Centre for Additive Manufacturing

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Formulation for 3D printing

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University of Nottingham

4th May 2017

Project Composition

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

gsk syngenta Unilever Malvern PPG

EPSRC
Engineering and Physical Sciences Research Council

University of Reading

UNIVERSITY OF BIRMINGHAM

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What is this 3D Printing all about?

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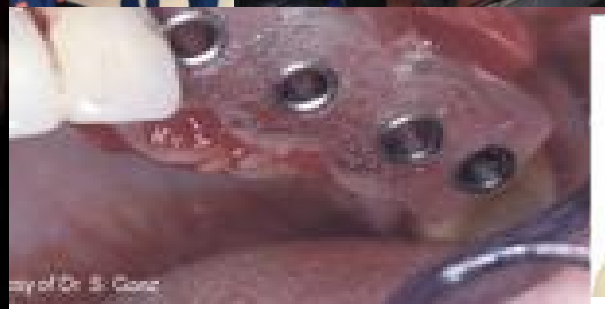
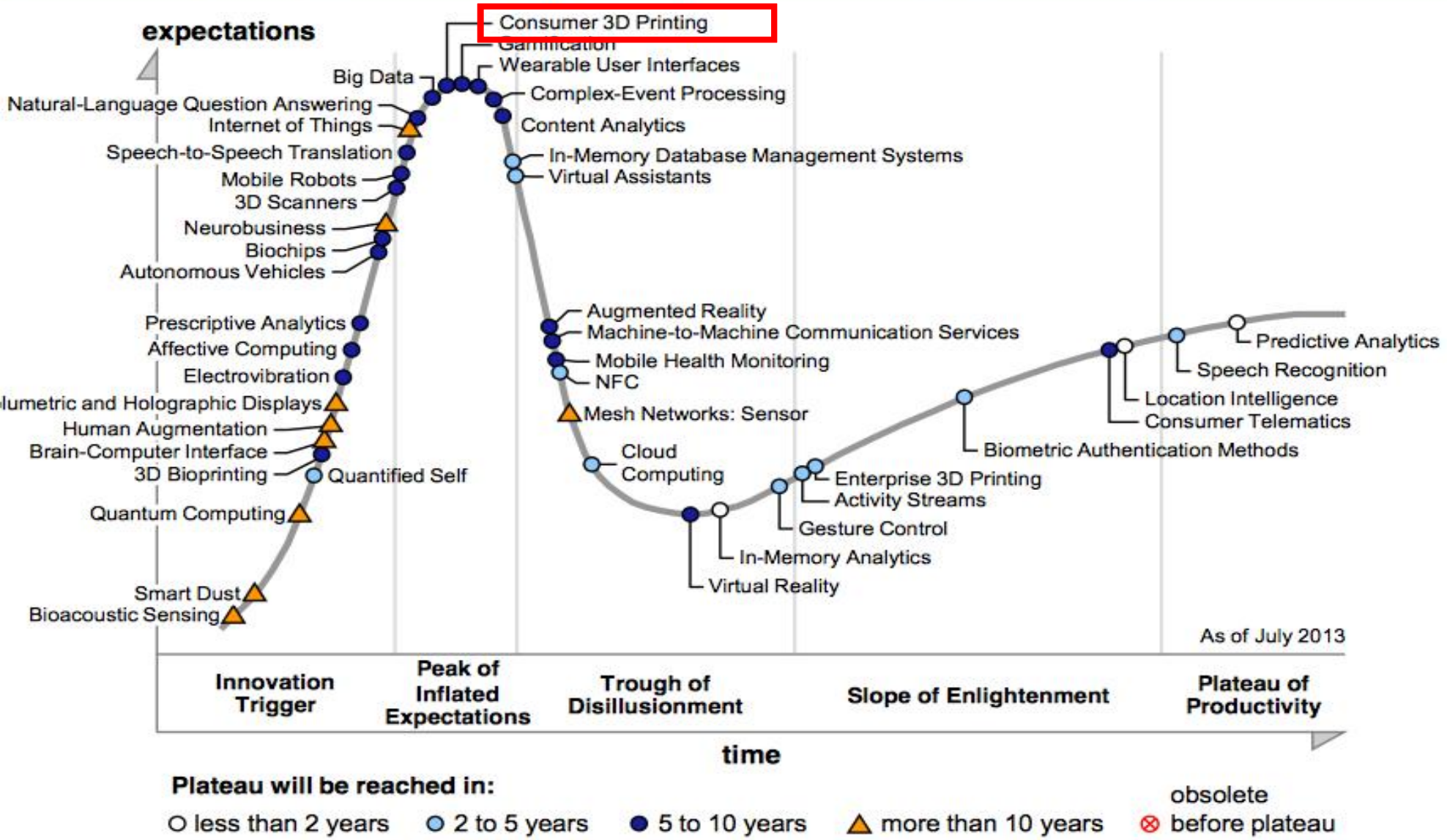




