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REVIEW

3D PRINTING PHARMACEUTICAL FORMULATION OF DRUGS IN PERSONALIZED THERAPY

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Abstract

3D printing offers the key for manufacturing new pharmaceutical forms and devices with complex structures and geometry that meet individual needs of patients, improving compliance, accessibility and affordability of medicines. Also, due to 3D printing technologies, on demand fabrication of pharmaceutical products in critical situations may be an easy task in the future. In this review we focused on the main 3D printing technologies, 3D printers and 3D software platforms widely used at present. Also, we discuss the most important achievements that have been obtained lately using 3D printing in the pharmaceutical field.

Rezumat

Metodele de fabricare aditivă 3D reprezintă o tehnologie cu rol esențial în obținerea unor forme și dispozitive farmaceutice noi, cu structuri și geometrii complexe, care corespund unor cerințe individualizate ale pacienților, ceea ce are ca efect creșterea complianței, accesibilității și afordabilității medicamentelor. Tehnologiile de printare 3D oferă, de asemenea, perspectivele producerii rapide și eficiente a unor produse farmaceutice în situații critice. Articolul descrie principalele tehnologii de imprimare 3D, imprimantele 3D și platformele *software* care sunt disponibile în prezent, precum și cele mai importante realizări ale tehnogiei de imprimare 3D în domeniul farmaceutic.

Keywords: additive manufacturing, 3D printing, pharmaceutical

Introduction

3D printing technology is different from traditional materials processing procedures. Sometimes considered a synonym for additive manufacturing, solid freeform fabrication, layered manufacturing or rapid prototyping [1, 2], 3D printing allows creation of three-dimensional objects by layer-by-layer deposition of printing materials [3]. This method has remarkable attributes like accuracy, repeatability and reliability [4].

3D printing uses Computer-Aided Design/Computer-Aided Manufacturing (CAD/CAM) applications to design and control fabrication processes. CAD/CAM systems are composed by: a scanner that translates geometric features of a 3D object in digital data; a software that process digital data received from the scanner and controls; a device that manufacture desired object using a specific technology [5].

3D printing has a great potential and applications in many fields, including medicine, electronics, aerospace, engineering and architecture. Various materials are used for 3D printing like sand, metals, ceramics and polymers [6].

The first commercial 3D printing technology, stereolitography, was invented in 1986 by Charles Hull, the co-founder and chief technology officer of 3D systems. In 1994 he received the Jacquard Award from the Numerical Controls Society. [7]

In time, different methods for 3D printing have been developed like Inkjet-Based 3D printing, continuous inkjet printing (drop-on-demand), nozzle-based 3D printing technologies (fused deposition modelling, pressure-assisted micro syringes technology) and laser-based writing methods (stereolithography, laser-induced forward transfer) [8, 9, 10].

Table I

3D printing methods [8, 9, 10, 11, 12, 13]

Type	Subtype		Basic Principle
Inkjet - based printing systems	Continuous inkjet printing (CIJ)		Continuous column of droplets are generated and deposited to selected positions on a target substrate.
	Drop-on-demand (DOD)	Thermal DOD	The pressure needed for ejection of the volatile printing material is performed by a heating device.
		Piezoelectric technology	The system contains a piezoelectric system that induce a rapid deformation of the fluid printing ink, thus generating the pressure required for ejection of the droplets.
Nozzle -based deposition systems	Fused deposition modelling (FDM)		Is based on heating and extrusion of a semi-liquid thermoplastic ink that is sequentially settled to obtain a 3D object using a removable scaffold.
	PAM (pressure-assisted micro syringes) technology		The viscous, semi-liquid ink is deposited layer by layer, according to a pre-designed 3D form, using a microsyringe moved by pressure generated by an air piston.
Laser-based writing system	Stereolithography (SLA)		UV laser transfers the energy to a photopolymerizable liquid resin. The 3D object is build layer by layer from the photochemical solidified resin.
	Laser-induced forward transfer (LIFT)		The energy of a high-powered laser pulse deposit the printing material on a receptor substrate. The system has a sacrificial layer (usually a metallic film volatilized under the laser pulse) and a transfer layer.

