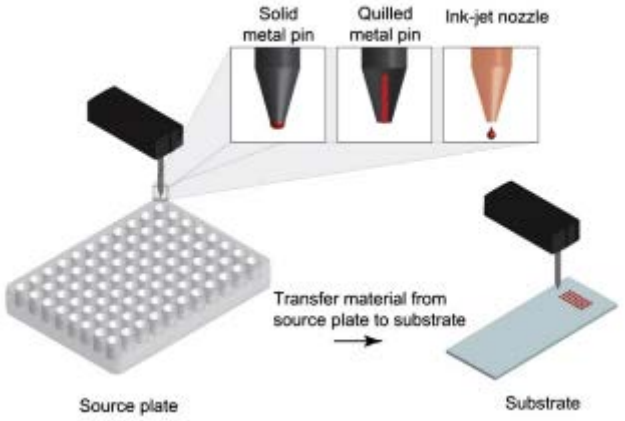
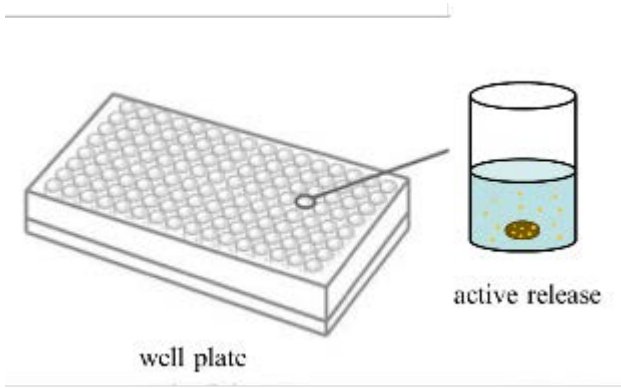
Assays and characterisation

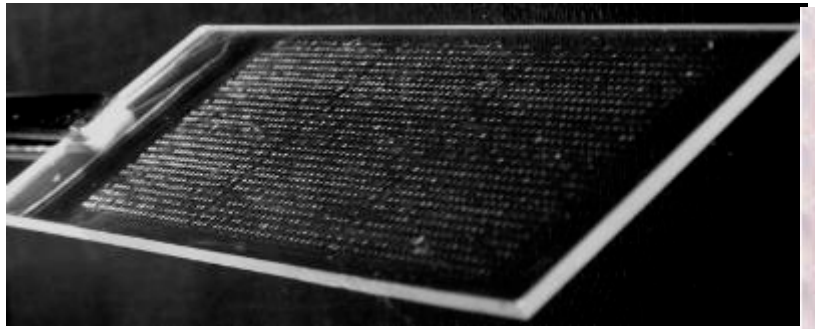
Material	Solvent	40 °C	50 °C	60 °C	70 °C
PCL	PEGDA	X	X	X	✓
PCL	NVP	✓	✓	✓	✓
PCLMA	PEGDA	X	✓	✓	✓
PCLMA	NVP	✓	✓	✓	✓
PCLMAA	PEGDA	X	X	X	X
PCLMAA	NVP	✓	✓	✓	✓
PLA	PEGDA	X	✓	✓	✓
PLA	NVP	✓	✓	✓	✓
PLAMA	PEGDA	X	✓	✓	✓
PLAMA	NVP	✓	✓	✓	✓
PLAMAA	PEGDA	X	X	X	X
PLAMAA	NVP	✓	✓	✓	✓
PTMC	PEGDA	X	✓	✓	✓
PTMC	NVP	✓	✓	✓	✓
PTMCMA	PEGDA	X	✓	✓	✓
PTMCMA	NVP	✓	X	X	X
PTMCMAA	PEGDA	X	✓	✓	✓
PTMCMAA	NVP	✓	✓	✓	✓

CREATING AN ARRAY OF SPOTS



CREATING A CYTOXICITY/DRUG RELEASE ASSAY / ARRAY

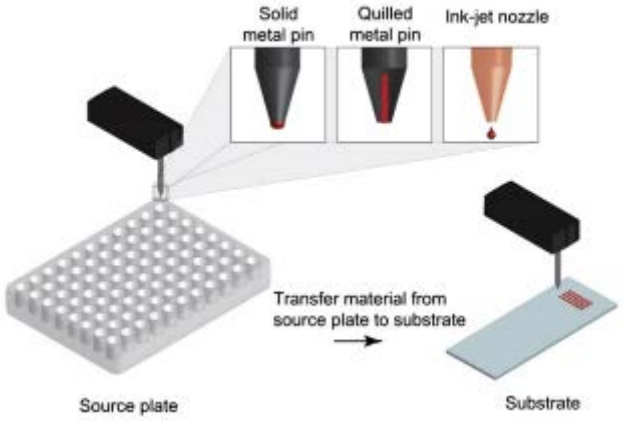


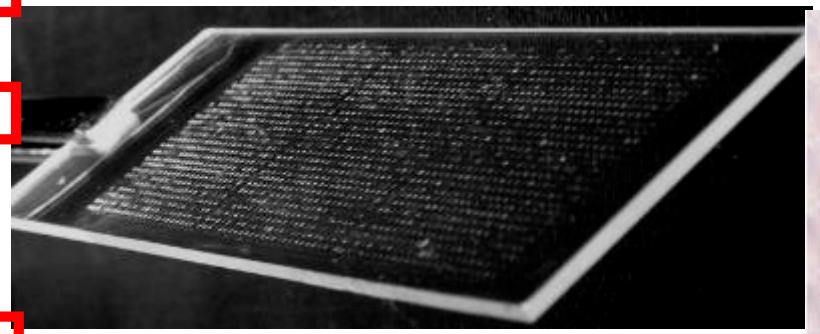


Assays and characterisation

Material	Solvent	40 °C	50 °C	60 °C	70 °C
PCL	PEGDA	X	X	X	✓
PCL	NVP	✓	✓	✓	✓
PCLMA	PEGDA	X	✓	✓	✓
PCLMA	NVP	✓	✓	✓	✓
PCLMAA	PEGDA	X	X	X	X
PCLMAA	NVP	✓	✓	✓	✓
PLA	PEGDA	X	✓	✓	✓
PLA	NVP	✓	✓	✓	✓
PLAMA	PEGDA	X	✓	✓	✓
PLAMA	NVP	✓	✓	✓	✓
PLAMAA	PEGDA	X	X	X	X
PLAMAA	NVP	✓	✓	✓	✓
PTMC	PEGDA	X	✓	✓	✓
PTMC	NVP	✓	✓	✓	✓
PTMCMA	PEGDA	X	✓	✓	✓
PTMCMA	NVP	✓	X	X	X
PTMCMAA	PEGDA	X	✓	✓	✓
PTMCMAA	NVP	✓	✓	✓	✓