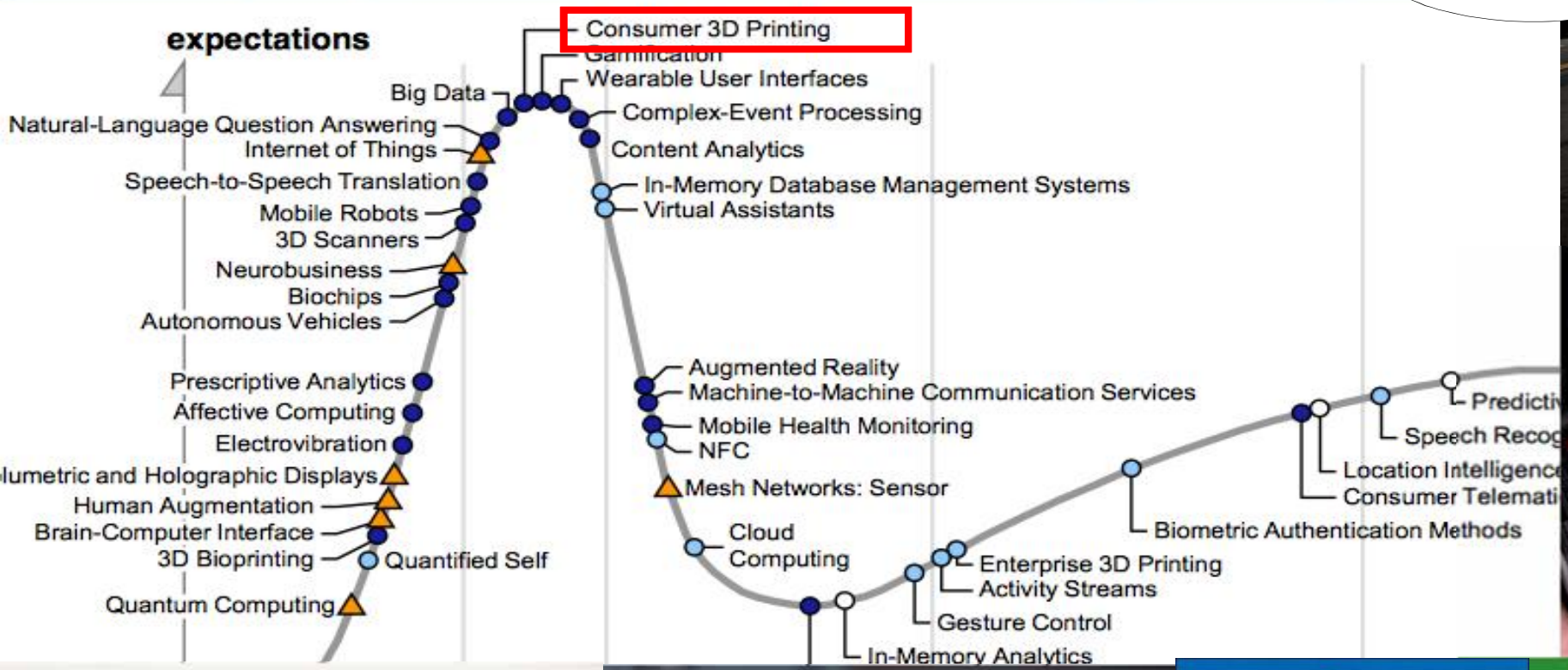

Emerging Technologies Hype Cycle, 2013

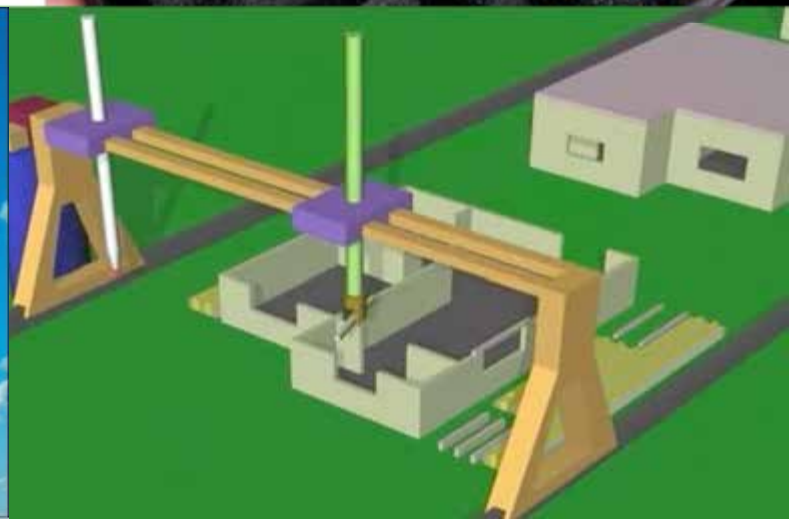


Gartner

esy of Gartner

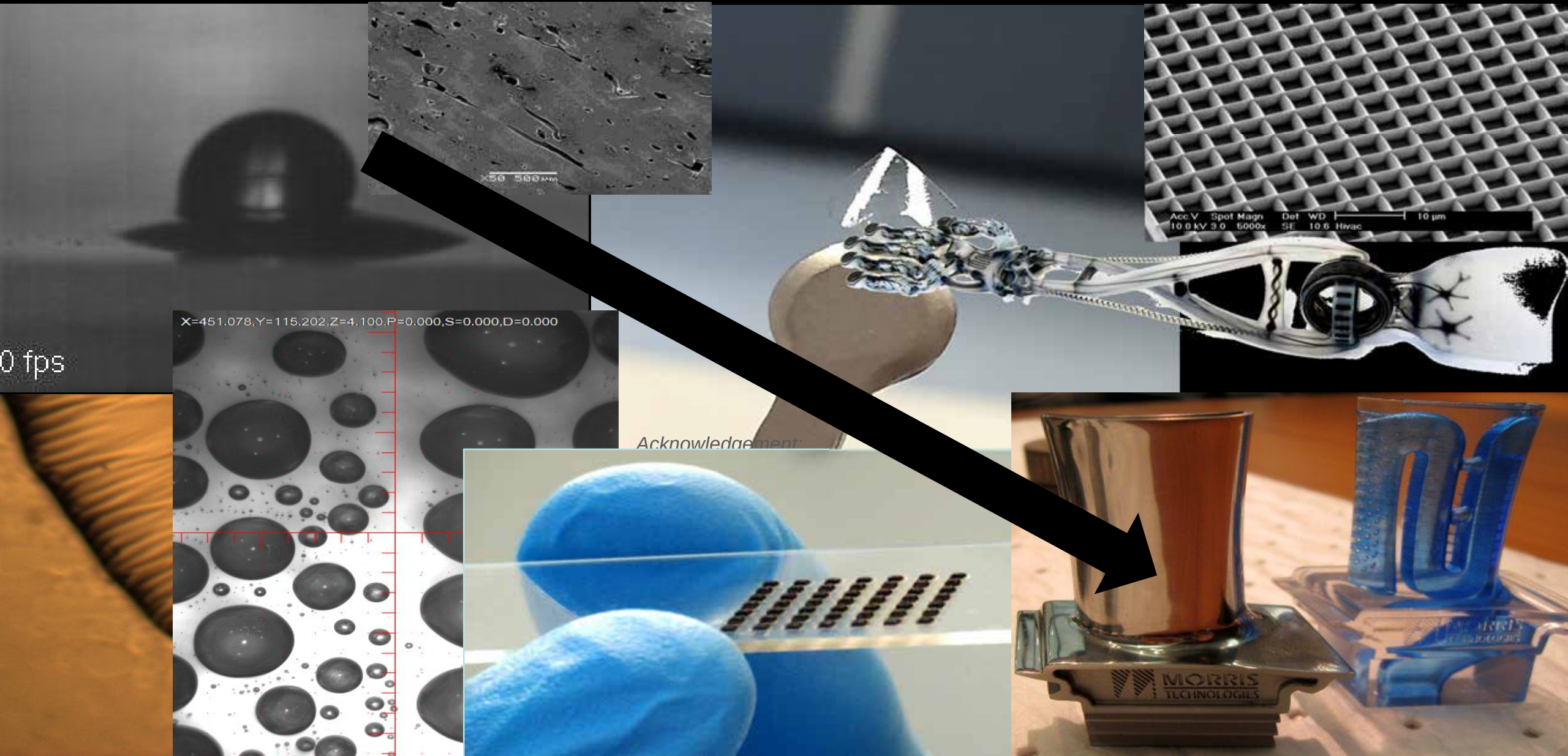
Emerging Technologies Hype Cy





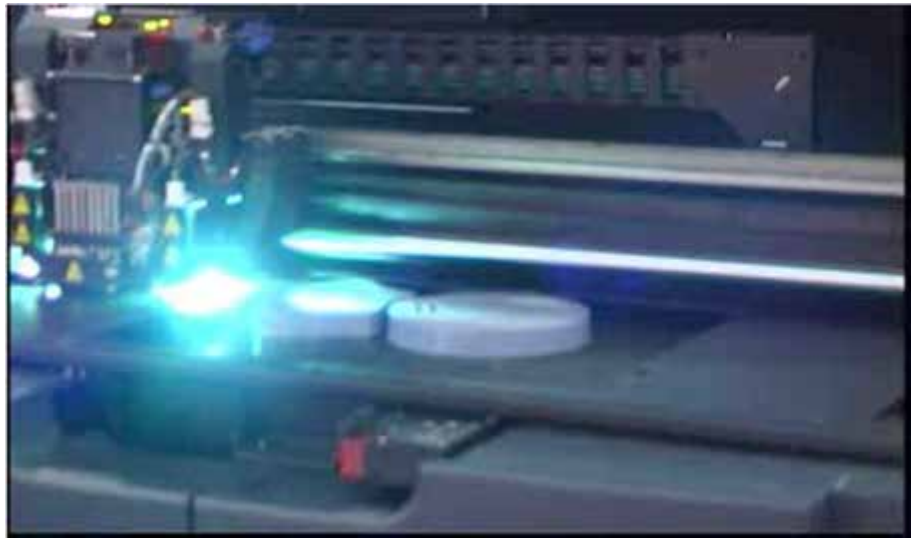
What we're trying to do

EPSRC Centre for Innovative Manufacturing in Additive Manufacturing



Acknowledgement:

How does it work?



SLM, SLS, SLA etc
Largely single material

Ink Jet based processes
Potential for multimaterial production

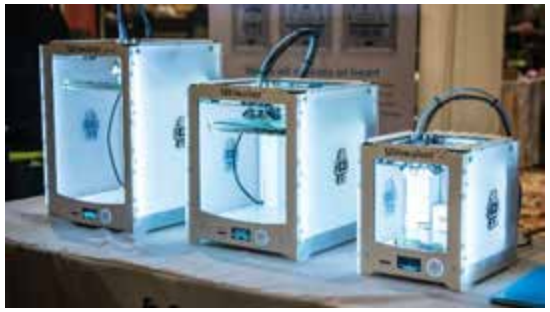
Three interesting processes (to us)

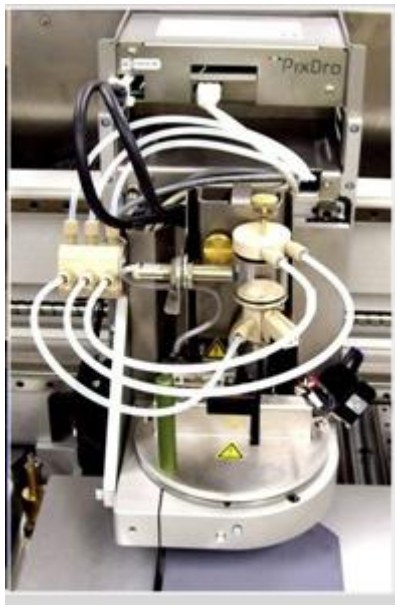
- Ink Jet Printing
- Hot Melt Extrusion
- Paste Extrusion

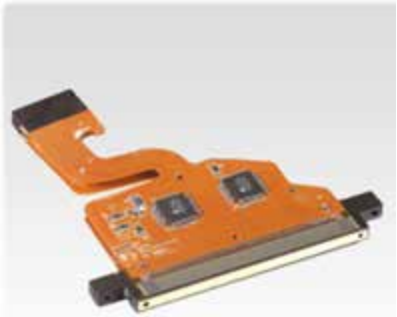
Plus related …

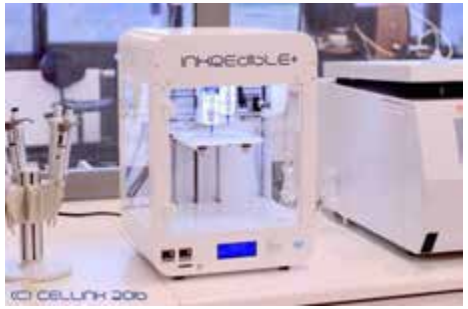
Vat Polymerisation

Multiphoton Polymerisation







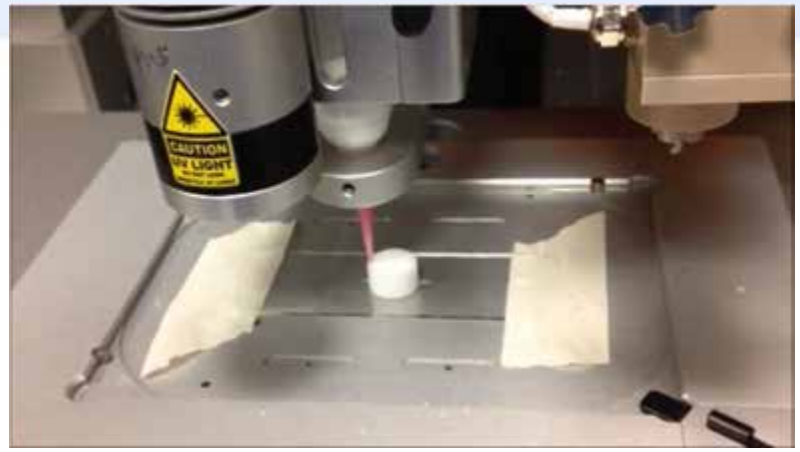


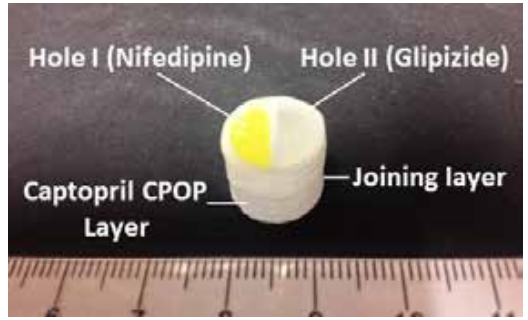
An application example is the 3D printing of solid dosage forms (tablets)

With 3D printing we could

- EMPOWER patients
- PERSONALISE treatments
- IMPROVE compliance
- CREATE tailored sensors
- INCORPORATE sensing and delivery

Dialled in release from multiple actives



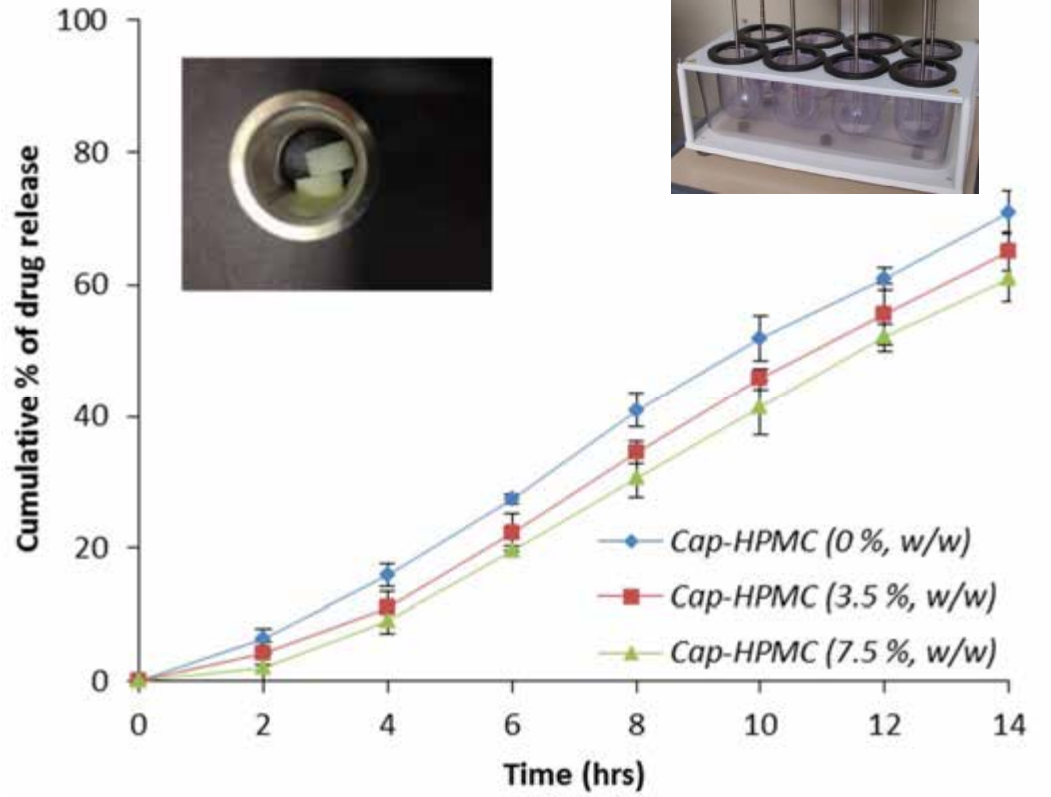


Captopril CPOP tablet

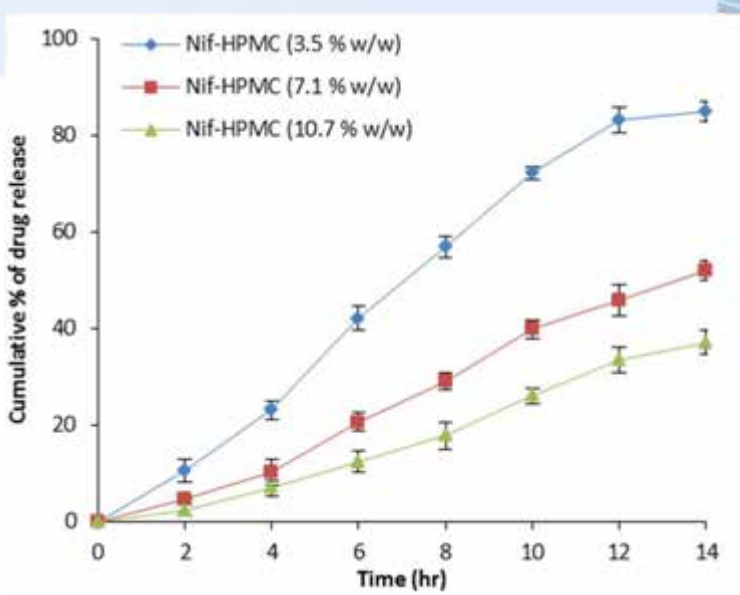
Nifedipine/Glipizide Sustained release tablets

