# BRINGING A WHOLE NEW DIMENSION TO LACTOSE

## Lactose Learnings and Evidence Building on 3D Printing in Pharma

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# Lactose learning and evidence building on 3D printing in Pharma

ARE YOU READY FOR THE FUTURE

From enabling personalised medicine to accelerating the drug development pathway, 3D printing offers huge potential in pharmaceutical manufacturing. In order to embrace this new world of opportunities, we need a deeper understanding of the materials, processes and techniques involved.

Information on the most effective use of excipients, for example, has, until now, been lacking. But a model of collaborative working, that has led to this detailed study on printed lactose, is starting to change that. While this area of research is still in its infancy and every use case is unique, the research set out in this whitepaper shows that lactose – and collaboration – are yielding results.

We now invite industry, innovators and academia alike to review the data and to continue working together with us to develop a deeper understanding of the 3D printing of pharmaceuticals. By pooling knowledge and expertise, we can quickly and efficiently build the evidence base we need to contribute to timely, patient-centred medicine development.

*K.A. van den Heuvel-Jansen &*
*C.J. Wiebinga*

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*Tablets need to adapt to the demands of 21st Century healthcare. They must be easier to make, easier to take and easier to personalise.*

# Challenges and opportunities

Despite tablets being the main mode of pharmaceutical delivery worldwide, there are major challenges both in the way they are made and the way they are taken.

Traditional facilities, accustomed to operating in the blockbuster drug era, are not geared towards the small-scale production needed for clinical trials or orphan drugs, or the creation of designer tablets for personalised medicine.

Taste, mouthfeel or solubility can make tablets hard to take, particularly for very young or old people. Matters only get worse when they need to take multiple tablets, because of co-morbidities or during complex clinical trials, for example.

Tablets also have a lack of dose flexibility that means breaking them into segments is the only way to deliver smaller measurements to children. This is imprecise and unscientific.

# 3D printing: the next frontier

As well as dose flexibility, 3D printing can mask taste, enhance solubility and modify shape, producing tablets that geriatric and paediatric populations find easier to take.

Tablets with multiple APIs are easy to fabricate, and 3D printing even allows for the delivery of multiple medications, with multiple time release options, in a single tablet.

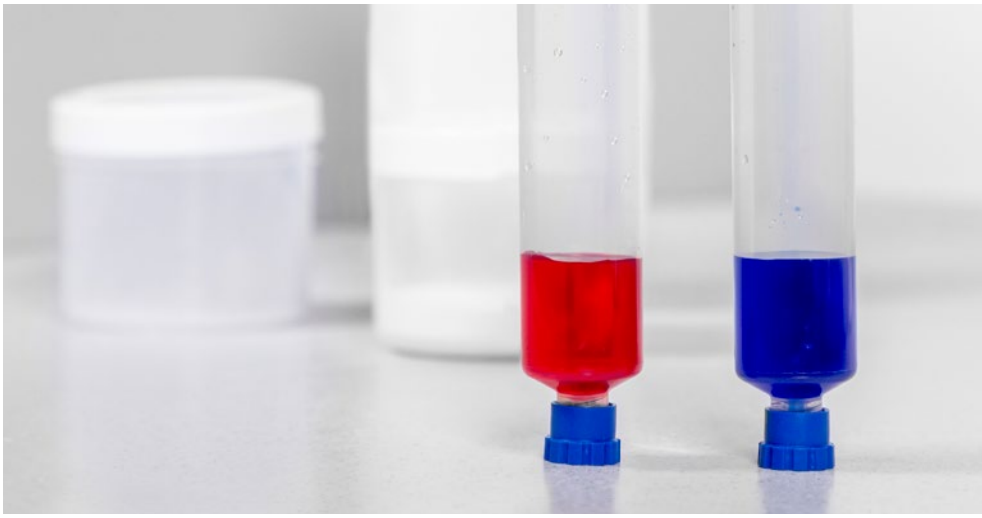
It enables patient-tailored medicine to be “printed” on demand in pharmacies or hospitals, making it particularly useful for orphan drugs and personalised medicines, and holds huge potential in the clinical trial space, which has a constant demand for bespoke, small-scale batches.

