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A Review of 3D printing methods for pharmaceutical manufacturing: Technologies and applications

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Abstract

The foundation of three-dimensional printing is the additive manufacturing principle. This type of technology could completely revolutionize manufacturing if it is capable of reducing time to manufacture from months or years down to hours. The pharmaceutical and healthcare sectors are just two of many that stand to benefit greatly from the revolutionary technology known as 3D printing, or additive manufacturing. Focusing on its capacity to improve patient-specific therapies, optimize drug release patterns, and produce customized medication formulations, this article investigates the possibilities of 3D printing in pharmaceutical production. Moreover, the article provides details on various methods of 3D printing including Fused Deposition Modelling (FDM), Inkjet Printing and Hot Melt Extrusion (HME) and the advantages, limitations, and application of these methods in the pharmaceutical industry. It also covers the application of 3D printing in the localization of the operative site, counseling and individualized manufacture of implants. Some of the technical, legal, and even financial barriers still remain to prevent the usage of 3D printing for the creation of pharmaceuticals despite the encouraging potential out there. This paper offers a comprehensive review of 3D printing's present state, difficulties, and potential future uses in the pharmaceutical industry, shedding light on how this technology has the potential to transform the pharmaceutical industry and personalized treatment.

Keywords: 3D Printing; Inkjet Printing; Pharmaceutical Manufacturing; Hot Melt Extrusion; Fused Deposition Modeling

1. Introduction

3D printing separates itself from the more traditional "subtractive manufacturing" methods by printing out individual layers of a model made in CAD software. The layered manufacturing process then builds the product from the ground up [1][2]. The robust research and development community in this field is directly responsible for the emergence of several innovative 3D printing technologies. Material extrusion, binder jetting, powder bed fusion, vat photo-polymerization, material jetting, directed energy deposition, and sheet lamination are the seven 3D printing techniques that have been cataloged by the American Society for Testing and Materials according to their underlying scientific principles [3][4]. The material, deposition method, manufacturing process for stacking, and end product properties used by each 3D printing technology are distinct.

The medical, aerospace, construction, and automobile sectors are just a few of the many that make extensive employ of 3D printing technology. There has been a recent uptick in the pharmaceutical industry's worldwide interest in 3D printing research [5][6]. When compared to more traditional preparation methods, 3D printing provides many benefits, including the ability to precisely regulate drug release, a great deal of leeway for the creative customization of medicines, and a substantial decrease in preparation development time. The building of complex three-dimensional forms within the dosage types of drugs and treatment regimes, the alteration of drug and combination formulas, and the rapid manufacture and model changes are some of the advantages [7][8].

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The various products that have been manufactured through 3D printing technology include the following: dispersible films, microneedles, implants, controlled-release tablets, transdermal patches and immediate-release tablets [9]. The pharmaceutical sector mostly uses Binding Jet 3Dprinting (BJ-3DP), FDM, SSE, Melt extrusion deposition (MED) in material extrusion, and Stereolithographic (SLA) as their 3D printing technologies [10].

The industry of making pharmaceutical products typically uses production line techniques that do not allow much variation in the process. In contrast, 3D printing allows for the creation of tailored drug formulations and dosage forms, offering solutions to challenges such as patient-specific treatment and rapid prototyping of new drug delivery devices [11]. This technique can help create new opportunities for pharmaceuticals by enabling bioprinter tissues, implants, capsules, and tablets, and many others dosage forms.

However, there exist a number of technical, legal and economic challenges that affect the application of 3D printing to the benefit of the pharmaceutical industry and its future outlook. Problems like optimization of the important print parameters, choice of right materials and others like scalability still pose as major challenges [12]. Also, safety efficacy and regulatory compliance of 3D printed drugs further open up another challenge of the integration of this kind of technology into the large-scale pharma manufacturing.

1.1. Motivation of the Study

Traditional pharmaceutical manufacturing has its limits, and the increasing demand for personalized medication is driving this study. Some of the crucial emerging technologies in medicine are 3D printing technology in the production of personalized drug doses and delivery systems, as well as personalized treatment of patients. 3D printing has the potential to solve problems like manufacturing complexity and production costs by accurately controlling medicine doses, release patterns, and pharmaceutical forms. This article explores the possibility of its impact on medication discovery and patient care and the potential role of 3D printing in drug manufacturing.

