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"3D PRINTING: A NEW AVENUE IN PHARMACEUTICALS"

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ABSTRACT

3D-printing (3DP) is the art and science of printing in a new dimension using 3D printers to transform 3D computer aided designs (CAD) into life-changing products. With 'SIPTRAM' the first 3D printed tablet acquiring FDA approval, has opened new avenues in pharmaceutical manufacturing. It is perched as the next technology revolution for the pharmaceutical and medical-device industries. Additive manufacturing classifies the 3DP process in namely seven categories i.e. material jetting, binder jetting, material extrusion, powder bed fusion, photopolymerisation, directed energy deposition and sheet lamination. This review objectively explores the potential growth, impact, quality assurance and regulatory problems of 3DP in pharmaceutical and medical devices industry.

KEYWORDS: 3D-printing, computer aided designs, fused deposition modeling, stereolithography, bioprinting.

3D printing technology

3D printing or additive manufacturing is a process of making three dimensional solid objects from a digital file. The creation of a 3D printed object is achieved using additive processes. In an additive process an object is created by laying down successive layers of material until the entire object is created.[1] Each of these layers can be seen as a thinly sliced horizontal cross-section of the eventual object. It acquired an impact as standard tool in the automotive, aerospace, and consumer goods industries. More recently, 3D printing has gained interest in pharmaceutical manufacturing, with FDA's approval of a 3D-printed drug product in August 2015.[2]

History

Early Additive Manufacturing (AM) equipment and materials were developed in the 1981. In 1981, Hideo Kodama of Nagoya Municipal Industrial Research Institute invented two AM fabricating methods of a three-dimensional plastic model with photo-hardening polymer, where the UV exposure area is controlled by a mask pattern or the scanning fiber transmitter.[3] July 16, 1984 Alain Le Méhauté, Olivier de Witte and Jean Claude André filed their patent for the stereolithography process.[4] The application of French inventors was abandoned by the French General Electric Company (now Alcatel-Alsthom) and CILAS (The Laser Consortium).[5] The claimed reason was "for lack of business perspective". It was three weeks before Chuck Hull[6-8] filed his own patent for stereolithography. Then in 1984, Chuck Hull of 3D Systems Corporation developed a prototype system based on a process known as stereolithography, in which layers are added by curing photopolymers with ultraviolet light lasers. Hull defined the process as a "system for generating three-dimensional objects by creating a cross-sectional pattern of the object to be formed". His contribution is the design of the STL (StereoLithography) file format widely accepted by 3D printing software as well as the digital slicing and infill strategies common to many processes today.

Advantages

1. Ability to customize products.
2. Rapid production of prototypes.
3. Low cost of production.
4. Increased employment opportunities.
5. No storage cost.
6. Improves the safety, efficacy, and accessibility of medicines.

Disadvantages

1. Intellectual property issues.
2. Unchecked production of dangerous items.
3. Limitations of size.
4. Limitations of raw material.
5. Cost of printers is high.

Working of 3D printing technology

It starts with making a virtual design of the object to be created. This virtual design is made in a CAD (Computer Aided Design) file using a 3D modeling program or with the use of a

3D scanner. 3D designs are typically converted to the STL file format, which describes the external surface of a 3D model. 3D printing programs "slice" these surfaces into distinct printable layers and transfers layer by-layer instructions digitally to the printer. After printing, products may require drying, sintering, polishing or other post-processing steps.[9]

To be more precise: since 2010, the American Society for Testing and Materials(ASTM) group "ASTM F42 – Additive Manufacturing", developed a set of standards that classify the Additive Manufacturing processes into 7 categories according to Standard Terminology for Additive Manufacturing Technologies. These are as follows:

