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3D PRINTING OF PERSONALISED MEDICINE: METHOD, APPLICATION AND FUTURE POTENTIAL A SYSTEMIC REVIEW

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ABSTRACT

Personalized medicine joins a new frontier in the development of treatment arrangements that take into account the personality, medical history and physiology. Precision medicine has gained a foothold in the medical field thanks to the use of revolutionary 3D printing technology. Compared to conventional methods, 3D printing allows for rapid production, design and printing. Pharmaceutical manufacturers are experimenting with creating compounds by layer-by-layer of pre-defined compatible polymers in various geometries, thicknesses, profiles and designs.[1] As this integrated and innovative technology continues to grow, patient-centered medical devices, prostheses and implants must comply with regulations and requirements to enter the market. This review explores the basics of 3D printing before diving into the techniques and strategies. The beam of light is on the logic of self-therapy. Applications of 3D printed integrated delivery and devices include dose tailoring, multidrug combinations, variable delivery systems, medical implants and population-specific diagnostics. Finally, some barriers and regulatory perspectives for 3D printing in the development of relevant drugs will be discussed.[1]

KEYWORDS: History of 3D printing, Methods, Application's, organ printing, Prostheses, Future potential.

INTRODUCTION

3D printing in personalized medicine refers to the use of additive manufacturing technologies to create medical products such as prostheses, implants, drug delivery systems and tissue models, tailored to needs and patient characteristics, and benefit from advances in the type of diagnosis, accuracy. Medicine and digital health technologies".

This definition includes many applications for 3D printing in personalized medicine, including.

Customized implants and implants

Personalized drug delivery systems

Fabrication of tissue and organ models for drug testing and modeling Disease modeling

Generating personalized guides and models

Creating personal robotic systems for minimally invasive surgery.

A new technique called medical application can benefit greatly from the use of three-dimensional (3D) printing. It can offer advanced solutions for people and the medical sector. 3D model that uses digital data collected by a 3D printer, 3D printing is a process that combines many technologies, methods to produce a 3D object. 3D printing is a process of creating 3D structures using a digital CAD file. The uniformity of shape and construction of many complex elements for use in simulation and simulation can be achieved through 3D printing technology. Therefore, it is a useful way of looking at the many challenges that face the daily work of the medical sector. 3D printing is considered one of the biggest advancements in the manufacturing industry. The nature of parts, components and tools have been changed to produce and develop this industry. Using conventional manufacturing techniques, 3D printing allows researchers and manufacturers to create structures with complex shapes that were previously thought of as dimensional structures. It also aids in the development of pharmaceutical products by providing a variety of delivery methods to meet unmet clinical needs. Using this technology, patient preferences can be accurately identified and support patient-centered therapy, including dose determination to treat specific disease states and groups. patient the range of printed materials and equipment research and development has increased due to the introduction of 3D and 4D printing technology in the medical sector.[2]

Purpose of this paper

- Explore the potential of 3D printing in personalized medicine
- Discuss the current state of 3D printing technology in biomedical research and healthcare- Explore the applications of 3D printing in personalized medicine, including braces, implants, drug delivery systems and tissue models.

Scope

- An overview of 3D printing techniques and their applications in biomedical and medical research
- Discussion of the benefits and challenges of using 3D printing in personalized medicine n
- Review of the current state of duplicating technology. the development of personalized medical devices[2]

HISTORY OF 3D PRINTING

In 1980, the concept of 3D printing or additive manufacturing was introduced. Chuck Hull invented stereolithography (SLA) in 1984, which allows objects to be created layer by layer using UV lasers and photopolymer resins[4] Development of other 3D printing technologies in the 1990s, including selective laser sintering (SLS) and sediment sampling. (FDM) has expanded potential application. Companies such as Stratasys and 3D Systems were founded during this[4] 2000s 3D printing began to gain commercial traction. Expiration of early patents increased competition and innovation, reducing free riding and entry.[4]

Researchers began experimenting with printing biological materials. In 2003, the first bioprinting patent was filed, leading to advances in printing tissues and organs.

2010s: The introduction of expensive desktop 3D printers, such as those from MakerBot, introduced access to the technology. Innovations in materials, such as metal printing and ceramics, expanded industrial applications.[4]

