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Review Article

3D PRINTING IN THE PHARMACEUTICAL INDUSTRY: A SPECIAL CONSIDERATION ON MEDICAL DEVICE AND ITS APPLICATIONS.

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ABSTRACT

3 Dimensional (3D) printing has seemed to be the technology of radical development for the pharmaceutical industry, particularly in medical device manufacturing. The current review elaborates on the applications of 3D printing, challenges, and potentials in pharmaceutical medical devices. The technology allows for complicated personalized devices with accuracy and cost-effectiveness as never before, bringing in the key applications for this technology in the fields of prostheses, orthoses, surgical guides, audiology devices, and bioresorbable implants. It brings along customization, better pre-operative planning, and new drug delivery systems, but there are quality control and regulatory challenges to be faced: material selection, process validation, sterilization, and scalability. In view of this upcoming technology, the regulatory bodies are having to update their guidelines to ensure continued safety and efficacy. On the road ahead, with artificial intelligence, nanotechnology, and 4 Dimensional (4D) printing, future developments could make sophisticated medical equipment and change the management and outcome of diseases. While 3D printing opens up newer routes of innovation in the pharmaceutical industry, there are major concerns on issues of scalability and regulatory matters. This technology will thus make a significant impact on healthcare delivery through these coming decades, with changes in the global research and regulatory landscapes.

Keywords: 3D printing, Medical devices, Pharmaceutical industry, Regulatory compliance, Personalized medicine, Additive manufacturing

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INTRODUCTION

The technology of 3 Dimensional (3D) printing has been embraced by pharmaceuticals, and it is being used in the manufacture of medical devices. This new manufacturing technique has taken the market by storm since now complex, very delicate, or highly specialized medical equipment can be created at the highest possible level of precision and cost-effectiveness [1].

Additive manufacturing or 3D printing is an innovative way of building up a device in small increments from digital blueprints. When compared to traditional methods of manufacturing, this approach provides many advantages. It makes it possible to develop intricate geometries, allows customization for individual patients, and speeds up trial production, thus shortening lead time for product development cycles [2].

Since there are no rules on how 3D printers should be used in medicine, they have been employed across different categories of medical devices as well. They can make artificial limbs, personalized implants, peculiar surgical equipment, and printed organs, which surgeons use for rehearsal before operations among other uses. This can optimize inventory control while improving supply chain dynamics in the sector through the ability of the technique to produce goods as required [3].

It is opening up new avenues of innovation in drug delivery systems within the pharmaceutical field since 3D printing allows the construction of devices with precision dose control and modified release profiles. It may finally lead to individually composed medications for the patient, which perhaps may improve treatment outcomes and compliance [4].

In a few years, when the technology further improves, 3D printing will change medical equipment design, development, and uses. The change is about ushering in an age of personalized healthcare solutions to improve results overall for patients [5]. The continuing development of 3D printing within both the pharma and medical device industries at large stands as evidence of its high potential to totally revolutionize health care into efficient, personalized care options for patients worldwide [6].

Search criteria

The selections of articles for the present review were searched from specialized databases (Range of years: 2000-2024), which includes Elsevier, PubMed, and Cambridge, using the keywords 3D printing, medical devices, additive manufacturing, and Regulatory consideration. Other selections include articles from Springer, and Wiley, information from Internet sources, and online published articles from the Food and Drug Administration (FDA).

Basics of 3D printing

Additive manufacturing or 3D printing is an innovative way to create 3D objects. From a digital model, it creates 3D objects, depositing layer by layer bit by bit. It will start off reading a computer-aided design (CAD) file sliced into very thin cross-sections to let it build an object from bottom to top with the help of materials which may range from plastics and metals to ceramics, and also some biological materials. Such technology provides the ability to create intricate, customized designs with a low volume of waste and multiples the benefits that cut across all the industrial fields, including medicine, aerospace, and consumer goods. It has attracted attention because of the possibility it presents to consumers, especially because of its capability to enable rapid prototyping, on-demand production, and the creation of shapes that are inaccessible or hard to produce [7].

The whole process often involves typically three main steps as given below.

Design

The digital 3D model of medical devices starts with selecting proper CAD software, for example, SolidWorks or Autodesk Fusion 360. The first step is the creation of 2 dimensional (2D) sketches to the needs of medicine, subsequently converted into 3D geometries with a set of CAD instruments. Parametric modeling can be easily modified, while assembly modeling is intended for complex devices. Surface modeling techniques are utilized in producing organic shapes. Material properties are defined to facilitate correct simulation. The design is subjected to finite element analysis, where it has to pass structural tests and other criteria of the design. The simulation result, combined with medical

feedback will allow iteration for optimizing the design. At the last stage, the CAD model is converted into a 3D-printable file and becomes ready for production. Throughout the process, documentation has been elaborated, and often, cloud-based platforms are utilized in cooperation between engineers and medical professionals.

Printing

The most basic steps of the process to bring a digital model to an actual, 3D-printed medical device include converting a CAD model into a Stereo lithographical (slt.) file. This involved projecting the surfaces of a model into triangles by approximating the model. Then, slicing software processes that file, which splits up the entire 3D model into layers at defined, thin horizontal sections and generates machine instructions for the 3D printer in geometry code. As the designs are fed into the device, layers on top of layers of the product are created during printing. Among the most common 3D printing technologies include fused deposition modeling (FDM), where molten thermoplastics extrude the product, Stereo lithography (SLA), which makes use of Ultraviolet (UV) light to cure the liquid resin, and Selective laser sintering (SLS) which utilizes a laser in fusing the powder material. Depending on the properties of the material required, resolutions, and the final application of the product for health care, then that will be the technology to apply. Most print devices require further post-processing steps, including cleaning of the supports off the material, finishing of the surfaces, and sterilization, for them to be used medicinally.

