

# 3-D Printing as A Tool for Applying Biotechnologies in Modern Medicine

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## 3-D Printing as A Tool for Applying Biotechnologies in Modern Medicine

HARUN ACHMAD<sup>1</sup>, ARNI IRAWATY DJAIS<sup>2</sup>, ELENA G. PETRENKO<sup>3</sup>, MARKOV ALEXANDER<sup>4,5</sup>, VIKHAREVA ANISA<sup>4</sup>, AMINUDDIN PRAHATAMA PUTRA<sup>6</sup>

<sup>1</sup>Department of Pediatric Dentistry, Faculty of Dentistry, Hasanuddin University, Indonesia

<sup>2</sup>Department of Periodontology, Faculty of Dentistry, Hasanuddin University, Indonesia

<sup>3</sup>Federal state budgetary educational institution of higher education "Kuban state agrarian university named after I. T. Trubilin"

<sup>4</sup>Tyumen State Medical University, Tyumen, Russian Federation

<sup>5</sup>Tyumen Industrial University, Tyumen, Russian Federation

<sup>6</sup>Department of Biological Education, Faculty of Teacher Training and Education, Lambung Mangkurat University, Banjarmasin, Indonesia

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### ABSTRACT

Three-dimensional printing techniques are increasingly used for the production of medical devices due to the ability to print specified designs with high dimensional accuracy. Indeed, the main merit in the widespread use of 3D printing methods in medicine is related to the ability of this method to prepare devices suitable for the patient, due to the limitations of traditional production methods, such as economic inefficiency and multi-stage processing for complex geometric shapes. This review manuscript is intended to provide a summary of the various concepts and technologies of three-dimensional printing used in the field of medicine. Biomaterials and bioprinting are defined. Finally, the pharmaceutical possibilities of three-dimensional printing are discussed.

**Keywords:** 3D printing, biotechnologies, modern medicine

### INTRODUCTION

3D printing involves a set of processes that link controlled materials together to create a 3D object. This process is usually performed in layers[11]. In another definition, 3D printing refers to any process by which 3D objects are formed when layers are combined in a row in a two-dimensional cross-section. This process is very similar to an event during which ink is sprayed onto paper in other types of printing that we know of, except that it occurs in 3D printing by crystallizing, solidifying, or combining a liquid material or powder at any point in the contact of the object that we want to print. The presence of a computer is a necessity in this process, since it is based on "computer-aided design" (CAD) [22].

Early 3D printing technology was observed in 1980. Dr. Kodama from Japan first invented this technology in his own name. At the time, this technology was called rapid prototyping (RP). This name was given because the technology was designed to quickly and cost-effectively create a prototype for mass production. Following this, Chuck Hull patented the invention of the stereolithography device (SLT) in his name in 1986 [13].

Needless to say, Hull invented his device in 1983, and in the meantime he was busy creating 3D Systems, which was then known as RP Systems and is now one of the largest enterprises in the field of 3D printing, where he built the first prototype of this device called SLA-1 and introduced it in 1987, which passed the first successful tests in 1988. At the same time, Carl Deckard, who studied at the University of Texas, performed the RP process with selective laser sintering (SLS) on his behalf in 1987. The patent for this invention was issued in 1989, then was issued to DTM Inc., and was later issued on the purchased 3D Systems. In the same year, 1989, Scott Crump, co-founder of Stratasys Inc., announced the patenting of his melting layer modeling machine and gave it to the company. So, the open source RepRap technology is very functional.

### RESULTS AND DISCUSSION

The term "3D printing" was originally dedicated to a specific process, patented by scientists from the University of Massachusetts Institute of Technology in 1993, and then the license for it was granted under contract to many manufacturers. Today, this term is used as a general name for many

related processes [16] in line with the current trend of digitalization [42]

Although there are different methods for 3D printing, their main steps are common. The first step in 3D printing is to create a 3D model for it on a computer. This is done using 3D modeling or CAD software. In some cases, reverse engineering and 3D scanning of the available part can also be used. The second step is to create an STL model file. The model must be converted to a format that can be read on the printer. To do this, the file must be converted to STL [22].

