University of Nottingham
UK | CHINA | MALAYSIA

Formulation for 3D Printing:

Creating a plug and play platform for a disruptive UK industry

Final Report
January 2017 – March 2021

Engineering and Physical Sciences Research Council

Centre for Additive Manufacturing

University of Birmingham

University of Reading

Contents

Overview

The project ‘Formulation for 3D Printing’ (Ff3DP) was funded by EPSRC in 2016 as part of a major call for proposals under the umbrella ‘Future Formulation’. We applied as a collaboration of three universities, Nottingham, Birmingham and Reading, and received contributions and support from five industrial partners, PPG, GSK, Syngenta, Malvern Instruments, Unilever – each representing sectors important to the UK economy. Our programme aimed to break the bottleneck for take up of 3D printing technologies in major industries, targeting both the lack of suitable materials, and the lack of the means to find them. Hence, our focus was to develop methodologies that could be easily translated into industry that would allow rapid identification of ‘printable’ inks, resins or feedstocks, and then demonstrate their use in industrially relevant products. It was here that our industrial partners were invaluable – they guided and informed our research to ensure that our materials and products were relevant.

Our project has now come to a close and we are able to look back at the challenges and the successes in delivering this project. This project was a huge collaborative effort, bringing together over 30 researchers and investigators into a coherent team, building lasting relationships that will continue to develop state of the art research. Our research culminated in over 30 publications, with up to 20 still in the pipeline. The project supported 11 PhD students, creating a cohort of trained 3D printing experts across multiple sectors. This project employed 14 post-doctoral researchers, developing their expertise and supporting their career development – 6 are now using their knowledge within industry, 4 have permanent academic positions, and 4 are continuing their research as post doctoral researchers. We are proud of the research that emerged from our work, which blossomed over the course of the project, and are proud that we have been able to create an environment through which talented researchers have been able to develop their skills and achieve their goals, be it in academia or in industry.

A fitting finale for the project was participating in the 2021 Royal Society Summer Science Exhibition. Originally planned for 2020, but delayed through the pandemic, our digital array of films, lectures and games ‘Personalised Printing for Pills!’ have already reached over 16,000 science inquisitive members of the public since July, demonstrating the level of interest and excitement in what 3D printing can do.

Ricky Wildman, Principal Investigator
‘Formulation for 3D Printing’

Key individuals **Investigators**

Professor Ricky Wildman
Professor of Multiphase Flow and Mechanics, Faculty of Engineering
University of Nottingham
Principal Investigator and RC1 Lead

Professor Clive Roberts
Professor of Pharmaceutical Nanotechnology, Head of the School of Pharmacy, Faculty of Science
University of Nottingham
Co-Investigator and RC2 Lead

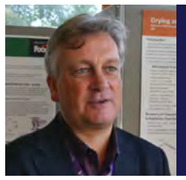
Dr Tom Mills
Senior Lecturer
School of Chemical Engineering
University of Birmingham
Co-Investigator and RC3 Lead

Professor Wayne Hayes
Professor of Polymer Chemistry
Department of Chemistry
University of Reading
Co-Investigator and RC4 Lead

Professor Ian Ashcroft
Professor of Mechanics of Solids
Faculty of Engineering
University of Nottingham

Professor Derek Irvine
Professor of Materials Chemistry
Faculty of Engineering
University of Nottingham

Professor Chris Tuck
Professor of Materials Engineering
Director of EPSRC CDT in AM and 3DP
University of Nottingham



Professor Tim Foster
Professor of Food Structure
University of Nottingham

Professor Morgan Alexander
Professor of Biomedical Surfaces
Faculty of Science
University of Nottingham

Professor Simon Avery
Professor of Eukaryotic Microbiology
University of Nottingham

Professor Richard Hague
Professor of Innovative Manufacturing, Director of the Centre for Additive Manufacturing
Faculty of Engineering
University of Nottingham

Professor David Amabilino
EPSRC/GSK Professor of Sustainable Chemistry
University of Nottingham

Dr Anna Croft
Associate Professor
Faculty of Engineering
University of Nottingham

Dr Fotios Spyropoulos
Reader in Formulation Engineering
University of Birmingham

Dr Anca Pordea
Associate Professor
Faculty of Engineering
University of Nottingham

Professor Ian Norton
Professor of Chemical Engineering
University of Birmingham

Key individuals **Research Fellows**

Dr Zuoxin Zhou
Research Fellow
Faculty of Engineering
University of Nottingham

Dr Saumil Vadodaria
Research Fellow
School of Chemical Engineering
University of Birmingham

Dr Laura Ruiz Cantu
Transitional Assistant Professor
Faculty of Engineering
University of Nottingham

Dr Lewis Hart
Research Fellow
Department of Chemistry
University of Reading

Dr Yinfeng He
Transitional Assistant Professor
Faculty of Engineering
University of Nottingham

Dr Azarmidokht Gholamipour-Shirazi
Research Fellow
School of Chemical Engineering
University of Birmingham

Dr Elizabeth Clark
Research Fellow
Faculty of Engineering
University of Nottingham

Dr Scott Wang
Research Fellow
Faculty of Engineering
University of Nottingham

Dr Adja Touré
Research Fellow
Faculty of Engineering
University of Nottingham

Dr Lea Santu
Research Fellow
School of Chemistry
University of Nottingham

Dr Simon Attwood
Research Fellow
Faculty of Engineering
University of Nottingham

Dr Xuesong Lu
Research Fellow
Faculty of Engineering
University of Nottingham

Dr Vincenzo de Bari
Senior Research Fellow
Faculty of Engineering
University of Nottingham

Mrs Hagit Gilon
Research Technician
Faculty of Engineering
University of Nottingham

Key individuals **PhD students**

Anna Lion – RC2
Multimaterial ink jet printing of hot waxes, University of Nottingham

Chris Strong – RC2
3D printing an artificial plant cuticle, University of Nottingham

Ling Xin Yong – RC1
Creating a library of antifungal 3D printable, materials, University of Nottingham

Yuyang Wu – RC1
Developing a reactive extrusion process for polyurethanes, University of Nottingham

Marica Malenica – RC2
Using microfluidic methods to creating microparticles suitable as 3D printing resin property modifiers, University of Nottingham

Eva Kingwood – RC2
Multimaterial 3D printing of tablets, University of Nottingham

Alice Andrea Konta – RC1
Extending the library of formulations suitable for two photon polymerisation, University of Nottingham

Glenieliz-Glyssa Dizon – RC4
Creating a library of organogel gelators for 3D printing applications, University of Nottingham

Sara Salimi – RC4
Supramolecular chemistry for designing novel 3D printing resins, University of Reading

Kilian Daffner – RC2
Creating dairy protein based 3D printing inks, University of Birmingham

Michael Kamlow – RC2
3D printing of edible hydrocolloid gels, University of Birmingham

Exploiting the clean room facilities at the University of Nottingham to create novel 3D printing formulations

Research Challenge 1

A sector specific library

Using a liquid handler based robot to automate the assessment of viscosity and surface tension, leading to high throughput screening of inkjet based 3D printing inks

Objective

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

Currently, the adoption of 3D printing has been limited owing to the lack of suitable materials, and those that are available are often tied to a specific process. In recent years some progress has been made in developing 3D printing ready materials, e.g. polyimides, polyurethanes and polyureas, self-healing materials, silver nanoparticle loaded inks, polycaprolactone and polyethylene glycols. However, in each of these cases a single material has taken a significant period of up to 6 months to prepare and optimise. Imagine though, if we were able to collect together many of the materials that might be useful, and rapidly ascertain which of these will be printable and which of these will result in properties that will be useful to important UK sectors. We took this concept and tailored it to 3D printing: we developed a suite of high throughput materials assessment systems for materials jetting.