Table II

3D printing technologies classification [14]

3D printing technologies	
Working principles	Binder jetting
	Material extrusion
	Directed energy deposition
	Powder based fusion
	Material jetting
	Vat photopolymerization
	Sheet lamination
Starting material states	Fluid material technologies
	Powder material technologies
	Solid material technologies
Energy sources	Inkjet-based printing
	Laser-based printing
	Force (extrusion)-based printing
	Ultrasonic-based printing
	Electron beam-based printing
	UV-based printing
Biological functions	Printing without living cells
	Printing with living cells (3D bioprinting)

Another 3D printing method is free-form spatial 3-D printing using part levitation that utilise acoustic or magnetic levitation of the printing material into space to form 3D objects. The method allows modification of the printed object by multiple print heads located in different positions. The 3D object can be moved and rotated to any angle without the need of a support structure [15].

The concept of 4D printing was developed by Skylar Tibbits from the Massachusetts Institute of Technology. He and his collaborators combined plastic filaments with a layer built of a "smart" material that is capable to undergo an auto contruction process in water [16]. In 4D printing, objects obtained by 3D printing are capable to self-transform into programmable, geometrically modified structures as a result to an extern stimulus (heat, pH, light etc.). 4D printing uses "smart materials" like electroactive polymers, shape memory alloys, shape memory polymers etc.

Software platforms for image processing in 3D printing.

Osirix® MD is a medical images viewer widely used by healthcare professionals from the entire world. The software is dedicated to post process 2D and 3D images, for 3D and 4D navigation and supports 64-bit computing. It is certified and validated for clinical use in medicine (FDA, CE, ANVISA) [17].

3D Slicer was developed by National Institutes of Health and other collaborators as a free, open source software for medical image informatics, image processing and three-dimensional visualization. It is used for analysis (including registration and interactive segmentation) and visualization (including volume rendering) of medical images and for research in image guided therapy [18].

Meshmixer version 3.2 by Autodesk Inc. is a free software that can analyse and fix the printing model, thus correcting errors or irregularities and saving time and efforts [19].

Mimic is another software platform for 3D scanning image capture, 3D design and reverse engineering, 3D inspections and analysis, 3D printable models rapid prototyping, parametric CAD modelling and NURB modelling. It can be successfully used in reverse engineering, rapid prototyping, inspection (quality control, first article and production line measurement, geometric dimensioning and tolerance, animation (face and body scanning, data acquisition for 3D character creation, 3D worlds from physical scale models), surgery, dentistry, archaeology, architecture etc [20].

3D printers

3D NovoGen MMX® Printer (San Diego Organovo) is dedicated to create high-resolution representations of human cancerous networks. Cancerous cells derived from human donors or tumour cell banks are grown and replicated in the lab and further used in a 3D printing process. Subsequently, the cells will form a viable tissue that can be studied and tested using different drugs [21, 22].

Aether® 1 printer (Aether Inc.) can create 3D objects formed by maximum 24 materials (viscous pastes, gels, ceramics, filaments, oils, liquids, resins etc.), in one printing process. The modular system contains 8 syringes, 2 hot-ends and 10 extruder fabrication systems. Optional attachments with different functions are available [23].

BioFactory (RegenHU) prints organotypic tissues with *in vivo* like morphology. The printing process can be performed in physiological conditions. The system utilizes multiple technologies and contains a laser unit for photopolymerisation and biomolecules immobilization. Tissue modelling is easy and rapid. BioCAD software can design models with complex structures without a prior 3D archetype or an image that contain medical informations [24].

3D Discovery Bench Top (RegenHU) is intended for research and development. It creates three-dimensional organomimetic models with composite structures for tissue engineering. The 3D Discovery BioSafety is a derivate of 3D Discovery Bench Top equipped with a class II biosafety cabinet [24].

Form 2 printer is dedicated to high-resolution 3D printing in digital dentistry. The system contains an integrated resin system in order to automatically fill in the tank printer during printing process and a 250 mW precision laser for high resolution. 3D Models are created with PreForm Software 2.12.3 [25].