1.2. Structure of the paper

The format of this document is as follows: An overview of 3D printing technology and its uses in a variety of sectors, including healthcare, is given in Section II. An application of 3D printing in the medical industry, including presurgical planning and customized instruments, is covered in Section II.1. Section III discusses 3D printing methods in pharmaceutical manufacturing. Section IV covers its applications in pharmaceuticals, such as bioprinting and personalized drug dosing. Section V provides a literature overview on the topic of 3D printing for pharmaceutical production, focusing on important results and difficulties.

2. Overview of 3d printing technologies

A process of printing 3-D objects by CAD files is based on the technique of layer-by-layer manufacturing [13]. An incredibly versatile technological platform, 3D printing has emerged as a truly innovative technology. It provides businesses hoping to increase the efficiency of their production a lot of optimism and opens up new options. Thermoplastics, ceramics, graphene-based materials, and metal are now all within the realm of possibility due to 3D printing [14]. It is possible that 3D printing technology may modify the production line and revolutionize entire industries. Manufacturing can be accelerated and expenses reduced by utilizing 3D printing technology [15]. The influence of customer demand on production, however, will be larger. The consumer has greater control over the final product and can modify it to meet their own requirements. The proximity of 3D printing facilities to consumers will also allow for better quality control and a more flexible manufacturing process [16]. The global demand for transportation can be significantly diminished by the utilization of 3D printing technologies. This is because production facilities can be located closer to the final destination, which saves both energy and time in distribution, due to fleet monitoring technology. Last but not least, using 3D printing technology may alter the business's logistics. Logistics departments can provide more comprehensive, end-to-end services by supervising the entire process [17]. Figure 1 depicts the 3D printing workflow discussed below:

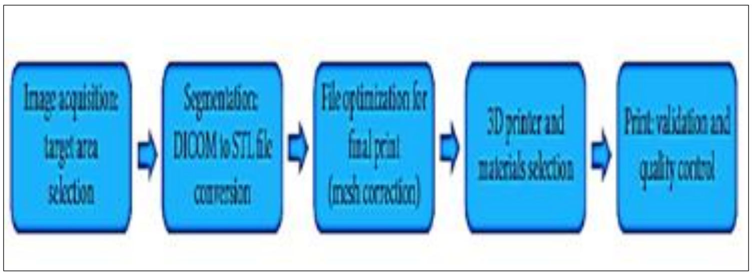

Figure 1 3D printing workflow

These days, 3D printing is all over the place. A growing number of sectors, including those dealing with food production, medicine, transportation, and aerospace, are making use of 3D printing technology for mass customization and the fabrication of open-source designs [18].

Thus, 3D printing may greatly enhance the training and education of future surgeons, the rapport between doctors and their patients, our understanding of the underlying disease, the ability to tailor surgical instruments and implantable devices to each individual patient, and the efficiency and economy of the surgical procedure[19][20][21]. A variety of printing methods and materials are now at our disposal, allowing for a more accurate reproduction of the patient's anatomy. With the use of a 3D printer, patients may have their medicine made specifically for them, with release profiles that are just right for them. Figure 2 depicts the working representation of 3D printing given below:

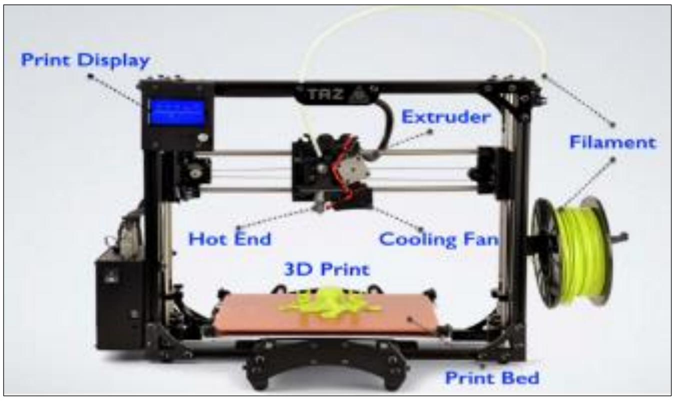

Figure 2 Working representation of 3D printing

Most printing materials are rigid, unlike genuine tissue, and are thus not ideal for printing delicate or flexible designs. The good news is that there are now materials that can potentially connect the dots between real and virtual anatomy, especially in the realm of soft tissue[22].

