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An overview on 3D Printed Medicine

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Abstract

Three-dimensional printing (3DP) is a digitally-controlled additive manufacturing technique used for fast prototyping. This paper reviews various 3D printing techniques like Selective Laser Sintering (SLS), Fused Deposition Modeling, (FDM), Semi-solid extrusion (SSE), Stereolithography (SLA), Thermal Inkjet (TIJ) Printing, and Binder jetting 3D Printing along with their application in the field of medicine. Normal medicines are based on the principle of "one-size-fits-all". This is not true always, it is possible medicine used for curing one patient is giving some side effects to another. To overcome this drawback "3D Printed medicines" are developed. In this paper, 3D printed medicines forming different Active Pharmaceutical Ingredients (API) are reviewed. Printed medicines are capable of only curing the diseases, not for the diagnosis. Nanomedicines have "theranostic" ability which combines therapeutic and diagnostic. Nanoparticles are used as the drug delivery system (DDS) to damaged cells' specific locations. By the use of nanomedicine, the fast recovery of the disease is possible. The plant-based nanoparticles are used with herbal medicines which give low-cost and less toxic medication called nanobiomedicine. 4D and 5D printing technology for the medical field are also enlightened in this paper.

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Introduction

3D Printing is the additive manufacturing (AM) technique, used for layer-by-layer material deposition in a defined cross-section. It generates customized complex geometries and shapes for a unique drug release pattern suitable for personalized drug therapy. 3D printers today are observed in many applications. In the aerospace industry, airplane engines are printed from industrial 3D printers. Engines printed have sophisticated geometries, defined aerodynamic and fluid dynamic properties, lightweight structures (up to 60 % less). The overall cost is lowered by printing low-cost superalloys. As a result environmental pollution can be reduced by a significant amount.[1] In the fashion industry, 3D printing has expanded creative possibilities for fashion design. Complex shapes and textures can be created without molds.[2] Astronauts used 3D printers

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to print objects like spare parts in the spaceship. The space stations are even planning to build a 3D-printed colony on the moon. Other industries like the military, FMGC, tissue engineering, etc. are using 3DP technology on a wide scale. During the current pandemic of COVID-19, 3D printing technology is used to print Copper 3D NanoHack mask, High-Efficiency Particulate Air (HEPA) mask, Lowell Makes mask, Hospital respiratory support apparatus, PPE kits, and even mask adaptors.[3]

3D Printing techniques

Depending upon the application requirement following 3DP technologies can be used.

- Selective Laser Sintering (SLS) – It is a fast prototyping technique that converts 3D CAD data into physical parts in a few hours. It is an AM technology that uses powdered nylon 11, nylon 12, and PEEK materials. Parts produced are lightweight, highly durable, heat resistant, and chemical resistant. The low-cost production parts are developed without any expensive tools required. First, the 3D CAD data is split into thin cross-sections of layers. After the data is split it is transferred to the SLS AM equipment. The machine creates the first layer of powdered material, then a leveling roller spreads it on the cross-section using a laser beam. After the completion of the first layer, the powder bed is made ready for the second layer by lowering it down. Layer by layer deposition is done until the required part is obtained.[4]
- Fused Deposition Modeling (FDM) – This technology is used for creating durable everyday objects. The 3D printer takes industrial-grade thermo-plastic filament which is melted then extruded on a tray to build a complete part layer by layer using a bottom-up approach. The limitation of this technique is the requirement of a high processing temperature for developing active thermo-labile compounds.
- Semi-solid extrusion (SSE) - Unlike FDM, it requires low temperature. In this process, a 3D object is created by using a semi-solid mixture as the starting materials which is extruded a syringe-based tool-head nozzle. The following parameters should be considered for optimized mechanical properties: processing temperature, material flow rate, and printing speed. In this technique post-processing steps of drying or cooling are required.[6]
- Stereolithography (SLA) – It is the oldest rapid prototyping technique, hence it is used for creating concept models, or as a master pattern for molding techniques. Initially, CAD data is sliced into cross-sections or layers and then transferred to an SLA AM system containing a vat of UV-curable photopolymer. The UV laser is used for creating the layer by X and Y scanning mirrors. When the laser impinges on the cross-section of the resin, the liquid material is hardened on contact. Once a layer is completed, the build platform is indexed down so that the next layer can be deposited. The layers are created one by one on top of each other using a bottom-up approach.
- Thermal Inkjet (TIJ) Printing – It is a non-contact technique, that uses electromagnetic, thermal, or piezoelectric technology to deposit tiny droplets of ink onto substrates depending upon digital instructions. In this printer, heat is created by resistors, and ink got vaporized to create a bubble. As the bubble expands, the ink is pushed out of a nozzle onto the substrate.
- Binder jetting 3D Printing- In this technique, various particle materials such as sand, plastics, or freely selectable powder materials. The main requirement is the CAD data of the part. The process starts with the application of the loose particle materials to the building platform by a recorder afterwards the printhead applies the binder selectively at the areas where the future parts have to be produced thus connecting the layers after the binder has been applied the building platform is lowered by the layer thickness. Each layer is printed one by one till the desired structure is obtained.