Captopril (hypertension), Nifedipine (hypertension) and Glipizide (diabetics type II)

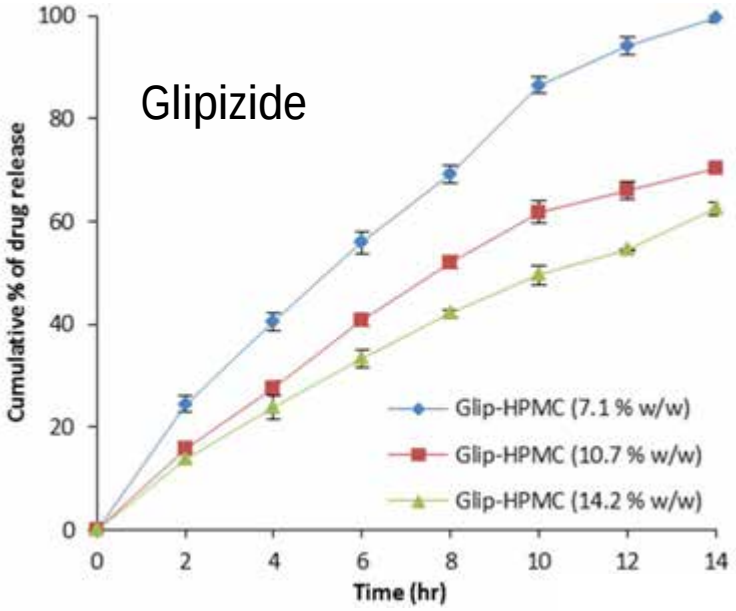
Release profiles



Drug release profile of Captopril; *Cap-HPMC (0 %, w/w)*, *Cap-HPMC (3.5 %, w/w)*, and *Cap-HPMC (7.5 %, w/w)*.



Glipizide



International Journal of Pharmaceutics
Volume 494, Issue 2, 30 October 2015, Pages 643–650

Our latest polypill, 5 drugs, separately controlled. Designed for cardiac treatment

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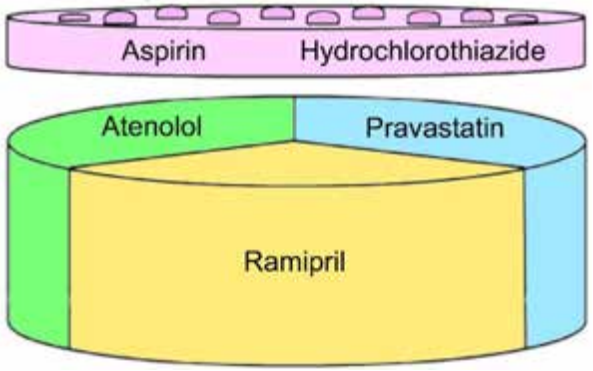

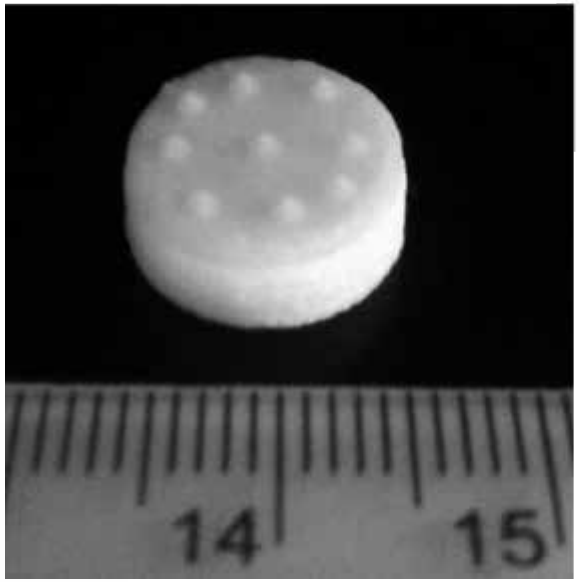

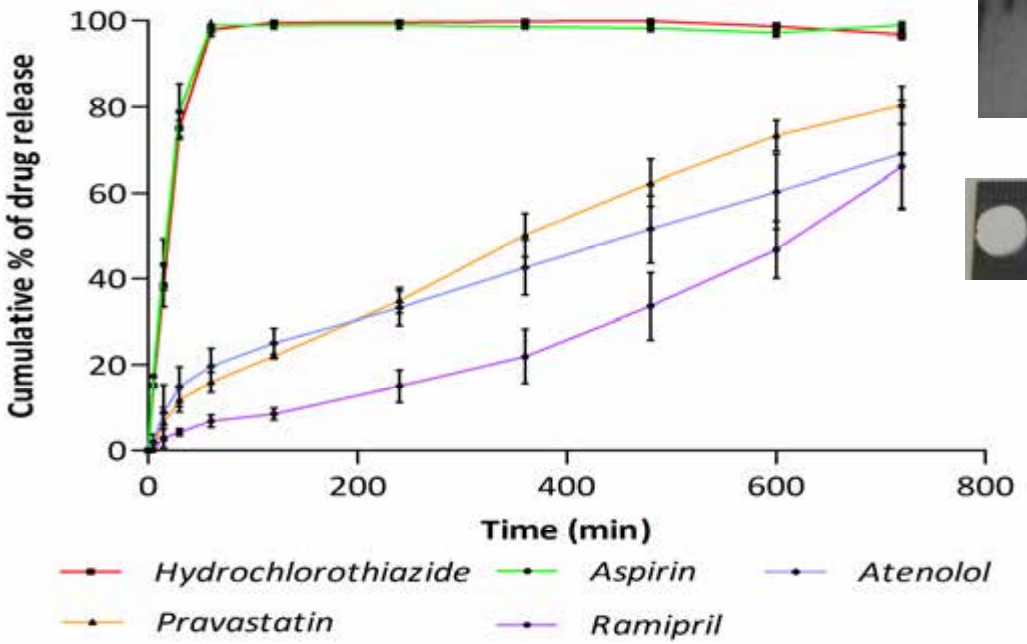

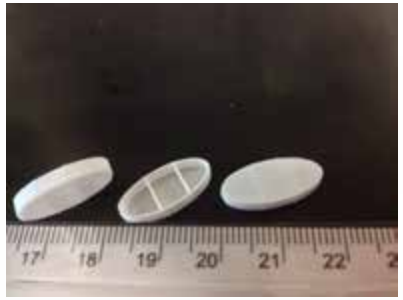

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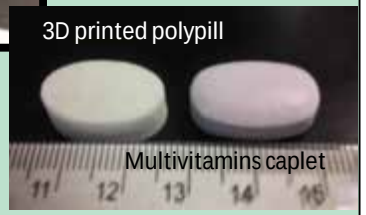
Other examples …

Printing the drug(s), the dose & the matrix to release when and where it is needed

A FLEXIBLE SINGLE PLATFORM FOR DOSAGE FORM INNOVATION AND MANUFACTURE.

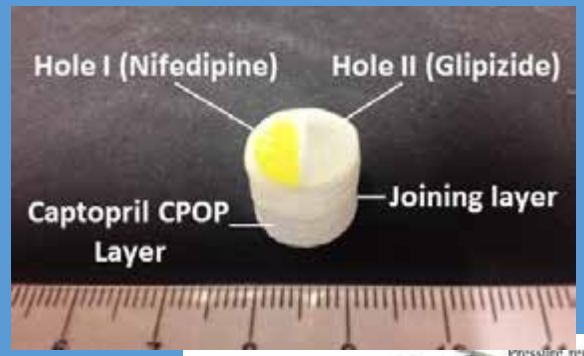
Fast melt tablet

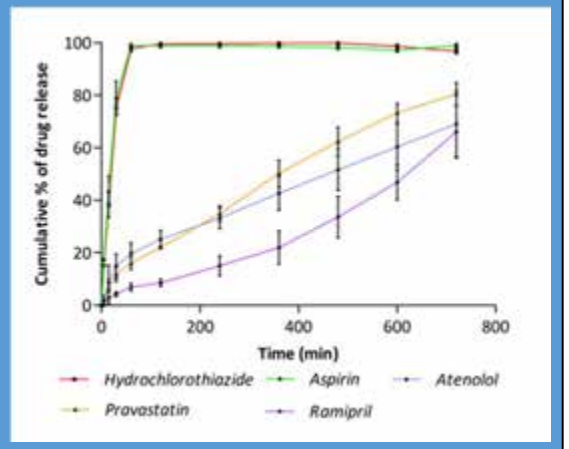


Fast disintegrating tablet

Ink Jet Printed GRAS IR Formulation

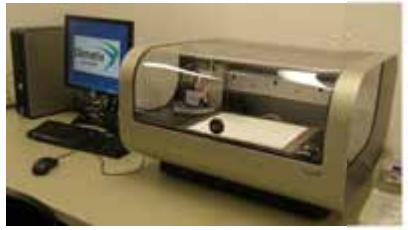
NEW GEOMETRIES,
NEW OPPORTINTIES.
THE POLYPILL MADE REAL.



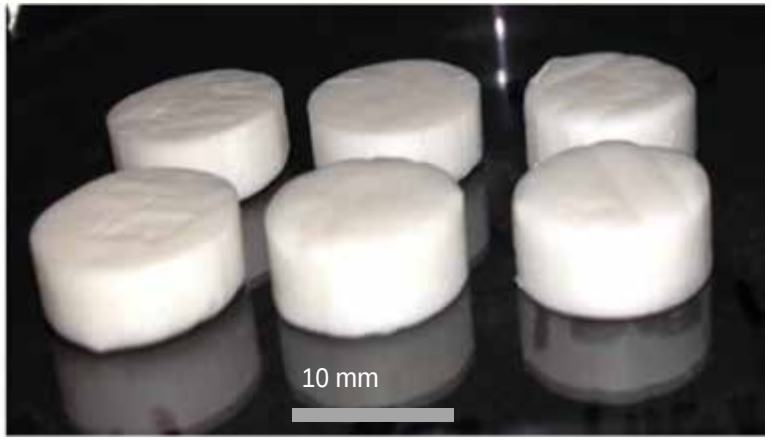


FACILITATING INNOVATION AND CHANGE IN DEVICE DESIGN.