Post-processing

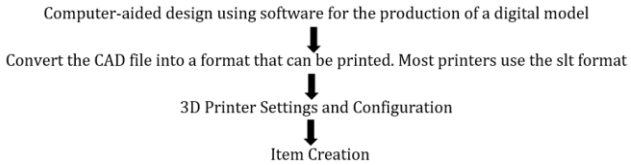
Post-processing is an important step in 3D printing medical products to ensure that the final product reaches stringent quality and safety requirements. First, support structures need to be removed. They are either manually removed or chemically dissolved based on the printing process. SLA/Digital Light Processing (DLP) resin-based prints undergo a thorough cleaning with isopropyl alcohol to remove uncured resin, followed by exposure to UV curing to attain full material strength. FDM prints can be surface finish enhanced with methods such as sanding or acetone vapor treatment. The metal prints are often heat-treated to relieve the internal stresses. All medical devices have precise dimensional checks and must undergo additional machining for critical features. Surface treatments with polishing or coating enhance both biocompatibility and functionality. Finally, the product is sterilized by a process such as ethylene oxide, gamma radiation, or autoclaving to ensure that the device is safe for medical application. All of these steps are documented for compliance with all demands of the regulatory body and for ensuring quality [2].

Need for 3D printing in the pharmaceutical industry

There are many benefits of 3D printing over traditional manufacturing methods, including a decrease in production and logistic expenses, easy production of complex and customized products, and more efficiency due to a reduction in material and energy usage [8]. 3D printing in medicine allows for faster and more affordable production of items compared to other means, such as machining. This is particularly valuable in product development, given that designs can be turned around quickly, products are easily customized, and small quantities can be produced affordably. In fact, this technology can really help slash the time taken to introduce new items into the market [9]. Compact and biocompatible electronic platforms are much needed for wearable devices and specific implants that will conduct real-time monitoring of chronic health conditions. The exploitation of 3D printing in medical devices is foreseen to go beyond anatomical models and prosthetics when electronic materials and additive manufacturing technologies with enhanced properties become available [10]. Such technology will aid in the creation of individualized or personalized electronic implants and other devices from a great variety of biocompatible materials. Success depends on getting enough feedback from health professionals and patients, but also on the opportunity to implement design improvements really fast. Fast feedback created by 3D printing accelerates the design refinement cycle [11, 12].

3D printing software

Technology for medical rapid prototyping has advanced significantly. The advancements in reconstruction techniques, image processing, and medical imaging techniques made them easier. Despite the diversity of technologies, the 3D printing process typically involves the majority of the following procedures:



Because this is a completely computer-driven process, it removes intermediary phases, hence requiring less manual labor. This technique comes with several advantages: cost savings, shortened production times, and development with any modifications if required [13].

3D printing materials and used in pharmacy

The selection of appropriate materials is crucial for the successful implementation of 3D printing in pharmacy, as these materials directly impact such as biocompatibility, mechanical properties, and degradation kinetics.

Biocompatibility

Biocompatibility is an important aspect of 3D-printed medical devices, particularly because the devices have direct contact with biological systems. The biocompatibility for a 3Dprinted medical device is therefore very necessary. For a safe and effective medical device in patients, restrictive testing is thus required by adherence to regulatory standards and continuous improvements in the field of materials and manufacturing processes [14].

Material selection

The biocompatibility of 3D-printed medical devices is very sensitive to material choice. The materials should not provoke any adverse biological responses. On the other hand, they should support tissue integration. For example, some polymers, metals, and ceramics are biocompatible [15].

Regulatory standards

In response, a few rigid standards have been set up by regulatory bodies for biocompatibility testing; this includes cytotoxicity, sensitization, irritation, and systemic toxicity studies [16].

Printing process implications

The 3D printing process itself can also affect biocompatibility due to variables such as printing resolution, layer adhesion, and other post-processing treatments associated with how materials will bind with biological systems [17].

Long-term stability

Another important factor is the biocompatibility for long periods. Materials shall not chemically degrade such that they cause harm to the patient or dysfunction of the device [18].

Customization and patient-specific devices

Although 3D printing allows customization to patient anatomy in the field of medical devices, this should not take away from considerations about biocompatibility. Materials and processes should be carefully matched both for safety and efficacy [19].

Mechanical properties

The mechanical performance of a 3Dprinted implant is expected to vary with the application involved, whether these are load-carrying implants or flexible systems, as in drug delivery. Required properties are appropriate: Strength and stiffness, Fatigue resistance, Wear resistance, and Elastic behaviour (for specific applications) [20].

Degradation kinetics

Material degradation

Depending on the nature of the application, the 3D-printed medical devices will have to bear degradation in biological environments.

Biodegradable polymers, for example, break down with time upon being resorbed or metabolized by the body. The kinetics of degradation for these materials provide the knowledge needed for the development of a device with the right lifetime [21].

Environmental factors

Many environmental parameters may be involved in degradation kinetics, such as temperature, pH, humidity, or even the presence of some enzymes or body fluids. Control and prediction of these parameters become, therefore, basic parameters for reliability and safety related to a 3D-printed medical device [22].

Long-term stability

In permanent implants, for example, orthopedic implants or dental prostheses, long-term stability and degradation resistance are very important. This means it should maintain its mechanical integrity along with biocompatibility as long as the device is intended to last [23].

