Three-Dimensional Hydrogel Bioprinting Technology as a Scaffold of Novel Drug Delivery and Biomedical Devices: A Comprehensive Review

Mohhammad Ramzan[1,*], *Mohammed* Sabir [2], *Sukhbir* Singh [3] and *Abhijit* Debnath [4]

[1]School of pharmaceutical sciences, Lovely Professional University,Phagwara-144411, Punjab, India
[2]School of pharmaceutical sciences, Lovely Professional University, Phagwara-144411, Punjab, India
[3]M M College of Pharmacy, Maharishi Markandeshwar University, Mullana, Haryana-133207, India
[4]Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida- 201306, Uttar Pradesh, India

*Corresponding author : Ramzan.pharma@gmail.com

Abstract. Polymer hydrogel used as computer-aided, non-biological arsenal utilize as a drug delivery vehicle overthe past few years.New advances in three-dimensional (3D) bioprinting technology have created new opportunitiesfor the use of hydrogel polymer-based medication delivery systems. 3D printing can deliver the ideal shapes or changecapabilities under specific circumstances which have a better adaptation to physiological function. The accuracy of 3Dprinting technology was significantly higher than that of conventional production techniques.A model bioink acquireproper physicochemical characteristics (mechanical and rheological) and biological properties important for proper functioning.It acts as additive manufacturing with complex spatial structure in biomedical research. In this review, we outlined the currentdevelopments in 3D printed polymer hydrogels as delivery and other platforms.

1 Introduction

Three-dimensional (3D) bioprinting is step by step addition bioink polymer (hydrogel) in order to build a 3D structure complex widely known as additive manufacturing (AM)[1]. AM is a group of cutting-edge technique initiates the use of computer-aided design (CAD) tools to produce a three-dimensional (3D) model of the intended object [2]. To create the appropriate item of concern accordingly the device ejects the inks as shown in fig.1. The well-known printing techniques are selective laser sintering (SLS), stereolithography (SLA), extrusion, inkjet 3D printing, laser-assisted printing, and selective laser melting (SLM) [3]. The bioprinting technology mainly applicable in various novel drug delivery systems (NDDS) in pharmaceuticals, orthodontics, and medical devices. This cutting-edge innovation is also becoming more prevalent in the clinical trial process. It also expands into other industries like fashion, automation, aircraft, cars, foods, energies, construction, and gastronomy [4]. A high number of implantable devices, prosthetics, tissue scaffold, and other devices for utilization are produced as a result of this ground-breaking invention which significantly improving the results. The main advantages of 3D bioprinting are quicker, more adaptable, more affordable, and customizable manufacturing, customer satisfaction, improved quality assurance. Further it has ability to save time and effort from the time raw ingredients are collected to when the item is finished, rapid prototyping, reuse and recycling, and environmental friendliness, which has caught the attention of the pharma company [5]. The employ of 3D printing is expanding in both medical and non-medical industries due to the numerous advantages of applying and advancing technology.The conventional scaffold fabrication techniques, viz. solvent casting, gas forming, membrane lamination, salt leaching, and fiber binding have limitations including intrinsic inability to mimic the complex microstructure of biological tissues. This current review provides concise information about the fundamental principles underlying 3D printing, including the technologies used, the bioinks that were used during fabrication, uses, difficulties, and future directions.

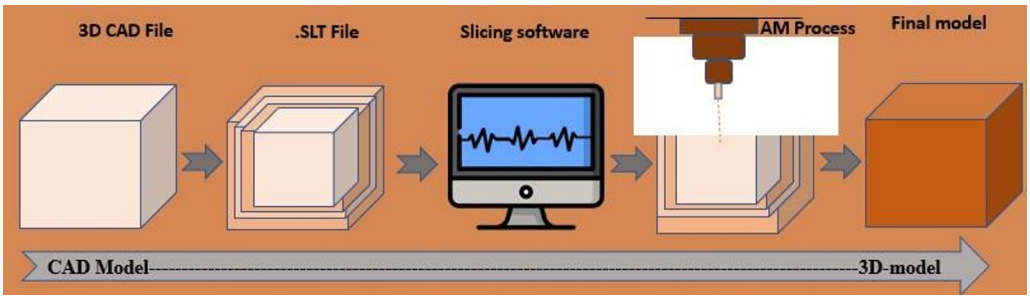

Fig. 1 Building Blockchain of Additive Manufacturing [3]

2 Approaches For 3d Bioprinting (3dbp)

3-D bioprinting is rapid associating substances as a film to give a frame to a 3-dimensional product. This is a unique advantage and advancement innovation that has the dormant to guide organizations into another period of fabrication and the rise of new plans of action [6].The modeling of the object is mostly done using different software, ideally computer-aided designing (CAD).

21 Fused Deposition Modelling (FDM)

Due to some of its business advantages for manufacturing, FDM is a widely utilized form of Rapid Prototyping (PR). The process involves spraying molten thermoplastic polymers successively to create layers. Typically, these materials are heated. Layers are added and fused together as the substances continue to build to the proper size to create the three-dimensional model as seen infig.2 [7]-[12]. The findings suggested that 3D bioprinting might be a feasible option for pharmaceuticals eluting implantation devices due to the ease of the technology [13]. It has been shown to be a successful and affordable technique for creating gastro-retentive delivery systems with the increased regulated release of drugs. [14].

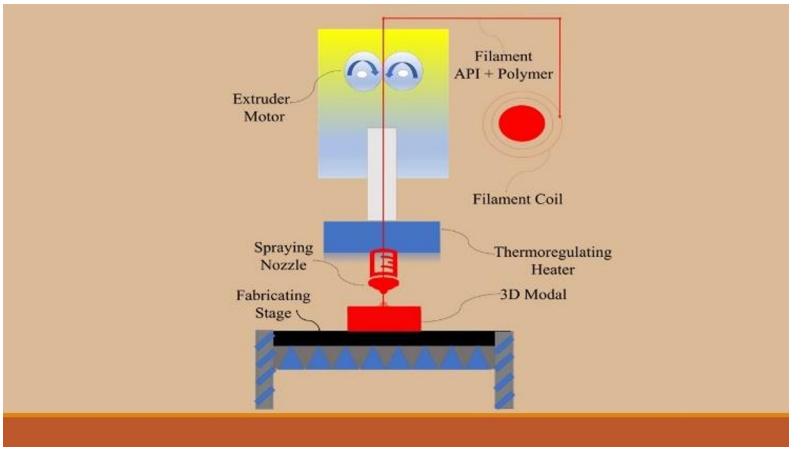

Fig. 2 Diagram illustrating fused deposition modelling (FDM) [12]

211 Stereolithography (SLA)

In this method, a unique polymer called a photopolymer is used, which when exposed to ultraviolet/Infrared light undergoes a chemical process that changes its physical and chemical properties illustrated infig.3. They have significant weaknesses such as resistivity, poor specific stiffness, and fragility. Additionally, their lifetime is limited since they lose physical character with time [15]. 2-Acetoxybenzoic acid and acetaminophen were utilized as experimental drugs in this investigation. The investigators looked at two distinct medication dosages and numerous polymers proportions. The drugs had a sustained release throughout the entire day. Furthermore, the therapeutic loading ability and release kinetics were also

improved because of 3D printing [16].

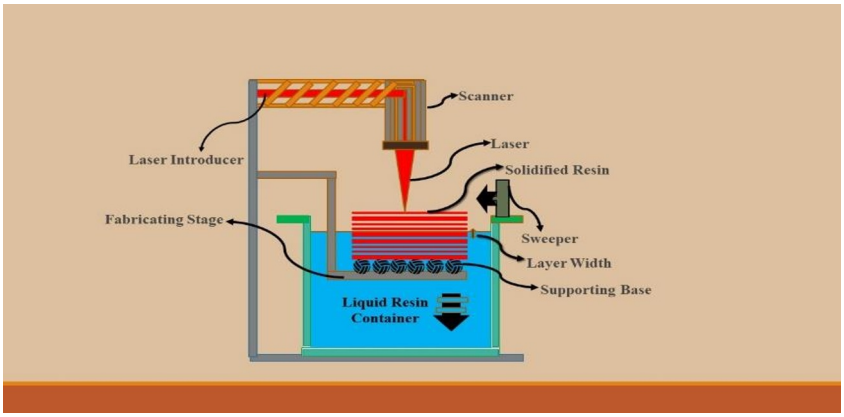

Fig 3 Stereolithography's basic operating concept is represented schematically[15]

212 Selective Laser Sintering (SLS)

In this technique, a light beam is utilized to melt and harden a photopolymerizable polymer mixture that contains a prescription drug. Carbon dioxide lasers, which release an plenty of power conformable with a variety of thermoplastic polymers, are a feature of the commercially practical SLS printers. The final required model is influenced by the manufacturing temperature, laser strength, scanning speed, and layer thickness. At ambient temperature, SLS technology can generate a model object with astronomical resolution. SLS technique and single path with high resolution objects containing Acetaminophen were constructed from a variety of polymers and concluded that this method might be used to tailor treatment performance to each patient's needs, eliminating the need to redesign the formulation mix in favour of a single uniform ink [17]-[20].

213 Selective Laser Melting (SLM)

SLM belongs to the same category as powder bed fusion. This method makes use of a layer of powder particle that have the required mass depicted infig.4. Heating source act as both a way for fusion of granules and a control mechanism for it. The construction material melts when laser light is sticking to a powder bed because it produces heat energy. As the temperature drops, the molten mass solidifies, even more, yielding the desired object. Some of the bed's original structure is still present and supports the subject of interest. Finally, after item fabrication is complete, the unused powder bed is removed[21].

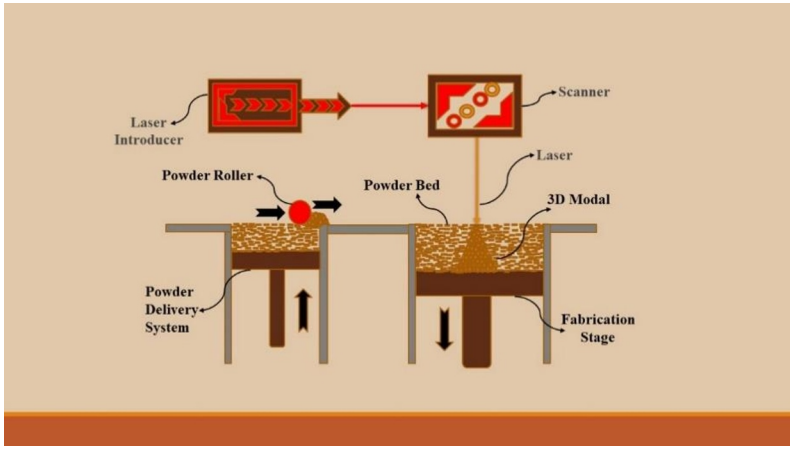

Fig. 4 Typical selective laser sintering [21]

214 Material Extrusion

The most well-known application of this method is fused deposition modelling. In order to do this, various polymer types must deposit and overlap one another. A specialized moving nozzle creates a pre-structured model with materials that are allowed access as it moves over the work area [22]. Extrusion is a method that uses thermoplastic polymers. The chosen polymers are first heated to a particular climate that is higher than their glass transition temperature. The polymer melts when heated, forming a layerobserved in fig. [12].

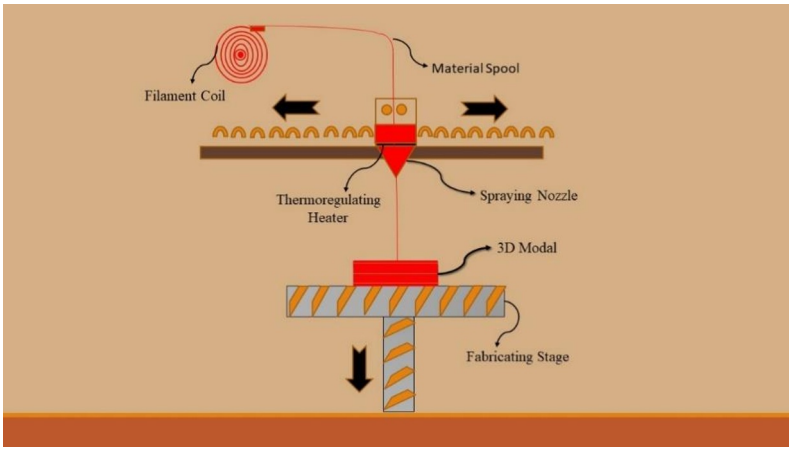

Fig. 5 Material extrusion illustration scheme[12]

Although the extrusion method featured some superior characteristics, such as simplicity and adaptability, it also had some potential drawbacks, such as the need for a cross-linker, the use of heat energy, and a slower printing speed.

215 Inkjet 3D Printing

Inkjet printing enables the delivery of a predetermined number of substances (polymer), commonly referred to as ink, onto a substrate to create a layer. The printing process is initiated by the proper command from computer software, and ink is ejected from the printer's head tank. Inkjet printers are categorized as either drop-on-demand (DOD) mode or continuous mode depending on the ink ejection modes[23]-[24]. In order to start the jet form, the continuous ejection mechanism applies pressure to the ink that is forced to flow constantly out of the printer. In order to divide the stream into exact droplets, pressured jets are used. Then, an actuator can provide pulses to cause the ejection of a single droplet with a predefined amount of ink [25].

22 Bioprinting Materials

The price of the polymer and the technique's applicability used are significant barriers to choosing.Organic polymers are especially relevant to 3D printing because of their similarities in both structure and composition to the tissue environment of the organism. Additionally, they consist of biocompatibility and biodegradability and enhance cellular response. Alginate is a polymer that has been the subject of substantial research on natural forms of chitosan, collagen, and hyaluronic acid. The main benefit of flexibility for synthetic origins is peaceful alterations to satisfy physicochemical properties. Polycarbonate, polyethylene glycol polyglycolic acid, and polylactic acid offer potential benefits as shown in Table 1[26]-[32]. Alginate is the most widely utilized natural polymer because of its capacity to create hydrogels, shear thinning characteristics, and exceptional bioavailability. Alginate hydrogel was used by Duin and his co-workers to print the functioning islets of Langerhans. The loss of the beta cells in the pancreas that produce insulin is the pathogenic aspect of type 1 diabetes [33].

Another substance with a natural origin is hyaluronic acid (HA), which is only present in the connective tissues and cartilages of animals. HA was used in much research. The condition of periodontitis was handled by Subramaniam et al.using a tissue engineering application. Collagenase complexes were created by researchers by complexing the polymers with calcium sulphate. These complexes replaced the regeneration of alveolar bone. To validate the bone augmentation, micro-CT pictures were used. [34].

Collagen is the vital protein framework that has been used in 3D printing. This proteinaceous polymer is used to plan the regeneration of cartilage and stiff connective tissues. Almeida et al. [35] customized camptothecin loaded in chitosan polymeric micelles using a 3D printing technique. The formulation was further insulated from the gastrointestinal tract by employing an enteric coating material to get past the adverse conditions.

According to the study, using nanomedicine and 3D printing in conjunction may have enhanced drug penetration in the intestine, protected the molecule from acidic condition and also avoided its discomfort [35].

