Future of Pharma: Developing Innovative Tablets Using 3D Printing

As the pharmaceutical industry steps into the future, companies which are developing excipient blends for the formulation of pharmaceutical drugs are investigating 3D printing as a new, innovative way to produce tablets. The technology is especially interesting whenever small batches of tablets are needed, such as in clinical trials

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Pharmaceutical production is a highly regulated field, but at the same time always in need of innovative technologies to keep pace with the rapidly developing demands of modern medicine. While in the past, 'blockbuster' drugs were produced in high quantities and given to a wide range of patients, drugs today are more diverse and tailored towards different patient groups. In clinical trials, too, drugs are only needed in small batches. This presents a challenge to traditional bulk manufacturing, much like special demands regarding drug properties and performance. For example, using traditional methods to combine excipients in a tablet with a high load of the active pharmaceutical ingredient (API) with fast dissolvability is not easily done. Producing tablets using 3D printing, however, represents a promising solution to these challenges.

Image 1: The contact angle meter OCA 50 from DataPhysics Instruments helps to characterise powder wettability. Copyright: DataPhysics Instruments

What 3D Tablet Printing Can Do For Pharma

The basic material of drugs produced in the form of tablets, capsules, or sachets, are so-called excipients, which are mixed with the API. Together, API and excipient determine the drug's properties, such as their dissolvability, flow, wettability, and compressibility.

DFE Pharma is one such company looking into the advancements of 3D printing. The company's 3D printing initiative is headed by Senior Product Developer Korinde van den Heuvel, and she explains the two significant benefits 3D printing can have as an innovative production technique for pharmaceuticals: "For clinical trials, which demand small batches and additionally call for variations of the API

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concentration for every drug tested, you only need a couple of thousand tablets. Such small quantities are not easily realised with traditional methods but can be produced with 3D printing technology." Moreover, she explains: "Using the same powder blend in a traditional compression machine and in a 3D printer yields different results, as the principle of binding the tablet together differs between approaches. Working with a 3D printer, multiple settings can be tweaked in a way that tablets with different characteristics are obtained, even with the same initial material mix." Hence, when there is a need for a certain special tablet, which cannot be produced with traditional methods, 3D printing can be the solution.

Image 2: 3D-printed lactose-starch tablets, developed by DFE Pharma.
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To date, the only fully FDA-approved 3D-printed tablet is the epilepsy drug Spritam, developed by the pharma company Aprecia in the US. Aprecia uses 3D printing to produce Spritam, because the technique allows the combination of fast dissolvability and a high drug load (i.e., API concentration). "The higher the drug load, the harder it is to create a tablet which falls apart easily. Aprecia has used 3D printing because it was the only way to combine both characteristics," explains van den Heuvel.

With all these benefits in mind, van den Heuvel, who is an organic chemist by training with over 10 years of experience in the pharma industry, works hard today to make 3D-printed tablets widely available in the world of tomorrow. For this purpose, she and her team are developing excipient-powder-blends, which constitute suitable starting materials for 3D-printed tablets.

3D Printing Explained

While there are several 3D printing methods available, those methods vary in suitability for printing tablets. The method used to produce Spritam is 'powder bed printing' – which is the technique that is also researched by DFE Pharma. "We believe that powder bed printing has the best qualities for tablet production compared to the other 3D printing methods which are available today," says van den Heuvel. Another advantage is that powder bed printing is closely related to an already widely used technique called wet granulation. With powder bed printing, it is even possible to handle thermosensitive APIs. Moreover, powder bed printing is scalable and applicable in real-life conditions.

The technique of powder bed printing works like building a brick wall, layer by layer. The ingredients are the aforementioned powder blend, which contains the excipient and the APIs, as well as an 'ink' (i.e., a liquid which is dosed onto the powder). This liquid is most commonly an ethanol-water-mix. First, a thin layer of the excipient-API-blend is spread out on a flat surface, forming the powder bed. Then, a nozzle sprays small drops of the liquid onto well-defined areas of the powder, where the tablets are to be built. Once the drops have solidified, a layer of fresh powder is added. Those steps are repeated until the desired tablet height is reached. Finally, the solidified tablets are scooped out of the powder bed.