1. Material Jetting-It differs substantially from binder jetting, and can be challenging to implement. Advantage of material jetting over binder jetting and other methods is resolution; inkjet droplets are about 100 μm in diameter and layer thicknesses for material jetting are smaller than the droplet diameter. Commonly jetted materials include molten polymers and waxes, UV-curable resins, solutions, suspensions, and complex multi-component fluids.[10]
2. Binder Jetting- The primary 3D printing technology used for pharmaceutical production is inkjet deposition on powder beds. Inkjet printers spray formulations of drugs or binders in small droplets at precise speeds, motions, and sizes onto a powder bed. The liquid formulation inside the printer may contain a binder only, and the powder bed may contain the active ingredient (API) with additional excipients. Alternatively APIs can be jetted onto powder beds as solutions or nanoparticulate suspensions[11]
3. Material Extrusion- The material is extruded from robotically-actuated nozzles. Unlike binder jetting, which requires a powder bed, extrusion methods can print on any substrate. Common type of extrusion printing is fused filament fabrication (FFF), also known by the trademarked name: fused deposition modeling™ (FDM®).[12] Thermoplastic polymers such as polylactic acid (PLA), polyvinyl alcohol (PVA), and acrylonitrile butadiene styrene (ABS) are used with the FDM process.
4. Powder Bed Fusion-It involves sintering (partial surface melting and congealing) or binding of high-melting-point particles with a low-melting-point binder.[12] It is a more rapid, complex, alternative to extrusion for heat processable materials like poly(lactic acid).[13]
5. Photopolymerisation-Also known as stereolithography[13] involves exposing liquid resins to ultraviolet or other high-energy light source to induce polymerization reactions. The

technique uses photopolymerizable raw material. An example drug delivery application is 3D printing of photopolymerizable hydrogels.[14]

6. Directed Energy Deposition-. Is a process where raw materials are melted by a focused energy source (ex: laser or electron beam) as they are being deposited. The method allows the use of powders or other raw materials that cannot be extruded.[13]
7. Sheet Lamination- Automated laser-cutting and sheet-by-sheet assembly of products. This process is quick and inexpensive but also low-resolution and more wasteful than most printing methods.[13]

3D PRINTING IN PHARMACEUTICALS

3D printing promises a future of drugs printed on demand, to custom doses, and the possibility that cost may no longer be a barrier to making niche medicines. And children could be among the patients to benefit most. “This technology could revolutionize the way we look at children’s medicines, both in terms of what they take and the ability to keep changing the dose as they grow,” says Steve Tomlin, consultant pharmacist at Evelina London Children’s Hospital, UK. Having a 3D printer in a hospital pharmacy could make weekly medication changes simple, personalised, and even fun.

“The potential of 3D printing is about being able to deliver what you want when you want,” says engineer Ricky Wildman from University of Nottingham in the UK. Wildman is trying to find the right materials that can be used as inks to make tablets with varying doses of drugs. In particular, Wildman is looking at inkjet 3D printing. He has replaced coloured inks with polymers, drugs and other materials used in pill manufacture. Using inkjet he is exploring the techniques by which suspensions and liquid-based materials can be triggered to make solids.

Simon Gaisford[3], a pharmaceutical scientist at University College London, is combining 3D printing and hot-melt extrusion (HME) technique. So far, Gaisford and his team have tested printing on two aminosalicylate drugs used to treat inflammatory bowel disease [1]. They applied a process related to HME called fused-deposition modelling, in which a heated polymer is squeezed out of the printer tip and then solidifies. They printed tablets in a range of shapes and found that the different shapes affected the rate at which the drug was released in the body example, a pill with a hollow middle dissolved at a different rate to one in which more of the middle was filled in.

Mohamed Albed Alhnan, pharmaceutical scientist at the University of Central Lancashire in Preston UK, says**,** the trouble with this technology is finding the right materials. He used fused deposition modelling (FDM) based 3D printer to fabricate extended release tablet of prednisolone loaded poly (vinyl alcohol) (PVA) filaments and to control its dose [15]. Any polymer used in drug manufacture needs to be biocompatible but also able to withstand the high temperatures used during the printing process, Alhnan says. He has found polymers that can be processed at high temperatures, although still lower than the typical 220–255 °C used in non-pharmaceutical 3D printing applications.