Table. 1 Bioprinting substance and utilization in 3d printing [32]

Sr. No.	Bioprinting substance	Subcategory	Polymer name	Uses
1.	**Hydrogels**	Biopolymers	Collagen, Chitosan, Fibrin, Alginate, Agar, Gelatin	Drug delivery (nanomedicine) and Tissue engineering (cartilage, bone)
2.	**Polymers**	Thermoplastics Thermosets	Polylactic acid (PLA) p-hydroxybenzoic acid (PHBA) Polycaprolactone (PCA) Urethane Resin	Drug modelling for cancer therapy Tissue engineering (Trachea, stem cell model)
3.	**Composites**	Matrix Fillers	Carbon fiber Silicon carbide Metal precursors Calcium phosphates	Prostheses, implant

Simultaneously numerous synthetic polymers are also acknowledged for usage as building blocks for 3D printing. Zhang et al. [36] presented a 3D model that uses melatonin-filled magnesium polycaprolactone as a powerful anticancer factor . The method was proposed as a means of treating bone cancer, or osteosarcoma. The research that was shown looked at how a drug model might help in demonstrating the antineoplastic accomplish. This concept created a brand-new innovative method of treating osteosarcoma [36]. A thermoplastic substance made from corn starch called polylactic acid (PLA) is completely biodegradable. Recent research suggested that the mechanical stability and biocompatibility of the abovementioned polymer support the assertions made in the process of model forming.

Asmaria et al. [37] was studied to reduce the risk of inner part of body dysfunction during surgery.. It was done to generate and validate the protocol modelling created with PLA. While the quantitative method inspect the damaged body part mock-up, the qualitative validation technique revealed an improvement in the modelling ability to visualize the patient's current situation. The outcome said that the created gallbladder model reflected similar biologically derived circumstances. [37].

A copolymer of polyglycolic acid and polylactic acid is known as poly (lactic-co-glycolic acid) (PGA). Paclitaxel and rapamycin were used as model pharmaceuticals in a study by Serris et al. [38] to make them use various grades of PLGA either together or with lidocaine alone. The extrusion-based method was the 3D printing technique used. The PLGA-PEG-PLGA hydrogel discs were used to express increased release kinetics in comparison to PLGA polymer when the release profile of pharmaceuticals made using PLGA was compared to those discs. The interactions between the medication and polymer matrix were reproduced by the molecular models. Because of the profile modification, the hydrogel discs offered better release patterns [38].

A hydrophilic polymer called polyethylene glycol (PEG) is frequently used in investigations on the engineering of tissues. Hot-melt extrusion was used to create biodegradable mats by Singh and Jonnalagadda [39]. The physicochemical and biological properties were enhanced by the polymer combination in a synergistic manner According to the reports, when neomycin was constructed utilizing 3D printing, the threshold was increased. Additionally, neomycin loaded PLLA has been used in tissue engineering and as a dermal mat, with advantage of PEG polymer enhancing its mechanical capability [39].

Numerous commercially available 3D printers depending on the various fabrication materials accessible. Choosing a 3D printer can sometimes be influenced by certain desirable characteristics, as shown in fig. 6

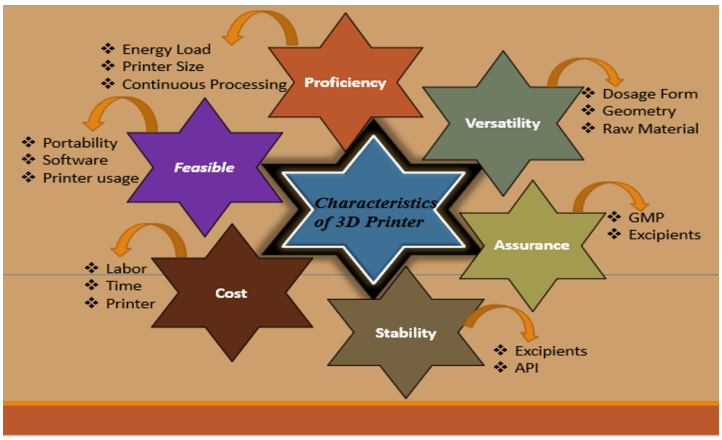

Fig. 6 Essential qualities for a 3D printer [39]

23 Applications Of 3d Bioprinting

There are various industrial uses for 3D bioprinting, and the ones that belong to the pharmaceutical industry are covered below in fig.7 [40].

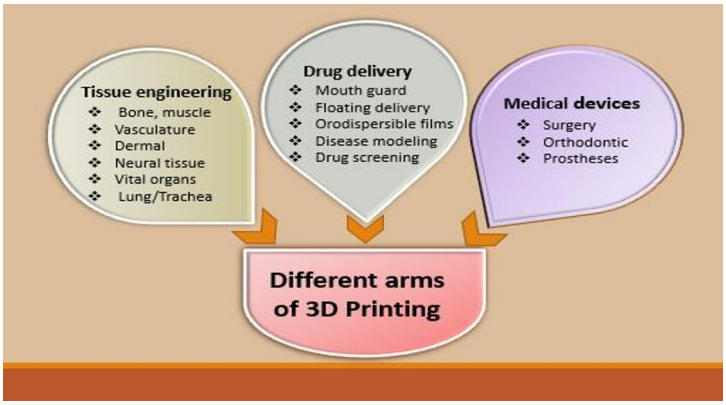

Fig. 7 Pharmaceutical uses for 3D printing [40]

231 Tissue Engineering

The issue of organ dysfunction must be tackled on a global scale. Even if organ transplantation is a great strategy to avoid the rejection of a particular body part, However there is a lot more to be done. The lack of organs and the ongoing need for immunosuppressive treatments are driving the demand for sophisticated technologies. As a result, employing bio-inks as building blocks, additive manufacturing has established itself in a number of fabricating organ, including hepatic, renal, and cardiac [40] Various bio-inks are appropriate for various types of tissue engineering. The choice of the right polymer is an important first step, but it's also important to take into account the properties of the bio-inks. For the researcher to choose the relevant components for the construction, they should possess a solid understanding [41]. These flexible tissue/organ models have great promise for high-throughput screening (HTS), drug design, in vitro disease modelling, and bringing attention to novel platforms like tissue/organ-on-chip. The printer is commanded to print the created computer models using polymer materials. Scaffolds are built based on the agreed requirements, depicted in Fig.8.

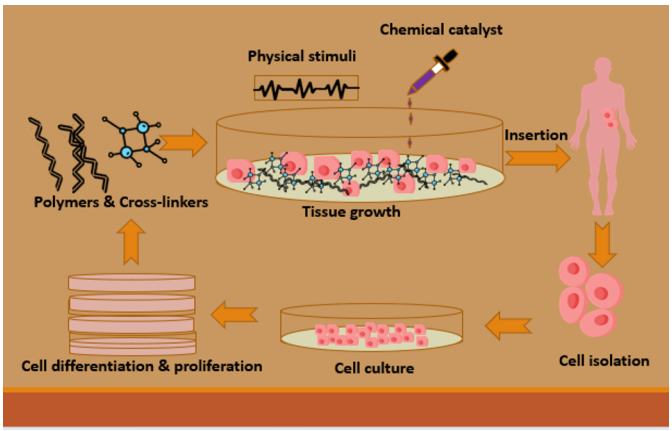

Fig. 8 Explanatory diagram of tissue engineering by a 3D printing technique [41]

2311 Bone Tissue

The internal structure of the bone is composed of a dense crosslinked matrix and is a hard connective tissue. Enhancing the capacity for regeneration and simulating the typical conditions of human bone are now the two main goals of bone regeneration [42]. In contrast, a lot of researchers use hydrogel-based models because they have easily adjustable properties. Hydrogel formulation was the main topic of attention for Bai et al. [43] when treating bone regeneration. When using hydroxyapatite or metal implants as the building materials, the proper therapeutic effect was not argued. Thus, the researchers asserted that hydrogels have a special ability. Other tissue engineering techniques and additional applications of hydrogels in bone regeneration were expressed [43].

2312 Cartilage Regeneration

A lot of the body's smaller organs are supported by cartilage. Nguyen et al. [45] used two bio-ink combinations—Nano fibrillated cellulose (NFC) with alginate (A) and NFC with hyaluronic acid—to create a 3D model of cartilage (HA). Modelling was done using induced pluripotent stem cells (iPSCs) obtained from humans. Researchers found that alginate copolymer displayed the best pluripotency activity and that adding more cells increased the density in the 3D modelling of cartilage creation [45].

Collagen was used by Isaeva et al. [46] to create a hydrogel formulation for a cartilage scaffold model. Due to its great biocompatibility, cartilage was incorporated in large amounts. Scholars investigated the in vitro and in vivo properties of collagen polymer to determine its applicability. In contrast to the latter study, which showed modest inflammation followed by the development of connective tissues and macrophages around the nucleus, the former demonstrated that cells lacked the ability to survive in specific contexts. They concluded that there were not enough chondrocytes present to start the formation of cartilage tissue [46].

2313 Skeletal Muscle Regeneration

The skeletal muscle structure is made up of myofibrils, which are its functional unit. This ordered layered structure's engineering was made possible through 3D printing. In this experiment, the tendon-muscle model was built using four different polymers. he rigidity and elongation of tendons are encouraged by the combination of polycaprolactone with a comparable hydrogel composition, which was used in the opposite study. The created model met the goal made possible by tissue engineering in terms of certain mechanical and biological features [47].

Muscle stimulation models, that was a significant barrier in many disorders like asthma and intestinal disease, was examined by Dickman et al. [48]. They showed how to get around this problem by using a 3D muscle model. Collagen polymer was the bio-ink material. A model that mimicked the respiratory system and the muscles involved in it was created. Drugs like histamine and salbutamol, respectively, were used to constrict and relax the created 3D model. Muscle contraction was seen throughout the course of a day, and as the number of days increased, the degree of the contraction also increased. In mature muscles that were agonist dependent, this contraction mechanism was very specialized. Fibrosis was encouraged to develop and maintain long-term changes in muscle behavior. The created model thus showed an encouraging similarity to biological muscle and worked as a platform for drug delivery to the muscle [48]-[50].

2314 Dermal Regeneration

The majority of the human body's surface is covered by the skin, which is made up of the three layers. The skin typically protects against mechanical trauma and maintains temperature homeostasis [51]. Trontium silicate microstructures were created and incorporated into the bio-ink polymer because the main goal of the research was to stimulate angiogenesis. The vascularized tissue that displayed angiogenic activity both in vitro and in vivo was modelled using the cell writing 3D printing approach. With the help of this research, vascularized skin with a quicker recovery rate could be created through tissue engineering [52].

2315 Neural Tissue Regeneration

The nervous system is not complete without neuronal tissue. Between various tissues and organs, these structures transmit information via electrical impulses. In this period, several neurodegenerative diseases are on the rise, which restricts the faulty neurons' ability to regenerate on their own. The most recent innovations in this field were handled by 3D printing technology. Peripheral nerve injury was treated by Liu et al. [53] by integrating a variety of 3D printing methods. In this study, the adjustable nerve tissue that has similar biological properties was designed and created. The results easily and potentiated the modelling techniques demonstrated the necessary adjustable features and resembled a typical human neuron [53]. To rebuild the peripheral nerve cell, Ye et al. [54] employed gelatin methacrylate in hydrogel form, a biodegradable polymer. This fabrication model addressed the huge gap in nerve injury using digital light processing.

2316 Spinal Cord Regeneration

The spinal cord serves as a communication channel between the brain and various other body organs. As a result, both neurons act as the appropriate carriers of the several stimuli. Injury to the spinal cord is a danger alert because the spinal cord contains a variety of cell types that are distributed widely in space, blocking most information from reaching the brain cells. Due to this, many spinal cord disorders had poor diagnosis capabilities and repairability. The development of tissue engineering through 3D printing effectively and repeatedly solved the issue. The researchers presented a framework that comprised collagen or chitosan polymers with neurotropic substances extracted from the brain.[55]. In the experimental animals, regeneration, scar reduction, and cavity creation were all seen to improve locomotor function. They concluded that this modelling would be useful for creating and expanding the spine network [55].

2317 Cardiac Tissue Regeneration

Circulatory and cardiac abnormalities can cause a wide range of diseases, many of which are fatal. The shortage of donors with minimal biological constraints made transplantation problematic. To solve this, a significant advancement in the ability to create specific tissues with the appropriate biological material inside of them through the use of 3D printing has been made. This has improved the transplantation's ability to meet requirements while also being compatible with the body's natural systems [56]. While the process of 3D printing has the possibility to be used in heart tissue regrowth, but the technology has limitations when it comes to precisely simulating biological action. Organ rejection was significantly reduced since the approach uses patient-specific cells. Bioprinting technology has already been employed extensively in several research projects for the treatment of congenital cardiac disease, malignancies, and other cardiac issues.[57–59]. Collagen was used by Lee and his collaborators [60], who created heart cells that closely resembled the original heart process. Since the collagen scaffold model made it impossible to functionalize biological tissue.The porous design of the model gave it stiffness and micro vascularization for the manufacturing process. In the hydrogel scaffold, tissue was created using cardiomyocytes. The suggested model described directed action potential transmission and synchronized contractions as possible approaches for modelling cardiac tissues [60] 3D printing was used by Zhang et al. [61] to create the myocardium. The model that produced the scaffold structure was made easier by the usage of bio-inks. The microfibre layers that made up the model were imprinted with endothelial cells. Additionally, endothelial cells were seeded inside the framework with cardiomyocytes that were derived from pluripotent stem cells. In order to complete the overall organ-on-chip model, researchers next placed the organoids inside a specially built microfluidic perfusion bioreactor. This cutting-edge model successfully replicated human cardiomyocytes and opened the door to regenerative medicine [61].

2318 Liver Regeneration

The most of intrinsic and extrinsic compounds that enter the body are metabolized by the liver, which is the most significant interior part of the human body. Organogenesis, pharmacological screening, and disease modelling are all accomplished via 3D printing. Liver scaffolding and its use in the management of last-level hepatic dysfunction were studied by Yang et al. [62] The utilization of specific biomaterial and 3D printing technologies allowed for the creation of liver cells. The cells were injected into animals lacking the Fumarylacetoacetate hydrolase gene after one week of regulated laboratory cell growth (mice). The results showed that several hepatic processes, including albumin production, glycogen secretion, and

drug metabolism, had better characteristics. The created model may therefore switch between organ transplantation from donor bodies [62] Using improved digital light technology, Mao et al. [63] produced hepatic microtissues that help cure final-stage liver disease. To enhance liver health, synthetic tissue was made to a specific specification. The liver-specific biomaterials were used in the fabrication process. Methacrylate gelatin and the extracellular matrix were combined to create these mixtures. In particular circumstances, the human-made liver cell was inserted into the general framework of the model. Mechanical strength, swelling property, and polymer compatibility were among the factors evaluated. Liver cell development was shown in the virtual three-dimensional model by a rise in albumin secretion and urea outflow. The model created served the purpose of being biologically comparable to the transplant's biological source [63].

2319 Islet Regeneration

An autoimmune disease known as type 1 diabetes triggers the pancreas to generate little or no insulin. Besides the lack of blood capillaries, the immune system attacks the pancreatic beta cells that secrete insulin which makes modelling difficult. The most common treatment for diabetes is insulin supplementation, while islet cell transplanting gave lifelong benefits. The development of 3D printing with hydrogel polymeric material was planned and perfected to meet the patient's expectations. Alginate and hydrogels made of gelatin were used by Lui and his coworkers [64] to construct a scaffold. The multilayer islets were altered using the coaxial printer. Characterization of the islet's cells revealed that they remained healthy across the modelling procedure. Further research is necessary to determine whether the scaffold structure's cells are compatible with transplantation because they resembled the growth of typical human cells [64].