Highlights:

- We developed a high-throughput method to rapidly screen materials for printability based on a liquid handler, to automate the measurement of viscosity and surface tension and coupled with a fluid mechanical model of flow through a nozzle.
- We synthesised a diverse library of biodegradable and biocompatible materials suitable for pharmaceutical applications and then showed how we can isolate the favourable properties and select the right materials for desired release.
- We screened a library of double-network supramolecular gels that showed superior mechanical properties to single network materials.
- We demonstrated that inkjet 3D printing yields controllable phase separation of polymers and that it can be predicted with the model-based Flory-Huggins interaction parameter.
- We fabricated a bioreactor for green chemistry using 3D printed polymer trapped enzymes, optimising the materials suitable so that both manufacture and the enzyme catalysed reaction can proceed.
- We developed biodegradable formulations for two photon polymerization that we used to 3D print implants to deliver treatment for the chronic eye disorder macular degeneration.

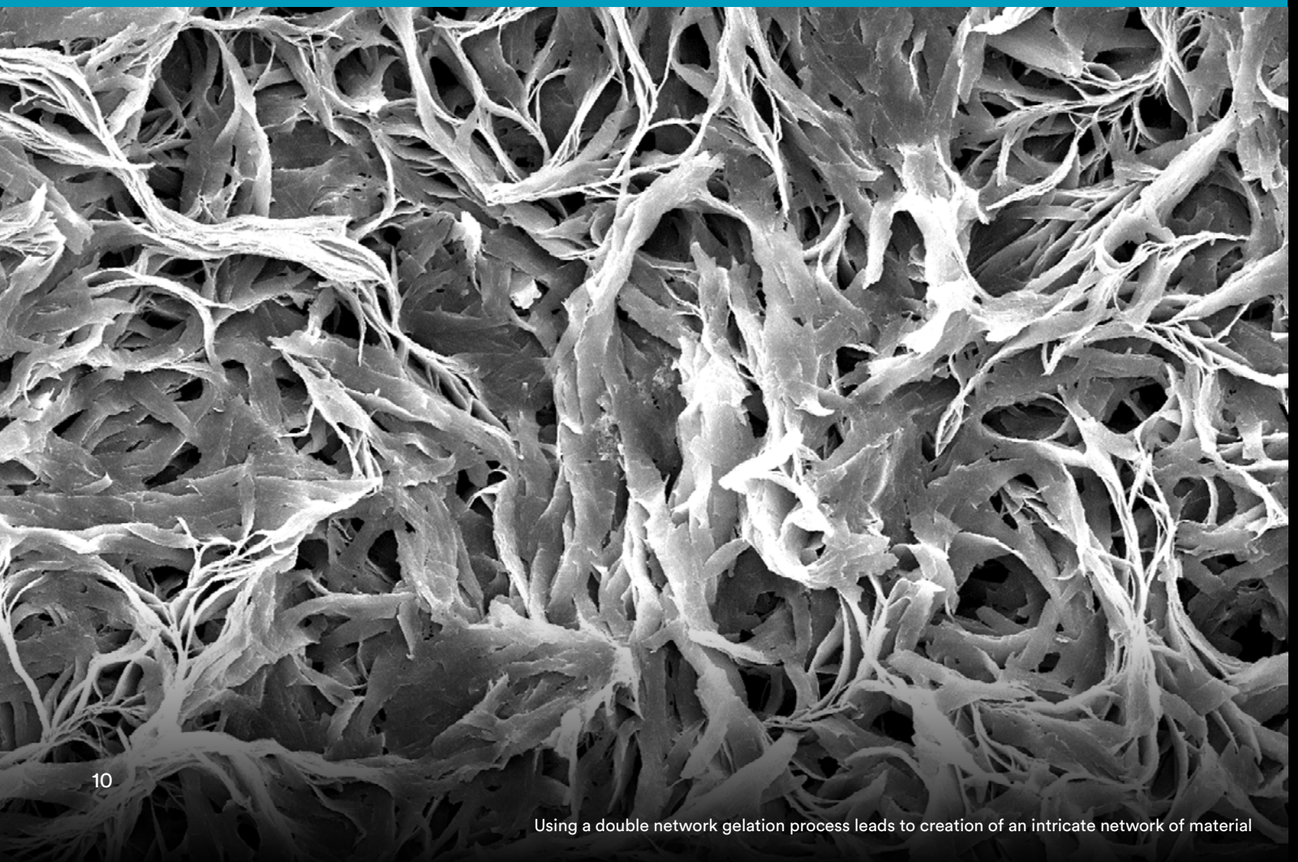
Dr Zuoxin Zhou

Printability high-throughput screening

Zuoxin developed a high-throughput screening approach that uses a liquid handler containing multi-pipette heads to achieve expedited formulation of new inks for material jetting Additive Manufacturing.
This approach essentially combines rapidly preparation inkjet formulations in a micro-array format, and subsequently measure the printability for each in a high-throughput manner. The throughput is 96 formulations per 13.1 working hours, 15 times more rapid than conventional methods. The methodology and the material database established using this high-throughput screening (HTS) technique will allow academic and industrial users to rapidly select the most ideal formulation to deliver printability and a predicted processing window for a chosen application.

Identification of double-network supramolecular gels to be processed using 3D printing techniques

In this project Zuoxin investigated gelation of 30 UV-curable monomers with 16 low molecular-mass organic gelators that have different chemical structures and gelation triggering mechanisms including temperature, pH, ultrasound, and hydrophobic association. Gelation speed, gel-sol temperature, and rheological properties have been obtained to identify the gel formulations that can trigger sol-gel transition upon deposition and subsequently form self-supportive structure prior to UV irradiation. Double-network gels constituting both physical and chemical networks are thus constructed which potentially benefit to mechanical performance, curing kinetics, self-healing capability and multi-drug loading.



Using a double network gelation process leads to creation of an intricate network of material

