INNOVATIONS IN 3D PRINTED PHARMACEUTICALS

In this article, Sarah Trenfield, PhD Researcher at University College London (UCL); Abdul Basit, PhD, Professor of Pharmaceutics at UCL and Co-Founder of FabRx; and Alvaro Goyanes, PhD, Co-Founder and Director of Development at FabRx, discuss the latest innovations in 3D printed pharmaceuticals.

Three-dimensional (3D) printing is causing a paradigm shift in the way medicines are designed, manufactured and administered. Conventional pharmaceutical manufacturing processes were first introduced around 200 years ago and, despite the significant technological advancements made so far during the 21st century, many of these are still in use today.

Although these methods are cost-effective for large-scale production, they can be inherently time-consuming, labour intensive and dose inflexible. This poses significant challenges for those patient groups that require tailored dosing (such as within paediatrics and geriatrics) or for certain medicines that require frequent dose adjustments based on blood levels (e.g. narrow therapeutic index drugs).

This often requires patients to split or crush and weigh formulations or pharmacists to extemporaneously prepare the formulations in hospitals, to achieve the correct dose – increasing the risk of medication error and inconsistency. To overcome these challenges, in recent years there has been a considerable push to move away from treating patients via a "one-size-fits-all" approach. Crucially, a report from NHS England (UK) showed that up to 70% of patients do not gain efficacy from the traditional mass manufacturing approaches.[1]

To achieve greater efficacy, the use of innovative technologies is required within pharmaceuticals to facilitate the production of small-scale, dose-flexible formulations. One technology which has great potential here is 3D printing – an additive manufacturing process enabling the design of

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Figure 1: FabRx's M3DIMAKER™ 3D printing technology for personalised medicine production.

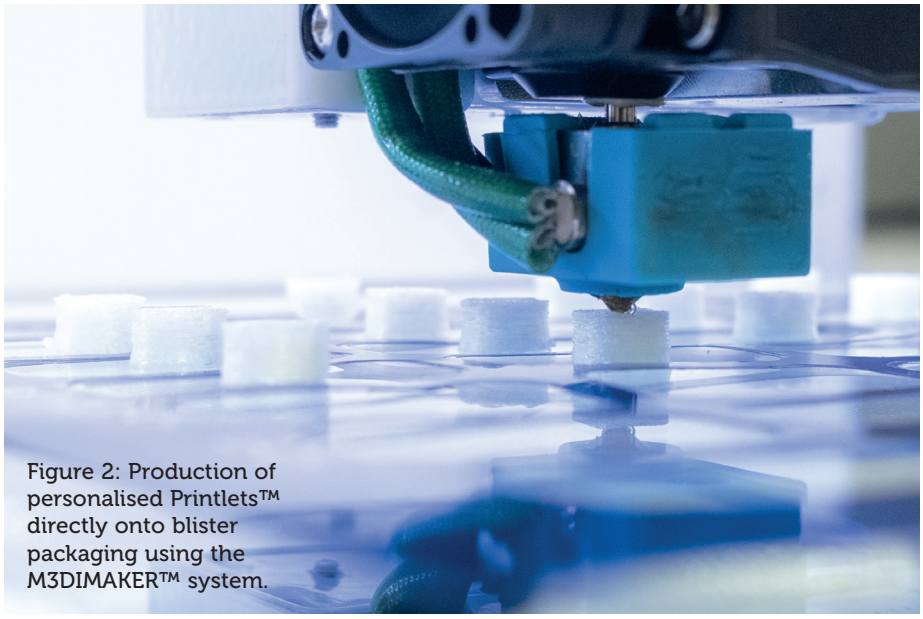

Figure 2: Production of personalised Printlets™ directly onto blister packaging using the M3DIMAKER™ system.

oral dosage forms using computer-aided design (CAD) software for the on-demand, layer-by-layer production of Printlets™ (3D printed tablets).[2,3]

Over the last seven years, FabRx has pioneered the use of 3D printing technologies for the production of personalised pharmaceuticals and medical devices, with a vision to revolutionise the way tablets are manufactured – moving away from a one-size-fits-all approach towards the production of personalised medicines at the point of care.

In 2020, FabRx launched the world's first 3D printer for personalised medicines (M3DIMAKER™) which is designed for the small-batch production of highly flexible drug products (tailored dosages, drug release, geometries and multiple drugs) to provide a truly personalised approach for patient care. Indeed, the M3DIMAKER™ platform could be used throughout the drug development timeline, ranging from research and development, preclinical studies, and first-in-human (FIH) clinical trials all the way through to front-line medical care.