23110 Lung Regeneration

Lung transplantation raises significant safety concerns due to the scarcity of organ donors and immunological refusal. Because of little number limitation, the transplanting was found to be impractical and required numerous restrictions. Lung transplantation raises significant safety concerns due to the scarcity of organ donors and immunological refusal. The transplanting was found to be impractical and required numerous restrictions. The challenge of a lack of lung transplants can be resolved by lung cells engineering. The use of 3D printing in conjunction with healthy cells is a potential method for the progress of lung cells engineering.
[65]. Huang et al. created nanofibers using 3D printing and special biomaterial. Silk fibroin and H2O2 were cross-linked, and oxidized bacterial cellulose was added to raise the thickness and improve the structural characteristics of the scaffold model. In order to strengthen the hardness and endurance of the model, the hydrogel was laminated more than ten times. he lung epithelial cells' alignment and continued growth were both aided by the nanofibers after they had been in the culture for seven days. The study suggests that nanofibers made from polymers could be a possible lung tissue engineering method [66]-[69].

232 Medical Devices

Our progress toward innovation is greatly influenced by medical equipment. They look for work in surgery, orthodontics, and prosthetics. They identify opportunities for people with unique needs. As a result, 3d printing opens up more opportunities for producing customized medical devices. To encourage people to adopt 3D printing, the Food and Drug Administration (FDA) authorized market access for some medical devices made with it. There are a few devices listed in Table 2 [70].

Table. 2 FDA approved 3D bioprinted medical devices [70]

Medical device	Medical application	Description
Unite3D bridge fixation system	Foot and ankle joint	It offers a reliable and deep-rooted remedy for fractured and osteotomy treatment, as well as joint arthrodesis, in the midfoot and hindfoot.
Lateral spine truss system	Spine	It serves as a support structure for bone formation and cell adhesion. Orthopedics growth is enabled via the open architecture. The bi-convex form of the implants places it closest to the adjacent bone.
HAWKEYE vertebral body replacement system	Spine	To reconstruct a cervical or thoracolumbar spine that has collapsed, been wounded, or become weak due to a tumor or trauma
Cellular titanium cervical	Spine	Injected with an anterior method to lengthen the

cage		intervertebral discs and promote the body to integrate during the cervical spine
ELEOS limb salvage system	Oncology	Operations requiring radical excision and substitution of the distal femur, proximal femur, shinbone, or complete femur, particularly in advanced stages of cancer.
Virto B-titanium hearing aids	Hearing aid	Individualized auditory devices that are very effective and automatically adapt to the environment
Teeth aligners (candid)	Orthodontics	Individually designed dental braces

2321 Orthodontics

The manufacture of orthodontist items based on the reference frame of the occlusal plane within the dental structures is made possible by three-dimensional diagnostic imaging, which allows for more precise diagnosis. Orthodontics and dentistry are undergoing a revolutionary change with to advancements in diagnostic imaging, 3D printing, and customizing equipment [71]. This technique thereby made it possible to create an orthodontic model from a range of materials, improved comfort, and faster recovery times. The viability of using 3D printing to create orthodontic braces was assessed by Redaelli et al. [72]. It was decided to use polyethylene terephthalate glycol-modified polymer for the fabrication procedure. The thermoformed polymers polyethylene and polypropylene were compared to the printed model in this manner. Toughness, price, mechanical properties, and adaptability of the prosthesis on healthy volunteers were the factors that were assessed for the investigationFindings showed that the suggested strategy fulfills the patient's current demand. The framework exhibited perfect morphological characteristics, and it was found that more adherence enhanced mechanical strength. This configurable model can also add medicinal medications to show pharmacological effects[72]. The orthodontic power arm model was produced by Thurzo et al. [73] using 3D printing. The model was made with the help of biocompatible materials. For biological purposes, the permeable alloy kind of titanium was perfect. The researchers employed finite element modelling to increase the power arm's resilience. The analyzed design may then be built when the model was linked to the dental shape. As a result of the production, the tensile arm strength increased by 7%, and the stress decreased by 82 %, highlighting the improvements over the conventional method [73]

2322 Prothesis

With the aid of 3D-printable devices, physicians and scientists may create simple operating prostheses, changing the nature of medicine. Because such devices are expensive and mostly cause user discomfort, the development of adaptable and additional convenience for persons is a problem that is encountered internationally. New technologies like 3D printing, that encourages the development of customized prostheses, can tremendously help prosthetists [74].

Zuniga [75]suggested a remedy to this frustrating issue to lower the threat of bacterial infection after amputation. In this work, a 3D printing material called Plactive with antibacterial capabilities was used. The intention was to highlight the usage of antibacterial elements in the creation of this model as well as to characterize it for its therapeutic characteristics. Two persons participated in the finger amputation test, with the severed portion being replaced with a 3D-printed prosthetic Patient convenience and satisfaction with the modelled prosthesis are improved by this technology [76].

A desktop 3D printer was used in a study by Honigmann et al. [76] to build scaphoid prostheses. Using the fuse filament process, the model was assembled. Polyetheretherketone (PEEK), a biopolymer used in construction, was selected as the building component. PEEK made it possible to minimize metal-metal debris while simultaneously lowering the danger of particle-induced implant loosening. This 3D model helped in class II biomedical assembly. This model received a lot of interest because it was a customized item. Medical and industrial biopolymers were compared one to the other. In conclusion, this prosthetics model showed enhanced integration and productive PEEK manufacture [76]. 3D model prostheses were contrasted with conventional prostheses by Xiao et al. [77]. Physical vapor deposition and stereolithography were both used in the model development. Polymers with a titanium coating were used in the fabrication, highlighting its advantages in the pharmaceutical and biological fields. We examined the mandibular model's crushing and compression strengths. The result was that the titanium model could withstand compressive stress of larger than 20% by also providing enhanced strength properties. According to an investigation, Future design, mechanical, and biological features are expected to benefit from finite element analysis [77]

2323 Surgery

The procedure of having surgery is extremely difficult and frequently has several serious consequences. The risk of perioperative and postoperative conditions was decreased by the use of sophisticated technology. The main goal is to shorten the operation's duration and associated risk simultaneously enhancing adherence and effectiveness. As a result, 3D printing creates a foundation for better surgical results in challenging circumstances. The introduction of this technique

aroused the interest of scholars and surgeons, leading to its applications in different sectors [78]. In the right hemi-colon cancer surgery, The mesenteric arteries were created via 3D printing by Chen et al. [79]. In the randomly chosen clinical investigation, three separate groups—3D printing, 3D image processing, and control—were employed. The primary variables were the length of the procedure, the amount of blood that was lost during it, and the number of lymph nodes present; however, secondary variables included postoperative complications, the length of the recovery process, and patient acceptance. The number of lymphatic nodes increased, and 3D printing technology significantly cut down on overall operating time. Additionally, the postoperative expectancy was enhanced, and the price of the treatment was significantly decreased. Investigators concluded that innovation improves accessibility to surgery as well as further lowers its cost and associated difficulties [79].

According to a different study, 3D printing can help sarcoma patients function better. Surgery was the basis of treatment, although it was challenging to handle. By representing the body's 3D anatomical structure, the technology enabled the development of 3D-modelled prostheses, that assisted in overcoming the constraints of conventional treatment. The electron beam melting approach was applied to replicate the bone make-up for the users who had primary bone sarcoma. In 23 individuals at random, the titanium metal was implanted. After a two-year follow-up, all participants were still surviving. Even while the technique is pricey and requires extensive preoperative planning, continued advancements will make it handier and may even lead to robotic surgery in upcoming times. The results showed that implantation in pelvic surgery had increased resection accuracy [80].

233 Drug Delivery

The administration of a medicinal substance to have a therapeutic effect has been better understood as a result of several studies. To achieve the anticipated medication administration, additional material discoveries have led to a wide range of innovative instruments, concepts, and tactics. In comparison to traditional methods, 3D printing offers substantial advantages in producing enormously complicated and customized models, making it more efficient in terms of both time and money [81]. Custom medications may be made in-house and on-demand because of 3D printing's adaptability. HME and FDM 3D printing are themost important methods for creating an innovative medication distribution system [82]-[83]. Most research used 3D printing for customized medication to create pellets [84], pills [85], tablets [86], capsules [87], and buccal thin films [88]. The solid dose formulation is primarily where this technology's benefits are visible.

Liang et al. [89] presented a portable, personalised mouthguard as an oral administration device in the first-in-human trial. 3D printing was utilized to create the product's adjustable structure and varying release profile (fused deposition process). As a sample medication and thermoplastic polymers, respectively, clobetasol propionate and polyvinyl alcohol (polylactic acid and polyvinyl alcohol) were used. These two polymers were used by scientists to produce three different types of mouthguards, each with a unique structure and material makeup. The simulated medication device system's extra versatility was tested on human test subjects. The model medication was steadily distributed over two weeks as per the in vitro dissolution experiment. This 3D printing manufacturing technique provides considerable time and performance advantages over currently used processes for making normal mouthguards, enabling the creation of such products for the urgent application. The immense opportunity of 3D printing to develop and use new therapeutic delivery methods for individualized therapy is exploding [89].

In an innovative investigation, theophylline was loaded as the model drug by Dumpa et al. [90] to construct the gastro-retentive floating pulsatile drug delivery system. Under this study, hot melt extrusion and a fused deposition modelling strategy were coupled, then direct compression was applied. The created device's purpose was to enhance asthmatic treatment he device underwent testing for thermal characteristics, stiffness evaluation, physical characteristics, bouncing. The lag time may be modified based on the requirements (30 min–6 h). Theophylline pulsatile release and medications that required a lengthy stay in the stomach might both be delivered using the floating pulsatile device that was recommended. With this approach, unwanted adverse effects were reduced, and patient satisfaction was elevated. In vivo experiments may be improved soon [90]

Oro-dispersible films (ODF) were customized by Yan et al. to improve patient acceptability of drug administration. Levocetirizine hydrochloride and hydroxypropyl methylcellulose were selected as the medication and additives, respectively. Additionally, plasticizers and fillers were employed to improve endurance and help in the breakdown. A semi-solid extrusive 3D printing technique was used to create this changeable film. The dosing forms specified various dose strengths. Along with being tested for drug content, dose uniformity, tensile characteristics, contact angle, and drug release estimation, the produced formulation also underwent several other tests. D printing seemed to be a practical method for creating customized ODFs. Because of their versatility and wetness characteristics, 3D-printed ODFs have the potential to be employed as an instant medicine delivery system. A drug dissolving test revealed that all ODFs released all of their medication components perfectly and quickly in under two minutes in vitro release of the drug. The wide range of applications of 3D printing in the production of uniform ODFs showed other prospects in hospital for a short-term

individualized drug delivery system [91]-[94].

2331 Drug Screening And Drug Modelling

Medication development involves significant funding and takes years, from the small scale to commercialization. The final product that is provided to the consumer is put under pressure as a result. Although significant initiatives have been conducted to minimize the time required for a pharmaceutical to hit the market while also improving therapeutic potential. In addition to improving the product model, 3D printing, and high-throughput processes help cut down on production costs, time, and regulatory requirements (92). 3D bio-printed cellular models for high-throughput drug screening have been introduced by bioprinting companies (93, 94). By offering an in vitro tissue model, such approach offers a tool for evaluating biomolecules at an early stage of development. With the use of this innovation, construction time and costs may be reduced by avoiding trial and error mistakes. Numerous preceding books provided depth understanding with a comprehensive description [95]-[96]. Traditional 2D cell culturing research and animal models were employed to clarify the cellular and molecular mechanisms underlying a range of human disorders, however, they had a slew of drawbacks. [97]-[98].

2332 Wound Healing

Wound dressing treatment comprises lowering the infection level and promoting the healing of wounds. This traditional method may cause other complex reactions. Because of this, 3D printing offers a patient-specific antibacterial effect in addition to other advantages including the ability to vary the dimensional properties of dressings, simple drug administration, usage of a variety of materials, and oxygen penetration because to porous structure [99].

Ilhan et al. [100], in the field of wound dressing, overcame a big challenge. A serious medical risk that may be controlled by 3D printing is acute injuries. Under this research, Satureja cuneifolia plant extract (SC) was utilized as a sample and it was discovered to be successful in healing diabetic ulcers. echanical, thermal, swelling, and degrading behavior investigations were done in addition to the dissolution studies. A few different kinds of dermal bacterium were found to have no microbiological activity. The outcomes were comparable to those of the wound healing experiment using the antibiotic ampicillin as a control. This proved that model was a suitable for 3D-printed wound mitigate [100]

24 Categorization And Approaches Of Hydrogels

Hydrogels are undoubtedly the most suitable substance for tissue engineering utilization. Before briefly outlining the many classifications of hydrogels, let's have a look at how it's used in a variety of tissue engineering implementation. This classification is crucial because it influences the parameters for formulating a method and the viability of using hydrogels based on their inherent mechanical and chemical properties.

According to their source (natural, synthetic, and hybrid), hydrogels are categorized. Proteins (such as collagen, and elastin), polysaccharides like alginate, and chitosan,) are used to create natural hydrogels. Synthetic hydrogels display more adaptable and simple-to-control physical and chemical properties than natural alternatives [101]. polycaprolactone (PCL), and all their derivatives are examples of synthetic hydrogels.

Hybrid hydrogels combine natural and artificial materials to create blended framework with favourable synthetic and natural properties [93]. According on their structural stability, hydrogels can either be long-lasting or biodegradable. While biodegradable hydrogels are made of natural polymers, are typically nontoxic, and exhibit fewer side effects than synthetic alternatives, stable hydrogels are typically synthetic and are physically harder than natively generated hydrogels. [102] Finally, the responsiveness of hydrogels to external stimuli can be used to further classify them.[103]-[104]. The physical and chemical characteristics of stimulus-responsive hydrogels, sometimes known as "smart hydrogels," [105]-[106]may be altered by reversibly changing their shape and volume [107] when exposed to changes in the pH level, [108]-[109] temperature, and other parameter. Table 3 presents a summary of the various polymeric hydrogel materials, cell types utilized, target tissue applications, and associated production techniques. [110]

Table. 3 Novel developed polymer-based hydrogels for tissue engineering uses[110]

Polymer Type	Cell Used	Specific Tissues Utilization	Synthesis Method	Reference

Alginate/bacterial cellulose nanocrystals-chitosan–gelatin	MC3T3-E1 cells	Bone	LBL	Yan et al. (42)
Gelatin	Human umbilical endothelial cells	Vascular	Microfluidics	He et al. (43)
Poly (ethylene glycol)-poly(N-isopropylacrylamide) (PEG-PNIPAAm)-poly(ε-aprolactone)	Human mesenchymal stem cells	Cartilage	Electrospinning	Brunelle et al. (44)
Peptide	Fibroblasts, dental pulp stem cells	Dental pulp	Self-assembly	Nguyen et al. (45)
Chitosan/PVA	Human mesenchymal stem cells	Bone	3D printing (extrusion)	Ergul et al. (46)

25 Case Studies

1. The purpose of this research is to identify Malaysia's major drivers and emerging trends in bioprinting. Under this analysis, both quantitative and qualitative methods were applied. The drivers and the situation for 3d printing in Malaysia were developed using a STEEPV (society, technical, economics, environmental, politics, and values) approach. An overall of 384 questionnaires had already been sent out to the pharmaceutical companies, and 37.26 percent of the total were returned. In the research's second stage, impact uncertainty was implemented. The two major factors identified have been the presence of financing for 3D bioprinting acceptance and the emphasis placed on 3d printing by doctors and scientists. At the conclusion of this research, four possibilities were put up, including success, gradual acceptance of 3D bioprinting, a lack of finance, and the destruction of technologies [111].
2. In this investigation, a new technique for creating gastrointestinal floating tablets (GRFT) combining hot-melt extrusion (HME) and fused deposition 3D printing is presented. HME was used to create theophylline-containing strands in a framework of hydroxypropyl cellulose. To confirm their drug concentration, float tendency, dissolving, and physicochemical features, 3DP tablets with various filling percent and shell widths were produced and tested. The results of the dissolving trials showed a connection between the 3DP tablet's drug release pattern and infill percentage/shell thickness. The created GRFTs were all capable of floating for 10 hours and showed 0 order release kinetics. The Peppas-Sahlin model suggests that the release of drugs is caused by a process that combines Fickian diffusion with swelling. The consistency of drug crystallization was observed across the procedure. When combined with HME, 3DP might be a powerful design to create controlled-release GRFTs, offering the benefits of ease and adaptability over more traditional approaches[14].
3. Individualized medication is now possible because to the development of three-dimensional printing, which has opened fascinating new options for the creation of pharmaceutical formulations. This work used stereolithography (SLA) to create oral dosage formulations of 2 therapeutic concentrations, 2.50 and 5.00 percent, utilizing a new photopolymerizable resin formulation based on a monomer combination that has not yet been published in the journals Acetaminophen and acetylsalicylic acid have been chosen as model drugs. Diphenyl (2,4,6-trimethyl benzoyl) phosphine oxide (Irgacure TPO) was used as the photoinitiator to create the dosage forms while varying the amounts of poly (ethylene glycol) diacrylate (PEGDA) and poly(caprolactone) triol. Creating 28 doses in one print process was feasible, and the printable dose forms' drug release characteristics were assessed. It was proven that these medications had a prolonged release throughout a 24-hour period. Additionally, the physical characteristics were examined, demonstrating that SLA allows for reliable printing of doses with some statistically relevant deviations from the desired dimensions limit, suggesting a potential area for technology development in the future. According to the research reported in this article, SLA can create tiny, customized batches that can be customized to a sufferer's particular requirements or enable the local manufacturing of pharmaceutical formulations[16].

