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3D Printing Technology: Shaping the Future of Pharmaceutical Dosage Design

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ABSTRACT

In the pharmaceutical industry, three-dimensional (3D) printing has become a ground-breaking technology that opens up new possibilities for the creation of customized dosage forms. In contrast to traditional medication production techniques, 3D printing enables exact control over a dosage form's size, shape, internal structure, and drug distribution. This technology makes it possible to produce medications that are specifically suited to the needs of each patient, which enhances therapeutic results and drug compliance.

Oral tablets, capsules, transdermal patches, and implantable medication delivery devices have all been successfully created using a number of 3D printing techniques, such as fused deposition modeling (FDM), inkjet printing, stereolithography (SLA), and selective laser sintering (SLS). Depending on the drug kind, intended release profile, and formulation ingredients, each approach has distinct benefits. Treatment convenience and efficacy can be improved by using digital design to modify the drug dose, release rate, and even mix several pharmaceuticals in a single dosage form.

The creation of rapid-dissolving tablets, patient-specific formulations, and controlled-release systems is further supported by the use of pharmaceutical-grade excipients and biocompatible polymers in 3D printing. Additionally, this method reduces material waste and enables on-demand manufacturing in pharmacies or hospitals. Despite these benefits, issues like quality control, reproducibility, and regulatory approval still need to be resolved to guarantee printed goods' safety and uniformity.

To sum up, 3D printing is a revolutionary development in dosage form design that provides accurate, adaptable, and patient-focused drug administration options. The future of pharmaceutical manufacture and personalized medicine could be drastically altered by 3D printing because to continuous developments in materials science, printing technology, and regulatory frameworks.

Keywords: 3D printing, Drug printing, Additive manufacturing, Pharmaceutical dosage forms

1.Introduction

Over the past few decades, there has been a significant surge in interest in three-dimensional (3D) printing. The methods that fall under this umbrella are frequently called an industrial revolution [1] and might potentially upend even well-established markets [2]. Many people believed that this transformation would spread swiftly in the pharmaceutical industry when the US Food and Drug Administration (FDA) approved the first 3D printed medication, Spritam®, in 2015. However, despite a huge surge in research articles on the subject, neither the FDA nor the European Commission have authorized any additional 3D printed medical items to date (after a proposal by the European Medicines Agency, or EMA). Nonetheless, a number of businesses are developing 3D printed goods. For instance, it has been claimed that Triastek has obtained investigational new drug (IND) clearance to permit delivery of at least four distinct 3D printed items that are currently in development over state boundaries in the United States of America [3]. Although the extrusion method used to make these items differs greatly from the ZipDose® approach used to make Spritam®, both techniques are part of 3D printing technology.

As seen in Fig. 1 [4], 3D printing is a manufacturing technology in which the final product is created by layering materials like plastics, metals, medications, cell cultures, etc. The Governmental Accountability Office (GAO) of the United States claims that 3D printing can use additive manufacturing to produce 3D structures from digital models [5]. It has numerous applications in a variety of industries, including as the toy, automotive, aerospace, food, and chemical sectors. 3D printing has been utilized in the healthcare sector to create artificial tissues and organs, medical equipment, prosthetics, and other drug dosage forms. It is not the same as 2D printing of pharmaceuticals, which prints thousands of dots on a flat surface or substrate using an ink based on a pharmaceutical. In order to screen the optimization parameters so that it can be scaled to 3D printing, the 2D printing approach can be utilized for testing various medications, drug loadings, or release features of different dosage forms [6]. The fourth dimension of 4D printing, a subset of 3D printing, is the final product's ability to change shape on its own after manufacturing, such as thermobiochemically triggered tetherless microgrippers [7], in response to a variety of stimuli like pressure, temperature, light, water, wind, and enzymes [8,9]

