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The future of pharmaceutics: 3D-printing?

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Abstract

Cephalosporins Over the last century pharmaceutical technology has progressed at an exponential rate, starting off from powder formulation, progressing through tablets, capsules, all the way the nano drug delivery systems. The industrial manufacturing appeared as a result to the increasing demand from the market. Large scale manufacturing setups relied on the one size fits all principle, aiming to serve the populational rather than individual needs. However, there are certain population groups (pediatric, geriatric, poly-medicated etc.) in need of special therapeutic adaptations. Three-dimensional printing (3D-printing, 3DP), due to its versatility and flexibility, can be considered a form of personalized medicine. Dose, release and form, by means of design, can be adapted based on individual needs and preferences, that ultimately can increase therapeutic outcomes, while bringing the manufacturing closer to the patient.

Keywords: 3D-printing, personalized medicine, digital health

GENERALITIES

Cephalosporins Three-dimensional printing (3D-printing, 3DP), alternatively called additive manufacturing (AM), as suggested by the nomenclature, involves the layer-by-layer construction of a three-dimensional geometry. The notion of 3DP includes a wide variety of techniques dependent on the main mechanism used in the structure formation. Table 1 gives an overview of the different 3DP techniques, with the most commonly used representative technologies.

In pharmaceutics melt extrusion [1-3], binder jet printing [4-6], SLA [7,8], SLS [9,10] and DLP [11,12] methods are employed. Notably, binder jetting was the first FDA approved 3DP pharmaceutical manufacturing technique via Spirtam® [13]. However, melt extrusion technologies are the most researched in the medical area, with more than 80 % of the articles published in the last five years relying on these technologies [14]. Each technology includes advantages and disadvantages. Products developed by binder jet printing are porous, characterized by rapid disintegration, however the ink viscosity and surface tension has to be controlled within a tight margin as to avoid process interruptions [5]. The use of organic solvents in binder jet printing and SSE is also a risk factor from the pharmaceutical perspective, which may cause stability issues with the active compound along the manufacturing and drying steps [15] and upon ingestion should be limited as per the permitted daily exposure [16]. Although the accuracy of SLA and DLP is superior, there is a limited number of photocrosslinkable polymers available, which are currently not recognized as safe (GRAS) excipients [12]. As for SLS, the limitation factors are the harsh printing conditions (temperature and laser) [10]. FDM is without a doubt the most popular option. The equipment used is small, cheap and easy to handle. The drawbacks are

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TABLE 1. The three-dimensional printing techniques [19,20]

3DP techniques	3DP construction principle	Representative technologies
Material extrusion	solid or semi-solid based printing, where material is selectively dispersed through a nozzle	Fused Deposition Modelling (FDM) Semi-solid extrusion (SSE)
Direct energy deposition	fusion is done by focused thermal energy (e.g. laser)	Laser Deposition (LD)
Powder bed fusion	thermal energy selectively fuses regions of a powder bed	Selective Laser Sintering (SLS)
Binder jetting	inkjet-based printing, where a liquid bonding agent is selectively deposited to join the powder material substrate	ZipDose®
Vat photopolymerization	liquid photopolymer in a vat is selectively cured by light-activated polymerization	Stereolithography (SLA) Digital Light Processing (DLP)
Material jetting	droplets of photopolymer build material are selectively deposited to form layers that are further cured	Polyjet Printing (PP)
Sheet lamination	sheets of material are bonded	Laminated Object Manufacturing (LOM) Ultrasound Additive Manufacturing (UAM)

the limitation to use thermal stable materials and necessity to produce filaments, which for pharmaceutical grade excipients is more problematic [17,18].

The manufacturing process is common for all technologies, involving projection and printing. Printing is done based on a previously defined digital design. The Computer Aided Design (CAD) can be created in various 3D modelling software or by using 3D-scanners, which use a laser to digitally capture the physical characteristics of the object that is desired to be printed. Once projected the design is transferred to the printer, where it is sliced into layers and translated into motion instructions. Additional design characteristics can be added at this level. Hollow structures can be created by infill settings, wall thickness and layer height can be controlled, different segments can be printed with different material substrates, etc.

Although there is an additional need of design, the overall manufacturing flow can be simplified. Complex forms can be produced by a relatively simple technological flow, which in conventional setups may require much more processing steps. Fig. 1 gives an exemplification by using FDM as a reference, which most commonly is used in conjunction with hot melt extrusion (HME).

The easy modulation of the design and the simplicity of the manufacturing process are the key factors that account for the flexibility of the technology.