CREATING AN ARRAY OF SPOTS





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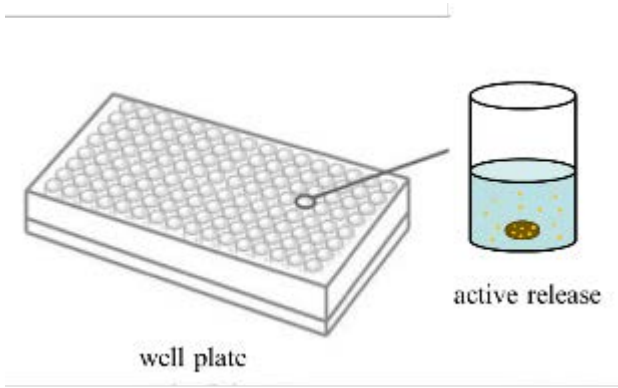
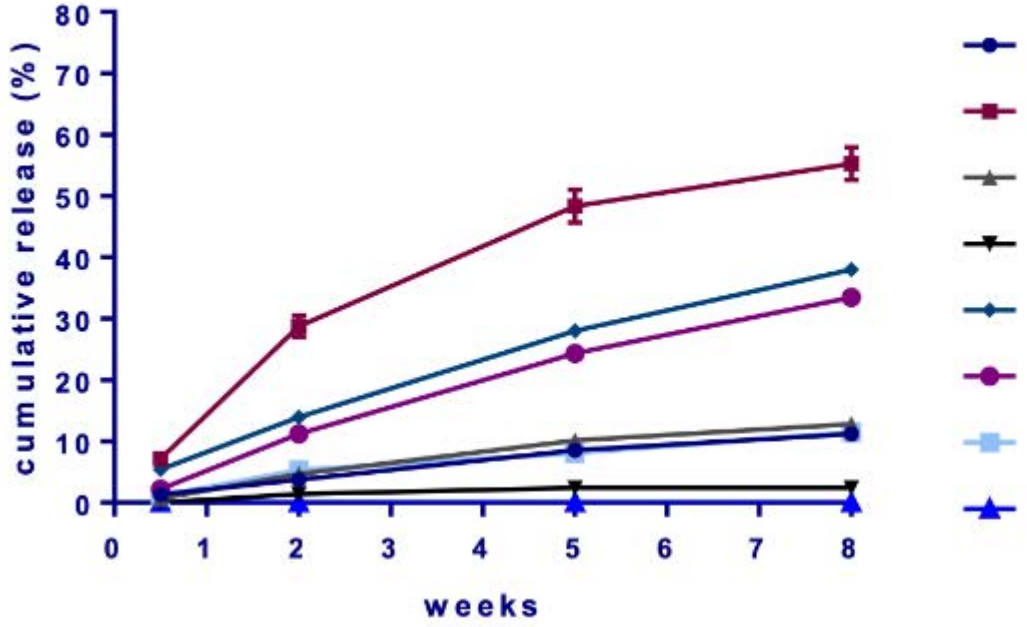


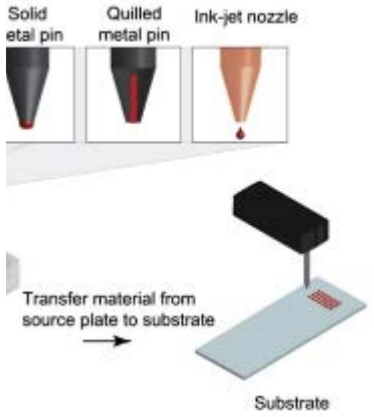
Assays and characterisation

Material	Solvent	40 °C	50 °C	60 °C	70 °C
PCL	PEGDA	X	X	X	✓
PTMC	NVP	✓	✓	✓	✓
PTMCMA	PEGDA	X	✓	✓	✓
PTMCMA	NVP	✓	X	X	X
PTMCMAA	PEGDA	X	✓	✓	✓
PTMCMAA	NVP	✓	✓	✓	✓

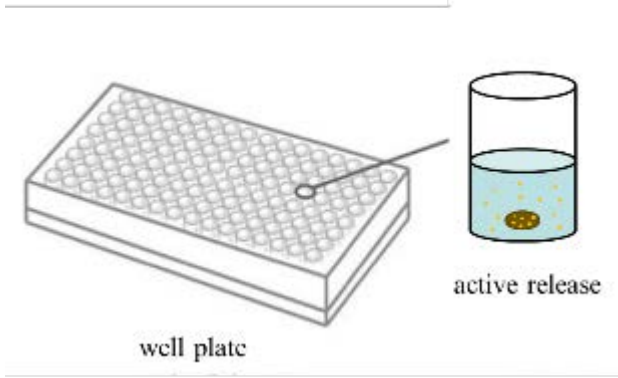


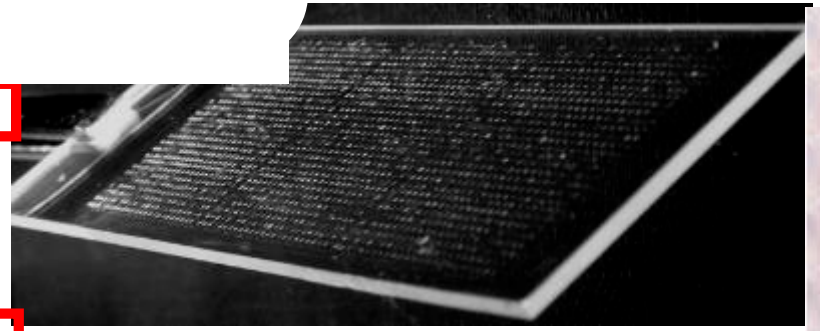
Varying combinations of printed materials