Also possible with ink jet printing …



FujiFilm Dimatix, DMP 2800



Kyobula et al, submitted to International Journal of Pharmaceutics

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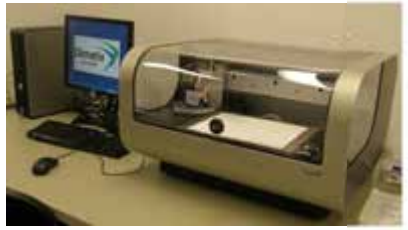

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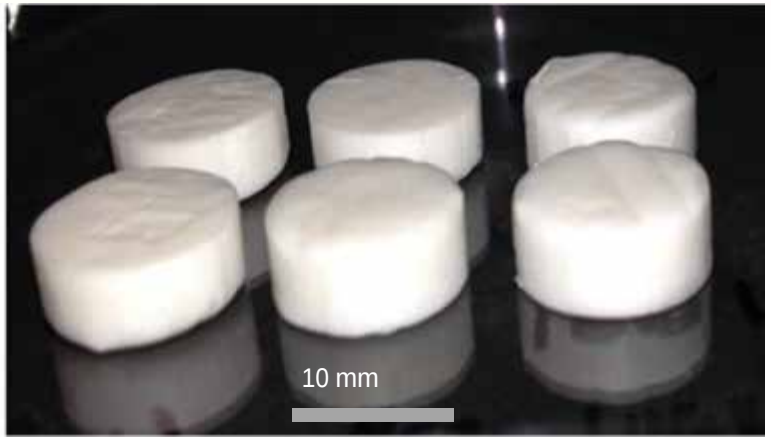

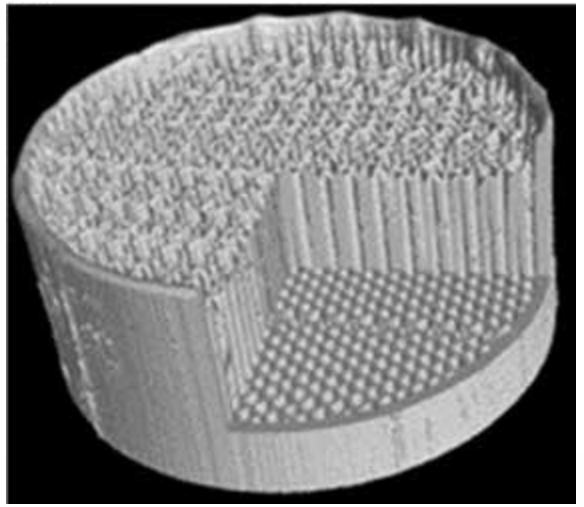

Example: Very fine control over geometry, surface area and drug distribution. Example shows a ‘honeycomb’ with two different cell sizes (A and B) and a 3D x-ray CT view

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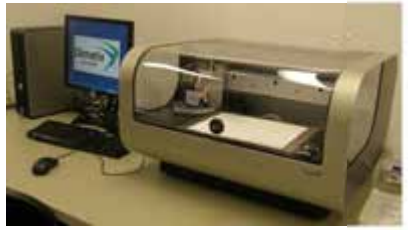

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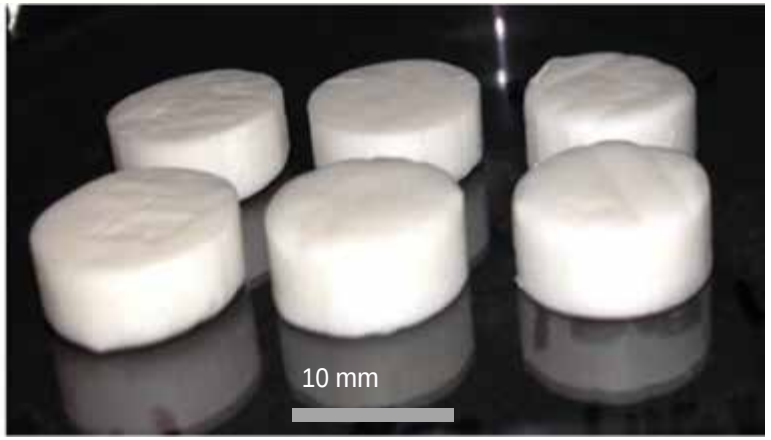

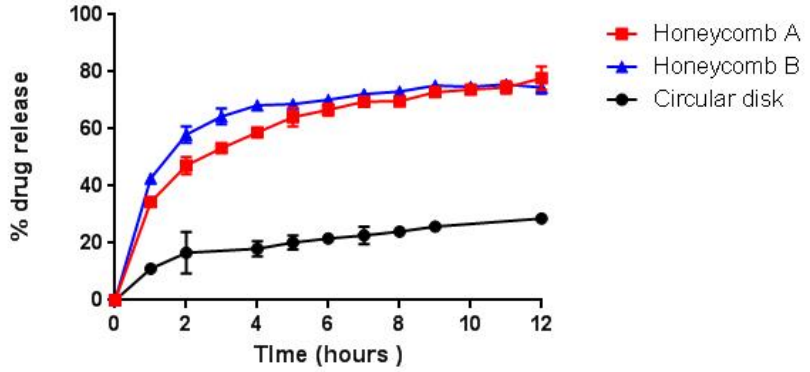

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So, what's the problem then?

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http://www.amnationalstrategy.uk/

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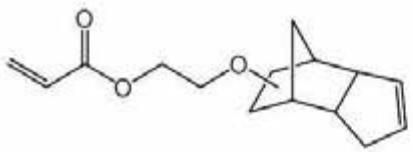
What are our options?

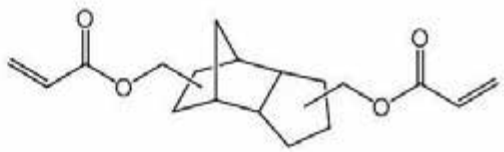
Option #1:Use established libraries as feedstock for 3DP

Use pre-existing libraries of materials with proven biological function and demonstrably UV curable:

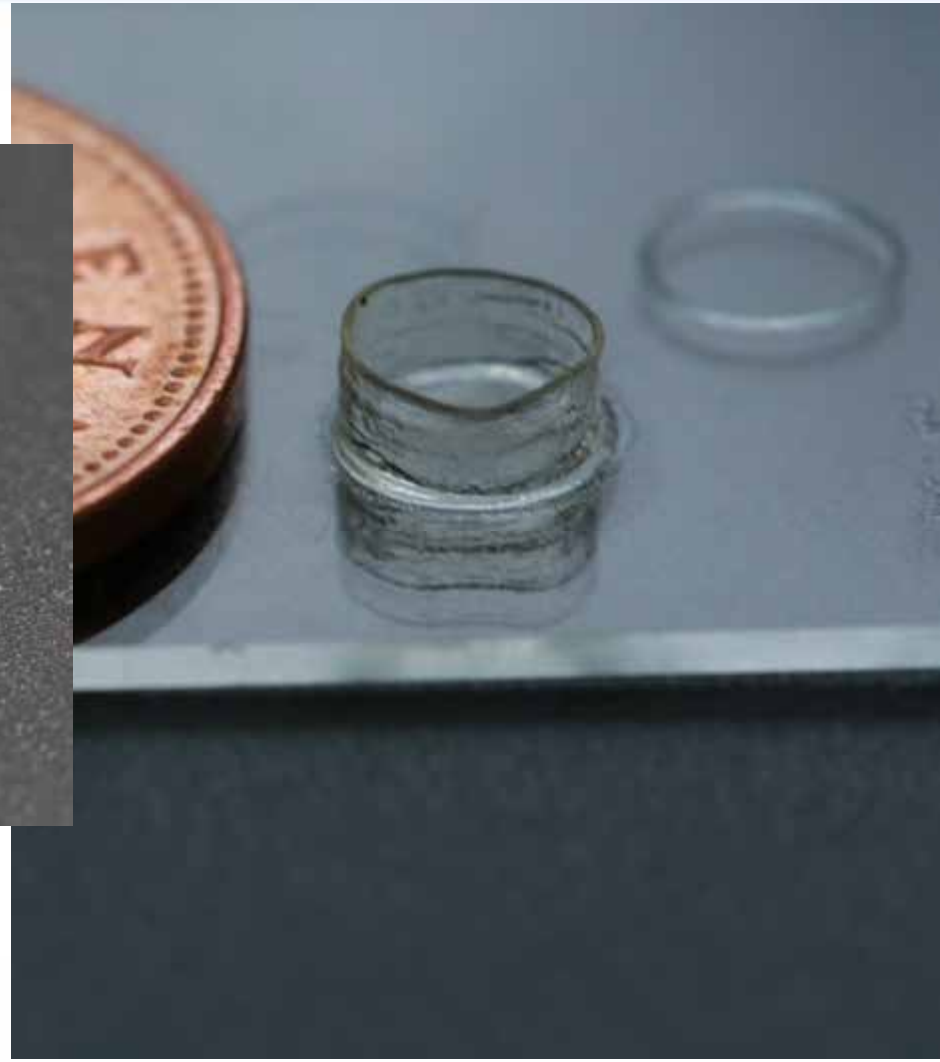
- Acrylates
- Beta amino acides
- Methacrylates



Ethylene glycol dicyclopentenyl ether acrylate



Tricyclo[5.2.1.0.2,6]decanedimethanol diacrylaye



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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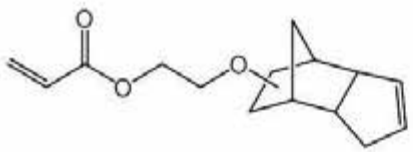

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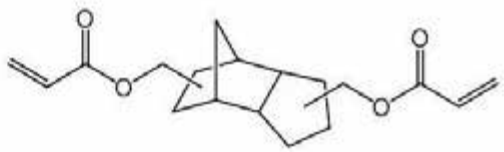

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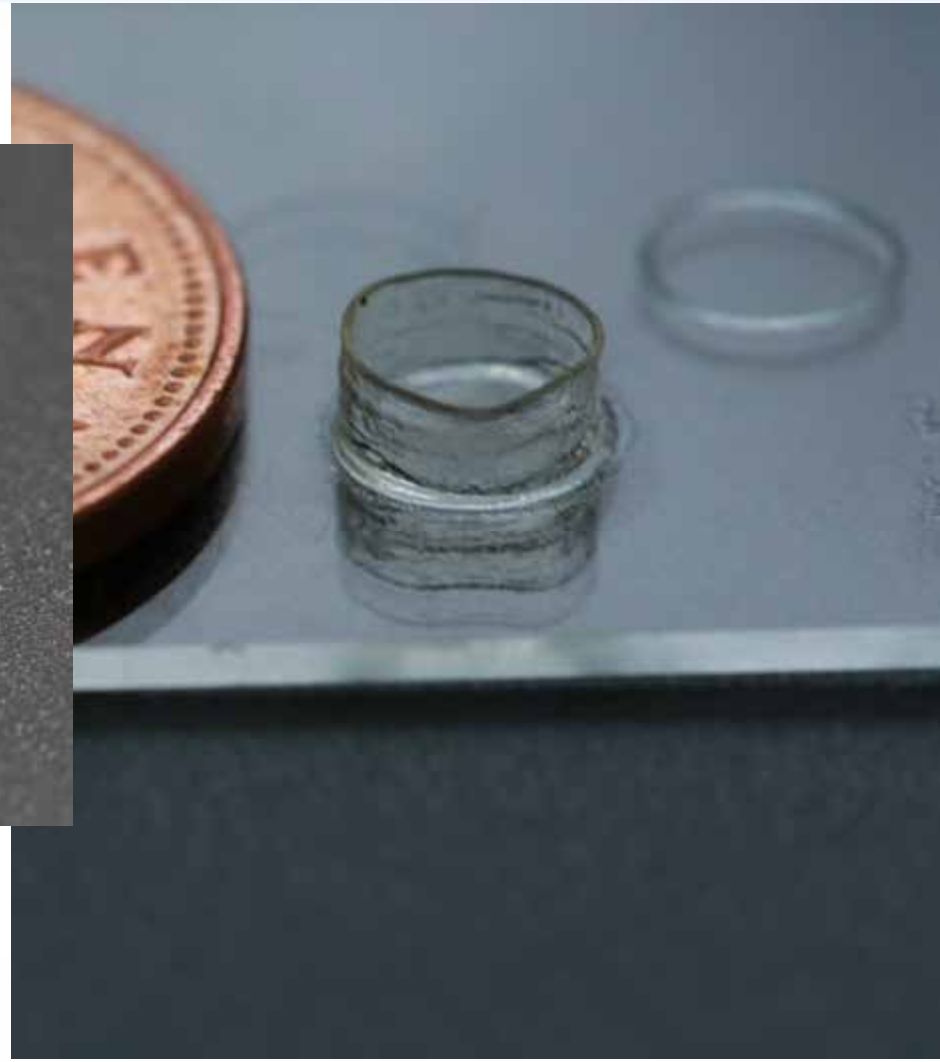