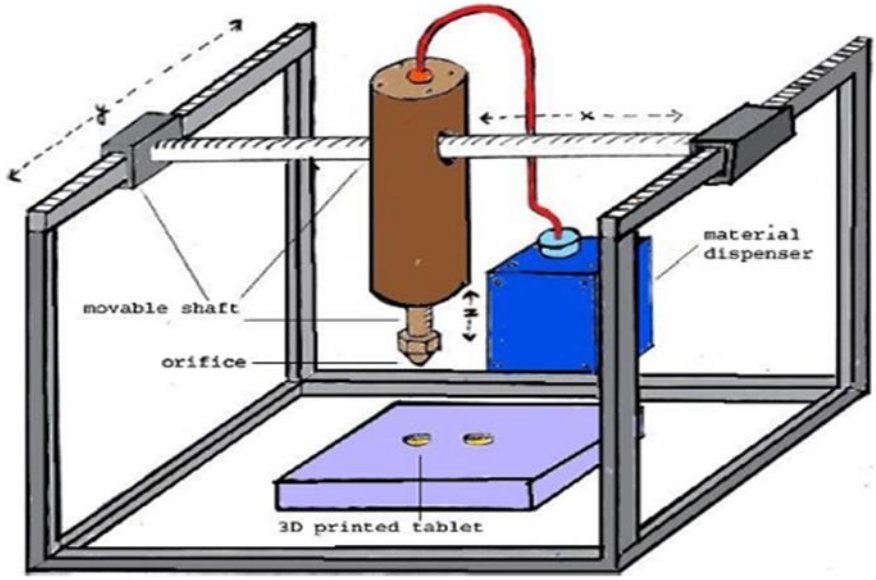


Fig. 1. 3D printer with different components

Many measures have been taken to incorporate and optimize various AM technologies in medication formulation and dosage forms, despite the fact that drug 3DP technology is still in its infancy. For example, a range of biocompatible bioinks used in inkjet 3DP have been developed [11], and new pharmaceutical-grade polymers were discovered to be appropriate for FDM 3DP operating at significantly lower temperatures (90°C) than conventional FDM printing, allowing printing of thermolabile active pharmaceutical ingredients (APIs) [10]. The primary cause of this AM explosion is the quick and steady decline in 3D printer pricing. FDM 3D printers are the best option for outfitting neighborhood pharmacies and other small healthcare institutions due to their affordable price. Furthermore, hot-melt extruders and FDM printers that adhere to good manufacturing procedures (GMP) have just been produced for continuous and large-scale production of drug-loaded filament [12], underscoring the imminent shift from proof-of-concept experiments to practical uses.

Coumarins have been the most often prescribed oral anticoagulants for more than half a century. [13] However, coumarin therapy has been linked to a significant degree of inter-individual variation in the dose necessary to obtain a therapeutic anticoagulation response, despite its widespread use. [14] For instance, giving a patient an excessive amount of warfarin can make them hypercoagulable or raise their risk of bleeding problems early in treatment. There is a 9.1% higher chance of significant bleeding after taking anticoagulants as a result of an over-anticoagulation reaction. [15]. An "induction" dose of 2 to 5 mg per day is recommended by the American College of Chest Physicians (ACCP), and it must be modified based on the patient's International Normalized Ratio (INR) [16]. Numerous factors, including patient age, body weight, dietary vitamin K intake, concurrent drugs, and different disease conditions, have a significant impact on the pharmacodynamics and pharmacokinetics of coumarins. [14] Therefore, frequent coagulation monitoring and dose adjustment are required to guarantee that the patient's INR stays within the desired range. [17]

Orodispersible films (ODFs) are another interesting dose type. Individual dose adaptation is made possible by the ability to cut drug-loaded ODFs made by solvent casting into various sizes [18–20]. The fabrication of various ODFs, including multilayered ODFs, can also be moved from a lab scale to a continuous manufacturing process, as Thabet et al. showed [21, 22]. Drug loading of up to 30% are possible, although higher drug loads alter the film formulation's inherent qualities [23]. ODFs typically have modest drug loads because of their low weight.

When it comes to appropriate production techniques for customized dosage, 3D printing shows great promise. 3DP claims to be able to create customized oral DDS with release profiles that can be altered. Creating a solid 3D object layer by layer is the uniform definition of the 3DP method [24]. Using computer-aided design (CAD) software, a template of the 3D item is created at the beginning of the 3DP process. The potential of 3DP for the idea of customized API dosage is demonstrated by these CAD-created designs. A wide range of options for printing the DDS are provided by the computer's ability to modify the template. In recent years, 3DP has made a name for itself in a variety of industries, including the automotive sector [25], tissue engineering [26], medical devices [27], and the manufacturing of pharmaceutical DDS [28]. The next section discusses the various methods that make up 3DP and how they are applied in the production of pharmaceuticals. The various 3DP methods utilized to produce DDS are depicted in Fig. 2.