2.1. Role of 3D Printing in Medical field

As time goes on, 3D printing finds ever-increasing uses in medicine, potentially saving and bettering lives in ways before thought possible [23]. Many branches of medicine have begun using 3D printing, including cardiothoracic, gastrointestinal, neurosurgical, ophthalmological, otolaryngologic, orthopedic, plastic, podiatric, pulmonological, radiotherapy oncological, transplant, urological, and vascular surgeries [24]. Although this technology has the potential to bring about many positive changes in the industry, the most obvious uses of 3D printing in healthcare are as follows:

- Aimed at individualized preoperative: therapy and planning. This will initiate a series of steps that, by combining data from imaging and clinical assessments, will ascertain the optimal course of treatment [25]. There is some evidence from a number of studies that suggests that surgeons may cut down on OR time and problems using patient-specific presurgical preparation [26]. Additionally, this has the potential to cut healthcare expenditures, reintervention rates, and postoperative stays. With the use of 3D printing, surgeons can now have a tangible representation of their patient's ideal anatomy, which can aid in accurate surgical planning in conjunction with cross-sectional imaging or even the creation of one-of-a-kind prosthetics or surgical instruments[27][28].

- Personalise surgical equipment and prostheses: Guides, surgical tools, and customized implants can all be made with 3D printing. Therefore, customizing surgical equipment and prostheses are less expensive due to the additive manufacturing method [29].
- Study of osteoporotic conditions: After a patient has taken a pharmaceutical medication, 3D printing may help verify the efficacy of the therapy. This allows for an improved surgical treatment decision-making process and a more precise assessment of the patient's bone health [30].
- Testing different devices in specific pathways: The reproduction of different circulatory patterns provides a direct illustration of how a cardiovascular system can be used to treat coronary artery disease and peripheral vascular disease. By using 3D printing, we can rapidly create models of potential new designs or enhancements to current gadgets [31].
- Improving medical education: Regardless of a trainee's career path, there is substantial evidence that patient-specific 3D-printed models may increase performance, speed up learning, and substantially enhance knowledge, management, and confidence [32]. The use of 3Dprinting in a classroom has several advantages, such as the fact that the models can be easily and safely produced, an ability to use a large dataset of images to model various types of anatomy (both normal and abnormal), and the fact that different institutions, particularly those with less resources, can share and use these models. The anatomical intricacies may be brought to light with the use of 3D printers that can print with varying densities and hues.
- Patient education: Most healthcare practitioners prioritize patient education as part of patient-centered care. However, patients may not accurately interpret 2D pictures depicting a 3D anatomy. Therefore, it's not always helpful to communicate imaging results orally or by showing patients their MRI or CT scans. However, by directly displaying the anatomic model, 3D printing has the potential to enhance doctor-patient communication [33].

3. 3D printing methods in pharmaceutical manufacturing

The adoption of 3D technology in the pharmaceutical industry has revolutionized drug development and manufacturing processes. This creative strategy makes use of cutting-edge manufacturing techniques to produce pharmaceutical goods that are precisely tailored to the drug release patterns, doses, and geometries. Various 3D printing techniques are utilized in pharmaceutics, each offering unique advantages and applications based on their operational mechanisms, material compatibility, and output quality [34]. The key techniques in 3D printing pharmaceutics discussed below:

3.1. Key 3D Printing Techniques/Methods in Pharmaceutics

3D printing describes a huge range of manufacturing techniques that create sophisticated three-dimensional items by depositing material in layers under computer control.

3.1.1. Thermal Inkjet Printing

A nozzle is used to drive ink droplets out of a fluid that has been heated to a vapor state in thermal inkjet printing [35]. Pharmaceuticals, biodegradable microspheres, liposomes, coatings, and drug-eluting stents are all products of its utilization. Additionally, it is a realistic and efficient way to make biological films that do not compress therapeutic action [36][37]. Figure 3 represents the visual structure of thermal inkjet printing mentioned below:

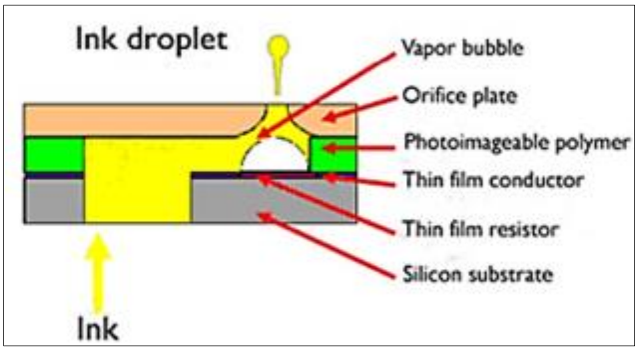

Figure 3 Thermal Inkjet Printing

3.1.2. Inkjet Printing

A "mask-less" or "tool-less" method, inkjet printing relies on the precise and repeatable movement of the substrate or inkjet nozzles to produce the required structure [2]. This method is ideal for liquid formulations and is categorized into CIJ and DOD[38]. Figure 4 represents the workflow of inkjet printing in 3D printing given below:

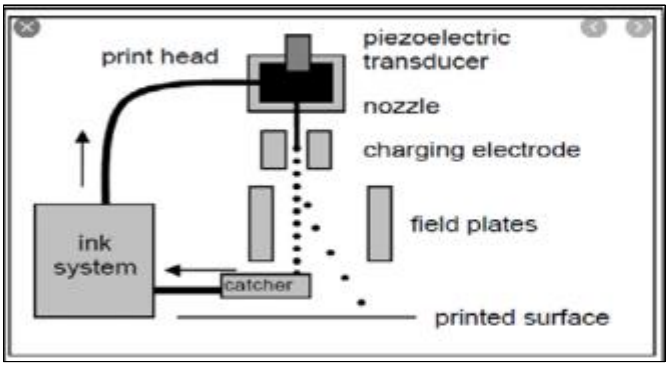

Figure 4 Inkjet Printing in 3D Printing

- Continuous Inkjet Printing (CIJ): Produces a continuous stream of droplets directed to a substrate.
- Drop on Demand (DOD): Generates droplets by heating or applying voltage to a piezoelectric crystal, depositing them onto a substrate.

3.1.3. Fused Deposition Modeling (FDM)

It is a typical method in three-dimensional printing whereby the ingredients are heated to a point where it melt in order to produce printed items. Using FDM, a variety of dose formulations are accessible. Fabrication of delayed-release print-lets without an exterior enteric coating and the provision of individually dosed medications are both facilitated by FDM 3D printing [39][40]. Figure 5 shows the visual structure of FDM technique given below:

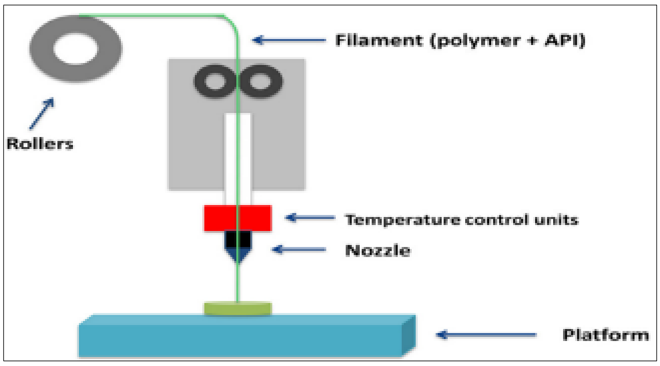

Figure 5 Fused Deposition Modeling (FDM)

3.1.4. Hot Melt Extrusion (HME)

A procedure of hot melt extrusion involves continually applying pressure to the instrument while the polymer and medication are heated to a melting point [41]. Feeding, heating, mixing, and shaping is all part of the continuous production process. It has been shown in recent years that HME may enhance the solubility and bioavailability of medications that are not very water-soluble [42][43]. Figure 6 represents the hot melt extrusion given below:

