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Review

3D printed medicines: A new branch of digital healthcare

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ABSTRACT

Three-dimensional printing (3DP) is a highly disruptive technology with the potential to change the way pharmaceuticals are designed, prescribed and produced. Owing to its low cost, diversity, portability and simplicity, fused deposition modeling (FDM) is well suited to a multitude of pharmaceutical applications in digital health. Favourably, through the combination of digital and genomic technologies, FDM enables the remote fabrication of drug delivery systems from 3D models having unique shapes, sizes and dosages, enabling greater control over the release characteristics and hence bioavailability of medications. In turn, this system could accelerate the digital healthcare revolution, enabling medicines to be tailored to the individual needs of each patient on demand. To date, a variety of FDM 3D printed medical products (e.g. implants) have been commercialised for clinical use. However, within pharmaceuticals, certain regulatory hurdles still remain. This article reviews the current state-of-the-art in FDM technology for medical and pharmaceutical research, including its use for personalised treatments and interconnection within digital health networks. The outstanding challenges are also discussed, with a focus on the future developments that are required to facilitate its integration within pharmacies and hospitals.

1. Introduction

Three-dimensional printing (3DP) has gained momentum in many industries as a new and revolutionary manufacturing tool. This additive system is rapidly changing the way goods are designed and produced; by using a 3D computer model, bespoke objects can be created in a layer-by-layer manner under automation. As such, this technology can bridge the gap between the worlds of imagination and reality. A variety of 3DP technologies are commercially available, however of all the systems, fused deposition modelling (FDM) is at present the most widely investigated 3DP technique within pharmaceuticals (Alhnan et al., 2016; Alomari et al., 2015; Awad et al., 2018; Goole and Amighi, 2016; Norman et al., 2017; Trenfield et al., 2018; Zema et al., 2017). As such, we anticipate that FDM is well suited for implementation in digital health.

FDM 3DP, a branch of material extrusion, is a diverse technology with its current applications ranging from aviation to automobiles, medicines, dentistry, art, jewellery, and footwear (Barnatt, 2016). Within pharmaceuticals, the adoption of FDM is forecast to initiate a paradigm shift in the drug design, formulation and production sectors (Berman, 2012). In particular, FDM 3DP could be applied as a fabrication tool within digital health for the remote manufacture and dispensing of personalised formulations having doses, shapes and sizes optimised to the patient. Such benefits provide flexibility and autonomy to the treatment process, potentially leading to the enhancement of therapy and medication adherence. This review provides an overview on the revolutionary prospects and opportunities that FDM 3DP holds for pharmaceutical formulation and production, whilst highlighting the outstanding technical and regulatory challenges that require consideration before its progression into common practice.

2. Material extrusion: an overarching principle

Material extrusion is a thermal process; the underpinning principle is the selective dispensing of a molten material through an orifice to generate fine semi-solid strands, which solidify on a build plate to create 3D objects. Materials used with this technology include thermoplastics, clays, waxes, gels, and pastes. As such, material extrusion is a broad term that expands to subsume other prominent techniques, including FDM and semi-solid extrusion. Whilst the terms material extrusion and FDM have often been used interchangeably, FDM deals only with thermoplastic materials (McMains, 2005).

FDM technology, also known as fused filament fabrication (FFF), was originated by Scott Crump in 1988 when he was attempting to craft

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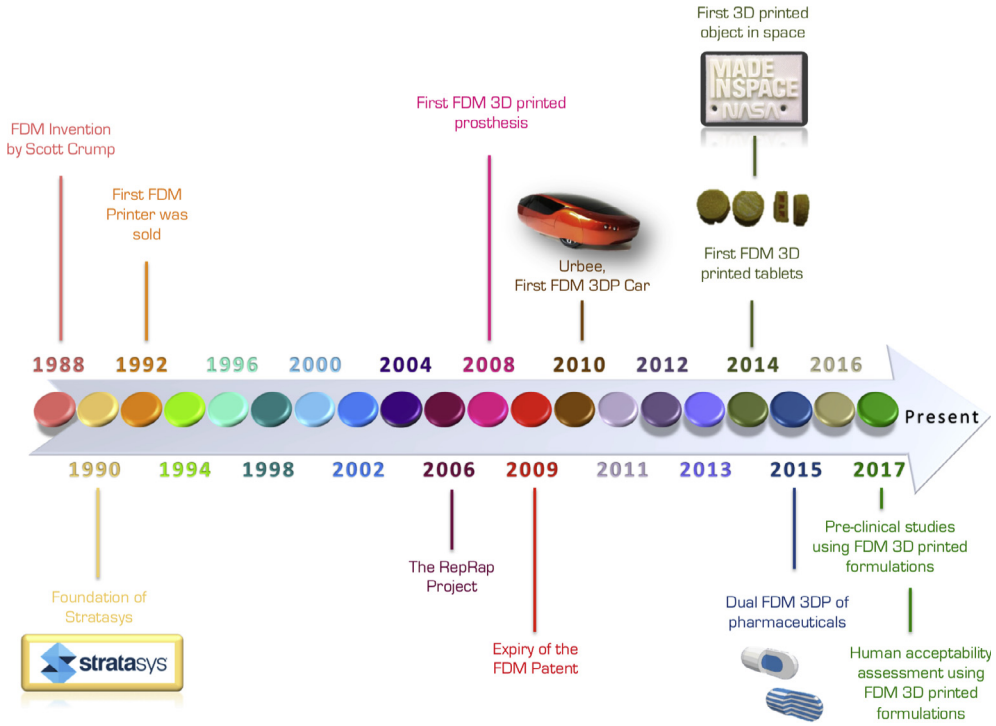