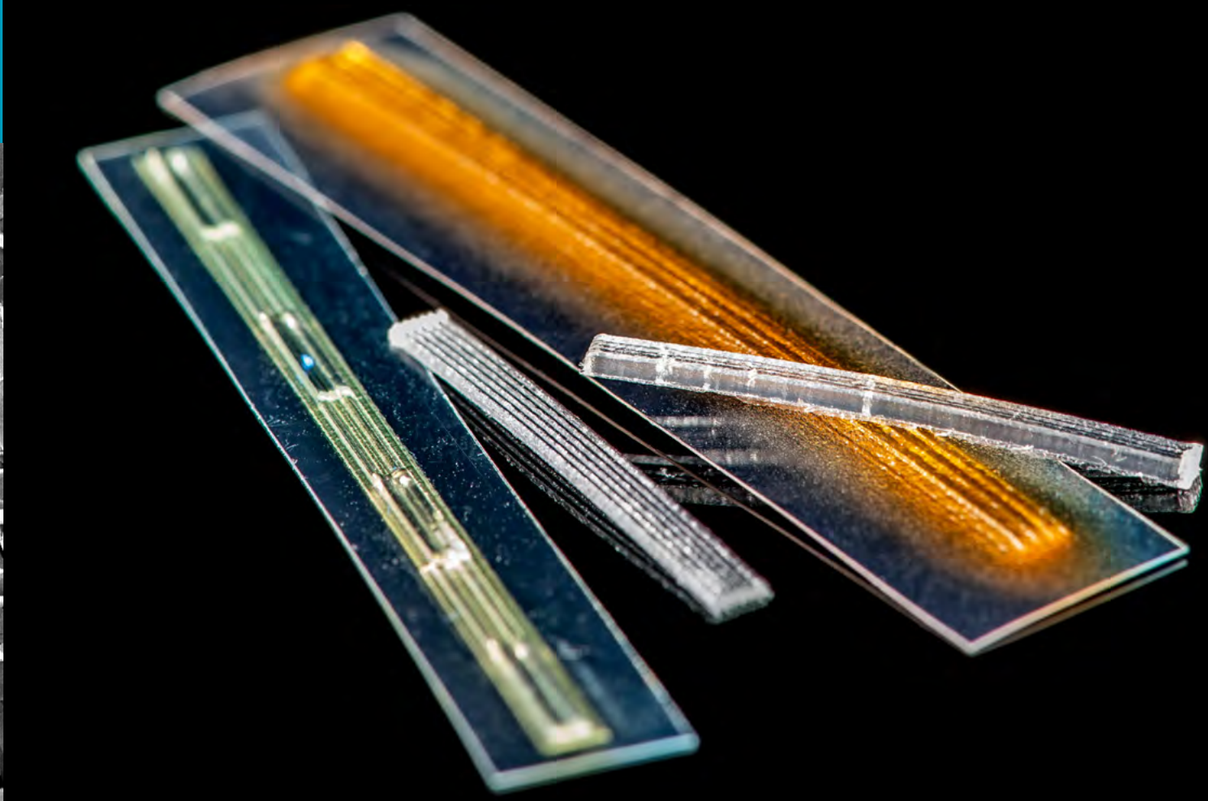
Dr Laura Ruiz Cantu

Materials library for pharmaceutical applications

Laura formulated a library of biodegradable and biocompatible materials that have different mechanical, thermal, crosslinking, degradation and drug release properties. The library is based in three FDA approved polymers (polycaprolactone, polylactic acid, polytrimethylene carbonate acrylate).

Then she set out to exploit the various mechanisms available for affecting drug release: polymer degradation rate, diluent dissolution rate and phase separation via the development of a library of formulations / inks that can be selected to enable the ‘dial up’ of release from a multiple-drug loaded 3D-printed implant.

In this project it was demonstrated that the microstructure generated by the phase separation of the ink components can be used to tailor spatial location of the drugs and thereby generate release profile of drug payload over periods ranging from one week to months. Finally, we exemplified our approach by fabrication a multidrug implant with release profiles that are tuneable through choice of material combination.



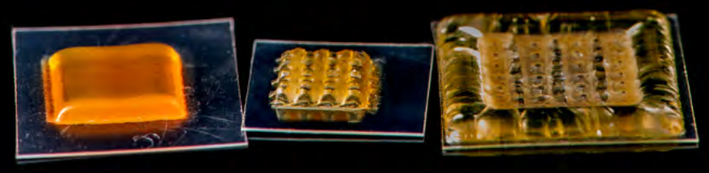
Multi-material inkjet printing, backed with screening of materials and microstructure, allows us to tune the structure and behaviour of drug loaded implants

Dr Adja Touré

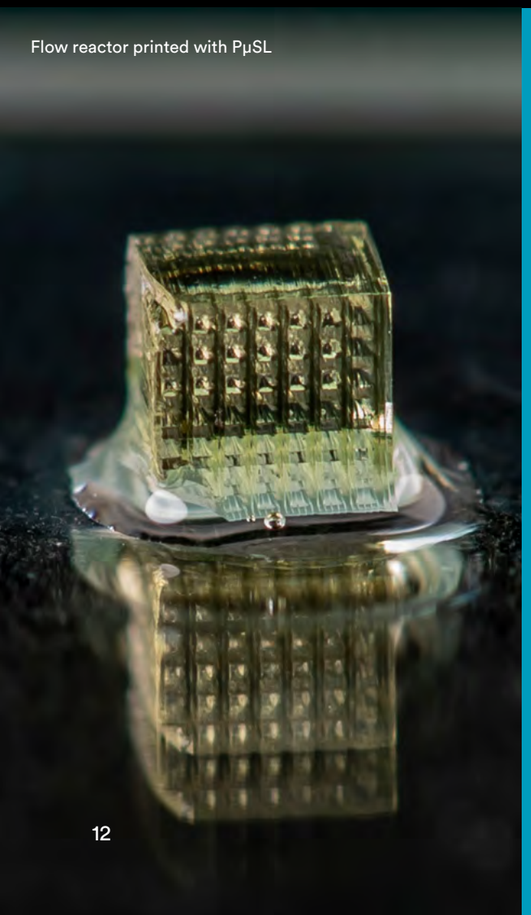
Library screening of self-assembly supramolecular polymer composites

Adja implemented the high-throughput screening methodology to quickly assess the printability and biocompatibility of a large library of materials developed by RC4. The material library is composed of 64 PCL-based hyperbranched polymers exhibiting self-assembly properties. We aim at determining their suitability for articular cartilage regeneration applications.

To screen the polymer library, their printability for inkjet printing was assessed using a liquid handler, measuring viscosity and surface tension. This led to selecting around 60% of the tested library. The high-throughput assessment of mechanical properties was enabled using a microarray strategy. Localised mechanical properties were determined using atomic force microscopy where materials exhibiting suitable elastic moduli were selected. Combination of these techniques with cytotoxicity screening led to the selection of suitable polymer candidates for the targeted application.



3D printed hyperbranched PCL polymer scaffolds for cartilage repair applications



Flow reactor printed with PμSL

Dr Simon Attwood

3D-printed polymer entrapped enzymes as bioreactors for green chemistry

Enzymes are nature's catalysts and have incredible potential for the field of chemical synthesis. They are capable of delivering exceptional yields with high chemical selectivity. Being of biological origin, their production and use avoids dangerous and harmful reagents and is therefore aligned with the principles of green chemistry. Using a state of the art Projection Micro Stereolithography 3D printer (PμSL) Simon created flow reactor components where enzymes are trapped within a hydrogel polymer matrix preserving their functionality and allowing them to be re-used over multiple cycles. These bespoke components contain micron scale channels that are designed to optimize flow of reactants in and products out, avoiding 'dead zones' where enzymes are underutilised due to poor localised flow. He is currently working towards integrating these components into fully functioning chemical flow reactors in order to maximize synthesis rates and provide an efficient and green alternative to conventional synthesis processes.

Alice Konta

Design of new materials for two photon polymerisation

The aim of this project was to develop biocompatible formulations for 2PP that could be used to manufacture drug eluting ocular implants. As part of the project, a new monoacrylate macromer, poly (trimethylene carbonate) acrylate (PTMCA), was developed and optimised for 2 photon polymerization printing by mixing it at different concentrations with diacrylate crosslinking monomers, like polyethylene glycol diacrylate diacrylate (PEGDA) or Tricyclo[5.2.1.$0^{2,6}$]decanedimethanol diacrylate (TCDMDA).
The formulations prepared with PTMCA+PEGDA manufactured structures with homogeneous dispersed phases. The mixtures prepared with PTMCA+TCDMDA produced both homogeneous and heterogeneous dispersed phases. Depending on the concentration used or the processing parameters selected (i.e., laser power, writing speed), these formulations allowed for a controlled phase separation that produced different microstructures in the samples.

