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Three-Dimensional Printing of Medicinal Products and the Challenge of Personalized Therapy

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ABSTRACT

By 3-dimensional (3D) printing, solid objects of any shape are fabricated through layer-by-layer addition of materials based on a digital model. At present, such a technique is broadly exploited in many industrial fields because of major advantages in terms of reduced times and costs of development and production. In the biomedical and pharmaceutical domains, the interest in 3D printing is growing in step with the needs of personalized medicine. Printed scaffolds and prostheses have partly replaced medical devices produced by more established techniques, and more recently, 3D printing has been proposed for the manufacturing of drug products. Notably, the availability of patient-tailored pharmaceuticals would be of utmost importance for children, elderly subjects, poor and high metabolizers, and individuals undergoing multiple drug treatments. 3D printing encompasses a range of differing techniques, each involving advantages and open issues. Particularly, solidification of powder, extrusion, and stereolithography have been applied to the manufacturing of drug products. The main challenge to their exploitation for personalized pharmacologic therapy is likely to be related to the regulatory issues involved and to implementation of production models that may allow to efficiently turn the therapeutic needs of individual patients into small batches of appropriate drug products meeting preset quality requirements.

Introduction

Three-dimensional (3D) printing enables the construction of solid objects of any shape through layer-by-layer addition of materials (additive manufacturing) based on a digital model.[1,2] In contrast to traditional subtractive manufacturing, which consists in successively cutting away material from a starting block to build up the final object, 3D printing allows production to be carried out with no waste of materials and no need for their disposal. Because objects are constructed automatically, according to preset digital models, relevant preliminary geometry study, production planning, and manual manufacturing steps can be limited or avoided. This results in major advantages in terms of reduced times and costs, irrespective of the extent of complexity of the item shape. The degree of conformity of an object to the electronic model by which it was generated (i.e., resolution) basically depends on the thickness of the single layers deposited and can, thus, be enhanced through proper modulation of this parameter.

3D printing encompasses a range of techniques differing from each other in the nature of the substrate (e.g., ceramics, metals, polymers, composites), deposition mode, mechanism of layer formation, printer used, and characteristics of the final product (e.g., morphology, texture, surface, thermal/mechanical/conductivity properties). According to the ASTM, these techniques are classified based on the additive process involved (Table 1).[3]

Independent of the specific technique applied, 3D printing processes generally entail common steps: the creation of a CAD file, its conversion into a *.stl* file, which will be transferred to the equipment, the printer set-up and proper fabrication of the object, its removal from the build plate, post-processes, and final cleaning

Abbreviations used: 2D, two dimensional; 3D, three dimensional; ABS, acrylonitrile butadiene styrene; API, active pharmaceutical ingredient; ASTM, American Society for Testing Materials; CAD, computer-aided design; DDS, drug delivery system; DPPO, diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide; EC, ethyl cellulose; EDTA, ethylenediaminetetraacetic acid; EVA, ethylene vinyl acetate; FDA, Food and Drug Administration; FDM, fused deposition modeling; HIPS, high-impact polystyrene; HME, hot melt extrusion; HPC, hydroxypropyl cellulose; HPMC, hydroxypropyl methyl cellulose; IM, injection molding; MCC, microcrystalline cellulose; PCL, poly-ε-caprolactone; PEG, polyethylene glycol; PEGDA, poly (ethylene glycol) diacrylate; PLA, poly (L-lactic acid); PLGA, poly (lactide-co-glycolide); PVA, polyvinyl alcohol; PVP, polyvinyl pyrrolidone; SLA, stereolithography; SLS, sodium lauryl sulfate; TEC, triethyl citrate; TPU, thermoplastic polyurethane; UV, ultraviolet.

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Table 1
Classification of the Main Additive Manufacturing Techniques

Technique	Substrate	Mechanism of Layering	Additive Process
Fused deposition modeling	Filament (thermoplastic polymer)	Melting/softening by an heated nozzle	Extrusion
Electron beam direct manufacturing	Wire (metal)	Melting by an electron beam	Direct energy deposition
Selective laser sintering	Solid particles	Melting by laser	Solidification of powder
Three-dimensional printing		Binding by wetting	
Stereolithography	Liquid (photopolymer)	Binding by UV ray	Photopolymerization
Laminated object manufacturing	Sheets (paper, metal, plastics)	Cutting by laser	Sheet lamination

step if needed (Fig. 1).[1,2] The entire manufacturing process occurs as a single step under computer control, thus avoiding intermediate stages of production and any manual task. Any change in the final object design can be achieved by modifying the relevant CAD file.

