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REVIEW ARTICLE

Additive Manufacturing Technologies in Tissue Engineering and Drug Delivery System

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ABSTRACT

3D printing is a technique that involves sequential deposition of materials in a layer-by-layer fashion to create three dimensional objects (hence also referred to as additive manufacturing) from a digital 3D model generated by computer-aided design (CAD) software which is obtained from a 3D scanner. Thus, objects generated using 3D printing have a broad spectrum of applications, ranging from rapid prototyping in electronics and robotic industries to 3D printing organoids using bio-ink in biomedical research. Recently, there has been a huge paradigm shift in the field of medicine toward personalized medicine. Hence, technologies that assist in modulating drug dosage based on genetic profiles have been vigorously evaluated, while technologies such as stereolithography, binder jetting and material extrusion have found profound applications in tissue engineering and other technologies such as fused deposition modelling, selective laser sintering, and material jetting. Many biomedical alloys used in implants are currently manufactured using direct energy deposition. The following article highlights its history, the difference between 3D printing and traditional manufacturing, the types of 3D printing techniques used, and the applications, advantages, and disadvantages of 3D printing.

Keywords: Additive manufacturing, Biomedical alloys, Bioprinting, Drug delivery, Scaffolds, Tissue engineering.

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INTRODUCTION

Three- dimensional printing (3DP) is a unique technology that has been in use for more than three decades. A brief history of the development of 3D printing technology in the pharmaceutical field is shown in Figure 1. The advent of bio-ink has revolutionised 3D bioprinting. Many milestones have been achieved in the field of biomedical engineering, including the generation of a fully functional kidney outside the human body, using stereolithography. There are three main steps involved in 3D printing. If the object of interest is pre-existing, then the object is sca nned to obtain a 3D design; otherwise, if the object is not pre-existing, we create a new design using CAD software such as Solid Works and Auto CAD. The STL file, which provides a sliced view, is then transferred to a 3D printer equipped with the corresponding technology. The material is deposited in a layer-by-layer pattern using various geometrics.[1-3] This process is also called solid-freeform fabrication. Three-dimensional (3D) printing offers many advantages over conventional manufacturing technologies, as listed in Table 1.

The 3D printing processes obtain prominence in the area of pharmaceutical and medical treatments because of the likelihood of speedy formulation of tailor-made items which can be useful in personalized therapy or medicine. The launch of 3D printing into the medical technology predominantly aims at the advancement of patient-centred dosage forms centred on structure design. It is still a new research path with probable to create the targeted release drug delivery systems in freeform geometries. Wide-ranging research are shown for oral dosage forms because that route of administration still remains major and favourite one. Some investigations are also focused on dosage forms for topical administration.[2] Capabilites of 3D printing technologies in Table 2. The major application of additive manufacturing technology in the field of pharmaceutical drug delivery system are enlisted in Table 3. The impact of additive production on biomedical field has increased rapidly since the 3D printing was established in the early 80s. It is since the technique allows formation of personally established materials of customized architecture and functionalities. It changed into effective tool for biomedical

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engineering providing formation of manufacturing implants that correspond to patient-specific anatomy, phantoms for education and surgical planning and disease models. The various additive manufacturing technologies were used for biomedical applications. Patient centric antimicrobial wound dressing using polycaprolactone, 3D printed scaffolds based on polyethylene glycol and homogenized pericardium were developed to stimulate wound healing. Besides the additive manufacturing technology also used in the fabrication of implants and prostheses. The fabrication of implants and prostheses by additive manufacturing has recently revolutionized the area of developing of medical devices fulfilling the growing demand for individualized therapy. The 3D printing enables preparation of tailormade goods that meet up individual needs developed from specific patient anatomy and pathology. Moreover, it provides the development of structures of site-specific mechanical and physical properties as well as spatial and temporal control of bioactive components. The clinical benefits of 3D printing are also noticeable in the field of implantable medical devices. Nylon-based uretic stents and laparoscopic trocars were printed and successfully developed in a female cadaver and in vivo porcine model. Besides the 3D printing technology also has been used in preparation of organ on chip bioprinting.[2]

