The Freeformer Allows a Tailor-Made Combination of Several Active Ingredients

Patient-Specific Tablets

Additive manufacturing has the potential to manufacture tablets individualized for the particular patient, and thereby further digitalize the pharmaceutical industry. In medication development, the properties of a tablet, such as its shape, dosage or release of the active substance, can be individually tailored – by making just a few changes to the digital 3D print file. Merck scientists have used a Freeformer for their lab tests.

Merck researcher Dr. Thomas Kipping (right) and Nabil Lamrabet value the advantages that the Freeformer offers as an open system. © Merck

The conventional method of pressing powder formulations from active ingredients and excipients is a tried-and-tested process with a long track record. It is especially efficient for manufacturing tablets with the same formulation by the billion. However, the method is less suitable when it comes to smaller amounts of experimental actives. "In the early phase of clinical development, dose escalation studies are performed to determine the best and safest dose for the patients. This requires numerous formulations with different amounts of active ingredients to be available," explains Dr. Thomas Kipping, who is head of Drug Carriers at Merck in the Life Science division (**Title figure**).

For some time, Merck, one of the world's oldest pharmaceutical and chemical companies, has been working on an alternative. Additive manufacturing not only speeds up clinical trials and thereby reduces the time until medications are available for patients. They can also benefit patients with rare illnesses and contribute to personalizing the medicine, since they allow the production of tablets with a precise dosage tailored to individual patients.

To drill down into this subject, Thomas Kipping's team rented a Freeformer from Arburg initially for one year. The machine is an open system that employs the patented APF process, Arburg Plastic Freeforming, to produce usually technical components by the layer-by-layer application of extremely small plastic droplets directly from 3D CAD data, and with qualified standard pellets. It is possible to make individual adjustments to the manufacturing process by influencing the layer-by-layer build-up by means of slicing, droplet size and process control.

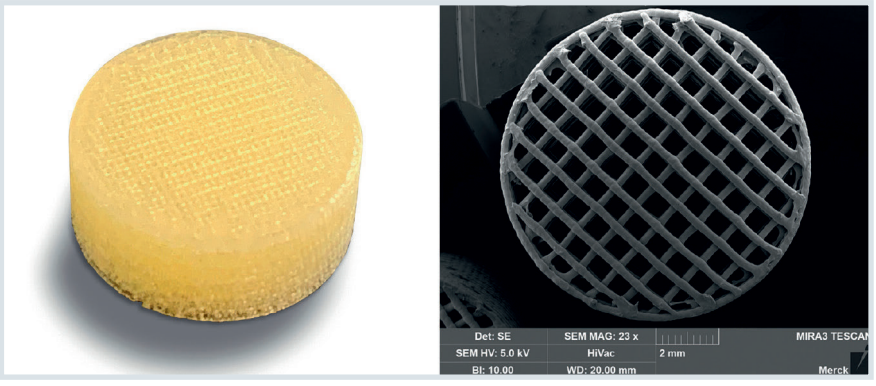

Fig. 1. The tablet (left) was manufactured with the Freeformer. The electron micrograph (right) shows its mesh-like structure. © Merck

Promising Tests with Various Model Active Ingredients

For the tests, various model active ingredients were used, which, together with a special polyvinyl alcohol (PVA, type: Parteck MXP) and additives such as a binder and flavor marker, are melted and homogenized in a twin-screw extruder. According to the manufacturer, the PVA polymer is approved as safe by the US Food and Drug Administration (FDA) for use in pharmaceuticals. Other advantages of Parteck MXP mentioned by Merck are

- the production of an amorphous solid solution to improve the solubility of active ingredients and therefore the bioavailability,
- stable, high active-ingredient loading under variable conditions,
- high thermal stability (above 250 °C), and a broad spectrum of active ingredients,
- a wide various of oral administration forms with individual release kinetics dependent on the particular formulation, and
- good reproducibility of the manufacturing process.

Here, the first advantage of the APF process came into its own: the Freeformer can apply the extruded and pelletized material directly without it needing to be processed into filaments and thereby be subjected to thermal or mechanical stressing again.

Polypills from the 3D Printer Are the Ultimate Goal

In addition, the open system allows various process parameters to be easily varied. For example, tests were carried out with filler loadings between 30 and 100 % (**Fig. 1**), in which the filler loading is recognizable by the porosity. "The test results overall are very positive. We ascertained that the active ingredient is very homogeneously distributed in the tablet. We can influence how much is released within a given time period by changing the filler loading," explains Kipping. This permits very accurate dosage, as is shown by the results of an active ingredient release analysis in a special apparatus (**Fig. 2**). Another possibility consists in combining several active substances in one tablet. "One day, we will produce small batches for particular patient groups," predicts Kipping. "These polypills from the 3D printer are the ultimate goal."

The requirements on the stability of the additively manufactured product were also analyzed and found to be good. After all, the tablets must, of course, not be broken during downstream process steps such as coating, packaging and transport. Ultimately, additive manufacturing can also contribute to decentralizing pharmaceutical manufacturing, adds Kipping. In the future, tablets could be manufactured in small amounts via the 3D printer directly in pharmacies. ■

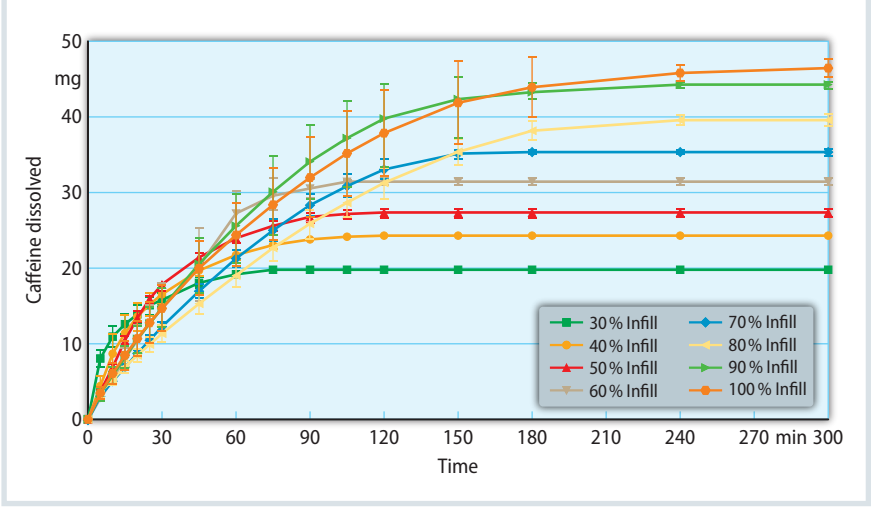

Fig. 2. The filler loading of the tablets can be used to control the release of active ingredient. Here, the polymer melt is loaded with 10 % caffeine in each case as a model active ingredient.

Source: Merck; graphic: © Hanser

Info

Text

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Company Profile

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