Goyanes A.[16] have explored the feasibility of fabricating controlled release budesonide tablet using fused deposition modeling (FDM) 3D printing technology with hot melt extrusion (HME) and fluid bed coating. Budesonide was loaded in polyvinyl alcohol filaments using HME. Capsule shaped tablets containing budesonide was prepared by engineering the filaments using a FDM 3D printer and were further overcoated with layer of enteric polymer. The formulation was tested in dynamic dissolution bicarbonate buffer system with commercial budesonide products. The new 3D printed caplet formulation showed sustained release throughout the distal intestine and colon.

Fig.1. Images of 3DP fabricated caplets (A) from left to right, caplet prior to coating, caplet after coating and cross section of coated caplet (scale in cm); (B, C) SEM images of internal structure of cross-section of a coated-3D printed caplet.[16]

He has also prepared drug-loaded paracetamol and caffeine—filaments of poly (vinyl alcohol) with fused-deposition modeling 3D printing.[17] The design configurations included a multilayer device, with each layer containing drug, whose identity was different to the drug in the adjacent layers, and a two-compartment device comprising a caplet embedded within a larger caplet (DuoCaplet), with each compartment containing a different drug.

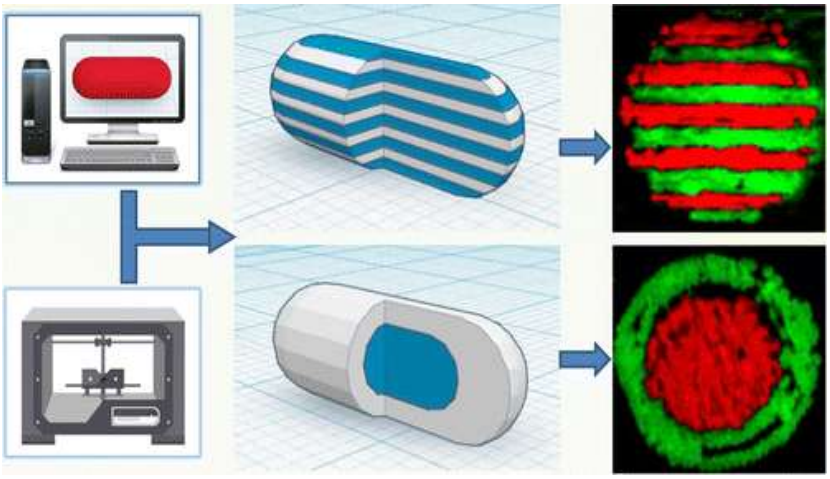

Fig.2. Caplet embedded within a larger caplet (DuoCaplet), with each compartment containing a different drug.[17]

Wang J.[39] evaluated the suitability of stereolithography (SLA) to fabricate drug-loaded tablets with modified-release characteristics. The SLA printer creates solid objects by using a laser beam to photopolymerise monomers. Polyethylene glycol diacrylate (PEGDA) was used by them as a monomer and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide was used as a photo-initiator. 4-aminosalicylic acid (4-ASA) and paracetamol (acetaminophen) were selected as model drug. Tablets were successfully printed and formulations with different properties were fabricated by adding polyethylene glycol 300 (PEG 300) to the printing solution. The loading of paracetamol and 4-ASA in the printed tablets was 5.69% and 5.40% respectively. In a realistic dynamic dissolution simulation of the gastrointestinal tract, drug release from the tablets was dependent on the composition of the formulations, but independent of dissolution pH. In conclusion SLA 3DP technology allows the manufacture of drug loaded tablets with specific extended-release profiles. In the future this technology could become a manufacturing technology for the elaboration of oral dosage forms, for industrial production or even for personalised dose.

Aprecia Pharmaceutical[40] based in Langhorne, Pennsylvania, filed its first 3D-printed product for approval to the US Food and Drug Administration (FDA) in October 2014. The company is developing a system that can print large doses of drugs in a formulation that makes them easy to swallow. **Aprecia's product, called ZipDose,** is built up from layer upon layer of powders of the drug bound together by droplets of liquid.