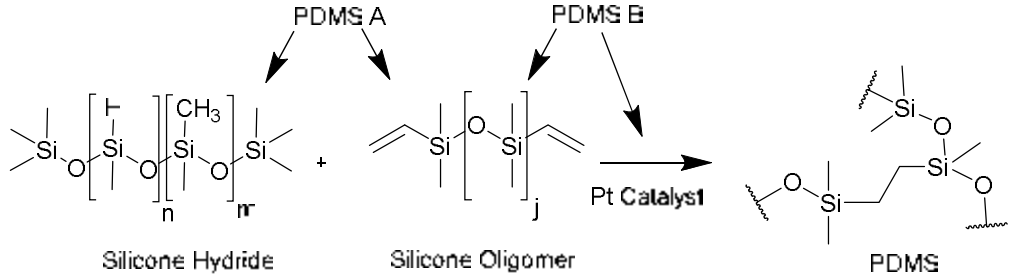
Works, but requires availability of libraries of materials with properties already determined

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

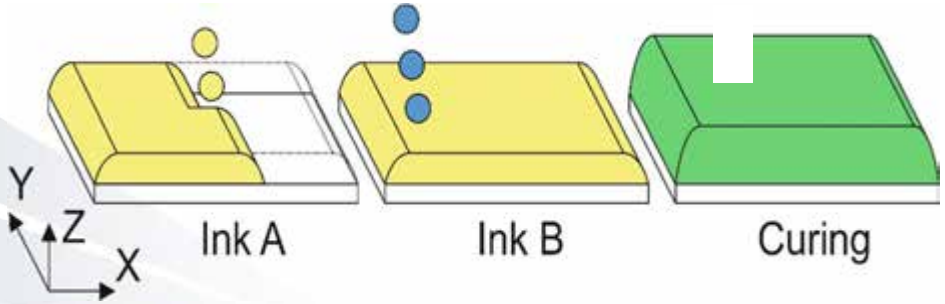
Option #2: Take known reactives and combine during printing

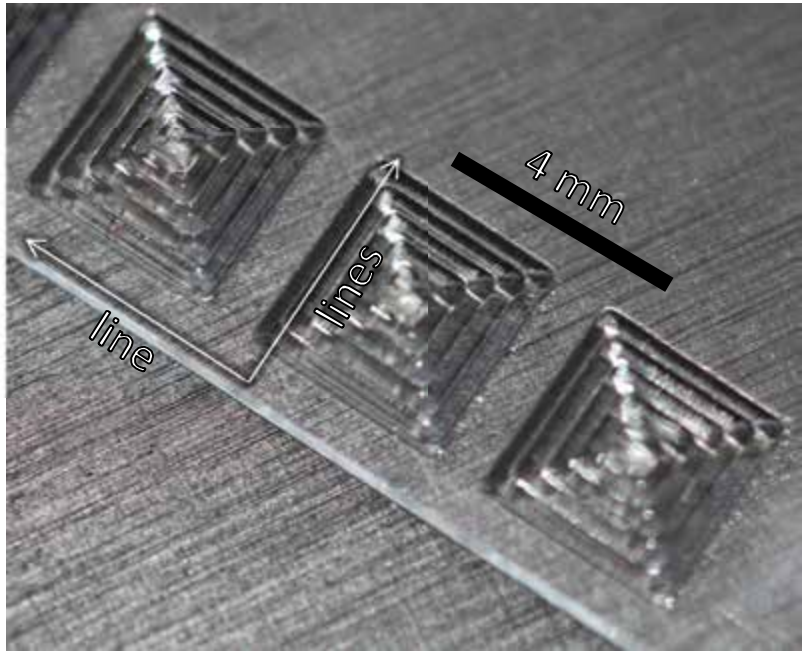
Reactive Ink Jet Printing of two part PDMS

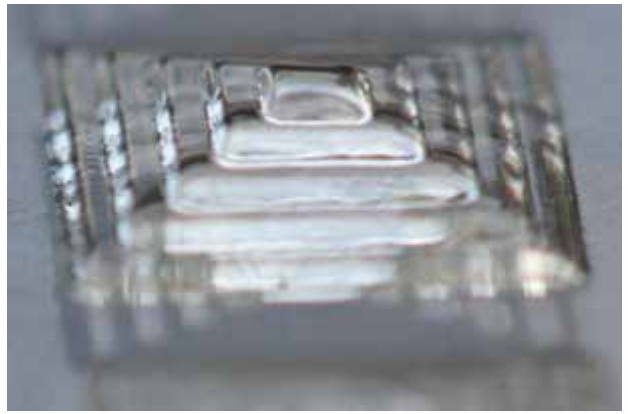
Two materials react in situ to form final product



Print layer by layer







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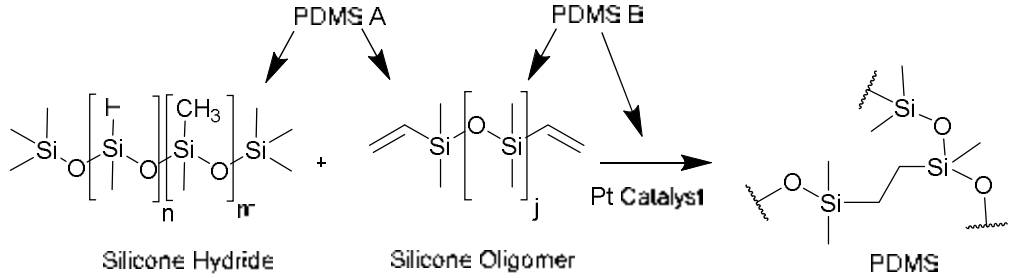

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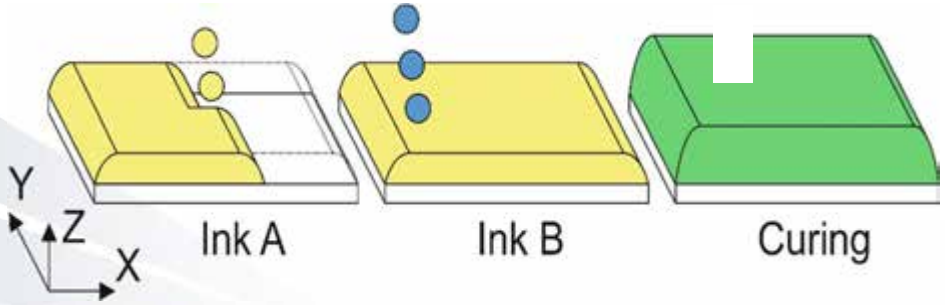
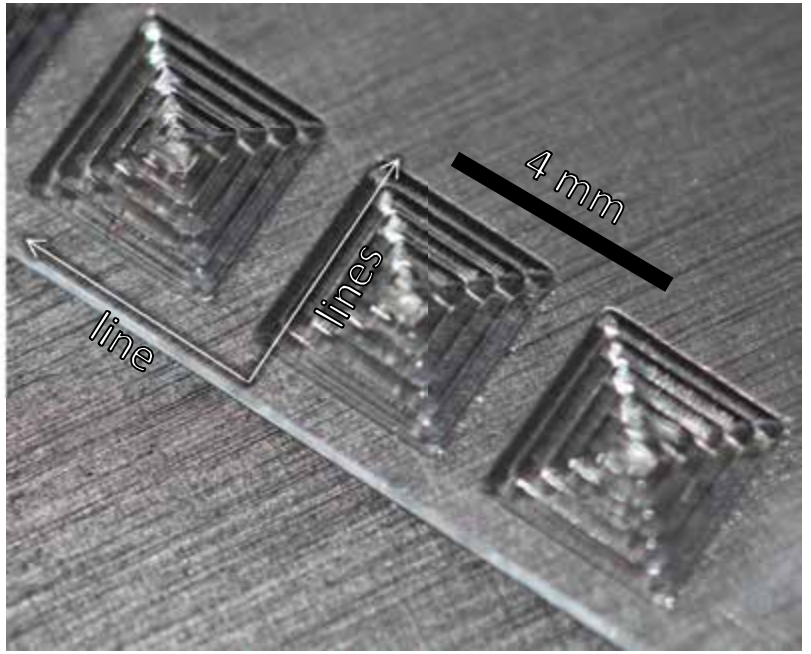
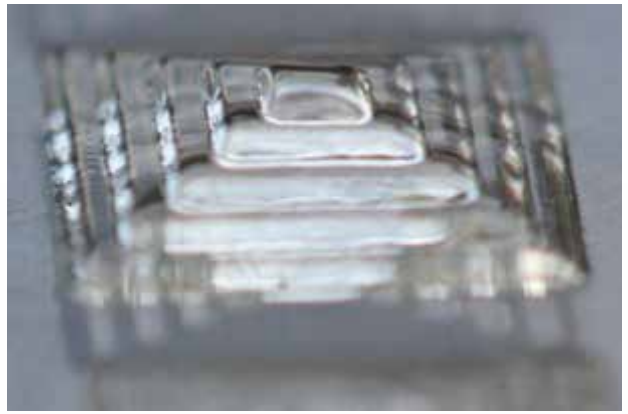


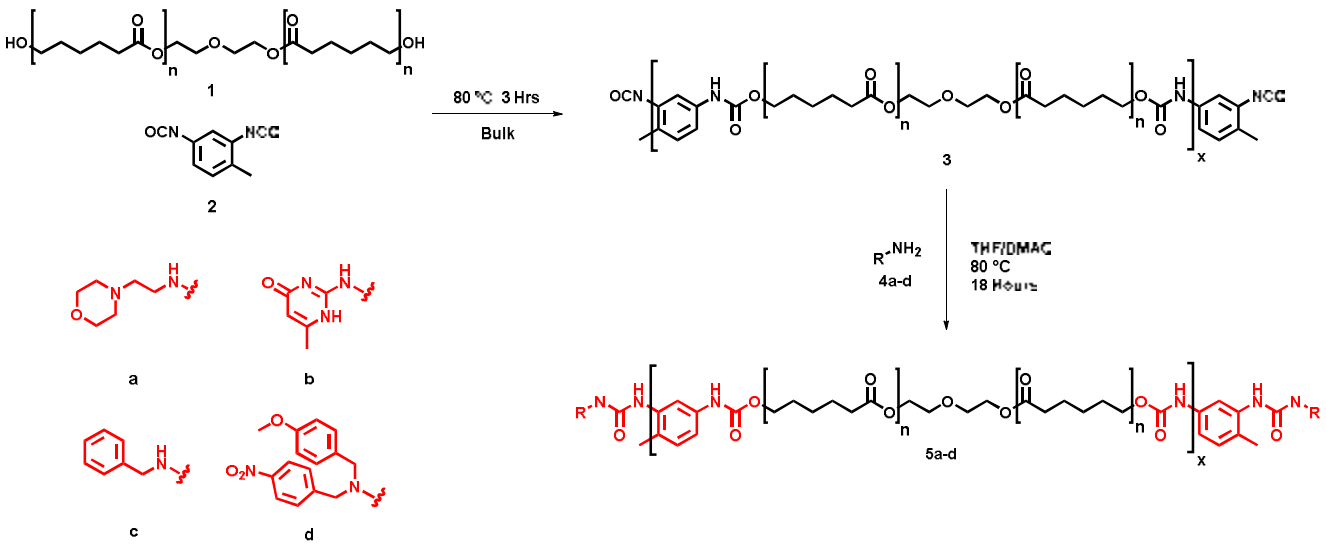


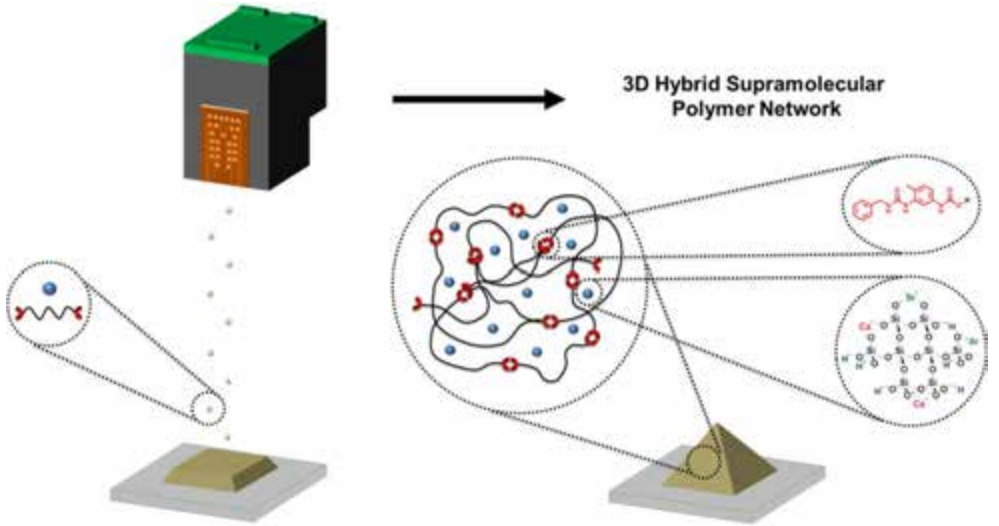


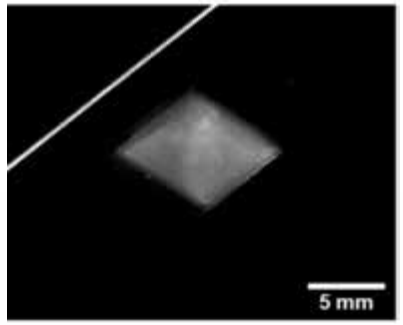
Promising, but time intensive to create and tune properties