N ARRAY OF SPOTS

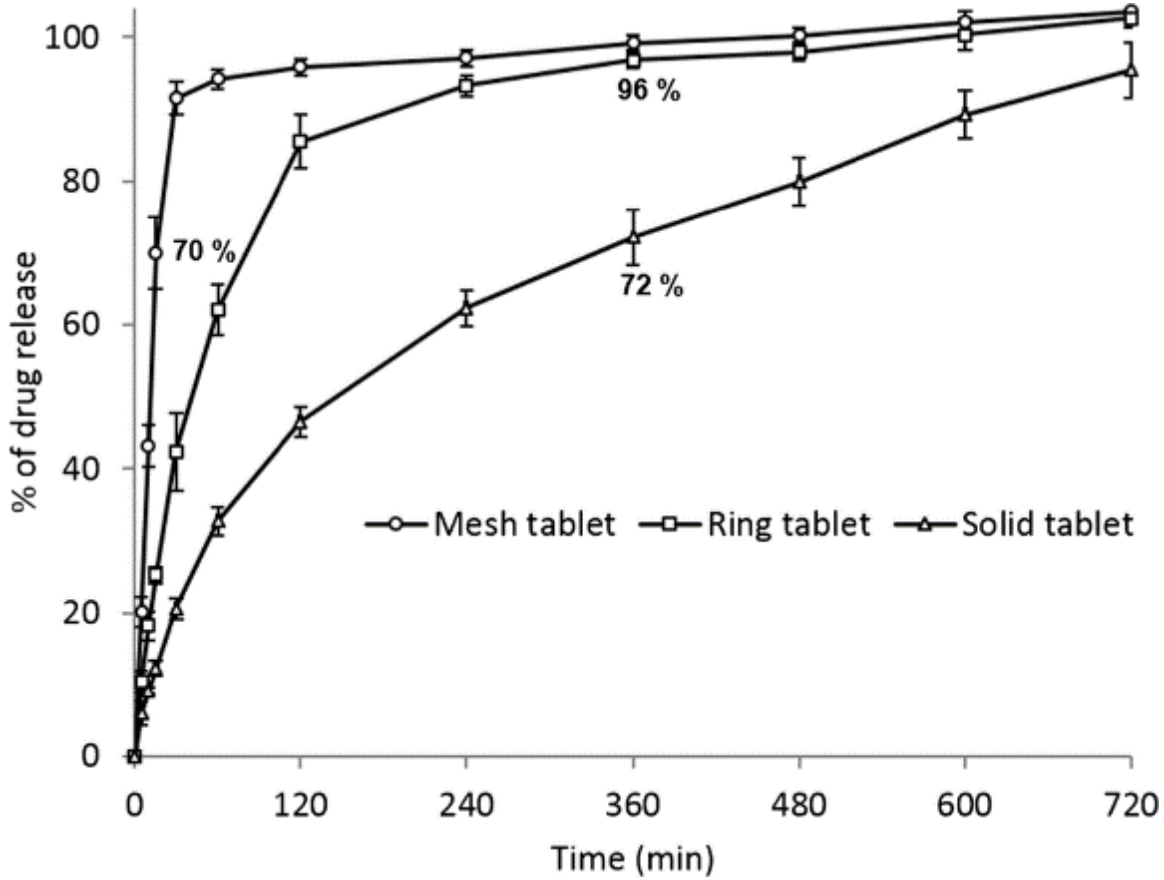


CREATING A CYTOXICITY/DRUG RELEASE ASSAY / ARRAY





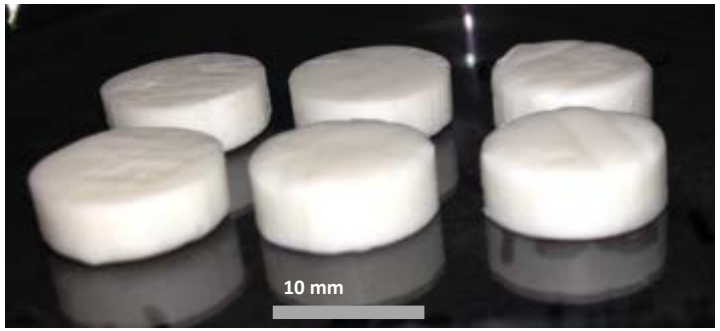
- One single formulation
- Multiple release rates
- Meets both IR and SR requirements
- Can meet all QTPP requirements

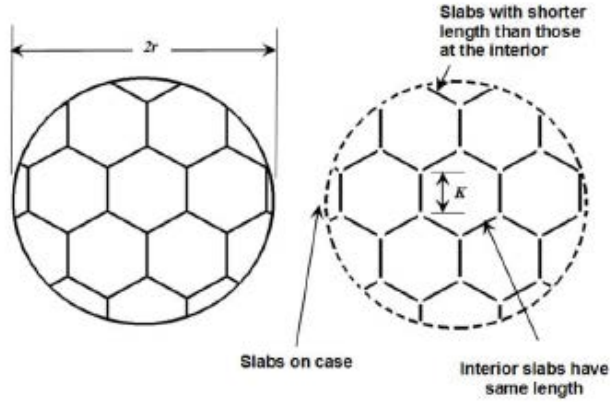


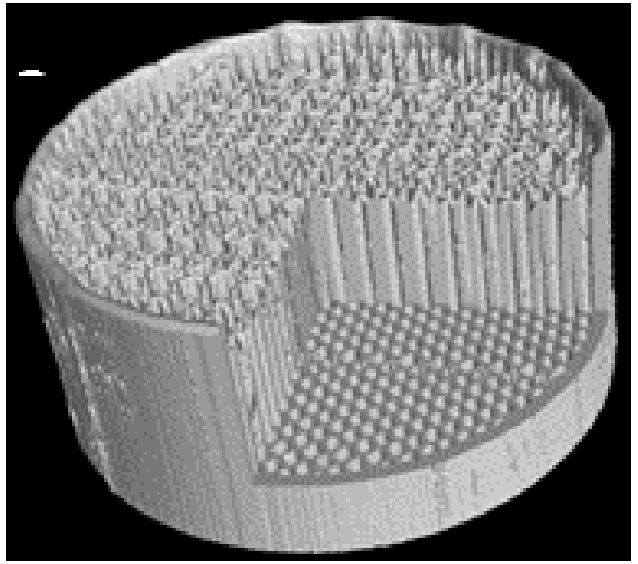
Extrusion 3D Printing of Paracetamol Tablets from a Single Formulation with Tunable Release Profiles Through Control of Tablet Geometry, Khaled, et al AAPS PharmSciTech, 2018

Geometrical control with ink jet printing and modelling

AstraZeneca



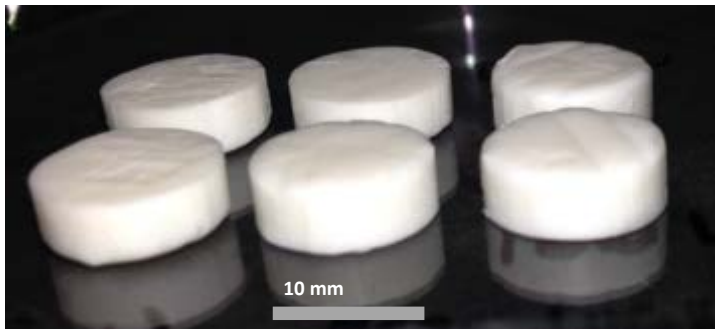


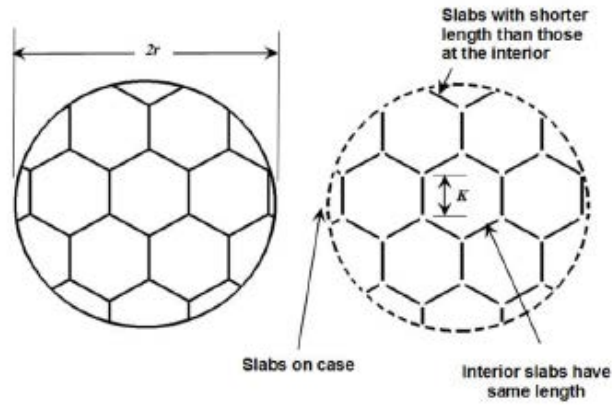


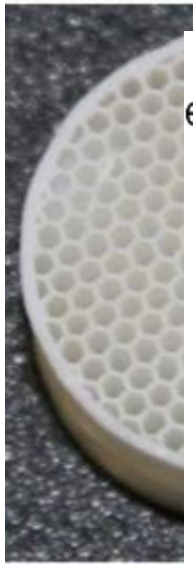
Kyobula et al, Journal of Controlled Release, 261 2017 207-215