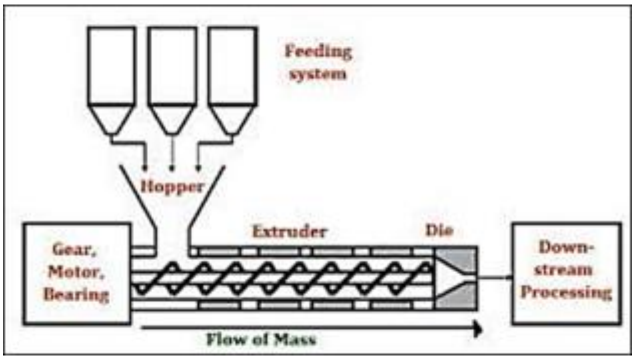

Figure 6 Hot Melt Extrusion

3.1.5. Extrusion-Based Printing

The 3D printing technique most often used is extrusion. The extrusion process involves the use of nozzles that are operated by robotics to extrude material. Printing using extrusion processes is substrate-independent, in contrast to binder deposition, which needs a powder bed. An assortment of semisolid materials, including molten polymers,pastes,colloidal suspensions, silicones, and others, can be extruded for the purpose of 3D printing. The fused filament fabrication process is a favorite among those who employ extrusion printing. This substance is only used in the production of expectorant tablets containing guaifenesin. FDM and HME are two of the methods that fall under this category [42].

3.1.6. Powder-Based Binding Method

This method makes use of inkjet printers to deposit a thin coating of powder or a power bed while also dropping liquid binder. To create the finished product, the ink (a mixture of binder and active pharmaceutical ingredients) is applied in a 2D pattern over a powder bed [39]. The approach could be more easily adjusted to the pharmaceutical production process compared to others, given the frequent use of powder and binder solutions in this industry. Making multi-layered 3D structures involves spraying a binder solution onto a powder bed.

3.1.7. Stereo-Lithographic 3D Printing

This method creates a three-dimensional object by curing photo polymerized materials, which are sensitized to light. By using a digital mirroring device to gradually scan a focused UV laser over a photo polymerizable liquid, SLA exploits a chemical reaction to induce the exposed region to gel. This procedure is iterated upon in successive layers to construct the whole component of the object [44]. This occurs because the illuminated resin in the subsequent layer polymerizes with the functional groups that have not yet interacted with the hardened structure in the first layer, guaranteeing adhesion and layer formation. Typically, a finished result needs post-print processing to round it out, strengthen its mechanical properties, polish it, or even remove the connected supports from the manufactured items[45][46]. However, this method could be harmful to your health because it uses resins that could cause cancer. The process is also very slow. Stereo lithographic 3D printing mentioned in the Figure 7 below:

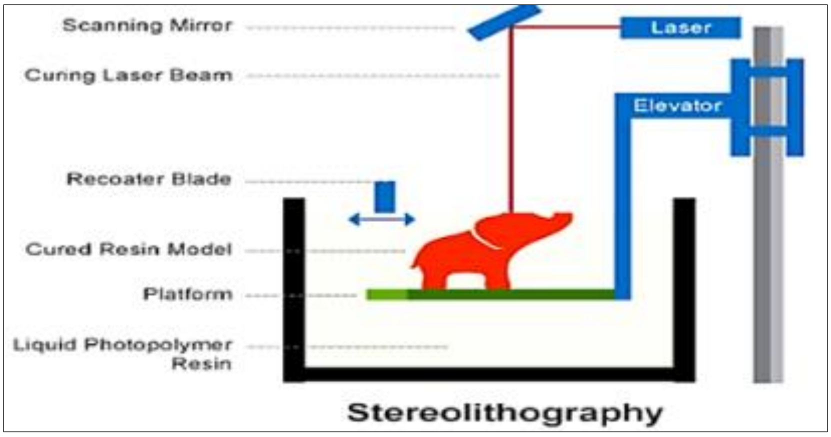

Figure 7 Stereo lithographic 3D printing

4. Applications of 3d printing in the pharmaceuticals

3Dprinting has now become a revolutionary tool for the medical industry due to its versatility applied to several uses. Personalized medicine has been transformed by its capability to develop models, devices, and implants based on patient data. From replacing limbs with prosthetics and fixing bones with orthopedic implants to printing out organs, tissues or an organ on a tissue chip through bioprinting, 3D printing is as precise as can be and as customized as human beings can be[47]. In pharmaceutical manufacturing it makes it possible to develop controlled release systems and multiple tablet combination systems. Figure 8 discusses the different medical applications of 3Dprinting technology discussed below:

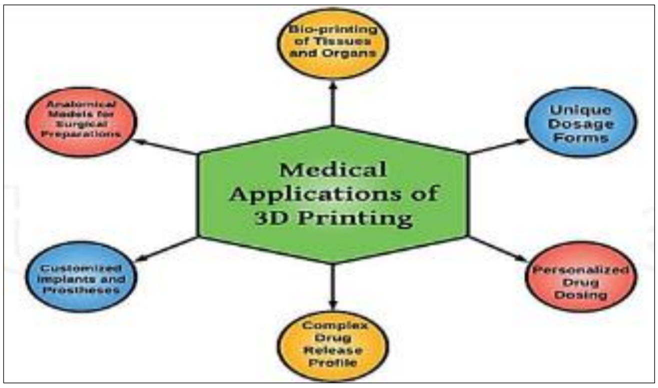

Figure 8 Different medical applications of 3D printing technology

4.1. Bioprinting of tissues and organs

3D bioprinting addresses critical medical challenges such as organ and tissue failure caused by accidents, congenital defects, or aging. Bioprinting lessens the need for immunosuppressant medications and the likelihood of rejection by making use of the patient's own cells. It offers advantages like precise cell placement, digitally controlled fabrication, and the ability to create functional tissues [4]. Applications include artificial ears, cartilage, bones, heart valves, and even liver tissue, demonstrating the immense potential of this technology in regenerative medicine.

4.2. Creation of unique dosage forms

The pharmaceutical industry uses 3D printing to come up with other types of dosage forms that include microcapsules, antibiotic micropatterns, and nanosuspensions. Inkjet-based and powder-based 3D printing makes it possible to develop highly sophisticated drug delivery systems that possess certain properties [48]. These improvements affirm drug stability and therapeutic effectiveness and create new opportunities for creating novel complex pharmaceutical corporeality’s [49].

4.3. Personalized drug dosing

3D printing enables personalized medication that incorporates traits like age, race, and genetic profile of the intended user [50]. It enables formation of multi-dose tablet products with multiple actives; this makes it easier for patients to adhere to their prescribed regimens [36]. It also promotes the creation of stable formulations and unconventional drug release mechanisms that deliver the required therapeutic outcomes accurately and efficiently [51].

4.4. Complex drug release profile

3D printing helps to design dosage forms with complex systems for managing the release of the medicine. This allows the formation of structures with multiple degrees of freedom in terms of porosity and geometry, where the drug release can be managed and scheduled [52]. Such examples include prostheses that have periodic release of different drugs and printed antibiotics for specific uses. These increases improve the precision and efficiency of delivery systems of drugs relative to what has traditionally be used[53].

5. Literature review

Table 1 below provides a section summary of the assessment of the current literature on the research focus of 3D printing and the pharmaceutical production industry.

In this study, Marinescu and Popescu (2020), the 3D-printed models facilitated better surgical planning, provided a personalized implant, improved team communication, reduced intervention time, and maximized medical equipment utilization through grip strengthening and repositioning. In the majority of the research published in the literature as well as in these clinical cases, positive results were recorded. While 3D printers aren't right for every patient or every emergency, they do make several orthopedic treatments that are currently available to both seasoned and novice surgeons [54].

In this study, Totu et al. (2017) present a novel polymeric nanocomposite for use in the production of three-dimensional printed dental restorations. A full denture might be made using the suggested nanocomposite: poly (methyl methacrylate) - TiO 2 nanoparticles. The availability of photocurable materials severely restricts the employment of the recently developed 3D printing technology for the manufacture of dental products. These days, this manufacturing method is limited to little dental bridges [55].

In this study, Lai et al. (2018) employ a molecular dynamics simulation method to investigate the physical characteristics of nanoscale titanium aluminum alloy powder as it is being fused in a powder bed sintering chamber in an additive manufacturing process. The 3D printing laser sintering method involves investigating and discussing the root mean square, neck width, and radius of gyration of various nanoscale titanium aluminum alloy powder sizes at varying heating speeds. Along with the observed changes in the physical parameters of the simulated nanoscale solid/hollow spherical titanium aluminum binary alloy powder, alterations in the internal lattice and the breadth of the neck are also noted [56].

In this study, Umair and Kim (2016) showcase our own 3D printing platform that enables users to design, purchase, trade, and manufacture 3D items. In addition to connecting members of the 3D printing community, the portal acts as a crowdfunding site. Participating organizations in the domains of dentistry, orthopedics, rehabilitation, and surgery also contribute 3D printing medical solutions to our suggested platform. Many companies have developed 3D medical solutions and online 3D printing service platforms in response to the industry-wide impact of 3D printing technology [57].