As 3D printing technology is continuously evolving, still, shape deformation is not possible for it. 4D printing incorporates the fourth dimension of time, which enables the 3D printed products to deform/ shape-shift upon external stimulation post-printing. If nanomaterials are involved with 4D printing then a new era will be started in the field of medicine.[6]

Areas Covered

The paper broadly discussed 3D printed medicines. 3D printed medicines are superior in comparison to normally available medicines because they can be customized, many in one or polypills are possible.

The medicines can be manufactured for individual patients as well as in bulk quantity. Patients who are unable to take multiple pills can take polypill to treat more than one disease. The 3DP medicines can treat the disease but the diagnosis is not possible. Nanomedicines are used for repairing and diagnosis of the damaged cells. It is also useful for the present pandemic COVID 19 situation can alter the reactive oxygen species (ROS) in our body to prevent virus infection.

Expert Opinion

3D Printed Medicines

Medicines are generally made for oral solid dosage forms in the form of tablets or capsules. The medicines are printed in multiple steps including complex additives. The active pharmaceutical ingredient (API) is the necessary ingredient for opening new opportunities for the enhancement of drug delivery systems. 3DP technology is used for pharmaceutical and biological applications because they exhibit excellent characteristics of controlling material and product characteristics with high precision.[7]

History of 3D Printed Medicines

In 2015, Aprecia Pharmaceuticals developed the first 3D printed orodispersible tablet Levetiracetam for seizure treatment. Seizures (tonic-clonic and partial-onset) in adults and children can be treated from this drug.[8] A molecular 3D printer, as the name says synthesize blocks of small molecules from the basic chemical pattern was developed at Howard Hughes Medical Institute. This printer serves as the great revolution in the field of 3DP medicines. They are currently working on the synthesis of protein tyrosine phosphatases for treating multiple forms of cancer. To date, API and PCL are combined and then implanted into a cancer-suffering pancreas. Currently, the medicines are manufactured in mass production which leads to the improper dosage which results in side effects to the patients. FabRX is working on personalized 3D printed medicines and drug-loaded medical devices (using SLA). Printlets (3D printed tablets) technology is used for personalized dosages to the patients. For young children and senior citizens, polypills, chewable and fast-dissolving tablets are printed. Polypills comprises many pills in a single medicine tablet, which reduces the number of tablet intakes. The National University of Singapore (NUS) has developed software for developing customized pills according to the patient's requirement. The software settings can be customized according to the number of tablets required. On the spot, pills can be produced for patients, or the pills can be produced on a large-scale for pharmaceutical companies. The Institute of Chemicals Technology and Tvasta, Mumbai, is developing a technique, in which multiple AM technologies are combined to produce tablets with controlled drug release. GlaxoSmithKline (GSK) is looking for the technique for large-scale 3D printed medicines. Another is to convert the API into a curable ink. Currently, 3D printing of medicine is not used worldwide, still, a lot of scope for development is there.[9]

Table 1 represents the list of 3D-printed medicines using SSE, SLA, SLS, FDM, and TIJ. Various types of medicines with different compositions are given in Table 1.

Limitations of 3D Printed Medicines

After so much advancement in the field, the technology growth is limited due to the unavailability of material for 3D printed medicines. Quality control and accuracy of 3D printed material is also one limitation. Defects are also observed in some types of 3D printers which are clinically unacceptable 3D printed drugs have a high loading capacity and more accuracy. Another drawback of 3D printed medicine is the low yield. It takes 2min to 2hour time for printing one tablet, whereas a batch of around 15000 tablets can be processed in a couple of minutes.[27] Minimum wastage of raw materials leads to minimizing production costs. The main limitation of medicine is that it should be taken orally for the treatment. They do not perform the diagnosis of the disease. For this purpose, nanomedicines are used which can be used for diagnosis. When the body cells are damaged at the molecular level which causes ill health and diseases. The tools used today for diagnostic and therapeutic modalities are imprecise, slow, and ineffective. Today the aim is early diagnosis of the disease so that the treatment can be started when the cells are in thousands instead of million cells for e.g. Cancer cells.