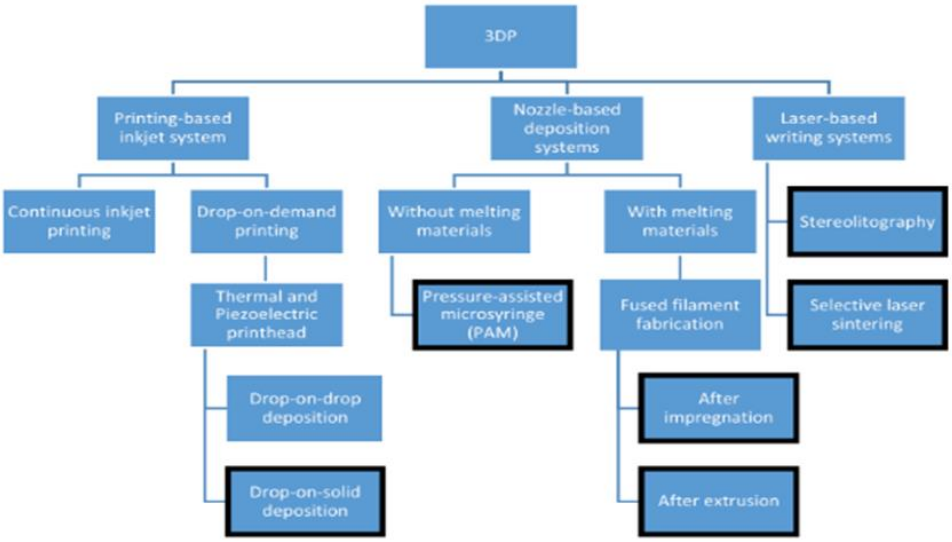


Fig. 2. Overview of the different 3DP techniques adapted and modified from Goole et al [29]

2.Historical Journey Of 3D Printing

The first 3D pharmaceutical trial using a printed multi-delivery device was carried out in 1996. Alizarin yellow and methylene blue dyes were placed in the device's three-dimensional form; its composition and microstructure were altered, and its release was controlled. Polyethylene oxide (PEO) was printed in a square pattern, and colors were positioned within the square. To seal it and stop diffusion, polycaprolactone sheets were printed on the top and bottom. The dye release profile from this device was multiphasic [30].

By altering the chemical characteristics and composition of the binder, the drug release of the 3D-printed tablet can be controlled. To create cellulose pills, a cationic methacrylic ester (Eudragit E-100) was utilized. To create tablets with regulated release characteristics, Eudragit RLPO was utilized. Dissolution tests in stimulated intestinal fluid showed that the longer drug release time was caused by an increase in the binder content in the tablet. The 3D printed tablet was as rigid and friable as compressed tablets that are sold commercially [31]. Chlorpheniramine was fabricated into immediate-extended-release tablets using E-100 and Eudragit RLPO as binder, respectively. The medicine was administered throughout the first half hour of the dissolving process by the immediate release (IR) portion. The medication was administered for six hours via the extended release (ER) segment.