3D Printer Families, Desktop, Prefactory, CDLM Printer, 3SP, VIRIDS3D, SLCOM, 3D-BIOPLOTTER, developed by Envision TEC use revolutionary DLP (digital light processing) technology. 3D-Bioplotter (starter, developer and manufacturer) Series print tissue, organs or other anatomical structures from biomaterials that solidify as a consequence of physical or chemical processes (hydrogels, melted polymers, ceramics, metals). The system uses air or mechanical pressure applied to a syringe, in highly accurate processes with X-Y repeatability down to 1 μm. Printers can be used in sterile biosafety cabinets at standards required for clinical trials. Mechanic properties and cellular adhesion can be easily controlled in printing processes for tissue engineering [26].

Table III

Bioprinters [27]

Printer	Company	Technology	Materials for printing	Price
3D Bioplotter Manufacturer Series + Developer Series	EnvisionTEC	Syringe extrusion	Hydrogels Silicon Hydroxyapatite Titan Chitosan	over $ 200,000
NovoGenMMX	Organovo	Syringe extrusion	Hydrogels	
3DDiscovery + Biofactory	RegenHU	Syringe extrusion	Bioinks Osteoinks	$ 100,000 - 200,000
BioBot1	BioBots	Syringe extrusion Blue light technology	Agarose Collagen Alginate PEG	$ 10,000
Inkredible	CELLINK	Syringe extrusion	CELLINK CELLINK A Others	€ 5,000 - 9,000

Printer	Company	Technology	Materials for printing	Price
Revolution	Ourobotics	Syringe extrusion	Collagen Alginate Others	€ 12,500
BioAssemblyBot	Advanced Solutions'	Syringe extrusion 6 axes	Different materials	$ 159,999
Bioscaffolder 2.1	GeSim	Syringe extrusion Piezoelectric pipetting	Polymers Pastes with high viscosity Alginate Calcium phosphate Silicon Solutions with proteins or cells	$180,000
Alpha & Omega	3Dynamic Systems	Syringe extrusion	Natural polymers Synthetic polymers Calcium phosphate Hydrogels	£ 12-18,000

Currency: $ - USD, € - EUR, £ - GBP

Top companies on the 3D printing market in healthcare field

Among the leading companies that offer innovative products and services for 3D printing we can list Stryker (U.S.), Zimmer Biomet (U.S.), Boston Scientific Corporation (U.S.), Smith & Nephew (U.K.), Biotronik (Germany), Tornier N.V. (The Netherlands), B.Braun (Germany), Science for Biomaterials (France), Kasios (France), Mediplus (UK).

Biotronik is a privately held company that offers medical technology and services for people with cardiac and circulatory diseases (pacemakers, stents, implantable defibrillators) in more than 100 countries [28].

Stryker, a leader in medical technology, provide a wide array of products and services in Orthopedics. It was founded as a hospital bed manufacturer in 1941. In the present, the company has three departments: Orthopedics, MedSurg (medical and surgical devices), Neurotechnology and Spine and delivers its devices in more than 100 countries. Some of Stryker's progressive innovations include robotics and 3D printing [29, 30]. In 2013, Stryker gained Mako system, that can be used in knee-replacement surgery, being able to create 3D models for fitting of the implant prior to the operation and to assist the physician during surgery. In 2017, Stryker launched its Mako Robotic-Arm Assisted Total Knee system made by Mako technology with Stryker's Triathlon Implant system. Stryker have been developed its own 3D printing process called AMagine (the "AM" - "Additive Manufacturing"). The company is focused on 3D printed metallic devices (titanium). The company received FDA approval in 2016 for Tritanium PL (Posterior Lumbar) Cage, a 3D printed spinal implant that mimics the natural structure of bones [30, 31].

Biomet Orthopedics is oriented to design and manufacture orthopaedic implants. The company developed Signature technology. In 2012, Biomet Orthopedics demonstrated how the Signature technology function in real time surgery processes. This technology utilizes MRI imaging to offer 3D data about patient's anatomy in order to increase effectiveness of the procedures and to simplify partial knee arthroplasty interventions [32, 33].