In this study, Sehnal et al. (2019) research is focused on the production of AgNPs that have been biomodified using compounds derived from three different plant extracts: T. serpyllum, S. officinalis, and T. pratense. Physicochemical techniques were used to study the produced nanoparticles in detail. The acrylonitrile butadiene styrene (ABS) substrate also supported their deposition. They used 3D printing to manufacture a novel antibacterial substance. In the assessment of their effectiveness, Sauers and E.coli were shown to be 20–40% inhibited. Microorganisms' resistance to antibiotics is gradually increasing. The creation of novel antimicrobial agents is a hot issue. Like the plant and animal components utilized in ancient medicine, metal nanoparticles have shown strong antibacterial activity[58].

Table 1 Presents the summary of literature review based on 3D printing Methods for Pharmaceutical Manufacturing

References	Objectives	Key findings	Challenges	Limitations	Future Work
[54]	Evaluate the impact of 3D-printed models in surgical planning and orthopedics.	Improved surgical planning, customized implants, enhanced communication, reduced intervention time, and optimized instrument usage. Positive outcomes in clinical cases.	It is not suitable for all cases or emergency situations.	Limited to specific orthopedic procedures; not broadly applicable across all surgeries.	Explore applicability in emergency and other surgical domains.
[55]	Introduce polymeric nanocomposite for 3D-printed dental prostheses.	Successfully manufactured complete dentures using poly(methyl methacrylate)-TiO2 nanoparticles. Highlighted	Availability of photo-curable materials for dental 3D printing is limited.	Currently applicable only for small dental bridges.	Develop advanced photo-curable materials for broader dental applications.

		limitations in photo-curable materials for dental applications.			
[56]	Investigate nanoscale titanium aluminium alloy powder characteristics during 3D printing laser sintering.	Analysed powder properties like the radius of gyration, neck width, and lattice changes during sintering under different heating rates.	The complexity of simulating nanoscale physical characteristics accurately.	Focused only on titanium aluminium alloy; other materials not considered.	Expand to other alloy systems and refine simulation methods for better accuracy.
[57]	Develop a 3D printing portal for creating, buying, selling, and printing 3D products, with medical solutions in various fields.	Proposed a multifunctional portal combining crowdfunding, social networking, and 3D printing services for dentistry, orthopaedics, rehabilitation, and surgery.	Integration of diverse services into a single platform is complex.	Limited participation and usage of the portal may affect scalability.	Expand platform adoption and include advanced 3D printing applications in medicine.
[58]	Synthesizesilver nanoparticles modified with biomolecules for antibacterial 3D printing applications.	Created antibacterial materials using 3D printing with 20-40% inhibition of S. aureus and E. coli. Highlighted the potential of AgNPs in combating antibiotic resistance.	The stability and consistency of AgNPs on 3D-printed materials need improvement.	Limited antibacterial efficacy (20-40% inhibition); broader microbial spectrum not tested.	Optimize nanoparticle synthesis and test efficacy against a broader range of microorganisms.

6. Conclusion and future work

The advent of 3D printing has been a game-changer in the pharmaceutical industry, opening up new possibilities for efficiency, accuracy, and personalization in the creation of new drugs. By enabling the creation of personalized drug formulations and controlled release profiles, 3D printing enhances patient care and accelerates the drug development process. Despite its potential, challenges such as material selection, process optimization, and regulatory compliance must be addressed to fully integrate this technology into mainstream pharmaceutical production. The advancements in 3D printing methods, coupled with ongoing research and development, suggest that the future of pharmaceutical manufacturing will be significantly shaped by these innovations.

Further research in 3D printing pharmaceuticals should zero in on the enhancement of the print quality and the variety of materials that can be printed, including biocompatible and biodegradable polymers. Furthermore, investigation into the durability, stability, toxicity, and effectiveness of 3D–printed medicines is essential in order to gain regulatory exemption. Exploring the scalability of 3D printing for mass production and developing standardized guidelines for quality control and testing will be essential for its widespread adoption. Furthermore, integrating artificial intelligence and machine learning with 3D printing could enhance the design and manufacturing processes, leading to even more efficient and personalized drug production.

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