4. A significant change has been made toward the progress of current medications because of the emergence of 3D printing in drug companies, comprising therapeutic items with various configurations and complicated geometry. The development of multi-drug packed formulations, which are now difficult to make using traditional pharmaceutical methods, has been investigated using 3D printing technology. This will help patients take their medications more consistently and minimize pill burden. In this work, a multi-layer 3D printed oral formulation (polyprintlet) containing four antihypertensive medicines, particularly irbesartan, atenolol, hydrochlorothiazide, and amlodipine, was created using stereolithography (SLA), a vat polymerization process. For the initial time, we disclose an unanticipated chemical interaction between a photopolymer and medication, despite being effective in its manufacturing. Both nuclear magnetic resonance (NMR) spectroscopy and Fourier transform infrared (FTIR) spectroscopy supported the notion that the main amine group of amlodipine and the diacrylate group of the photoreactive monomer performed a Michael addition process. The work presented here emphasizes the significance of selecting photosensitive resins with caution to create drug-packed oral drug formulations using the SLA 3D printing technique[18].
5. In drug companies, three-dimensional printing (3DP) is picking up steam and providing cutting-edge possibilities to produce medications. We just exposed the pharma sciences to a unique, greater resolution, single-step printing process called selective laser sintering (SLS). The purpose of this research was to develop print lets (three-dimensional printed tablets) with cylindrical, gyroid lattice, and bi-layer architectures that could have their release properties customized using SLS 3DP. Using SLS 3DP, constructions containing acetaminophen were made from four distinct pharma-grade polymers, including polyethylene oxide, Eudragit (L100-55 and RL), and ethyl cellulose. All 4 polymers' release of drugs might be controlled by the new gyroid lattice. This study is the first to show that it is possible to customize the drug release characteristics of multiple polymers quickly and affordably utilizing SLS, without having to change the formulation's content. It is consequently feasible to alter medication distribution by using these constructions, which in turn could make it feasible to adapt drug efficacy to the individual by only modifying the 3D architecture[19].
6. This study used the photo-sensitive medicine nifedipine (NFD) to examine the effects of experimental condition and synthesis components on drug loss, crystalline nature, and quality characteristics (symmetries, toughness, breakdown time) of 3D printed dosage forms made utilizing selective laser sintering (SLS). Among the laser origin utilized in selective laser sintering (SLS) procedures is a visual laser with a wavelength of about 455 nm, and medications like nifedipine can accumulate light at variable intensity along these wavelengths. This concept could result in chemical degradation and solid-state conversion, which was examined for nifedipine in preparations processed under various SLS circumstances using various proportions of the vinyl pyrrolidone-vinyl acetate copolymer (Kollidon VA 64) and potassium aluminum silicate-based pearlescent pigment (Candurin). Following an initial assessment, Candurin, surface temperature (ST), and laser speeds (LS) were found to be the independent components. More to comprehend the correlation patterns and measure the influence on deterioration (%), crystalline nature, and quality characteristics (symmetries, toughness, breakdown period), a 17-run, random, Box-Behnken design was created utilizing the selected independent parameters. The experiment design and mathematical analyses demonstrate that ST had a significant positive association with drug loss, nanocrystalline transformation, and toughness of the 3D-printed pharmaceutical formulations, so although LS and Candurin (wt.%) had a significant negative relationship on drug loss, toughness, and mass. Based on the results of this investigation, it can be inferred that composition and process variables have a significant influence on structure and reliability; as a result, these factors should be assessed and improved before subjecting pharmaceuticals that are susceptible to light to SLS operations[20].
7. This paper presents the findings of an in-depth investigation on the use of inkjet 3D printing for the creation of microfluidic geometries. Four different printers were used to generate test constructions that were created in CAD. Every printout's shape and size accuracy, structural conformance, and surface irregularity were examined. It was discovered that a correctly printed microfluidic channel needed to be at least 200 μm in breadth or height. Despite the printers' apparent clarity being an order of magnitude greater, tiny constructions were either produced considerably deformed or not at all. It has also been discovered that the withdrawal of the base material is an essential part in the one-step creation of embedding microchannels. We also go through the cause of printing errors and offer a system for comparing different printers. To create a microfluidic framework for the spectrophotometric characterization of drinks, the prints from the 4 distinct printers were analyzed, and the best printing method and printer were then chosen. This microfluidic structure was used to gather UV/VIS absorbency properties, proving that the manufactured spectrophotometric chips worked as intended. As a result, a proof-of-concept for the creation of microfluidic structures utilizing inkjet 3D printing was generated [26].
8. To mimic the porosity shape and matrix robustness of normal bone fragments, a 3D bio-printed pseudo-bone drug carrier platform was created. The 3D bio printed scaffold was created using computer-aided design (CAD) software. The scaffold was further optimized using MATLAB software and artificial networks of neurons (ANN). Polypropylene fumarate (PPF), free radical-polymerized polyethylene glycol-polycaprolactone (PEG-PCL-PEG), and pluronic were the polymers used to

create the 3D scaffolding (PF127). Simvastatin was added to the 3D bioprinted scaffold more to enhance their capacity for bones repair and regeneration. The 3D bioprinted scaffold was assessed for its functionality to be used as an implanted structure at the site of broken bone by looking at its biochemical, morphology, mechanics, and in vitro drug release studies kinetics.A modified release system using the ANN-optimized 3D bioprinted framework successfully demonstrated release of the drug for 20 days. Using a model of a normal clavicle skeleton that had been fractured by a butterfly, the 3D bioprinted substrate also demonstrated creation as a pseudo-bone matrix. According to tests measuring the pseudo-bone matrix's matrix softness (MH) and matrix robustness (MR), the durability of the pseudo-bone matrix was found to be identical (99% MH and 98% MR) to normal adult clavicle bone [29].

9. Numerous advancements have been made in pancreatic islet transplants over the ages, making it a potential treatment option for certain people with type 1 diabetes who have uncontrolled blood-glucose control. Encapsulating transplant islets in a hydrogel, with alginate being the most extensively studied, can preserve them from the immune response. Under this work, islet encapsulation is coupled to 3D extrusion bioprinting, an additive manufacturing technique that allows the manufacture of conformations having exact morphology to build macroporous hydrogel constructions with encapsulated islets. Pancreatic islets may be enclosed in macroporous 3D hydrogel structures of predetermined geometries while keeping their survivability, appearance, and functioning by employing a plottable hydrogel mix made of clinically approved ultrapure alginate and methylcellulose (Alg/MC). The implanted islets constantly manufacture insulin and glucagon during the observation and continue response to glucose stimuli, although to a smaller extent than standard islets. Diffusion of glucose and insulin in the Alg/MC hydrogel is equivalent to diffusion in plain alginate [33].
10. Bioengineering is a rapidly expanding field of study that is of tremendous interest due to its potential to create bionic grafts that can substitute for autologous tissue. Precellularization of comparatively tiny vascular grafts continues to be a research problem even after several modelling techniques have been attempted. Thus, by merging nanofiber electrospinning and a specifically created rotatable bioprinter, an unique method for generating bionic comparatively tiny vascular arteries is produced. Excellent flexibility is provided by electrospun poly(-caprolactone), and the electrospinning alteration is advantageous for endothelial cell attachment and functionalization. Following weeks of culture, PCL's surface forms a flat monolayer. The conventional two half (3D) bioprinter was modified to enhance the rotating of the central point and employ two motors to boost stability while creating. This made it possible to bioprint a homogeneous, thick methacrylated gelatin (GelMA) structure with cells of smooth muscle that are placed in a straight line along the horizontally rotational axis. Throughout the culture procedure, the two types of cells retain their survivability and propagation in the framework. Additionally, the bionic construction has stronger suture holding and anti-burst force than a native blood artery. This research could offer a fresh approach to creating bionic blood vessels or other tubular structures [49].
11. The mechanism of tissue formation requires the repair of dermal blood vessels. Nevertheless, there are significant barriers to persistent dermal substitution in bioengineering, including the absence of vascular structure, poor angiogenesis stimulation, and inefficient graft-host anastomosis of the present skin replacements. This research successfully creates homogeneous strontium silicate (SS) microcylinders, integrates them into the biodegradable polymer ink to behave as steady cell-induced aspects for angiogenesis, and afterward uses a "cell-writing" bioprinting method to produce a workable dermal replacement depending on a vascularization-induced biocompatible multicellular structure. The multilayer systems incorporating SS demonstrate exceptional angiogenesis action both in vitro and in vivo due to its unique coupling of vascular skin-mimicking morphology and vascularization-induced functioning. The 3d bioprinting skin replacements therefore encourage graft-host integration and vasculature skin rejuvenation in 3 experimental animals, which dramatically speeds up the recovery of both acute and chronic injuries. In order to create biocompatible multicellular structures with angiogenesis-induced functionality for the rejuvenation of vascularized sophisticated and hierarchy tissues, the research presents a preferable method [52].
12. The main component of the extracellular matrix in the human body is collagen. Making collagen frameworks that can mimic the composition and operation of organs and tissue has proven to be difficult. We describe a technique for engineering segments of the human cardiac at different sizes, from capillary to the whole organ, utilizing freeform removable embedded suspended hydrogels (FRESH). Management of pH-driven gelation gives tensile stability for manufacturing and perfusion of multiscale vasculature and tri-leaflet valves, a permeable microstructure that permits fast cell infiltration and micro vascularization, and 20-micrometer strand accuracy. We discovered that FRESH 3D-bioprinted hearts faithfully replicate the anatomy identified by micro-computed tomography in sufferers. Human cardiomyocyte-printed cardiac ventricles displayed coordinated contractions, directed action potential propagation, and wall thickening of up to 14 percent at maximum systole [60].

26 Criteria For Hydrogel In Tissue Engineering

Hydrogels must fulfil several design requirements in order to perform as intended, promote the growth of new tissue, and trigger little or no immunological response in the recipient. The physical properties of hydrogels, like physical properties, biodegradability and swelling behaviour, moreover their biological performance, just like their biocompatibility, vascularization, and bioactivity, primarily determine the satisfactory design and material selection of hydrogels. The intended use and environmental exposure of these elements define them. For instance, hydrogels used to produce artificial skin and artificial bones must differ from one another. This means that a particular composition and structure of hydrogel may be advantageous for many projects involving tissue engineering.

261 Biological Performance

Biocompatibility*:* - Researchers looking to create hydrogels with applications in biological systems are primarily interested in biocompatibility [112] Hydrogels should be created as biomaterials with little or no immune response to the live tissues. The simultaneous breakdown of the hydrogel matrix and the growth of new tissues are signs of biocompatibility [103]. The matrix ought to be physiologically secure and noncytotoxic. It has been observed that several man-made polymers, which incorporates polyesters and acrylates, exhibit biocompatibility with the human body [113]. To create biocompatible hydrogels, poly (amino acids),and other bioderived materials have also been employed [114].

Cell adhesion: - It is anticipated that hydrogel scaffolds will have an adhesive quality for cell binding. It should be noted that many synthetic polymers have poor cell bio-adhesion. The synthetic polymers PEG, PVA, and Poly (2-hydroxyethyl methacrylate) (PHEMA) that show weak cell binding are among the most often used in tissue engineering [115].

Vascularization: - Implanted tissues with higher levels of survivability have developed a capillary network that carries nutrients to the cells, which is known as vascularization. Common techniques for improved vascularization include proper scaffold design, angiogenic agents [116] Of these strategies, it has been discovered that appropriate hydrogel model shape and size with sufficient interconnectivity, branching, and exact pore size can affect the rate of vascularization following insertion [117]-[118].

Bioactivity: - The term "bioactivity" describes a material's capacity or inclination to induce or promote a biological response in a live system when it is introduced [112]. A typical bioactive scaffold should have strong osteoconductivity and osteoinductivity, tissue connectivity, and binding capabilities, and growth factors and biological signals that encourage cell differentiation, adherence, and formation [119]. Because of their distinctive structure, hydrogels can also regulate and sustain the release of bioactive substances, enabling the creation of a persistent vascular system and the bone scaffold. Controlled hydrogel degradation and molecular diffusion rates might be achieved by structurally modifying the composition and adjusting the amounts of polymers and crosslinkers [120]

262 Topographical Characteristics

Mechanical properties: - The mechanical properties of the hydrogel used in tissue engineering applications must be compatible with the tissues present at the place of insertion. These characteristics might be modified to satisfy certain end-use needs. As an example, adding crosslinking agents, blocking polymerization, forming interpenetrating networks (IPNs) or semi-interpenetrating networks (SIPNs), and adding nanofiller materials like graphene, nano silica, carbon nanotubes, and their derivatives can all increase the mechanical strength of hydrogels [121-[122]. Additionally gel elasticity is crucial because it allows crosslinked chains to flex and makes it easier for bioactive substances to migrate or diffuse [113].

Biodegradability/absorbability: - When functional tissues are formed because of the replacement of old cells with new ones, hydrogels should generally have bioresorbability and adjustable rates of breakdown and resorption. One of the fundamental demands for hydrogels during their predicted lifetime is the maintenance of both cell growth and appropriate distribution [102],[103],[106]. Which remains after they have fully degraded. In order to create efficient and practicable hydrogels for tissue engineering applications, biodegradation rates are essential.