3D printing has been utilized for the fabrication of medical implants and devices, such as stents and catheters and dosage forms such as tablets. Table 1 draws attention to literature pertaining on fabrication of various dosage forms using 3D printing technology.

Gaisford has started a company based in Ashford, UK, to commercialise his technology, called FabRx. And pharmaceutical giant GlaxoSmithKline (GSK) is running a research and development project looking at 3D printing of drugs in its Upper Merion, Pennsylvania.

Table1. Literature pertaining to fabrication of various dosage forms using 3D printing technology.

Dosage Form	Drug	3D technique	Reference
Implant, CR	Dye	FDM	[18]
Coated Stent	Fenofibrate, Zotarolimus	Inkjet	[19]
Implant, CR	Rifampicin, Levofloxacin	Powder bed inkjet	[20][21]
Coated Orthopedic Implant	Rifampicin (RFP), Biphasic calcium phosphate (BCP, bioceramic)	Inkjet	[22]
Implant, SR	Dexamethasone-21-phosphate disodium salt	Custom	[23]
Catheter	Nitrofurantoin	FDM	[24]
General Device	Gentamicin sulfate (GS), Methotrexate (MTX)	FDM	[25]
Functionalized Coating	Dye, Fluorescent dextran	Custom	[26]
Implant	Nitrofurantoin, hydroxyapatite	FDM	[27]
Tablet, ER	Acetaminophen	Powder bed inkjet	[28]
Tablet, ER	Pseudoephedrine HCl	Powder bed inkjet	[29]
ODT	Acetaminophen	Powder bed inkjet	[30]
ODT	Levetiracetam	Powder bed inkjet	[31]
Tablet, ER	Acetaminophen	Powder bed inkjet	[32]
Tablet, IR/ER bilayer	Guaifenesin	FDM	[33]
Tablet, SR	Captropril (CAP), Nifedipine (NIF), Glipizide (GLI)	FDM	[34]
Tablet,	Pravastatin,	FDM	[35]

IR/SR	Atenolol, Ramipril, Aspirin, Hydrochlorothiazide		
Tablet	Fluorescein	FDM	[36]
Tablet, MR	5-ASA, 4-ASA	FDM	[17]
Tablet, ER	Prednisolone	FDM	[15]
Tablet	Acetaminophen	FDM	[37]
Tablet, MR	Acetaminophen	FDM	[38]

3D PRINTING IN MEDICAL DEVICES AND BIOMATERIALS

Atala A.,[41] at Wake Forest Institute for Regenerative Medicine used molding techniques to produce a synthetic human bladder scaffold. Boland T.,[42] received the first patent for a bioprinting technique based on inkjet technology. Forgacs G.,[43] at the University of Missouri created multicellular spheroids for 3D printing which is regarded as the key step towards scaffold free printing of cells. Chisey D.,[44] at the Naval Research Laboratory applied laser technology to print bio-inks and mammalian cells into 3Dimensional structures. Derby B., Chrisey D. and Mironov V.,[45] defined bioplotting or bioprinting as "the use of material transfer processes for patterning and assembling biologically relevant materials–molecules, cells, tissues, and biodegradable biomaterials – with a prescribed organization to accomplish one or more biological functions."Organovo and Invetech[46] produced the first commercial bioprinter. Atala A.,[47] at Wake Forest University produced printed skin constructs which are considered to be the bioprinting attempt nearer to functional tissue replacements. Further achievement in bioprinting has come in the form of ear shaped constructs[48] and heart valve models.[49] At first in 2014, Organovo[50] applied bioprinting techniques to produce the commercially available liver tissue model. As the technology has become archetypal the influence it has in medical and biological fields is awfully precise. Recent reviews brief the growing use of these technologies for clinicians, especially in the fields of radiology[51], cardiovascular[52] and reconstructive surgery.[53] In the research milieu the technology has transformed tissue engineering[54] with prominence on bone[55-56] skin[57] and myocardial[58] tissue models. For example, printed tissue mimics can be pertinent as disease models[59] and acellular constructs can function as structured scaffolding for bone grafting materials.[56] Bioprinting is also competent for the development of high-throughput assays and drug discovery.[60]