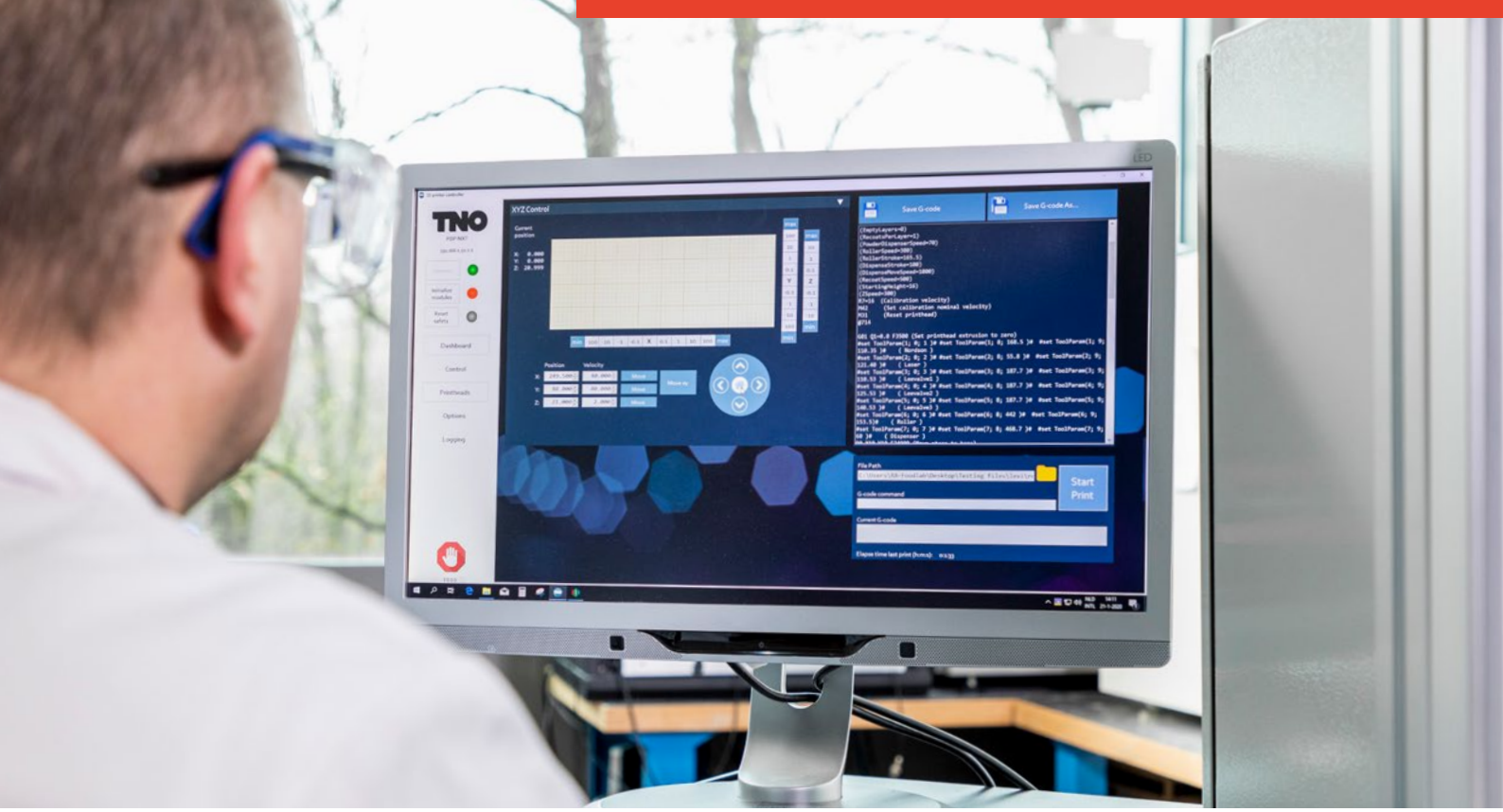
What’s more, the 3D printing of medications can, potentially accelerate the scaling up of manufacturing when compared to traditional processes.

Embracing these opportunities depends on a thorough understanding of the techniques and procedures involved. The use of excipients in the process, for example, is currently lacking in both research and application.

Lactose, which is well-established and has regulatory approval, is a logical place to start the journey of understanding.

And, as this study shows, it certainly has an important role to play in embracing the opportunities of pharmaceutical 3D printing.






# Building the evidence

In 2015, Spritam (levetiracetam) was the first 3D-printed medication to receive FDA approval. The epilepsy drug delivers a high dose via a tablet that dissolves on the tongue with a small amount of water. It illustrates the possibilities but has not been widely replicated.

While industry and academia have both taken their first foray into the technology, advances have been slow, due, at least in part, to the siloed nature of the research.