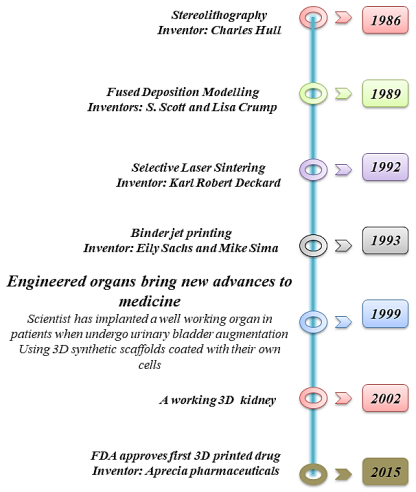

Figure 1: A brief history of 3D printing technology development in the pharmaceutical field.

MATERIALS AND METHODS USED IN DIFFERENT 3D PRINTING TECHNOLOGIES

Stereolithography (SLA)

SLA is the first and oldest technique in 3D printing for rapid prototyping. It involves the use of photopolymers, which are light sensitive materials that solidify upon exposure to certain wavelengths of light. It includes materials such as polyethylene, polypropylene, and many others.[9] The SLA setup has four sections: a vat tank filled with liquid photopolymer resin, a platform dipped in a tank, a high-power ultraviolet laser, and a computer interface that manages both the platform and UV laser movements.[10,11] The build platform moves down as the deposition progresses.[12] This phenomenon is iterated until the product formation is complete. The SLA technology is shown in Figure 2. *Lan. P. X. et al.*;[12] designed, and prepared three-dimensional (3D) porous scaffolds based on a PPF polymer network using microstereolithography (MSTL). The 3D scaffold was well fabricated, with a highly interconnected porous structure and a porosity of 65%. These results suggest a novel scaffold fabrication method for tissue engineering. Various other applications of stereolithography are presented in Table 4 (Figure 2).

Fused Deposition Modelling (FDM)

The FDM was invented by Scott Crump in 1989, who was also the co-founder of Stratasys Ltd. This technique is also called fused filament fabrication (FFF) because it is based

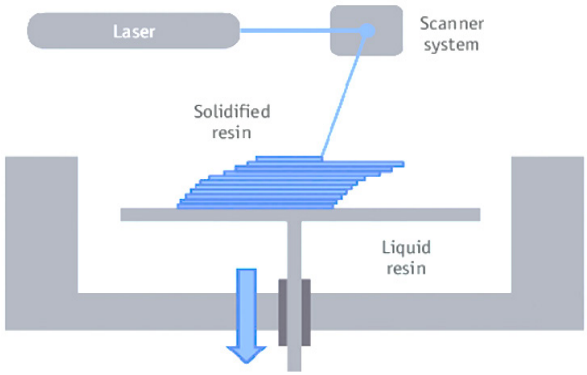

Figure 2: Stereolithography (SLA)

Table 1: Difference between 3D printing and traditional manufacturing.

3D printing  3D Printer	*Traditional manufacturing* 
Reduction of prototyping cost by 70%.	The cost of production is higher due to conventional moulding and milling techniques.
Complex geometries can be easily achieved.	Complex shapes cannot be generated easily
Since it involves manufacturing deposition of materials in a layer-by-layer fashion, lesser amount of waste is produced.	The subtractive method will compromise on precision and a larger amount of waste is produced.
Customized products or medicines leads to successful therapy	Customization is not possible
Demand happens parallel to production	Demand surpasses the production

Table 2: Capabilities of 3D printing technologies.

3D printing technique	*Material Jetting*	*Binder Jetting*	*Powder bed fusion*	*Vat polymerization*	*Material extrusion*	*Direct energy deposition*	*Sheet lamination*
Examples	Material jetting, Drop-on-demand, Nanoparticle jetting	Binder jetting	Selective laser sintering, Selective laser melting, Material jet fusion,	Stereolithography, Direct light processing, Continuous digital light processing	Fused-deposition modelling, Semi-solid extrusion	Laser engineering net shape (LENS), Electron beam additive manufacturing (EBAM)	Laminated object manufacturing
Material Type	Photopolymer resin	Powder based material with binder	Power material with dye	Photocurable liquid resin	Solid filament/ Semi-solid mass	Metal alloys	Thermoplastic plastic or paper
Surface finish and build speed	Surface finish is smooth and build speed is fast	It has an average surface finish and Speed of building is fast.	It has an average surface finish and Speed of building is fast.	It has a smooth surface finish, and the speed of building is on average.	It has a rough surface finish, and the Speed of building is low.	Less smooth surface and build speed is low	Surface finish is rough and build speed is fast

Table 3: Drugs with modified drug delivery with help of 3D Printing.

