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REVIEW ON 3D BIOPRINTING FOR TISSUES AND ORGANS

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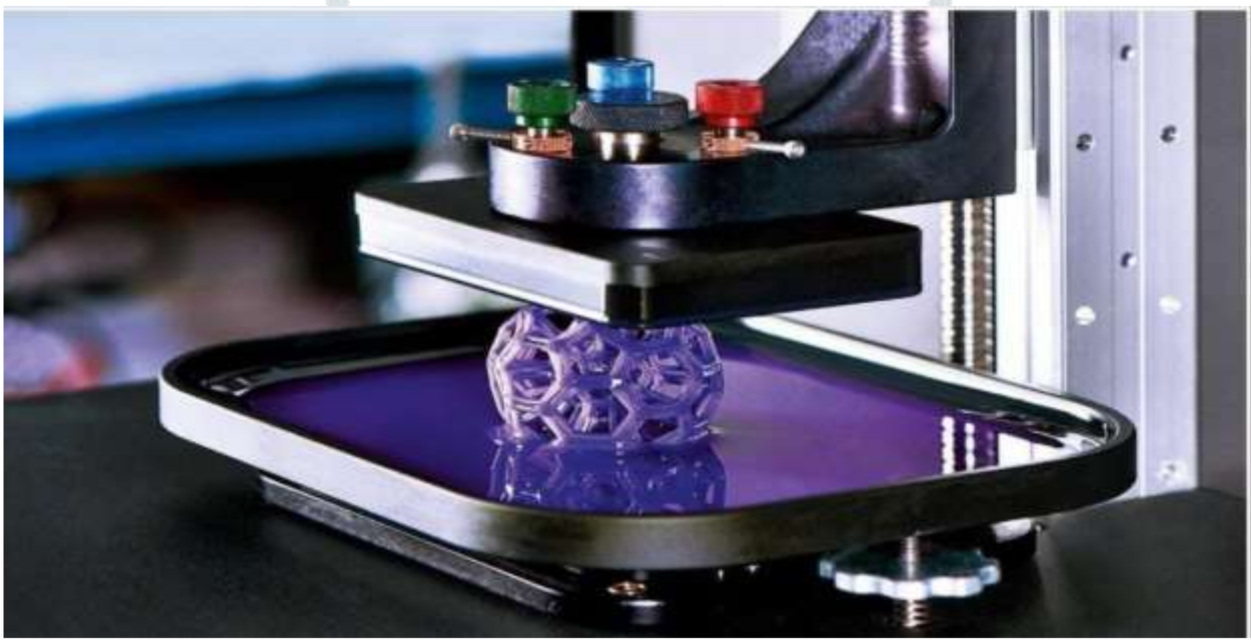
ABSTRACT

Cumulative manufacturing, else known as three- dimensional (3D) printing, is driving major inventions in numerous areas, similar as engineering, manufacturing, art, education and drug. Recent advances have enabled 3D printing of biocompatible materials, cells and supporting components into complex 3D functional living tissues.3D bioprinting is being applied to regenerative drug to address the need for tissues and organs suitable for transplantation [1]. The ongoing advancement of new biomaterial inks has enabled manufacturing of models and in vitro implants able of achieving some position of success in preclinical trials. Remarkable progress in cell biology and biology- inspired computational design has supported in achieving the rearmost corner with planned tissue- or organ- suchlike constructs having specific situations of functionality. Still, biofabricated constructs still have a long way to go before reaching clinics [2]. The goal of researchers is to replace a human organ with Bioprinted organ successfully. The most printed organs with this technology are liver, cartilage, skin, heart and bone tissues etc. This review discusses the state of the art of the technology, along with a broad range of biomaterials used for 3D bioprinting. It provides an update on recent developments in bioprinting and its operations[3]. Biomedical operations are described in detail in relation to major tissues or organs considered in the human body. Current specialized limitations, challenges, future prospects and advancements are critically outlined and discussed [4,5].

KEYWORDS: 3D Bioprinting, bioinks, biomaterial inks, Biofabricated, biomedical operations

1.INTRODUCTION

3D bioprinting is a technology where bioinks, mixed with living cells, are printed layer-by-layer into a natural tissue-like three-dimensional structures.Bioprinting was first demonstrated in 1988 by Dr.Robert J. Klebe when he used a standard office inkjet printer to deposit cells on substrate material. The principle of bioprinting can be defined as the placement of cells within biomaterials into spatially defined structures using automated 3Dbioprinter technologies. The process of bioprinting requires a delivery medium for cells which can be deposited into designed shapes acquired from computer-aided design (CAD) models. The CAD models can be generated using 3D medical images obtained through magnetic resonance imaging (MRI), computed tomography (CT)scanning, and other techniques. Soft biomaterials loaded with living cells are called bioink, and are the "raw material" of bioprinting processes. The development of bioink materials allows scientists to manipulate biological and biochemical environments as well as living cells to create complex biological constructs. The milestones of success are measured by sustained viability of cells during short- and long-term culture, cell spreading and proliferation, cell-cell and cell-extracellular matrix (ECM) interactions, and functionality of the bioprinted constructs [6,7].



2. BACKGROUND

3D printing has become more important in recent decades. 3D printing allows three- dimensional renderings to be realized as physical objects with the use of a printer. 3D-printed objects can be used to study complex cases, to practice procedures, and to teach students and patients.