It is unclear how many drug manufacturers are investigating the mechanisms of 3D printing, as generated evidence is rarely shared. The information we have originates from academia, yet there is a clear data gap.

This gap could be addressed by universities, innovators and industry working together, collaborating on research and sharing their data.

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# Where we are: techniques & excipients

*"Breaking out of data silos is important – sharing knowledge and working together accelerates learning and progresses science for the good of the whole industry.*

*That's why Deakin University has worked with DFE Pharma to combine our organisations' expertise on powder physics. Together, we have developed the sector's understanding of the wetting, flow and consolidation properties of lactose, starch and microcrystalline cellulose (MCC) in 3D printing."*

***Professor Karen Hapgood,***
*Executive Dean, Deakin University.*

Fused deposition modelling (FDM), long the staple 3D printing method across sectors, is relatively cheap and accessible. It means universities have created the beginnings of a dataset using this technique.

While it is inexpensive and scalable, though, it is not suitable for thermosensitive APIs and it can struggle to provide complete API release. Crucially, no perfect polymer, or building material, has been identified in drug production.

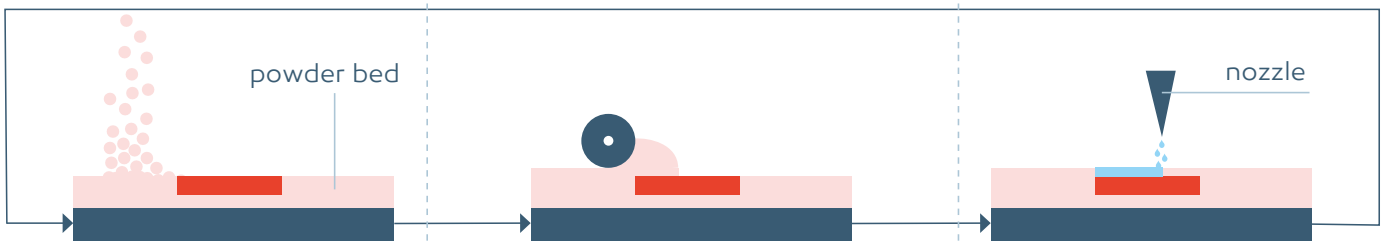
Powder bed printing, which was used to develop levetiracetam, is arguably the best method for pharmaceutical manufacturing. Unlike FDM, it can provide fast and complete API release and is suitable for thermosensitive APIs.

R&D equipment and kit capable of producing large batches suitable for clinical trial preparation is commercially available, but it is expensive, and this has blocked access for many academic investigators.

The whole sector stands to benefit from the creation of a centralised database that unites industry, innovators and academia in the common aim of providing patient-centred care.

# How does it work?

A nozzle sprays small droplets of water- or ethanol-based ink onto a thin bed of powder with a smooth surface. Once solidified, another layer of powder is deposited on the powder bed and the cycle repeats until the desired height is obtained. The API will be contained in the powder or the ink, depending on the use case.




# Where we are: excipients

Key to addressing the data gap is developing an understanding of how to use excipients, as different substances will affect the powder parameters that are central to the success of the 3D printing process in different ways.

The flowability, wettability and consolidation of the powder used to print tablets will determine the resulting tablet's hardness, friability and disintegration.

**Powder parameters and their importance in the 3D printing of pharmaceuticals**

| Parameter | Definition | Importance in the 3D printing of pharmaceuticals |
|---|---|---|
| Flowability | The ability of a powder to flow | • Powder needs to be able to flow easily through the 3D printer's deposition mechanism and be able to create a flat bed<br>• Powder with poor flowability can clog machinery |
| Wettability | The ability of a powder to absorb liquid | • Poor wettability can lead to balling of the surface<br>• Bleeding is a result of non-optimal wetting. It happens when the liquid penetrates further in the powder bed then intended<br>• Wettability impacts on tablet disintegration. This affects the dissolution rate and release characteristics of the resulting tablet<br>• Wettability impacts on the tablet strength |
| Consolidation | The ability of a powder to bind together | • Powder granules must be able to bind during the 3D printing process in order to form a tablet<br>• Consolidation impacts on tablet hardness and friability |

**Tablet parameters and their impact on 3D printed pharmaceuticals**

| Parameter | Definition |
|---|---|
| Hardness | The breaking force of a tablet |
| Friability | The tendency of a tablet to crumble, chip or break |
| Disintegration | The tendency of a tablet to break down into granules/powder particles once it becomes in contact with an (aqueous) liquid |

We need to build the knowledge of how excipients impact on these parameters in 3D printing before we can begin to understand the most appropriate materials or techniques for each use case.
A repository of excipient usability and applicability, along with their impact on powder parameters and those of the resulting tablet, would provide investigators of all backgrounds with an invaluable tool.