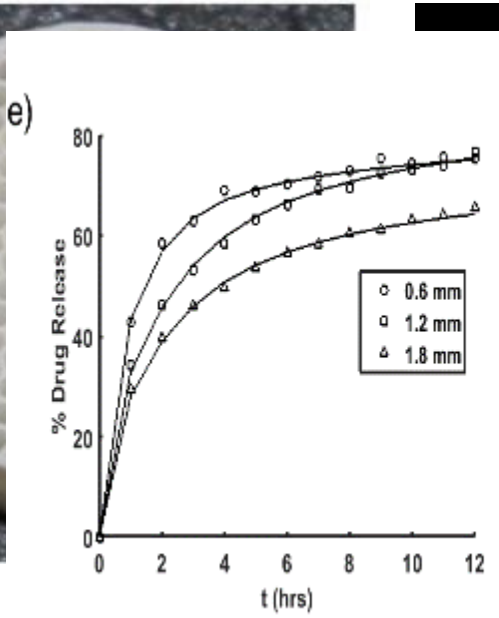
Geometrical control with ink jet printing and modelling

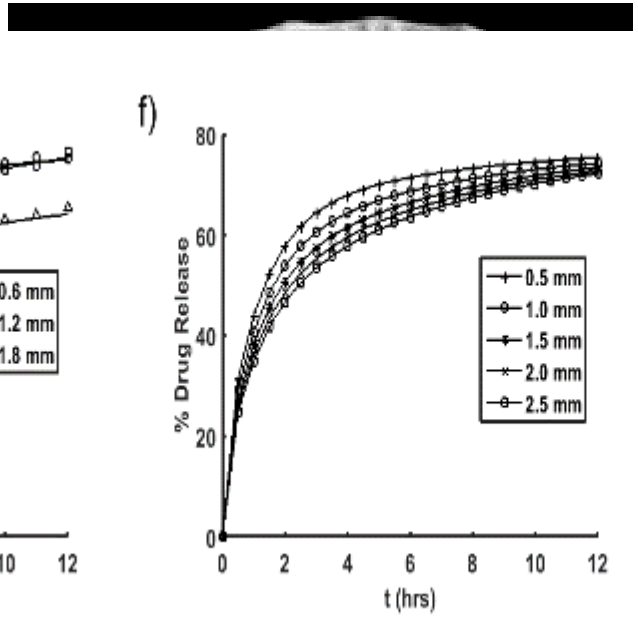
AstraZeneca

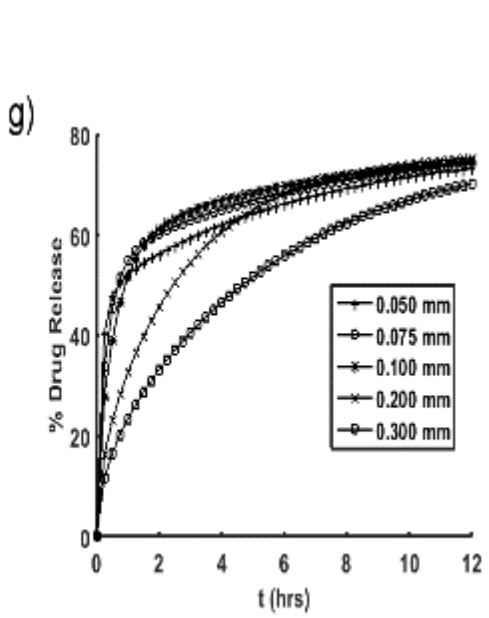






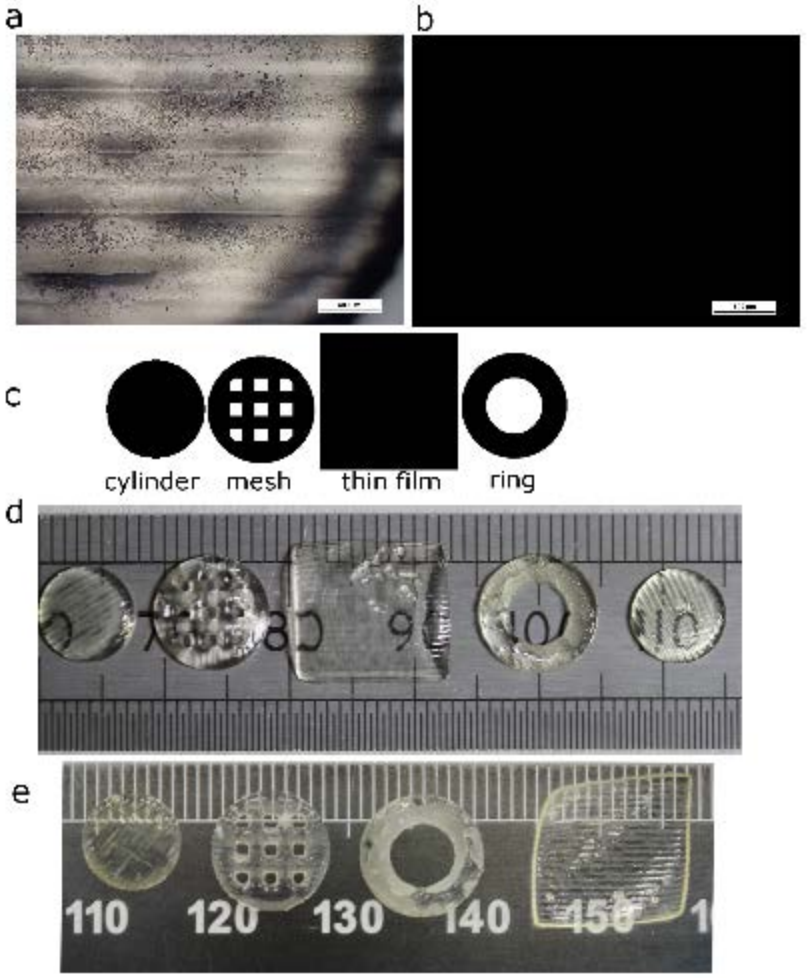




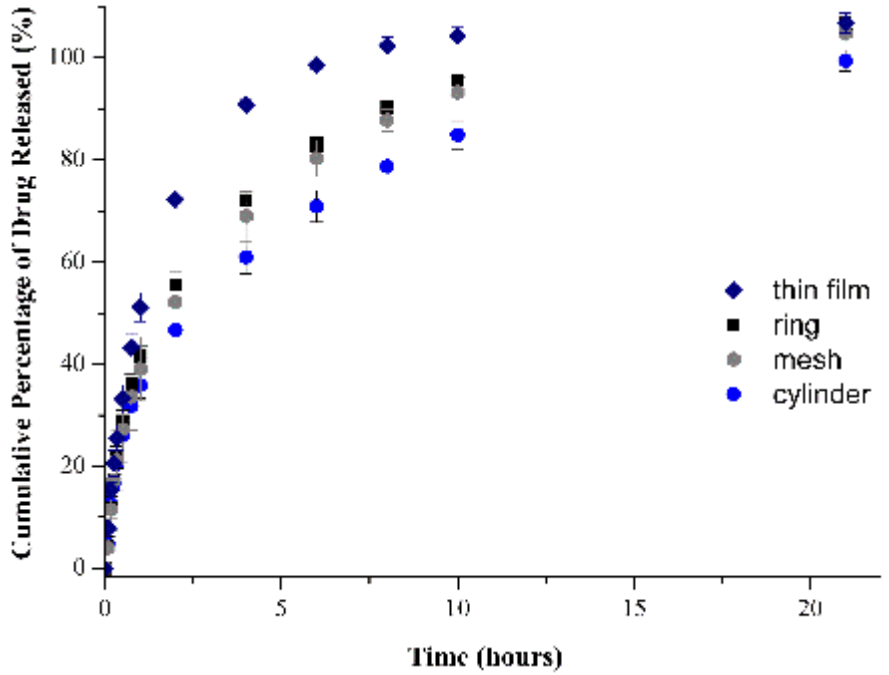


Kyobula et al, Journal of Controlled Release, 261 2017 207-215

UV curable materials for solid dosage forms: poorly soluble



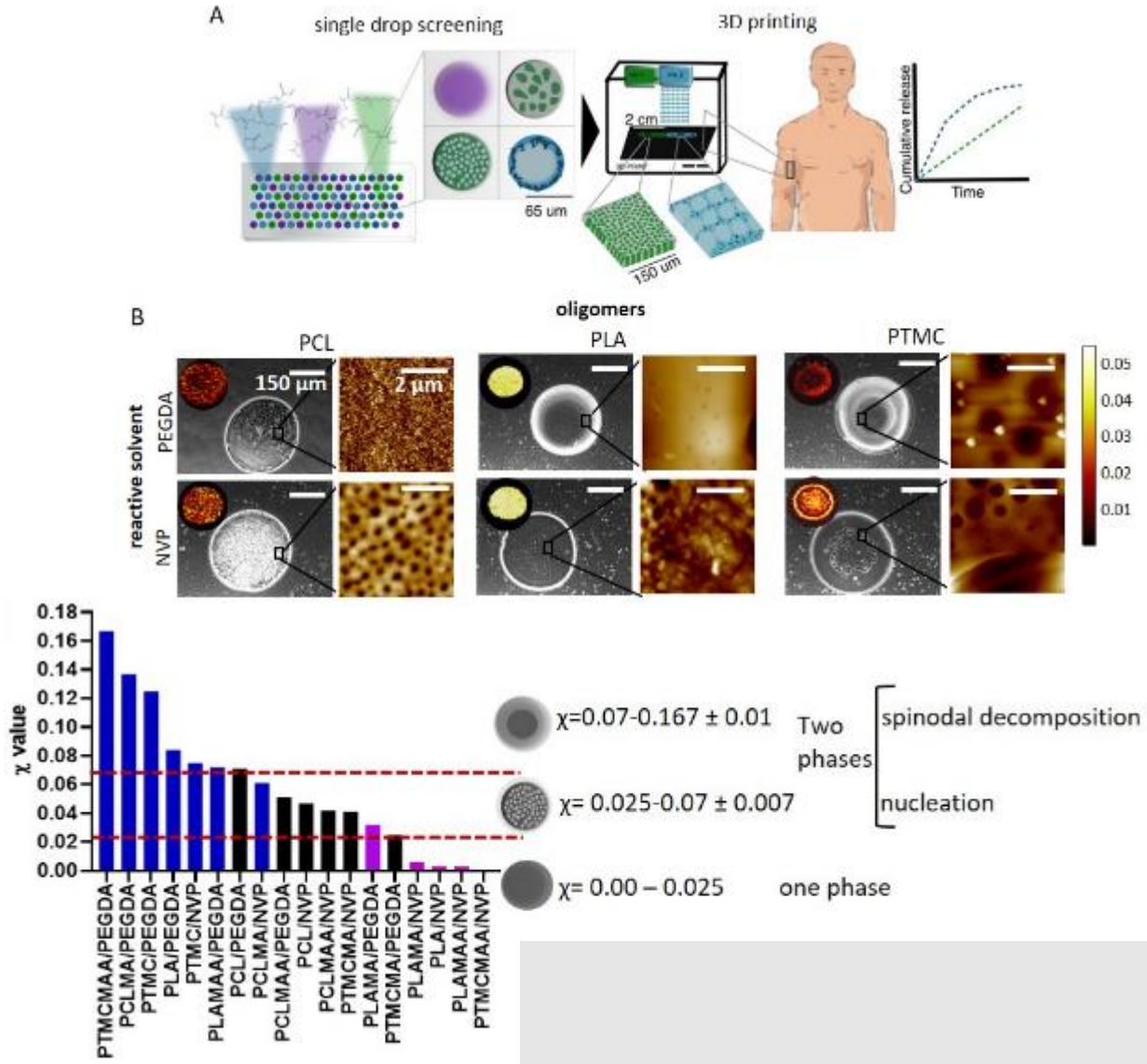
Irgacure 2959	0.50 wt%
Carvedilol	10.00 wt%
N-vinyl 2-pyrrolidone (NVP)	73.06 wt%
PEGDA (M_n= 250 g/mol, Sigma-Aldrich)	16.44 wt%



Clark et al. 'Making tablets for delivery of poorly soluble drugs using photoinitiated 3D inkjet printing'
International Journal of Pharmaceutics, 578 2020 118805

Microstructure that arises from 3DP directs release behaviour

- Different mixtures give different microstructure
- Microstructure is a determinant for release
- Microstructure can be predicted by Flory-Huggins