3D printing and OBJ formats are less popular than other formats. In STL format, polygons or triangles are used to represent the model on the printer. The STL file is imported into a program that slices layers of files and is called a slicer [22]. The slicer receives the model and converts it to a G-code containing instructions for CNC machines and 3D printers. The third step involves printing the model. There are many machines, each of which uses its own mechanism to print the model. As for the fourth step, concerning the removal of printed parts, it should be noted that in some devices, the removal of parts is quite simple and without any problems. However, in more industrial models, this process is quite technical and precise. The last step, step five, is post-processing, which depends on different technologies. In some cases, the part must be treated with UV rays.

The term "additive manufacturing" (AM), commonly referred to as 3D printing, is described by ISO / ASTM standards as the process of joining materials to create parts from 3D model data, often layer by layer, in contrast to the methods of forming production and subtractive production [19].

A common feature of all 3D printing methods, called AM, is their sequential or step-by-step processing. Unlike casting or forging, which require a one-step process or solidification process, or what is obtained from a cubic mass when sheet metal is shifted, or mechanical processing that follows a subtractive process, creating based on 3D printing methods has significant advantages and disadvantages compared to previous traditional methods.

Modern medicine uses three-dimensional printing technologies based on biomaterials. Biomaterials are natural or synthetic materials that interact biologically with human fluids and are used to prepare products to replace any organ or compensate for damaged tissues in the body in a safe and physiologically approved way. Biomaterials can effectively solve many health problems using new materials. They are

applicable in controlled drug delivery systems, as well as in the engineering and cultivation of soft and hard tissues and organs [46,47,48]. What's more, biomaterials can allow clinicians to optimize products for people using 3D printing.

Depending on the chemical nature of biomaterials, they are divided into four different types, including metals, ceramics, polymers, and composites. Due to the excellent mechanical properties of metal biomaterials, they are mainly used in dentistry or orthopedics [24].

In addition to the crucial role of metal biomaterials in reconstructive surgery, they have also recently been used in non-bone tissues. Moreover, ceramic biomaterials can have excellent mechanical properties, as well as excellent wettability, wear-resistance and biocompatibility. Unlike most metals, ceramics are resistant to high temperatures. The advantages of polymer biomaterials are acceptable mechanical properties, stability and elasticity. Polymers are widely used in various biomedical applications, such as prosthetics, implants, controlled drug delivery, and so on.

It should be noted that there are various subtypes of AM, such as three-dimensional printing, direct digital production (DDM), and RP. The term "subtractive manufacturing" (SM) refers to traditional manufacturing approaches such as machining, casting, molding. These approaches are usually equivalent to complex processes that require equipment, tools, robots, computers, and so on to develop three-dimensional parts. AM significantly reduces or completely avoids the use of tools, allowing you to fully customize projects by simply changing the 3D model in the software, which leads to lower costs during the prototyping stage [18].

New materials are being used in Biomedicine, and AM approaches are being developed. One of the main factors in increasing the availability of this technology is related to the expiration of earlier patents that allow manufacturers to create new 3D printing systems. The cost of 3D printers has been reduced due to the latest developments. Thus, their use has been expanded in homes, schools, laboratories, and libraries.

There is a growing general agreement to adapt the 3D production system over traditional methods due to some advantages, such as high-precision construction of complex geometries, flexible design, individual customization, and maximum material savings. 3D printing uses a wide range of materials, such as polymers, metals, concrete, and ceramics [10].