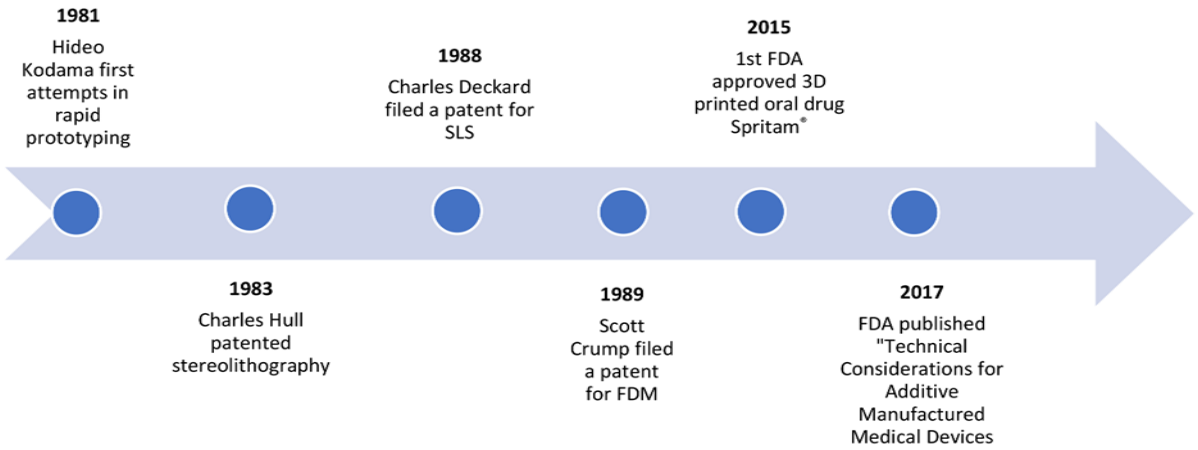


Fig.3 Historical journey of 3D printing

3.Materials And Methods

3.1 Materials

BASF (Burgbernheim, Germany) donated grade 25 ibuprofen. We bought gelatin and 99.0% paracetamol from Sigma-Aldrich in Darmstadt, Germany. J.M. Loveridge Ltd. (Andover, UK) provided the glycerol EP. We bought locust bean gum (derived from Ceratonia siliqia seeds) from Sigma-Aldrich in Pool, UK. FastColours LLP, located in Huddersfield, UK, provided the food dyes, Lake Allura Red and Brilliant Blue.

3.2 Preparation of Embedding and Embedded Materials

Each oral dose form consisted of an embedding medium (gelatin-based gel) and a suspension of either ibuprofen or paracetamol powder in locust gum solution (paste).

3.2.1 Embedding Medium

The ideal weight ratio for a thermoresponsive embedding medium was 45:25:30 for water, glycerol, and gelatin. After heating the water to 75 degrees Celsius, the gelatin was added and stirred until it completely dissolved.

3.2.2 Embedded Drug Paste

To suspend model drug particles in the media, a 2.98% w/w locust bean solution was utilized (at 80 C). Suspensions (100 g) of paracetamol were made in locust bean solution at various drug concentrations: 20%, 30%, 40%, 50%, or 60%. Ibuprofen suspensions (100 g) were made in locust bean solution at various drug concentrations: 16%, 22%, 28%, 34%, or 40% w/w. In order to homogenize the suspensions, 5 mg of Lake Allura Red (ibuprofen) and Brilliant Blue (paracetamol) were added, and they were manually agitated for two minutes.

3.3 Modification Of Dual FDM 3D Printer

A MakerBot Replicator Experimental 2X dual FDM 3D printer (MakerBot Industries, Brooklyn, NY, USA) was modified to provide a method for producing new soft dosage forms using e-3DP, as shown in Supplementary Data, Figure S1. Both FDM nozzle heads are present in the 3D printer. A liquid dispenser based on a syringe was used in place of the twin 3D printer's right extruder/head. Acrylonitrile butadiene styrene (ABS) filaments (MakerGear LLC, Beachwood, OH, USA) and an M2 MakerGear FDM 3D printer were used to 3D print the various pieces of the dispenser, which was based on an open-source design (Thingiverse, 2017). The 2.5 mL or 10 mL syringe was fitted to the dispenser head once it was installed. Using the motherboard's built-in housing connectors, a Nema 17 1.5 A 4-lead stepper motor (MakerBot Industries, Brooklyn, NY, USA) was connected [32].

3.4 Design Of Template And Pattern

Using an M2 MakerGear FDM 3D printer, ABSfilaments (MakerGear LLC), and Simplify 3D software (Simplify 3D LLC, Cincinnati, OH, USA), the template design was created by 3D printing. The proof-of-concept that e-3DP may be used to create a complex form and a design that children are familiar with was tested using a Lego-like design. Making use of polylactic acid (PLA) filament (MakerBot), a Lego-like template was created. Autodesk® 3ds Max® Design version 2018 was used to create the pattern for printing the paste with active ingredient (Autodesk Inc., San Rafael, CA, USA). Version 4.1 of the Simplify 3D program (Simplify 3D LLC, Cincinnati, OH, USA) was used to import the STL-formatted design. Simplify 3D software and a modified MakerBot Replicator Experimental 2X were used to print the paste containing the active ingredient in the appropriate pattern during the experiment. The embedded printing pattern's dimensions, which were tailored to fit inside a Lego-like block made of gelatin (40 25 15 mm), were X Y Z = 20 29.52 0.45 mm. The designs' X and Z dimensions were the same for the 25%, 50%, and 75% printing patterns, but the Y axis was 8.1, 15, or 22.5 mm, respectively.