S. No	*API*	*Formulation*	*Reference*
1	Acetaminophen	Fast disintegrating tablet	34
2	Chlorpheniramine maleate & Diclofenac sodium	Oral pulsatile tablet	35
3	Hydrochlorothiazide	Tablet	36
4	Nifedipine, glipizide and captopril	Multiactive tablet (polypills)	36
5	Paracetamol	Oral modified-release tablet	37
6	Budesonide	Controlled released tablet	38
7	4–amino salicylic acid	Oral modified-release tablet	39
8	Acetaminophen	Tablet	40
9	Prednisolone	Extended-release tablet	41
10	Nitrofurantoin	Catheter implant	42
11	Salicylic acid	Antiacne patch	43
12	Salbutamol sulfate	Solution	44
13	Felodipine	Solid dispersion	45
14	Folic acid	Nano suspension	46
15	Pseudoephedrine hydrochloride	Capsule with immediate release core and a release rate regulating shell	47
16	Rifampicin and Calcium phosphate	Nanocomposite structure	48
17	Acetaminophen	Oral pulsatile capsule	49
18	Dexamethasone	Drug encapsulate film of PLGA, PVA	50
19	Saline solutions	Microfluidic pump	51
20	Rifampicin, isoniazid	Multidrug implant	52
21	Tetracycline	Patterned micron scaled	53
22	hydrochloride	structures	
23	Rifampicin	Compartmental oral drug	54
24	andisoniazid	delivery	
25	Berberine	Topical polymeric film	55
26	Olanzapine	Immediate release tablet	56
	Berberine	3D printed nanocomposite	57
27	Drug loaded	pills	58
	nanostructured lipid	Mouth dissolving wafers	
	carriers		59
	Berberine chloride	Enteric coated hollow capsular device	

on the material extrusion principle.[13-17] An FDM has three main components: printer platform, nozzle, and raw material (made of thermoplastic polymers, such as nylon, acrylonitrile butadiene styrene (ABS), polycarbonates, polystyrene, and thermoplastic urethane.[18] In FDM, the raw material is extruded from the rollers and heated in the nozzle (printing head).[19] The nozzle movement occurs in the x-, y-, and z- axes to facilitate the extrusion of the filament in any direction along the bed. Upon extrusion, the filament solidifies as soon as it touches the platform bed which is composed of metal, ceramic, or hard plastic.[20] Filip; *et al.* prepared an individualised multi material wrist orthosis was designed using a CAD system.

Table 4: Various 3D printing technique, principle, description, and its application in drug delivery