Acrylonitrile butadiene styrene (ABS) and polylactic acid (PLA) are the main polymers used in 3D printing of composites. Modern alloys and metals

are commonly used in the aerospace sector, as traditional procedures are more expensive, difficult, and slow. Ceramics are mainly used in medical 3D printing platforms, and concrete is the main material used in building construction. However, the poor mechanical characteristics and anisotropic behavior of 3D printed components still limit the possibilities of large-scale printing. Thus, to control anisotropic behavior and sensitivity to defects, it is critically important to have an optimal 3D printing sample [29]. 3D printing technology is used by clinicians to solve a wide range of problems in the field of health and medicine. Optimizing medical products for individuals is one of the most prominent features of this technology in biomedical applications. In addition, the production of complex structures of implants, prostheses, surgical devices and models is another advantage of 3D printing in medical applications. In most 3D printing processes, the raw material consists of a soft plastic or metal powder. The powder is usually contained in cartridges or layers, as it is distributed in very small quantities and fed by a roller or blade mounted in the frame on which the part of the model is made. The thickness of these layers, taken together, does not exceed the size of the powder particles of the source material, which can reach 5 microns [26]. Early 3D printers were mostly able to create relatively rough sculptures out of plastic, ceramics, and sometimes plaster; but over time, more advanced printers were created that could print volumes of metal with greater accuracy and durability. Currently, 3D printers are used to print polymers, ceramics, and metals in various forms of raw materials, including powder, filament, and bio-ink. Significant advances in 3D printing technologies have allowed surgeons to eliminate most of the disadvantages associated with traditional methods of manufacturing medical devices, such as multiple stages of production and expensive tools, and can help in the manufacture of devices for specific patients. The various types of 3D printing process used in medical applications will be discussed later [26]. In the FDM modeling approach, a continuous filament made of a thermoplastic polymer is used in layers of 3D printing materials. To achieve a semi-liquid state, the thread is heated in a nozzle, and then it is extruded over layers that were previously printed, or on a platform. An important feature of this approach is the thermoplasticity of the polymer thread, which allows the threads to melt during printing and solidify at ambient temperature after printing. The layer thickness, orientation and width of the threads, as well as

the air gap (between layers or in one layer) are the main processing factors that affect the mechanical characteristics of printed parts. The main cause of mechanical instability is interlayer distortion.

The main advantages of modeling deposited metal include acceptable speed, low cost, and simplicity of the process. Its main disadvantages include weak mechanical characteristics, poor surface quality, layered appearance, and a limited number of thermoplastic materials. The development of fiber-reinforced composites by surfacing simulation can improve the mechanical performance of 3D-printed parts. However, the binding between the matrix and the fiber and the formation of voids, as well as the orientation of the fibers, are the main obstacles that arise when using three-dimensional printed composite parts [18].

In the field of healthcare, the future of medical devices and medicines will be personalized for different patients, allowing the use of AM functions to visualize patients and highlight consistent devices. According to the literature, FDM is the only method used to develop personalized catheters with promising results. FDM is a potential method for manufacturing surgical instruments, implants, orthoses, and prosthetics.

AM inkjet printing is used to print complex ceramic structures, such as frames for fabric engineering. In this approach, a fixed ceramic suspension, such as zirconium oxide powder in water, is pumped, and it accumulates as droplets through an injection nozzle on the substrate. Then a continuous pattern of drops is formed, which harden with sufficient strength to hold the next layers of printed materials. This is an efficient and fast approach that provides flexibility when printing and designing complex structures [11].

Liquid suspensions and wax-based inks are the two main types of ceramic inks. To solidify, wax-based paints are heated and applied to a cold base, and liquid evaporation is used to solidify liquid suspensions. Factors that determine the quality of inkjet printed parts include the particle size distribution of ceramic particles, extrusion speed, ink viscosity and hardness, printing speed, and nozzle size. The main disadvantages of this approach include the coarse resolution, the continuing workability and lack of adhesion between the layers.

Inkjet printing is a complex technique that requires various time and long scales. Therefore, different scales and assumptions are used when using different materials for inkjet printing.