**Test, learn and share: A study in lactose**

To date, we know that powder bed printing can result in significant dust formation during the process, and high friability in the resulting tablets.

In a bid to overcome this known challenge, DFE Pharma worked with the Netherlands Organisation for Applied Scientific Research (TNO) to look at the use of lactose as an excipient in some detail.

Despite lactose being a well-known, well-established and widely used pharmaceutical excipient, its use in the 3D printing of pharmaceuticals is rare – possibly because it isn't easy without the right expertise and access to materials.

The research team tested 20 lactose grades, all with varying morphology, and explored their effects on selected criteria, such as hardness friability and disintegration.

The primary objective was to develop a lactose with sufficient flow, wetting and binding to be used effectively in the powder bed 3D printing of pharmaceuticals.

**Background**

Lactose is a commonly used, regulatory-approved, water-soluble filler for the pharmaceutical industry and a logical choice as filler material in powder bed printing.

**Method**

- Twenty grades of lactose were used to produce various powder blends for the 3D printing of tablets. The powders were assessed on wettability, flowability and consolidation. The resulting tablets were tested for hardness, friability and disintegration
- The impact of factors such as line spacing, print direction and rotation were also examined

**Key findings**

- Differing grades of lactose produced differing results in terms of the main investigative parameters
- Our study showed that specific grades of lactose monohydrate can be utilised effectively in the 3D printing of pharmaceutical tablets
- Twenty grades of lactose were tested for the purposes of this study. For illustrate purposes, the table below details key findings from tests on the two most effective grades

| Parameter | Method | Top line findings |
|---|---|---|
| Wettability of lactose during 3D printing | In order to study the impact of particle size distribution (PSD) on powder bed printing, wetting tests were performed by printing a single layer with different line spacings | The findings concluded that the d10 value should be larger than 6µm, and preferably in excess of 10µm |
| Flow of lactose during 3D printing | Based on the wettability findings, two lactose grades (A+ and B^) with a higher than 10µm d10 value were blended with 10% fully pregelatinized starch* and measured on flowability, density and particle size | Both blends had a flow function (FFC) above 10 and a compressibility index below 15. This is an indication of excellent flowability and a low compressibility |
| Consolidation of lactose during 3D printing | Circular, 9mm tablets with a height of 2.8mm were 3D printed using lactose grades A and B | Both grades resulted in tablets with an acceptable variation in tablet mass, diameter and height  *Left: Grade B Right: Grade A* |

*+ Lactose grade A was milled and classified lactose with a d10 above 20µm*

*^ Lactose grade B was sieved lactose with a d10 above 20µm*

**Lactose alone does not have sufficient binding to result in a robust tablet, so it is advisable to add 10 to 20% binder to the powder blend to obtain a strong formulation. These results refer to tests using formulations of 10% fully pregelatinized starch as a binder*

**What else did we learn?**

- *Milled/sieved lactose monohydrate gave better results compared to anhydrous lactose (less wettability but smoother layer)*
- *Milled/sieved lactose monohydrate gave better results compared to spray-dried lactose monohydrate (less wettability but improved consolidation)*
- *Tablets formed with fully pregelatinized starch as a binder had less bleeding and friability than those produced using polyvinylpyrrolidone*
- *Print direction and linespacing impacted on tablet appearance, friability and disintegration*
- *Wettability was improved by replacing the aqueous ink with ethanol, which has a lower surface tension than water (95% water is 56 σ/mN m−1 compared to 22 σ/mN m−1 for 100% ethanol). However, technical issues such as powder sticking to the roller and spilling on the powder bed remained. As such, the team concluded that using an aqueous ink and lactose with the larger d10 value, as described above, was the best solution*
- *The addition of silica resulted in an improved flow, and slightly improved wettability. However, this is not always the preferred option due to safety and handling considerations*

*Full details of this study are available on request from the research team.*
*Email learningaboutlactose@dfepharma.com for more information.*

# What this tells us about the 3D printing of lactose tablets

*"TNO was excited to combine its knowledge of printing with DFE Pharma's knowledge of powders to carry out this fundamental piece of research.*