PERSONALISED MEDICINE EARLY CONCEPT

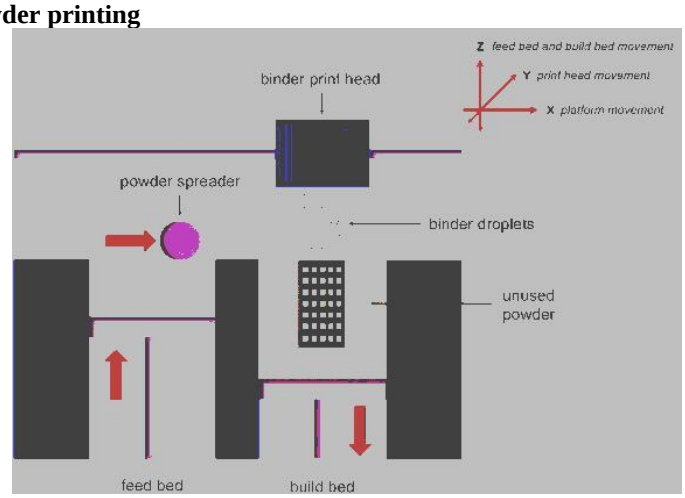
Pharmacogenomics: The study of how genes influence a person's response to drugs laid groundwork for personalized medicine. In the 1990s, the Human Genome Project released massive data that pushed the field forward.[3]

Customized dosage forms: In the early 2000s, customized dosage forms were developed to allow for the tailoring of medications to the needs of specific patients. Integration with 3D Printing - Custom Implants and Implants: The use of 3D printing to create custom implants and implants is of great interest to patients who are beginning to engage in the principles of personalized medicine.[3]

- Drug delivery systems: 3D printing has made it possible to create complex drug delivery systems that can deliver drugs at rates and times appropriate to the patient's condition.[3]

DIFFERENT METHODS AND MATERIAL USED IN 3D PRINTING

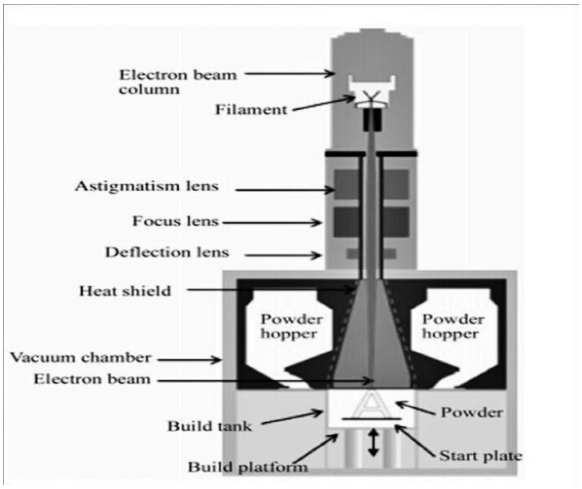
1. Three-dimensional powder printing



3D powder printing (3DPP) works by using an adhesive that is selected on the powder, mainly gypsum and starch. Powder layers are distributed in a forming chamber using a nozzle, and then a liquid paste is applied to the powder in a defined pattern by an inkjet head[5,6] When one layer is finished, the powder layer is lowered slightly by the swing, and a new layer of powder is spread on top. This process is repeated until the structure is complete. During manufacturing, the powders are not bound to support the object being printed.[7] After printing, various finishing operations such as cleaning and assembling of the printed material can be performed to improve the surface or mechanical strength of the part. However, one of the main disadvantages of using sintering as a finishing process is that it can cause parts to slip. If there is a need to increase the mechanical strength of the unit, this should be considered to reduce the production unit.[7] The resolution of 3DPP printing is 40-50 µm .

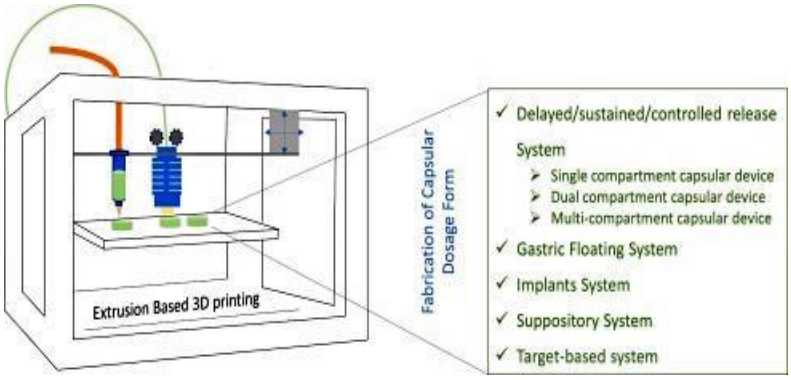
2. Electron beam melting: In electron beam melting (EBM), an electron beam is used to melt a metal powder in a vacuum chamber, creating a desired pattern or shape that solidifies upon cooling. When one layer is

completed, another layer of powder is spread over the previous layer and this process is repeated[8] EBM can produce metal parts with complex structures that are dense or porous in nature. Typically, EBM systems include an electron gun and focusing device, a build table in a vacuum chamber, and powder coating.



