



Cover Story

3D printing of 5-drug polypill



The processes and tools for producing tablets, the dominant form of drug taken by patients, have changed relatively little for over a century. We have seen much innovation in excipients and processes for manufacturing suitable powders as well as vast improvements in speed and quality of manufacture. While this approach serves the industry and patients very well for the majority of drugs, it remains limited in its capacity to create complex dosage forms, for example with specific distributions of materials or containing multiple drugs. It is also limited in producing bespoke formulations tailored for an individual or small sub-population. The ability to produce multiple drugs in one tablet (known as 'polypill') would significantly improve patient compliance through reduced tablet burden. Polypills become even more valuable, if the loaded drugs have independent release kinetics. The paper by Professor Clive Roberts and his colleagues in this issue demonstrates the manufacture of a 5-drug polypill using an alternative manufacturing method based on 3D printing [1].

A 3D printer is able to manufacture, via an additive process, exquisitely complex geometries with multiple materials from 'inks' (i.e., formulations) of metastable fluids or pastes that can be triggered to form solid objects post-deposition. The 5-drug polypill manufactured here exploits a particular version of 3D printing based upon extrusion from a paste, but it is important to recognize that this is in fact only one of several currently recognized distinct methods of 3D printing (or more correctly Additive Manufacture). Modern 3D printing also has the potential to meet the requirements of a more traditional centralized manufacturing model. This year, the FDA has approved the first tablet formulation manufactured by 3D printing [2]. The tablets, made by Aprelia, use an aqueous fluid to hold together multiple layers of powder during printing in a reformulation of the anti-epileptic seizure drug levetiracetam. The tablet can have a very high drug loading and is very porous due to how it has been printed and hence it very quickly disintegrates in liquid or in the mouth. Currently, the tablets are expected to be manufactured at traditional 'central' facilities, and thus, in this sense 3D printing of such tablets is not any different from manufacturing of traditional tablets in a well-controlled good manufacturing practice (GMP) environment.

While the 3D printing is an exciting development, such excitement should not overcast the real important issues. For 3D printing of polypills to be truly revolutionary in providing individually tailored formulations for different patients, it has to overcome multitude of regulatory problems to ensure suitable control of the manufacturing process and patient safety. After all, the most important aspects of any formulation is to deliver the right amounts of drugs at the right time to be effective and safe. Thus, it is unimaginable under current

guidelines that the Food and Drug Administration (FDA) will approve the use of individual 3D printing devices in locations convenient for patients all around the country, e.g., local pharmacies. Under such a scenario, each 3D printer needs to be treated as an independent manufacturing machine, and each pharmacy has to be approved as a GMP site. To achieve such a goal the 'local' manufacture must be under total and secure control, and for this requires significant technical advances as well as regulatory changes.

In the end, the cost of the final formulation and the clinical benefit that can be achieved will be the deciding factors. Will the cost of producing personalized 3D printed pills be low enough for everybody to afford? The first 3D printed levetiracetam is basically a fast dissolving tablet. There are currently several low cost methods of making the fast dissolving formulations. What can justify the potentially high price of 3D printed pills, when the drug efficacy remains the same? What are the practical advantages of 3D printed tablets over the existing tablets that have the same function? The 5-drug polypill developed by the Roberts team is certainly an exciting advance in drug delivery systems. But the reality is that when different drugs are combined into a single tablet formulation, it is regarded, at least by the FDA, as a new formulation requiring clinical studies to show the safety and efficacy.

There is no doubt that the introduction of new technologies will eventually improve the quality of the products we use. But in the pharmaceutical field, being new is not enough. The new formulation has to show its efficacy and safety through well-controlled clinical studies. Knowing the difficulties to overcome will make the 3D printing process more practical. It is hoped that the new, exciting 3D printing process of polypills described by the Roberts team becomes a truly useful new tablet manufacturing process ready for the personalized medicine in the near future. As with most other technological advances occurring quickly, governing agencies lag behind in providing regulatory guidance. Formulation scientists should be properly trained to know the regulatory hurdles to overcome for translating this emerging 3D printing technology to clinical application as fast as possible.

References

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