M3DIMAKER™: FABRX'S PHARMACEUTICAL 3D PRINTER

FabRx's breakthrough 3D printer, the M3DIMAKER™, aims to deliver unique personalised medicines with appearance and dosages that can be tailored directly to the patient on demand (Figure 1).[4] The groundbreaking additive manufacturing technology can produce Printlets™ with a precise dose and tailored drug release – and can even combine multiple medications into a single "polypill" for patients with complicated medication regimens.

The M3DIMAKER™ consists of a sleek hardware system that is controlled by specialised user-friendly software, enabling the required dose to be easily selected by the pharmacist or user to achieve the needs of the patient or research outcome (Figure 2).

The key features of FabRx's M3DIMAKER™ technology include:

- User-friendly software – FabRx's specialised software enables the required dose to be easily printed by the pharmacist or user according to the needs of the patient or research aims.
- Multi-nozzle printing system – the M3DIMAKER™ is an alternating nozzle system, giving users the choice between three different extrusion printing nozzles and so allowing the user to easily adapt the system to their manufacturing needs.
- Able to be validated to GMP – the M3DIMAKER™ has been developed in close communication with regulatory agencies (e.g. the UK MHRA, the Spanish AEMPS, the US FDA and the EU EMA) and hospital end users in order to create a system that is fit for purpose.[5] Due to the hardware design and materials used in production, the M3DIMAKER™ is able to be validated to GMP requirements for research and clinical manufacture.
- Assured quality control and security – the system is fitted with advanced in-line quality control and security measures, alongside camera monitoring of the printing process, to track the progress and detect any faults during manufacture. Incorporation of a modern fingerprint access control alongside a data matrix reader ensures manufacturing reliability, enabling only qualified personnel to have access to the technology's features.
- High throughput and low wastage – the preparation of one-month's medication (28 Printlets™) can be carried out in approximately eight minutes, revolutionising the drug manufacture timeline.
- Compact and versatile – as the printer is compact (bench-top size) and easily portable, an on-demand manufacture of pharmaceuticals in a wide variety of settings (research, clinical trials and within clinical settings) can be achieved.
- Affordable cost – the M3DIMAKER™ has been designed with the budgets of the end users in mind, providing a cost-effective approach to small-batch manufacture.

The M3DIMAKER™ system can formulate a wide variety of drugs, ranging from small molecule compounds through to large molecules and biologics, including antibodies. These advantages could benefit clinical practice, specials manufacturing companies and pharmaceutical companies seeking to deliver their active in a personalised and more cost-effective manner. Using the FabRx M3DIMAKER™, the drug products produced may generate increased revenue due to enhanced medication adherence and improved efficacy and safety profiles, as well as increased product margins via premium pricing.

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WORLD FIRST CLINICAL STUDY

As a world first, FabRx's personalised medicine 3D printer was integrated into a hospital setting to treat children (3–16 years) with a severe metabolic disorder – maple syrup urine disease (MSUD).[6] The first-line therapy for MSUD involves the personalised oral supplementation of isoleucine; the dose of which is tailored according to blood levels. In current clinical practice, however, practitioners are required to extemporaneously prepare formulations (via weighing powder and manually filling capsules) due to the lack of commercially available oral treatments for MSUD.

To overcome these challenges, FabRx's 3D printer was integrated into the pharmacy department of the University Clinical Hospital in Santiago de Compostela (Spain). This innovation enabled the production of chewable and palatable Printlets™ containing isoleucine in a variety of dosages, colours and flavours (Figure 3), which were evaluated for patient acceptability and therapy control. The researchers found that 3D printing enabled tighter control over target blood concentrations compared with the standard therapy (capsules) – and that the flavours and colours of the 3D printed dosage forms were well accepted amongst all patients.

This study was a significant milestone in 3D printing history and demonstrated the true benefits of such technology in the pharmaceutical arena.