Testing and validation

Run accelerated aging studies and *in vitro*/*in vivo* degradation studies to understand the degradation kinetics of a 3D-printed medical device. The results of such studies are highly valued while gaining regulatory approval and acceptance at the clinical level [24].

Table 1: Common polymers used in 3D printing

Name	Melting point	Advantages	Limitations
Acrylonitrile butadiene styrene (ABS)	105 °C	Good strength and flexibility	They are non-biodegradable and reduce in size when in contact with air.
Polylactic acid (PLA)	175 °C	Good mechanical properties; Low cost.	Long-term biocompatibility [25]
Polycaprolactone (PCL)	60 °C	Good rheological and Excellent viscoelastic properties upon heating and are minimal cost.	Long degradation time (3 y) [26]
Polycarbonate (PC)	110 °C	Tuneable mechanics and porosity.	They intake moisture from the air which can affect the performance and printing resistance [27]
High-performance polymers-PEEK (polyetheretherketone), PEKK (Polyetherketoneketone), ULTEM (polyetherimide)	350 °C	The material is highly resistant to mechanical and thermal stresses. Besides, it is an extremely strong and at the same time much lighter material than some metals.	High melting point [28]

Types of 3D printing technologies applicable in pharmacy

Stereolithography (SLA) technology

3D printing in pharmacy involves several different technologies, such as stereolithography. SLA is an additive manufacturing technique whereby a UV laser or projector hardens liquid resin into plastic. The main parts composing an SLA printer are the light, build platform and resin tank. This is a fast-prototyping method that generates fine details using an ultraviolet laser and requires only a few hours to print an object. Digital Light Processing is an older technology in 3D printing that uses lamps, increasing the printing speed by drying layers in seconds [29, 72].

Digital light processing (DLP)

DLP belongs to the additive process for producing medical devices whereby a digital projector is used to cure photopolymer resin layer by layer. It projects a 2D image onto the resin, thereby solidifying an entire layer at once. This has high precision, smooth surface finish, and faster printing speeds compared to other technologies. DLP finds a lot of applications in creating complex medical devices, like dental implants, hearing aids, and surgical guides. This is where the manufacturing of customized devices with complex geometries and fine details for the patient can be done. The ability to use biocompatible resins opens a plethora of possibilities for this technology in many medical applications, which will enhance personalization and potentially improve the quality of care delivered [72].

Continuous liquid interface production (CLIP)

The CLIP process is a fast VAT photopolymerization method that makes use of Digital Light Synthesis technology to shine a series of UV images onto a 3D printed part's cross-section, which aids in controlling the curing process with very fine resolution. The whole part is then subjected to a thermal bath or oven, raising a diversity of chemical reactions that eventually harden the part.

Material jetting

Material jetting technologies represent the newest developments in the field of 3D printing and are increasingly being explored for pharmaceutical applications. Liquid materials photopolymers are deposited as small droplets in a layer-by-layer process and subsequently cured by UV light. It presents great promise for personal medicine: from tailored dosage formats and complex geometries in controlled release to multi-drug combination products. In this respect, material jetting may be considered an attractive technique in drug delivery because of its high precision and possibilities for the elaboration of structures. The range of suitable materials is highly limited, and there are regulatory hurdles and scaling up for mass production in the way of this industry. This technology may yet hold some revolutionary techniques for the drug-manufacturing industry, such as rapid prototyping or on-demand production of tailored pharmaceutical products.

Binder jetting

Binder jetting is an additive manufacturing process wherein liquid binding agents are applied selectively to hold the layers of powdered material together. Droplets of binder come out of a print head and are dispensed onto thin layers of powder. The powder has been spread across a build platform, and then the same process occurs for each layer until a 3D object is created. Binder jetting is compatible with different materials, such as metals, ceramics, and polymers. It is particularly useful for the production of complex geometries and large parts. In medical applications, it allows for the manufacture of custom implants, surgical models, and drug-delivery devices. This technology is suitable for both prototyping and production-scale manufacturing of medical devices, with relatively fast build speeds and the ability to print multiple parts at one time [72].

Fused deposition modeling (FDM)

Fused deposition modeling works through an extrusion-based technique whereby thermoplastic filament is heated and deposited on a substrate by layer to create a 3D object. The same involves the extrusion of molten plastic via a moveable nozzle onto a build platform in a specified path. As each layer cools and solidifies, it can bond with the previous layer. It finds broad application in medical device prototyping and production due to the flexibility, cost-effectiveness, and biocompatible raw materials the technology offers. These include applications for orthotics and prosthetics, models of anatomy, and surgical guides. Although FDM may offer lower resolution compared with some other 3D printing methods, it generally displays good mechanical properties and allows the fabrication of parts that have functionality within them to be rapidly created.

Selective laser sintering (SLS)

SLS is a form of Powder Bed Fusion that produces 3D objects by the fusion of small particles of powder by the use of a high-power laser.

A high-powered laser scans each layer of the powder bed and selectively fuses the particles, and then the process is repeated as the bed is lowered.

Multi-jet fusion (MJF)

In multi-jet Fusion, the powder is laid down by a sweeping arm; binder is applied selectively on top with an inkjet-equipped arm. Precision comes from the application of a detailing agent around said area. The application of thermal energy then initiates a chemical reaction. Direct Metal Laser Sintering, on the other hand, is similar but it uses metal powder.

Directed energy deposition (DED)

Directed Energy Deposition is one of the methods mainly used in the metal industry. A 3D printing device is attached to a multi-axis robotic arm with a nozzle that applies the metal powder. It works by melting the material, applied as a powder to a surface, by use of some energy source, and immediately creating solid objects [30, 31].