Zimmer Biomet is another top company oriented to design foot and ankle joint fusion systems with 3D printing and OsseoTi porous metal technology. In 2016 the company announced FDA Clearance for Unite 3D Bridge Fixation System foot and ankle joint fusion system that has a structure that resemble the one of the cancellous bone and contains an osteoconductive material for embodiment of biological factors [34].

Smith & Nephew is one of the best provider of joint replacement systems for knees, hips and shoulders. On 1 March 2016 the company launched REDAPT Revision Acetabular Fully Porous Cup with CONCELOC Technology. The product applicability is intended for revision cases with injuried bone that generate complications in implantation procedures. The porous implant is produced by a 3D manufacturing process and mimics the structure of the cancellous bone [35]. The company developed the Syncera program in order to lower hip and knee products prices by 40% to 50% for the market of 5% to 10% of U.S. hospitals [36].

St. Jude Medical, Inc. (US) announced on October 2013 the FDA approval for Ilumien Optis PCI optimization system, an innovative technology produced to support physicians with an allinclusive disease evaluation tool for people that suffer of coronary artery disease (CAD). The platform assists medical specialists in order to manage the disease in optimal conditions. The OCT imaging technology provides 3D reconstruction of the patient's vessel in real-time, making effortless for doctors the visualization of the treated area [37].

BioBots was founded as a 3D bioprinting start-up. The first product is BiotBots 1 that can print living tissues or non living scaffolds at a resolution of 100 micrometres using biomaterials, binding factors and cells that are pulled together in a device, extruded out of a syringe and cured with blue light or UV light. The system produce tissues that can replace the animals in tests currently performed in pharmaceutical and medical filed [38].

Therics Inc. is a Princeton-based biopharmaceutical company oriented to develop innovative products with a revolutionary 3D printing technology. With TheriForm micro-fabrication technology, the company is able to manufacture complex products that could not be produced by now-a-days conventional manufacturing technology. In 2008, Therics was taken over by Integra LifeSciences Holdings Corp [39].

Aprecia is a company that produces Spritam, the first FDA approved drug produced by 3D printing. Spritam uses ZipDose technology to assemble multiple layers of powder with an aqueous fluid, producing a porous, water-soluble structure that rapidly disintegrates if exposed to a liquid. This technology allowed the development of orodispersible formulations with high doses (up to 1,000 mg) of pharmacologically active substances [44].

Rainbow Biosciences is a division of Rainbow Coral Corp. that created the 3D BIO Assay, the first 3D bioprinting system for drug's toxicity screening. The system prints 3D structures made from biocompatible magnetic nanoparticles and cells [41].

Personalized Pharmaceutical 3D printing

It is predicted that 3D printing of drugs will have an endless impact on drug discovery and personalized therapy producing medicines with maximum efficacy and minimum toxicity [42]. It is generally accepted that 3D printing has three exclusive features in pharmaceutical field that improve the effect, safety and accessibility of drugs: it allows manufacturing of complex pharmaceutical products, personalization and on-demand production of medicines [43]. Last but not at least, 3D printing provides the solutions for fabrication of pharmaceutical products in various critical situations like natural disasters, military operations, in emergency and operating rooms and in healthcare units when time and resources are limited [44].

3D printing technology provides an infinite number of opportunities for fabrication of patient-specific drug delivery devices and dosage forms for personalized drug therapy [45]. Currently, versatile therapeutic systems are developed with tailor-made formulas of different active pharmaceutical substances, in various doses and with various kinetic profiles. 3D printed pharmaceutical forms with particular designs and compositions offer the advantages of fabrication of multiple separate chambers that can be loaded with different substances, thus modulating the bioavailability of drugs [46].

3D printing of new pharmaceutical products

The new era of medicine address the issues of safety and efficacy of drugs, requesting new methods for production and evaluation of pharmaceutical forms [48]. In the last years, 3D printing received a constant attention from pharmaceutical sector and important steps have been made promising prospective success of implementing new methods for design and production of high quality medicines by these state of the art technologies [48].

3D Pharming (the direct printing of pharmaceutical comprimates) represents a new innovative process for manufacturing controlled release drug delivery systems.

There are many examples of new pharmaceutical forms produced by 3D printing.