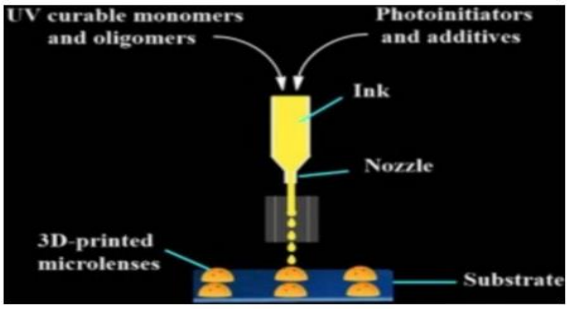
An electron gun creates an electron beam that is then focused to achieve a high energy density. Using a vacuum chamber ensures an oxygen-free environment, reduces the potential for hydrogen absorption, and increases the cleanliness of the print. After casting the desired parts from the previous layer, it is important to paint the powder by spreading a new layer of powder. This new layer of powder acts as a support for the ridges that appear below the subsequent layers.[9] The production process begins with EBM to create the outer boundary of the layer, and then melt the powder in that layer. When one layer is finished, the powder coater spreads another layer of powder, and the whole process is repeated until the part is finished. Although parts manufactured using EBM have high mechanical strength, the accuracy of the process is limited by the particle size of the metal powder. The resolution of the EBM document is 50-100 µm.

3. Extrusion based: Extrusion-based (EB) production is a common and cost-effective process that involves removing a material as a continuous filament layer by layer, using a piston, screw, or high pneumatic force.[10,11] Depending on its characteristics, the transmitted material can be combined electronically or simply removed. After completing a layer, the head of the printer is raised by the robot and a new layer is started.[11] This process continues until the 3D structure is completed. The resolution of EB printing is 20-100 µm. EB printers include a material management system, an extraction system, and a heat-sensing area. The extraction system consists of one or more recording heads that can move in the x- and z-axis, and the stage moves in the y-axis[11,5] Different combinations of drawing phase and head movement direction are also possible. However, one of the main disadvantages of EB printing is that it heats up the printed material, creating high shear stresses that significantly reduce cell life.[10]



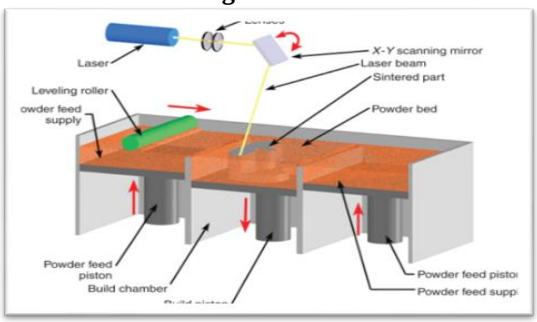
4. inkjet: Inkjet (IJ) printing technologies, also known as application-based technologies, were originally adapted from 2D inkjet printers.[10,11] IJ artists work by placing controlled volumes of fluid into predefined patterns on top of the print layer by layer until the desired 3D structure is achieved. Volumes of water are ejected from the nozzle using pressure pulses either thermally or piezoelectrically.

When thermal pressure technology is used, it is heated up to 300 °C, and it takes a long time. 2 µs. Fortunately, this local heating does not affect cell viability because the ink temperature rises below 10 °C above ambient. In general, the amount of water dispensed is in the picolitre range.[10] IJ printers are widely used for biological and non-biological printing applications.[11] The resolution of the IJ is 20-100 µm. Two major advantages of IJ printers are low cost and fast printing.[6] However, one of the main disadvantages of IJ printers is that the printing material must be water-resistant. This is usually achieved by UV or chemical bonding methods. Furthermore, it is difficult to create structures with biologically relevant cell densities due to the low concentration of cells in the ink. The reason for using a low concentration of cells in the ink is to reduce the problems of nozzle swelling and improve the formation of droplets.[11]



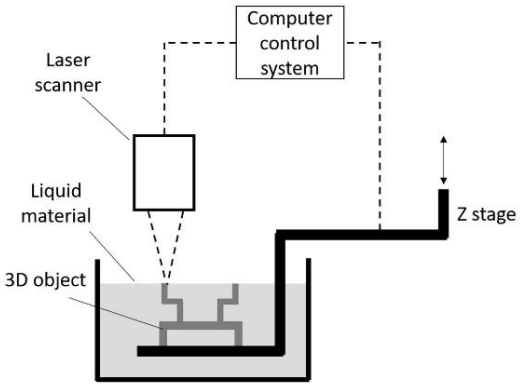
5. Multi head deposition system: The Multi-Head Deposition System (MHDS) represents a fusion of the Inkjet (IJ) and Electron Beam (EB) printing techniques. MHDS includes 2–6 printing heads that have the capability to dispense various synthetic or natural polymers, proteins, or hydrogels simultaneously.[13] The printing heads themselves bear resemblance to, or are identical to, those utilized in EB and IJ printing techniques. Furthermore, it is possible to control the movement, pressure, and temperature of each printing head individually.[13] The printing resolution of MHDS ranges from 100 to 200 µm.[13] In the field of MHDS, polymer materials are typically employed for establishing the framework of the structure, whereas hydrogels predominantly aid in the development of living tissue and can be accurately administered in quantities as minimal as 1 µL.[13] The MHDS printing method was developed to overcome the constraints associated with the separate applications of IJ and EB printing methods. Printing techniques utilizing hydrogels encounter difficulties in preserving a consistent three-dimensional structure.[13] Conversely, EB printing techniques can generate consistent 3D structures; however, they might not offer environments that are as favorable for cell proliferation as a blend of EB with IJ. Two point one point six. Poly Jet technology is a fusion of Stereolithography (SLA) and Inkjet (IJ) printing techniques. The process employed by PJ involves the application of a photopolymer resin onto the build surface, followed by the curing of each layer with a UV light, and subsequent repetition of these steps until the construction is finalized. In instances where auxiliary materials are required for the construction process, a gel-like substance is introduced via one of the support nozzles, and it can be readily eliminated after construction either by rinsing with water or manual removal.[14] The printing resolution of the PJ device ranges from 30 to 40 micrometers according to sources . PJ provides a variety of benefits, including the elimination of post-curing requirements[14] and achieving a higher level of accuracy, specifically 0.49% and 0.61% more precise than 3DPP or Selective Laser Sintering, respectively. Furthermore, PJ has the ability to print layers with a thickness of 16 µm and in various colors. An additional benefit lies in the capability to fabricate items with varying degrees of rigidity. Nevertheless, the primary drawback of utilizing PJ technology is that these benefits are accompanied by a significant increase in cost, with prices ranging between USD $20,000 and $120,000.[15]