What are medical device and implants?

Medical devices and implants can be summed up as those products of the pharmaceutical industry used in healthcare that are not drugs themselves, yet in most cases, help pharmaceuticals achieve the diagnosis, prevention, or cure of an ailment. These may include simple devices and tools at one end to highly complicated implants at the other. They also intersect with drug development, delivery, and administration within the context of the pharmaceutical industry.

The major points for consideration about medical devices and implants in the pharmaceutical industry include:

Drug-device combination products

3Dprinted drug-device combination products inlay pharmaceutical components into the medical device itself to improve therapeutic outcomes from that single entity. Customized, patient-need-based, and localized drug delivery systems can be designed through such a process. By 3D printing, complex geometries can be produced with precise drug incorporation to achieve increased efficacy and reduced side effects. Applications are currently being made in drug-eluting stents, antibiotic-infused implants, and targeted cancer treatment devices, providing innovative solutions in personalized medicine and improved care for patients [32].

Drug delivery systems

These 3D-printed medical devices allow for the controlled, accurate release of drugs through their delivery systems. Such structures can be tailored for targeted delivery, optimized release kinetics, and patient-dependent needs. 3D printing enables both complex geometries and multi-drug configurations; therefore, it increases therapeutic efficacy while decreasing side effects. Applications range from implantable devices to transdermal patches that can revolutionize personalized medicine and treatment strategies across a broad swath of medical fields [33].

Diagnostic devices

Medical instruments are employed to recognize illnesses or follow conditions that can impact medicines administered by the drugs. It offers customized, rapid, and cost-effective solutions for the diagnosis and monitoring of diseases through 3D-printed diagnostic devices in medical technology. These diagnostic devices can be tailored to patients' requirements or any testing needs, hence fulfilling the concept of point-of-care diagnostics. 3D printing enables the realization of complex microfluidic structures, biosensors, and lab-on-a-chip devices that increase sensitivity and accuracy in diagnostics. Their applications include portable testing kits, wearable health monitors, and individual biomarker detection systems that further precision medicine and the identification of diseases at an incipient stage [34].

Implantable drug reservoirs

3D-printed implantable drug reservoirs offer an avenue for medical devices capable of targeting sites with controlled medication delivery. Complex geometries, part of integrated structures that optimize the release kinetics, can maintain at specific sites the release of a drug. Such devices offer features that support patient-specific design, multiple compartments for different drugs, and stimuli-responsive functionalities, which possibly will help to enhance treatment efficiency while reducing systemic side effects for a range of medical applications [35].

Smart devices

These electronic gadgets can take care of a patient's health status and adjust dosages of drugs as far as possible where necessary [36].

Table 2: Comparison of traditional and 3D-printed medical device

Category	Traditional medical devices	3D-printed medical devices
Manufacturing Process	Normally mass-produced through conventional techniques such as injection molding and machining.	It is fabricated using additive manufacturing techniques wherein an object is created layer by layer [37]
Customization	Normally limited to usual sizes or configurations.	Normally limited to usual sizes or configurations [7]
Design Complexity	It is constrained by manufacturing processes' limitations.	Enables complex geometries and internal structures [3]
Materials	It is restricted to only material types that can be conventionally manufactured.	Expanding spectrum of biocompatible materials, including some that have the potential to exhibit properties, such as that of tissues [38]
Applications in Drug Delivery	It is influenced to a great extent by a lot of manufacturing-related defects.	It allows for Multiple complicating drug release profiles under one dosage form with tailored [39]

Applications of 3D printed medical devices

Prosthesis

An artificial limb, simply put, is known as a prosthesis an artificial device designed to replace the missing body part, be it in the form of a hand or a foot, or in any other shape less natural, designed to allow amputees to perform any day-to-day activity with ease.

Prosthetics can be fabricated from many materials, of which plastics like polypropylene and polyethylene constitute prosthetics and polypropylene and polyethylene are in larger use. It has been a major and primary element in the rehabilitation of amputees and has been able to function for many years of their lives. Unlike conventional prostheses in which the materials are 'molded and cast', 3D printed models are tuneable around your unique anatomy. This can result in a much softer and more aesthetically pleasing product with much less challenge in responding to their lifestyle. During the design, the orthopedic surgeon, together with the designer, employs a blend of clinical data, CAD, and software tools in making the final product. It allows for a more personal and efficient product because it can be manufactured more easily at a lower cost and is durable [41].

Orthotics

An orthoses is a device used to assist the body in performing its functions. Generally, orthoses protect the body, limit movement, support body weight, provide movement, and prevent/correct deformities. They have been used on an extensive basis in helping patients with physical dysfunction and disability due to muscular problems like fractures, sprains, arthropathy, tendinopathy, or even

neurological disorders in the brain, spinal cord, and peripheral nerves.

The conventional technique of orthoses production is rather time-consuming. Again, the shape and dimensions of the orthoses have to be pre-adjusted on a patient's body manually. Further, creating several customized, high-quality orthoses is difficult, and sometimes realization of the complex designs is also hard.

Through 3D printing, the technology becomes dimensionally accurate for orthoses by computer graphic software. This offsets the limitation of the traditional method due to the high precision of a 3D printer.

Using 3D printing, design software enables the production of orthoses with correct dimensional values and complex structures that, otherwise produced manually, would be impossible.

Unlike custom-made orthoses, which take approximately a week, a 3D printer can make an orthoses within one day, hence provoking great interest in orthoses created using 3D printing technology [42].