The need for improved visualization and surgical outcomes has given rise to 3D-printed anatomical models, patient-specific guides, and 3D-printed prosthetics. The growing surgical applications of 3D printing have made it interesting to analyze the current implementation of this new technology. This article gives an overview of the current usage of 3D-printing techniques in human medicine, more specifically surgery [7].

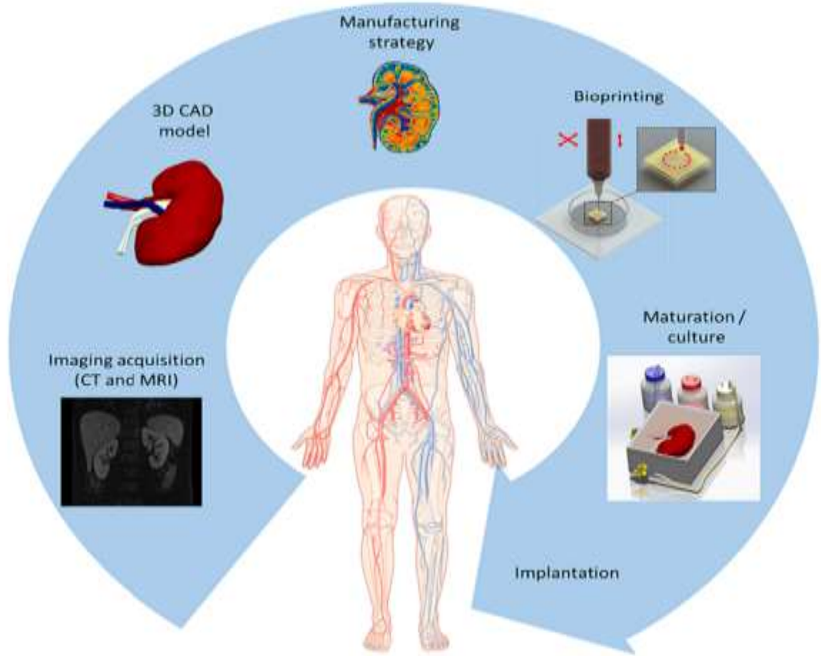


Fig. 1. Schematic illustration of the steps required to generate bioprinted tissue structures. Reproduced with permission from Ref. [31] Copyright 2020 ACS.

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3. ORGAN PRINTING

Organ printing is defined as a layer by layer additive robotic computer-aided bio fabrication of functional 3D organ constructs with using self-assembling tissue spheroids according to digital model. Information technology and computer-aided design software's are instrumental in the transformation of virtual 3D bioimaging information about human tissue and organs into living biological reality during 3D bioprinting. Information technology enables design blueprints for bioprinting of human organs as well as predictive computer simulation both printing and post-printing processes [8].

4. ORGAN BIOPRINTING PROCESS

Bioprinting processes can be broadly classified under four main categories namely, (i) Laser-based bio printing, (ii) Droplet-based bioprinting, (iii) Extrusion-based bio printing, and (iv) Stereo lithography - based bioprinting.

4.1 Laser-based Bioprinting

Laser-based bioprinting processes utilise laser energy to pattern cell-laden bio inks in a three- dimensional spatial arrangement with the aid of Computer-aided Design and Manufacturing (CAD/CAM). Laser radiation, being highly monochromatic, coherent, and highly focussed, was used for precise patterning of metals like Ag, $BaTiO3$, and NiCr into active and passive mesoscopic circuit elements including conductors, capacitors and resistors, with a high spatial resolution of 1-3µm. High resolution and reproducibility of this process made it a viable option for use in biomedical applications such as cell printing. Laser-induced Forward Transfer (LIFT) is a common laser-based bioprinting method used for cell patterning and bioprinting of tissue constructs. Laser-based bioprinting possesses many unique advantages. It is a non-contact process and hence, result in high post-printing cell viabilities. Being a nozzle-free approach, the problem of clogging is eliminated.

4.2 Droplet-based Bioprinting

Droplet-based Bioprinting processes eject cell-laden bioinks out of the nozzle onto a substrate in the form of droplets. They can be classified further into Inkjet bioprinting (CIJ and DOD - Thermal, Piezoelectric and electrostatic), electro-hydrodynamic jetting (EHD-jetting), acoustic bioprinting and microvalve-based bioprinting.

4.2.1 Inkjet Bioprinting.

Inkjet bioprinting is adapted from the inkjet printing technology, with the printing ink cartridges replaced by cell-laden bioink cartridges. Inkjet bioprinting can be broadly classified under two headings, namely continuous inkjet (CIJ) and drop-on-demand (DOD) inkjet printing. DOD inkjet bioprinting techniques eject droplets on demand or only when a trigger is given, aiding in precise control and positioning of droplets. Based on the type of trigger, the DOD inkjet bioprinting could be thermal, piezo-electric, or electrostatic DOD systems. Inkjet bioprinting had been used for printing cells and tissue constructs of bone, cartilage, skin, etc.

4.2.2Electro-hydrodynamic jetting (EHD-jetting)-based Bioprinting

In EHD-jetting-based Bio printing, a high voltage (0.5-20 kV) is applied between the nozzle and the substrate as a back-pressure supply delivers the bioink to the nozzle tip. When the applied electric field force overcomes the viscoelastic force of the bioink and surface tension force at the nozzle tip, droplets of bioink are ejected out of the nozzle by the formation of a Taylor cone.