Verstraete *et al* used fused deposition modelling technology to manufacture thermoplastic polyurethane (TPU)-based personalized pharmaceutical forms loaded with high concentration of drugs (up to 60% w/w) [49].

Li *et al* used 3D printing for generation of gastro-floating tablets with a hydrophilic component made from hydroxypropyl methylcellulose. The extrusion molding agent was microcrystalline cellulose and the active compound was dipyridamole, a drug used to prevent blood clots formation after heart surgery, strokes and heart attacks [50].

Acosta-Vélez *et al* prepared a biocompatible photocurable polymeric ink for 3D printing of pharmaceutical products with hydrophilic drugs. The printing polymer was obtained from hyaluronic acid functionalized with norbornene moieties. This compound goes through a rapid polymerization process in the presence of Eosin Y as photoinitiator and poly(ethylene)glycol dithiol, if it is exposed to visible light. Ropinirole HCL was used as active compound for tablets formulation [51].

In 2015, FDA authorized the first 3D manufactured drug, Spritam®, that contains as active pharmacologic substance an anti-epileptic drug, levetiracetam [52, 53, 54]. Levetiracetam has unique properties compared with other drugs with the similar pharmacologic activity [54, 55]. It can be used for treatment of partial onset seizures, myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures [56]. Spritam® is produced by an innovative technology (ZipDose technology) developed by Aprecia, a drug delivery platform company. ZipDose technology can be used to manufacture rapidly disintegrating orodispersible formulations of drugs by 3D printing [40].

ZipDose Technology prints a porous matrix made from multiple layers of powder fixed with an aqueous fluid that is further used to produce premeasured orodispersible formulations of drugs that disintegrate in the mouth with small quantities of liquids. Currently, is the only platform for formulation of pharmaceutical products that disintegrate rapidly and contain high quantities of active substances [40]. The advantages of ZipDose technology rely on the rapid disintegration of the tablets even at high dose of pharmaceutical compound (up to 1,000 mg), on the potential of using a large number of taste-masking excipients and on unit-doses delivery that increase patient compliance [57].

"Polypill" describe a pharmaceutical tablet that contains a mixture of several drugs. These comprimates have a great potential for cardiovascular therapy. Also, they could represent an inexpensive alternative to pharmaceutical forms used in current practice [58]. To date, conclusions about polypill's efficacy in cardiovascular diseases events and mortality are inaccessible and are investigated in clinical trials at present [59]. The CNIC-Ferrer polypill is the only product for which a marketing authorization has been granted in the EU, in other European countries and in Latin-America [60]. The Fuster-CNIC-Ferrer CV polypill (Trinomia®, Sincronium®, Iltria®) was developed in order to provide to patients accessibility to a simplified treatment, in an economical way. This polypill was designed, produced and patented by Ferrer. Active ingredients (atorvastatin, ramipiril and acetylsalicylic acid) are printed in a single capsule. Pharmacological substances properties remain unaffected and physico-chemical incompatibilities do not occur (between atorvastatin, ramipiril and acetylsalicylic acid there is a chemical incompatibility), 3D printing technologies allowing strict control of active ingredients location within the polypill and drug release kinetics [61].

Khaled *et al* used (3D) extrusion printing to obtain polypills for the treatment of cardiovascular diseases with five separate sections, each of them being loaded with a single drug. The polypill released the drugs according to two pharmacokinetic release profiles. The tablet contained an immediate release reservoir with aspirin and hydrochlorothiazide and three sustained release compartments with pravastatin, atenolol and ramipril [62]. The same author also obtained by 3D extrusion printing a polypill containing a guaifenesin bilayer tablet, that matches the international standards stated in the US Pharmacopeia [63].

Development of new medical devices

Cannabinoids are involved in analgesia and in anti-inflammatory processes and can be used to treat various conditions like chronic pain [64, 65]. The major components of cannabis are Δ9-tetrahydrocannabinol with psychotropic action and cannabidiol, a non-psychotropic component, with anti-inflammatory effects [66, 67, 68].