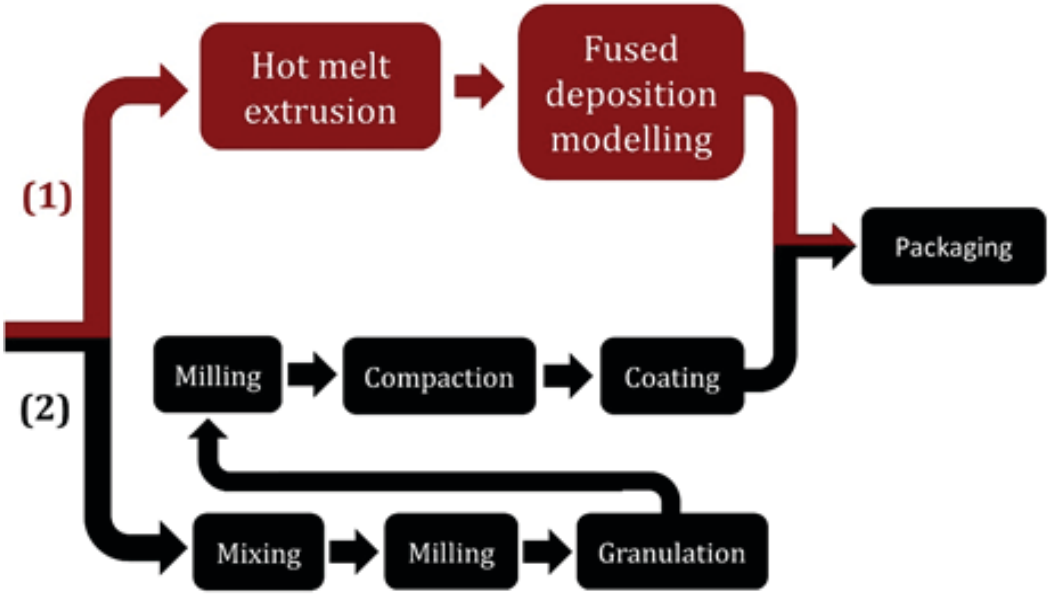

FIGURE 1. The production flow for complex products in modern 3DP (1) and traditional (2) manufacturing

POTENTIALS

The aspect which sets apart 3DP from other technologies is the ability to produce complex geometries. This was the characteristics based on which the integration to the medical field was considered. The technology first appeared at the beginning of the 1980s. However, being patent protected, the exploitation was limited for several years. In the medical domain, the first 3DP attempts were related to producing medical devices. The findings along this path are further along, the United States Food and Drug Administration (FDA) having already the Technical Considerations for Additive Manufactured Medical Devices guideline [21] in place to help the integration of the technology.

The integration of 3DP in pharmaceutics is a relatively new research topic. The first publications appeared in 2006 [22,23], still, it became a hot topic only after the approval of Aprecia's Spirtam® in 2015, which reassured professionals that the pharmaceutical domain was ready to accept 3DP as an alternative manufacturing process. Spirtam® is a Levetiracetam loaded product which is manufactured using the ZipDose®, binder jetting technology, and was developed with the purpose to assure rapidly disintegrating high-dose formulations that can be used in imminent epileptic seizures for people that may potentially suffer from dysphagia from the pediatrics to the geriatrics [24].

Pediatrics and geriatrics are special population groups in need of individualized formulations and doses. Due to the flexibility of the 3DP manufacturing process, shape and dose can easily be modulated at design by projecting smaller or bigger structures. Besides material considerations, release can also be controlled by design. By understanding how each design feature contributes to dose and release eventually enables the personalization of the drug delivery systems [25-27].

The variety of shapes that can be obtained by 3DP is high. Conventional and particular geometries can be formed as to for solid oral dosage forms or drug eluting devices. The systems can be adapted to the destined anatomical site or based on preferences. When designing implants, the most essential characteristic is the appropriateness or fit. The systems must fit to the site in order to be tolerable. As such, in some cases, 3D-scanning would be needed in order to obtain a 3D model of an anatomical feature adapted to the morphology of the individual [8]. A large variety of shapes could be produced by different 3DP techniques, e.g. dental fillers with FDM [28], hearing aids with DLP [29], intrauterine devices with SLS [30] etc.

In the same time, shape is a key feature when discussing compliance in children. Starting from this premises, research groups have developed drug delivery systems with Starmix® [31] or cartoon designs [32] and dosage forms that resemble conventional gummies [33]. Based on a previous study, among DLP, FDM, SSE and SLS, DLP was found to produce the most visually appealing printlets for children [34].

For compliance dosing is also important. Having more medications in the therapeutic scheme increases the risk to leave out doses. The most at risk is the poly-medicated geriatric population. With 3DP so called polypills can be obtained, which, within the same product, combine several active substances with common or individual release profiles. The most complex product documented was obtained by SLA and combines 6 active substances within the product [35].

