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ROLE OF 3D BIOPRINTING TECHNOLOGY IN PHARMACEUTICAL SCIENCE

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ABSTRACT
The novel three-dimensional printing technology is discovered with the long-term goal to produce human tissues and the organs for the transplants and the surgical therapy, which is mainly based on the layer-by-layer additive fabricated method and 3D imaging. The aim of this review paper is to give an overview of bioprinting existing literature and the principles and software used to demonstrate how a digital information is transferred into the biological models that imitate the biomimetic organs. This review paper surveys the multiple application of bioprinting technology by demonstrating the current developments and the limitations of bio-materials, the paper highlights the goals, and objectives of the bioprinting and then the brief introduction of new materials and their specific and critical parameters for printing as well as the broad applications areas, and a possible way to sort out the serious problem in shortage of human organs in tissue engineering and regenerative medicines ,this paper also highlights the key factors of the printing process, and also the existing challenges of the 3D bioprinting in the selection of cell and material, and the various limitation that prevent approaches in usual clinical practice which includes the unsatisfactory properties of materials, high cost, and relatively long processing durations.

Keywords: Bioprinting, Additive manufacturing, Biomaterials.

INTRODUCTION

3D BIOPRINTING TECHNOLOGY Bioprinting technology has emerging as the most powerful tool for the building of biomimetic organ structures and the tissues in the field of tissues engineering, 3D printing technology has gained the lots of attention because of the wide applications in multiple fields and its ability to resolve and overcome the engineering challenges encountered in the field of tissue engineering. As per the definition, bioprinting was defined as the use of material transferring process for the assembling and patterning the biologically relevant materials with a prescribed organization to accomplish the one or more biological functions and activities.

IDEA BEHIND 3D BIOPRINTING When the simple idea of additive manufacturing is combine with biomedical engineering, the novel research is born ; 3D bioprinting. At present scenario, 3D bioprinting can be seen from the two different point of view i;e narrow view point and the broad view point, if we go through the concept behind the broad view point, the 3D bioprinting was established when the biomedical applications were meet up with 3D printing to used in the printing ofmedical aids, polymers, ceramics and the scaffolds, and if we talk about Narrow view point, the concept refers to the 3D cell assembling with the printing, so it might be similarly referred to as the cell printing or the organ printing.

In the 1980s the rapid prototyping technology is invented called, 3D PRINTING TECHNOLOGY, The applications of this novel technology in the medicine and the life science has gradually become the multi-disciplinary field which is termed as 3D Bioprinting, which also been applied in the customized model, permanent implants of humans, biomimetic scaffolds, drug testing models and also in the controlled drug delivery systems, and this technology plays a vital role in the modern biomedical fields. The materials used in the 3D bioprinting technology are mainly cells, biological materials and the inks and the growth factors, etc. from the past several years, the 3D bioprinting have made the new process in the many aspects, like printing models, materials, printing methods and so on. The first known 3D printer was developed and patented by Charles W. Hull in 1986. In his patent he explains a way in which it is possible to name things with reinforcing layers of image polymer (resin). [2,4,5]

FRAMEWORK

Transplantation of organ is an effective way of medical treatment for those patients who have suffered from the severe organ damage. Meanwhile the contraindications between the number of organs donated and the organs in the demands is keep rising due to the rapid increasing demands of organs in the worldwide, so in the 80s the emergence of the tissue engineering technology brought the rays of hope for solving these contraindications. Tissue engineering is a new research field that combines the multiple field that is biology, material science, engineering, surgery, molecular technology , the main aim of which is to resolve the current predicament of the organ shortage by the

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fabrication of the tissues substitutes with the biological functions,but there are still remained some defects to be solve: the first one is its costs too long to produce tissues organs which mainly delays the treatment and it is unable to carry out the multi-cell implantation and the cells and tissues cannot achieve the distribution with the high density and the precision spatial position. distribution with the high density and the precision spatial position. [2,3,]

The main goals of these 3D bioprinting technologies is to print living cells in layers using CAD models to produce bioactive constructs. Recent advances in the development of the 3D bioprinters have significantly enhanced their applications and demands in the producing of scale-up tissues and organs, such as the skin, myocardium, nerve, liver, cartilage, bone, and the blood vessel.

