The Future of Drug Manufacturing Innovation

Korinde van den Heuvel, Senior Product Developer at DFE Pharma, discusses how excipient innovation and 3D powder bed printed tablets research can help pharma companies achieve worldwide security of supply

***PMPS:* What are the main challenges facing tablet production today?**

Korinde van den Heuvel: Despite tablets being the main mode of pharmaceutical delivery worldwide, there are major challenges in the way they are made and the way they are taken. Traditional facilities are not geared towards the small-scale production needed for clinical trials, orphan drugs, or the creation of designer tablets for personalised medicine. Taste, mouthfeel, or solubility can make tablets hard to take. Tablets also have a lack of dose flexibility. Smaller measurements are often delivered by breaking tablets into segments, which results in imprecise dosing.

Why should pharma companies consider 3D printed tablets?

From enabling personalised medicine to accelerating the drug development pathway, 3D printing offers huge potential to meet the above challenges. It offers opportunities in shape modifications, dose flexibility, solubility enhancement, and multiple pills with multiple active pharmaceutical ingredients (APIs). There is huge potential to deliver bespoke, small batches in the clinical trials market. When it comes to patient-centred medicine, 3D printed tablets, which can be created on demand in local healthcare settings could open up a new era of personalised medicines. What's more, the 3D printing of medications can potentially accelerate the scaling up of manufacturing.

Why is 3D tablet printing a growth area?

Aside from the reasons above, the ongoing COVID-19 pandemic has led both pharma companies and global political leaders to recognise potential supply challenges, and reinforced the need for worldwide stocks. Because of this, we have seen renewed interest in 3D printing. This technology has the potential to offer global security of supply. Instead of one large facility, local 3D printers can be given recipes for

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production of specific medicines relevant to their location's healthcare needs.

Are there any other changes you see as a result of the pandemic?

We have already seen huge changes in the use of medicines and demand for new vaccines as a result of COVID-19. There has also been a shift in demand for existing therapies, and changes in both patient and research participant behaviour with greater use of remote consultations and decentralised clinical trials. Disruptions in the supply chain due to manufacturing shutdown and international restrictions have highlighted the urgent need for a reliable and consistent supply.

What do you need to consider when producing 3D printed tablets?

Critical material attributes are vital when selecting excipients for a 3D-printed formulation. Flowability, wettability, and consolidation are the main characteristics for 3D printing using powder bed printing technology. This differs from conventional tablets where compaction and flow behaviour are crucial.

Why use powder bed printing?

Fused deposition modelling has long been the staple 3D printing method across sectors because it is relatively cheap and accessible. However, it is not suitable for thermosensitive APIs and can struggle to provide complete API release. Crucially, no perfect polymer or building material has been identified in drug production. Powder bed printing is arguably the best method for pharma manufacturing because it can provide fast and complete API release and is suitable for thermosensitive APIs.

Are there regulatory considerations?

The overall approach to acceptance, validation, and registration of 3D printed tablets is similar to that of any other product. There must be a risk assessment, followed by evaluation and validation of critical parameters. However, limited data on 3D printing and the relatively low number of products on the market could make this more challenging. A key advantage of powder bed 3D printing is that it has already been commercialised and approved by the FDA. In 2015, Spritam (levetiracetam), produced using ZipDose Technology from Aprecia Pharmaceuticals, was the first 3D-printed medication to receive FDA approval.

Are there any excipient-specific considerations?

We know powder bed printing can result in significant dust formation during the process, and high friability in resulting tablets. Lactose is a good option to overcome the challenges found in the 3D printed tablet production process. However, greater understanding of the impact of different lactose grades is needed. This is why we recently carried out a research project on the

use of lactose as an excipient for 3D tablet printing in collaboration with independent research organisation, The Netherlands Organisation for Applied Scientific Research (TNO).

What more is needed?

The whole sector would benefit from the creation of a centralised database on 3D-printed tablet research. This database should bring together industry, innovators, and academia. We need to develop an understanding of how to use excipients. Bridging the data gap on how different excipients impact the powder parameters central to the success of the 3D printing process is vital. This will help us learn which materials or techniques are appropriate for each case. Once that is achieved, we need to study the interaction between the different excipients themselves, and their effect on both hydrophobic and hydrophilic APIs. We envisage a repository including data on excipient usability and applicability and their impact on powder and tablet parameters. This would provide investigators with an invaluable tool, and help unite us all in the common aim of providing patient-centred care.

How did your recent research help address this data gap?

The primary objective of our research was to develop a lactose-based blend with sufficient flowability, wettability, and binding to be used effectively in powder bed 3D tablet printing. 20 lactose grades, all with varying morphology, were screened in a lactose binder blend and tested for 3D powder bed tablet printing. We explored the effects of the lactose grades on criteria including hardness, friability, and disintegration. We also examined the impact of factors such as line spacing, print direction, and rotation. Formulations with acetaminophen and diclofenac sodium were printed. The results show how hydrophilic and hydrophobic APIs can be successfully formulated into 3D powder bed printed pharmaceutical tablets.

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How did the results compare to traditional tablets?

Our research resulted in 3D-printed products with properties that, while not yet equal to traditional tablets, are approaching the industry standard for hardness and friability. However, it is worth noting 3D printed tablets will always look more irregular and have a rougher surface area than traditional tablets.

What were the findings on wettability?

Wetting tests were performed by printing a single layer with different line spacings. The findings concluded that the PSD was of importance, and in particular, the d10 value. It was found that the d10 value should be larger than 6µm, and preferably in excess of 10µm.

How are flow and consolidation impacted?

Blends of two lactose grades with a higher than 10µm d10 value were blended with 10% fully pre-gelatinised starch and measured on flowability, density, and particle size. Both blends had a flow function above 10 and a compressibility index below 15. This is an indication of excellent flowability and a low compressibility. Circular 9mm tablets with a height of 2.8mm were 3D printed using these lactose grades. Both grades resulted in tablets with an acceptable variation in tablet mass, diameter, and height.

How do your findings impact the future of 3D printed tablets?

This study shows lactose is an ideal excipient for a 3D powder bed tablet printing platform. However, it also has a wider impact. It contributes to the common evidence base for 3D printing in the pharma industry and highlights the power of collaborative working. This research is the first step towards creating a centralised dataset, which could accelerate progress throughout the industry.

What would you like to see happen now?

Pooling the knowledge and expertise of established pharma companies, innovators, and academia will allow us to make huge strides towards a person-centred clinical trials and medicines future offering a truly global supply.

In what other areas can we expect to see new developments?

The stabilisation of biological drugs is challenging, as they are sensitive to temperature and light, susceptible to shearing and degradation, and not as durable and robust as small molecules. Sucrose has a stabilisation effect on biologics during the formulation, and new kinds of stabilisers are now being used to support COVID-19 vaccine supply challenges.

Having joined **DFE Pharma** in April 2014, **Korinde van den Heuvel** is a Senior Product Developer who has worked on multiple oral solid dose (OSD) projects, as well as focusing on 3D printing of pharmaceutical tablets. Prior to working at DFE Pharma, Korinde worked in formulation development at Synthon for 10 years developing various generic and OSD forms, such as orally disintegrating, immediate release, and modified release tablets and capsules. Korinde holds a Master's degree in Organic Chemistry from the Radboud University in Nijmegen, The Netherlands.