Reshaping drug development using 3D printing

Atheer Awad[1,‡], Sarah J. Trenfield[1,‡], Alvaro Goyanes[2], Simon Gaisford[1,2] and Abdul W. Basit[1,2]

[1] UCL School of Pharmacy, University College London, 29–39 Brunswick Square, London WC1N 1AX, UK
[2] FabRx Ltd, 3 Romney Road, Ashford TN24 0RW, UK

The pharmaceutical industry stands on the brink of a revolution, calling for the recognition and embracement of novel techniques. 3D printing (3DP) is forecast to reshape the way in which drugs are designed, manufactured, and used. Although a clear trend towards personalised fabrication is perceived, here we accentuate the merits and shortcomings of each technology, providing insights into aspects such as the efficiency of production, global supply, and logistics. Contemporary opportunities for 3DP in drug discovery and pharmaceutical development and manufacturing are unveiled, offering a forward-looking view on its potential uses as a digitised tool for personalised dispensing of drugs.

Introduction

Three-dimensional printing (3DP) has the potential to cause a paradigm shift in the way that drugs are designed, manufactured, and used. For centuries, civilisation has experienced periodic radical transformations, often described as industrial revolutions. With the advent of steam engines, the textile industry and mechanised factories, the first industrial revolution was pronounced [1]. Motivated by the harnessing of electrical energy for mass production, the second industrial revolution evolved [2]. Subsequently, the third industrial revolution was established by the adoption of automation [3]. Robotised and customised systems, such as cloud computing, the internet of things (IoT), and 3DP, have already been implemented to bridge the gap between the physical and virtual worlds [4]. Now, 3DP is at the forefront of the next industrial revolution.

3DP has created a technological paradigm by triggering boundless opportunities in diverse fields. It is an additive manufacturing technique that enables the fabrication of bespoke objects in a layered manner. By combining digitisation and mechanisation, this disruptive tool avoids the constraints often imposed by conventional tooling methods. Owing to its additive nature, 3DP delivers finalised products rapidly, with minimal waste production [5]. Additionally, because the object designs are digitised, their customisation, storage and transference can be achieved with ease, avoiding the need for labour and space occupancy. Collectively, this permits the straightforward instantaneous creation of complex bespoke objects. Thus, this singular platform has a multitude of applications, from aviation to automobiles, drugs, dentistry, art, jewellery, and footwear [6].

In the pharmaceutical field, the drug development process is a multistage procedure, requiring significant resources and time. Since the 1960s, this sector has been experiencing a dormant stage, with limited manufacturing advancements. Recently, 3DP has offered contemporary opportunities to revolutionise the pharmaceutical industry. In particular, 3DP can be used to fabricate 'printlets', which refers to 3D printed solid oral dosage forms (e.g., tablets and capsules). As such, this multidisciplinary tool could be implemented across the entire drug development process, enhancing the quality of treatment in healthcare.

Although most research in this area is primarily focused on personalised drugs, a multitude of opportunities remain underexplored (Fig. 1). In our previous review, we discussed the motivations and potential applications of 3DP in clinical research and practice, providing a practical viewpoint on its integration in a pharmaceutical setting, while highlighting the challenges and hurdles that come alongside [7]. Here, we focus on the technical

Corresponding author: Basit, A.W. (a.basit@ucl.ac.uk)
‡ These authors contributed equally to this work.