3D-printed surgical guides

Additive manufactured surgical guides have been at the forefront of changing the face of personalized medicine. Patient-specific tools created from advanced modalities of imaging computed tomography or magnetic resonance image allowing for accurate preoperative planning and intraoperative guidance. One of the main advantages associated with 3D-printed surgical guides is that they enhance surgical accuracy.

For instance, a study conducted by the researchers concluded that in spinal surgery, 3D-printed surgical guides can increase the accuracy of pedicle screw placement, thereby reducing the risk of neurological complications. The accuracy rate reported for 3D printed guide-assisted screw placement was 92.8%, compared to 86.6% using the freehand technique [43].

Their working applications throughout a wide surgical spectrum in orthopedic surgery, 3D printed guides have changed the landscape for total knee arthroplasty by demonstrating that the patient-specific instrumentation-including 3D printed guides-improved overall prosthetic component alignment, which likely improves the long-term results in patients [44].

3D-printed hearing aids

This additive technology enables devices with a high level of customization, improving comfort and acoustics in comparison with devices that have been conventionally manufactured. The process mostly incorporates digital scanning of the patient's ear canal, followed by making a personalized shell design and creating the same through 3D printing.

Integrating the 3D printing procedure in the manufacturing process of the hearing aid device gave several benefits. Those are:

Improved comfort and fit

Commit accurate customization provides an excellent fitting, reducing feedback and other problems to provide more comfortable wear.

Ready in no time

The manufacturing time for custom hearing aids has come down drastically with 3D printing.

Consistency

Because it is a digital process, repeatability is assured at a high level of quality control.

The 3D printing in the hearing aid industry was simply overwhelming. The custom in-the-ear hearing aids fabricated using 3D printing have moved not only the quality of products to another level but also eased manufacturing with reduced workers, time, waste of materials, and energy [45].

Bioresorbable implant

Bioresorbable implants and tissue scaffolds have taken a new dimension of advancement in the area of 3D printing of pharmaceutical and medical devices. These structures support tissue regeneration and degrade within the body; thus, no removal surgery will be required, which minimizes long-term complications that come due to permanent implants.

3D-printed bioresorbable implants are under study for many medical applications, in particular, in orthopedics and craniofacial surgery. Such devices render temporary support, undergoing degradation in some time and allowing natural body healing processes.

3D-printed polycaprolactone and hydroxyapatite composite scaffolds were frontline for bone regeneration. These scaffolds showed good biocompatibility and sufficient mechanical strength compared to natural bone [19].

Tissue scaffolds

3D printed tissue engineering scaffolds are, therefore, essential in regenerative medicine, providing structures that will very finely duplicate the extracellular matrix to support the growth of cells and the formation of tissues.

3D bioprinting techniques for tissue engineering applications: In 3D printing, there is the potential ability to control scaffold architecture, porosity, and mechanical properties so that they are conducive to cell adhesion, proliferation, and differentiation [46].

Tailored dosage forms

Tailored dosage forms have revolutionized the production in the pharmaceutical industry brought about by the emergent technology of 3D printing. This innovation gives the opportunity for making personalized medicines with corresponding exact dosing, shape, and size for the needs of individual patients. Using 3D printing, the pharmacist and healthcare provider may use a patient's age, weight, metabolism, and even genetic makeup in tailoring their medication decisions. This kind of individualized therapeutic regimens would have more pronounced therapeutic outcomes by ensuring optimal drug absorption and efficacy. Complex geometries may be prepared for modulating the rates of release of drugs, such that multi-layered tablets combine several drugs with different release profiles in one dose. This type of strategy increases patient compliance while minimizing the side effects, which are generally associated with conventional, one-size-fits-all drugs.

Controlled release mechanisms

3D printing allows for the creation of highly complex controlled-release mechanisms for drug release. Such systems could be designed to give the necessary rate of medication delivery over much more extended periods, maximizing efficacy in therapy while offering easier management for patients. However, by manipulation of the internal architecture and composition of 3D printed devices, the researchers may be able to create matrices that can uniformly and precisely control drug diffusion or erosion. As such, it allows for complex release profiles; indeed, pulsatile or chronotherapeutic delivery systems comparable to, yet respectful of, the circadian rhythm of the body can be designed. 3Dprinted implants and inserts can also be designed for the sustained release of drugs over several weeks or months, which might modify the treatment strategies of chronic diseases and the number of drug administration's [71].

Advanced inhalation devices

3D printing paved new ways in advanced inhalation device design and manufacturing for respiratory drug delivery. Devices may be designed tailored to the patient's lung volume and breathing pattern and his or her particular therapeutic need. By 3D printing on inhalers, complex internal geometries that optimize the size distribution of particles and the dynamics of flows can be achieved. The technology can also lead to multi-dose inhalers having in-built dose counting with smart features to enhance tracking for better adherence. It also supports fast prototyping and iteration of inhaler designs, accelerating the product development process and can save costs in the long term.

Transdermal and microneedle systems

The transdermal and microneedle systems are an excellent advancement in non-invasive drug delivery. 3D printing allows the

creation of specific dimensions shapes and density arrays for maximum skin penetration and drug release with 3D-printed microneedles. These systems can deliver a wide range of therapeutics, from small molecules to large proteins and vaccines, with improved bioavailability compared to traditional transdermal patches. The ability to customize microneedle geometry allows for tailoring the depth of penetration and the rate of drug release to suit different skin types and therapeutic needs. Besides, the capability to combine multiple drugs into a single microneedle patch by 3D printing can present the potential for combination therapies or staged drug delivery. The same technology may be used in order to advance the development of dissolvable microneedles that do not leave sharps waste; thus providing safety and convenience in self-administration scenarios [73].