4.Various Techniques Used in 3D Printing

Traditional techniques for creating solid dosage forms involve a lot of processing processes, such as granulation, mixing, and milling. The likelihood of batch failure or inadequate quality may rise with the number of preparation processes. Significantly fewer processes are needed with 3D printing, which means there are less quality control and regulatory concerns [33]. The 3D printing methods used in manufacturing are listed below:

4.1 Binder Deposition

This is the main method for using 3D printing to produce pharmaceuticals. This method uses binder ink, such as polyvinyl alcohol and maltodextrin [34], in tiny droplets that are sprayed on a powder bed at precisely calibrated speed, movement, and size. To create the most basic drug product, the powder bed may contain a combination of API and excipients, whereas the ink used may merely contain binder solution. An alternative to this API can be employed in nanoparticulate suspension or in solution form with binder [35]. This method works best with poorly soluble medications, such as those in classes II and IV of the Biopharmaceutical Classification System (BCS). Folic acid (a BCS class IV medicine) and other excipients were combined to create a nanosuspension by Pardeike et al., which was printed on edible paper to be rolled and sealed in a capsule at the appropriate dosage [36]. The process by which a medicinal product is solidified is comparable to that of wet granulation. This approach has a range of comparable evaluation methodologies and rapid regulatory approval because of these methodology commonalities.

4.2 Material Jetting

Inkjet printing does not always require the use of a powder bed. after ejecting drop after drop, which solidifies simultaneously like stalagmites, it may print free-form structures. Waxes, molten polymers, different types of resins, suspensions and solutions, and multi-component fluids are among the materials utilized in jetting. The entire formulation is designed for jetting, which solidifies quickly. The droplet's ejection path, impact, and surface wetting dictate the formulation's final form [35]. Using thermal inkjet printing, Buanz et al. applied a single layer and several layers of salbutamol sulfate to a potato starch film within ±5% of the theoretical dosage [37]. Cheow et al. synthesized ciprofloxacin (BCS class IV) nanoplexes with dextran sulfate and used inkjet printing to place the resulting nanosuspension on cellulose substrate [38].

4.3 Extrusion

The most popular 3D printing method that has generated a lot of attention in the pharmaceutical industry is extrusion. It operates by use of automated nozzles to extrude melt [39]. It can print on any substrate and is not reliant on a powder bed. For drug printing, this method typically calls for scaffolding to hold the extruded material, including tribasic calcium phosphate [40] and eudragit E, in place. Sadia et al. used the hot-melt extrusion process to create immediate-release tablets of prednisolone, theophylline, and captopril [40]. This process can be used to extrude a wide range of materials, including silicones, semisolids and pastes, molten formulations, and colloidal suspensions. Potential drawbacks of this method include the incompatibility of thermolabile medications such as abatacept [42], adalimumab, and bovin serum al bumin [41], which break down when the melt is created at high temperatures [35].

4.4 Powder Bed Fusion

In both circumstances, a laser is used as a heat source to sinter or bond materials with a high melting point utilizing a low melting point binder [43]. Tayel et al. made a sublingual tablet of the anti-asthmatic medication ketotifen fumarate using a starch/mannitol mixture as filler and a fast-melting blend of polyethylene glycols 400 and 600 [44]. Although more complicated, this method is quick and can be used as a substitute for extrusion [35].

4.5 Photopolymerization (Stereolithography)

Using this method, liquid resins like PLA and PVA [45] are exposed to high-energy light sources like UV radiation in order to trigger a polymerization reaction. Using polyethylene glycol dia crylate as a monomer and diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide as a photo-initiator, Wang et al. created modified release tablets containing paracetamol and 4-amino salicylic acid [46]. The limited availability of photopolymerizable materials is a drawback of this approach. The final product and residual resins following polymerization may have toxicity problems, such as genotoxicity. Its speed of printing and good resolution are its only advantages [35].

4.6 Pen-Pased 3D Printing

This is a modernized hand-held gadget that uses the extrusion process to create desired structures that are typically efficient. Researchers are also thinking about how important it is for the deposition of 3D structures in surgery.

5.Classification Of 3D Printing

5.1 Inkjet Printing Method

This approach involves the precise spraying of a mixture of excipients and active medicinal substances onto the substrate in the form of droplets using two different techniques: continuous and drop on demand. During continuous jet printing, the droplet stream is constantly sprayed onto the substrate or diverted toward the waste line when not in use. In contrast, the drop-on-demand technique sprays the substrate with the necessary number of droplets and closes when not in use. As a result, it is more beneficial and avoids waste that continuous jet printing cannot [47]. With polyvinyl pyrrolidine as an excipient and felodipine as a hypertensive, a controlled release tablet was created using inkjet printing [48].