The Syqe Inhaler® was developed by Syqe Medical, a start-up company from Tel Aviv. Is the first-in-class pocket-sized selective-dose cannabis inhaler that have been made with 3D printing technology (80% of The Syqe inhaler was 3D printed using Stratasys MED610 biocompatible material with Stratasys Objet 350 3D Printer). The device can be connected to a Wi-Fi network on a smart phone or tablet. pSyqe Inhaler Exo® is the inhaler's variant that can be used in hospital units [69]. The devices maintain an excellent ratio between pharmacological action and psychoactivity. Eisenberg *et al* studied the pharmacokinetics, safety, tolerability and efficacy of Syqe Inhaler® device in a trial program and proved the efficacy of this 3D printed instrument according to the required pharmaceutical standards [69, 70].

We can also mention non printed pharmaceutical products that contains cannabinoids, like those ones obtained by 4GW Pharmaceuticals, a leader company that design and develops pharmaceutical forms with cannabinoids for the treatment of rare types of epilepsy syndromes [71, 72]. Some of these products have already been tested in studies FDA approved. Epidiolex® is an oral solution with cannabidiol (CBD) extracted from plants. The company received the FDA authorization for a clinical trials program [72]. Sativex® (US approved name: nabiximols) is an oromucosal spray of a formulated extract of the *Cannabis sativa* plant that contains the principal cannabinoids delta-9-tetrahydrocannabinol (THC) and CBD in a 1:1 ratio, and specific minor cannabinoids and other non-cannabinoid components. Sativex® has been approved in 30 countries so far (outside the United States) [72]. In Germany, Sativex® administration was approved in 2011. THC-containing capsules and oil are not approved yet in this country (German Narcotic Drugs Act) [73].

Table IV

Cannabinoids approved by the U.S. Food and Drug Administration (FDA) for clinical use [74, 75]

Cannabinoid	Active substances	Formulation	Company	Indications
Cesamet®	Nabilone a dimethylheptyl analog of THC	Capsules for oral administration	Meda Pharmaceuticals, Somerset, NJ, USA	Severe nausea and vomiting associated with chemotherapy neuropathic pain and pain associated with cancer and fibromyalgia
Marinol®	Dronabinol THC	Capsules for oral administration	AbbVie, Inc., North Chicago, IL, USA	Nausea and vomiting in patients receiving cancer chemotherapy who failed to respond to conventional antiemetics appetite stimulant for patients with wasting diseases such as cancer and HIV/AIDS
Sativex®	*Cannabis* extract 50:50 THC and CBD	oromucosal spray	GW Pharmaceuticals, Cambridge, United Kingdom	Treatment of chronic pain that is unresponsive to opioids

3D printing of pharmacologically active substances

3D printers can be transformed in successful automated minilabs for chemical synthesis of pharmaceutical compounds, as Professor Cronin and his collaborators from the University of Glasgow have been already proved. They produced a nonsteroidal anti-inflammatory drug, ibuprofen, by a three-step process, using a modified open source 3D printing platform, RepRap. Professor Cronin has provided, at the same time, a low-cost solution for 3D printing of pharmacologically active substances. The cost associated with the 3D printer used in this study was about 600-700 € [76].

Legal issues concerning 3D printing of drugs and medical devices

FDA is reviewing 3D printed products and evaluated the safety and efficacy of 3D printed medical devices and 3D printed drugs [77]. Two laboratories in the FDA's Office of Science and Engineering Laboratories, Functional Performance and Device Use Laboratory and Laboratory for Solid Mechanics, are investigating the future of 3D printing in healthcare field [77].

In 2016, the FDA distributed a guide book with Technical Considerations for Additive Manufactured Devices that contains recommendations for developers who produce equipment through 3D printing techniques [77].

Conclusions

Currently, applications of 3D printing innovative technologies are the most powerful and promising tools in the pharmaceutical field. Even there are numerous difficulties regarding technical resources, safety and security concerns and lack of a legal base, the scientists and physicians already foreknow the great opportunities are raising from 3D printing technology applications in healthcare. The pharmaceutical world will be inevitable changed in the next future by 3D printed medicines, opening new directions for personalization of drug therapy or development of new pharmaceutical forms and solving important problems that occur daily in drug therapy. The 3D printed market will forcefully expand as a result of innovative healthcare solutions, improving the life quality for a large number of patients.

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