Techniques	*Description*	*Materials*	*Advantages/ Disadvantages*	*Applications*	*Ref.*
Material Jetting (MJ)	Material Jetting builds object into a similar method to a 2D inkjet printer. Multiple materials can be used in in one process and the material can be changed during the build stage. Material is jetted onto the build platform surface in droplets, which are formed using oscillating nozzle	Photopolymer or casting wax	Advantages: 1) High resolution Disadvantages: Drying after print Build speed is low	Orthopaedic Implant Microneedles	38
Laminated Object manufacturing (LOM)	Thin sheet of material (usually supplied via a system of feed rollers) are bonded together layer bylayer to form a single piece that is cut together layer by layer to form a single piece that is cut into a 3Dobject	Metal such as steel, titanium and ceramics	Advantages: 1) Hybrid manufacturing has possible Disadvantages: 1) Tedious cleaning	1) Porous ceramics	47
Direct Laser Deposition (DLD	The laser or electron beam source isused to melt the material, the moltenmaterial deposited and solidify to form solid layer	Metal and ceramics	Advantages: 1) No use of binder solution Disadvantages: 1) High laser power	Knee arthroplasty implant Biomedical alloy	49,50
Stereolithography (SLA)	Photopolymerization of photocurable resin in presence of photo initiator under the influence oflight to form a layer-by-layer object	Photocurable resin (photocurable monomers like Polyethylene glycol diacrylate, Polyethylene glycol methacrylate withTPO as photo initiator	Advantages: Improved resolution Accuracy Disadvantages: 1) Resin availability	1)Microneedle assay 2)Intravesicular bladder device	60,61
Fused deposition modelling (FDM)	Thermoplastic polymers in the form of filament are extruded through the printer head at a specific temperature at definite directions	Solid filaments (Polylactic acid, Polyvinyl alcohol grades, etc)	Advantages: Low cost Absence of postprocessing Disadvantages: Low resolution Chances of drug degradation	Drug delivery Tissue engineering Bone tissue engineering	62, 63, 64
Selective Laser Sintering (SLS)	It uses laser radiation to sinter (superficial melting) or fuse the powder materials and form a 3D object, instead of a liquid binder to glue the layers	Powdered material with laser absorbent dye	Advantages: 1) Porous structure can be prepared Disadvantages: Sintering speed Required post finishing	Drug delivery Bone tissue engineering	65, 66
Binder Jetting (BJ)	Powder is distributed layer by layer, either by a roller (powder layering system) or by a powder jetting reservoir (powder jetting system), and the layers are fused together in presence of binder solution	Polymers, ceramics, hydroxyapatite, bio glass, polycaprolactone etc.	Advantages: Room Temperature process Porous product Disadvantages: 1) Required special facility	1) Drug Delivery	67, 68

Every portion of this orthosis comprises two diverse ingredients that fulfil different purposes. Using the double-head fused deposition modelling 3D printer, they fabricated all the parts into one without the necessity for supplementary assembly operations.[21] Chaudhari *et al;* explored the FDM technique to prepare a mouth-dissolving wafer for effective oral delivery of nanostructured lipid carriers to mitigate oral cancer (Figure 3).

Selective Laser Sintering (SLS)

The SLS consists of a laser beam (heat source), powder roller, and build platform. The fused powder material forms a 3D structure, as directed by the information coded in CAD.[22-24] The powder material is spread over the build platform upon which the laser beam scan due to which the powder material is fused, upon which another powder material is spread over the previously fused powder layer. The following process iterates until several layers are formed, and the build platform gets a lower side for the formation of a new layer by the roller on the previous layers. This process occurs repeatedly until a 3D object is formed. In this process, a high-power laser is used, such as a carbon dioxide laser. The polymers

used in SLS include polyamide (PA), polystyrene (PS), polyaryletherketone (PAEK), and thermoplastic elastomers (TPE).[25,26] SLS technology is showed in Figure 4. Allahham *et al.;* explored the possibility of using selective laser sintering (SLS) 3D printing (3DP) to formulate oro-dispersible tablets (ODPs) containing ondansetron. Ondansetron was first mixed with the drug-cyclodextrin complexes and then pooled with the diluent mannitol. Two 3D printed tablets with different ratios of mannitol were fabricated and tested, and a commercial ondansetron orally disintegrating tablet (ODT) product (Vonau® Flash) was also investigated for comparison (Figure 4).

Binder Jetting (BJ)

In BJ, powder and binding agents are the two materials used. Metals, sand, and ceramics are commonly used as powder materials is binder jetting. The recoating blades spreads the powder material onto the build platform, and the nozzle-containing binder solution is gradually deposited over the powdered material layer. Once the layer is formed, that is, completes the formation of layer, the build platform moves to the lower side, and the recoating blade again spreads the powder material over the previously formed layer.[27-29] The binding solution helped to form a 3D layered structure of the powdered material. The first FDA approved 3D printed tablet Spritam by Aprecia Pharmaceuticals was prepared by modifying the binder jet printing process.[30,36] The BJ technology is shown in Figure 5. Zuoxin Zhau *et al.* explored different water-soluble adhesives to increase the 3D printability of HA powder using binder jet 3D printing technology. Using the ideal powder composition used in this study could possibly enhance the structural, mechanical, and biological functions of HA-based 3D scaffolds prepared using the binder-jetting AM process for bone tissue engineering applications (Figure 5).