Nanomedicines

In 1959 Richard Feynman the Physicist said "There's plenty of room at the bottom" which indicates minimization is possible for every field of technology.

Medicines size can also be reduced in nanometer (1 to 100nm) range to form nanomedicines. Nanomedicine is the branch of science that combines chemistry (deals with the chemical structure of the drugs), biology (deals with living organisms, functions, nanoparticles as nanocarriers).

Table 1: Summary of 3D printed medicines

3D Printed Technology Used	Formulation	API	Reference
SSE	Bi-layered tablets (polypill)	Guaifenesin	10
SSE	Multiactive tablets (polypill)	Nifedipine, Glipizide, and captopril	11
SLA	Hydrogels	Ibuprofen	12
SLA	Facial mask	Salicylic acid	4
SLS	Tablets	Paracetamol	13
SLS	Drug delivery device	Progesterone	14
FDM	Caplets	Caffeine	15
FDM	Tablets	Hydrochlorothiazide	16
FDM	Oral films	Aripiprazole	17
Binder jet printing	Tabular devices	Methylene blue and alizarin yellow (dyes)	18
Binder jet printing	Cubic tabular devices	Pseudoephedrine	19
Binder jet printing	Tablets	Chlorpheniramine meleate and fluorescein	20
Binder jet printing	Orodispersible tablets	Levetiracetam	21
Inkjet 3DP	Implant	Levofloxacin	22
Inkjet 3DP	Nanosuspension	Folic acid	23
Inkjet 3DP	Nanoparticle	Rifampicin	24
3D printing	Multidrug implant	Rifampicin and isoniazid	25
TIJ	Solution	Salbutamol sulfate	26

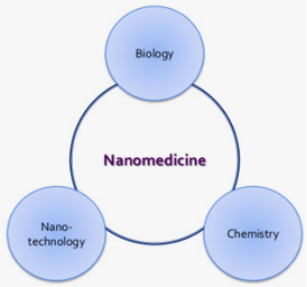

Fig. 1: Nanomedicine basic diagram[28]

As per the report obtained by Grand View Research, Incorporation of the global market for nanomedicine will reach 350.8 billion USD by 2025.[28] In the UK and the USA, the expected rise in the employment opportunities in the field of nanomedicine by 2025 is 200%. Nanomedicines can monitor, diagnose, repair through therapy, construct, and control the biological systems at the molecular level using engineered microstructures. Nanomedicine is majorly used for cancer therapy and diagnosis ranging from blood, liver, brain, and lung cancer. It includes a component that is designed to connect nanoparticles with a particular damaged cell type or tissue.[29] Nanomedicine derives its technological, rhetorical, and scientific strength from the scale on which it operates (1to100nm). Nanomedicine was depicted as the creation of 'nanobot' devices in the form of nanoparticles that would pass through the human body in search of the disease and then curing it. These nanoparticles behave as specific markers or contrasting agents in the form of invasive medical imaging tools to the cells. These markers deliver the drug to the specific damaged cell and not to the healthy cell. Nanomedicine in its simplest forms was able to put drugs in nanoparticles that are small enough to put thousands of them side by side in the cross-section. The nanoparticles can be administered systematically under the immune system's radar to find diseased tissue and then release the drug. Unlike the conventional methods where the drugs get washed out through the kidney.

Nanoparticles:(Drug Delivery System)

Nanoparticles are preferred because of their small particle size. If the particle size is too small then the total surface area will be higher which indicates greater contact with surrounding material and therefore reactivity will be higher. Nanoparticles are designed in such a way that they can swim through a non-Newtonian fluid-like bloodstream around the lymphatic system or even across the slippery goo on the surface of the eyeballs. The nanoparticles should be stable, biocompatible, biodegradable, and uniform distribution in the system without side effects. Drug-bearing nanoparticles are injected into the bloodstream and they should cross the layer of endothelial cells that line blood vessels before encountering damaged or target tissue cells.[29] The nanoparticles get attached easily because they have surface extensions (tiny finger-like structures at the surface). After the drug delivery, the fluorescence spectra light up to signal where exactly the disease is. These signals are given by the nanoparticles in a variety of optical ways. Encapsulation of API into nanocarriers is aimed toward enhancing the stability and solubility of the drug, protecting the drug from the environment.[30]

Types of Nanoparticles

Different types of nanoparticles are used for drug delivery which is as follows:

Metal-Based Nanoparticles

These are inserted inside the body with some inert material and then these particles are activated with the help of light rays or ultrasonic rays.