Porousness: - The porousness of a hydrogel indicates the existence of void spaces within its overall structure. For effective nutrition and metabolic waste transport as well as for ideal cell migration, a significant degree of scaffold permeability or hierarchical transportation characteristics is required. In order to promote healthy cell proliferation and movement and to enhance surface area equivalent to the necessary scaffold volume, hydrogels should have an adequate number of interconnected porosity networks. Particularly in the absence of a functioning circulatory system, such severe, linked porosity can benefit cell ingrowth and homogeneity [123],[101].

Swelling: - Swelling is defined by the hydrogel's natural ability to grow as a result of liquid absorbing through the spaces

within its polymer chains systems. Swelling is frequently related to the substance's physical characteristics, that result exhibits a relationship with the crosslinking strength and hydrogel content. Furthermore, swelling is important for material dispersion and movement inside and across the hydrogel [124],[106]. The rate and ability of swelling are also important factors since they can affect how well hydrogel materials work. The rate of swelling for particular in vivo use must also be taken into consideration because they can give an indication of the defect filling rates during a given surgical technique [123].

27 Challenges In Manufacturing Of Hydrogel-Based Biological Tissue

There are still several significant obstacles and restrictions facing different tissue-engineered technologies that have passed satisfactory medical studies. These problems are brought on by the use of synthetic hydrogel model and the associated manufacturing techniques to mimic natural ECMs, (103) which help cells proliferate, differentiate, and synthesize new cells [125] Up to this point, improved printers have been able to print hydrogel structures with a satisfactory resolution (0.3 mm) [126]-[127].

Due to the poor efficiency of cell infiltration rates, the majority of the difficulties with these devices is uneven cell seeding. This finding is mostly the result of the size, shape, and insufficient monitoring in the spatial and temporal components of cell movement and multiplication [128],[129]. Hydrogels with an uneven distribution of crosslink density indicate a phenomenon called spatial inhomogeneity, which lowers the hydrogel strength[130],[119]. Additionally, there are challenges in integrating hydrogel systems into the human body because these systems must react continually and periodically with a variety of pathologic and physiologic events. [131],[132]. Even though hydrogels are now regarded as smart materials and their production techniques are more advanced, they still need to have better vascularization if they are to behave in a way that mimics the complex structure of genuine tissues. As a result, this step would remove the obstacle to the development of complex organs [129].

When used as a scaffolding material, the characteristics of biomaterials, particularly their mechanical characteristics, have a minor but considerable effect. Therefore, while creating appropriate scaffold constructions, including biomaterials, the goal is supposed to be to convert the mechanical qualities of the tissue of interest into the physical characteristics of the created construct. In light of this, it was discovered that hard tissue regeneration requires mechanical strengths between 0.4 and 350 MPa, whereas soft tissue regrowth needs values between 10-1500 MPa [130].At both the macro- and microscopic levels, it is discovered that hydrogel structures have weak mechanical characteristics. As a result of the uneven placement of crosslinkers in their network, their ability to withstand physical strain is fairly low [133]. Their uses are therefore still restricted to soft tissues without loads on them. ECMs with this structural modification may eventually resemble their native forms in form of makeup and operation In addition, handling and loading hydrogel systems can be delicate and fragile [130],[134].

Additionally, Synthetic hydrogels can provide problems with biodegradability and biocompatibility. High molecular weight and viscous materials can be created by chain-growth addition polymerizing hydrogels to create their crosslinked structures. Monomers slowly diffuse as viscosity is raised, which prevents their full utilization and leaves behind unusable leftover monomers in the framework that are frequently polluted. As a result, sterilisation suffers and could get much more challenging if there are still water molecules present. [124], [129], [135].

28 3d Bioprinting Based On Natural Biopolymer

When compared to synthetic polymers, natural biopolymers usually exhibit features that are more suited to biological surroundings and are frequently impossible to imitate synthetically [136]. The most extensively researched naturally occurring hydrogel polymers for biomedical applications are collagen, gelatin, and alginate. Adapting or changing these materials while preserving their original organizational structure is difficult. The extracellular matrix (ECM) contains a large amount of collagen, which makes it possible to extract and print vast amounts of collagen. Additionally, collagen has great biodegradability and biocompatibility [136],[137]. These characteristics have prompted researchers to improve collagen's capacity to be 3D printed directly or copolymers. [138]. According to several characterization approaches, PLA-Col-MH-cHA model showed mechanical and biological characteristics that were highly similar to those of bone structures.

Murphy et al. [139] produced star-like dendrimers using peptide copolymer monomers using extrusion-based printing techniques. The method was combined with a after-print UV ray therapy to create controllable microstructure hydrogels that are mechanically stable. Degradable hydrogels created by functionalizing L-glutamate and L-valine were unable to stop the Balb/3T3 cell line from functioning. By adding the small molecule medicine doxorubicin hydrochloride to the hydrogel, the degradation was taken advantage of in order to show the possibility of controlled drug release.

Thiolate heparin combined with glycidyl methacrylate Hyaluronate and different growth factors was employed by Wang et al. [140] to create stable hydrogel structures using digital light projected (DLP) 3D printing method. To investigate the dimensional influence on regulated discharge of growth factors, a variety of geometries were built layer by layer, with growth factors in each layer [141].

29 3d Bioprinting Based On Synthetic Hydrogel Biopolymer

In tissue engineering, synthetic polymers have become more popular as feasible printing substances for the creation of de-novo hydrogel. Even while many synthetic polymers lack an equivalent extent of bioactivity and biocompatibility as natural biopolymers, there are advantages to using them.. Natural biopolymers are not as flexible as synthetic polymers when it comes to creating 3D printed polymer hydrogels. For example, Various monomers and crosslinkers can be utilised, with respect to the characteristics that are wanted, such as molecular weight, degree of functionalization, and surface form [142].

Due to its high biocompatibility, PEG has taken over as the preferred material for hydrogel manufacturing in tissue engineering. It resists the adsorption of proteins and adheres to cells, enabling more precise regulation of tissue development[142],[143]. Because PEG's molecular weight is strictly controllable, its physical characteristics may be modified to suit a particular purpose., PEG may be safely eliminated by the body. Because of the polymer chain is only partially digested [142]. It has been demonstrated that PEG may create copolymers with other species that can be polymerized. This compatibility adds a degree of control to changing the characteristics of PEG-derived polymers [143]. To increase mechanical qualities like toughness and impact strength, units of a certain polymer backbone can be introduced. The preservation of biocompatibility requires careful PEG copolymer selection. The release of PEG bits requires the degradation of nearby PEG blockchain systems [142].

Using the SLA 3D printing approach, Christensen et al. [144] created hydrogel structures. Micro-cantilever frameworks integrated in a medium rich in cells were used to encourage tissue development.. with turnable features provided by altering PEGDA concentration and cantilever width. Due to the cantilevers' ability to withstand varying degrees of tension, tissue strips can form without causing harm. Fluorescent microscopy was used to confirm biocompatibility and regulated cellular proliferation.

For application in tissue engineering, Tessmar and Göpferich (1982) investigated a variety of PEG-copolymer compounds. The biomimetic properties necessary for the growth of cells were mainly produced through cross-linking and extremely moist PEG-based polymers. The use of certain short peptide chains as crosslinkers allowed for the targeted breakdown of the cross-linked units with the addition of particular proteinases. Cellular adhesion can be boosted by choosing crosslinked peptide sequences with sections that are recognized by receptor substrates. Through the scaffolded network, directed migration may be produced by the targeted cellular adhesion. [145],[146].

Application

The creation of tissues like dermal tissues, bone tissue, cardiovascular tissue, cardiac valve, and neurological tissue is one use for 3d-printed hydrogel-based bio-inks. Collagen, and agarose, are among the hydrogel polymers employed. There are numerous drawbacks to the traditional method of tissue engineering that 3D printing can help to overcome. Inkjet, thermal inkjet, piezoelectric and laser-assisted bioprinting are some of the methods that have been utilized to create hydrogel-based bio-inks in three dimensions [147].

210 Challenges And Opportunities

In order to eliminate the need for organ donors in the long term, investigators seek to inject 3D-printed scaffolds with the proper bioactive substances. If this is accomplished, patients' specific 3D printed parts can be produced in a much faster, more reliable manner. Collagen is a good option for use in hydrogel scaffold production in tissue engineering applications [148].The purpose of the study is clear, and it would have significant ramifications for treating difficulties with heart abnormalities and failures, even though the technology and knowledge required to transform a duplicate like this into a functioning human heart are not now available. A working device of this kind could considerably increase the expected lifespan of an individual. because cardiac failure is regarded as a leading cause of death around the world.

Players who engage in physical activities like baseball, rugby, and volleyball frequently have knee problems. The frequent and rapid direction changes necessary to compete in these games at a high standard create many opportunities for knee injury. The meniscus is an important ligament in the knees and is designed like a wedge. Although a ruptured meniscus can be repaired surgically, this ligament injury can lead to long-lasting persistent pain. Zhang et al. [149] looked at the viability of producing an artificial meniscus in a 3D printer that might replace a torn or damaged ligament. With the aid of soft acrylamide, phenyl acrylate, and cellulose nanocrystal, this powerful synthetic meniscus was 3D printed. An interesting finding was the ability to create a print that had qualities that were comparable to or even better than those of an actual human meniscus. However, this type of application still faces difficulties, such as effectively attaching the meniscus to the bone and material property persistence over time. However, because of the communal and economic benefits they offer, these goals are beneficial to undertake.

Urine can leave the bladder through a pipe structure called the urethra. Urologists face a challenging and common problem with inherited or congenital diseases of the urethra. Medical specialists struggle greatly to repair the injury and restore the functioning of the urethra when it is distorted or injured. Until now, most procedures have been based primarily

on tissue grafting, which can sometimes be successful but could sometimes result in graft rejection. Xu et al. [150] examined the viability of printing a synthetic and biodegradable urethra tube. The resulting print's elastic characteristic enables structure restoration and makes it the perfect choice for this application. It has also been difficult to create high-resolution 3D-printed hydrogels using numerous extrusion-based printing methods, which is still a problem in the field of additive manufacturing. To attain high print resolution, a variety of techniques have been used. For instance, light-based 3D printing methods like DLP and SLA have been utilized to produce things more quickly than FDM.[151]-[154]. Due to the strong transmissibility of the solution, nevertheless, unwanted light penetration might impair the resolution on transparent resins. This problem was solved by Shin et al. (1995) by adding melanin nanoparticle-infused silk fiber (SFM) to a poly (ethylene glycol)-tetra acrylate solution that was otherwise clear (PEG4A). To irradiate the resin more precisely, the opacity of the mixtures can be adjusted by the introduction of SFM.

Incorporating hydrophilic photo blockers that can significantly absorb photons, such as chlorophyllin and tartrazine, can also help produce high print quality when utilizing these photopolymerization-based techniques [155]. With a larger dye quantity used, however, a longer curing period is needed to achieve the same film widths. The fabrication of high-resolution printed structures with a size of up to 100 nm for use in tissue regeneration, drug administration, biosensing, and other applications is also possible using two-photon polymerization (2PP) [156],[158].

On the other hand, by printing several polyurethane-gelatin (PU gelatin) compositions with an orifice diameter of 80, 200, and 320 μm, Hsieh et al. [157] showed the capability for extrusion-based, 3D-printed hydrogels. When compared to hydrogel structures printed with 200 and 320 μm diameters, cell proliferation was maintained with only a slight decrease in viability of cells. After being treated with Ca2+ ions and then thermally cured, the 3D-printed structures' mechanical characteristics were further improved. The PU-gelatin matrix experienced a chelating effect because of the addition of Ca2+, which enhanced the structural stability of the printed pieces.[159]

211 Future Perspectives

Even while 3D printing makes it possible to create a variety of intricate designs, the microstructures it produces remain stagnant.[160] Therefore, 4D printing generates a complicated framework that alters with period and reacts to outside stimulation in the appropriate manner.[161] The scaffolded model is not anymore stationary and may be transformed into intricate architectures by changing the model's dimensions, layout, characteristics, and functionality in reaction to outside signals [162]. This method is time-limited and does not depend on a printer, dissimilar to 3D printing.[163] Structures created with 4D printing should be carefully demonstrate, keeping in mind any anticipated time-dependent constituent structure.[164] One more key component of 4D printing is substances that can become highly extendable, flexible, or stretchable in response to external forces [165].

3 Conclusion

Additive manufacturing is being applied in a variety of fields, including energy technology, medical, and lightweight manufacturing, in addition to its conventional application.

- Among the most promising methods for creating cell-loaded frameworks that might specialize and multiply deeper is 3D bioprinting. A significant technological advance is the emergence of individualized implantation and multiactive medication.
- Patient-specific medications eliminate several negative aspects of the typical dose types.
- Biomaterials used in the manufacturing process have also been shown to increase the potency and efficacy of drugs. Although the expensive nature of the devices and polymers utilized, technology is advancing quickly, and costs would eventually fall to a level that would make sometimes large-scale production feasible.
- The benefits of this discovery are expanded for patients, healthcare experts, and learners. In comparison to traditional therapeutic approaches, the standard of living has increased due to the increasing use of grafts to larger social group.
- We may anticipate the most reliable technique with enhanced qualities in the pharmaceutical industry. The integrated cell lines would maintain mechanical stability over time, but the complete extent of their flexible biological nature remains a challenge.
- Machine learning algorithms are anticipated to play a significant role in enhancing the procedure and quality of a product as 3D bioprinting develops and becomes more widely used. Hydrogels, then moved on to the technical specifications for producing biopolymers (i.e., physical and biological properties), before talking about the substance antecedents for 3d - printed hydrogels.
- The usage of hydrogel materials for bioengineering will be made possible by the integration of novel printing techniques, and 4D printing. The evolution of this field necessitates multidisciplinary and cooperative efforts to solve any manufacturing challenges.
- The potential for 3D printing hydrogels in the future in conjunction with novel materials, production techniques,

and therapeutic research was also emphasized.