CLASSIFICATION: BIOPRINTING TECHNOLOGY

On the basis of classification, 3D bioprinting technologies can be divided into four main classes based on the working principles:

1. Inkjet 3D Bioprinting
2. Pressure Assisted 3D Bioprinting
3. Laser Assisted based 3D Bioprinting
4. Stereolithography

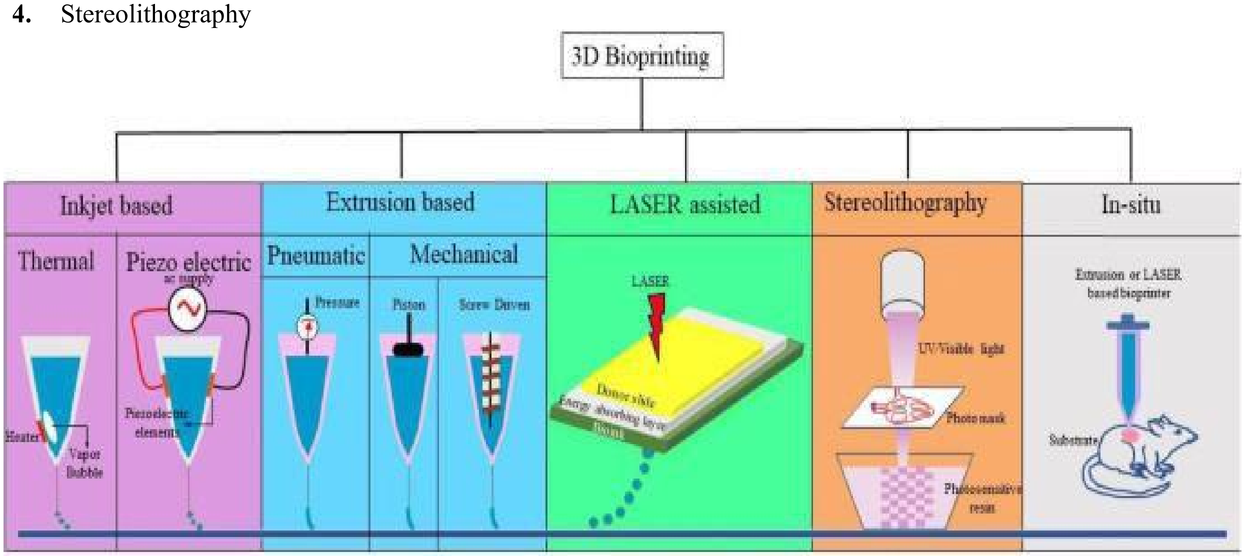

Figure. 1

BASIC REQUIREMENTS FOR ORGAN 3D BIOPRINTING

Different 3D bioprinting technologies have different requirements for organ transplantation. The key components of a common 3D bioprinting organ are duplication of important morphological, physical (especially mechanical and environmental), chemical, and organic organisms (e.g. partner). To produce a complete organ replacement for body function, a few basic issues must be addressed first:

1. A powerful construction tool, such as a multi-nozzle 3D printer and a systematic addition of an integrated mold system, is needed to integrate many biomaterials, including cell types, growth materials, and other bioactive agents, in a predefined 3D structure;
2. efficient soft- / hard-ware prefers to automatically achieve complex geometric points (or patterns) of the target organ, including vascular and sensory networks;
3. a large enough source (number) of cells, especially stem cells and related growth factors;
4. natural and synthetic polymers, such as gelatin, polyurethane (PU) and poly (lactic acid-co-glycolic acid) (PLGA), with excellent biocompatibility to support many cellular functions , multi-tissue formation, multicellular fusion, and anti-suture anastomoses;
5. the ability to understand the key characters of the target organs, in relation to cellular sites, building structures and biological functions. Among all the basic issues, the powerful 3D printer, the proposed “bioinks” and the adequate cellular resources are essential elements of the process of producing fully automated organs.[5,6,7]

ORGAN 3D BIOPRINTING PROCEDURES

An effective organ 3D bioprinting process requires several steps of application:

- Structure planning ahead
- Starting property and preparing a construction tool, including skill. multi-nozzle 3D printer and polymer "bioinks" (including cells, polymers and growth elements)
- 3D bioprinting

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- Body maturation after printing.