6. Selective laser printing and selective laser sintering



Selective Laser Melting (SLM) and Selective Laser Sintering (SLS) employ identical processes with the exception of one significant distinction. In Selective Laser Melting (SLM), the powder material undergoes complete melting, whereas in Selective Laser Sintering (SLS), the powder material is solely subjected to sintering. Both Selective Laser Melting (SLM) and Selective Laser Sintering (SLS) entail the utilization of a laser characterized by high-power density to melt or sinter consecutive layers of powder, culminating in the creation of a three-dimensional object. The systems utilized for Selective Laser Melting (SLM) and Selective Laser Sintering (SLS) comprise a fiber laser equipped with a beam focuser, a build table housed within a build chamber, and a powder recoater. The build table has the capacity to be heated to a temperature of 200 ◦C, while the build chamber is commonly purged with an inert gas to maintain a high level of purity. The powder recoater is a device that applies a new layer of powder with a thickness ranging from 20 to 100 μm once the previous layer has been finished.[8] The printing resolution of Selective Laser Melting (SLM) ranges from 20 to 50 μm, as reported in references . The printing resolution of SLS ranges from 50 to 100 micrometers. The typical procedure for printing with Selective Laser Melting (SLM) and Selective Laser Sintering (SLS) entails initially constructing the outer perimeter of the layer, followed by melting or sintering the powder contained within said layer.[8,16] Upon completing a single layer, the powder re-coater proceeds to apply a new layer of powder, continuing this process iteratively until the component is fully constructed. The benefits of utilizing Selective Laser Melting (SLM) encompass the ability to create components with intricate designs and superior mechanical properties, whether they are porous or fully compacted. Nevertheless, the precision of the printing process is restricted by the size of the powder particles, necessitating strict atmospheric control. Moreover, Selective Laser Sintering (SLS) offers a cost-efficient and effective approach for fabricating porous scaffolds featuring intricate internal and external geometries. An additional significant benefit of SLS lies in its versatility, as it has the capability to utilize virtually any powdered biomaterial that can undergo fusion without decomposition when exposed to a laser beam. Nevertheless, a notable drawback of Selective Laser Sintering (SLS) lies in its incapacity to bond bio ceramics. As a result, a polymer binding agent must be added to the powder mixture for applications involving bio ceramic substances.[16]

7. Stereolithography: The essential elements of the SLA system comprise a UV laser, a reservoir containing a photosensitive liquid resin, and a construction platform situated inside the reservoir.[6]



SLA functions through the precise exposure of a fine layer of photosensitive liquid resin to a UV laser in the x and y-axes, leading to the specific photopolymerization of these regions. After finishing one layer, the build platform gently descends by 50–200 μm, accommodating the chosen resolution of the build, enabling the new liquid resin to smoothly cover the already solidified layer.

The process continues in this manner until the construction is finished, at which point the liquid resin is drained and the component is washed. If necessary, additional post-processing like UV flooding can be carried out after the completion of the build to improve its strength. The SLA printing resolution ranges from 70 to 300 micrometers.[17] SLA presents several benefits, including exceptional print precision, the capacity to produce sizable prints, and a relatively affordable cost.