4 References

[1] Gibson, Ian, David Rosen, Brent Stucker, Mahyar Khorasani, Ian Gibson, David Rosen, Brent Stucker, and Mahyar Khorasani. "Introduction and basic principles." *Additive manufacturing technologies* (2021): 1-21.
[2] Campbell, Thomas, Christopher Williams, Olga Ivanova, and Banning Garrett. "Could 3D printing change the world." *Technologies, Potential, and Implications of Additive Manufacturing, Atlantic Council, Washington, DC* 3 (2011): 1-16.
[3] Sames, William J., F. A. List, Sreekanth Pannala, Ryan R. Dehoff, and Sudarsanam Suresh Babu. "The metallurgy and processing science of metal additive manufacturing." *International materials reviews* 61, no. 5 (2016): 315-360.
[4] Pavan Kalyan, B. G., and Lalit Kumar. "3D printing: applications in tissue engineering, medical devices, and drug delivery." *Aaps Pharmscitech* 23, no. 4 (2022): 92.
[5] Chia, Helena N., and Benjamin M. Wu. "Recent advances in 3D printing of biomaterials." *Journal of biological engineering* 9, no. 1 (2015): 1-14.
[6] Niaki, Mojtaba Khorram, and Fabio Nonino. "The management of additive manufacturing." *Birmingham: Springer* (2018).
[7] Gao, Chaohua, Chenyu Wang, Hui Jin, Zhonghan Wang, Zuhao Li, Chenyu Shi, Yi Leng, Fan Yang, He Liu, and Jincheng Wang. "Additive manufacturing technique-designed metallic porous implants for clinical application in orthopedics." *RSC advances* 8, no. 44 (2018): 25210-25227.
[8] Karayel, Elif, and Yahya Bozkurt. "Additive manufacturing method and different welding applications." *Journal of Materials Research and Technology* 9, no. 5 (2020): 11424-11438.
[9] Thompson, Mary Kathryn, Giovanni Moroni, Tom Vaneker, Georges Fadel, R. Ian Campbell, Ian Gibson, Alain Bernard et al. "Design for Additive Manufacturing: Trends, opportunities, considerations, and constraints." *CIRP annals* 65, no. 2 (2016): 737-760.
[10] Jayanath, Shiyan, and Ajit Achuthan. "A computationally efficient hybrid model for simulating the additive manufacturing process of metals." *International Journal of Mechanical Sciences* 160 (2019): 255-269.
[11] Konta, Andrea Alice, Marta García-Piña, and Dolores R. Serrano. "Personalised 3D printed medicines: which techniques and polymers are more successful?." *Bioengineering* 4, no. 4 (2017): 79.
[12] Pranzo, Daniela, Piero Larizza, Daniel Filippini, and Gianluca Percoco. "Extrusion-based 3D printing of microfluidic devices for chemical and biomedical applications: A topical review." *Micromachines* 9, no. 8 (2018): 374.
[13] Stewart, Sarah A., Juan Domínguez-Robles, Victoria J. McIlorum, Elena Mancuso, Dimitrios A. Lamprou, Ryan F. Donnelly, and Eneko Larrañeta. "Development of a biodegradable subcutaneous implant for prolonged drug delivery using 3D printing." *Pharmaceutics* 12, no. 2 (2020): 105.
[14] Giri, Bhupendra Raj, Eon Soo Song, Jaewook Kwon, Ju-Hyun Lee, Jun-Bom Park, and Dong Wuk Kim. "Fabrication of intragastric floating, controlled release 3D printed theophylline tablets using hot-melt extrusion and fused deposition modeling." *Pharmaceutics* 12, no. 1 (2020): 77.
[15] Xing, Jin-Feng, Mei-Ling Zheng, and Xuan-Ming Duan. "Two-photon polymerization microfabrication of hydrogels: an advanced 3D printing technology for tissue engineering and drug delivery." *Chemical Society Reviews* 44, no. 15 (2015): 5031-5039.
[16] Healy, Andrew V., Evert Fuenmayor, Patrick Doran, Luke M. Geever, Clement L. Higginbotham, and John G. Lyons. "Additive manufacturing of personalized pharmaceutical dosage forms via stereolithography." *Pharmaceutics* 11, no. 12 (2019): 645.
[17] Xu, Xiaoyan, Pamela Robles-Martinez, Christine M. Madla, Fanny Joubert, Alvaro Goyanes, Abdul W. Basit, and Simon Gaisford. "Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: Case study of an unexpected photopolymer-drug reaction." *Additive Manufacturing* 33 (2020): 101071.
[18] Awad, Atheer, Fabrizio Fina, Alvaro Goyanes, Simon Gaisford, and Abdul W. Basit. "3D printing: Principles and pharmaceutical applications of selective laser sintering." *International Journal of Pharmaceutics* 586 (2020): 119594.
[19] Fina, Fabrizio, Alvaro Goyanes, Christine M. Madla, Atheer Awad, Sarah J. Trenfield, Jia Min Kuek, Pavanesh Patel, Simon Gaisford, and Abdul W. Basit. "3D printing of drug-loaded gyroid lattices using selective laser sintering." *International journal of pharmaceutics* 547, no. 1-2 (2018): 44-52.
[20] Thakkar, Rishi, Daniel A. Davis Jr, Robert O. Williams III, and Mohammed Maniruzzaman. "Selective laser sintering of a photosensitive drug: impact of processing and formulation parameters on degradation, solid state, and quality of 3D-printed dosage forms." *Molecular Pharmaceutics* 18, no. 10 (2021): 3894-3908.
[21] Sahini, Deepak Kumar, Joyjeet Ghose, Sanjay Kumar Jha, Ajit Behera, and Animesh Mandal. "Optimization and simulation of additive manufacturing processes: challenges and opportunities–a review." *Additive manufacturing applications for metals and composites* (2020): 187-209.

[22] Stansbury, Jeffrey W., and Mike J. Idacavage. "3D printing with polymers: Challenges among expanding options and opportunities." *Dental materials* 32, no. 1 (2016): 54-64.
[23] Highley, Christopher B., Christopher B. Rodell, and Jason A. Burdick. "Direct 3D printing of shear-thinning hydrogels into self-healing hydrogels." *Advanced Materials* 27, no. 34 (2015): 5075-5079.
[24] Sridhar, Ashok, Thomas Blaudeck, and Reinhard R. Baumann. "Inkjet printing as a key enabling technology for printed electronics." *Material Matters* 6, no. 1 (2011): 12-15.
[25] Mohebi, Mohammad Masoud, and Julian RG Evans. "A drop-on-demand ink-jet printer for combinatorial libraries and functionally graded ceramics." *Journal of combinatorial chemistry* 4, no. 4 (2002): 267-274.
[26] Walczak, Rafał, and Krzysztof Adamski. "Inkjet 3D printing of microfluidic structures—on the selection of the printer towards printing your own microfluidic chips." *Journal of Micromechanics and Microengineering* 25, no. 8 (2015): 085013.
[27] Ferracini, Riccardo, Isabel Martínez Herreros, Antonio Russo, Tommaso Casalini, Filippo Rossi, and Giuseppe Perale. "Scaffolds as structural tools for bone-targeted drug delivery." *Pharmaceutics* 10, no. 3 (2018): 122.
[28] Arai, Kenichi, Shintaroh Iwanaga, Hideki Toda, Capi Genci, Yuichi Nishiyama, and Makoto Nakamura. "Three-dimensional inkjet biofabrication based on designed images." *Biofabrication* 3, no. 3 (2011): 034113.
[29] Kondiah, Pariksha Jolene, Pierre PD Kondiah, Yahya E. Choonara, Thashree Marimuthu, and Viness Pillay. "A 3D bioprinted pseudo-bone drug delivery scaffold for bone tissue engineering." *Pharmaceutics* 12, no. 2 (2020): 166.
[30] Song, J. Hillstrom, R. J. Murphy, R. Narayan, and G. B. H. Davies. "Biodegradable and compostable alternatives to conventional plastics." *Philosophical transactions of the royal society B: Biological sciences* 364, no. 1526 (2009): 2127-2139.
[31] Liu, Jun, Lushan Sun, Wenyang Xu, Qianqian Wang, Sujie Yu, and Jianzhong Sun. "Current advances and future perspectives of 3D printing natural-derived biopolymers." *Carbohydrate polymers* 207 (2019): 297-316.
[32] Carrow, James K., Punyavee Kerativitayanan, Manish K. Jaiswal, Giriraj Lokhande, and Akhilesh K. Gaharwar. "Polymers for bioprinting." In *Essentials of 3D biofabrication and translation*, pp. 229-248. Academic Press, 2015.
[33] Duin, Sarah, Kathleen Schütz, Tilman Ahlfeld, Susann Lehmann, Anja Lode, Barbara Ludwig, and Michael Gelinsky. "3D bioprinting of functional islets of langerhans in an alginate/methylcellulose hydrogel blend." *Advanced healthcare materials* 8, no. 7 (2019): 1801631.
[34] Subramaniam, Sadhasivam, Yen-Hsin Fang, Savitha Sivasubramanian, Feng-Huei Lin, and Chun-pin Lin. "Hydroxyapatite-calcium sulfate-hyaluronic acid composite encapsulated with collagenase as bone substitute for alveolar bone regeneration." *Biomaterials* 74 (2016): 99-108.
[35] Almeida, Andreia, Vicente Linares, Gloria Mora-Castaño, Marta Casas, Isidoro Caraballo, and Bruno Sarmento. "3D printed systems for colon-specific delivery of camptothecin-loaded chitosan micelles." *European Journal of Pharmaceutics and Biopharmaceutics* 167 (2021): 48-56.
[36] Zhang, Weilin, Wei Zhao, Qin Li, Duoyi Zhao, Junxing Qu, Ziyang Yuan, Zhihong Cheng, Xiaojuan Zhu, Xiuli Zhuang, and Zhiyu Zhang. "3D-printing magnesium–polycaprolactone loaded with melatonin inhibits the development of osteosarcoma by regulating cell-in-cell structures." *Journal of Nanobiotechnology* 19, no. 1 (2021): 1-20.
[37] Asmaria, Talitha, Djusman Sajuti, and Khusnul Ain. "3D printed PLA of gallbladder for virtual surgery planning." In *AIP Conference Proceedings*, vol. 2232, no. 1. AIP Publishing, 2020.
[38] Serris, Ioannis, Panagiotis Serris, Kathleen M. Frey, and Hyunah Cho. "Development of 3D-printed layered PLGA films for drug delivery and evaluation of drug release behaviors." *AAPS PharmSciTech* 21 (2020): 1-15.
[39] Singh, Mahima, and Sriramakamal Jonnalagadda. "Design and characterization of 3D printed, neomycin-eluting poly-L-lactide mats for wound-healing applications." *Journal of Materials Science: Materials in Medicine* 32 (2021): 1-13.
[40] Derakhshanfar, Soroosh, Rene Mbeleck, Kaige Xu, Xingying Zhang, Wen Zhong, and Malcolm Xing. "3D bioprinting for biomedical devices and tissue engineering: A review of recent trends and advances." *Bioactive materials* 3, no. 2 (2018): 144-156.
[41] Hospodiuk, Monika, Madhuri Dey, Donna Sosnoski, and Ibrahim T. Ozbolat. "The bioink: A comprehensive review on bioprintable materials." *Biotechnology advances* 35, no. 2 (2017): 217-239.
[42] Ashammakhi, Nureddin, Anwarul Hasan, Outi Kaarela, Batzaya Byambaa, Amir Sheikhi, Akhilesh K. Gaharwar, and Ali Khademhosseini. "Advancing frontiers in bone bioprinting." *Advanced healthcare materials* 8, no. 7 (2019): 1801048.
[43] Bai, Xin, Mingzhu Gao, Sahla Syed, Jerry Zhuang, Xiaoyang Xu, and Xue-Qing Zhang. "Bioactive hydrogels for bone regeneration." *Bioactive materials* 3, no. 4 (2018): 401-417.
[44] Seok, Ji Min, Jae Eun Jeong, Sang Jin Lee, Seung Hyun Im, Jun Hee Lee, Wan Doo Kim, Kangwon Lee, and Su A. Park. "Bio-plotted hydrogel scaffold with core and sheath strand-enhancing mechanical and biological properties for tissue regeneration." *Colloids and Surfaces B: Biointerfaces* 205 (2021): 111919.
[45] Nguyen, Duong, Daniel A. Hägg, Alma Forsman, Josefine Ekholm, Puwapong Nimkingratana, Camilla Brantsing, Theodoros Kalogeropoulos et al. "Cartilage tissue engineering by the 3D bioprinting of iPS cells in a nanocellulose/alginate bioink." *Scientific reports* 7, no. 1 (2017): 658.

[46] Isaeva, E. V., E. E. Beketov, V. V. Yuzhakov, N. V. Arguchinskaya, A. A. Kisel, E. P. Malakhov, T. S. Lagoda et al. "The use of collagen with high concentration in cartilage tissue engineering by means of 3D-bioprinting." *Cell and Tissue Biology* 15 (2021): 493-502.
[47] Merceron, Tyler K., Morgan Burt, Young-Joon Seol, Hyun-Wook Kang, Sang Jin Lee, James J. Yoo, and Anthony Atala. "A 3D bioprinted complex structure for engineering the muscle–tendon unit." *Biofabrication* 7, no. 3 (2015): 035003.
[48] Dickman, Christopher TD, Valerio Russo, Katherine Thain, Sheng Pan, Simon T. Beyer, Konrad Walus, Spiro Getsios, Tamer Mohamed, and Sam J. Wadsworth. "Functional characterization of 3D contractile smooth muscle tissues generated using a unique microfluidic 3D bioprinting technology." *The FASEB Journal* 34, no. 1 (2020): 1652-1664.
[49] Jin, Qianheng, Yi Fu, Guangliang Zhang, Lei Xu, Guangzhe Jin, Linfeng Tang, Jihui Ju, Weixin Zhao, and Ruixing Hou. "Nanofiber electrospinning combined with rotary bioprinting for fabricating small-diameter vessels with endothelium and smooth muscle." *Composites Part B: Engineering* 234 (2022): 109691.
[50] Hann, Sung Yun, Haitao Cui, Timothy Esworthy, Xuan Zhou, Se-jun Lee, Michael W. Plesniak, and Lijie Grace Zhang. "Dual 3D printing for vascularized bone tissue regeneration." *Acta Biomaterialia* 123 (2021): 263-274.
[51] Daikuara, Luciana Y., Xifang Chen, Zhilian Yue, Danielle Skropeta, Fiona M. Wood, Mark W. Fear, and Gordon G. Wallace. "3D bioprinting constructs to facilitate skin regeneration." *Advanced Functional Materials* 32, no. 3 (2022): 2105080.
[52] Ma, Jingge, Chen Qin, Jinfu Wu, Hongjian Zhang, Hui Zhuang, Meng Zhang, Zhaowenbin Zhang et al. "3D printing of strontium silicate microcylinder-containing multicellular biomaterial inks for vascularized skin regeneration." *Advanced Healthcare Materials* 10, no. 16 (2021): 2100523.
[53] Liu, Suihong, Liguo Sun, Haiguang Zhang, Qingxi Hu, Yahao Wang, and Murugan Ramalingam. "High-resolution combinatorial 3D printing of gelatin-based biomimetic triple-layered conduits for nerve tissue engineering." *International Journal of Biological Macromolecules* 166 (2021): 1280-1291.
[54] Ye, Wensong, Haibing Li, Kang Yu, Chaoqi Xie, Peng Wang, Yating Zheng, Peng Zhang et al. "3D printing of gelatin methacrylate-based nerve guidance conduits with multiple channels." *Materials & Design* 192 (2020): 108757.
[55] Liu, Xiao-Yin, Chong Chen, Hai-Huan Xu, Yu-sheng Zhang, Lin Zhong, Nan Hu, Xiao-Li Jia et al. "Integrated printed BDNF/collagen/chitosan scaffolds with low temperature extrusion 3D printer accelerated neural regeneration after spinal cord injury." *Regenerative biomaterials* 8, no. 6 (2021): rbab047.
[56] Liu, Nanbo, Xing Ye, Bin Yao, Mingyi Zhao, Peng Wu, Guihuan Liu, Donglin Zhuang et al. "Advances in 3D bioprinting technology for cardiac tissue engineering and regeneration." *Bioactive Materials* 6, no. 5 (2021): 1388-1401.
[57] Goo, Hyun Woo, Sang Joon Park, and Shi-Joon Yoo. "Advanced medical use of three-dimensional imaging in congenital heart disease: augmented reality, mixed reality, virtual reality, and three-dimensional printing." *Korean journal of radiology* 21, no. 2 (2020): 133-145.
[58] Al Jabbari, Odeaa, Walid K. Abu Saleh, Avni P. Patel, Stephen R. Igo, and Michael J. Reardon. "Use of three-dimensional models to assist in the resection of malignant cardiac tumors." *Journal of cardiac surgery* 31, no. 9 (2016): 581-583.
[59] Gardin, Chiara, Letizia Ferroni, Christian Latremouille, Juan Carlos Chachques, Dinko Mitrečić, and Barbara Zavan. "Recent applications of three dimensional printing in cardiovascular medicine." *Cells* 9, no. 3 (2020): 742.
[60] Lee, A. R. H. A., A. R. Hudson, D. J. Shiwarski, J. W. Tashman, T. J. Hinton, S. Yerneni, J. M. Bliley, P. G. Campbell, and A. W. Feinberg. "3D bioprinting of collagen to rebuild components of the human heart." *Science* 365, no. 6452 (2019): 482-487.
[61] Zhang, Yu Shrike, Andrea Arneri, Simone Bersini, Su-Ryon Shin, Kai Zhu, Zahra Goli-Malekabadi, Julio Aleman et al. "Bioprinting 3D microfibrous scaffolds for engineering endothelialized myocardium and heart-on-a-chip." *Biomaterials* 110 (2016): 45-59.
[62] Yang, Huayu, Lejia Sun, Yuan Pang, Dandan Hu, Haifeng Xu, Shuangshuang Mao, Wenbo Peng et al. "Three-dimensional bioprinted hepatorganoids prolong survival of mice with liver failure." *Gut* 70, no. 3 (2021): 567-574.
[63] Mao, Qijiang, Yifan Wang, Yang Li, Sarun Juengpanich, Wenhuan Li, Mingyu Chen, Jun Yin, Jianzhong Fu, and Xiujun Cai. "Fabrication of liver microtissue with liver decellularized extracellular matrix (dECM) bioink by digital light processing (DLP) bioprinting." *Materials Science and Engineering: C* 109 (2020): 110625.
[64] Liu, Xiao, Sarah-Sophia D. Carter, Max Jurie Renes, Juewan Kim, Darling Macarena Rojas-Canales, Daniella Penko, Cameron Angus et al. "Development of a coaxial 3D printing platform for biofabrication of implantable islet-containing constructs." *Advanced healthcare materials* 8, no. 7 (2019): 1801181.
[65] Tebyanian, Hamid, Ali Karami, Mohammad Reza Nourani, Ebrahim Motavallian, Aref Barkhordari, Mohsen Yazdanian, and Alexander Seifalian. "Lung tissue engineering: An update." *Journal of Cellular Physiology* 234, no. 11 (2019): 19256-19270.