Fig. 1. Graphical timeline from 1988 to 2018: Current advances of the FDM technology. (Images reprinted with permission from (Goyanes et al., 2014; Goyanes et al., 2015d; Krassenstein, 2014; Stratasys, 2013, 2017b)).

a toy for his daughter using a simple glue gun (On3DPrinting.com, 2013). He replaced the conventional glue stick with a blend of polyethylene and candle wax and utilised it to construct the toy layers one over the other. The idea was then expanded and an automated version of the process was developed. In 1989, Crump and his wife patented the technology and co-founded their own company, Stratasys, to commercialise their product (Crump, 1992; Stratasys, 2017a). The technology was coined and trademarked as FDM™. A timeline of the current advancements in the FDM process are outlined in Fig. 1.

Like any other 3DP technology, the FDM method follows "the 3D's of 3DP" (Trenfield et al., 2018): (a) design: a 3D shape is designed using a computer-aided design (CAD) software. This shape is digitally divided into horizontal layers and is then loaded into the software of the printer in the form of a stereolithography (.stl) file (Stratasys, 2017a); (b) develop: a suitable thermoplastic drug-loaded filament is developed and then fed into the printer, where it is melted and extruded through a metal nozzle at a specific temperature (McMains, 2005). Most printers allow user-selection of the print head temperature and so an FDM printer can be used to print different polymers and polymer blends; (c) dispense: the extruded filament is subsequently deposited on the flat base of the printer, known as the build plate or platform. The print head moves in a rastor pattern, to create the first layer of the object. Upon the completion of each layer, the platform is lowered to allow enough space for a new layer to be deposited. As the filament cools down, it attaches to the previous layer. The process is then repeated until the completion of the object (Fig. 2). The resolution of the printed object is dependent upon the thickness of the extruded filament, typically 100 μm in a commercial printer.

By simply changing the polymer being printed, FDM has the ability to create complex objects with unique characteristics, such as high mechanical strength and thermal resistance. In medicine, surgeons have explored the possibility of utilising this technology to print anatomical guides and organs specifically adapted to patients, enabling them to train for challenging surgeries (Maxey, 2013). By integrating electronic sensors, these models can provide quantitative analysis on the surgical technique (e.g. duration of a surgery and success rates), and have thus

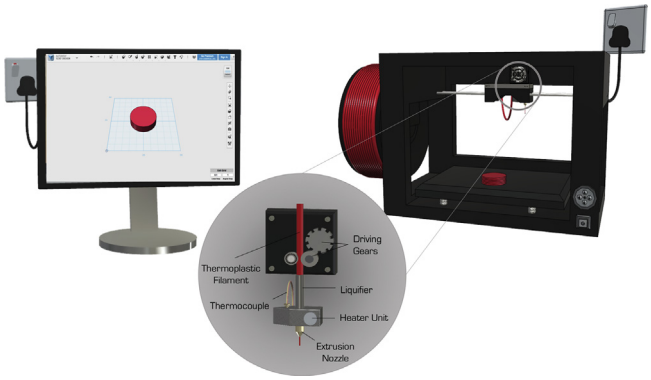

Fig. 2. Graphical representation of the FDM process.

been termed "smart surgical aids" (Qiu et al., 2018). In addition, organ models based on human data obtained using well-established imaging techniques, such as computed tomography (CT) or magnetic resonance imaging (MRI), can also be utilised as means of testing; a process termed biomodelling. For instance, an FDM 3D printed induction port (IP) model, based on the CT scan of a patient's trachea, was found to be superior to pharmacopoeial IPs, providing more insight into the *in vitro* evaluation of pressurised metered dose inhalers (Berkenfeld et al., 2018). However, compared with other 3DP technologies, for instance stereolithography (SLA), which has been used to print an airway model for inspiratory flow simulation (Collier et al., 2018) or nasal casts for the prediction of drug deposition from nebulisers (Warnken et al., 2018), FDM organ models have limited use as means for *in vitro* evaluation. This can be attributed to the limited resolution of these printers, resulting in a lower printing accuracy or the need for the use of support materials to create complex models.

Additionally, bespoke osteoid casts have been developed as a form of advanced therapy using FDM (Karasahin, 2013). These functional devices utilise low-intensity pulsed ultrasound (LIPUS) to stimulate bone healing. This induces mechanical stress on the cells of the