Yuyang Wu

Development of 3D printing materials for Reactive Extrusion (REX)

Yuyang worked on developing a new formulation for reactive extrusion 3D printing, using polyurethane or polyurea chemistry. The objective of this project was to tackle the intrinsic anisotropic issue related to 3D printing, both improve the interlayer adhesion and enhance mechanical strength of the extrusion-based 3D-printed objects. It is anticipated that the in-situ reaction during printing could synchronise the development of shear modulus and the crosslinking between layers. The potential curing at ambient temperature could mitigate the thermal distortion during the printing.

He designed one polyurethane formulation which is suitable for REX system, by balancing the reaction kinetics and rheology profile. He studied a number of parameters related to polyurethane reaction, including the different isocyanates (di or poly-functional); different diols (ABA or BAB block copolymers, where A stands for polyethylene glycol and B stands for polypropylene glycol); different filler type and level; catalyst level. Besides, the printing parameters including printing speed, dosing speed and Z-gap have also been investigated.

Ling Yong

Development of materials for fungal and bacterial resistance for bio functional devices

Ling's research aim is to screen for potential flexible polymers with antimicrobial properties to be used as a UV curable Additive Manufacturing material. The use of anti-microbial polymer for applications such as medical devices would in turn reduce the mortality rate from microbial infection and also reduce complications in patients' health from frequent changes of medical devices. Voice prosthesis and catheters are examples of such devices. Additive manufacturing method would then be advantageous in terms of low-volume manufacturing and customisation. In Ling's project, she applied the high-throughput methodology to screen materials especially flexible co-polymer materials to explore the formulation candidates for voice prosthesis application. By screening low glass transition photoreactive monomers involved formulations that reduce the overall glass transition point of the copolymer chain, Ling was able to find anti-microbial copolymer composition that not only has anti-microbial properties but also with good flexibility at room temperature.

Research Challenge 2

Researching formulations for multi-active compartmentalisation and delivery

pμSL printed hydrogel lattices with triggerable releasing profiles with the presence of peptides

Objective

Establishment of formulations required to deliver multiple actives in one system

There is substantive cross-sector need for formulating multi-active delivery vehicles, with ‘actives’ required to deliver different functions, often at different times or conditions. This spans across several industries: in home care, food, agrochemicals and pharmaceuticals there are overlapping interests in delivering ‘actives’, controlling release and keeping ‘actives’ apart until use/delivery. It is challenging to meet these needs by established mass-manufacturing methods that lack fine control of 3D geometry and material distribution. Our concept is to generate a library of materials that will enable advantage to be taken of the ability of 3D printing to place materials in 3D without the need for complex reformulation and manufacturing strategies.

We focused on both inkjet-based and extrusion based multi-material 3D printing techniques in order to manufacture customizable delivery vehicles that are able to deliver multiple actives in a controlled manner. To achieve this goal we have worked from two aspects: developing new molecules and formulations that are compatible with the multi-material 3D printing process; modifying our multi-material 3D printers to make it more tolerable for a wider group of materials.

Highlights:

- A group of photoreactive excipients were developed and successfully printed through inkjet-based 3D printing process, including commercially available photoreactive monomers and new photoreactive monomers synthesised for drug delivery application.
- A reactive prodrug based formulating strategy was established through which pills with an extended releasing period can be manufactured. The formulations are compatible with the multi-material inkjet 3D printing process. This strategy offers more design freedom when developing ink formulations and is capable of realising customizable pills with a sustained release period and allows for a high drug loading.
- A hot melt-based multi-material inkjet 3D printing system was modified to allow us to manufacture polypills that can be tuned for desired by spacially varying the composition of the tablet.
- Photoreactive excipient materials were processed with a jet mixer and microfluidic device to produce continuous and efficient processes capable of creating monodisperse drug loaded particles. Implantable polydrug delivery devices were also printed from highly diverse polymer/monomer libraries leading to highly tailorable and predictable sustained release delivery systems.

Creating biomedical devices that can be personalised and manufactured on demand

Dr Yinfeng He

Yinfeng's project focused on developing functional polymeric ink formulations for printing drug delivery system. He explored a formulation involving attaching the drug molecules to the photoreactive monomers. The drug molecule was temporarily attached to a photoreactive monomer through a degradable covalent bond. Once the application environment is reached, the drug molecule can detach and release while the releasing speed and releasing condition can be tuned by choosing different temporal covalent bonds and adding hydrophilic monomers.

This work has been published in Advanced Therapeutics as a cover article in which a series of drug attached reactive monomers were synthesised using ibuprofen as a proof of concept work. The drug molecules were attached through ester bonds which can then hydrolyse to release the drug molecules. Such a system can enable sustained release of a drug which can be tuned by altering the composition and also allow for very high loading without adverse polymorphic changes in the drug (up to 60wt% drug loading) to be manufactured for long term drug-releasing applications. Formulations were developed for inkjet-based 3D printing and successfully printed. We were able to show that the drug-elution rate can be tuned with environment pH as well as through composition, showing the possible complete elution ranges from 5 to 400 days.

Dr Elizabeth Clark

Elizabeth's project focused on developing photoreactive excipient materials that are compatible with inkjet-based 3D printing of delivery devices for both pharmaceutical and agricultural applications. She has successfully developed the first fully inkjet printed Parkinson's medicine with a novel photoreactive excipient ink formulation that can continuously deliver the loaded drug (Ropinirole HCL) within 4 hours. This work was achieved in collaboration with GlaxoSmithKline (GSK) and has been published in the International Journal of Pharmaceutics. This work opens the possibility for the translation of scalable, high precision and bespoke inkjet-based 3D printing to the pharmaceutical sector. She also looked into other formulating strategies to incorporate poorly soluble drugs in 3D printable formulations without disturbing processability. By using carvedilol as an exemplar of poorly soluble drug, she achieved inkjet 3D printed tablets with 10wt% drug loading which is high for such drugs. This new photoreactive excipient formulation also has an extended releasing period (up to 24 hours) to ensure the highly loaded drug can release in a controlled manner. The success of developing such formulations for inkjet-based 3D printing also offered the capability to print tablets with customizable geometries that provide a further strategy to design and control the release of the loaded drug.

Rapidly dissolvable materials that are sustainable and environmentally friendly

Dr Shaban Khaled

Shaban mainly worked on the design, formulation, manufacture and testing of oral drug delivery dosage forms with extrusion-based multi-material 3D printing techniques. Compared to inkjet-based 3D printing, extrusion more easily allows the use of regulatory approved excipient materials common in the pharmaceutical industry. Therefore, this technique has the advantages of a more established material database and easier acceptance by the pharmaceutical industry, in this aspect at least. Shaban was responsible for a series of seminal high-impact papers in 3D printing applied to tablet manufacture. In this project, he focused on using regulatory approved excipients to make them compatible with the extrusion-based 3D printing process. By including functional materials and ingredients, he was able to design customised tablets containing multiple active ingredients, each independently controlled, an osmotic pump tablet and the first demonstration of immediate and sustained release from the same formulation using tablet geometry alone as the controlling factor. This latter is an important practical development that could ultimately simplify supply chains and ease regulatory issues in using 3D printing in a distributed manufacturing model.

Dr Xuesong Lu

Xuesong explored and developed the concept of reactive extrusion, in collaboration with PPG Inc. The principal interest of this project was how to optimise printing in order to achieve high conversion, stable printing and avoid/mitigate the production of bubbles that have the effect of reducing the mechanical properties and affecting the optical clarity of the structures. This project explored the use of a library of components that would feed into the reaction, the reaction/mixing modes and their relationship to the quality of the product.