Material Jetting-Inkjet Printing

In the material projection process (MJ), a print head selectively deposits material droplets onto the construction plate. The most used technology based on MJ printing is drop-on-demand technology. The two furthermost communal actuation methods for DOD print heads are thermal and piezoelectric. In thermal print heads, resistance generates heat that quickly creates a steam bubble in the material tank. Consequently, a smaller volume of material is emitted from the nozzle in the form of droplet. A potential problem with this technique is that; it elevates the local temperature in the material reservoir which degrades the thermolabile medicament. However, piezoelectric print heads are implanted with piezoelectric essentials (i.e., crystals or ceramics) which produce machine-driven movements upon the application of an electrical current. This distortion procedure yields the mandatory pressure to drive the liquid out of the nozzle in the droplet form. The method uses less volatile liquid at room temperature; thus, these types of print heads are more common in pharmaceutical applications.[37]

Gu *et al.* fabricated antibiotic- and calcium-eluting bioresorbable nanocomposite micropatterns for orthopaedic implants using the inkjet printing technique. The authors demonstrated the ability of the piezoelectric ink jet print head to deposit the rifampicin microparticles on orthopaedic

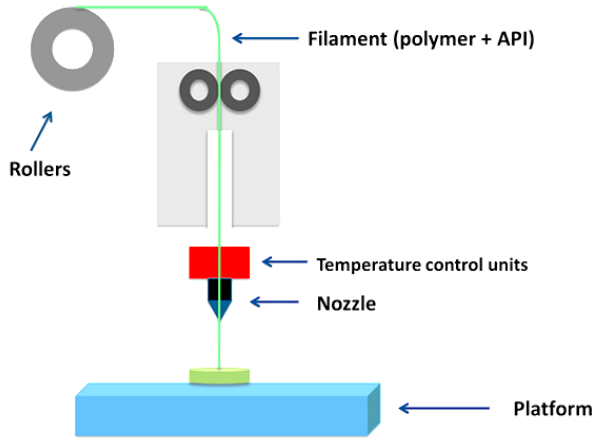

Figure 3: Fused Deposition Modelling (FDM)

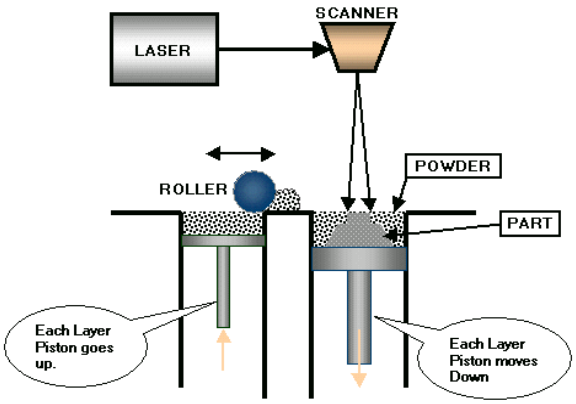

Figure 4: Selective Laser Sintering (SLS)

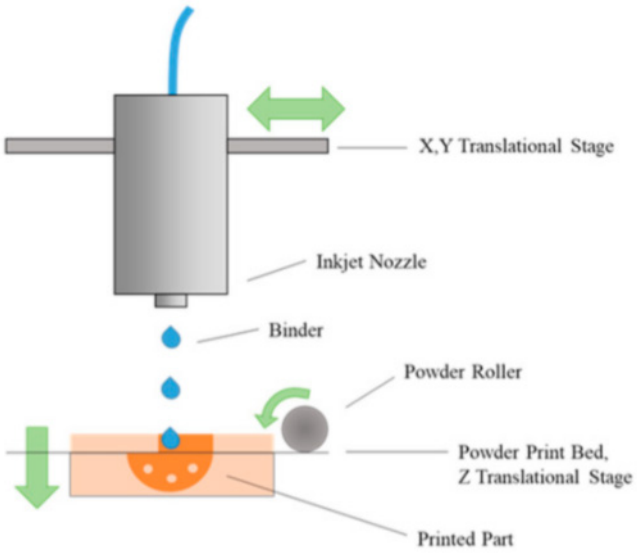

Figure 5: Binder jet (BJ)

implants.[38] Tarcha *et al*. prepared a coated stent for controlled delivery of fenofibrate and zotarolimus. The authors also demonstrated the efficiency of inkjet printing in coating stents.[39] Sanjana *et al*. demonstrated, the ability of inkjet printing to fabricate precise micropatterns of cell adhesion materials for neural cell culture.[40] The material jetting process is shown in Figure 6.