Stereolithography (SLA) is one of the main AM approaches created in 1986. UV light (or electron

beam) is used in this approach to initiate a chain reaction on a resin layer or monomer solution. Monomers (mainly based on epoxy resin or acrylic) are UV-active, and they immediately turn into polymer chains after their activation (radicalization). After polymerization, the pattern solidifies inside the resin layer to hold the subsequent layers. When printing is complete, the unreacted resin is removed. For some printed parts, post-processing such as photo-curing or heating can be used to achieve optimal mechanical performance. You can use the dispersion of ceramic particles in monomers to print ceramic-polymer composites or certified polymer-based monomers such as silicon oxycarbide. SLA provides printing of high-quality parts with a good resolution of up to 10 microns. However, it should be noted that this is expensive, relatively slow, and there is a very limited set of materials for printing. In addition, the curing process and reaction kinetics are complex. The main factors that determine the thickness of the layers are the energy of the light source and the exposure. SLA can be effectively used to create complex nanocomposites.

As for the SLA's ability to create large-sized objects with submillimeter errors, products for several patients have been successfully prepared to date, such as Invisalign<sup>®</sup>, which is an orthodontic device, and hearing aids. Moreover, thanks to the development of resolution, the expansion of applicable materials, porosity control, and the production of patient-oriented devices, SLA has proven its ability to be used as a potential manufacturing method for tissue engineering [8].

Due to SLA's ability to create cross-linked polymer structures through photopolymerization, this is a potential method for high-resolution low-temperature fabrication. These features of SLA methods make it an excellent candidate for controlled drug production, tissue engineering (TE), and regenerative medicine (RM).

One of the three-dimensional printing technologies is the use of powder layer Fusion (PBF). PBF processes consist of thin layers of fine powders that are dispersed and tightly packed on a platform. Powders are deposited in each layer by a binder or laser beam. The next layers of powders are joined on top of the previous layers, and they merge so that the last three-dimensional detail is created. The excess powder is then removed by vacuum. If necessary, further detailing and processing, such as impregnation, sintering or coating, are performed. The most important factors affecting the effectiveness of this approach include the particle size distribution and

powder packaging, which determine the density of the printed part [19].

The laser can only be used for powders with a low sintering / melting temperature, otherwise a liquid binder should be used. SLS is used for various polymers, alloy powders, and metals, while selective laser melting (SLM) is only used for certain metals, such as aluminum and steel. The powders do not completely melt during laser scanning in SLS, and the increased local temperature on the grain surface leads to the fusion of the powders at the molecular level. In addition, with selective laser sintering, the powders completely melt and melt after laser scanning, resulting in better mechanical performance provides a detailed description of the various applications and materials that use SLS.

PBF has shown great potential for use as production methods for tissue engineering and bio-devices. It was used to make metal frames with the desired porosity for bone grafting.

Digital light processing (DLP) is also used. This technology works with the photopolymer in the same way as SLA. The main difference between these two methods is their source of radiation. In DLP, a typical light source is used together with a liquid crystal display (LCD) or a digital micromirror (DMD) screen that affects the entire surface of a reservoir containing a photopolymer resin at one moment; indeed, it creates each layer in one moment, so it is usually faster than stereolithography technology. As with SLA, DLP technology creates parts with great accuracy, although it has the same problems. One of the advantages of this method over SLA is that light processing requires a reservoir containing a very low depth of resin. This reduces the cost and saves expensive raw biomaterials, thus increasing the overall health sector performance [41]. Compared to other 3D printing technologies used in healthcare, DLP technology has high resolution, speed, and efficiency. The use of this technology began in 2006, and due to its outstanding characteristics, it has attracted a lot of attention in the field of medicine. Its applications in various fields include medical devices (medical models, implants, functionalized devices), tissue engineering (liver, lungs, bones, heart, spinal cord, etc.), and pharmaceuticals (drug discovery and development, drug delivery) [10].

Multiphoton polymerization (MPP) uses the same high-resolution SLA method. Three-dimensional printing in micro-scales and less than microns, which has recently attracted a lot of attention, is a process based on polymerization of multiphotons using an ultrashort pulse laser. This nonlinear

optical process occurs by polymerizing a light-sensitive material by simultaneously absorbing several photons with a higher wavelength, which is in the range of 780-820 nm. Typically, parts made by the MPP method are much smaller. Therefore, they are not suitable for the fabric frame of implants. But on the other hand, it is used to understand the interactions of the cell framework.