3D printed tablets using beeswax

Chris Strong

Chris's project investigated the possibility of printing a wax film of known composition to enable investigation of surfactant, agrochemical and fungal interactions with controlled wax film. The aim was to generate a film that modelled the behaviour of the Solanum lycopersicum fruit cuticle. The success of this project will help to further our understanding of why plant cuticles of different composition present their unique physical properties with the aim to predict these properties from the wax composition alone. This has significant implications with respect to agrochemical and surfactant development and the development of fungal resistant strains of plants. The development of such films was successful with variable properties depending on wax composition with the behaviour of these waxes being partially understood. Penetration of agrochemicals through the wax films has been achieved with a limited subsection of waxes and the crystalline properties that enable such behaviour identified.

Anna Lion

Anna's project focused on the design and development a solvent free, hot-melt based inkjet 3D system capable of producing multi-material solid dosage forms with tailorable release profiles. She has discovered a group of excipient materials that are suitable for pharmaceutical application as well as compatible with the hot-melt inkjet 3D printing process. Further analysis of their crystalline state, chemical composition and response to thermal stress where performance through the use of FTIR, XRD, DSC and TGA. These studies confirmed both excipient and active ingredient are chemically stable during and after the printing process. Based on the geometry and drug position within the printed tablet, this project has successfully achieved printed tablets with controlled release profiles: immediate, extended, delayed and pulsatile.

Marica Malenica

Despite its potential in creation of personalised and complex-shaped medical products (tablets, implants, medical devices), additive manufacturing is still underutilised in the biomedical industry, due to the lack of processable materials. This is particularly true for selective laser sintering (SLS). In order to circumvent the issue, core-shell particles have been designed that contain a shell made of biodegradable material which melts at low temperature and can be processed by SLS, and a core which remains unaffected. Three types of particles were prepared: all of them contained polycaprolactone as a shell material, while the core was made by photocuring one of the following monomers: 1,4-butanediol diacrylate; 1,6-hexanediol diacrylate or divinyl adipate. The particles were produced via: jet mixing, microfluidics and homogenizing, and jet mixing showed highest potential for continuous production of higher quantities of particles (up to several kg/hour). Finally, particles were successfully processed via selective laser sintering and binder jetting which proved their potential in additive manufacturing of biomedical products.

Evie Kingwood

Additive Manufacturing (AM) has been proven to show unique potential in the formulation of bespoke, personalised drug therapy due to its geometrical freedom. The utilisation of inkjet-based AM allows for multi-material deposition, widening the design scope further in terms of a device's material composition, and therefore increasing control and precision of drug placement and loading. Evie's project aimed to develop and exploit these technological advantages to produce biodegradable personalised implantable devices using RC1's generated poly(trimethylene carbonate methacrylate)-based inks with surface eroding tendencies to create a repeating pulsatile release pattern. Experimental areas include a vast range of material, part characterisation and process optimisation techniques including: NMR spectroscopy, Differential Scanning Calorimetry, Rheology, Drop Shape Analysis, Confocal microscopy, UV-Vis Spectroscopy, Dynamic Mechanical Analysis, Degradation testing, Dissolution testing, amongst others.


Making complex objects that are self-supporting

Research Challenge 3

How to formulate for structure and texture via the medium of 3D printing

Objective

Identifying edible materials suitable for printing and for control of textural and breakdown properties

The ability to selectively deposit materials or molecules within a 3D volume and hence gradate the composition (e.g. via direct manufacture of pores) offers the possibility for the control of complex structures for altering texture, taste and morphology in food products. Manipulation of microstructures by regulating mix and selective deposition of materials can allow regulation of fracture, breakdown or dissolution mechanics during product use, giving the possibility of a range of functional and novel foods.

While such manufacturing techniques are largely unheard of in large scale food production, there is significant interest and innovation in crude 'macro' scale food printing for the catering industry and niche food product markets. To drive this technology forward a significant increase in the knowledge of potential food materials for printing is needed, coupled with a focus on controlling structures at a smaller scale to build more complex multicomponent systems as ingredients for more conventional processes. With this knowledge significantly more sophisticated and personalised products can be offered when coupled with a point of sale or distributed manufacturing model.

Highlights:

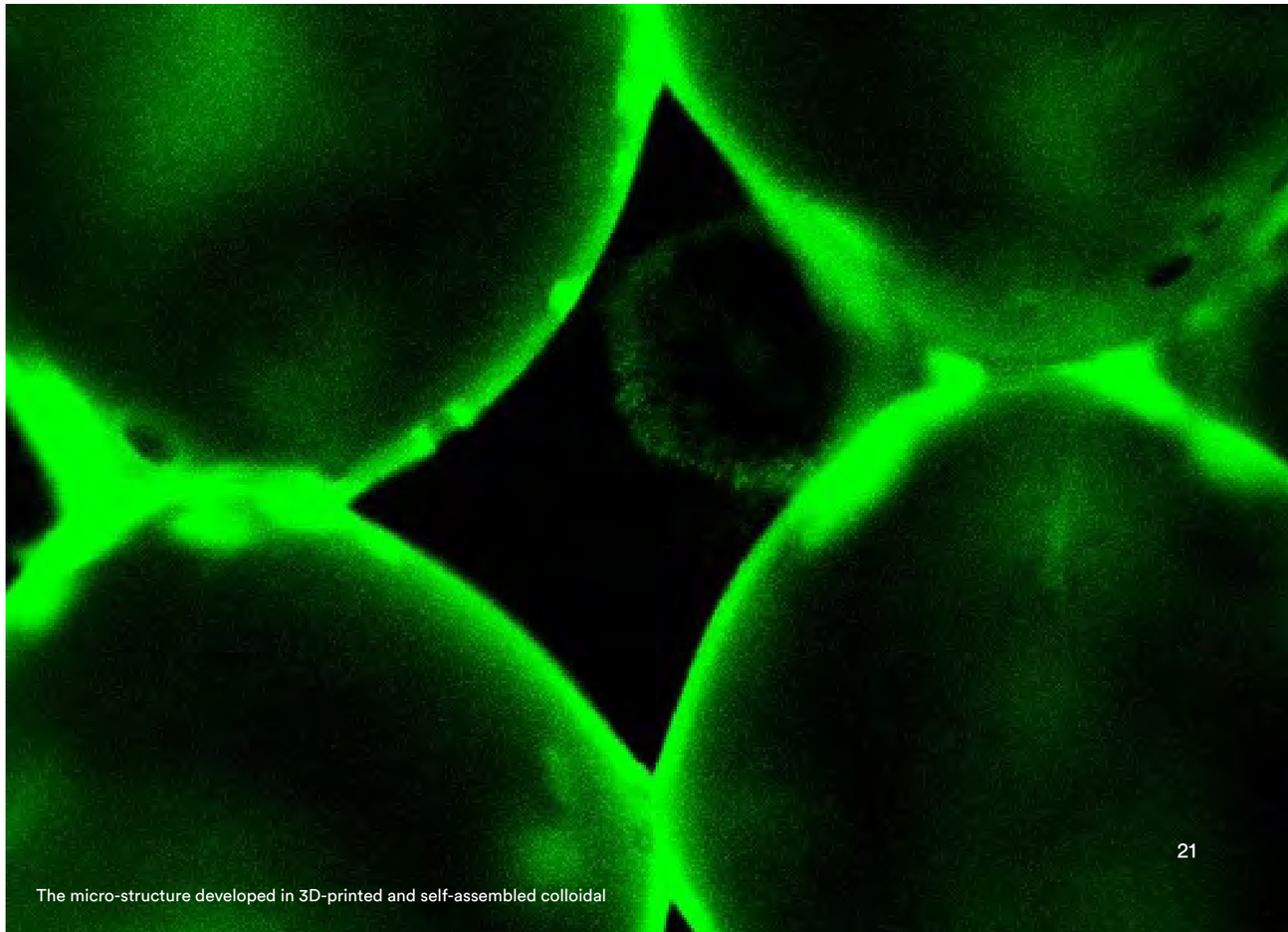
- We were able to demonstrate how 3D printing can be used to create food materials and utilise the design freedoms to create products with complex properties and shapes utilising commonly available foodstuffs combined in a way to realise new textures.
- We were able to show how 3D printing, due to its layer-by-layer approach, can lead to novel microstructures that emerge during the manufacturing process. These microstructures, which do not appear when using traditional techniques, can strongly affect flavour and texture and lead to ways in which we can create new tailored, food products.