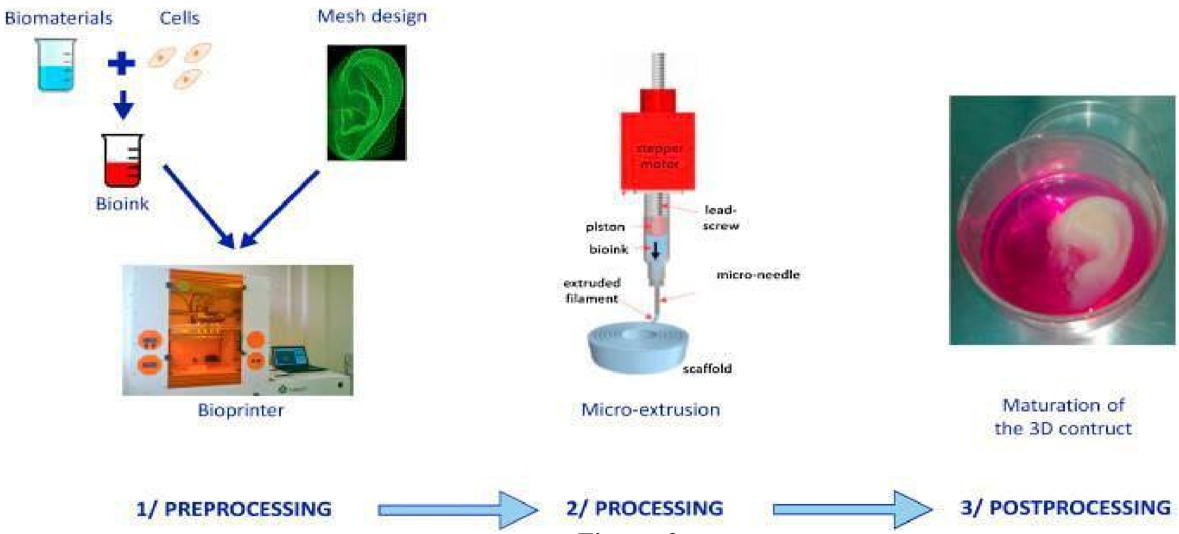

Figure. 2

BIOPRINTING MATERIALS

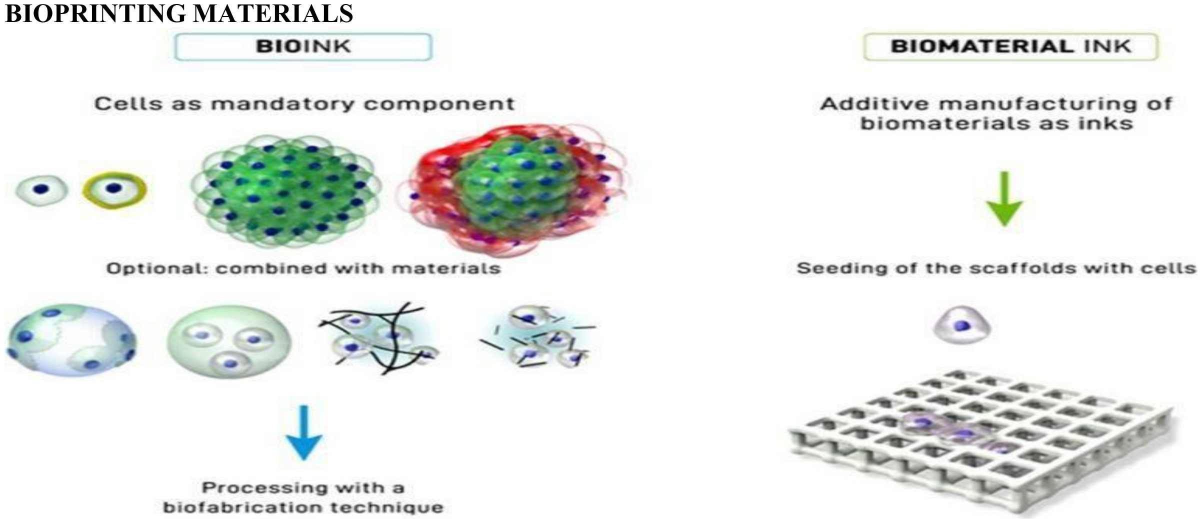

Figure. 3

Biological inks is typically consisted of a hydrogels pre-polymer solutions and cells and derived from the natural polymers, and very sensitive to the harsh processing environments and often have high water content. Therefore, they are printed at the very low-temperature and the conventional three-dimensionals printing and the mild crosslinking agentsor the conditions are used. These mild conditions also ensure the cell viability. The components are also selected for their structural, sacrificial, functional, or supportive characteristics. Bioink can be defined as the bioprintable material consisting of the living cells, proteins and the other biologics loaded into the matrix. They mimic the extracellular matrix (ECM) for the supporting of the cells. An ideal properties of bioink materials should be biocompatible, bioprintable, affordable, cell-friendly, mechanically strong and structurally stable, and possesses the solidification ability by means of cross-linking i.e; enzymatic, physical and ionic or the aggregations of the cells. Both naturals polymers (such as polyethylene glycol, poly lactic acid, and the polycaprolactone) are mainly used as a bioinks. Printability is an important features of an ideal bioinks. On the basis of materials base, bioinks can be classified into two major categories including; scaffold-based and scaffold-free bioinks[1,3,4

SCAFFOLD-BASED BIOINK: Scaffolds based bioinks consist of cells which is dispersed within the hydrogels or decellularized matrix components, or seeded on the microcarriers that help in the maintain a conducive environment for cell proliferation as well as providing the structural support. Both stem cells and differentiated cells can be used

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in the bioinks. Ideal bioinks are the accurate when printed, crosslinkable, maintain their properties after the polymerization, biocompatible, and undergo controlled degradation and the ECM production. The most common type of bioinks are the hydrogels, which can be natural or synthetic.[3]

SCAFFOLD-FREE BIOINKS Cells in the scaffold- free constructed are bioprinted without a supporting hydrogel and the cells are loaded in the higher concentrations. Pellets, tissue strands, or spheroids can be created. They deposit their own ECM components, which help in the providing support as well as facilities cell to cell communications and the maturation**.**