Personalization

The current popularity of 3D printing in various fields is often described as a new industrial revolution.[4,5] Although in the last centuries, industries were focused on mass manufacturing, automation, and standardization to reduce costs and increase profit, with the advent of 3D printing, they are shifting to on-demand production of either a small number of objects or even 1 object at a time (small batches), possibly customized, at affordable prices. Products characterized by complex geometries can also be fabricated and real-time modified to meet individual needs at little or no extra costs. 3D printing is spreading throughout all manufacturing stages of production, from the prototyping step to the fabrication of consumer products. By shortening the design, manufacturing, and production cycle, thus simplifying the manufacturing chain, this new technology has brought the site of object fabrication closer to that of demand. Moreover, it has proved effective as a rapid prototyping tool useful to evaluate the form, fit, and function of many objects before their production on a large scale. Finally, because items are fabricated on request, waste and inventory can be reduced, and issues related to overproduction are circumvented.

Personalized Medicine

Within the health care field, 3D printing has grown in step with the concept of personalized medicine, which has been attracting more and more attention in the last.[6-10] Personalized medicine generally consists in tailoring medical treatments to the characteristics, needs, and preferences of each single patient, and it involves purposely run diagnosis, therapy, and follow-up. The concept could be extended to include pre-emptive medicine aimed at reducing the risk of diseases a subject has shown susceptible to, by changing his lifestyle, diet, and habits and by advising him on the use of peculiar supplements or drugs. Personalized medicine is not actually a new idea: physicians have noticed over time that patients with similar symptoms may have different illnesses and that medical treatments may work in some subjects while not being as much effective in others apparently suffering from the same disease. Recent advances in various medical and biomedical fields, from genomics to imaging, have already allowed patients to be treated and monitored more properly, in closer and closer agreement with their individual needs. By way of example, genetic tests are used before diagnosis, thereby enabling earlier intervention, more efficient drug selection, and increased safety. Indeed, the goal of personalized medicine is to drive clinical decision making by distinguishing in advance those patients who are most likely to benefit from a given treatment from those who would incur costs and side effects without gaining equivalent benefits. In this respect, 3D printing could provide the answer and instrument for moving from mass production based on the one-size-fits-all approach to manufacturing of small batches of individually developed products that can be modified in real time and possibly fabricated at the point of care.[11-14]

Personalized Therapy

In the medical field, 3D printing was initially used by surgeons as an aid in creating 3D models of patients to better visualize their anatomy, particularly in the case of individuals with unique structures or anomalies, which would require complex surgeries.[15,16] With respect to tissue engineering, medical devices, especially scaffolds and prostheses, currently represent one of the most interesting manufacturing applications of 3D printing.[17] This technique has partially replaced more established ones (e.g., solvent casting and particulate leaching, membrane lamination, molding) because it enables fabrication, starting from biocompatible materials, of items perfectly fitting the anatomical characteristics of the patient as highlighted by diagnostic imaging tools (e.g., X-ray, computed tomography, nuclear magnetic resonance). Scaffolds are intended for different functions, such as space filling,

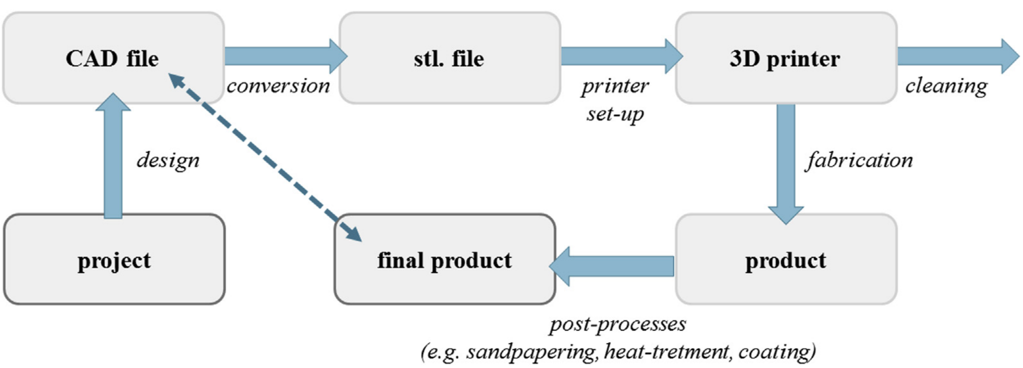

Figure 1. Outline of common steps generally entailed by a 3D printing process.