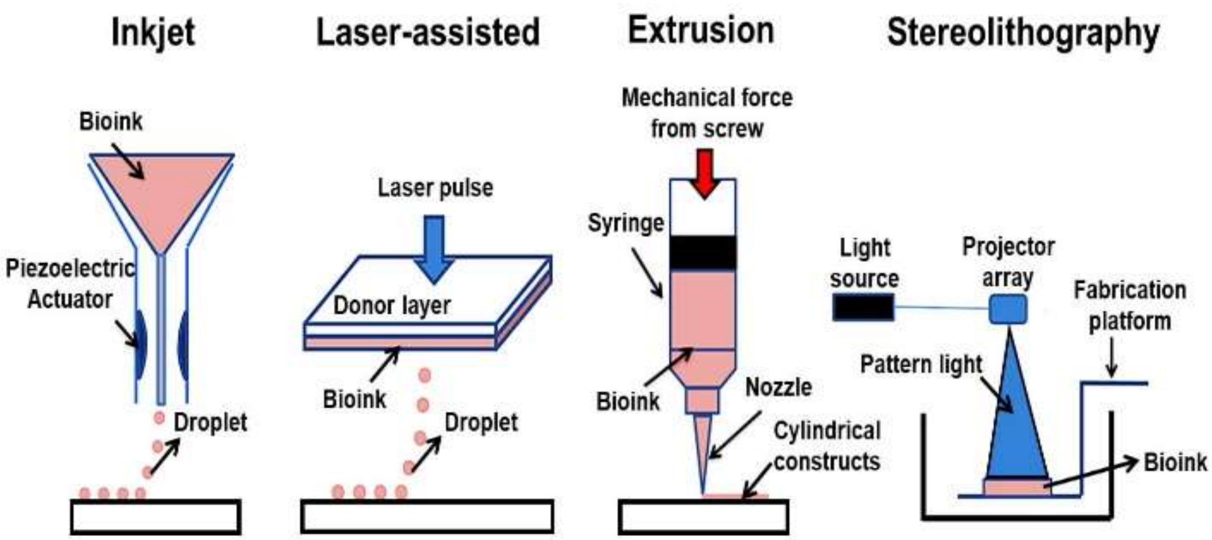
4.3.) Extrusion based Bioprinting

It is the most widely used of all bioprinting modalities. The bioink is extruded out of the nozzle using pneumatic pressure or mechanical force by means of a piston or screw. Extrusion -based bioprinting had been used to bio print cells, tissues, organ modules, and organ-on-a-chip devices, for tissue engineering, cancer research, drug testing, and transplantation. Several tissue types including but not limited to bone, cartilage, skeletal muscle, skin, cardiac tissue, nervous tissue, and liver. Extrusion -based bio printing has many advantages. The first and foremost advantage of this method is the scalability i.e. the ability to print human-scale tissue, which is impossible with any of the other bioprinting methods.

4.4.) Stereolithography Bioprinting

Stereolithography, though developed in 1996 by 3D Systems, is still a fledgling technology in the bioprinting space. Briefly, a layer of photopolymer resin is cured (or polymerized) by light (usually UV) irradiation, the light movement controlled by a computer code / images / CAD files, forming a 3D structure as the build stage is translated vertically building the object layer by layer [8].

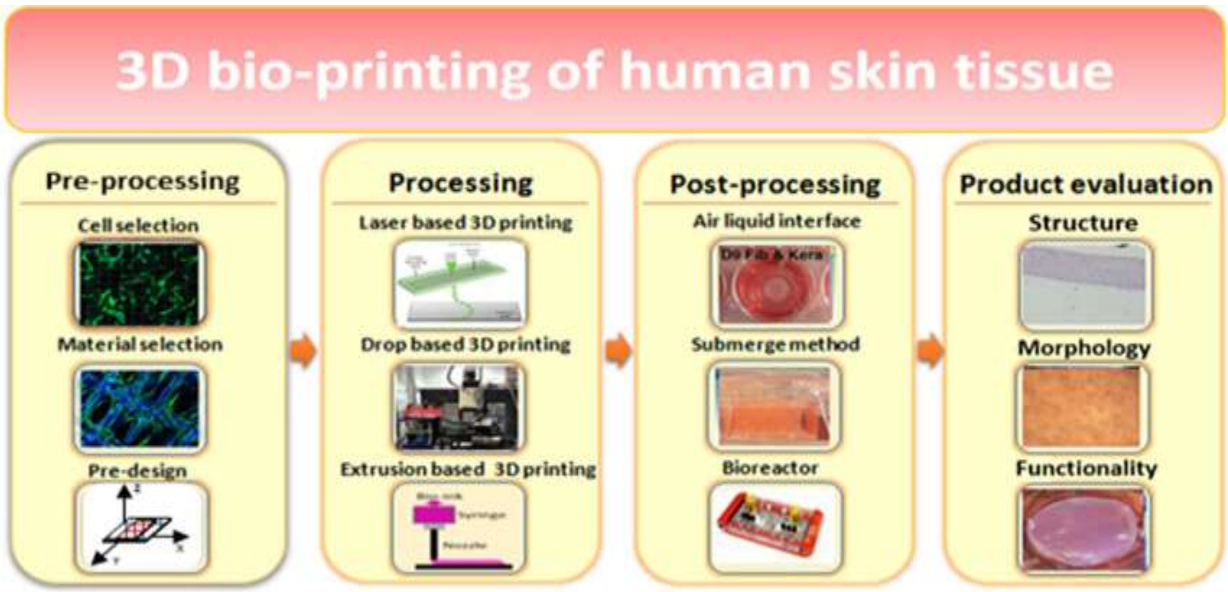
Table 1. Comparison of four types of bioprinting technique [8].