Ruiz-Cantu el al, ChemArxiv https://doi.org/10.26434/chemrxiv.12440015.v1

Microstructure that arises from 3DP directs release behaviour

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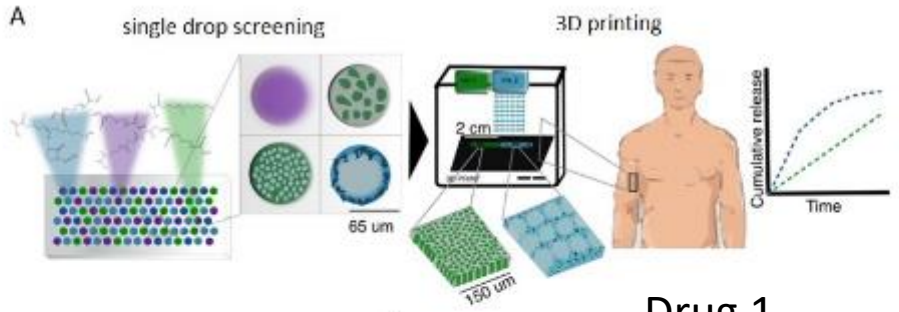
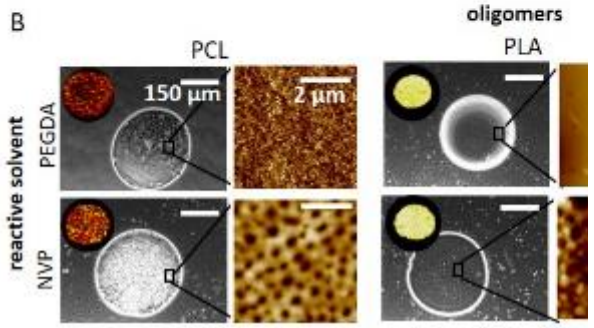
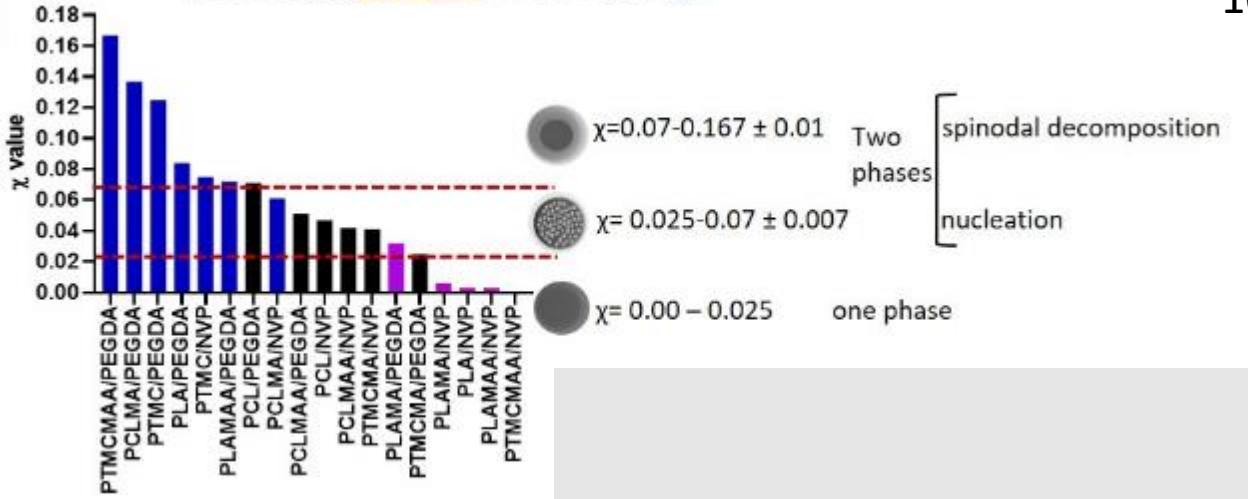


