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3 D Printing a Revolutionary Approach in Medicinal Science-Review

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ABSTRACT

3 D printing for design and manufacturing Medicinal seems to be new science fiction and breakthrough solution for various medicinal problems. The novel technology is simple time saving and rapid designing and manufacturing of most complex things. This system seems to take science and technology to new heights.

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1. INTRODUCTION

3 D printing has to raise biosynthesis of artificial organs to a new height. Medical uses for 3D printing are categories into, tissue and organ fabrication; synthesis of customized prosthetics, implants, and anatomical models; and pharmaceutical research regarding drug dosage forms, delivery, and discovery.[3] The application of 3D printing in medicine can provide many benefits, including the customization and personalization of medical products, drugs, and equipment; cost-effectiveness; increased productivity; the democratization of design and manufacturing; and enhanced collaboration.[4] Three-dimensional (3D) printing is a manufacturing method in which objects are made by fusing or depositing materials—such as plastic, metal, ceramics, powders, liquids, or even living cells—in layers to produce a 3D object. This process is also referred to as additive manufacturing (AM), rapid prototyping (RP), or solid free-form technology (SFF).Some 3D printers are similar to traditional inkjet printers; however, the end product differs in that a 3D object is produced. 3D printing is expected to revolutionize medicine and other fields, not unlike the way the printing press transformed publishing. [5]These technologies can build a 3D object in almost any shape imaginable as defined in a computer-aided design (CAD) file.[6] In a basic setup, the 3D printer first follows the instructions in the CAD file to build the foundation for the object, moving the print head along the x–y plane. The printer then continues to follow the instructions, moving the print head along the z-axis to build the object vertically layer by layer. It is important to note that two-dimensional (2D) radiographic images, such as x-rays, magnetic resonance imaging (MRI), or computerized tomography (CT) scans, can be converted to digital 3D print files, allowing the creation of complex, customized anatomical and medical structures.3D printing has been used to create car parts, Smartphone cases, fashion accessories, medical equipment and artificial organs. 3D printing has also helped save lives.[9]

2. Medical applications of 3D printing

3D printer produces bones, ears, exoskeletons, windpipes, a jaw bone, eyeglasses, cell cultures, stem cells, blood vessels, vascular networks, tissues, and organs, as well as novel dosage forms and drug delivery devices. The current medical uses of 3D printing can be organized into several broad categories: tissue and organ fabrication; creating prosthetics, implants, and anatomical models; and pharmaceutical research concerning drug discovery, delivery, and dosage forms.