[66] Huang, Li, Wei Yuan, Yue Hong, Suna Fan, Xiang Yao, Tao Ren, Lujie Song, Gesheng Yang, and Yaopeng Zhang. "3D printed hydrogels with oxidized cellulose nanofibers and silk fibroin for the proliferation of lung epithelial stem cells." *Cellulose* 28 (2021): 241-257.
[67] Filippou, Valeria, and Charalampos Tsoumpas. "Recent advances on the development of phantoms using 3D printing for imaging with CT, MRI, PET, SPECT, and ultrasound." *Medical physics* 45, no. 9 (2018): e740-e760.
[68] Park, Jae-Hyun, Jeong-Kee Yoon, Jung Bok Lee, Young Min Shin, Kang-Woog Lee, Sang-Woo Bae, JunHee Lee et al. "Experimental tracheal replacement using 3-dimensional bioprinted artificial trachea with autologous epithelial cells and chondrocytes." *Scientific reports* 9, no. 1 (2019): 2103.
[69] Kim, In Gul, Su A. Park, Shin-Hyae Lee, Ji Suk Choi, Hana Cho, Sang Jin Lee, Yoo-Wook Kwon, and Seong Keun Kwon. "Transplantation of a 3D-printed tracheal graft combined with iPS cell-derived MSCs and chondrocytes." *Scientific Reports* 10, no. 1 (2020): 4326.
[70] Zhou, Huan, and Sarit B. Bhaduri. "3D printing in the research and development of medical devices." In *Biomaterials in translational medicine*, pp. 269-289. Academic Press, 2019.
[71] Grauer, Dan. "Quality in orthodontics: the role of customized appliances." *Journal of Esthetic and Restorative Dentistry* 33, no. 1 (2021): 253-258.
[72] Redaelli, Davide Felice, Valentina Abbate, Fabio Alexander Storm, Alfredo Ronca, Andrea Sorrentino, Cristina De Capitani, Emilia Biffi, Luigi Ambrosio, Giorgio Colombo, and Paolo Fraschini. "3D printing orthopedic scoliosis braces: a test comparing FDM with thermoforming." *The International Journal of Advanced Manufacturing Technology* 111, no. 5-6 (2020): 1707-1720.
[73] Thurzo, Andrej, Filip Kočiš, Bohuslav Novák, Ladislav Czako, and Ivan Varga. "Three-dimensional modeling and 3D printing of biocompatible orthodontic power-arm design with clinical application." *Applied Sciences* 11, no. 20 (2021): 9693.
[74] Zuniga, Jorge M., Jean Peck, Rakesh Srivastava, Dimitrios Katsavelis, and Adam Carson. "An open source 3D-printed transitional hand prosthesis for children." *JPO: Journal of Prosthetics and Orthotics* 28, no. 3 (2016): 103-108.
[75] Zuniga, Jorge M. "3D printed antibacterial prostheses." *Applied Sciences* 8, no. 9 (2018): 1651.
[76] Honigmann, Philipp, Neha Sharma, Ralf Schumacher, Jasmine Rueegg, Mathias Haefeli, and Florian Thieringer. "In-hospital 3D printed scaphoid prosthesis using medical-grade polyetheretherketone (PEEK) biomaterial." *BioMed Research International* 2021 (2021).
[77] Xiao, Ran, Xiaobin Feng, Rong Fan, Sijie Chen, Jian Song, Libo Gao, and Yang Lu. "3D printing of titanium-coated gradient composite lattices for lightweight mandibular prosthesis." *Composites Part B: Engineering* 193 (2020): 108057.
[78] Tsoulfas, Georgios, Petros I. Bangeas, Jasjit S. Suri, and Vasileios N. Papadopoulos. "Introduction: the role of 3D printing in surgery." In *3D Printing: Applications in Medicine and Surgery*, pp. 1-6. Elsevier, 2020.
[79] Chen, Yigang, Linjie Bian, Hong Zhou, Danping Wu, Jie Xu, Chen Gu, Xinqi Fan et al. "Usefulness of three-dimensional printing of superior mesenteric vessels in right hemicolon cancer surgery." *Scientific reports* 10, no. 1 (2020): 11660.
[80] Bianchi, Giuseppe, Tommaso Frisoni, Benedetta Spazzoli, Alessandra Lucchese, and Davide Donati. "Computer assisted surgery and 3D printing in orthopaedic oncology: A lesson learned by cranio-maxillo-facial surgery." *Applied Sciences* 11, no. 18 (2021): 8584.
[81] Melocchi, Alice, Marco Uboldi, Alessandra Maroni, Anastasia Foppoli, Luca Palugan, Lucia Zema, and Andrea Gazzaniga. "3D printing by fused deposition modeling of single-and multi-compartment hollow systems for oral delivery–A review." *International journal of pharmaceutics* 579 (2020): 119155.
[82] Vo, Anh Q., Jiaxiang Zhang, Dinesh Nyavanandi, Suresh Bandari, and Michael A. Repka. "Hot melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine." *Carbohydrate polymers* 246 (2020): 116519.
[83] Lee, Jaemin, Chanwoo Song, Inhwan Noh, Sangbyeong Song, and Yun-Seok Rhee. "Hot-melt 3D extrusion for the fabrication of customizable modified-release solid dosage forms." *Pharmaceutics* 12, no. 8 (2020): 738.
[84] Awad, Atheer, Fabrizio Fina, Sarah J. Trenfield, Pavanesh Patel, Alvaro Goyanes, Simon Gaisford, and Abdul W. Basit. "3D printed pellets (miniprintlets): A novel, multi-drug, controlled release platform technology." *Pharmaceutics* 11, no. 4 (2019): 148.
[85] Robles-Martinez, Pamela, Xiaoyan Xu, Sarah J. Trenfield, Atheer Awad, Alvaro Goyanes, Richard Telford, Abdul W. Basit, and Simon Gaisford. "3D printing of a multi-layered polypill containing six drugs using a novel stereolithographic method." *Pharmaceutics* 11, no. 6 (2019): 274.
[86] Thakkar, Rishi, Amit Raviraj Pillai, Jiaxiang Zhang, Yu Zhang, Vineet Kulkarni, and Mohammed Maniruzzaman. "Novel on-demand 3-dimensional (3-D) printed tablets using fill density as an effective release-controlling tool." *Polymers* 12, no. 9 (2020): 1872.
[87] Yu, Ilhan, and Roland K. Chen. "A feasibility study of an extrusion-based fabrication process for personalized drugs." *Journal of Personalized Medicine* 10, no. 1 (2020): 16.

[88] Musazzi, Umberto M., Francesca Selmin, Marco A. Ortenzi, Garba Khalid Mohammed, Silvia Franzé, Paola Minghetti, and Francesco Cilurzo. "Personalized orodispersible films by hot melt ram extrusion 3D printing." *International journal of pharmaceutics* 551, no. 1-2 (2018): 52-59.
[89] Liang, Kun, Simone Carmone, Davide Brambilla, and Jean-Christophe Leroux. "3D printing of a wearable personalized oral delivery device: A first-in-human study." *Science advances* 4, no. 5 (2018): eaat2544.
[90] Reddy Dumpa, Nagi, Suresh Bandari, and Michael A Repka. "Novel gastroretentive floating pulsatile drug delivery system produced via hot-melt extrusion and fused deposition modeling 3D printing." *Pharmaceutics* 12, no. 1 (2020): 52.
[91] Yan, Ting-Ting, Zhu-Fen Lv, Pan Tian, Min-Mei Lin, Wei Lin, Si-Yu Huang, and Yan-Zhong Chen. "Semi-solid extrusion 3D printing ODFs: an individual drug delivery system for small scale pharmacy." *Drug development and industrial pharmacy* 46, no. 4 (2020): 531-538.
[92] Gao, Ge, Minjun Ahn, Won-Woo Cho, Byoung-Soo Kim, and Dong-Woo Cho. "3D printing of pharmaceutical application: drug screening and drug delivery." *Pharmaceutics* 13, no. 9 (2021): 1373.
[93] Vaidya, Manasi. "Startups tout commercially 3D-printed tissue for drug screening." *biomedicine* 7, no. 8 (2015): 3.
[94] Nelson, Bryn. "3-dimensional bioprinting makes its mark: New tissue and organ printing methods are yielding critical new tools for the laboratory and clinic." *Cancer cytopathology* 123, no. 4 (2015): 203-204.
[95] Ma, Xuanyi, Justin Liu, Wei Zhu, Min Tang, Natalie Lawrence, Claire Yu, Maling Gou, and Shaochen Chen. "3D bioprinting of functional tissue models for personalized drug screening and in vitro disease modeling." *Advanced drug delivery reviews* 132 (2018): 235-251.
[96] Ozbolat, Ibrahim T., Weijie Peng, and Veli Ozbolat. "Application areas of 3D bioprinting." *Drug discovery today* 21, no. 8 (2016): 1257-1271.
[97] Clevers, Hans. "Modeling development and disease with organoids." *Cell* 165, no. 7 (2016): 1586-1597.
[98] Zhang, Boyang, Anastasia Korolj, Benjamin Fook Lun Lai, and Milica Radisic. "Advances in organ-on-a-chip engineering." *Nature Reviews Materials* 3, no. 8 (2018): 257-278.
[99] Nadhif, Muhammad Hanif, Hanif Assyarify, Muhammad Irsyad, Arindha R. Pramesti, and Muhammad Suhaeri. "Recent advances in 3D printed wound dressings." In *AIP Conference Proceedings*, vol. 2344, no. 1. AIP Publishing, 2021.
[100] Ilhan, Elif, Sumeyye Cesur, Ece Guler, Fadime Topal, Deniz Albayrak, Mehmet Mucahit Guncu, Muhammet Emin Cam et al. "Development of Satureja cuneifolia-loaded sodium alginate/polyethylene glycol scaffolds produced by 3D-printing technology as a diabetic wound dressing material." *International Journal of Biological Macromolecules* 161 (2020): 1040-1054.
[101] Spicer, Christopher D. "Hydrogel scaffolds for tissue engineering: The importance of polymer choice." *Polymer Chemistry* 11, no. 2 (2020): 184-219.
[102] Khansari, Maziyar M., Lioudmila V. Sorokina, Prithviraj Mukherjee, Farrukh Mukhtar, Mostafa Rezazadeh Shirdar, Mahnaz Shahidi, and Tolou Shokuhfar. "Classification of hydrogels based on their source: A review and application in stem cell regulation." *Jom* 69 (2017): 1340-1347.
[103] El-Sherbiny, Ibrahim M., and Magdi H. Yacoub. "Hydrogel scaffolds for tissue engineering: Progress and challenges." *Global Cardiology Science and Practice* 2013, no. 3 (2013): 38.
[104] Yan, Huiqiong, Xiuqiong Chen, Meixi Feng, Zaifeng Shi, Dashuai Zhang, and Qiang Lin. "Layer-by-layer assembly of 3D alginate-chitosan-gelatin composite scaffold incorporating bacterial cellulose nanocrystals for bone tissue engineering." *Materials Letters* 209 (2017): 492-496.
[105] He, Jiankang, Ruomeng Chen, Yongjie Lu, Li Zhan, Yaxiong Liu, Dichen Li, and Zhongmin Jin. "Fabrication of circular microfluidic network in enzymatically-crosslinked gelatin hydrogel." *Materials Science and Engineering: C* 59 (2016): 53-60.
[106] Vickers, Neil J. "Animal communication: when i'm calling you, will you answer too?." *Current biology* 27, no. 14 (2017): R713-R715.
[107] Nguyen, Peter K., William Gao, Saloni D. Patel, Zain Siddiqui, Saul Weiner, Emi Shimizu, Biplab Sarkar, and Vivek A. Kumar. "Self-assembly of a dentinogenic peptide hydrogel." *ACS omega* 3, no. 6 (2018): 5980-5987.
[108] Ergul, Necdet Mekki, Semra Unal, Ilyas Kartal, Cevriye Kalkandelen, Nazmi Ekren, Osman Kilic, Lin Chi-Chang, and Oguzhan Gunduz. "3D printing of chitosan/poly (vinyl alcohol) hydrogel containing synthesized hydroxyapatite scaffolds for hard-tissue engineering." *Polymer Testing* 79 (2019): 106006.
[109] Lode, Anja, Michael Meyer, Sophie Brüggemeier, Birgit Paul, Hagen Baltzer, Michaela Schröpfer, Claudia Winkelmann, Frank Sonntag, and Michael Gelinsky. "Additive manufacturing of collagen scaffolds by three-dimensional plotting of highly viscous dispersions." *Biofabrication* 8, no. 1 (2016): 015015.
[110] Jang, Tae-Sik, Hyun-Do Jung, Houwen Matthew Pan, Win Tun Han, Shengyang Chen, and Juha Song. "3D printing of hydrogel composite systems: Recent advances in technology for tissue engineering." *International Journal of Bioprinting* 4, no. 1 (2018).
[111] Wahab, Eta, Alina Shamsuddinb, Wan Nurul Karimah Wan Ahmadc, Nurazwa Ahmadd, and Law Xin Weie. "Identifying future prospect of 3D bioprinting in Malaysia." *Journal of Critical Reviews* 7, no. 8 (2020).