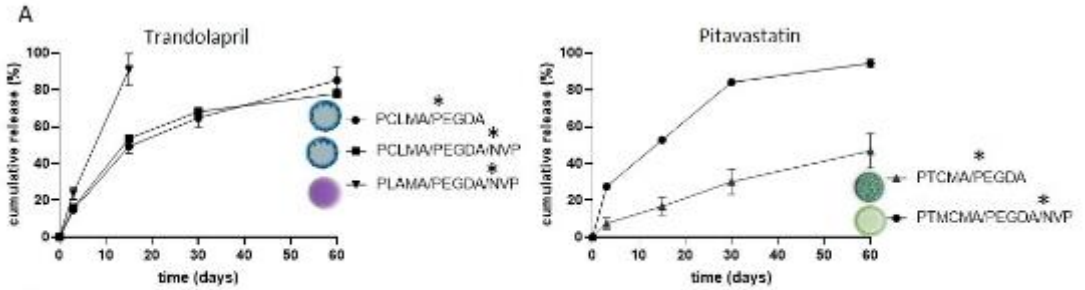
Drug 1

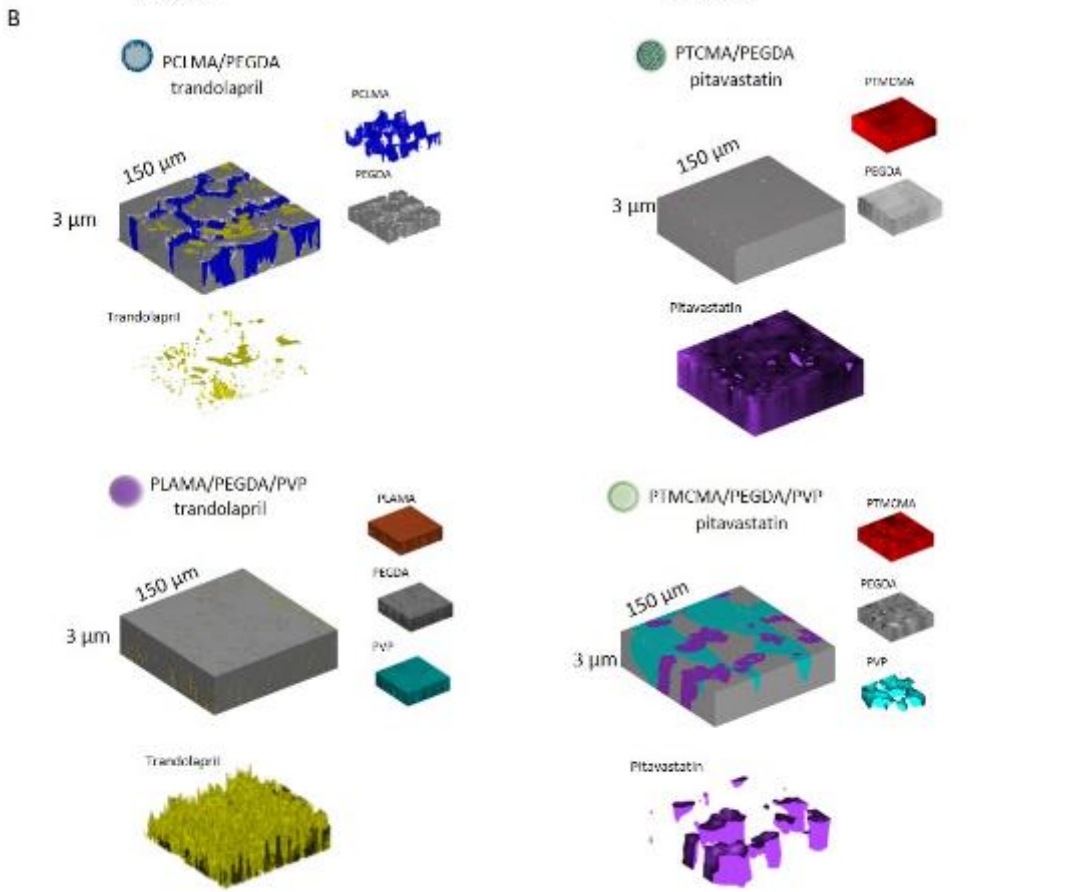
Drug 2



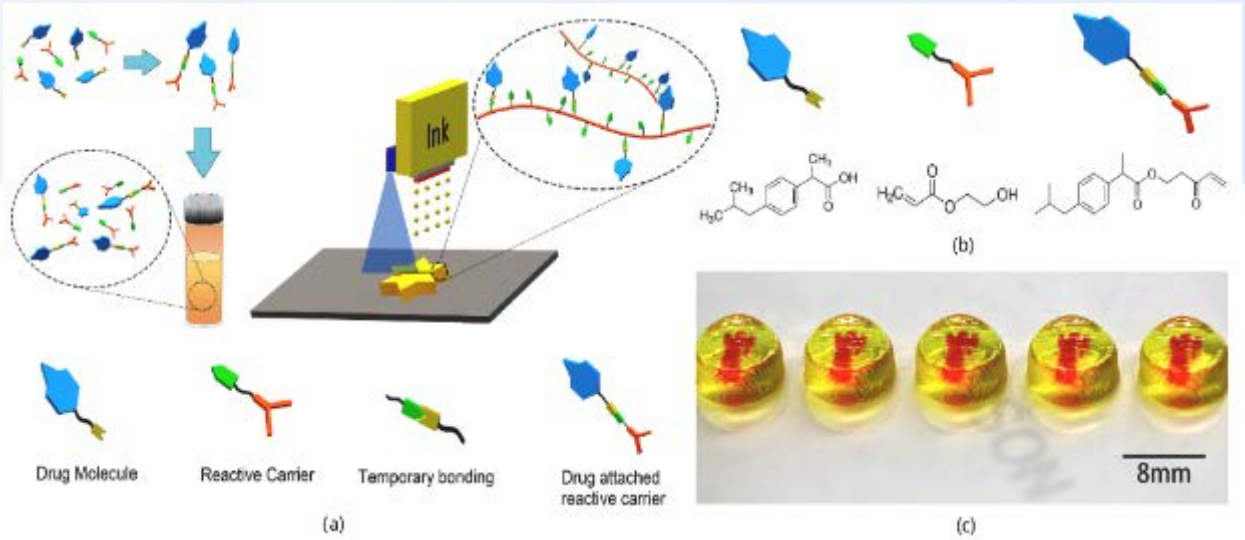
10 mm

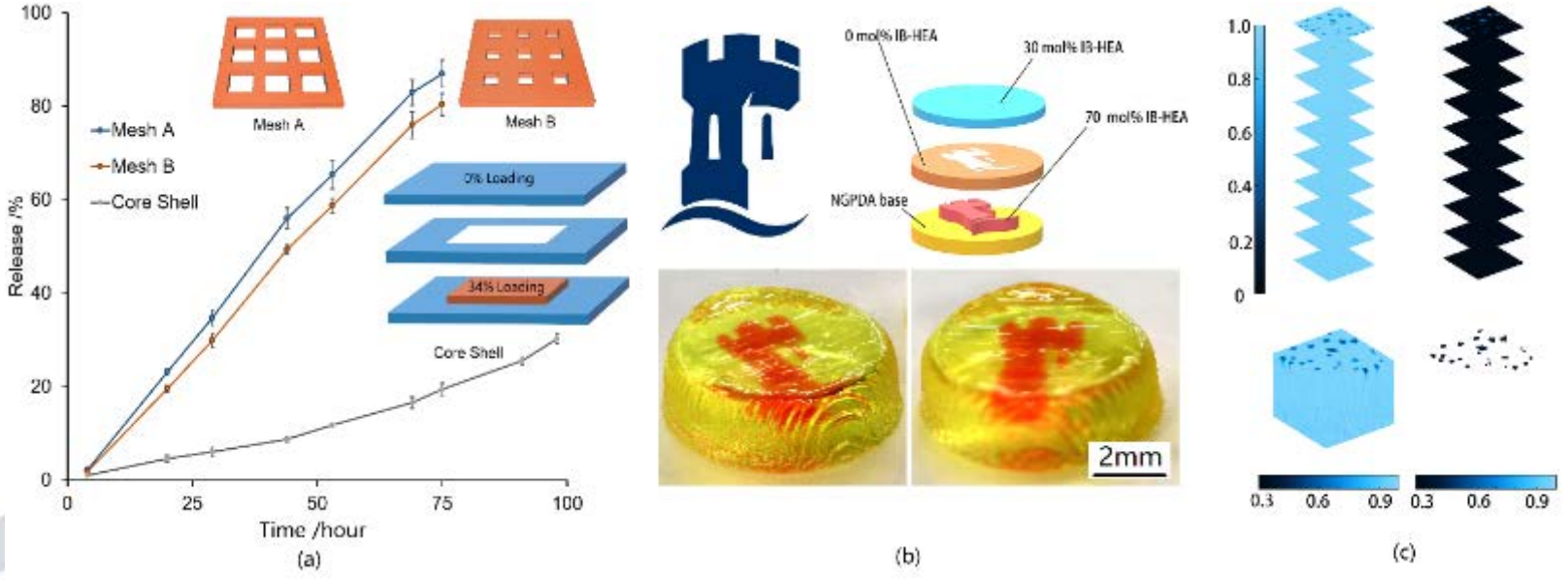






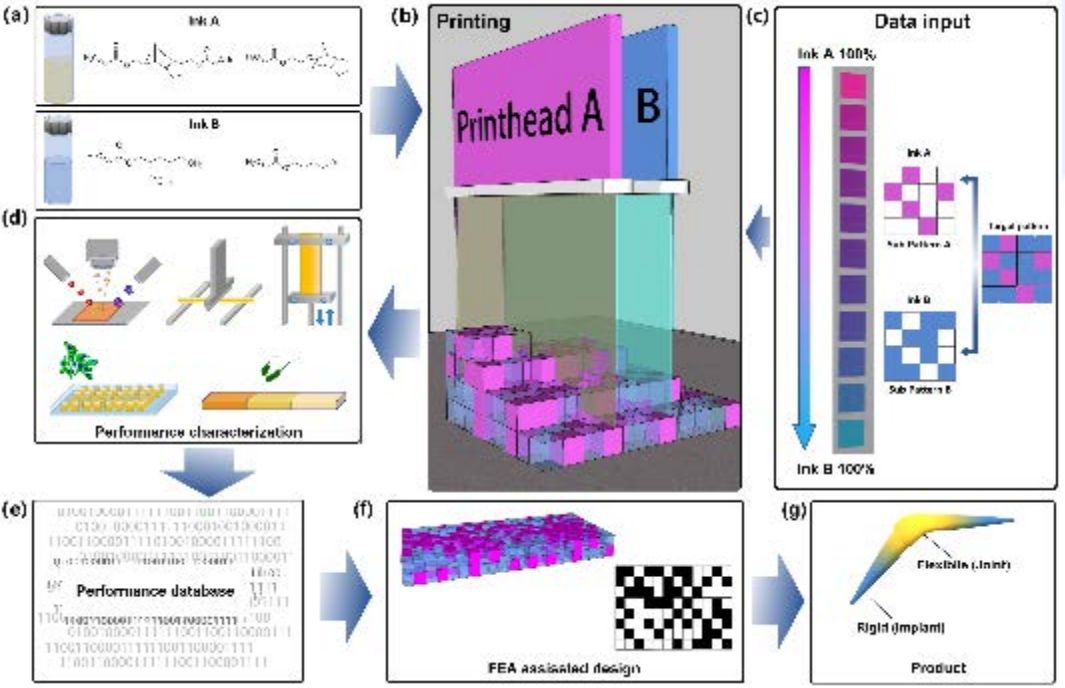
Ruiz-Cantu el al, ChemArxiv https://doi.org/10.26434/chemrxiv.12440015.v1