Material Extrusion Semi-solid Extrusion 3D Printing

Semi-solid extrusion (SSE) printing is most suitable for soft materials. The preliminary ingredients (commonly a semi-solid mixture) are extruded through a syringe-based tool-head nozzle to create a 3D object.[37] The most used are gels or pastes that are formulated by mixing the ideal ratio of substances with solvents to attain an optimum viscosity appropriate for printing.[41] Physicochemical and mechanical properties, such as rheological properties, viscosity and miscibility of materials, influence on the processing (i.e., excess material flow at low viscosity or insufficient material flow at high viscosity). Printing parameters such as material flow rate, processing temperature, and printing speed are carefully optimized and controlled to achieve a decent finished product with good mechanical properties. Compared with fused deposition modelling which requires high temperatures to restrict the use of heat-labile drugs, SSE printing technology minimises the limitations of FDM 3D printing as it allows a heat-labile drug to print.[37] The firmness of this method is occasionally inferior to FDM as the procedure uses superior dimensions orifices with a dimension of 0.5–0.8 mm, which can disturb the reproducibility Shaben A. Khaled *et al*. employed three-dimensional (3D) semi-solid extrusion-based printing as a medicine manufacturing technique for the production of multi-active tablets with well-defined and separate controlled release profiles for three different drugs. This 'polypill' made by a 3D semi-solid extrusion-based technique showed that multifaceted medication systems can be pooled in a sole tablet and that it is feasible to formulate and 'dial up' this single tablet for the particular needs of an individual.[41] Chen *et al*. prepared a core-shell system (CSS) containing a low-density drug-loaded shell and a floating core using multi-nozzle semi-solid extrusion (SSE) 3D printing technology. The prepared CSS and floating core structure provides a novel perspective for constructing a stable gastric floating drug delivery system.[42] The practice of soft materials is more common in the food industry[43] and biological applications (bioprinting); thus, this the technique has been extensively implemented for tissue engineering.[44] The material extrusion process is shown in Figure 7.

Laminated Object Manufacturing (Sheet Lamination 3D Printing)

In 1991, Helisys was the first corporate player to introduce sheet lamination technology to the market. The organisation's laminated object manufacturing method attaches sheets of material and uses a digitally guided laser to cut away the looked-for object. LOM allows for additive building of parts by stacking subsequent layers of material sheets on top of each other. Each layer was cut to its shape using a knife or laser beam, according to the 3D CAD data, before it was laminated by a thermoplastic adhesive on top of the previous layer. The adhesive is activated by a heated roller; that laminates the layers at a temperature between 60ºC and 80ºC and a pressure of 10 to 30 MPa.[45] Zhang *et al.* proposed a new aqueous slurry-based laminated-object manufacturing method for porous ceramics. The prepared porous ceramic framework and template not only lessened the possibility of harm to the green body but also