Dr Saumil Vadodaria

Saumil worked towards the development of two-part edible inks which could be 3D printed using jetting-based printers, i.e. pneumatic jet and inkjet, to yield soft structures. The inks designed for pneumatic jet, through supramolecular interactions, transformed into complex gels with previously unreported microstructure upon printing. These complex gels could potentially be used for delivering flavours, nutrients and pharmacologically active compounds. On the other hand, the inks designed for inkjet led to thin films of water-in-oil emulsions with monodisperse size and a regular spatial distribution of water droplets, with potential applications in moisture-resistant barriers and transdermal delivery. Besides jetting-based printing, Saumil also contributed towards the development of thermoreversible gel formulations to be printed using Fused Deposition Manufacturing (FDM) type 3D printing. He facilitated the printing of these formulations by systematically transforming the printing equipment to suit the formulations.

Dr Azar Gholamipour-Shirazi

Azar's work focussed on developing design rules and predictive models of printability of food grade materials. Over the course of the project a library of printable yield stress hydrocolloids was developed. This library formed a springboard for material selection in associated work in controlled release. In addition a rheological property based model to predict printability was created to fast track screening of future cold extrudable materials. Proof of principle studies included the use of printed gels to control folic acid release in the presence of electric fields.


The micro-structure developed in 3D-printed and self-assembled colloidal

Dr Vincenzo Di Bari

Vincenzo's research aimed at mimicking plant epicuticular wax micro-architecture via hot-melt ink-jet 3D printing for water repellent biomimetic innovation. Natural plant waxes, currently an underutilised secondary by-product of the edible oil industry, were selected as feedstock materials. To exploit waxes thermo-reversible and self-assembly behaviour, the research focused on building a bottom-up-approach linking the chemical profile through the rheological, thermal and mechanical properties, to their 3D printing behaviour. The work demonstrated that wax-based multi-layered, composite structures can be successfully printed by tailoring wax feedstock and processing parameters.

Kilian Daffner

The objective of this research was to investigate high dairy protein-based formulations regarding applications for extrusion-based 3D-printing via the pH–T-route, inclusive a sol–gel transition of the feedstock. These dairy protein-based raw materials (casein and whey protein), which offer health benefits and have high satiating effects, were used to create and tailor novel edible formulations for applications in thermal extrusion printing. In-depth characterisation of high dairy protein-based formulations was conducted to expand the available feedstock of printable materials for thermal extrusion printing.

Rheological results were applied to mimic extrusion behaviour during potential printing applications and formulations differing in product and process parameters were analysed. The addition of whey protein and the change in process parameters allowed to modify the composition of the casein micelle, to change the type of casein–whey protein complexes and to manipulate the sol–gel transition temperature as well as the aggregation rate. Formulations differing in the concentration of the two main proteins as well as of the additional product parameter dairy fat, the pH at heating and the acidification pH were investigated in order to successfully print novel edible feedstock.

Michael Kamlov

Michael's work has been on the 3D printing of edible hydrocolloid gels, specifically focusing on kappa-carrageenan gels which undergo a sol-gel transition when lowered below its gelling temperature. This makes it very well suited to hot-extrusion 3D printing. While there are several studies on 3D printed hydrocolloid gels, there are few, if any, examining their performance compared to traditionally manufactured cast gels. This has been the primary goal of the research, with the first study testing 3% w/w 3D printed kappa-carrageenan gels against the cast equivalent through texture profile analysis and microscopy. After loading a model molecule (vitamin B1), the release kinetics from 3D printed kappa-carrageenan gels was studied. After this, an oil phase was introduced into the kappa-carrageenan solutions to create emulsion gels. The effect of increasing oil concentration (0-40% w/w sunflower oil) and two different emulsification agents (whey protein isolate and Tween 20) on the gels and their printability was assessed. A comparison was made against the cast and printed kappa-carrageenan emulsion gels by oscillatory rheology and texture profile analysis, as well through confocal light scanning microscopy to image the differences in the bulk structures. The work shows 3D printed hydrocolloids can be created with complex microstructure and be used for controlled release profiles that differ from cast gels alone.

Research Challenge 4

Feeding the pipeline for high-throughput formulation

Objective

Identifying and developing novel materials for 3D printing

To support the research objectives of RC1, 2 and 3, RC4 has and continues to produce organic-based materials that are designed to meet the process constraints of 3D printing whilst affording functional materials that address sector specific needs. Two methodologies, namely polymers and gelators, have been explored to create a portfolio of organic materials which can be used in a combinatorial approach to realise novel jetting inks.

Highlights:

- We were able to identify a family of gelators that work synergistically with (meth)acrylate or acrylamides to create dual network polymer systems, leading to highly favourable properties that one cannot achieve with single materials.
- Development of a library of supramolecular chemistries that have been screened to identify their potential as biomedical materials, where their diversity of structure leads a diversity of properties that can be exploited to target different tissues. Creation of composite materials based on silica nanoparticles that allow fine tuning of 3D printed object properties.

Preparing high-throughput deposits for testing critical mechanical and functional properties

Dr Lewis Hart

In order to discover the next generation of organic-based materials for 3D printing this work package is producing a diverse library of polymers (both covalent and supramolecular in nature, > 200 polymers) for a variety of 3D printing technologies. Biocompatible polyurethanes have been synthesised from a suite of initiators, monomers, linkers and terminal motifs to afford materials with desirable physical and mechanical properties. Future studies to be carried out in collaboration with Research Challenge 1 will focus on the development of detailed structure-property assays, the physical and mechanical characteristics of these materials will be established prior to formulation for inkjet printing feasibility studies of the optimum materials. 3D constructs will then be deposited for assessment in pharmaceutical and agrochemical delivery applications.

Dr Lea Santu

A library of small molecular weight gelators with hugely varying chemical functionality has been synthesised and their suitability for formulation of a large range of carrier media has been characterised. In addition, a comprehensive investigation of carrier composition and rheology effect on certain lead gelator structures has been assessed. To determine their printability parameters, gelators that act as viscosity modifiers are formulated as additives for 3D printing so that they can make single or multiple colloidal networks. The novel blends (gelator and monomers) are under investigation for preliminary jetting to select ideal candidates for 3D printing applications.

We are presently applying physicochemical models that will lead to knowledge that will be disseminated in publications, for example the synthesis and characterisation of sustainable sugar-derived gelators and the design and predictive application of low molecular weight gelators for the generation of new composite materials for 3D printing.