OTHER FABRX 3D PRINTING TECHNOLOGIES

Alongside the M3DIMAKER™, FabRx has extensive experience in formulation development and a wide range of 3D printing technologies, including fused deposition modelling (FDM), selective laser sintering (SLS) and stereolithography (SLA). FDM is an extrusion-based technology which has the capability to manufacture multiple-drug combinations (polypills) as well as sustained- or delayed-release tablets. SLS incorporates a laser which is used to create drug-loaded Printlets™ with various characteristics, ranging from orodispersible to controlled-release dosage forms.[7] To manufacture sustained-release medical devices and drug-loaded Printlets™, FabRx can use SLA 3D printing, which is capable of using a light to transform a liquid into solid parts.

Furthermore, in 2019, FabRx developed a revolutionary new 3D printing system for the production of pharmaceuticals. The novel printing system, known as direct powder extrusion (DPE), enables the production of drug products in a single-step process directly from powdered materials – avoiding the time-consuming steps usually required to produce 3D printer filament feedstock used in FDM printing.[8] This technology enables flexible and tailored dosing with minimal development times, showing promise in the field of preclinical studies or early phase clinical trials.

"The benefits of 3D printing could also have a wide-reaching impact on global health."

LATEST INNOVATIONS IN 3D PRINTED MEDICINES

Due to the highly flexible nature of 3D printing processes, this technology enables the generation of drug products that would be impossible to produce using conventional manufacturing processes. For example, using SLS, the University College London (UCL) and FabRx team was able to produce orodispersible Printlets™ that were designed to have Braille and Moon patterns on the surface, providing an innovative and practical medicine strategy for patients with visual impairment (Table 1).[9]

In particular, Printlets™ with different shapes were fabricated to offer additional information, such as the medication indication or its dosing regimen. Despite the presence of the patterns, the Printlets™ were found to retain their original mechanical properties and dissolution characteristics and disintegrated within approximately five seconds, avoiding the need for water and facilitating self-administration of medications. Such a concept could revolutionise medicine taking for patients with visual impairment, e.g. by reducing medication errors and supporting increased independence.

The benefits of 3D printing could also have a wide-reaching impact on global health, tackling the challenges arising from opioid abuse. The UCL and FabRx team, in collaboration with Nisso Chemical Europe (Düsseldorf, Germany), devised a

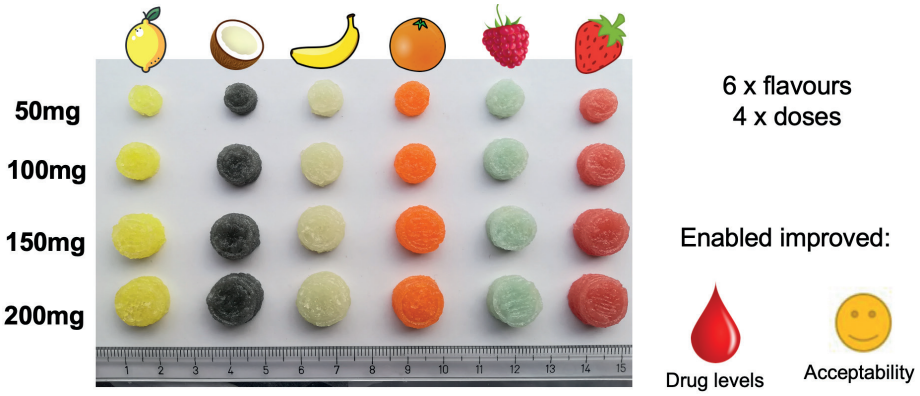


Figure 3: FabRx formulations used in a clinical study for the treatment of children with a severe metabolic disease – MSUD.