5.2 Fused Deposition Method

Because of the drawbacks of inkjet printing, Scott Crup, a co-founder of Stratasy Ltd., created the FDM technology, which he patented. In this process, the raw material or polymers are melted, extruded, and deposited layer by layer. After that, the substance solidifies and forms the intended object. The raster thickness, angle, distance between rasters, and rheological parameters can all be changed to change the object's shape and pore size [49]. This process can be used to produce solid dosage forms such fast-dissolving, multi-layered, and zero order release tablets. An extended-release tablet of polyvinyl alcohol (PVA) filaments filled with prednisolone was created using the fused deposition modeling approach [48].

5.3 Direct Inkjet Writing Method

Direct inkjet printing makes it possible to construct intricate 3D-shaped tablets or other objects without the need for costly tools or equipment. This results in structures and shapes of finer sizes. This technique uses a computer-controlled stage where an ink deposition nozzle or pattern-generating device moves to produce a product with precise 3D size and shape. The direct writing technique uses a variety of ink designs, including gels, waxes, diluted fluids, polymer melts, and colloidal suspensions. The following techniques are then used to solidify these inks: solvent and temperature phase shifts, gelation, or liquid evaporation [50].

5.4 Zip Dose Method

MIT created this method in the latter part of the 1980s. This technique uses an aqueous solution to hold the powder layers together. This method is employed to create a tablet that dissolves quickly and has a high dosage [51]. This method involves applying a liquid or binding fluid to a layer of powder that has been placed as a substrate in order to create an interaction between the powder and liquid binder. Until the desired product with the ideal size and shape is produced, this process is repeated multiple times. As a result, a very porous dosage form with high drug loading is formed.

5.5 Thermal Inkjet Printing Method

When current is induced, a resistor in these printers generates heat, which warms the aqueous ink solution and turns it into a vapor that exits a nozzle in the form of droplets. The high temperature needed for this procedure could cause the heat-sensitive material to deteriorate. As a result, its pharmacological uses are diminished [52, 53].

6. Computational Approaches In Pharmaceutical 3D Printing

6.1 General Considerations

The design and production of 3D tablets may take a new turn when computational techniques and 3D printing technology are coupled [54]. This technique enables the creation of structures with intricate microstructures while maintaining precise control. Additionally, computational methods are useful for forecasting the structural characteristics and ensuing intended drug release, which significantly reduces the number of experimental repeats.

6.2 Printability, Drug Loading, and Drug Dissolution

Currently, rheological characterizations are underrepresented in formulations that are 3D printed. A mathematical model that forecasts the printability of fused deposition modeling 3D-printed tablets (printlets) was created in a study using viscosity data [55]. Additionally, a prediction model for passive diffusion drug loading on filaments utilized in FDM 3D printing of oral dosage forms has been established. This pre-screening technique may assess material miscibility and choose the best combination that can offer a high drug loading based on Hansen solubility parameters (HSP) and the idea of HSP distances (Ra) between drug, solvent, and filament [56].

6.3 Design of 3D Structure

In this regard, a computational method for creating porous materials was developed and put into practice [57]. The method was used to polymer filaments like polylactic acid and polyurethane to produce porous products. The geometries were created using a twin nozzle melt deposition technology that is sold commercially. It can be applied to a wide range of potential applications using different additive manufacturing processes, scales, and materials.

6.4 Artificial Intelligence Methods

Neural network-based scaffold design and fabrication have been the subject of numerous investigations since the emergence of artificial intelligence in recent years. The combined effects of layer thickness, lag time, and pressure direction on the porosity and compressive strength of the scaffold were examined in a study using an artificial neural network [58]. In order to assess the structural characteristics of scaffolds and identify the right mechanical behavior for tendon and ligament regeneration, some researchers have employed a neural network approach in addition to pressure settings [59].

6.5 Limitations

Research on the design and fabrication of three-dimensional structures is increasingly employing computer-aided techniques. However, successful modeling, manufacturing, and simulation are hampered by significant constraints and challenges [60]. The various 3D printing techniques lack the accuracy needed to construct structures of this size because the microstructure of the scaf fold is frequently on the micrometer or even nanometer scale.

7. Conclusions

We are now much better able to reproduce the complicated intricacies of the TME thanks to three-dimensional tumor models. The immune compartment's primary function inside the TME has been thoroughly described due to its immunosurveillance and regulatory activities. However, there is still a lack of complete models that accurately include the immune system, even with the widespread use of 3D TME models. The integration of these two compartments in vitro should be the main focus of future research in order to develop models that closely resemble the physiological interactions between immune cells and malignancies. These advancements have the potential to clarify the invisible processes that propel immune trafficking to the tumor mass and the immunosuppressive milieu in TDLNs.

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