3D-printed tablets for personalised medicine

Dr Scott Wang

Converting gelators into 3D printing materials is not trivial. To achieve this we considered the rheological conditions, such as whether the material had a yield stress or was thixotropic, to screen potential formulations for 3D printing. Particularly important was the re-gelling time, which is the time taken for a material to reform a gel after it has been broken. This is critical in extrusion 3D printing since this defines how long it takes for a material to create self-supporting network that can support multiple layers of material deposited upon it.

3D printed complex interweaving structures through extrusion of supramolecular polymer melts

Sara Salimi

Sara's project focused on supplying functional supramolecular polymeric materials for different applications of 3D printing. Whilst high molecular weight polymers are desirable, they can be challenging to print as a result of high viscosity and poor processability. Supramolecular polymers are desirable as a result of their versatility as well as processability under 3D printing condition while exhibiting satisfactory mechanical properties. Dissociation of the supramolecular interactions in melt or solution gives rise to a formulation with low viscosity suitable for deposition. Consequently, the supramolecular material self assembles on the substrate surface to form pseudo-high molecular weight polymer networks with attractive physical characteristics to generate high-quality and high-resolution structures. The main objective of her project was to propose, research and investigate different methods of improving the mechanical properties of supramolecular materials by maintaining their processability. A variety of approaches including the incorporation of inorganic filler such as silica or iron oxide nanoparticles as well as organic fillers i.e. Low Molecular weight Additives (LMWAs) and Gelators (LMWGs) were studied and reported. For example, we were able to 3D print a bar sample using a Reactive Extrusion Printer to generate a part with mechanically gradient properties which has been produced by variation of the concentration of LMWAs along the axis during deposition.

Glenieliz-Glyssa Dizon

In recent years, low molecular weight gelators (LMWGs) have been the subject of intensive research. They are an important class of functional materials, finding application in various industries such as cosmetics, food processing, healthcare and additive manufacturing. This research successfully synthesised novel 'green' LMWGs containing acetal groups from naturally occurring sugar alcohols. These compounds were characterised and tested for their gelation abilities in organic solvents, aqueous solutions and UV curable monomers. The formed gels in the UV curable monomers were polymerised via radical polymerisation. Dynamic mechanical analyses were studied on the materials (gels and the polymers) to determine and compare the strength of their networks. The results show that the gelators positively influence the rheology of the materials. The effect of solvent on the self-assembly morphology of these gelators was investigated via scanning electron microscope (SEM). By virtue of π-π interaction, on a particular lead gelator, 1,3:2,4-di(4-isopropylbenzylidene-D-sorbitol (DBS-iPr) undergoes gelation in polar solvents to form smooth non-helical fibres. In contrast, gelation in non-polar solvents such as cyclohexane, aided by hydrogen bonding interactions, results in helical fibres. The investigation of 3D printing application inks using the synthesised gelators will be the subject of future work.

Publications

Nöbel S, Seifert B, Daffner K, Schäfer J, Hinrichs J. (2021). Instantaneous gelation of acid milk gels via customised temperature-time profiles: Screening of concentration and pH suitable for temperature triggered gelation towards 3D-printing. *Food Hydrocolloids,* doi: 10.1016/j.foodhyd.2020.106450

Ruiz Cantu L, F Trindade G, Taresco V, Zhou Z, He Y, Burroughs L, Wildman RD. (2021). Bespoke 3D-Printed Polydrug Implants Created via Microstructural Control of Oligomers. *ACS applied materials & interfaces,* doi: 10.1021/acsami.1c07850

Jacob P, Ruiz Cantu L, Pearce A, He Y, Lentz J, Moore J, Taresco V. (2021). Poly (glycerol adipate) (PGA) backbone modifications with a library of functional diols: Chemical and physical effects. Polymer, doi: 10.1021/acsami.1c07850

He Y, Abdi M, Trindade GF, Begines B, Dubern JF, Prina E, Wildman RD. (2021). Exploiting Generative Design for 3D Printing of Bacterial Biofilm Resistant Composite Devices. Advanced science (*Weinheim, Baden-Wurttemberg, Germany*), doi: 10.1002/advs.202100249

He Y, Vallières C, Alexander MR, Wildman RD, Avery SV. (2021). Inkjet 3D Printing of Polymers Resistant to Fungal Attachment. *Bio-protocol,* doi: 10.21769/bioprotoc.4016

Zhou Z, Samperi M, Santu L, Dizon G, Aboarkaba S, Limón D, Wildman R. (2021). An imidazolium-based supramolecular gelator enhancing interlayer adhesion in 3D printed dual network hydrogels. *Materials & Design*, doi: 10.1016/j.matdes.2021.109792

Daffner K, Vadodaria S, Ong L, Nöbel S, Gras S, Norton I, Mills T. (2021). Design and characterization of casein–whey protein suspensions via the pH–temperature-route for application in extrusion-based 3D-Printing. *Food Hydrocolloids*, doi: 10.1016/j.foodhyd.2020.105850

Ding J, Baumers M, Clark E, Wildman R. (2021). The economics of additive manufacturing: Towards a general cost model including process failure. *International Journal of Production Economics*, doi: 10.1016/j.ijpe.2021.108087

Clark EA, Alexander MR, Irvine DJ, Roberts CJ, Wallace MJ, Yoo J, Wildman RD. (2020). Making tablets for delivery of poorly soluble drugs using photoinitiated 3D inkjet printing. *International journal of pharmaceutics,* doi: 10.1016/j.ijpharm.2019.118805

Gholamipour-Shirazi A, Kamlow MA, T Norton I, Mills T. (2020). How to Formulate for Structure and Texture via Medium of Additive Manufacturing-A Review. Foods (*Basel, Switzerland*), doi: 10.3390/foods9040497

He Y, Foralosso R, Trindade G, Ilchev A, Ruiz Cantu L, Clark E, Wildman R. (2020). A Reactive Prodrug Ink Formulation Strategy for Inkjet 3D Printing of Controlled Release Dosage Forms and Implants. *Advanced Therapeutics*, doi: 10.1002/adtp.201900187

Daffner K, Hanssen E, Norton I, Mills T, Ong L, Gras S. (2020). Imaging of dairy emulsions via a novel approach of transmission electron cryogenic microscopy using beam exposure. *Soft Matter*, doi: 10.1039/D0SM00582G

Dizon GC, Atkinson G, Argent SP, Santu LT, Amabilino DB. (2020). Sustainable sorbitol-derived compounds for gelation of the full range of ethanol-water mixtures. *Soft matter, 16*(19), doi: 10.1039/D0SM00343C

Samperi M, Limón D, Amabilino D, Pérez-García L. (2020). Enhancing Singlet Oxygen Generation by Self-Assembly of a Porphyrin Entrapped in Supramolecular Fibers. *Cell Reports Physical Science*, doi: 10.1016/j.xcrp.2020.100030

Vadodaria S, He Y, Mills T, Wildman R. (2020). Fabrication of surfactant-polyelectrolyte complex using valvejet 3D printing-aided colloidal self assembly. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, doi: 10.1016/j.colsurfa.2020.124914

Vallieres C, Hook AL, He Y, Crucitti VC, Figueredo G, Davies CR, Avery SV. (2020). Discovery of (meth) acrylate polymers that resist colonization by fungi associated with pathogenesis and biodeterioration. *Science advances,* doi: 10.1126/sciadv.aba6574