Lipid-Based/Starch-Based Nanoparticles

The lipids are mixed in an organic solution which is evaporated later. For hydrating, the sonication method is used to divide liposomes into small parts.

Synthetic/Polymer-Based Nanoparticles

These are less toxic because of degradation due to ester's bond hydrolysis. The alkyl alcohol and cyanoacrylic acid are the by-products produced which are eliminated during kidney filtration. These nanoparticles are alkyl-cyanoacrylates used for skin wounds and surgical glues and as a tissue adhesive.

Inorganic/Gold Nanoparticles

These are used for rapid tests for pregnancy and ovulation, gold shell particles for biomedical imaging, magnetic nanoparticles for cell sorting in clinical diagnostics, silica nanoparticles for diagnostic imaging, superparamagnetic iron oxide particles for MRI. The nanoparticles are functionalized with different ligands such as surfactants, dendrimers, small molecules, polymers, and biomolecules.[31]

Plant-Based Nanoparticles

If the plant-based nanoparticles are used then "Nanobiomedicines" which proves to be a great innovation in the field of "Ayurveda" is formed. Nanobiomedicines are combining nanotechnology with herbal medicines to form nano-phytomedicines. Herbal medicines are preferred because of their great anti-oxidant properties. For reliable products, physiochemical, biological, and pharmacotoxicological properties of nano-phytomedicines should be improved. These medicines are expected to be useful for cancer treatment.[27]

The advantage of using nanoparticles in nanomedicine are

- Encapsulation/Packaging protection
- Comparatively less drug is required
- Prolonged circulation half-life and excellent specificity
- Concentrate in tumor sites due to EPR effect (<300nm)
- Minimal side effects
- Early diagnosis and protects the drug from degradation
- Assist drugs in penetrating biological barriers
- Targeted delivery to specific cell types
- Dosing frequency is less

Limitation

To make nanomedicine for the liver because the liver has a filtration system that filters out all the foreign particles to supply drugs to the liver. The immune cells in the liver eat these foreign nanoparticles and seize the drug delivery. Many biological nanoparticles are already present in the body in the human saliva, pancreatic liquid, etc. These nanoparticles do not get filtered by the liver and can be used for drug delivery. A large variety of nanoparticles are available so it is hard to standardize these nanoparticles' safety to further complicate things. If the size or shape of the nanoparticle is varied. The risk/benefit ratio is not yet estimated If 3D printed nanomedicines

are not suitable for the patient, then the 5D printing technology can be used. 5D printing technology creates personalized models of patients' pathology.[32]

Conclusion

The present paper furnishes the importance of 3D printing technology in the field of medicines and nanomedicines. Various 3D printing technologies can be used for printing medicines (polypill, tablet, Orodispersible tablets, implants, etc.) forming different APIs like Paracetamol, Aripiprazole, Levetiracetam, and other useful day-to-day life drugs are reviewed. The use of nanoparticles for implementing nanomedicines is also discussed. Nanoparticles based on metals, polymers, lipids, and inorganic are discussed. It also emphasizes how nanomedicines are useful for cancer treatment for various body parts. It will be useful for COVID-19 situations as well due to their capability of controlling the reactive oxygen species (ROS) in the human body. There is still a lot of scope of research in the field of nanomedicines for organ printing, tissue engineering, etc. The future of nanomedicine is early detection of pathological or biological changes at the molecular level by using unambiguous imaging methods and less invasive treatment of the patient with individually tailor-made medicines as soon as the disease is in the development stage.[33] Great innovation is expected in the field of "Ayurveda" when nanotechnology (using plant-based nanoparticles) is combined with herbal medicines to form nano-phytomedicines (nanobiomedicines). Herbal medicines are preferred because of their great anti-oxidant properties. For reliable products, physiochemical, biological, and pharmacotoxicological properties of nano-phytomedicines should be improved. These medicines are expected to be useful for cancer treatment as well. In the future, nanobiomedicines can be 3D-printed for more cost-effective and high-yield products. If the printed nanomedicines are unable to cure the patient then the horizon can be expanded up to 5D, creates personalized models of patients' pathology.

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Conflict of interest

No conflict of interest is declared by the authors.

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