The following section described the details about bioink materials:

NATURAL POLYMERS	
Alginate	Sodium alginate is a raw material which is extracted from the brown seaweed. Alginate is a polysaccharide and anionic in the nature and having the linear block co-polymers M and G domains. Alginate has the properties of biomimetic structures, a suitable viscosity, gelatin at the ideal temperatures and the high compatibility, which makes the alginate suitable for the bioprinting. Moreover, bio-printing alginates constructs of the thick tissues with the well interconnected pores which is yet to be achieved.
Collagen	Collagen is a protein which is a naturally occurring protein in tissues which is constitutes largely of the amino acids such as hydroxyproline, proline, glycine and the trace amounts of sulfur which contains the amino acids and the aromatic amino acids. These Maintain the tertiary structure of the collagen. Collagen is a major extracellular matrix protein which controls all the cellular fate processes. It is used as a scaffold material for the various tissue engineering applications but its poor mechanical properties limit its suitability in the bioprinting.
Gelatin	Gelatin is denatured form of the collagen and has fewer tertiary structures, it is usually existing in the coiled form at the 40-degree centigrade and after the colling it can again regain the triple helix form. This transition property is important for the bioink to improve the integrity of the constructs post-print.
Hyaluronic acid	It is a linear polysaccharide made of beta 1,4-linked D glucuronic acid and the N-acetyl-D-glucuronic acid and N-acetyl-D-glucosamine disaccharides. It is a biodegradable, viscoelastic and highly biocompatible polymers. But the main drawback with hyaluronic acid is its high hydrophilicity limits.
Silk Fibroin	Silkworm derived the fibrous protein which is called silk fibroin, which is an amphiphilic block copolymer. The main heavy chain of silk fibroin has twelve repeating domains with the frequent occurrence of G-X-G-X-G-X where the G is glycine and the X may be serine or alanine. The repeating units are separated by the hydrophilic peptides that have the eleven amorphous regions. Silk fibroin is not used individually, for improving the ink flow it is blended with the gelatin, and gelatin also used in silk fibroin for improving the cellular compatibility