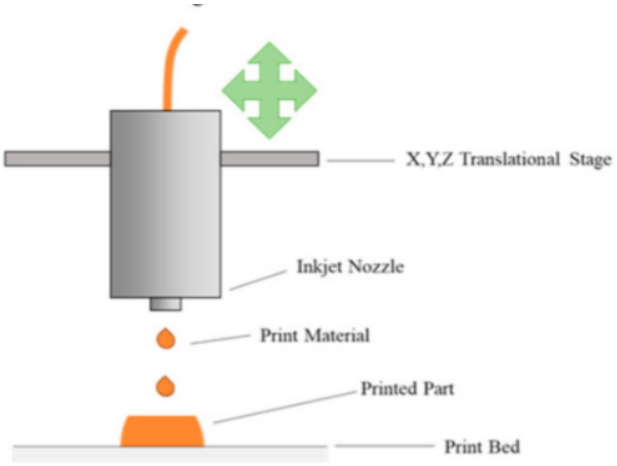

Figure 6: Material Jetting Inkjet Printing

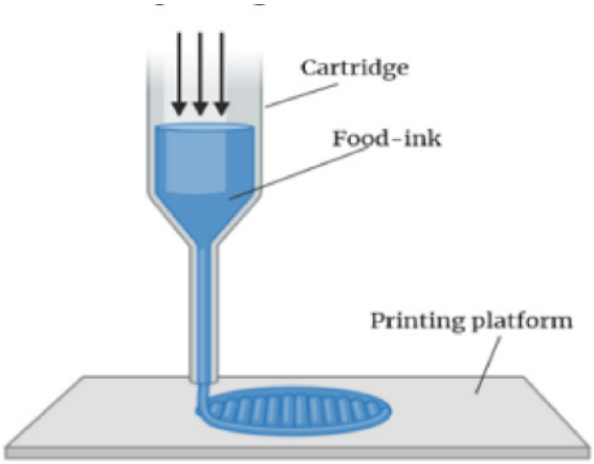

Figure 7: Material extrusion process

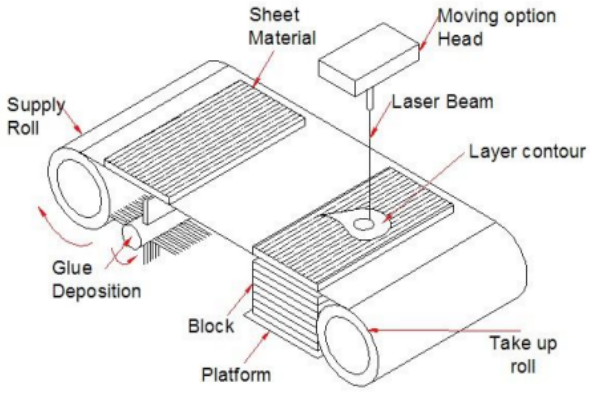

Figure 8: Laminated object manufacturing

safeguarded the symmetry, uniformity, and connectivity of the micron-scale pore network.[46] In addition, laminated object manufacturing additive manufacturing technology has been explored for the preparations of Al2O3 green ceramics.[47] The laminated-object manufacturing process is shown in Figure 8.

Direct Energy Deposition

DED, also referred to as blown powder AM or laser cladding, involves the introduction of metal powder to a heat source, such as a laser, which melts the metal particles together as they are deposited. Because of the technology's ability to inject metal powder directly into the heat source, which is often attached to a 4- or 5-axis arm, DED systems are not limited to 3D printing onto a flat substrate. Instead, it is possible to print metal onto curved surfaces, such as the existing metal structures Tarun Bharadwaj *et al.* proposed the Direct Energy Deposition - Laser Additive manufacturing (DED-LAM) method for the deposition of β-type titanium molybdenum (Ti-15Mo) which is a biomedical alloy. The direct energy deposition is shown in Figure 9.

Applications

3D printing technology has wide applications in the pharmaceutical industry and medical devices.[31,32] 3D printing has various applications in drug delivery. However, the approval of orally disintegrating tablets by the FDA in 2015 under the trade name Spritam, opened a new chapter on 3DP in the manufacturing of pharmaceutical products.[6] It is made using zip-dose technology, with a porous structure that helps to disintegrate the tablet in the mouth within seconds.[36] Currently, it is used in targeted drug delivery for cancer patients (comprising nanoparticles), where the release of drugs with a narrow therapeutic index can be optimised according to the pharmacogenetic profile. It is also used in manufacturing capsules, implants, microneedles, and transdermal patches using 3D printing. Medication facilitates the modulation of drug doses during drug fabrication,[4,5] facilitating personalised medicine (Table 3) shows drugs that are being modified by 3D printing of different drug delivery systems. 3D printing is also used to create scaffolds for tissue design, printing artificial organoids that serve as models for better understanding of various biological phenomena, and to accelerate the drug design process and fabrication of biomedical devices and diagnostics.[7,8] Additive manufacturing technologies possess certain advantages over traditional manufacturing, as shown in Table 1.