5. STEPS IN 3D BIOPRINTING

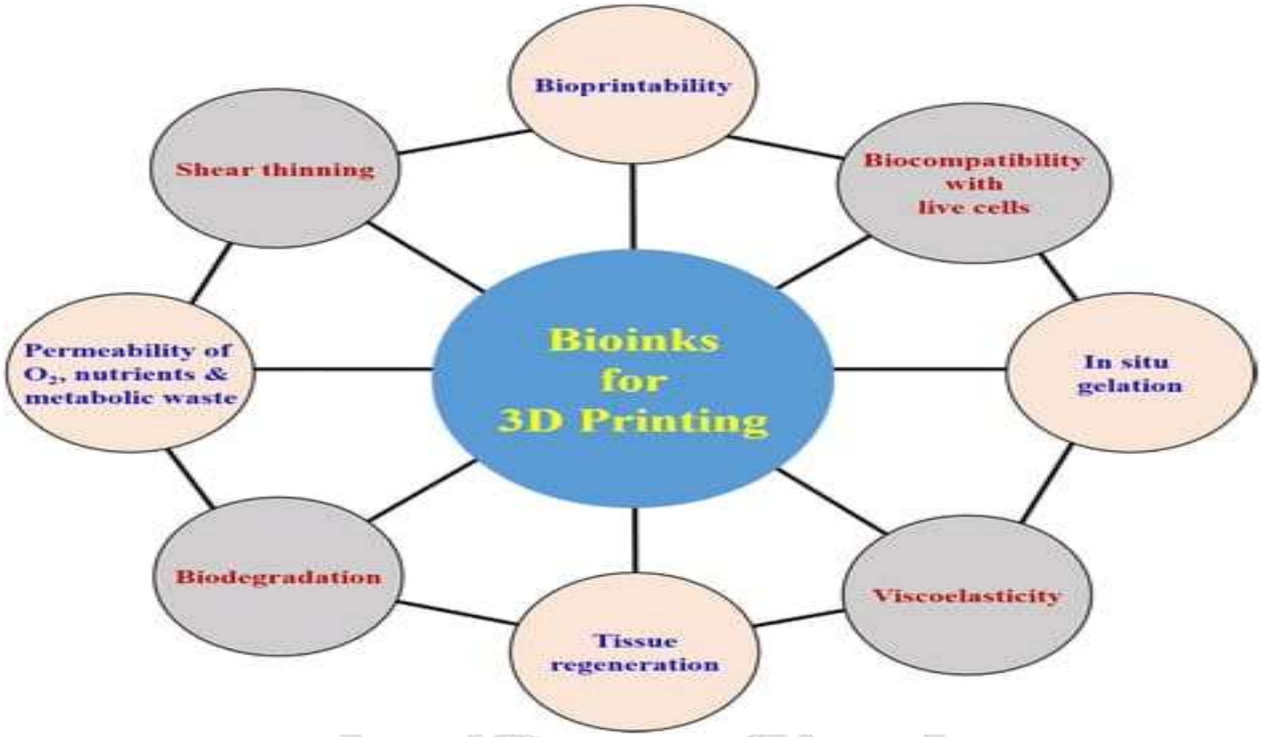
A typical bio printing process consists of three major steps namely pre-processing, processing and post-processing. Pre-processing involves imaging of the tissue or organ using computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound imaging techniques and reconstruction of 3D models from the imaging. The generated 3D models are living tissues would be to use the patient's own cells. Suitable bio inks with properties mimicking the intended tissue to be printed are selected and the cells are suspended in these bio inks. The cell-laden bio inks are then converted into STL file format, which is a commonly accepted file format by most of the commercially available bio printers. The processing step starts with harvesting primary cells from patients, culturing and expanding it ex vivo for the bio printing process. Though cancer cell lines and other non-human cells are being used, the ideal condition for fabricating transplantable into required 3D living tissue / organ according to the 3D model using a bio printer. Post-processing involves maintaining the bio printed tissue / organ in a bio printer for tissue maturation before being transplanted into patients or used as in vitro models for disease modelling, or drug testing [8].

Figure no2. 3D BIOPRINTING OF HUMAN SKIN.