PROSPECTS

The specific notions most used to define the potentials of 3DP are: personalization, print-on-demand, point-of-care. Personalization, as discussed earlier, is due to the potential to adapt design as per individual needs.

Print-on-demand is given by the flexibility of the technology. The equipment used is small, cheap and easy to handle and the technology is simple and flexible, with the possibility of making technology transfer to local manufacturers easy. Most possibly, if approved, 3DP will be used in local hospitals and pharmacies, at point-of-care, bringing the manufacturing process close to the patient. Being able to manufacture at small scale will enable the possibility to personalize pharmaceutical dosage forms based on needs and preferences, but it will also enable the possibility to produce clinical trial samples and orphan drugs [17]. By producing what is necessary in the exact amounts that are required, drug shortages could be prevented, but also unnecessary waste.

3DP can also enable the concept of digital pharmacy [36] potentially completing the digital health cycle

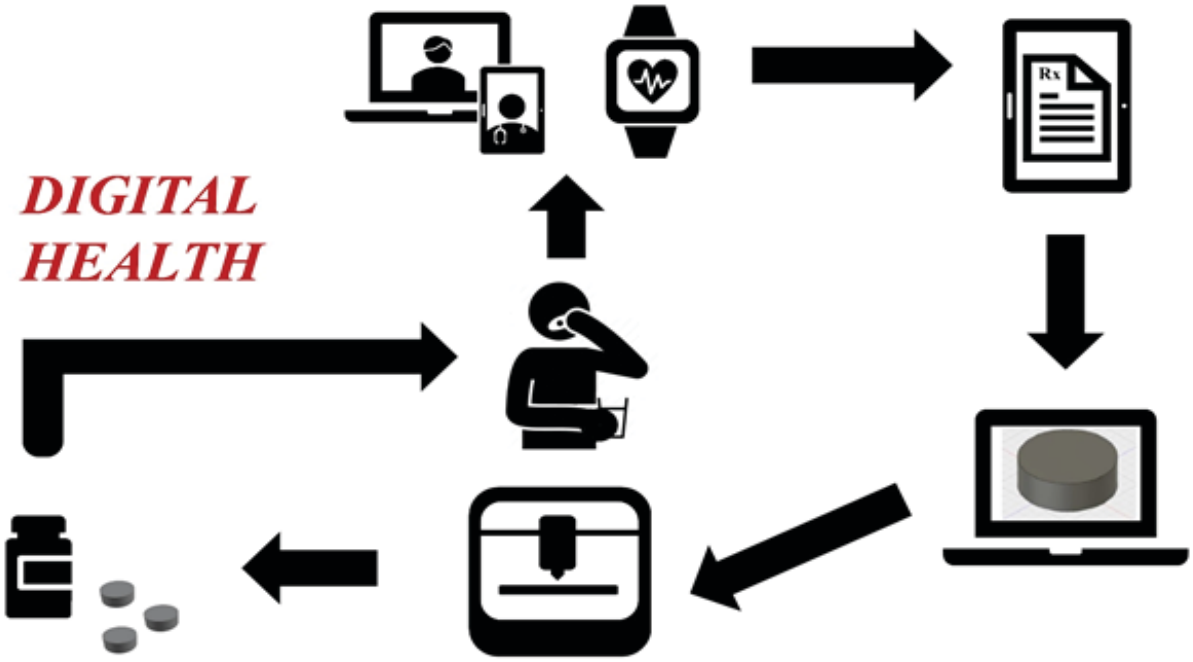

FIGURE 2. The Digital Health concept

(Fig. 2). The other elements included in cycle are telemedicine, with the virtual consultation of the patient, smart devices, that complete the medical decision, and ultimately electronic prescriptions which could guide the manufacturing process.

CONCLUSIONS

3DP is a technology not to be neglected. The recent proceedings show that in the near future 3DP will infiltrate in several common areas of everyday life.

The outbreak of the coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus highlighted the disadvantage of mass manufacturing and globalization. The supply chain was disrupted, with alarming product shortages appearing in various domains. 3DP came as a rapid response to correct the voids created by the crisis situation. Non-traditional manufacturers and community responders helped to produce personal protective equipment (PPE) and medical devices that were missing from the local market.

In pharmaceutics the technology proposes the shift from populational to individual dosage forms with manufacturing done on small rather than on large scales. During COVID-19 pandemic 3DP might not have been able to help in resolving drug shortages, but the created circumstances might speed up its regulatory acceptance. The therapeutic potentials are diverse and, undoubtably, 3DP is set to revolutionize pharmaceutical manufacturing.

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