2.1 Designing and manufacturing Tissues and Organs[7]

Tissue or organ failure due to aging, diseases, accidents, and birth defects is a critical medical problem. Current treatment for organ failure relies mostly on organ transplants from living, however; there is a chronic shortage of human organs available for transplant. In 2009, 154,324 patients in the U.S. were waiting for an organ. Only 27,996 of them (18%) received an organ transplant, and 8,863 (25 per day) died while on the waiting list. As of early 2014, approximately 120,000 people in the U.S. were awaiting an organ transplant. Organ transplant surgery and follow-up are also expensive, costing more than $300 billion in 2012. An additional problem is that organ transplantation involves the often difficult task of finding a donor who is a tissue match. This problem could likely be eliminated by using cells taken from the organ transplant patient’s own body to build a replacement organ. This would minimize the risk of tissue rejection, as well as the need to take lifelong immunosuppressants[3]. Therapies based on tissue engineering and regenerative medicine are being pursued as a potential solution to the organ donor shortage. The traditional tissue engineering strategy is to isolate stem cells from small tissue samples, mix them with growth factors, multiply them in the laboratory, and seed the cells onto scaffolds that direct cell proliferation and differentiation into functioning tissues. Although still in its infancy, 3D bioprinting offers additional important advantages beyond this traditional regenerative method (which essentially provides scaffold support alone), such as highly precise cell placement and high digital control of speed, resolution, cell concentration, drop volume, and diameter of printed cells. Organ printing takes advantage of 3D printing technology to produce cells, biomaterials, and cell-laden biomaterials individually or in tandem, layer by layer, directly creating 3D tissue-like structures. Various materials are available to build the scaffolds, depending on the desired strength, porosity, and type of tissue, with hydrogels usually considered to be most suitable for producing soft tissues.[6] Although 3D bioprinting systems can be laser-based, inkjet-based, or extrusion-based, inkjet-based bioprinting is most common. This method deposits “bio- ink,” droplets of living cells or biomaterials, onto a substrate according to digital instructions to reproduce human tissues or organs. Multiple print heads can be used to deposit different cell types (organ-specific, blood vessel, and muscle cells), a necessary feature for fabricating whole heterocellular tissues and organs. A process for bio printing organs has emerged: 1) create a blueprint of an organ with its vascular architecture; 2) generate a bioprinting process plan; 3) isolate stem cells; 4) differentiate the stem cells into organ-specific cells; 5) prepare bio-ink reservoirs with organ-specific cells, blood vessel cells, and support medium and load them into the printer; 6) bioprint; and 7) place the bioprinted organ in a bioreactor prior to transplantation. Laser printers have also been employed in the cell printing process, in which laser energy is used to excite the cells in a particular pattern, providing spatial control of the cellular environment.[1] Although tissue and organ bioprinting is still in its infancy, many studies have provided proof of concept. Researchers have used 3D printers to create a knee meniscus, heart valve, spinal disk, other types of cartilage and bone, and an artificial ear. Cui and colleagues applied inkjet 3D printing technology to repair human articular cartilage. Wang et al used 3D bioprinting technology to deposit different cells within various biocompatible hydrogels to produce an artificial liver. Doctors at the University of Michigan published a case study in the *New England Journal of Medicine* reporting that use of a 3D printer and CT images of a patient's airway enabled them to fabricate a precisely modeled, bioresorbable tracheal splint that was surgically implanted in a baby with tracheobronchomalacia. The baby recovered, and full resorption of the splint is expected to occur within three years. A number of biotech companies have focused on creating tissues and organs for medical research. It may be possible to rapidly screen new potential therapeutic drugs on patient tissue, greatly cutting research costs and time. Scientists at Organovo are developing strips of printed liver tissue for this purpose; soon, they expect the material will be advanced enough to use in screening new drug treatments. Other researchers are working on techniques to grow complete human organs that can be used for screening purposes during drug discovery. An organ created from a patient's own stem cells could also be used to screen treatments to determine if a drug will be effective for that individual.

2.2 For building 3D VascularizedOrgans[1]

Proof-of-concept studies regarding bioprinting have been performed successfully, but the organs that have been produced are miniature and relatively simple. They are also often avascular, aneural, alymphatic, thin, or hollow, and are nourished by the diffusion from host vasculature. However, when the thickness of the engineered tissue exceeds 150–200 micrometers, it surpasses the limitation for oxygen diffusion between host and transplanted tissue. As a result, bioprinting complex 3D organs will require building precise multicellular structures with vascular network integration, which has not yet been done. Most organs needed for transplantation are thick and complex, such as the kidney, liver, and heart. Cells in these large organ structures cannot maintain their metabolic functions without vascularization, which is normally provided by blood vessels. Therefore, functional vasculature must be bioprinted into fabricated organs to supply the cells with oxygen/gas exchange, nutrients, growth factors, and waste product removal—all of which are needed for maturation during perfusion. Although the conventional tissue engineering approach is not now capable of creating complex vascularized organs, bioprinting shows promise in resolving this critical limitation. The precise placement of multiple cell types is required to fabricate thick and complex organs and for the simultaneous construction of the integrated vascular or microvascular system that is critical for these organs to function. TIJ printers are considered to be the most promising for this use. However, various 3D printing techniques and materials have been applied successfully to create vasculature as simple as a single channel, as well as more complex geometries, such as bifurcated or branched channels. Recently, collaborators from a network of academic institutions, including the University of Sydney, Harvard University, Stanford University, and the Massachusetts Institute of Technology, announced that they had bioprinted a functional and perfusable network of capillaries, an achievement that represents a significant stride toward overcoming this problem.[1]