Photobioprinting is a newly developed AM method that is widely used in TE and RM. MPP is considered one of the most important methods of bioprinting due to the excellent cell viability, since there is no external force when printing the product. However, MPP is associated with low speed and expensive tools, which in some cases makes it difficult to use [14].

One of the newest 3D printing methods used in medicine is 3D printing on suspensions. This method can be implemented through both SLA and sintering. In this method, the photo-cured matrix as a binder can be combined with various ceramic powders to form suspensions. The suspension is then photo-cured using a light source to give the final three-dimensional shape to be used for the intended applications. As for the sintering process, the laser is used to heat the suspension and then RUB it, while in SLA the suspension is cured by light.

This method is most often used for dental implants. Today, dentists use three-dimensional suspension printing to make dental implants using zirconium dioxide (ZrO<sub>2</sub>). The suspension consists of a photo-cured resin, a methanol solvent, and a ZrO<sub>2</sub> powder.

For core-shell printing, a coaxial nozzle is used, which makes it possible to print on two different materials simultaneously. One of the materials is considered the inner part or core, and the other that covers the core is called the shell. Until now, coaxial printing has been used to make core shells and hollow threads. However, none of them could provide good mechanical properties along with cell viability. It is very important that the use of two biomaterials in core-shell printing can help optimize the mechanical properties of 3D printed objects. As for making the framework using this method, by choosing a cross-linking agent as the core and a biomaterial as the shell, it would be possible to create a hollow tube in just one manufacturing step. This one-step manufacturing method is considered the most economical [18].

Core-shell printed frames are applicable in applications such as TE, such as vascular structures. The nozzles are made of metal to prevent any deformation during the 3D printing process and can provide rapid cross-linking of

raw materials, resulting in one-step production of hollow filaments. This method is used for manufacturing microchannels, in which hollow filaments are supporting structures that ensure the mechanical stability of the product, and microchannels serve as a way to deliver nutrients to cells [39].

4D printing is a type of 3D printing. When the 3D printing process uses functional and intelligent materials that can function due to external stimuli such as heat, pH changes, and so on, This process is called 4D printing. It has a high potential for application in biomedical fields such as organ regeneration, tissue processing, implants, and drug delivery.

Initially, 4D printing was considered as a technique that links AM with time. In fact, in early research in 2013, the proposed strategy involved designing a 3D-printed part that undergoes a controlled shape change. According to the Atlantic Council of the United States, 4D printing is described as "an AM of objects that have the ability to self-transform in function or shape when exposed to a predetermined stimulus, such as heat, osmotic pressure, ultraviolet light, current, etc. energy sources." Consequently, 4D printing is a programmable aspect of the 3D printing field with the ability to change the functionality of available materials or hybrids of materials that are designed to be self-assembled in precise shapes and locations. For this reason, recent developments in this field show that the focus is on intelligent materials [2].

4D bioprinting is an application of 4D printing in medicine and technology that is directly related to the maturation of incorporated cells. The process of cell maturation is carried out through self-organization using the fourth dimension, i.e. external stimuli. Various materials such as lipids, biopolymers, and hydrogels were printed using 4D printing for biomedical applications. One of the most applicable materials in the 4D printing process is hydrogels that respond to stimuli, including synthetic and natural ones. The advantages of using hydrogels in 4D printing are their excellent interconnectedness and adjustable porosity [11].

In the literature, bioprinting is described as "the use of computer transfer processes to assemble and form non-living as well as living materials using a given three-dimensional or two-dimensional organization to create bioengineered structures that serve in pharmacokinetics, regenerative medicine, and basic cell medicine - that is "biological research". To obtain a three-dimensional structure of human tissues and organs, it is necessary to use precise and well-controlled methods for manufacturing suitable

biomaterials and living cells. With the above requirements in mind, four types of three-dimensional bioprinting methods have been developed that can print based on the principle of biological release. These methods include bioprinting systems based on extrusion, inkjet printing, laser printing, and stereolithography [17].