Application of 3D printing

1 3D bio printing: Another broad application of 3D printing involves 3D bioprinting. 3D bio-printing is the process of using cell-loaded biomaterials to create intricate living tissues or organs with specific functions.[18] In the field of regenerative medicine, it has been utilized to create tissues such as skin, bone, and cartilage. Therefore, an alternative technical method that is suitable for depositing living cells is required. Several benefits of this method comprise scalability, precise control of cell placement, superior resolution, customization, and cost-efficiency.[19] Bio-inks are delicate formulations consisting of cells and possibly containing biomaterials and biologically active

components. The cells come in diverse shapes and settings, and can also be implanted into different carriers. Nano-fibrillated cellulose with shear thinning properties and alginate with excellent cross-linking ability were utilized in creating cartilage structures. These substances were found to be non-cytotoxic and exhibited good cell viability.[20] Bioactive bone scaffolds were designed to boost bone regeneration by utilizing poly-lactic acid as the foundation. These were enveloped in gels containing mucic acid. The application of this coating enhanced their physical and chemical characteristics, promoting the differentiation of osteoblasts. Another team utilized 3D bio-printing to create small diameter blood vessels consisting of two separate cell layers. Decisive cell growth and development of blood vessels were noted in the study. 3D bio-printing has been utilized for creating neuronal tissues as well. Researchers have achieved the printing of a human heart, including blood vessels, ventricles, and chambers, using human cells. Bio-printing encounters some challenges, such as maintaining cell viability and regulating cell proliferation, despite its advantageous aspects. The materials and cells used should also be suitable for the printing process. A significant consideration in the field of bio-printing revolves around ensuring its safety. The materials utilized need to be biocompatible and safe.[21]

2. Combination table polypills: A significant application of 3D printing in personalized medicine involves the concept of a "polypill. " A polypill consists of a combination of multiple drugs in a single tablet that can be customized for an individual experiencing polypharmacy. Furthermore, the drug release can be customized according to individual requirements. This concept has the potential to significantly benefit the elderly demographic by enhancing patient compliance and medication adherence through a reduction in the daily pill intake. The fabrication of 3D printed polypills containing three drugs has been achieved successfully. This medication has the potential to be used for individuals with diabetes and hypertension. The tablets consist of an osmotic compartment containing captopril, as well as sustained-release compartments containing nifedipine and glipizide.[22] The identical team also developed a polypill containing five compartments that symbolized a regimen for cardiovascular treatment. The tablet is formulated with aspirin and hydrochlorothiazide in two immediate-release compartments, as well as pravastatin, atenolol, and ramipril in three sustained-release chambers. A different team has devised polyvinyl alcohol (PVA)-based combination pills incorporating four medications: lisinopril, amlodipine, rosuvastatin, and indapamide, which were investigated for their multilayer and unimatrix formations. The unimatrix tablets yielded a slower drug release rate compared to the individual tablets. In multi-layered polypills, the release of the drug was impacted by its specific placement within the various layers.[23] Fabricated multilayered polypills, consisting of six drugs (paracetamol, prednisolone, aspirin, chloramphenicol, naproxen, and caffeine) with varied geometries, such as cylindrical and ring-shaped, were produced utilizing an SLA 3D printer. In this instance, the printer underwent modifications to enable halting of the printing process, removal of the resin tray, and substitution with alternative resin solutions.[24] Subsequently, advancements in 3D printing technology were made to facilitate the production of polypill capsules featuring diverse release profiles for numerous medications. This achievement was accomplished by integrating FDM with hot-filling syringes. Two capsule skeletons were created featuring four distinct compartments. One capsule design incorporated a concentric configuration with two outer compartments for early release and two inner compartments for delayed release. The other design consisted of a parallel configuration utilizing non-dissolving capsule shells with unrestricted passageways and dissolution rate-limited pores to achieve both early and delayed release. The capsule shell is made up of polyvinyl alcohol and polylactic acid. Customized release profiles were achieved by modifying the shell thickness in the concentric arrangement or adjusting the size of the rate limiting orifices in the parallel arrangement.[25]

3. Dose personalization: 3D printing has the potential to provide flexibility in tailoring doses to meet the specific requirements of patients. A significant demographic that often requires dose adjustments is the pediatric population, as the appropriate therapeutic dosage varies based on the age and weight of children. Different forms of medication as listed earlier can be effectively customized with the use of 3D printers to provide the most suitable dosage for individual patients. In ODF formulations, adjusting the liquid API amount dispensed onto the film can be achieved effortlessly. ODFs may also undergo alterations in shape and size to personalize treatments.[26] Similarly, the dosage strength can be adjusted in alternative forms such as tablets or patches to cater to the specific requirements of patients. An instance of this can be seen in the work of Pietrzak and colleagues. FDM and HME technologies were utilized for printing theophylline tablets, with doses ranging from 60 to 300 mg, through adjustments in the printing scale.[27] Tablet splitting, manually or with a splitter, has historically been employed to allow for dose customization. It has been shown that this approach is ineffective because the different characterization parameters of the divided tablets do not consistently meet the Pharmacopeial standards. Zheng and colleagues conducted a study comparing split tablets with 3D printed subdivided tablets. The research found that the 3D printed divided tablets were more precise, secure, and offered customization possibilities. Newly developed 3D printed pellets, also known as mini-print lets, are customizable mini-tablets. They can be utilized to merge two distinct medications as well. Mini-print lets can also be tailored and enclosed in a way that matches the required dosage for personalized effect.[28]