2.3 For synthesis of Implants and Prostheses[2]

Implants and prostheses can be made in nearly any imaginable geometry through the translation of x-ray, MRI, or CT scans into digital. 3D print files. In this way, 3D printing has been used successfully in the health care sector to make both standard and complex customized prosthetic limbs and surgical implants, sometimes within 24 hours. This approach has been used to fabricate dental, spinal, and hip implants. Previously, before implants could be used clinically, they had to be validated, which is very time-consuming.

The ability to quickly produce custom implants and prostheses solves a clear and persistent problem in orthopedics, where standard implants are often not sufficient for some patients, particularly in complex cases. Previously, surgeons had to perform bone graft surgeries or use scalpels and drills to modify implants by shaving pieces of metal and plastic to a desired shape, size, and fit. This is also true in neurosurgery: Skulls have irregular shapes, so it is hard to standardize a cranial implant. In victims of head injury, where bone is removed to give the brain room to swell, the cranial plate that is later fitted must be perfect. Although some plates are milled, more and more are created using 3D printers, which makes it much easier to customize the fit and design. There have been many other commercial and clinical successes regarding the 3D printing of prostheses and implants. A research team at the BIOMED Research Institute in Belgium successfully implanted the first 3D-printed titanium mandibular prosthesis.[2] The implant was made by using a laser to successively melt thin layers of titanium powders. In 2013, Oxford Performance Materials received FDA approval for a 3D-printed polyetherketoneketone (PEKK) skull implant, which was first successfully implanted that Year. Another Company, Layer Wise, manufactures 3D-printed titanium orthopedic, maxillofacial, spinal, and dental implants.[6] An anatomically correct 3D-printed prosthetic ear capable of detecting electromagnetic frequencies has been fabricated using silicon, chondrocytes, and silver nanoparticles. There is a growing trend toward making 3D-printed implants out of a variety of metals and polymers, and more recently implants have even been printed with live cells. 3D printing has already had a transformative effect on hearing aid manufacturing. Today, 99% of hearing aids that fit into the ear are custom-made using 3D printing. Everyone's ear canal is shaped differently, and the use of 3D printing allows custom-shaped devices to be produced efficiently and cost-effectively. The introduction of customized 3D-printed hearing aids to the market was facilitated by the fact that class I medical devices for external use are subject to fewer regulatory restrictions. Envisaging braces are another successful commercial use of 3D printing, with 50,000 printed every day. These clear, removable, 3D-printed orthodontic braces are custom-made and unique to each user. This product provides a good example of how 3D printing can be used efficiently and profitably to make single, customized, complex items.