Table. 1

SYNTHETIC POLYMERS

These are the better choice for the bioprinting application, as comparison to the natural polymers. These offers the multiple parameters like biocompatibility, strong mechanical properties, degradation profile and allow the chemical modifications to alter the structure and modify the functions of the polymers. The ease of processability also make the synthetic polymer as a good choice candidate, bioactive molecules are incorporated to modify these polymers which help in the inducing specific cellular responses.[1,2,4,6]

Different types of synthetic polymers are as follows;

SYNTHETIC POLYMERS	
POLY (lactic-co-glycoside) (PLGA)	PLGA is a copolymer of the lactide and the glycoside, which is synthesized via ring opening polymerization mechanism. It can also synthesize with the different copolymer ratios. It is one of the promising bioink which is used for the printing of the multiple tissue's structures.
POLY (ethylene glycol) (PEG)	It is a biocompatible and a hydrophilic polymer which is used for the various biomedical devices. PEG has been used in the various applications such as nanoparticle coating to prevent the aggregation, bioink for the printing scaffolds

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	and the encapsulations of the cells. It is water soluble but required the chemical modifications to forms the gels. This polymer can easily form the physical and the chemical crosslinked networks after the process of acylation.
POLY (L-LACTIC acid) (PLA)	It is an aliphatic polymer with the glass transition and also have the excellent mechanical strength. It is a biocompatible, biodegradable and the semicrystalline polymer which is used for the multiple tissue engineering applications. As a bioink, it is less viscous in the nature and can be easily ejected through the needle.

Table. 2

HYDROGELS: Hydrogels are the class of the materials that are mainly composed of the water. These are the water insoluble, cross linked of 3D networks of the polymers chains and water, where the water mainly fills the voids between the polymer chains. Crosslinking facilitates the insolubility in the water and provides the required mechanical strength and the physical integrity. Multiple properties like biocompatibility, ability to protect the cells, good nutrient transport and the different in vivo functions have made the hydrogels the most important star material. Hydrogels could be classified in the variety of the ways which mainly depending on the cross-linking, physical or chemical bonding or the physical structure of the polymer chains, and In the bioprinting are used as a bio-inks materials or as cell delivery vehicles, and many types of cells have been encapsulated within the hydrogels and tested.[6,7,9]

CELLS PRINTING: Crucial for the application of the cell printing is a high survival rate and there is no damage to the genotypes and the phenotypes of the cells. Cell-aggregate-based bioinks could be homogenous, and containing a single-cell type, or the hetrogenous, prepared by coculturing the several cells types. The cell-aggregate-based bio inks typically used are tissues spheroids, cell pellets and the tissue strands. In addition to the hydrogels and cell aggregate-based bio-inks, decellularized matrix components have been recently considered as a new bio-ink types.[7]

SCAFFOLDS AND CONSTRUCTS: Scaffolds and constructs are the backbone of the tissue engineering, as they provide the necessary frameworks to the support cell attachment and the tissue regeneration. Printing of the scaffolds and the constructs laden with the cells and the materials is one of the most common type of the biofabrication carried out. In the bioprinting technology a substrate is usually acts as a bioprocessable scaffolding material, which is contributing as a biological and the structural support for the cells to attach, proliferate and the differentiate. The different parameters have to be maintained in the scaffolds, those properties are; biocompatible, nontoxicity, rapid solidification, dispensability and the functionality with the growth factors for the high cell viability.[8]