[112] Williams, David. "Revisiting the definition of biocompatibility." *Medical device technology* 14, no. 8 (2003): 10-13.
[113] Saroia, Jabran, Wang Yanen, Qinghua Wei, Kun Zhang, Tingli Lu, and Bo Zhang. "A review on biocompatibility nature of hydrogels with 3D printing techniques, tissue engineering application and its future prospective." *Bio-Design and Manufacturing* 1 (2018): 265-279.
[114] Hutmacher, D. W., J. C. H. Goh, and S. H. Teoh. "An introduction to biodegradable materials for tissue engineering applications." *Annals-academy of medicine singapore* 30, no. 2 (2001): 183-191.
[115] Drury, Jeanie L., and David J. Mooney. "Hydrogels for tissue engineering: scaffold design variables and applications." *Biomaterials* 24, no. 24 (2003): 4337-4351.
[116] Rouwkema, Jeroen, Nicolas C. Rivron, and Clemens A. van Blitterswijk. "Vascularization in tissue engineering." *Trends in biotechnology* 26, no. 8 (2008): 434-441.
[117] Druecke, Daniel, Stefan Langer, Evert Lamme, Jeroen Pieper, Marija Ugarkovic, Hans Ulrich Steinau, and Heinz Herbert Homann. "Neovascularization of poly (ether ester) block-copolymer scaffolds in vivo: Long-term investigations using intravital fluorescent microscopy." *Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials* 68, no. 1 (2004): 10-18.
[118] Yang, Shoufeng, Kah-Fai Leong, Zhaohui Du, and Chee-Kai Chua. "The design of scaffolds for use in tissue engineering. Part I. Traditional factors." *Tissue engineering* 7, no. 6 (2001): 679-689.
[119] Leijten, Jeroen, Jungmok Seo, Kan Yue, Grissel Trujillo-de Santiago, Ali Tamayol, Guillermo U. Ruiz-Esparza, Su Ryon Shin et al. "Spatially and temporally controlled hydrogels for tissue engineering." *Materials Science and Engineering: R: Reports* 119 (2017): 1-35.
[120] Bai, Xin, Mingzhu Gao, Sahla Syed, Jerry Zhuang, Xiaoyang Xu, and Xue-Qing Zhang. "Bioactive hydrogels for bone regeneration." *Bioactive materials* 3, no. 4 (2018): 401-417.
[121] Goenka, Sumit, Vinayak Sant, and Shilpa Sant. "Graphene-based nanomaterials for drug delivery and tissue engineering." *Journal of Controlled Release* 173 (2014): 75-88.
[122] Eivazzadeh-Keihan, Reza, Karim Khanmohammadi Chenab, Reza Taheri-Ledari, Jafar Mosafer, Seyed Masoud Hashemi, Ahad Mokhtarzadeh, Ali Maleki, and Michael R. Hamblin. "Recent advances in the application of mesoporous silica-based nanomaterials for bone tissue engineering." *Materials Science and Engineering: C* 107 (2020): 110267.
[123] Lee, Jung-Hwan, and Hae-Won Kim. "Emerging properties of hydrogels in tissue engineering." *Journal of tissue engineering* 9 (2018): 2041731418768285.
[124] Vedadghavami, Armin, Farnaz Minooei, Mohammad Hossein Mohammadi, Sultan Khetani, Ahmad Rezaei Kolahchi, Shohreh Mashayekhan, and Amir Sanati-Nezhad. "Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications." *Acta biomaterialia* 62 (2017): 42-63.
[125] Kim, Youhwan, Hyojin Ko, Ik Keun Kwon, and Kwanwoo Shin. "Extracellular matrix revisited: roles in tissue engineering." *International neurourology journal* 20, no. Suppl 1 (2016): S23.
[126] Gregor, Aleš, Eva Filová, Martin Novák, Jakub Kronek, Hynek Chlup, Matěj Buzgo, Veronika Blahnová et al. "Designing of PLA scaffolds for bone tissue replacement fabricated by ordinary commercial 3D printer." *Journal of biological engineering* 11, no. 1 (2017): 1-21.
[127] Zhang, Xiaoying, and Yangde Zhang. "Tissue engineering applications of three-dimensional bioprinting." *Cell biochemistry and biophysics* 72 (2015): 777-782.
[128] Akther, Fahima, Peter Little, Zhiyong Li, Nam-Trung Nguyen, and Hang T. Ta. "Hydrogels as artificial matrices for cell seeding in microfluidic devices." *RSC advances* 10, no. 71 (2020): 43682-43703.
[129] Mantha, Somasundar, Sangeeth Pillai, Parisa Khayambashi, Akshaya Upadhyay, Yuli Zhang, Owen Tao, Hieu M. Pham, and Simon D. Tran. "Smart hydrogels in tissue engineering and regenerative medicine." *Materials* 12, no. 20 (2019): 3323.
[130] Lu, Qijin, Kavitha Ganesan, Dan T. Simionescu, and Narendra R. Vyavahare. "Novel porous aortic elastin and collagen scaffolds for tissue engineering." *Biomaterials* 25, no. 22 (2004): 5227-5237.
[131] Chung, Johnson HY, Sina Naficy, Zhilian Yue, Robert Kapsa, Anita Quigley, Simon E. Moulton, and Gordon G. Wallace. "Bio-ink properties and printability for extrusion printing living cells." *Biomaterials Science* 1, no. 7 (2013): 763-773.
[132] Jabbari, Esmaiel. "Challenges for natural hydrogels in tissue engineering." *Gels* 5, no. 2 (2019): 30.
[133] Zhao, Hongbo, Min Liu, Yajie Zhang, Jingbo Yin, and Renjun Pei. "Nanocomposite hydrogels for tissue engineering applications." *Nanoscale* 12, no. 28 (2020): 14976-14995.
[134] Stratton, Scott, Namdev B. Shelke, Kazunori Hoshino, Swetha Rudraiah, and Sangamesh G. Kumbar. "Bioactive polymeric scaffolds for tissue engineering." *Bioactive materials* 1, no. 2 (2016): 93-108.
[135] Annabi, Nasim, Jason W. Nichol, Xia Zhong, Chengdong Ji, Sandeep Koshy, Ali Khademhosseini, and Fariba Dehghani. "Controlling the porosity and microarchitecture of hydrogels for tissue engineering." *Tissue Engineering Part B: Reviews* 16, no. 4 (2010): 371-383.

[136] Tetsuka, Hiroyuki, and Su Ryon Shin. "Materials and technical innovations in 3D printing in biomedical applications." *Journal of Materials Chemistry B* 8, no. 15 (2020): 2930-2950.
[137] Advincula, Rigoberto C., John Ryan C. Dizon, Eugene B. Caldona, Robert Andrew Viers, Francis Dave C. Siacor, Reymark D. Maalihan, and Alejandro H. Espera. "On the progress of 3D-printed hydrogels for tissue engineering." *MRS communications* 11 (2021): 539-553.
[138] Martin, Victor, Isabel A. Ribeiro, Marta M. Alves, Lídia Gonçalves, Ricardo A. Claudio, Liliana Grenho, Maria H. Fernandes, Pedro Gomes, Catarina F. Santos, and Ana F. Bettencourt. "Engineering a multifunctional 3D-printed PLA-collagen-minocycline-nanoHydroxyapatite scaffold with combined antimicrobial and osteogenic effects for bone regeneration." *Materials science and engineering: C* 101 (2019): 15-26.
[139] Murphy, Robert, David P. Walsh, Charles A. Hamilton, Sally-Ann Cryan, Marc in het Panhuis, and Andreas Heise. "Degradable 3D-printed hydrogels based on star-shaped copolypeptides." *Biomacromolecules* 19, no. 7 (2018): 2691-2699.
[140] Wang, Pengrui, David Berry, Amy Moran, Frank He, Trevor Tam, Luwen Chen, and Shaochen Chen. "Controlled growth factor release in 3D-printed hydrogels." *Advanced healthcare materials* 9, no. 15 (2020): 1900977.
[141] Liu, Qiongqiong, Qingtao Li, Sheng Xu, Qiujian Zheng, and Xiaodong Cao. "Preparation and properties of 3D printed alginate–chitosan polyion complex hydrogels for tissue engineering." *Polymers* 10, no. 6 (2018): 664.
[142] Li, Jinhua, Chengtie Wu, Paul K. Chu, and Michael Gelinsky. "3D printing of hydrogels: Rational design strategies and emerging biomedical applications." *Materials Science and Engineering: R: Reports* 140 (2020): 100543.
[143] Tessmar, Joerg K., and Achim M. Göpferich. "Customized PEG-derived copolymers for tissue-engineering applications." *Macromolecular bioscience* 7, no. 1 (2007): 23-39.
[144] Christensen, Rie Kjær, Christoffer von Halling Laier, Aysel Kiziltay, Sandra Wilson, and Niels Bent Larsen. "3D printed hydrogel multiassay platforms for robust generation of engineered contractile tissues." *Biomacromolecules* 21, no. 2 (2019): 356-365.
[145] Mohanty, Soumyaranjan, Martin Alm, Mette Hemmingsen, Alireza Dolatshahi-Pirouz, Jon Trifol, Peter Thomsen, Martin Dufva, Anders Wolff, and Jenny Emnéus. "3D printed silicone–hydrogel scaffold with enhanced physicochemical properties." *Biomacromolecules* 17, no. 4 (2016): 1321-1329.
[146] Janarthanan, Gopinathan, Hyun Soo Shin, In-Gul Kim, Pyung Ji, Eun-Jae Chung, Chibum Lee, and Insup Noh. "Self-crosslinking hyaluronic acid–carboxymethylcellulose hydrogel enhances multilayered 3D-printed construct shape integrity and mechanical stability for soft tissue engineering." *Biofabrication* 12, no. 4 (2020): 045026.
[147] Ramiah, Previn, Lisa C. Du Toit, Yahya E. Choonara, Pierre PD Kondiah, and Viness Pillay. "Hydrogel-based bioinks for 3D bioprinting in tissue regeneration." *Frontiers in Materials* 7 (2020): 76.
[148] Lee, A. R. H. A., A. R. Hudson, D. J. Shiwarski, J. W. Tashman, T. J. Hinton, S. Yerneni, J. M. Bliley, P. G. Campbell, and A. W. Feinberg. "3D bioprinting of collagen to rebuild components of the human heart." *Science* 365, no. 6452 (2019): 482-487.
[149] Zhang, Zimeng, Ruochen Liu, Herman Zepeda, Li Zeng, Jingjing Qiu, and Shiren Wang. "3D printing super strong hydrogel for artificial meniscus." *ACS Applied Polymer Materials* 1, no. 8 (2019): 2023-2032.
[150] Xu, Yifan, Qinghua Meng, Xin Jin, Feng Liu, and Jianjun Yu. "Biodegradable scaffolds for urethra tissue engineering based on 3D printing." *ACS Applied Bio Materials* 3, no. 4 (2020): 2007-2016.
[151] Benjamin, Aaron D., Reha Abbasi, Madison Owens, Robert J. Olsen, Danica J. Walsh, Thomas B. LeFevre, and James N. Wilking. "Light-based 3D printing of hydrogels with high-resolution channels." *Biomedical Physics & Engineering Express* 5, no. 2 (2019): 025035.
[152] Zhang, Biao, Shiya Li, Hardik Hingorani, Ahmad Serjouei, Liraz Larush, Amol A. Pawar, Wei Huang Goh et al. "Highly stretchable hydrogels for UV curing based high-resolution multimaterial 3D printing." *Journal of Materials Chemistry B* 6, no. 20 (2018): 3246-3253.
[153] Shin, Sungchul, Hojung Kwak, and Jinho Hyun. "Melanin nanoparticle-incorporated silk fibroin hydrogels for the enhancement of printing resolution in 3D-projection stereolithography of poly (ethylene glycol)-tetraacrylate bio-ink." *ACS applied materials & interfaces* 10, no. 28 (2018): 23573-23582.
[154] Hsieh, Cheng-Tien, and Shan-hui Hsu. "Double-network polyurethane-gelatin hydrogel with tunable modulus for high-resolution 3D bioprinting." *ACS applied materials & interfaces* 11, no. 36 (2019): 32746-32757.
[155] Benjamin, Aaron D., Reha Abbasi, Madison Owens, Robert J. Olsen, Danica J. Walsh, Thomas B. LeFevre, and James N. Wilking. "Light-based 3D printing of hydrogels with high-resolution channels." *Biomedical Physics & Engineering Express* 5, no. 2 (2019): 025035.
[156] Zhang, Biao, Shiya Li, Hardik Hingorani, Ahmad Serjouei, Liraz Larush, Amol A. Pawar, Wei Huang Goh et al. "Highly stretchable hydrogels for UV curing based high-resolution multimaterial 3D printing." *Journal of Materials Chemistry B* 6, no. 20 (2018): 3246-3253.
[157] Hsieh, Cheng-Tien, and Shan-hui Hsu. "Double-network polyurethane-gelatin hydrogel with tunable modulus for high-resolution 3D bioprinting." *ACS applied materials & interfaces* 11, no. 36 (2019): 32746-32757.

[158] Shin, Sungchul, Hojung Kwak, and Jinho Hyun. "Melanin nanoparticle-incorporated silk fibroin hydrogels for the enhancement of printing resolution in 3D-projection stereolithography of poly (ethylene glycol)-tetraacrylate bio-ink." *ACS applied materials & interfaces* 10, no. 28 (2018): 23573-23582.
[159] Chu, Honghui, Wenguang Yang, Lujing Sun, Shuxiang Cai, Rendi Yang, Wenfeng Liang, Haibo Yu, and Lianqing Liu. "4D printing: a review on recent progresses." *Micromachines* 11, no. 9 (2020): 796.
[160] Choi, Jin, O-Chang Kwon, Wonjin Jo, Heon Ju Lee, and Myoung-Woon Moon. "4D printing technology: a review." *3D Printing and Additive Manufacturing* 2, no. 4 (2015): 159-167.
[161] Jilte, R.D., Kumar, R. and Ahmadi, M.H., 2019. Cooling performance of nanofluid submerged vs. nanofluid circulated battery thermal management systems. *Journal of Cleaner Production*, *240*, p.118131.
[162] Singh, A.P., Pradhan, N.R., Luhach, A.K., Agnihotri, S., Jhanjhi, N.Z., Verma, S., Ghosh, U. and Roy, D.S., 2020. A novel patient-centric architectural framework for blockchain-enabled healthcare applications. *IEEE Transactions on Industrial Informatics*, *17*(8), pp.5779-5789.
[163] Panda, S.K., Aggarwal, I., Kumar, H., Prasad, L., Kumar, A., Sharma, A., Vo, D.V.N., Van Thuan, D. and Mishra, V., 2021. Magnetite nanoparticles as sorbents for dye removal: a review. *Environmental Chemistry Letters*, *19*, pp.2487-2525.
[164]Bashir, S., Thakur, A., Lgaz, H., Chung, I.M. and Kumar, A., 2020. Corrosion inhibition efficiency of bronopol on aluminium in 0.5 M HCl solution: Insights from experimental and quantum chemical studies. *Surfaces and Interfaces*, *20*, p.100542.
[165]Kumar, H., Bhardwaj, K., Sharma, R., Nepovimova, E., Kuča, K., Dhanjal, D.S., Verma, R., Bhardwaj, P., Sharma, S. and Kumar, D., 2020. Fruit and vegetable peels: Utilization of high value horticultural waste in novel industrial applications. *Molecules*, *25*(12), p.2812.