2.4 Designing anatomical models in surgical preparations[1]

The individual variances and complexities of the human body make the use of 3D-printed models ideal for surgical preparation. Having a tangible model of a patient's anatomy available for a physician to study or use to simulate surgery is preferable to relying solely on MRI or CT scans, which aren't as instructive since they are viewed in 2D on a flat screen. The use of 3D-printed models for surgical training is also preferable to training on cadavers, which present problems with respect to availability and cost.[3]Cadavers also often lack the appropriate pathology, so they provide more of a lesson in anatomy than a representation of a surgical patient. Researchers at the National Library of Medicine generate digital files from clinical data, such as CT scans, that are used to make custom 3D-printed surgical and medical models. 3D-printed neuroanatomical models can be particularly helpful to neurosurgeons by providing a representation of some of the most complicated structures in the human body. The intricate sometimes obscured relationships between cranial nerves, vessels, cerebral structures, and skull architecture can be difficult to interpret based solely on radiographic 2D images. Even a small error in navigating this complex anatomy can have potentially devastating consequences. A realistic 3D model reflecting the relationship between a lesion and normal brain structures can be helpful in determining the safest surgical corridor and can also be useful for the neurosurgeon to rehearse challenging cases. Complex spinal deformities can also be studied better through the use of a 3D model. High-quality 3D anatomical models with the right pathology for training doctors in performing colonoscopies are also vital since colorectal cancer is the second leading cause of cancer-related deaths in the U.S.3D model used for surgical planning by neurosurgeons at the Walter Reed National Military Medical Center. Although still largely exploratory, 3D-printed models have been used in numerous cases to gain insight into a patient’s specific anatomy prior to a medical procedure.[6] Pioneering surgeons at Japan’s Kobe University Hospital have used 3D-printed models to plan liver transplantations. They use replicas of a patient’s organs to determine how to best carve a donor liver with minimal tissue loss to fit the recipient’s abdominal cavity. These 3D models are made of partially transparent, low-cost acrylic resin or polyvinyl alcohol—materials that have water content and texture similar to living tissues, allowing a more realistic penetration by the surgical blades. Other surgeons have used a 3D-printed model of a calcified aorta for surgical planning of plaque removal. A premature infant’s airway was also reconstructed in order to study aerosol drug delivery to the lungs. It has been reported that an orthopedic surgery trainee used CT image scans and 3D modeling software to create print files representing a patient’s bones. The files were then sent to Shape ways to print custom models used for planning surgery. The cost for 3D printing was a fraction of what it would normally cost to have custom models made, and the turn-around time was faster. 3D-printed models can be useful beyond surgical planning. Recently, a polypeptide chain model was 3D printed in such a way that it could fold into secondary structures because of the inclusion of bond rotational barriers and degrees of freedom considerations. Similar models could be utilized to aid the understanding of other types of biological or biochemical structures. Pre- and postcomprehension study results have shown that students are better able to conceptualize molecular structures when such 3D models are used.

2.5 For designing novel Dosage Forms and Drug Delivery Devices[1]

3D printing technologies are already being used in pharmaceutical research and fabrication, and they promise to be transformative. Advantages of 3D printing include precise control of droplet size and dose, high reproducibility, and the ability to produce dosage forms with complex drug-release profiles. Complex drug manufacturing processes could also be standardized through the use of 3D printing to make them simpler and more viable. 3D printing technology could be very important in the development of personalized medicine, too.

2.6 For making drug dosing personalized[1]

The purpose of drug development should be to increase efficacy and decrease the risk of adverse reactions, a goal that can potentially be achieved through the application of 3D printing to produce personalized medications. Oral tablets are the most popular drug dosage form because of ease of manufacture, pain avoidance, accurate dosing, and good patient compliance. However, no viable method is available that could routinely be used to make personalized solid dosage forms, such as tablets. Oral tablets are currently prepared via well-established processes such as mixing, milling, and dry and wet granulation of powdered ingredients that are formed into tablets through compression or molds. Each of these manufacturing steps can introduce difficulties, such as drug degradation and form change, possibly leading to problems with the formulation or batch failures. In addition, these traditional manufacturing processes are unsuitable for creating personalized medicines and restrict the ability to create customized dosage forms with highly complex geometries, novel drug-release profiles, and prolonged stability.[2] Personalized 3D-printed drugs may particularly benefit patients who are known to have a pharmacokinetic polymorphism or who use medications with narrow therapeutic indices. Pharmacists could analyze a patient's pharmacokinetic profile, as well as other characteristics such as age, race, or gender, to determine an optimal medication dose. A pharmacist could then print and dispense the personalized medication via an automated 3D printing system.[5] If necessary, the dose could be adjusted further based on clinical response.[1] 3D printing also has the potential to produce personalized medicines in entirely new formulations—such as pills that include multiple active ingredients, either as a single blend or as complex multilayer or multi-reservoir printed tablets. Patients who have multiple chronic diseases could have their medications printed in one multidose form that is fabricated at the point of care. Providing patients with an accurate, personalized dose of multiple medications in a single tablet could potentially improve patient compliance. Ideally, compounding pharmacies could dispense 3D-printed drugs since their customers are already familiar with purchasing customized medications.