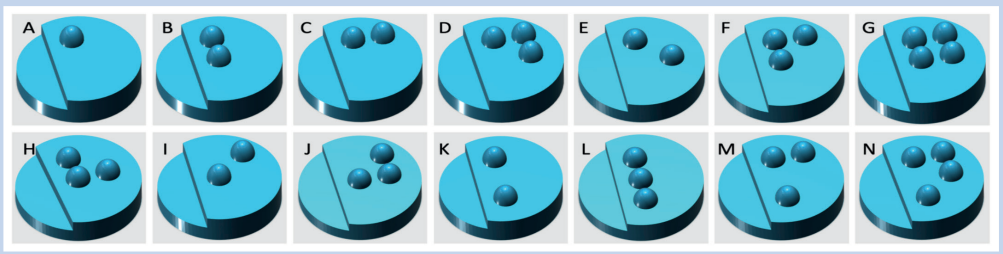
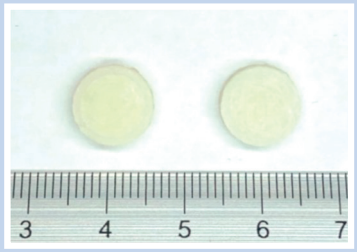
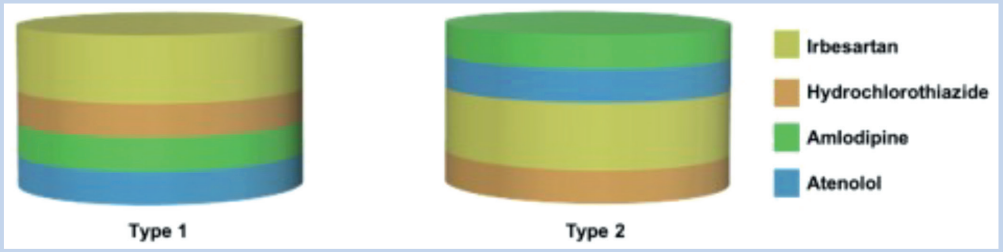
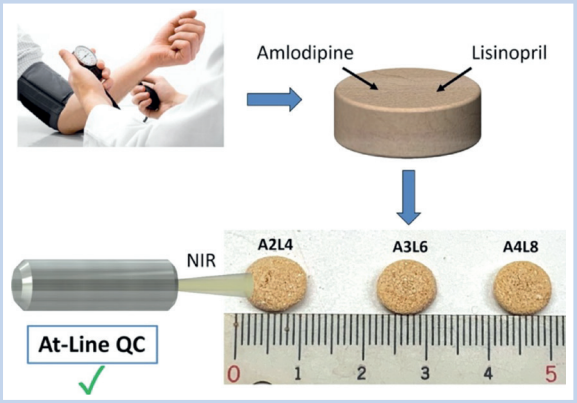
Description	Image	Reference
3D printed tablets with Braille and Moon patterns for visual impairment		9
3D printed tablets with opioid abuse-deterrent properties		10
Four layered polypill in two conformations		12
Dose verification of 3D printed antihypertensive polypills		13

Table 1: Novel applications of 3D printing using FabRx 3D printing technologies.

novel formulation strategy whereby abuse-deterrent 3D printed formulations were produced using DPE, a technology devised by FabRx (Table 1). In this study, DPE enabled the production of modified-release drug products containing tramadol in a single-step process directly from powdered materials.[10] This technology was capable of preparing drug products with both alcohol-resistant and abuse-deterrent properties, offering a novel approach for the safe and effective use of opioids.

3D printing could also be useful for patients who are prescribed complex medication regimes, such as in the case of polypharmacy – the administration of more than one medicine – which can lead to confusion and errors in medication management. FabRx has used SLA to print multiple drugs into the same dosage form to create 3D printed polypills (aka polyPrintlets™).[11]

As an example, four different drugs were printed in two multi-layered configurations, reducing the number of tablets from four a day to just one (Table 1).[12] In another study, the team produced antihypertensive polyPrintlets™ using SLS containing personalised dosages of two drugs (amlodipine and lisinopril) which then underwent a real-time quality control process using spectroscopic methods to confirm the dosage of the APIs within the formulation.[13] Such a concept revolutionises the capability for on-demand quality control and dispensing of 3D printed dosage forms at the point of care.

CONCLUSION

The potential for 3D printing to transform pharmaceutical practice is evident. Indeed, 3D printing systems can revolutionise formulation production to move away from mass manufacture to the production of highly flexible and personalised dosage forms on demand, providing benefits from research and development through to clinical care. The April 2020 launch of the world's first personalised medicine 3D printer, FabRx M3DIMAKER™, is a significant milestone in

the history of this technology, and is driving forward the use of 3D printing technologies in pharmaceuticals to make treatments safer and more effective for patients around the world.

ABOUT THE COMPANY

FabRx was established in 2014 by leading academics from UCL and is experienced in the application of 3D printing technology for medicines and medical devices. Since its initiation, FabRx has developed more than seven different types of pharmaceutical 3D printers and, in 2017, won the TCT Best Start Up Award. In 2018, FabRx was awarded a grant totalling nearly £1 million from Innovate UK to develop the world's first personalised medicine 3D printer (M3DIMAKER™) and conducted a world first clinical study using its Printlets™ technology in 2019.