In addition to the usual 3D printing problems, 3D bioprinting problems include cell inclusion problems. On the other hand, in case of problems with 3D printing, the bio-ink must be biocompatible and provide good structural stability. On the other hand, cell-related problems consist of cytocompatibility of biosensitive elements and cell viability. The most important parameters in the further development of 3D bioprinting are cytocompatibility and good printability. In addition to these problems, a successful three-dimensional bioprinting process requires a sterile environment with a constant temperature set at 37 ° C. In addition, shear stress is another important factor affecting cells in large quantities. Currently, there is a limited number of successful approaches, that meet all the requirements of three-dimensional bioprinting, such as partial gel crosslinking.

Three-dimensional bioprinting has developed significantly over the past decade and is rapidly developing. One of the promising achievements of this method is the printing of organs. Organs are defined as a complex combination of tissues. The term "organ printing" was first noticed in 2003, which is described as "a rapid prototyping technology for computer 3D printing based on the use of layer-by-layer deposition of cells and / or cell aggregates in a 3D gel with sequential maturation of the printed structure into vascularized and perfused living organs or tissues". "Printing of Organs" is still used frequently; it is especially used in popular literature. However, it is currently broader than its relatively narrow original definition [13].

Further advances in biotechnology make it easier and more possible to create products with a higher percentage of imitation of natural tissues and organs. Biofacturing is described as "the automatic production of biologically functional products with a structural organization of bioactive molecules, living cells, cellular aggregates such as microtubules, biomaterials, or hybrid cell-material structures, through bioassembly or bioprinting and subsequent tissue maturation processes. It is used to describe natural processes such as biomineralization, and technological processes in various disciplines such as catalysis, biotechnology, sensing, synthetic biology, and especially TE and RM.

The choice of suitable materials for use in bioprinting, as well as the characteristics of these materials in a particular application, depends on various factors:

a) Printing capability is characteristics that facilitate the application and use of the bioprinter include rheological properties, viscosity, and gelation approaches.

b) Biocompatibility. Materials should not stimulate undesirable systemic or local host responses, and they should make an active and controlled contribution to the functional and biological elements of the structure.

C) By-products and degradation kinetics. The rate of degradation should correspond to the ability of cells to produce their own ECM; the by-products of decomposition should not be toxic; the materials should have appropriate contractile or swelling properties.

d) Mechanical and structural characteristics- Materials are selected based on the required mechanical characteristics of the structure, which range from soft hydrogels for cell compatibility to rigid thermoplastic polymer fibers for strength.

E) Biomimicry of materials is the development of optimal dynamic, function and structural characteristics of the material should be based on knowledge of the tissue-specific compositions of endogenous materials [18].

Implants are one of the most useful 3D printing products in healthcare, which has been widely developed using various 3D printing technologies and materials. The term "implant" is described as a device that is surgically transplanted or inserted, permanently or temporarily, into the body to improve, support, or maintain function or improve / change contour. Implants can be made from synthetic materials, such as a hip prosthesis, or from soft tissues, such as blood vessel grafts, which are mostly inert.

The following definition is the most recent consensus definition given at the 2018 conference: it is a medical instrument made from one or more biomaterials that are partially or completely placed in the body[8].

Consider the advantages of 3D printing over medical implants

A) shortening the duration of the operation : the duration of the operation is shortened by planning and replacing implants based on the preliminary pathology, and the surgeon and surgical team know exactly the stages of the operation.

b) Reduction of intraoperative bleeding: if you have prior knowledge about the stages of the operation and reduce the time of operation, the total number of bleeding during the operation

can be reduced. Thus, the return to normal conditions is faster than usual.