4. Micro needles: Microneedles, also known as MNs, are small needle devices that are minimally invasive and can be made from different materials like biomaterials, metals, polymers, ceramics, and composites. These devices are specifically designed to penetrate the skin's outer layer, known as the stratum corneum, for a wide range of applications. Microneedles are designed with the purpose of delivering bioactive materials, vaccines, and pharmaceutical agents, as well as obtaining bio-signals and substances from the body in a minimally invasive manner. The efficacy of drug administration via the gastrointestinal tract has been limited by factors such as inadequate absorption of orally consumed medications and the body's pharmacokinetic processes. As a result, only a small portion of the drug reaches its desired therapeutic effectiveness. Patients' adherence to using hypodermic needles in the traditional manner has decreased notably over time because of the pain, anxiety, and discomfort associated with their use. A more attractive method that allows for controlled release, although requiring longer administration time, is transdermal drug delivery (TDD) with a microneedle patch. Nonetheless, the effectiveness of TDD is significantly hindered by the fact that the majority of individual drug particles struggle to permeate the skin at the required therapeutic levels, mainly because of the formidable barrier presented by the skin's stratum corneum.[29] Various methods have been explored to enhance the skin's permeability, such as the use of chemical lipid enhancers, applying electric fields through iontophoresis, and utilizing electroporation or pressure waves generated by ultrasound or photoacoustic effects . A different method includes forming a pathway of tiny needles to make minuscule holes on the top layer, known as the stratum corneum, by using microneedles crafted from silicon, metal, or polymer material. Microneedle arrays show great potential for enhancing transdermal drug delivery. Microneedles have been developed to effortlessly access the abundant blood supply in the deeper dermal layers, facilitating a comfortable and painless administration of various medications through the skin.[30] Microneedles offer painless application, quicker recovery, convenient use, and enhanced control over drug release speed. Microneedle patches fall into five categories solid, coated, dissolvable, hollow, and hydrogel-based microneedles. Different types of microneedles are crafted through specific fabrication methods and are designed for specific application areas. The term "microneedle" was initially mentioned in 1921 by Chambers in the context of micro-dissecting echinoderm eggs.[31]

A.) Solid microneedles, B) hollow microneedles, C) coated microneedles, D) dissolving microneedles, and hydrogel-forming microneedles are all types of microneedles. The methods mentioned include (a) First-generation stereolithography (b) Selective laser sintering (c) Digital light processing (d) Fused Deposition Modeling € Continuous liquid interface production and (f) Two-photon polymerization process.[32]

5. 3D printed nano medicine: 3D printing techniques have been utilized in the production of nanomedicines. The concentration of nanoparticles plays a significant role in 3D printing since agglomerated particles can act as flaws, leading to a reduction in the strength of the printed structure.[33] Typically, it is quite challenging to achieve high drug-loading nanoparticles in a polymer matrix due to the attractions between nanoparticles and the aggregations induced by Van der Waals forces. In order to enhance the uniformity of particles in a liquid suspension, it may be necessary to implement a preliminary step, like utilizing ultrasound, incorporating surfactants, ball milling, and similar methods.[34] Polymeric PCL nano capsules were used to encapsulate redispersible 3D-printed solid dosage forms incorporating polyphenols such as curcumin and resveratrol. The former were incorporated into a hydrogel 3D-printed with carboxymethyl cellulose by PAM. The polyphenols were gradually released over an 8-hour span, although not all of the active components were liberated from the Nano capsules, presenting a persistent challenge to address. Curcumin was encapsulated in liposomes and then incorporated into 3D-printed tissue scaffolds. Curcumin is known for its potent antioxidant, anti-cancer, and bone-strengthening properties, although its effectiveness is hindered by its low solubility in water. The integration of loaded liposomes into 3D-printed calcium phosphate scaffolds resulted in notable cytotoxic effects on osteosarcoma cells, while simultaneously enhancing the viability of osteoblasts.[35] Smoothly put, solid dosage forms made of 3D-printed solid lipids were created using dissolvable polymers. These forms were made with PLA and PVA, featuring various compartments for incorporating a second-step solid lipid formulation into a unified dosage form. The emulsions were carefully crafted with Gelucire 44/14, Gelucire 48/16, and Kolliphor P188 in combination with fenofibrate or Clofazimine, lumefantrine, and halofantrine as model drugs. The mixture was gently prepared by heating and stirring before being carefully filled into the compartments of the solid dosage form. After reaching room temperature, the solid lipid system solidified. Various release profiles were attained based on the lipid ratio applied in the production of solid lipid systems.[36] Solid Self Nano-Emulsifying Drug Delivery Systems were effectively fabricated into a tablet form. A semisolid paste was created using the fusion method, which included dapagliflozin, caproyl 90, poloxamer 188, PEG 6000 and 400, and Cremophor EL. The lipid system is comprised of a fluid phase housing oils and cosurfactants, alongside a solid phase consisting of a solid matrix integrated with a surfactant. Once all excipients and drugs had completely melted, they were moved to a PAM cartridge for the purpose of 3D printing. The immediate release profile of the 3D-printed tablet loaded with dapagliflozin in SNEDDS exhibited rapid dissolution, with more than 75% released within 20 minutes.[142] PAM employed a similar technique to create 3D-printed Lidocaine-loaded