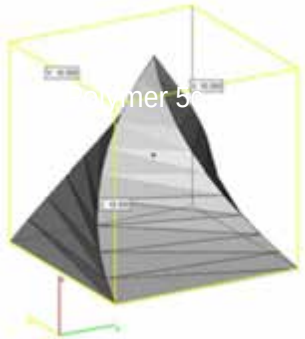
Option #3: Create new molecules

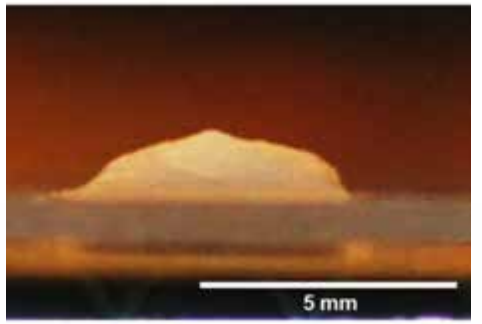
Designing 3D printable biocompatible supramolecular polymer hybrids for biomedical scaffolds











Hart, L. R.; Li, S.; Sturgess, C.; Wildman, R.; Jones, J. R.; Hayes, W. *ACS Appl. Mater. Interfaces* 2016, *8*, 3115–3122.

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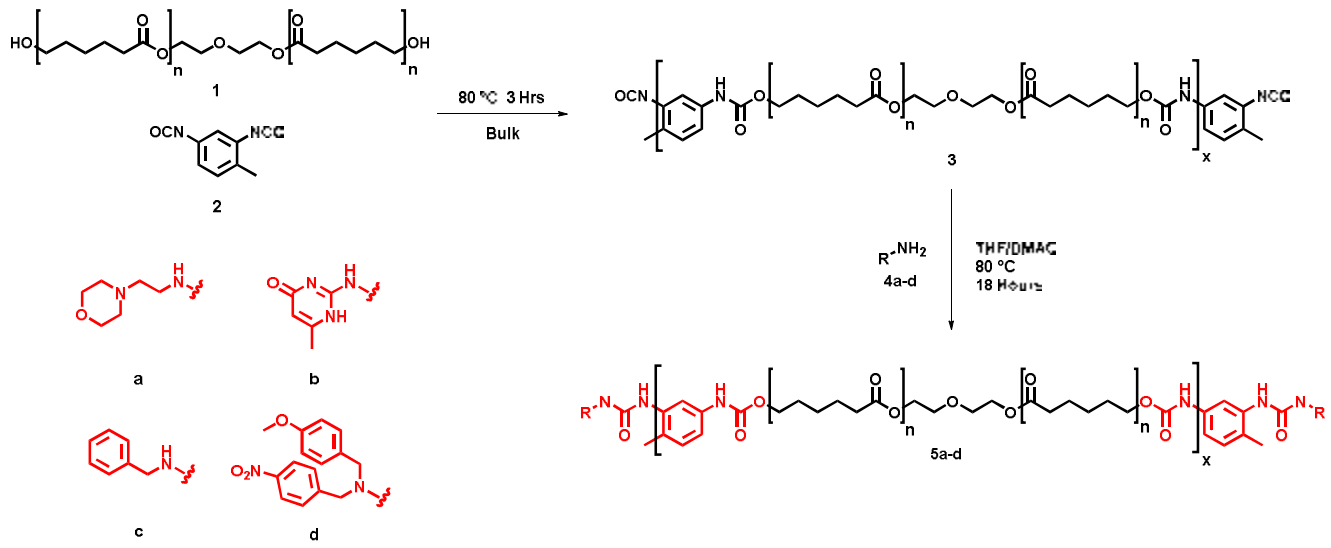
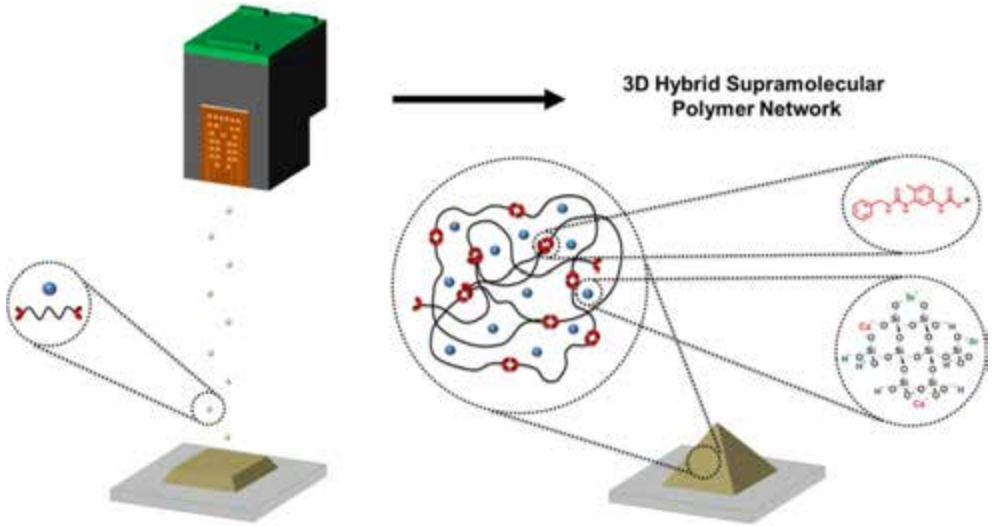
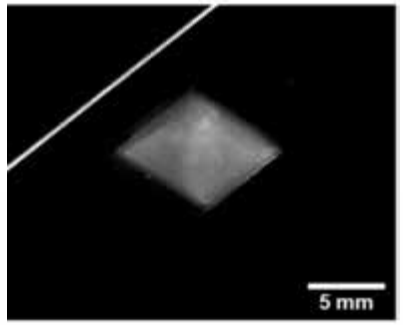
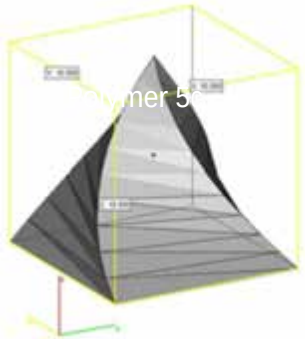
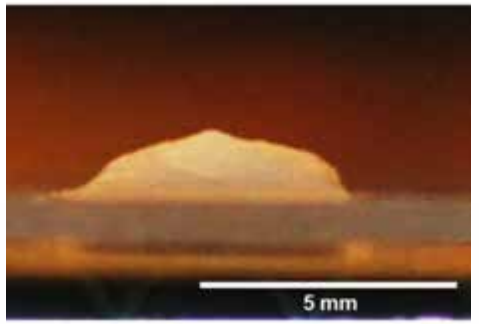




Requires new molecules that are *designed* and these are not readily available

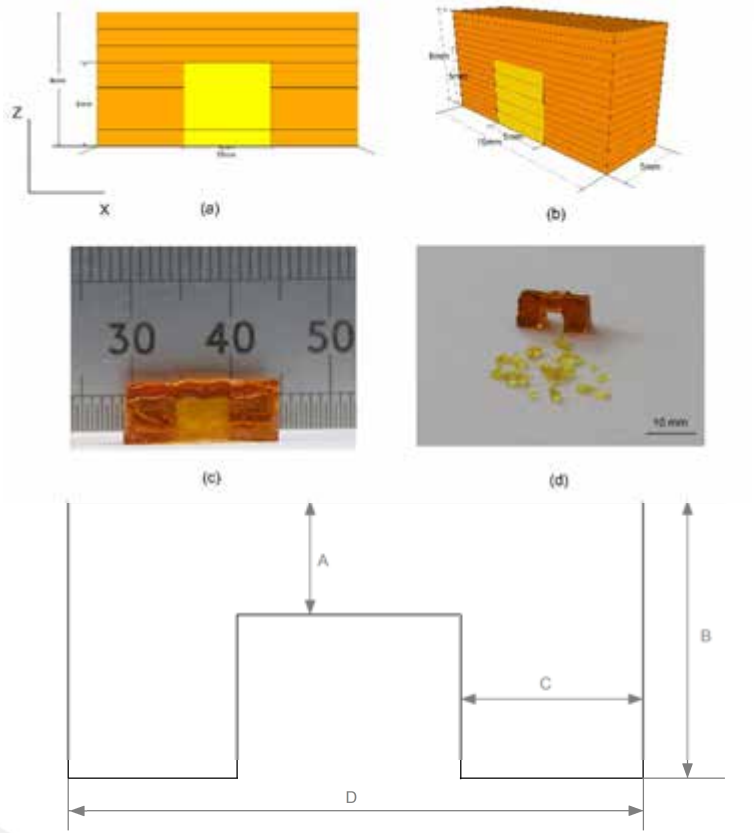


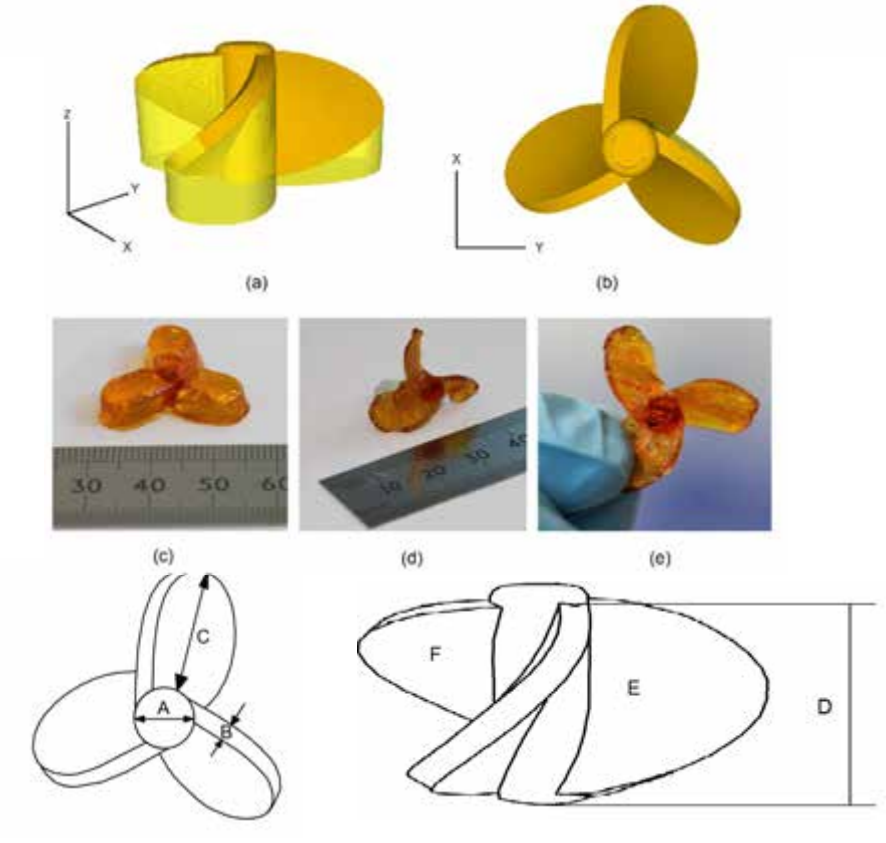




Hart, L. R.; Li, S.; Sturgess, C.; Wildman, R.; Jones, J. R.; Hayes, W. *ACS Appl. Mater. Interfaces* 2016, *8*, 3115–3122.