Regulatory authorities

Regulator bodies

The Food and Drug Administration (FDA) oversees three primary categories of products: 1) drugs overseen by the Centre for Drug Evaluation and Research, 2) device-related products overseen by the FDA's Centre for Devices and Radiological Health, and 3) Blood vaccines overseen by the FDA's Centre for Biologics Evaluation and Research. Regarding medical device regulation, firms that manufacture devices distributed in the United States have several basic regulatory responsibilities. It covers registration of facilities (21Code of Federal Regulations (CFR) Part 807), listing of devices for medical application (21 CFR Part 807), premarket application notification 510 (k) (21 CFR Part 807 Subpart E), premarket approval (21 CFR Part 814), exemption for clinical investigation of a device for investigational use (21 CFR Part 812), quality system regulation (21 CFR Part 820), regulation for labeling requirements (21 CFR Part 801), and Medical Device Reporting (MDR)(21 CFR Part 803) [48].

Medical devices are ensured through the monitoring by the United States Food and Drug Administration's Centre for Devices and Radiological Health that companies manufacturing, repackaging, relabelling, or importing medical equipment for sale in the US market adhere to the medical device regulations. In terms of setting up a regulatory framework for 3D printed medical devices, this would mean that the former would be treated as any other traditional medical device regarding manufacturing processes and control requirements.

Medical devices are classified into three classes according to the FDA: Class I, Class II, and Class III, depending on the given level of device risk, with the greater class number signifying increased controls. These classes determine the controls that would be implemented for each device type. Devices under class I are mainly low-risk and normally would not require 510(k) clearance. Those under class II are generally considered of moderate risk and require a Premarket Notification, 510(k). Generally, device types that have been classified as high-risk or novel (Class III) must support a Premarket Approval (PMA) [49].

Inspection at the site of device manufacturing of higher-risk devices in Class C or D of some classification systems within 60 days of receipt of the marketing application for compliance with the requirements of quality management. The team prepares a comprehensive inspection report at the end.

Upon getting this report, the regulating agency has 45 days in which it may reach a decision. It may license the medical device for production and distribution or reject the application upon its findings [50].

Medical devices classification as per United States Food and Drug Administration (USFDA)

Medical devices are thus categorized into three classes by the USFDA regulations based upon the associated level of risk and also the regulatory measures required to ensure that they are safe and effective. What follows is a brief description of how they are classified:

Table 3: Medical device classification as per USFDA

Class I devices	Class II devices	Class III devices
The risk associated with these devices is minimal.	The devices are considered a medium-level risk-associated	These devices belong to the highest-risk device category.
These are controlled only by general controls.	These devices are, therefore, subject to both general controls and special controls.	They are associated with clinical data under the general controls and premarket approval categories for supporting claims of safety and effectiveness.
Most of the devices are exempt from the requirement for 510(k) premarket notification.	Most of these require the 510 premarket notifications.	
Examples include elastic bandages, examination gloves, and hand-held surgical instruments.	Examples include powered wheelchairs, infusion pumps, and surgical needles.	Examples include pacemakers and deep-brain stimulators.

The class of the device is determined by the FDA based on:

Intended use of the device, how it is to be used, and any potential risk to patients and users.

Devices are liable to be reclassified upon reception of new information with respect to the safety or effectiveness of a device [51].

The FDA has laid down various routes through which medical device manufacturers can get their products into the marketplace or be approved for use. All of these routes ensure that medical devices manufactured with 3D printing technology, amongst others, are safe and effective. Details for each type of submission include:

The 510(k) Premarket notification provides the common pathway to market for many medical devices, including several 3D printed ones. This, therefore means manufacturers have to bear the burden of proving that a device is essentially equivalent to another lawfully marketed predicate device. This route is commonly quicker and less burdensome than applying for Premarket Approval [52].

Probably, the most rigorous process for marketing medical devices is premarket approval (PMA). The PMA process itself has been developed to be applied for those medical devices that are associated with high risk and for which no substantially equivalent predicate device is available. This may include, concerning 3D printed devices, implantable devices, or other products for which safety and effectiveness have to be established by a large amount of data on their clinical and non-clinical performance [53].

Humanitarian device exemption, this pathway is for Devices indicated for a condition or disease that annually affects under 8,000 Americans are eligible for a humanitarian device exemption. Unlike PMA devices, although it is assumed that they will be less effective in general for all cases a built-in incentive for rare disorders is the rule [54].

De Novo classification, A new device can be placed in a low-to-moderate risk classification pathway where the FDA has the discretion to have a device that has not been previously approved and is not substantially equivalent to any other device [55].

The Investigational device exemption (IDE) process provides the opportunity for limited exemption of certain portions of the Act, allowing for an investigational device to be used in a clinical trial to gather safety and effectiveness data. This occurs before PMAs or 510(k) applications are submitted, and it involves cases where new

3D-printed devices require clinical data to back up a marketing application [56].

The type of submission required for 3D printed devices will depend on many factors, including the risk class of the device, the intended use, whether the design or material is novel, and whether suitable predicate devices are available. This regulatory pathway is influenced by several unique aspects of the 3D printing technology, including the ability to make patient-specific devices with complex internal structures.