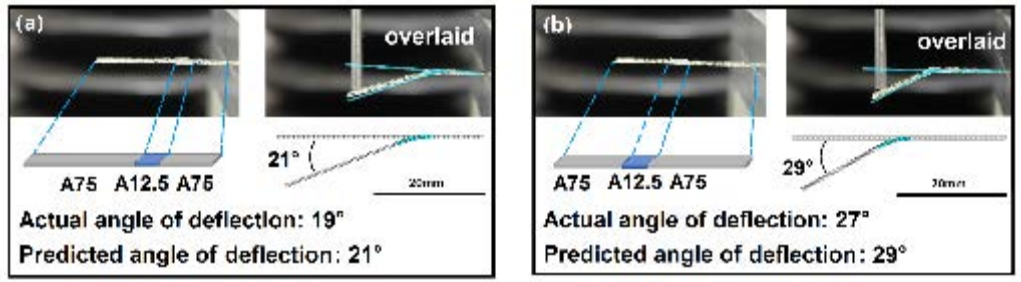


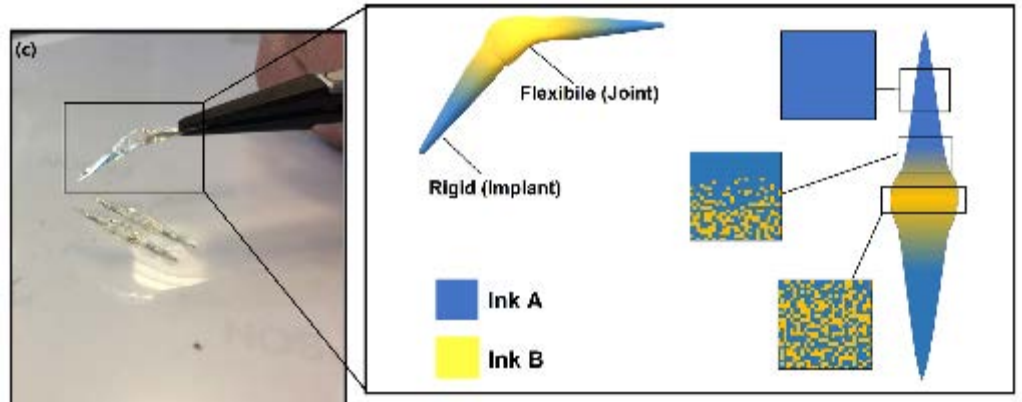


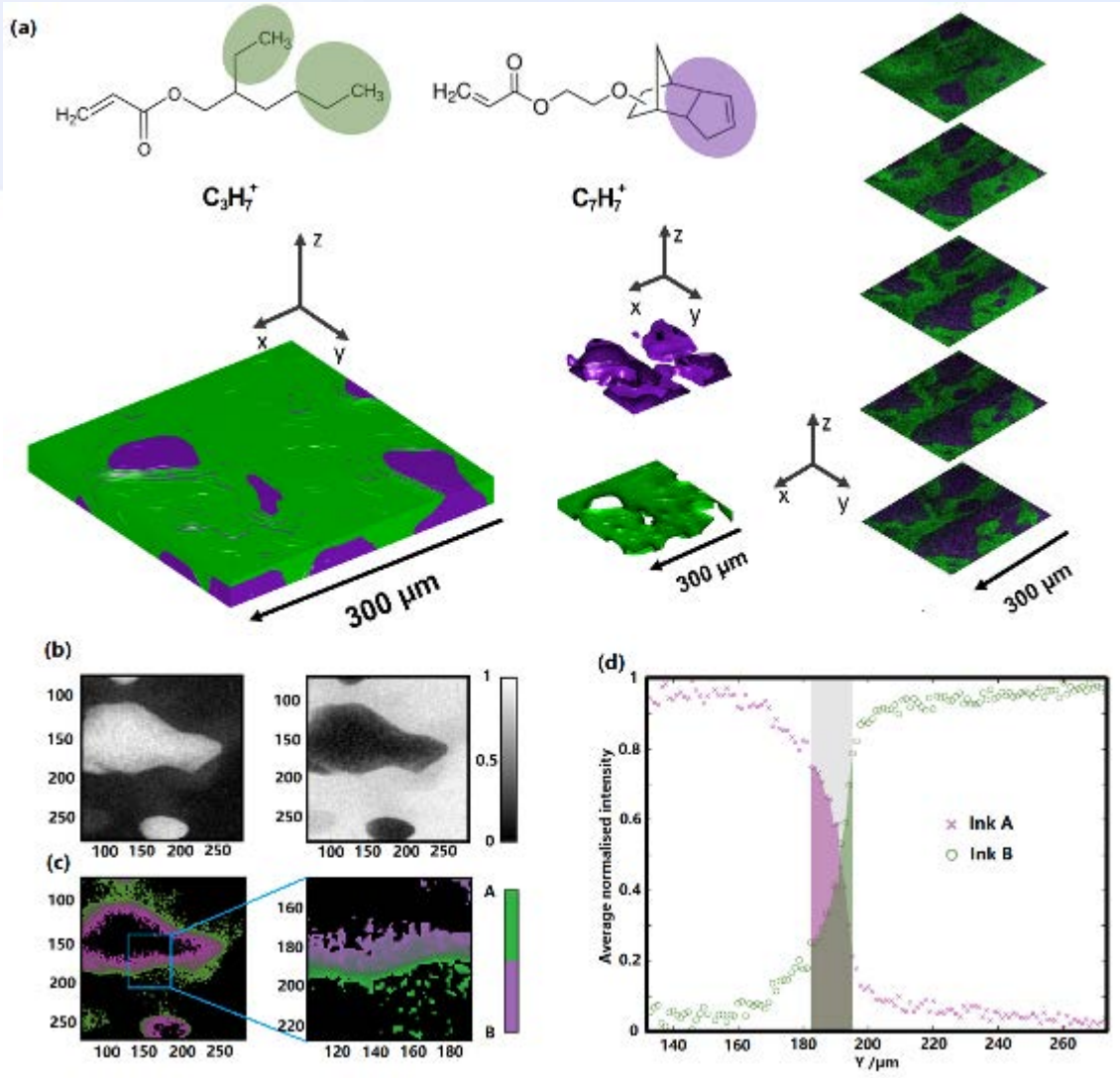
- High Dose (> 80% wt%)
- Multimaterial – possibility for multiple APIs
- High personalisable and tailorable
- Avoids issues with solubility / stability

He et al. '**A reactive prodrug ink formulation strategy for inkjet 3D printing of controlled release dosage forms and implants',** Advanced Therapeutics https://doi.org/10.1002/adtp.201900187









- Multimaterials co-printed
- Possibility to dial up behaviour
- High personalisable and tailorable
- Multifunctionality enabled

Concluding points

- Additive Manufacturing / 3D Printing can be an effective ‘on demand’ manufacturing tool
- It isn’t just about ‘shape freedoms’
- There are many levers that can be used to control functionality
- Design by Shape, by multimaterial / functional Composition, by Microstructure
- Materials identification screening works – now for materials and formulation *control*

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University of Reading

Thanks!

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Richard Hague (UoN)
Chris Tuck (UoN)
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Mark East (CfAM/TS)