PHYSIOCHEMICAL ASPECTS OF BIOPRINTING

The main aim of printing technology is to fabricate 3D artificial tissues and the composed of a scaffolds, cells and providing a suitable microenvironment that mimic the exact environment that mimics the real environment of the human body. meanwhile a highly effective and the most accurate method for the fabrication of highly complex artificial tissues in vitro, and the printing achieves these various necessary components (biomaterials, cells and cell factors).

1. **BIOMATERIALS PARAMETERS:** Generally, biomaterials are one of the most important brick in tissue engineering, biomaterials can be categorized into a very large variety of hydrogel, creamic, metallic, polymeric and composite materials. The physical characteristics of biomaterials parameters determines the optimal printing typeFor eg; low- viscosity materials are more attractive for bioprinting because cells can grow well in the lower pressurized environment. And the other material properties such as interconnectivity and the pore size, also influence the encapsulated cells.

2. **BIOCOMPATIBILITY** During the printing, biocompatibility of the materials is the very first parameters which is considered during the fabricating of scaffolds and significantly limits the number of suitable materials. the material for the scaffolding process must accommodate the encapsulated cells and the recipients body. Therefore the implants must be cyto-compatible and support the growth of the cells, proliferation, attachment and the migration but safe for the host and not cause severe inflammation or immunologic rejection.Hydrogels are the one of the most usable and attractive materials for the bioprinting because of their enormous three-dimensional network of polymers chains which holds the mass of water. Mainly for the processing of the physical hydrogels, a polymer network is expected to form from the physical junctions between the hydrogel macromolecules. The use of some photo initiatiors and monomers during hydrogel crosslinking mainly affects the cell viability depending on the radical concentration and the length of the exposures. Meanwhile further more complex functional and biocompatible hydrogels can be fabricated using the bioprinting technology.

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3. **POROSITY AND INTERCONNECTIVITY:** volume, size, pore shape and geometry all these parameters directly affect the behavior of cells after the adhesion to the scaffolds. The different pore sizes in the matrices can affect the extracellular matrix development and are strictly correlated with the cellular organization, collagen assembly and mineralization. Porosity and the interconnectivity play an important roles in the ingrowth of surrounding tissues. Open and interconnected pores helps in the transporting of the oxygen and nutrients into the interior and eliminate the waste which is genered by the cellular metabolisms. After the various research and the analysis, researchers found that the cell adhesion, viability and proliferation are strongly influenced by the pore size and shape, whereby large quadrangular pores enhanced the viability and proliferation. The cell morphology did not seem to be affected by the pore topology.

4. **MECHANICAL PROPERTIES:** Physical characteristics are the indispensible parts of the tissues engineering scaffolds, particularly for the regeneration of the hard tissues mainly cartilages and bones. Appropriate mechanical strength should match the natural bones strength. When the artificial bones with high elasticitic moduli are implanted, further which may produce the stress shielding and hinder new formation. The mechanical parameters of the human cortical and cencellous bones should also characerterised. The different of component of the bioink materials are derived from the current materials which is mainly used in the tissue engineering and the limited application of the printing scaffolds. Whereby in addition of good biocompatibility, high porosity and the matching mechanical properties. The ideal material must have the appropriate hydrophilicity, pH neutrality and degradability without the formation of toxic macromolecules. The future development of the manufacturing technology will be enabling the printing of biofunctional scaffolds that will be perfectly mimic the extracellular matrix to provide cells with a microenvironment for the adhesion, proliferation and the directional differentiation.
   -