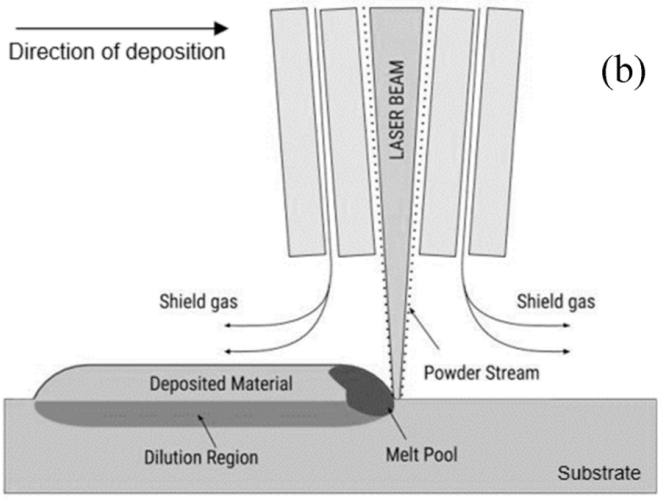

Figure 9: Direct energy deposition

Tel Aviv researchers have created the world's first 3D printed heart with vascularisation using the patient's cells and other organic materials. Bio-printed tissue models are an important application of 3D printing techniques. In addition, a 3D printed model of a calcified aorta was used for surgical planning of plaque removal was used by surgeons. In addition, the titanium mandibular prosthesis was printed and successfully implanted at the BIOMED Research Institute, Belgium. Several implants and prostheses can also be customised and printed according to the requirements, which can be either a CAD design or a scanned image obtained with the help of MRI, CT scan, and X-ray imaging systems. In addition, hearing aids can also be manufactured using 3DP.

Viewpoint

3DP provides an effective (time-saving) approach for preclinical evaluation of new drugs. It is especially important to test for new drugs.[33-35] 3D printing assists in achieving personalised medicine, as it modulates drug dosages and delivery of drugs in the pharmaceutical industries.[33-35] Medicines formulated by the 3D printing technique avoid the manufacturing costs of large pieces of equipment in industries by reducing distribution costs. Hence, they are more cost-effective than most other manufacturing methods.[35] However, just like the two sides of a coin, there are few disadvantages. It is associated with hazardous gases that emerge from printers, such as ultrafine particles and volatile organic compounds, which are toxic and may lead to asthma, loss of coordination, headache, and irritation of the eyes and nose upon long-term exposure.

CONCLUSION

Various 3D printing technologies use different materials and methods. They are classified into different subgroups based on their working principles. It is possible to manufacture extremely complicated and composite dosage forms of drugs by using 3D printing. This has transformed the way products are made in the pharmaceutical industry. This advances design manufacturing and decreases the guide time and tooling price for innovative products. In addition, not all products fabricated using 3D printing match the mechanical properties of those manufactured using conventional techniques. Hence, various strategies are currently employed to overcome this problem, such as advancements in processing technologies, the use of materials with better properties, and the usage of composite materials and many others. While additive manufacturing in the pharmaceutical sector is still in an experimental phase, the medical devices industry grew rapidly. The overall market size of 3D printing is huge and improving exponentially year on year. The international 3D printing healthcare market volume

is estimated to reach US$3692 million by 2026, growing at a compound annual growth rate (CAGR) of 18.2% from 2019 to 26. Authorisation of Spritam® sparked great attention from international pharmaceutical manufacturers, particularly from North America, Europe, China, and Japan. To speed up product agreement, regulatory agencies also need to be ready with a thorough understanding of the technological details and pathways for product review. These additional demands connecting the gaps between all stakeholders, including researchers, pharmaceutical producers, and regulators, for understanding the patient's needs to transform theory to realistic and revolutionary solutions. Above all, evaluation of the real-time safety and efficacy of 3D-printed products in clinical practice is also warranted to result in highly flexible and personalized dosage forms on demand.

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