Salimi S, Wu Y, Barreiros M, Natfji A, Khaled S, Wildman R, Hayes W. (2020). A 3D printed drug delivery implant formed from a dynamic supramolecular polyurethane formulation. *Polymer Chemistry*, doi: 10.1039/D0PY00068J

Samperi M, Pérez-García L, Amabilino DB. (2019). Quantification of energy of activation to supramolecular nanofibre formation reveals enthalpic and entropic effects and morphological consequence. *Chemical science,* doi: 10.1039/C9SC03280K

Zhou Z, Ruiz Cantu L, Chen X, Alexander M, Roberts C, Hague R, Wildman R. (2019). High-throughput characterization of fluid properties to predict droplet ejection for three-dimensional inkjet printing formulations. *Additive Manufacturing*, doi: 10.1016/j.addma.2019.100792

Begines B, Alcudia A, Aguilera-Velazquez R, Martinez G, He Y, Trindade GF, Prado-Gotor R. (2019). Design of highly stabilised nanocomposite inks based on biodegradable polymer-matrix and gold nanoparticles for Inkjet Printing. *Scientific reports*, doi: 10.1038/s41598-019-52314-2

Cader HK, Rance GA, Alexander MR, Gonçalves AD, Roberts CJ, Tuck CJ, Wildman RD. (2019). Water-based 3D inkjet printing of an oral pharmaceutical dosage form. *International journal of pharmaceutics,* doi: 10.1016/j.ijpharm.2019.04.026

Gholamipour-Shirazi A, Norton I, Mills T. (2019). Designing hydrocolloid based food-ink formulations for extrusion 3D printing. *Food Hydrocolloids*, doi: 10.1016/j.foodhyd.2019.04.011

Rodriguez-Salvador M, Ruiz Cantu L. (2019). Revealing emerging science and technology research for dentistry applications of 3D bioprinting. *International journal of bioprinting,* doi: 10.18063/ijb.v5i1.170

Ruiz Cantu L, Pearce A, Burroughs L, Bennett T, Vasey C, Wildman R, Taresco V. (2019). Synthesis of Methacrylate-Terminated Block Copolymers with Reduced Transesterification by Controlled Ring-Opening Polymerization. *Macromolecular Chemistry and Physics*, doi: 10.1002/macp.201800459

Salimi S, Hart L, Feula A, Hermida-Merino D, Touré A, Kabova E, Hayes W. (2019). Property enhancement of healable supramolecular polyurethanes. *European Polymer Journal*, doi: 10.1016/j.eurpolymj.2019.05.042

Hermida-Merino D, O'Driscoll B, Hart L, Harris P, Colquhoun H, Slark A, Hayes W. (2018). Enhancement of microphase ordering and mechanical properties of supramolecular hydrogen-bonded polyurethane networks. *Polymer Chemistry*, doi: 10.1039/C8PY00604K

Khaled SA, Alexander MR, Wildman RD, Wallace MJ, Sharpe S, Yoo J, Roberts CJ. (2018). 3D extrusion printing of high drug loading immediate release paracetamol tablets. *International journal of pharmaceutics,* doi: 10.1016/j.ijpharm.2018.01.024

Khaled SA, Alexander MR, Irvine DJ, Wildman RD, Wallace MJ, Sharpe S, Roberts CJ. (2018). Extrusion 3D Printing of Paracetamol Tablets from a Single Formulation with Tunable Release Profiles Through Control of Tablet Geometry. *AAPS PharmSciTech, 19*(8), doi: 10.1208/s12249-018-1107-z

Louzao I, Koch B, Taresco V, Ruiz Cantu L, Irvine D, Roberts C, Alexander M. (2018). Identification of Novel "Inks" for 3D Printing Using High-Throughput Screening: Bioresorbable Photocurable Polymers for Controlled Drug Delivery. *ACS Applied Materials & Interfaces,* doi: 10.1021/acsami.7b15677

Clark EA, Alexander MR, Irvine DJ, Roberts CJ, Wallace MJ, Sharpe S, Wildman RD. (2017). 3D printing of tablets using inkjet with UV photoinitiation. *International journal of pharmaceutics,* doi: 10.1016/j.ijpharm.2017.06.085

Sathyanarayanan G, Rodrigues M, Limón D, Rodriguez-Trujillo R, Puigmartí-Luis J, Pérez-García L, Amabilino D. (2017). Drug-Loaded Supramolecular Gels Prepared in a Microfluidic Platform: Distinctive Rheology and Delivery through Controlled Far-from-Equilibrium Mixing. *ACS Omega*, doi: 10.1021/acsomega.7b01800

Lion A, Wildman RD, Alexander MR, Roberts CJ, (2021) Customisable Tablet Printing: The Development of Multimaterial Hot Melt Inkjet 3D Printing to Produce Complex and Personalised Dosage Forms. *Pharmaceutics,* doi: 10.3390/pharmaceutics13101679

He Y, Begines B, Luckett J, Dubern J, Hook A, Prina E, Rose F, Tuck C, Richard H Irvine D, Williams P, Alexander M, Wildman R (2020) Inkjet based 3D Printing of bespoke medical devices that resist bacterial biofilm formation, *BioRxiv,* doi: 10.1101/2020.06.30.180596

He Y, Luckett J, Begines B, Dubern J, Hook A, Prina E, Rose F, Tuck C, Richard H, Irvine D, Williams P, Alexander M, Wildman R (2021) Ink-jet 3D printing as a strategy for developing bespoke non-eluting biofilm resistant medical devices, Biomaterials, doi: 10.1016/j.biomaterials.2021.121350

Outreach

The Royal Society Summer Science Exhibition

The 'Formulation for 3D Printing' team had the exciting opportunity to be part of the "Summer Science hub" at The Royal Society Summer Science Exhibition 2021 with the theme "Can we print your perfect pill". We made a movie[1], a virtual game[3] and a lightning lecture[2], with contributions across the team, allowing the public to take a virtual step into our lab and learn about how and why we are working to create 3D printed medicine.

With our movie we told the story of how polypills can lighten the pill burden, while with our game we put the player in the shoes of a pharmacist who has to manage a queue of patients! Our lightning lecture was seen by over 16,000 people and was hosted by Dr Ruiz Cantu and Dr He who told the story of why we need to 3D print tablets.

During the exhibition, we were delighted to talk about our research with BBC Radio 4 programme 'Inside Science', with BBC Radio Nottingham and had a spot on Al Jazeera English TV.

[1] www.youtube.com/watch?v=m4nUbSjKsII&ab_channel=TheRoyalSociety

[2] www.youtube.com/watch?v=C05tBuY2PEw&list=PLg7f-TkW11iVmGf4Sexj_akSICGQ6vyEa&index=3&ab_channel=TheRoyalSociety

[3] https://limitless-beach-00824.herokuapp.com/

University of Nottingham
UK | CHINA | MALAYSIA

ROYAL SOCIETY OF CHEMISTRY

Centre for Additive Manufacturing

Al Jazeera English TV crew filming in the CfAM lab

Lead collaborators

Martin Wallace
GlaxoSmithKline

Faheem Padia
Syngenta

John Duffy
Malvern Panalytical Ltd

Adam Kowalski
Unilever

David Fenn
PPG

For general enquiries please contact

The Centre for Additive Manufacturing
Faculty of Engineering
Advanced Manufacturing Building
Jubilee Campus
University of Nottingham
Nottingham
NG8 1BB

CfAM@nottingham.ac.uk

nottingham.ac.uk/CfAM

This publication is available in alternative formats:
+44 (0)115 951 5559

Printed March 2022.