Fibronectin and laminin have been bioinkjet printed in accurate patterns and shown to consequently affect cell organization.[61] Fibrin has been printed for cartilage engineering.[62] Growth factors can also be patterned onto culture surfaces with high stability. Fibroblast growth factor-2 (FGF-2) and ciliary neurotrophic factor (CNTF) have been inkjet patterned onto culture surfaces to inhibit or strengthen the differentiation of neural stem cells into astrocytes.[63] Similarly, FGF-2, bone morphogenetic protein-2 (BMP-2) and insulin-like growth factor II (IGF-II) have been printed to influence the differentiation of muscle-derived stem cells toward osteogenic or skeletal muscle lineages.[64] This technique has also been used to generate lipid vesicles[65] and enzymes, such as glucose oxidase have been printed.

In bioprototyping, SLS has most productively been applied to fabricate bone replacements FDA approved[66] OsteoFab bone grafts utilize a proprietary process which combines laser sintering technology and a powder formulation (OXPEKKR)

Quality Assurance and regulatory problems for 3D Printing pharmaceuticals, medical devices and biomaterials

The Food and Drug Administration is the regulatory agency that governs medical devices and materials intended for human use in the United States. Presently the FDA doesn't have a category for bioprinted products, but rather classifies them either as drugs, biologics, medical devices or combination products.[67] Each of the product types is regulated by a different office within the FDA, either the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER) or the Center for Devices and Radiological Health (CDRH).[68] New medical device are federally regulated product which must be tested through clinical trials before it can be used.

3D printing techniques do not support well with current regulatory standards which rely on the manufacturing process to be standardized, validated and continuously monitored.[69] The customizable nature will require a strategy to assure quality control in every step of the process: production of raw materials, design control of the 3D printed model, validation of the manufacturing process along with its governing software, and finally end product testing.

Sandler N.,[70] investigated applicability of near infra-red (NIR) hyperspectral imaging technique in quality control of printed personalised dosage forms. This method takes tens of thousands of spectral images at one time across an entire sample, with each spectrum

becoming a pixel in an overall image of what the sample contains, chemically, at each point. He performed inkjet 3D printing on anhydrous theophylline as a model drug.

Market forecast for 3D printing technology

The world 3D printing healthcare market was evaluated at $579.0 million in 2014 and is estimated to acquire $2,363.8 million by 2020, registering a CAGR of 26.2% during the forecast period 2015- 2020.[71] As of 2015, North America holds the largest share of the global 3D printing medical devices market, followed by Europe.[72] A number of factors, including increased government funding to enhance 3D printing applications in the healthcare industry, augmented R&D investments, rapidly expanding customer base, increasing scope of biomedical applications and extensive research and development activities at the academic and industrial level has increased the market growth. The Asia-Pacific market is expected to grow at the highest CAGR from 2015 to 2020. However, lack of skilled professionals and high cost of 3D printing systems restricts its demand in the developing Asian countries.

Stratasys Ltd. (Israel & U.S.), 3D Systems Corporation (U.S.), EnvisionTEC GmbH (Germany), EOS GmbH Electro Optical Systems (Germany), Renishaw plc (U.K.), Materialise NV (Belgium), 3T RPD, Ltd. (U.K.), Arcam AB (Sweden), Concept Laser GmbH (Germany), and Prodways (France) are the key players operating in the global 3D printing medical devices market.

CONCLUSION

There is a growing trend towards personalized and customized medicines. This technology may transform the pharmacy practice by allowing medications to be truly individualized and tailored to a patient. Moreover the technology enables preparation of dosage forms with accurate deposition of materials, greater spatial control and geometric flexibility. There is a great hope of 3D bioprinting in producing reproducible biological constructs for producing structures for studies into implantation, regenerative medicine and automated assays for high throughput in vitro drug and toxicity studies in lab developed tissues.

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