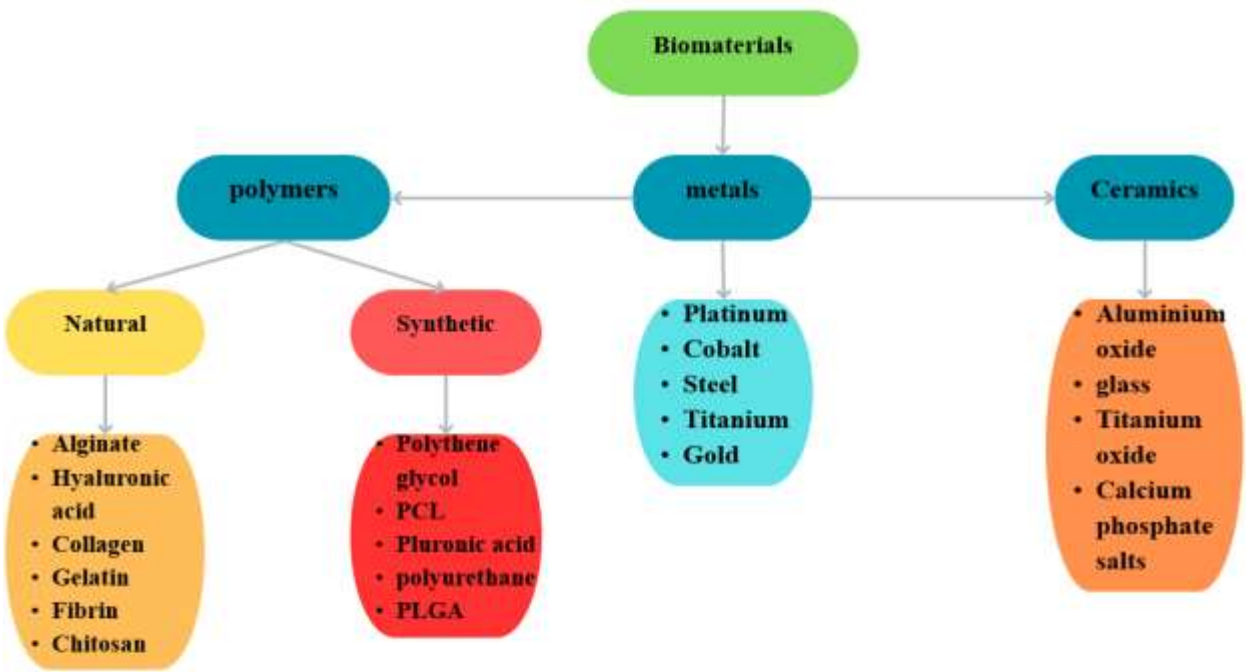


6. REQUIREMENTS OF BIOINK FOR 3D BIOPRINTING

Biomaterial properties include printability, mechanical properties biodegradation, modifiable functional groups on the surface and post printing maturation. Biological requirements mainly include biocompatibility (not only non-toxic to the other tissues/cells, but also live cells' viability inside bioink), cytocompatibility, and bioactivity of cells after printing [9,10]. The important requirements for selecting a bioink for 3D printing in biomaterials aspects. The other important desirable aspects for a bioink include high resolution during printing, in situ gelation, visco elastic properties, low cost, readily available, industrial scalability, bio mimicking the tissue internal structures, mechanical integrity, short post printing time for maturation, and immunological compatibility, when implanted in vivo and wide variety of different types of cells should be employed. Permeability of oxygen gas, metabolic wastes and nutrient transport are also important. These basic requirements are very important while selecting a successful bioink material for 3D bioprinting [4,11].



7. BIOINK MATERIALS AND THEIR PROPERTIES



According to the requirements of the desired tissues and organs, the bioink should be selected and may be modified to regenerate the appropriate tissue structure and organs.

Agarose-based bioinks

Agarose, a marine polysaccharide obtained from sea- weed, is one of the highly used bio Polymer in the bio- medical field for diverse applications because of its excellent gel formation properties. Agarose has a linear polymer chain with an agarobiose repeating unit. This agarobiose backbone chain consists of disaccharides namely D-galactose and 3,6-anhydro-L-galactopyranose]. Though the gelation, mechanical and biocompatibility properties of the agarose are commendable, however, its ability to support cell growth is limited as reported earlier. Hence, the researchers started using blends of functional biomaterials along with the agarose gel. Kreimendahl et al. (2017) reported the use of agarose-based bioink consisting of collagen and fibrinogen, separately. They demonstrated the ability of these agarose-based blend biomaterials to form stable 3D structures and support endothelial and fibroblast cell growth.