Challenges and limitations

The challenges of 3D printing technology in the field of pharmaceutical medical devices are:

Selection and validation of raw material

Firstly, stringent selection and validation of the raw material must be ensured in the quest for quality control. It would include the active pharmaceutical ingredients and different polymers along with additives used in printing. Manufacturers are working on evolved testing protocols for proving the purity, stability, and compatibility of raw materials with the technology of 3D printing and the intended medical application [1, 71].

Material and manufacturing constraints

The futuristic domain of 3D printing in medical devices encounters significant challenges in material science and manufacturing processes. Additive manufacturing promises unparalleled geometric freedom, but it also struggles with a very limited bio-compatible palette that can withstand the rigorous demands of medical applications. Layer-by-layer deposition inherently forces the creation of anisotropic mechanical properties, which can be deleterious to the structural integrity of the final product; yet, these state-of-the-art 3D printing technologies are still challenged by multi-material integration-the crux in mimicking the complexity of biological systems' heterogeneous structures. These limitations not only limit what can be produced but also impact long-term lifetime and functionality in vivo [1, 71].

Process validation and monitoring

Another critical pillar in the area of quality maintenance is process validation. This will involve the establishment and tracking of key process parameters such as temperature, speed, and resolution at which printing is carried out. The aim of the process will be to have lot-to-lot reproducibility and to ensure that the final product possesses the desired physical and chemical characteristics. Toward this goal, the pharmaceutical industry is currently investigating state-of-the-art process analytical technologies that support in-process monitoring and adjustments in real-time [5].

Characterization and testing of products

Characterization of the finished 3D printed devices is very necessary to assure quality. Characterization typically includes a suite of analytical techniques, many of which involve spectroscopic and imaging techniques to confirm the uniformity of the drug content, structural integrity, and surface characteristics, among others. For the devices releasing medication, special attention is paid to dissolution testing and drug release profiling to prove that the medication will be released as intended [2].

Sterilization and control of contamination

Unique in nature, 3D-printed medical devices have particular challenges regarding sterilization and contamination control. Traditional methods of sterilization may not be appropriate for 3D-printed devices; therefore, innovative ways have been explored. The need to maintain a sterile printing environment and to use proper post-production sterilization techniques has grown to become paramount in the manufacturing process [57].

Regulatory compliance and adaptation

The regulatory setting for 3D-printed medical devices in pharmaceuticals will be complex. Indeed, such products often occupy the space where device and drug regulations blur. Time is of the essence as companies rush to tailor existing Good Manufacturing Practices (GMP) and set new standards unique to 3D printing technologies while staying compliant with the changing regulatory frameworks [3, 71].

Standardization efforts

The standardization efforts that would be put in will ensure that common practices for the design, manufacture, and testing of such novel devices are streamlined. It calls for the development of standard file formats for 3D designs, calibration procedures for printing equipment, and unified test methods for the finished products [58].

Personal medicine considerations

The field, moving into personalized medicine, shall also need to consider strategies for quality control with the possible customization of devices for individual patients. This brings a unique challenge in balancing consistency and safety against the flexibility that makes 3D printing so attractive for personal healthcare solutions [59].

Post-market surveillance and traceability

Post-market surveillance and traceability of 3D printed medical devices assume new significance. Tracking products effectively through an established system for the collection of real-world data on product performance for continued quality assurance and improvement of innovative products is key to quality [60].

Scalability and economic viability

3D printing indeed does well in producing customized, low-volume medical devices. However, there is a big limitation to 3D printing regarding the scaling-up requirements of mass production. From this aspect, 3D printing is economical in terms of building time and material cost, which is a condition for large-scale standardized manufacturing. Another factor is that the 3Dprinted medical devices have post-processing requirements, including removal of supports, surface finishing, and sterilization. The majority of the processes are labor-intensive and, therefore, affect scalability. A high entry threshold at the outset with great capital investment for the production of industrial-grade biomedical 3D printers presents a huge entry barrier to smaller medical device firms. These economic factors are compounded by the current limitations of technology, which severely limit applications of 3D printing to high-value, customized medical devices, which constitute a tiny fraction of the total market for medical devices [60].

Future of 3D printing in medical devices

Personalized drug delivery systems of the future

Advanced sensor technologies and responsive materials may be incorporated into next-generation, 3D-printed drug delivery systems. Such systems could have the capability of monitoring parameters of the physiological state in real-time and tailoring drug release. For example, an implant printed by 3D printing for the treatment of chronic pain could monitor inflammation markers, modulating in turn the delivery of analgesics and, therefore, optimize the relief of pain with minimal side effects. Such systems would represent a phenomenal improvement in the personalization of medicine and might offer improved treatment efficacy and quality of life [61, 71].

Bio-printed organs: simple to complex

While completely functional 3Dprinted organs are currently hoped for the future, researchers are making huge inroads in the bioprinting of less complex tissues and organ parts. Clinical use of bio-printed skin grafts for burn victims or 3Dprinted blood vessels for cardiovascular treatments may not be far off. This could be the first step that eventually leads to more biosynthetic organs, allowing us to extinguish the organ shortage and reduce rejection rates for transplants [62].

On-demand pharmaceutical manufacturing

Future pharmacies could use advanced 3D printing technologies to manufacture the drugs in stores in doses tailored to the patient's

requirements. This would be a breakthrough in the formulation of drugs that would allow more precise dosages and tailored release profiles, maybe even several drugs combined in one easy-to-swallow form. This would be especially important in regions relatively inaccessible or at times of health catastrophe due to the fast local production of critical drugs [61].