REFERENCES

1. *"Improving Outcomes Through Personalised Medicine". NHS, September 7, 2016.*
2. *Trenfield SJ, Awad A, Madla CM, Hatton GB, Firth J, Goyanes A, Gaisford S, Basit AW, "Shaping the future: recent advances of 3D printing in drug delivery and healthcare". Expert Opin Drug Deliv, 2019, Vol 16, pp 1081-1094.*
3. *Basit A, Gaisford S, "3D Printing of Pharmaceuticals". Springer International Publishing, 2018.*
4. *"FabRx's pharmaceutical 3D printer for personalised medicines, M3DIMAKER™, is now available!". Press Release, FabRx, April 6, 2020.*
5. *"FabRx meet with the MHRA and AEMPS to discuss 3D printing for personalised medicines". Press Release, FabRx, April 11, 2019.*
6. *Goyanes A, Madla CM, Umerji A, Duran Piñeiro G, Giraldez Montero JM, Lamas Diaz MJ, Gonzalez Barcia M, Taherali F, Sánchez-Pintos P, Couce ML, Gaisford S, Basit AW, "Automated therapy preparation of isoleucine formulations using 3D printing for the treatment of MSUD: First single-centre, prospective, crossover study in patients". Int J Pharm, 2019, Vol 567, 118497.*
7. *Allahham N, Fina F, Marcuta C, Kraschew L, Mohr W, Gaisford S, Basit WA, Goyanes A, "Selective Laser Sintering 3D Printing of Orally Disintegrating Printlets™ Containing Ondansetron". Pharmaceutics, 2020, Vol 12 (2), pp 110.*
8. *Goyanes A, Allahham N, Trenfield SJ, Stoyanov E, Gaisford S, Basit AW, "Direct powder extrusion 3D printing: Fabrication of drug products using a novel single-step process". Int J Pharm, 2019, Vol 567, 118471.*
9. *Awad A, Yao A, Trenfield SJ, Goyanes A, Gaisford S, Basit WA, "3D Printed Tablets (Printlets™) with Braille and Moon Patterns for Visually Impaired Patients". Pharmaceutics, 2020, Vol 12, pp 172.*
10. *Ong JJ, Awad A, Martorana A, Gaisford S, Stoyanov E, Basit AW, Goyanes A, "3D printed opioid medicines with alcohol-resistant and abuse-deterrent properties". Int J Pharm, 2020, Vol 579, 119169.*
11. *Robles-Martinez P, Xu X, Trenfield JS, Awad A, Goyanes A, Telford R, Basit WA, Gaisford S, "3D Printing of a Multi-Layered Polypill Containing Six Drugs Using a Novel Stereolithographic Method". Pharmaceutics, 2019, Vol 11 (6), pp 274.*
12. *Xu X, Robles-Martinez P, Madla CM, Joubert F, Goyanes A, Basit AW, Gaisford S, "Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction." Additive Manufacturing, 2020, Vol 33, 101071.*
13. *Trenfield SJ, Tan HX, Goyanes A, Wilsdon D, Rowland M, Gaisford S, Basit AW, "Non-destructive dose verification of two drugs within 3D printed polyprintlets". Int J Pharm, 2020, Vol 577, 119066.*

ABOUT THE AUTHORS

Sarah Trenfield is a PhD Researcher at UCL specialising in developing 3D printed technology for pharmaceuticals. She qualified with a first-class Pharmacy degree from Cardiff University in 2015 and undertook her pre-registration year at Merck Sharpe and Dohme. In 2016, Ms Trenfield successfully registered as a Pharmacist and began studying for her PhD on 3D printed medicines. Since then, she has authored more than 21 publications on the topic and has received a number of prestigious awards.

Abdul Basit holds the position of Professor of Pharmaceutics at the UCL School of Pharmacy. He is a leading authority on oral drug delivery, digital health and innovative pharmaceutical technologies including 3D printing. Professor Basit is also a world authority on translational research; he has founded two spin-out companies (FabRx and Intract Pharma) and has invented several drug products that have entered the clinic.

Alvaro Goyanes is the Co-Founder and Development Director at FabRx, as well as an honorary lecturer at UCL and a lecturer at the University of Santiago de Compostela (Spain). He was one of the first researchers assessing opportunities of 3D printing to manufacture personalised oral dosage forms and medical devices. Dr Goyanes is a recognised world expert in the 3D printing of medicines and has worked as a Registered Pharmacist so has first-hand knowledge of pharmaceutical needs in clinical settings.