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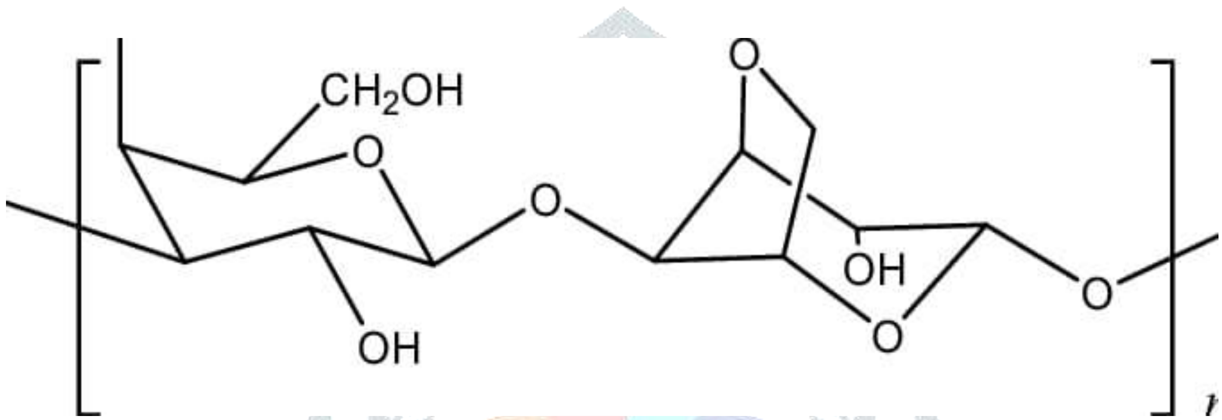
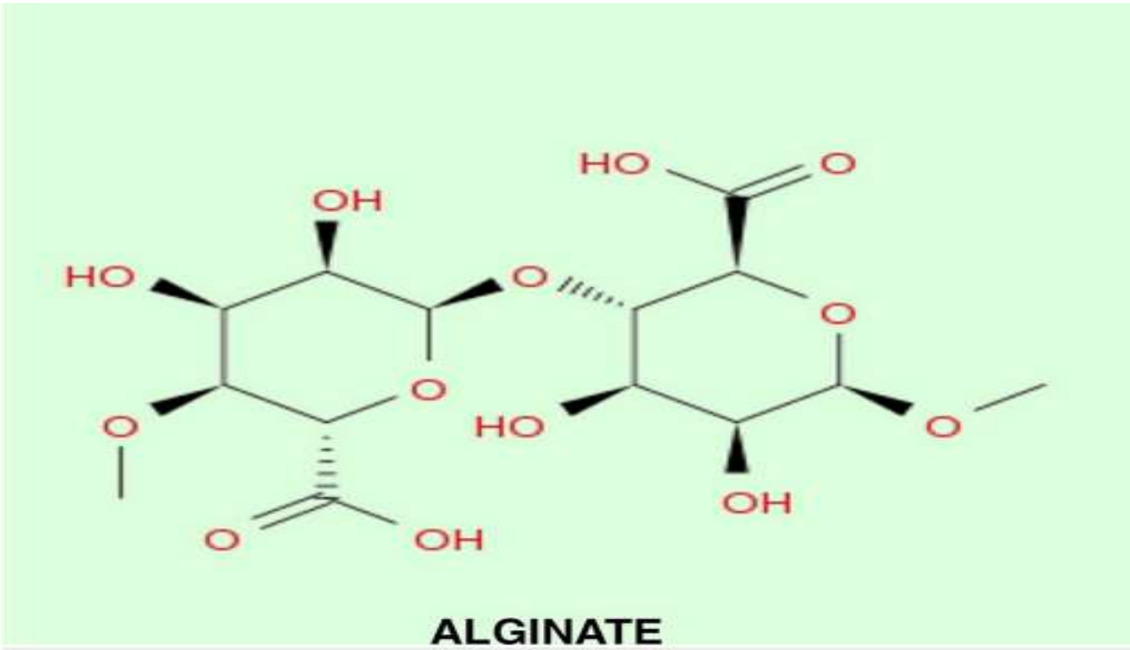


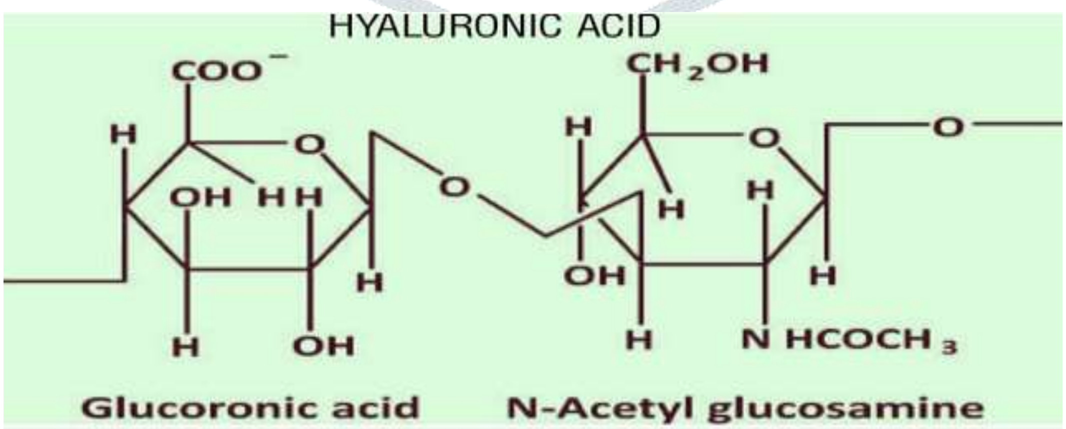
Alginate-based bioinks

Alginate is a natural biopolymer attained from brown algae, which is cheap and also called as algin or alginic acid. This characteristic property is ideal for 3D bio printing bio inks. Thus, Zhang et al. (2013) used this alginate-based bioinks with cartilage cells to print hollow constructs. These vessels-like print- able microfluidic channels are capable of transporting oxygen, nutrients, and biomolecules through the construct and also can support cell growth.



Hyaluronic acid-based bioinks

HA is one of the prominent biomaterials which are used in 3D bioprinting for developing 3D structures. Like other natural polymers, HA has low mechanical properties and slow gelation behaviour, considering the synthetic polymer hydrogels. Ouyang et al. reported a HA-based 3D printed construct using a secondary crosslinking methodology. Sakai et al. (2017) reported HA-gelatin based bioinks which can be polymerized using visible light with the help of Ruthenium-based complexes. They demonstrated the ability of these biomaterials to enhance cell viability and differentiation of human adipose stem cells. In an- other recent work, highly tunable HA-carboxymethyl cellulose gels were reported. The mechanical properties and cell viability of the different concentrations were analyzed, suggesting that high concentration may yield higher cell viability and stability to the 3D printed structures. These recent studies show the advantages HA as bioinks in 3D bioprinting technology.