The Importance of Powder Wettability

When developing powder blends for 3D printing, three parameters are of importance: the wettability of the powder, its flow, and the consolidation of the printed tablets (1). While the wettability determines how the powder interacts with the liquid drops, the flow governs how easy it is to spread the powder. Furthermore, the consolidation after 3D printing describes the integrity of the printed tablets when dried.

Van den Heuvel knew from the beginning of her research that wettability was an important parameter to gain more insights into the usability of different powder blends. Hence, she decided to invest in dedicated measurement equipment for wettability studies.

Methods to Study Powder Wettability

Technical measurement experts from DataPhysics Instruments could offer van den Heuvel two established techniques for studying powder wettability. One possibility is to use a tensiometer and conduct the Washburn method. For this method, the powder is filled into a small cylindrical vessel with a porous bottom, which is fixed to a high precision scale in the top part of the tensiometer. A sample container filled with a liquid is then positioned below the vessel and lifted by the electrical sample stage until the liquid touches the bottom of the vessel. Driven by capillary forces,

the liquid enters the vessel through the porous bottom and soaks through the powder. While the powder gets soaked with the liquid, the weight of the vessel increases. The instrument's software then calculates, based on the weight's increase rate, the liquid's advancing contact angle on the powder as a measure for its wettability.

The second available method does not use a tensiometer but an optical contact angle meter. In this case, the powder is spread flatly on a substrate, which is placed on the instrument's sample table. The liquid is filled into a dosing system, such as a syringe, which then doses precisely controlled, single drops of liquid onto the powder. The entire process is closely monitored by a high-performance camera of the contact angle meter, whose comprehensive software executes a detailed video image evaluation.

"The measurements with the contact angle meter mirror the process of powder bed printing," explains van den Heuvel. The system doses liquid drops on a powder bed, just as happens in a 3D powder bed printer. In addition, the interaction of the liquid drop with the powder bed can be analysed in detail evaluating the captured video images. DFE Pharma is not alone with its decision to look at drop penetration times for its powder wetting studies. Universities doing research in the field of 3D printing, like Deakin University, Australia, or the University of Connecticut, US, are also using drop test experiments for their measurements (2, 3).

Fundamental Studies for 3D Printed Tablets

When van den Heuvel had a contact angle meter at her disposal, she and her team started conducting extensive wettability tests on their different excipient-API-blend powders. She explains: "In detail, we are measuring the penetration time (i.e., how long it takes for the drop to be absorbed by the powder once it comes to rest on it)." If a powder does absorb the liquid quickly, the blend is suitable for further investigation.

Of course, with prior knowledge of 3D printing, van den Heuvel and her team were eager to do more than just standard measurements with their contact angle meter. So, in order to adapt the instrument to their specific measurement needs, they worked with the contact angle meter service team to programme it to work as a 'prototype printer'. "This gives a first indication if a blend is suitable or not," says van den Heuvel.

In addition to the wettability tests, the flow of the powder is measured. "Only if those preliminary tests for wettability and flow are satisfactory do we start printing tablets in the 3D prototype printer and study their disintegration and hardness," explains van den Heuvel. "Only if the disintegration and hardness of the first printed tablets is satisfactory, we move on to the official testing stage to gain a bigger data set," says van den Heuvel.

On the Journey Towards the Future of Pharmaceutical Manufacturing

DFE Pharma strongly believes in the enormous potential of 3D printing, which has already made a significant impact in many industries. For the company, the innovative technique is a promising way into the future of pharmaceutical manufacturing. Van den Heuvel says: "When I started my position at DFE Pharma, little research had been published on 3D printing in the pharma industry – and even less about specific questions like which excipients to use and which particle sizes are needed for powder bed printing." Van den Heuvel and her colleagues decided to change that: In 2021, they published a paper in the scientific journal *Powder Technology* for which they evaluated different lactose and lactose-starch formulations as excipient blends for 3D printed tablets. The research was conducted together with TNO, the Netherlands Organisation of Applied Scientific Research, which provided the 3D-printing-equipment for the study.

Exploring new ways to tap into the advantages of 3D printing, DFE Pharma is about to embark on an exciting journey. However, the company does not want to go alone. Van den Heuvel says: "We would like to invite other organisations to work with us. We are looking forward to collaborations in the area of 3D printing and are more than happy to supply our partners with advice or customised blends. Other industries have already committed to 3D printing and gained a lot from it. We hope the same will be possible in the pharma industry."

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