More complex structures need (disposable) supports …

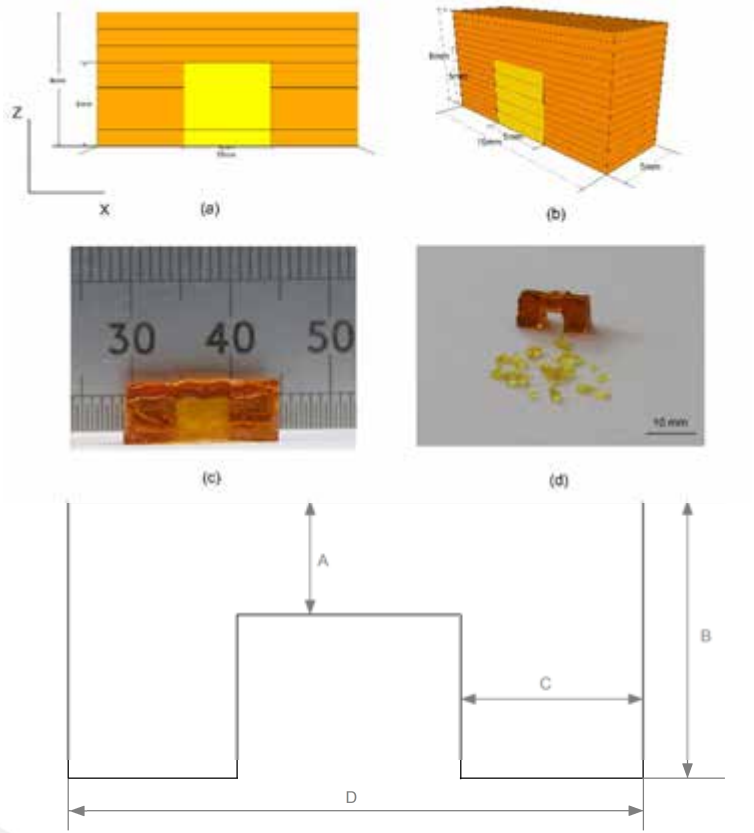


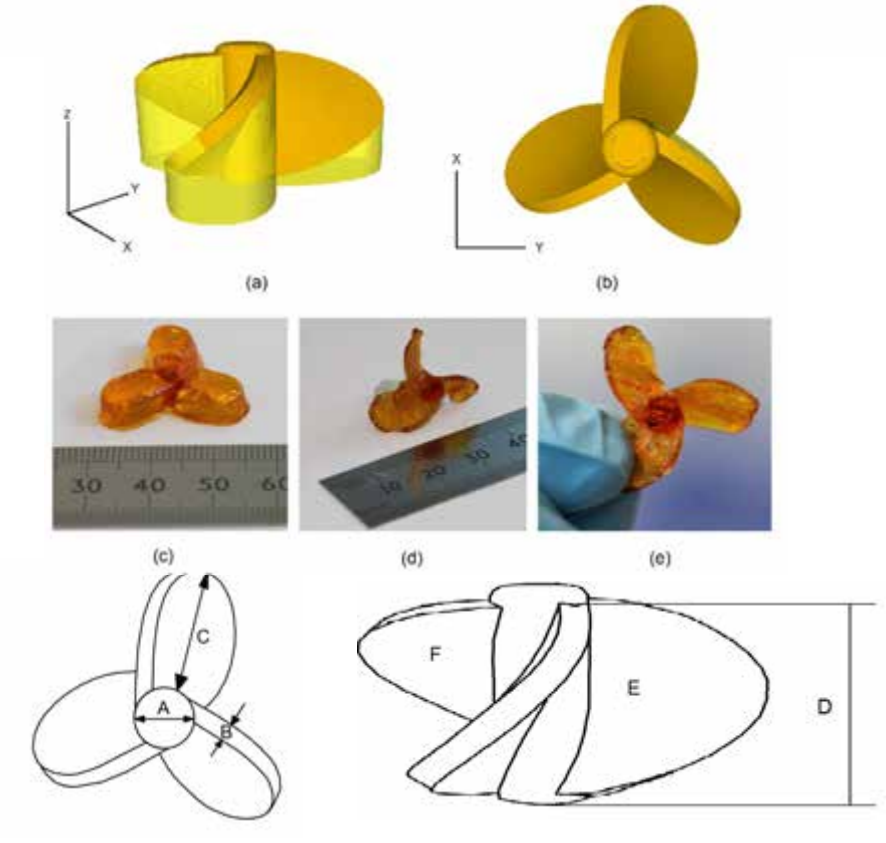


Support material created from a mix of tripropylene glycol diacrylate and triethylene glycol monomethyl ether – easily removable mechanically

He et al, Submitted to Additive Manufacturing Journal

More complex structures need (disposable) supports …





Support material created from a mix of tripropylene glycol diacrylate and triethylene glycol monomethyl ether – easily removable mechanically

Requires iterative formulation to achieve desired properties

He et al, Submitted to Additive Manufacturing Journal

The problem

- Our experience shows it can take up to 6 months to identify a single formulation for a given function – very intensive

- High throughput methods can help us narrow down the possible options – allow us to rapidly identify candidate materials
- We can use HT assessment to identify many possible formulations for a given function – achieve assessment of multiple formulations
- A library of available formulations and their properties can be shared for all

Our plan

- **Research Challenge 1: A sector specific library**

  Objective: Development of a system for rapidly formulating and characterising 3D printing inks

- **Research Challenge 2: Researching formulations for multiactive compartmentalisation & delivery**

  Objective: Establishment of formulations required to deliver multiple actives in one system

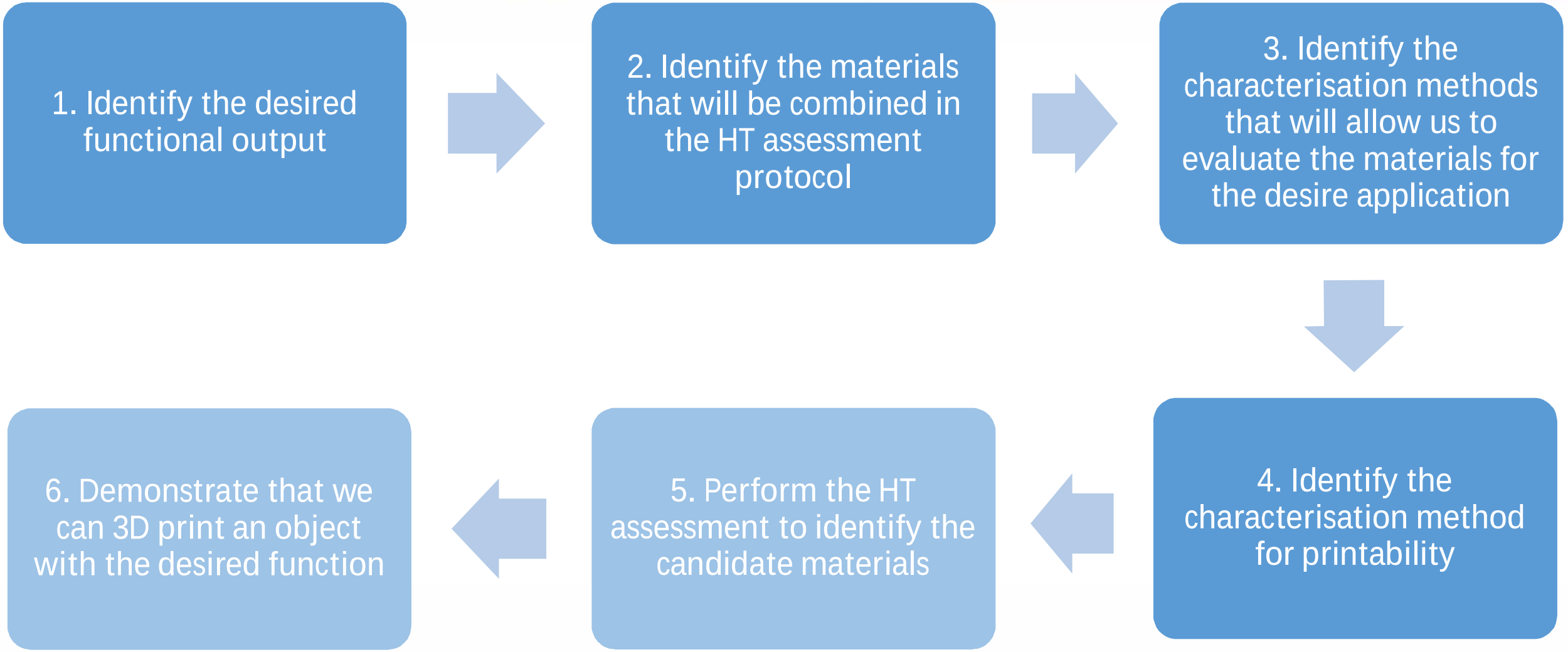
- **Research Challenge 3: How to formulate for structure & texture via the medium of 3D printing**

  Objective: Identification of edible materials suitable for printing and for control of textural and breakdown properties.

- **Research Challenge 4: Feeding the pipeline for high throughput formulation**

  Objective: Development of new materials for 3DP.

A High Throughput Methodology for 3DP



An example of how it works

AIM: Identify 3D Printable bioresorbable materials for zero order delivery of drugs from implants

Our steps:

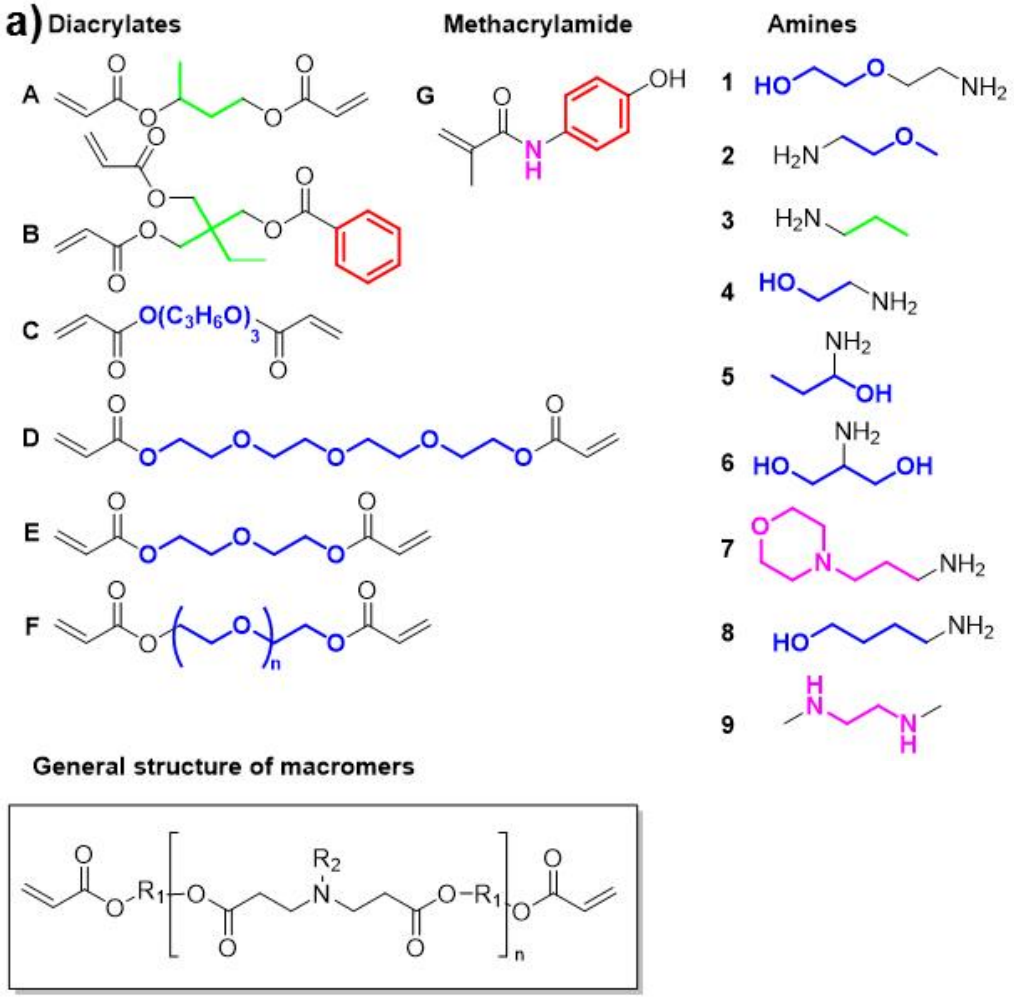
1. Identify class of bioresorbable materials
2. Use HT methods to select for zero order release
3. Identify toxicity of candidate materials
4. Determine which candidate materials are printable
5. Optimise and scale up for 3D printing