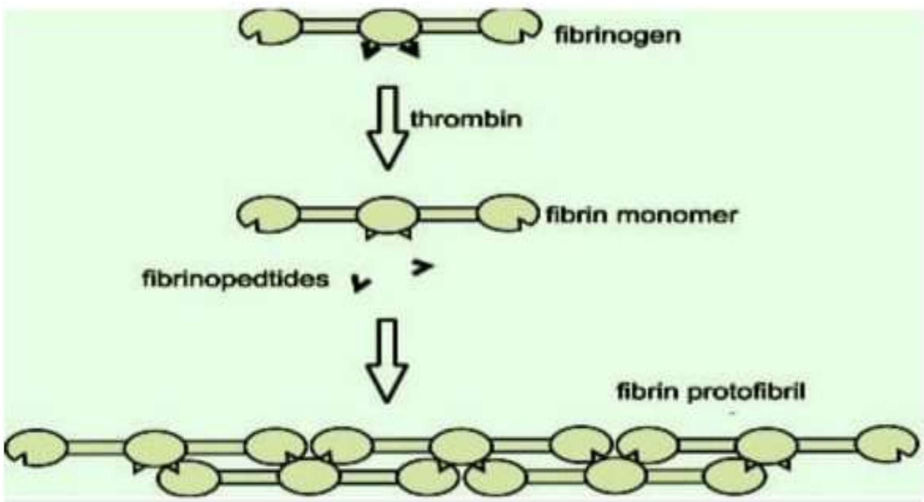


Various other bioinks used in 3D printing

The numerous bioinks used in 3D printing including fibrin, cellulose, silk, ECM-derived bioinks, cell aggregates, cell spheroids, collagen –based bioinks.

Fibrin-based bioinks

Fibrin is a protein which is seen in the blood and helps in clotting. Fibrin hydrogel can be made from fibrinogen by enzymatic treatment of thrombin. This hydrogel has excellent biocompatibility and biodegradation properties, but it has weak mechanical properties. Zhang et al. used fibrin hydrogels along with PCL/PLCL to develop 3D constructs of urethra and seeded multiple cell types to investigate the in vitro effects of this material.

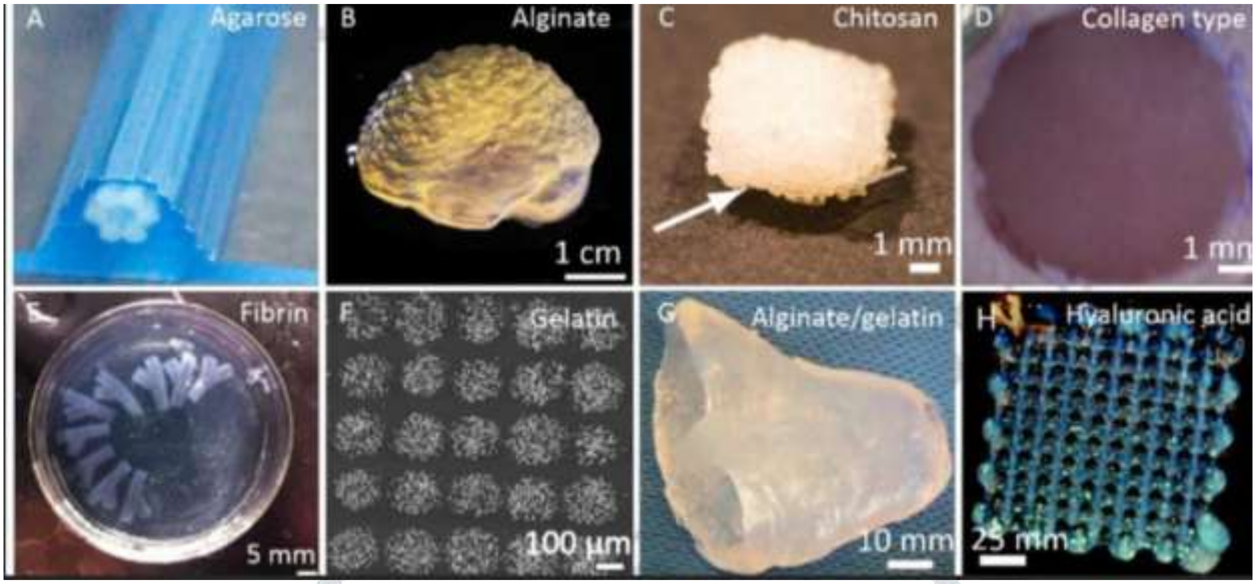


Cellulose-based bioinks

CMC can be converted into environment-sensitive hydrogen by altering its concentrations, molecular weight, salts and degree of methyl grafting appropriately. The aqueous solution of CMC can form gels below 37 °C. For bone regeneration, CMC along with bioactive glass was to develop 3D constructs with high mechanical properties. Markstedt et al. also reported a nanocellulose alginate-based bioinks for cartilage tissue engineering with improved cell viability and mechanical properties of the printed 3D constructs.

Extracellular matrix (ECM)-based bioinks

ECM is the mixture framework which consists of different components such as collagen, glycosaminoglycans, chondroitin sulphate, elastin, etc. where cells are present. Decellularized ECM (dECM) materials are obtained from the desired tissues where cells are removed by a sequential procedure leaving the ECM intact. The obtained constituents are crushed to form a powder-like state and dissolved in a buffer solution and used as bioink for 3D printing. Further, to enhance the printability of the dECM -based bioink, different polymeric hydrogels may be added to the solution. Pati et al. used PCL to improve the printability of the dECM bioink obtained from different tissue types and used it for 3D printing of tissue constructs by cells [4,12].