Advanced methods

Artificial intelligence (AI) aided development in 3D printed medical devices

It is very much possible that AI, integrated with 3D printing, will revolutionize the creation and production of personalized medical devices. Algorithms in artificial intelligence open up great opportunities for analyzing complex data on patients, which includes anatomical scans and measurements, for the development of exactly tailored medical devices. For instance, AI could predict gait changes for a patient's prognosis over time—then, theoretically, a change in the prosthetic fit, if applied, might result in initially poor comfort and function but better long-term comfort and function with less frequent adjustments or replacement [63].

Moreover, machine learning models applied in AI technology can detect and correct anomalies during printing in real-time, thereby improving the 3D printing process. Increased reliability and consistency of 3D-printed medical devices boost their adoption and regulatory approval for use in the future. For instance, AI-driven platforms developed by 3D Systems and Enhanced automate design and delivery for patient-specific medical devices, making them streamlined to cover growing demands for healthcare solutions personalized to a particular patient [64].

Nano technique

Applying nanotechnology to 3D-printed medical devices opens new transformative opportunities for performance and efficiency at a molecular scale. Some researchers have found ways recently in which nanoparticles can be embodied within printable biomaterials, bringing forth advanced medical devices laden with new functionalities. Good examples include the control of drug release that comes with embedding nanoparticles into 3D-printed implants. These implants could deliver drugs at an exactly controlled rate or in response to determined biological triggers, thus offering a new paradigm in localized, long-term drug delivery [65].

Another application that looks promising is 'smart' implants with the use of Nanosensors. These microscopic sensors could read continuously in the local tissue environment, detecting the first appearances of infection, inflammation, or rejection of an implant. This data can be transferred wirelessly to health providers against the background of readings by those sensors, allowing a real-time information system on the performance of an implant and the health status of a patient. This development would, therefore, greatly improve patient outcomes through timely medical interventions based on precise and real data [66].

4D medication: the upcoming frontier

4D drugs delve into 3D printing, elevating the dimensionality with time or stimuli responsiveness. How the field in its nascent form could progress is mentioned here:

Shape-shifting drug-delivery systems

Such 4Dprinted pharmaceuticals could be designed to change their form or structure depending on lost stimuli within the body. For instance, a pill may unfold in the stomach to increase the retention time in the gastric region, whereby in the long run, it would result in prolonged release of the entrapped entity. For example, another option is a drug-releasing system whose surface area changes with pH, suiting better absorption in different parts of the gastrointestinal tract. This dynamism thus adapts to a change that realizes more and better delivery of the drugs [67].

Programmable release

4D drugs can be developed from the formation of highly complex programmable release means. This implies the release of different drugs or dosages at selectively controlled times or predetermined sequences in response to different physiologic signals. This can vastly increase the effectiveness of combination therapies in cancer, infectious diseases, and other serious diseases [68].

Environment-responsive drugs

Drugs in the future will be able to adapt to the internal environment of the patient. For instance, an anti-inflammatory drug will adjust the release of the medication in response to markers that suggest the state of inflammation, thereby providing an appropriate, individualistic dose that is tuned in real-time to the patient's needs. This level of personalization will allow optimal therapeutic effects with a decrease in potential side effects [69].

Targeted activation

The 4Dprinted nanoparticles or microstructures can be designed to be activated when reaching certain targets within the body. It would increase the treatment's precision by a big margin, therefore limiting side effects, while drugs will be active at the right locations.

This will go further into the future, whereby we have self-regulating 4D medication systems capable of monitoring their effectiveness and self-modifying their behavior appropriately. They could be interlinked with wearable health monitors or implantable sensors to establish a closed-loop system of optimal drug delivery. Truly, this will make a quantum jump toward personal and adaptive healthcare [70].

CONCLUSION

It is expected that this kind of integration would further leap toward personalized healthcare in both the pharmaceutical and medical device industries. In the case of 3D printing, customized device and implant designing and drug-delivery systems are feasible according to the requirements of a patient. Such capabilities in creating complex geometries, merging independent materials, and advanced features like Nano sensors or responsive elements make this new frontier of treatment and care unprecedented.

With the evolving technology, the development of 4D printing is visible, where time or stimuli-responsiveness is added as a dimension to the printed objects. We can foresee that this will ultimately lead to shape-shifting drug delivery systems and self-regulating medications responding in real-time to the physiology of the patient.

However, their adoption is challenged by scalability, cost-effectiveness, and regulatory compliance. Guarantees of quality control and standardization during the production of customized products remain a great obstacle. Nevertheless, 3D and 4D printing will continue to remain very promising frontiers of pharmaceutical and medical device innovation because of the potential for better patient outcomes, reduced healthcare expenses, and easier drug development processes.

Further down the road, as research continues to push further forward and regulatory frameworks change, we may see these technologies diffuse into changing how we think about treatment options and disease management in the decade ahead.

ABBREVIATIONS

3D (3 dimensions), 2D (2 dimensions), 4D (4 dimensions), CAD (Computer-aided design), stl.(stereolithography format), ABS (Acrylonitrile butadiene styrene), PEEK (polyetheretherketone), PEKK (Polyetherketoneketone), ULTEM (polyetherimide), UV (Ultraviolet), Stereolithography technology (SLA), Digital light processing (DLP), Continuous liquid interface production (CLIP), Fused deposition modeling (FDM), Selective laser sintering (SLS), Multi-jet fusion (MJF), DED (Directed Energy Deposition), FDA (Food and Drug Administration), USFDA (United States Food and Drug Administration), CFR (Code of Federal Regulations), MDR (Medical Device Reporting), PMA (premarket approval), IDE (investigational device exemption), GMP (Good manufacturing practice), AI(Artificial intelligence).

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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