SNEDDS suppositories for the treatment of haemorrhoids.

Future potential

1 surgical planning: Performing surgery on a complex congenital heart condition demands a surgeon with advanced skills and extensive experience, able to swiftly make critical decisions throughout the procedure[38] Rushing into decisions during surgery can result in extended operating durations, potentially affecting the outcome of the procedure negatively. Vodiskat and colleagues. A 3D printing model of the congenital heart defect was utilized for preoperative planning. Two distinct commercially available 3D printing technologies (Poly jet Object Eden 350, Maker Bot Replicator) were applied to reconstruct the congenital heart defect in three patients. They determined that with high-quality CT scan data at hand, a cost-efficient 3D printed model can be crafted for preoperative preparations. Repairing an old pelvis fracture poses a significant challenge due to its complexity. The intricate anatomy of the pelvis and the challenging access to operational sites primarily contribute to this. The study conducted by Wu and colleagues. They analysed the utilization of 3D printed pelvic models for preoperative planning.[39] Throughout a span of four years, they examined nine distinct clinical cases, assessing the effectiveness of their surgical reconstruction by relying on the 3D printed models of the fractured pelvises. They showed a strong correlation between the preoperative planning and the postoperative results obtained from X-ray evaluations in all instances. It was suggested that a larger sample size of patients is needed to thoroughly evaluate the potential benefits of utilizing 3D preoperative models for pelvic fracture surgeries. Truscott and colleagues. Three case studies were showcased, demonstrating how 3D printing models can aid surgeons in preoperative planning. They developed 3D models of the pelvis, femur, eye socket, and scapula based on the CT scan data.[41] Subsequently, they employed laser-sintering technology with 3D printing to craft an eye socket using Titanium material. They reached the conclusion that this technique reduces material wastage when compared to a CNC process.

2 prostheses: In a study conducted by Suaste-Gómez et al., an ear prosthesis was 3D printed using polyvinylidene fluoride (PVDF).[40] The prosthesis response to pressure and temperature was studied using an integrated astable multi-vibrator circuit. Their novel 3D-printed PVDF-made ear prosthesis showed high sensitivity to pressure changes. This is a promising result for extensions of this technique to other fields of biomedical engineering.

Commercial patient-specific cranioplasty prostheses are very expensive. Alternatively, acrylic bone cement is widely used in the field as a cost-efficient approach. However, the manual fabricating of the bone cement is cumbersome and may not lead to a satisfactory implant in many cases. Tan et al. created a 3D printed skull from high resolution CT scan data using FDM.[42] The Mould was used as a template to shape the acrylic implant. They showed that their approach to make patient-specific acrylic cranioplasty implants with a low-cost 3D printer is successful; however further studies are required to assess the application in the clinical setting. 3D printed skull and Mould (D,F) from high resolution CT scan data (C,E) using the fused deposition modelling method.[40] Ahlheim et al. combined the 3D printing lithography-based ceramic manufacturing technique with so-called freeze-foaming technique in order to achieve inherent open-porous-interconnected foam structures of the bone.[43] They demonstrated that these novel potential bone replacement structures might serve as possible next-generation material which can be used for personalized implantation. In a study conducted by Parthasarathy et al., a novel design approach for creating periodic cellular structures was proposed. The material was fabricated using a metal 3D printed technique. They concluded that 3D printed implants, made out of the proposed material, would fulfil the need for lighter implants and meet the esthetic and functional requirements for patients with skull defects.

3D printing techniques have been used recently to reproduce patient-specific tissue-mimicking materials. In a study by Wang et al., two types of dual-material 3D printed meta-materials were designed to replicate the properties of soft tissues.[44] They showed that the proposed 3D printed materials have great potential in fabricating patient-specific tissues. Advantages included accurate mechanical properties, which can vary depending on gender, age, ethnicity, and other physiological/pathological characteristics.