2.7 Unique Dosage Forms[2]

The primary 3D printing technologies used for pharmaceutical production are inkjet-based or inkjet powder-based 3D printing. Whether another material or a powder is used as the substrate is what differentiates 3D inkjet printing from powder-based 3D inkjet printing. In inkjet-based drug fabrication, inkjet printers are used to spray formulations of medications and binders in small droplets at precise speeds, motions, and sizes onto a substrate. The most commonly used substrates include different types of cellulose, coated or uncoated paper, microporous bioceramics, glass scaffolds, metal alloys, and potato starch films, among others. Investigators have further improved this technology by spraying uniform "ink" droplets onto a liquid film that encapsulates it, forming microparticles and nanoparticles. Such matrices can be used to deliver small hydrophobic molecules and growth factors. In powder-based 3D printing drug fabrication, the inkjet printer head sprays the "ink" onto the powder foundation. When the ink contacts the powder, it hardens and creates a solid dosage form, layer by layer. The ink can include active ingredients as well as binders and other inactive ingredients. After the 3D-printed dosage form is dry, the solid object is removed from the surrounding loose powder substrate. These technologies offer the ability to create limitless dosage forms that are likely to challenge conventional drug fabrication. 3D printers have already been used to produce many novel dosage forms, such as microcapsules, hyaluronan-based synthetic extracellular matrices, antibiotic printed micropatterns, mesoporous bioactive glass scaffolds, nanosuspensions, and multilayered drug delivery devices. Ink formulations used in 3D drug printing have included a variety of active ingredients, such as steroidal anti-inflammatory drugs, acetaminophen, theophylline, caffeine, vancomycin, ofloxacin, tetracycline, dexamethasone, paclitaxel, folic acid, and others. Inactive ingredients used in 3D drug printing have included: poly (lactic-co-glycolic acid), ethanoldimethyl sulfoxide, surfactants (such as Tween 20), Kollidon SR, glycerin, cellulose, propylene glycol, methanol, acetone, and others.

2.8 Complex Drug-Release Profiles[1]

The creation of medications with complex drug-release profiles is one of the most researched uses of 3D printing. Traditional compressed dosage forms are often made from a homogeneous mixture of active and inactive ingredients and are thus frequently limited to a simple drug-release profile. However, 3D printers can print binder onto a matrix powder bed in layers typically 200 micrometers thick, create a barrier between the active ingredients to facilitate controlled drug release. 3D-printed dosage forms can also be fabricated in complex geometries that are porous and loaded with multiple drugs throughout, surrounded by barrier layers that modulate release. Implantable drug delivery devices with novel drug-release profiles can also be created using 3D printing. Unlike traditional systemic treatments that can affect nonaffiliated tissue, these devices can be implanted to provide direct treatment to the area involved. Bone infections are one example where direct treatment with a drug implant is more desirable than systemic treatment. Fortunately, powder-based 3D-printed bone scaffolding can be created in high-resolution models with complex geometries that mimic the natural bone extracellular matrix. The printing of medications with customized drug-release profiles into such bone implant scaffolds has been studied. One example is the printing of a multilayered bone implant with a distinct drug-release profile alternating between rifampicin and isoniazid in a pulse release mechanism. 3D printing has also been used to print antibiotic micropatterns on paper, which have been used as drug implants to eradicate *Staphylococcus epidermis*. In other research concerning drug-release profiles, chlorpheniramine maleate was 3D printed onto a cellulose powder substrate in amounts as small as 10 to 12 moles to demonstrate that even a minute quantity of drug could be released at a specified time. This study displayed improved accuracy for the release of very small drug doses compared with conventionally manufactured medications. Dexamethasone has been printed in a dosage form with a two-stage release profile. Levofloxacin has been 3D printed as an implantable drug delivery device with pulsatile and steady-state release mechanisms.

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