C) higher accuracy: surgeons will be able to plan the operation better if an accurate model is available. Depending on the shape and size of the bone, implants can be pre-formed. This increases the accuracy and reduces the duration of the operation.

d) patient Education: it is now easier to Explain the pathology and procedure of surgery to patients, as patient knowledge and awareness are increased by the availability of the 3D printing model. This is useful for informing patients and they will be aware of the expectations of the surgery procedure.

e) Trials: patients will be better informed about expectations by using the models guide. This improves communication between the patient and the doctor, and consequently reduces the number of medical disputes.

e) tools and devices that are specific to the patient : people are different, so the size of the bones is also different. Using this technology, you can adjust the implants to the exact size of the patient and prepare the devices.

3D printing is also used in pharmacy. Traditional processes such as grinding, granulating, pressing, and mixing used in the pharmaceutical industry sometimes result in irregular end product qualities that depend on factors such as drug release, drug loading, drug stability, and pharmaceutical dosage. Three-dimensional printing as a reliable tool technology has competitive advantages such as increased safety, increased research and development productivity, drug availability, and efficiency. The main advantages of 3D printing that make it more attractive are listed below:

a) Personalization (personalized medicine). It involves adapting treatment to the characteristics, preferences, and needs of each individual patient. This includes targeted diagnosis, treatment, and follow-up. The concept of personalized medicine can be expanded to include preventive medicine aimed at reducing the risk of diseases to which the patient has shown a predisposition, by changing the patient's diet, habits and lifestyle, as well as by providing recommendations for the use of certain medications. medications or supplements.

b) creating complex shapes: using 3D printing, complex shapes can be formed with the exact dose of medication or active pharmaceutical ingredients, even with 10-12 mol per tablet, which helps reduce the side effects observed due to excessive doses. Compared to traditional approaches, when complex geometric shapes were not possible, this can be easily achieved using 3D printing. In addition, different sizes and

shapes lead to different release profiles. Complex forms result in modified release, adjusted drug loading, and masking the taste of the drug.

C) slow release: 3D printing makes it easy to monitor and target drug release. By printing the binder in layers of matrix powder, it can be used. This creates a barrier between API levels that allows you to change the release profile.

d) Unique dosage form: 3D printing can be used in the pharmaceutical production process to create an unlimited number of unique dosage forms. 3D printing is used to create a new dosage form.

e) Mini dispenser: the installation of a 3D printer requires minimal space, which allows these printers to fit into any environment, and it is economical. Three-dimensional printing is an automated design. This means that 3D printing can be controlled using computer software and a network. In addition, 3D printing technologies make it possible to individualize medicines. Based on these properties, the 3D printer works like a mini dispenser, potentially bringing tablet production closer to patients.

e) Integration with the healthcare network: pharmacists and doctors can make changes to the next dose or combination of medications depending on the patient's needs. 3D printers are controlled remotely. This way, patients can easily access 3D printing. This increases patient compliance and reduces the time of clinical response to the patient's needs (gram).

## CONCLUSION

According to the literature, you can see that 3D printing technologies are successfully used in medicine and healthcare and are the proper representation of health development as a meta-institution [43]. Today, a significant number of traditional manufacturing technologies are being replaced by new 3D printing technologies due to their ability for more controlled processing, higher dimensional accuracy, and patient-oriented devices. However, there are some limitations when printing viscous raw materials, which leads to modification, optimization, or replacement of some parts. The commercialization of the technologies highlighted in the text is also unclear, even though the core potential of those technologies to facilitate territories' economic development is rather obvious [44] since many territories make an emphasis on their effort to anchor various innovation-driven business in bio-tech and med-tech [45]. Perhaps these technologies can simply be used for research and never get a chance to commercialize, for example, those medical devices that have not yet

been approved by the Food and Drug Administration.

To combine the results of 3D printing systems, you need to check the stability and repeatability of the final products. However, it is difficult to predict how widely 3D printing covers medical applications. Although 3D printing applications and products in medicine, biology, and healthcare have made significant progress, they still need to be carefully evaluated for compliance with standards based on efficiency, energy consumption, and sustainability. Moreover, it should be noted that related industries should support academic developments in this area, because without their financial support, this technology cannot develop quickly and effectively.

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