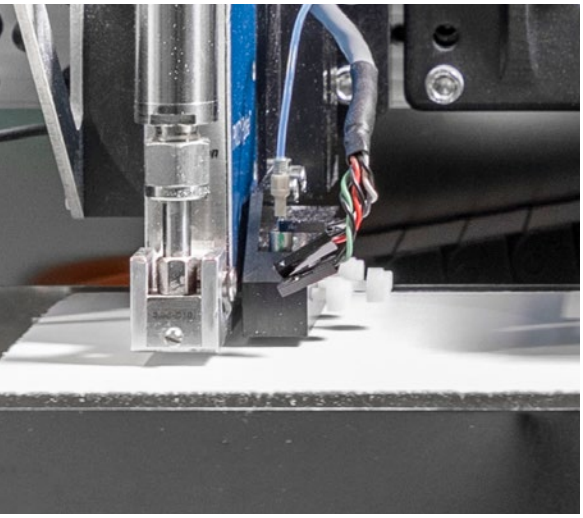
*The scientific approach to the study of lactose as an excipient in the 3D printing of pharmaceuticals provides us with robust evidence on which to base our understanding of how these products work.*

*The whole sector stands to benefit from this collaborative piece of research, which provides valuable insights into the optimal PSD of lactose in this setting."*

*Kjeld van Bommel*
*PhD, Senior Consultant, TNO*

With the initial selection of excipient grades, and the range of printer settings tested, we achieved 3D printed tablets with properties that, while not yet equal to traditional pills, are approaching the industry standard for hardness and friability (i.e. <1%). Ultimately, lactose works.

It's worth noting that 3D printed tablets will always look more irregular and have a rougher surface area than those produced using traditional methods.




# Towards data sharing

While there is still much to learn about how different grades of lactose can impart various qualities onto tablets, this study demonstrates that it is a suitable excipient for the 3D printing of pharmaceuticals.

What's more, it contributes to the common evidence base for 3D printing in the pharmaceutical industry and highlights the power of collaborative working in this space.

We are taking the tentative first steps towards creating the centralised dataset that we believe is the key to accelerating progress, and we will continue our research in this area.

We would invite other organisations to work with us, our knowledge of 30 types of lactose and our ability to customise grades to suit each use case, so that we can all find out more.

By pooling the knowledge and expertise of industry, innovators and academia, we can truly move the dial on 3D printing in pharmaceuticals, and in doing so take huge strides towards delivering the person-centred clinical trials and medicines future.

This is something we take very seriously. At DFE Pharma we have a dedicated researcher who is committed to driving development in this space and strong relationships with institutions such as TNO and respected academic centres like Deakin University.

To find out more about possible collaborations or to request full details on our lactose in 3D printing study, get in touch on learningaboutlactose@dfepharma.com

# 3 We are committed to excellence

*"For just over a year I have been DFE Pharma's dedicated researcher for 3D printing.*

*Allowing me to gain fundamental insights in this application, and collaborate with academia and commercial organizations.*

*We are proud to share these first results and looking forward to collaborate with you as well."*

***Korinde van den Heuvel-Jansen***
*MSc, Senior Product Developer, DFE Pharma*

As the leading manufacturer of excipients in the world, we need to make sure you can rely on us. That's why we only work with highly skilled people, resulting in excellent and consistent excipients.

**We are committed to excellence in innovation**
Our innovation team has functions dedicated to the furtherance of medical science and understanding of continuous manufacturing, 3D printing and biologics.

**We are committed to excellent people**
We know how a company culture defines its performance. Therefore, we invest in a culture of excellence. A culture that puts customers first, is process oriented and cultivates reliability. A culture that inspires and challenges our team of 360 highly motivated people. People that come from all over the world and have a profound knowledge of formulation technology and the pharmaceutical market. People who have experience in a wide area of fields. People who deeply understand your needs.

**We are committed to excellent quality**
- We supply from manufacturing sites all over the world.
- Our facilities are dedicated to the manufacture of pharmaceutical excipients.
- We have implemented a single, uniform quality system based on ISO 9001:2015 and IPEC* PQG** cGMP and where applicable ICH Q7***, at all manufacturing sites, including those of the parent companies.
- A program to monitor the effectiveness of the quality system is in place and ensures continuous improvement.
- Our customers are welcome to audit our manufacturing facilities in order to verify our quality status.

**IPEC: International Pharmaceutical Excipients Council; **PQG: Pharmaceutical Quality Group; ***ICH Q7: applicable for inhalation grade lactose.*

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## Learn More About DFE Pharma


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*Photographs courtesy of Netherlands Organisation for Applied Scientific Research (TNO)*

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