Identification of Novel 'Inks' for 3D Printing Using High Throughput Screening: Bioresorbable Photocurable Polymers for Controlled Drug Delivery

Louzao *et al*, submitted to Advanced Materials

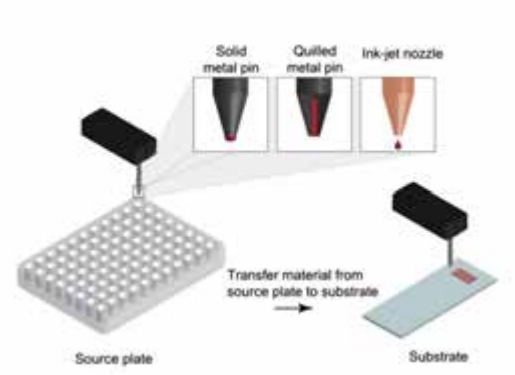
Materials

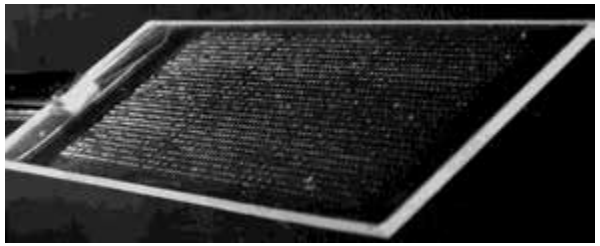
- Select materials likely to be printable / degradable
- Form macromers through combination of diacrylates and amines
- Formulate into printable versions via addition of photoinitiator and diluent/solvent



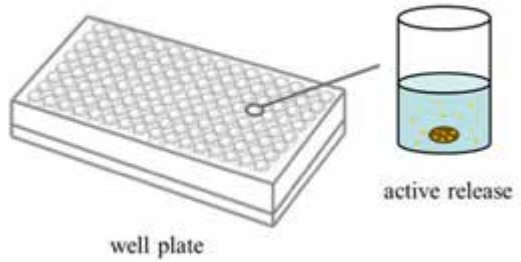
Assays and characterisation

Spotting of library materials on to a slide
- Mechanical characterisation





Deposition into well plates
- Drug release
- Cell testing



Degree of conversion
- Raman spectroscopy

Mechanical properties
- AFM

Cytotoxicity
- Cell viability study (LIVE/DEAD)

Miscibility

Drug release

Degradation
- Anderson et al 2006

Algahtani, M. S., Scurr, D. J., Hook, A. L., Anderson, D. G., Langer, R. S., Burley, J. C., ... Davies, M. C. (2014). High throughput screening for biomaterials discovery. Journal of Controlled Release, 190, 115–126.

Printability

How to predict whether a formulation will *3D print*

Key variables:

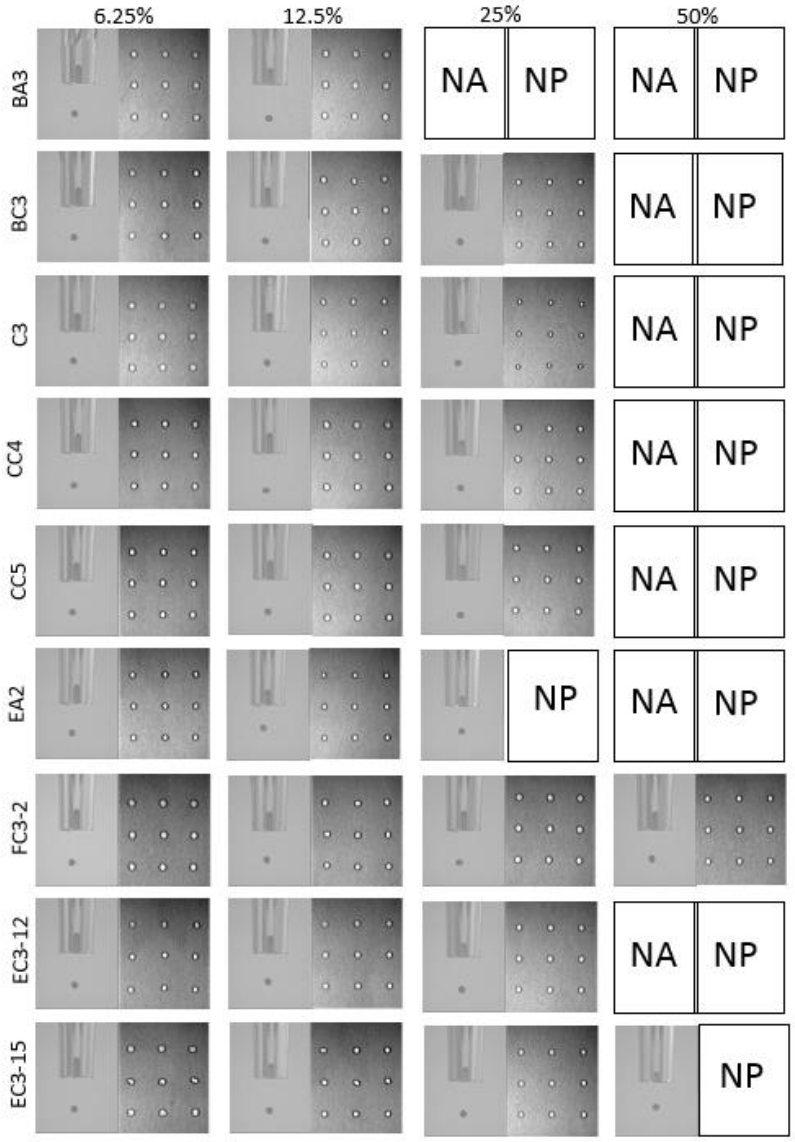
- Viscosity
- Surface Tension

Difficult to determine in a high throughput way

First assessment done on a proxy printing system that can aspirate/deposit many materials onto slides or well plates.

Determine which materials are ‘easy’ or ‘difficult’ to print and select candidates.

Project will lead to a more quantitative route to candidate selection.



Candidate selection and scale up

Take materials that are

- Have zero order release for chosen API
- Printable
- Reasonable mechanical properties
- Non cytotoxic

a)

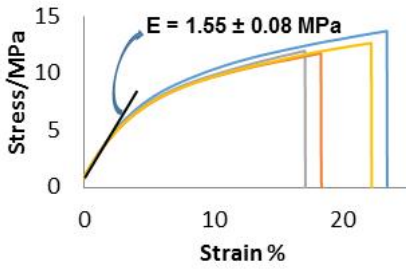
ink %	25%		50%	
ink	A	E	A	E
BA3	X	X	X	X
BC3	✓	✓	X	X
C3	✓	✓	X	X
CC4	✓	✓	X	X
CC5	✓	✓	X	X
EA2	✓	X	X	X
FC3-2	✓	✓	✓	✓
EC3-12	✓	✓	X	X
EC3-15	✓	✓	✓	X

b)

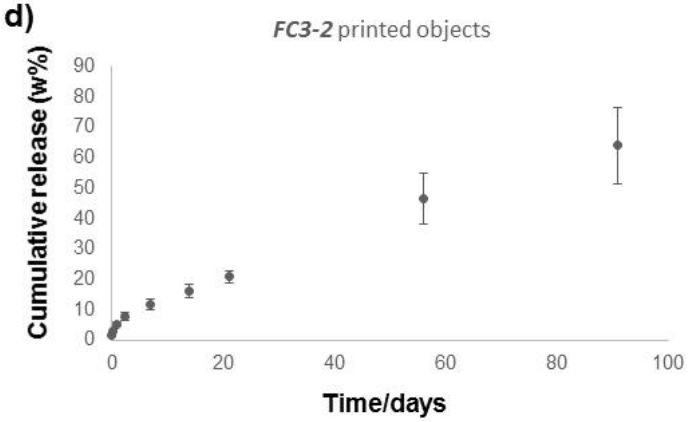
Ink formulations	Viscosity [mPa.s] [a]	Surface tension [mN/m] [b]	Surface tension [mN/m] [c]
FC3-2	13.08 ±0.36	32.81±0.21	33.11±0.23
EC3-15	10.61 ±0.10	31.96±0.11	32.75±0.38
GC3	15.94±0.14	33.84±0.92	33.40±0.18
GB	13.85±0.12	36.34±0.17	36.90±0.26

[a] Data at printing temperature T=60, 60, 65, 45C respectively from top to bottom [b] RT, [c] containing 1mg/mL paroxetine hydrochloride

c)

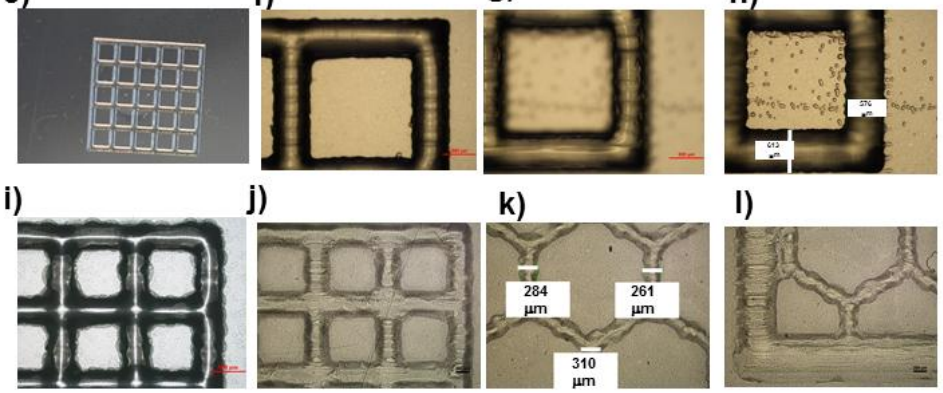


d)



e) f) g) h)

i) j) k) l)



Successful test 3D printing and release

Findings

In the same time as it would take to formulate one printable material we

- Assessed 312 combinations of new materials
- Determined 19 formulations with the correct drug delivery *function*
- Found 4 formulations that were 3D printable and ready for scale up

Summary

- 3D printing has huge potential in a wide variety of sectors
- Very limited set of materials available
- Time intensive to formulate for each individual application
- High throughput methods offer us a speedy way to find suitable candidate materials

Thanks

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W Hayes University of Reading