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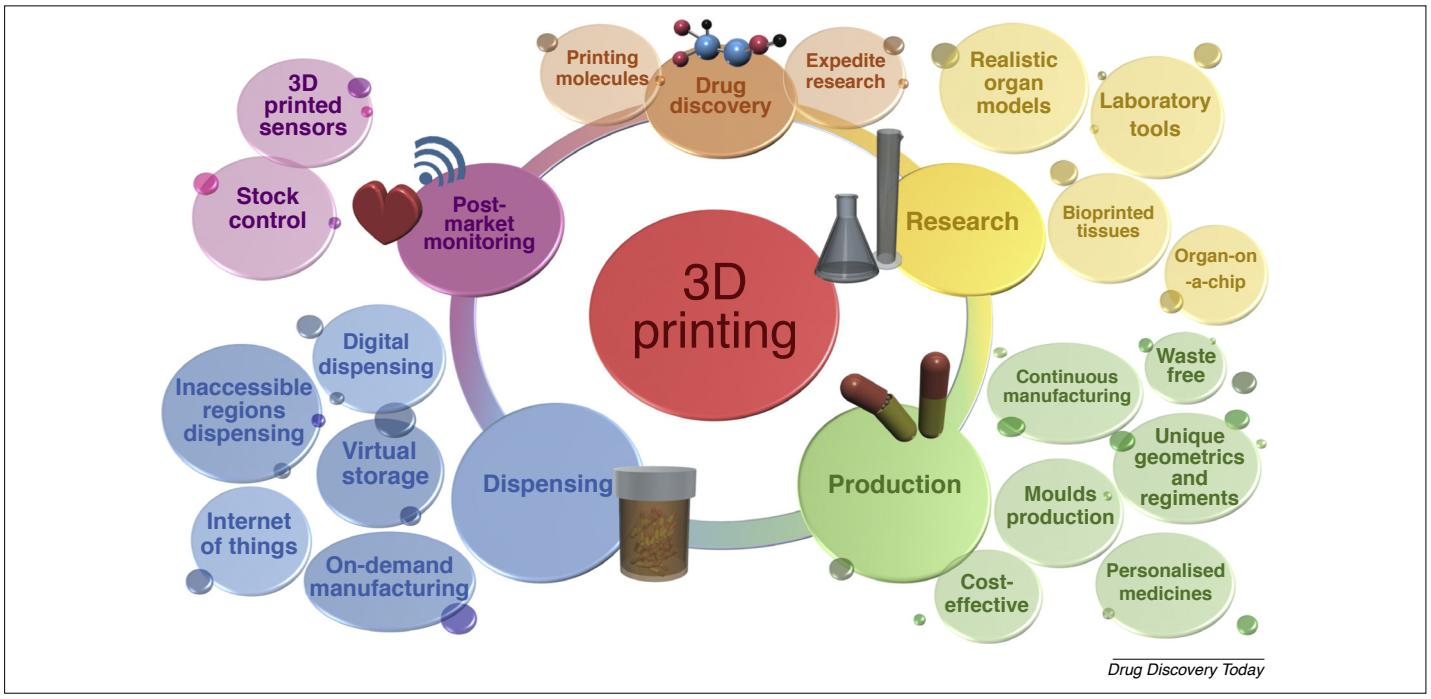

FIGURE 1

Graphical representation of the opportunities in which 3D printing (3DP) can be implemented.

aspects, offering an overview of the novel prospects via which 3DP can be applied to the different drug development phases, including early-phase screening, testing, manufacturing, and dispensing, while discussing some of the technological hurdles associated with the adoption of these processing for pharmaceutical production.

3D printing to support drug discovery

The drug failure rate is high during early phase development [8], creating a substantial financial burden for the pharmaceutical industry. In 2013, the cost of taking a new chemical entity (NCE) to commercialisation was estimated at ~US$5 billion dollars (www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/) and this value will only continue to increase over the next decade. As such, there is a growing need for innovative technologies to support drug development, in particular, by enabling rapid identification of suitable drug candidates at a minimal cost. 3DP could prove advantageous for this application by producing small or 'one-off' batches of formulations (and even drugs) in a cost-effective, efficient and flexible manner. Using such technology could expedite the drug development process.

Early-phase drug development covers the fields of drug discovery, preclinical studies, and first-in-human (FIH) clinical trials. Within drug discovery, 3DP has already been used to produce active pharmaceutical ingredients (APIs). Chemists from the University of Glasgow fabricated a series of reaction vessels (comprising polypropylene) using fused deposition modelling (FDM). The RepRap printer used was modified to incorporate liquid handling components, whereby liquid reagents could be dispensed into the reaction vessels after fabrication to carry out simple chemical reactions on a small scale [9]. Thus far, the group has produced ibuprofen and aim to make other molecules using this novel approach. Furthermore, Kitson *et al.* [10] successfully undertook the multistep synthesis of baclofen within a 3D-printed miniaturised reactor cascade, thus demonstrating the ability of 3DP to remotely digitise blueprints for print and synthesis.

3DP of miniaturised reaction vessels for API synthesis on demand could provide more flexibility to scientists. Compared with conventional methods, 3DP could help to support the synthesis of a range of different molecules on a small scale, particularly useful for those of high cost or poor stability [11]. Moreover, it could enable researchers to evaluate different chemical reactions and reaction conditions, enabling synthesis pathways to be more efficiently established. Printing reaction vessels on demand could also enable API synthesis to be performed at locations that could otherwise not support such processes, such as within remote locations or even for expensive personalised medicines in the clinic. However, there are limitations to the process, including consideration of solvent incompatibilities and heat tolerance of the printed materials, requiring more research to be performed in this area before integration [12]. Other considerations surrounding decentralising production are discussed below.

These benefits could also be extended to preclinical drug development. Through advancements in bioprinting, researchers have been able to 3D print animal and human tissues, which could be suitable for acute and chronic drug toxicity screening, as well as metabolic studies. For example, Organovo specialises in 3D bioprinting of structurally and functionally accurate human tissue models (such as liver and kidney tissue) that can be used for medical and therapeutic research (http://organovo.com). Moreover, 3DP has been used to create 'organs-on-a-chip', designed to mimic the structure and function of human or diseased tissue. Researchers at Harvard University 3D printed the first cardiac microphysiological device, which was used to study drug responses as well as contractile development of laminar cardiac tissues [13]. This has also been taken