3. Medical education and training

Typically, 3D-printed models exhibit anatomical precision, contingent upon the availability of high-quality CT scan data. Nevertheless, in numerous instances, 3D-printed models are generally rigid, thereby posing challenges in their utilization for scenarios concerning delicate tissues like the brain. Ploch et al. A rapid and cost-effective method was suggested, incorporating 3D printing, moulding, and casting techniques to produce accurate and deformable models of human brains[45] A surrogate material akin to gelatin was employed due to its close resemblance to the mechanical properties of the human brain. It was concluded that the aforementioned methodology has the potential to be applied in the creation of individualized deformable brain models, serving purposes such as aiding in surgical preparation or facilitating medical education. Research conducted by McMenamin and colleagues. The study presented critical factors that have a direct or indirect impact on the precision of the 3D printed replicas of human anatomical objects intended for training purposes.[46] They deliberated on the necessary quality of image data, which has the potential to yield replicas of superior quality. They additionally provided a cost analysis of producing a 3D printed

replica when compared to different alternatives. It was concluded that 3D printing represents the swiftest and most cost-effective method for replicating human specimens intended for medical education purposes. It was demonstrated that a considerable number of scans are necessary to create authentic 3D printed replicas.

4. Organ printing: Cornell University researchers showcased the advanced technique of 3D bioprinting complete tri-leaflet heart valves by utilizing hydrogels as a supportive framework for the cells. They precisely printed two distinct cell types – aortic smooth muscle cells and aortic valve leaflet interstitial cells – onto the pre-made hydrogels. The sections infused with cells maintained their strength and remained viable for seven days when cultured. The printed cells exhibited excellent spreading, leading to a strong structure and retaining their phenotype effectively, revealing their intended functionality. They point out that the tensile strength of the prototypes produced was insufficient for optimal functioning as a heart valve and provided various suggestions for future improvements. These comprise incorporating microfluidics to enhance the resilience of cell proliferation. The process of bioprinting an aortic valve conduit. Printing a layer of SMC on a computer model, followed by printing a layer of VIC. Taking a fluorescent image of the first two layers results in the printed aortic valve conduit.[47] In Edinburgh, researchers have detailed the creation of operational "mini-livers" through the use of 3D printing. Their inventive approach involves printing delicate hips cells into a 3D alginate hydrogel matrix while preserving their viability and pluripotency. The cell structure remained viable for a period of 24 days following the printing process. Pluripotency was assessed through the secretion of albumin, reaching its highest level 21 days post-printing. The focus of the project is on conducting drug trials without animal testing and developing personalized medicine. The study demonstrates the potential of 3D printing technology, which involves using patient-specific cells to create 3D structures that remain functional as a real liver for weeks after being printed. Ultimately, the ability to develop organs that rival the intricacy of natural organs opens up the potential for enhancing these organs in the future or even crafting brand-new organs tailored for specific purposes.[48] A team of international researchers in evolutionary biology has gone beyond conventional methods to develop a 3D morpho-space.

This new tool enables them to characterize not only biological features in human organs but also cells and anatomical structures in animals, including invertebrates.[49] The design space encompasses three essential axes: cognitive complexity, solid/liquid, and developmental complexity. It has been observed that a significant portion of the design space remains uncharted, yet bioprinting methods provide a unique opportunity to delve into this unexplored territory, unveiling novel biological structures and delving into profound inquiries regarding evolution.

5. Drug delivery: At University College London, researchers have developed advanced topical drug delivery systems through the innovative technique of 3D bioprinting. They explored two cutting-edge methods, fused deposition modelling (FDM) and stereolithography (SLA), to create devices designed to be worn on the nose. These devices are engineered to deliver salicylic acid effectively for the treatment of acne. Salicylic acid is incorporated into commercial polymer filaments through the process of hot melt extrusion. 3D printing is ideal for this procedure, as it allows scanned images of the patient's anatomy to be utilized for producing custom devices that perfectly fit, ensuring optimal contact and uniform drug dosage delivery. It was discovered that although both methods yielded satisfactory results, the SLA method proved to be more convenient for the fabrication process. The dosage can be adjusted accordingly based on the preparation of the filaments used for printing. Khaled and colleagues showcased the ability of 3D printing to create high-quality drug tablets suitable for prescriptions. Researchers at the University of Nottingham tried to create Guaifenesin Bilayer tablets, also known as Mucinex, by utilizing a desktop 3D printer that cost less than $1,000..[50] The team evaluated the drug release patterns of their prototypes and identified one design that closely mirrored the release profile of the market product, with only a 10% deviation, throughout a 14-hour dosing period. They also assessed the tablets they manufactured for weight variation, hardness, thickness, and friability. With the newfound design flexibility that 3D printing offers in the pharmaceutical field, Goyanes and colleagues. They examined how various tablet shapes impacted the drug release patterns.[51] The shapes included torus, pyramid, cube, sphere, and cylinder, which were created using an FDM technique to produce paracetamol-filled PVA filaments. They initially showed that the drug's stability remained intact throughout the printing process. They proceeded to examine the drug release rate from each tablet, revealing a predictable correlation with the surface area to volume ratio. According to them, creating these intricate geometries using conventional powder compaction techniques would be unattainable, while also providing enhanced management of drug release patterns.

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