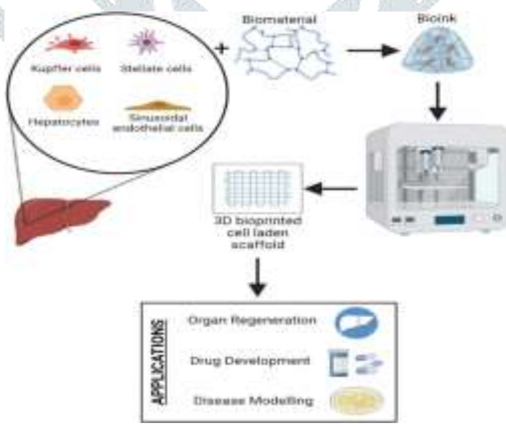


8. BIOPRINTING APPLICATIONS-

The creation of the artificial human organ with life has become possible with help of organ printing which runs on basic principle of 3D printing or rapid prototyping. In most of the cases these Organ are not only printed with life but also with functional.

Human Liver with life

Liver is one of the complex organs in the human body. In the current world millions of people were suffering from liver failure. There are no sufficient donors for them, due to this lot of people are struggling with life. Fortunately with help of bioprinting we can print as many as livers, which can save many lives by transplanting these artificial printed livers in the near future.



Bioprinted artificial human heart

Heart is one of the critical organs for the survival of human life. In every corner of the world there are people suffering from heart failures. For eg. 2 years baby named Mina had a hole in the heart when she was born, doctors fixed the problem successfully with help plastic model printed with inside structure of the heart. Thus 3D printed model save life of a 2 year mina. In some other cases the heart cannot function for longer time and these cases requires the replacement of entire heart from a donor or an artificial bio printed heart should replace the original heart (as shown in Figure

Printing human skin

As per the research studies lead by Wake Forrest School of Medicine under Anthonyalata developed a printer which is capable of printing human skin.This 3D printer can print the cells inside the lab from the own Patients cells as shown in Figure 2. In the near future, Doctors may scan the wounds and decide to spray required number of 3D printed layers to heal the wound quickly. For this these doctors have done a case study on the mice where they took some mice with similar kind of wound and for some of the mice they sprayed the cell layers with help of 3D bio printer and some are kept in a closed group with currently available healing techniques. This technology of skin printing is going to change the rules of the medical healing. even in this technology also patient needs to take rest for some days to fuse the entire cells in to body, but the major advantage is the recovery time comes down drastically [13].

9. RECENT ADVANCES IN BIOPRINTING TECHNOLOGY-

The application of the internet of things (IoT) with the technology of bioprinting has led to breakthroughs in surgical techniques. The ultimate goal is to break the chain of years and years of waiting for a donor organ and to print an entire organ that will be structurally and functionally similar. The main organs on focus to print are our heart, bone, skin, cartilage, and tendon. Besides focusing on printing an entire organ, 3D bioprinting has been used in various other branches, which have been described in Table 3 [12].

Industries	Uses
Dental	Crowns, filling, implants, fixtures
Pharmacy	Drug delivery
Medicine	Pharmacy, prosthetics, hearing aids, orthopedic screws/plates
Food	Cookie, candy, pizza
Automobile industry	Prototypes, spare parts

TABLE 3: Summary of Application of Bioprinting in Different Industries

10. CHALLENGES / DIFFICULTIES IN BIO PRINTING

To continue life of the organ from the pre -processing stage to till implant of organ in to the body is one of the major challenges, other is to control unwanted biological reactions in the organ. The major challenge in this area is to control diffusion of cells, required vascularisation and desired cell density. The major challenge in the entire cycle is life of the cell should be continued and should not have any unwanted biological reactions or to be away from any kind of contamination. This organ printing also consists of some difficulties, some of them were generation of required amount of life cells which suites to appropriate organ. Complete printing process should be carried out in contamination free environment. Even though printing process is carried out by machine lot of human intervention is required in pre and post processing [13].

11. 3D BIOPRINTING INDUSTRIES

In commercial industry 3D, bio-printing is swiftly developing and manifesting the eminence of a mature market with mountainous potential. Several companies are already established the bio-printing technology and raising their finance through various paths. Envision TEC was founded in 2002, has high status for manufacturing the reliable manufacturing system. The product of Envision TEC is 3D-Bioplotter® System, which is used to organize the biomaterials using a computer. Organovo was developed in 2003 to print the organs, applications of drug discovery, and producing fully human tissues. Hydrogels are used as a temporary support. The printing process starts with bio-ink. Using hydrogel and bio-ink, the Blood vessel is designed layer-by-layer. (Courtesy of Organovo Inc.). GeSiM is another privately held company having the properly controlled software. The product of this company is Bio Scaffolder that is able to print scaffolds as well as living cells. It consists of a Z – stepper. Z-drives discretely print enormous materials. It is a standard instrument platform which can fix up to four independent Z axes for relinquish materials. Cyfuse Biomedical K.K. Also develops 3D tissues and their Product is (Regenova®) [14].

12. CONCLUSION

3D printing is already well integrated in medical practice and the literature. Applications vary from anatomical models (mainly for surgical planning) to surgical guides and implants. The main advantages stated by the authors of the selected papers are reduced surgical time, improved medical outcome, and decreased radiation exposure. Unfortunately, the subjective character and lack of evidence supporting majority of these advantages does not allow for conclusive statements. The increased cost of this new technology, and the often limited or unproven advantages, make it questionable whether 3D printing is cost effective for all patients and applications. Several authors have indicated that medical 3D printing has greater advantages when used to handle complex cases and with less experienced surgeons [7].

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