5. **INK FORMULATIONS:** A wide variety of biomaterial inks which basically categorized the polymers, ceramics, hydrogels and composites are developed in the printing technology as compare to polymers and ceramics, hydrogels inks received much more attention and the significant progress have already been made to design novel ink formulations. The lag of diversity in the inks of biomaterial is becoming the barriers to the widespread applications of 3D printing techniques. uv light , chemical crossling, and the high temperature in the materials machining negatively impact the most biologically activities . however, utilizing the cellularized matric shell which mainly lagged the initial mechanical strength the balanced between structural strength and the biocompatible processing is hardly satisfied the researchers and scientist . meanwhile in the future more bioactive and mechanically stable bioinks must be developed for the bio-printing of complicated organs and tissues.[7,8,9]

SOFTWARE USED IN BIOPRINTING TECHNOLOGY

The bioprinting of tissues and heterogeneous organ is a very complicated and crucial issue and there are two main research field of bioprinting organs: printing of living cells and organs mainly for the purpose of printing living organism, while the printing of living cells consist of tissues or a whole organ for the purpose of research and medicine mainly for Pharmaceutical research, surgery, and tests, transplantation , and for drug testing instead of using lab animals. In the field of bioprinting technology , the printing of living cells which mainly includes skin, bones, cartilage and vascularized tissues is the most widespread and many others physiologically relevant tissues printing for the research and development in pharmaceutical field and for the therapy of cancer treatment.[10]

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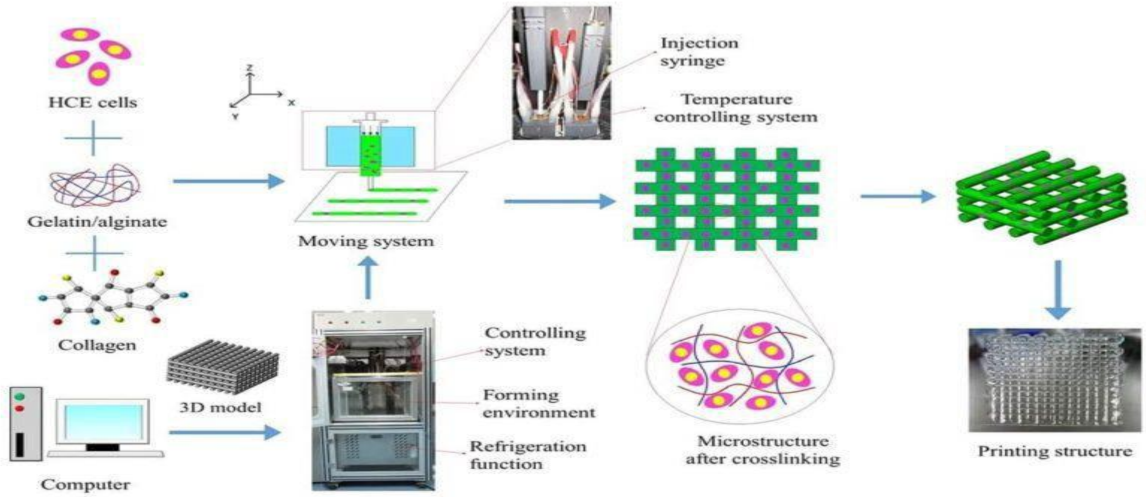

Figure. 4

PRINTING PROCESS

Without any instructions bioprinters cannot print anything, for the successfully creating bioprinted tissues, it is necessary to generate the printing paths, select appropriate bioinks, control the bioprinters and maintain the quality control after the printing process, mainly typical bioprinting process has following steps:

- Printing geometry designs by the designers and manually verification of its feasibility
- designers select the appropriate cell types and the hydrogels and then load the bioinks into the bioprinting systems.
- through control language and protocoals and the lab view and then designed paths are forwarded to the bioprinting system.
- the bioprinters build structures by depositing bioinks under the control of a computer
- Bio printed tissues are checked manually via Microscopy after printing

After the bioprinting process, the printed constructs are transferred to an incubator for the culturing. The printing process is not currently highly automated and multiple manual operations at a variety of the steps can result in a slow processing speeds and increase the chance for the errors and mistakes. To ensuring the quality of printing and to improve the printing process, many of the researchers have investigated Computer-aided design (CAD) and the modeling technology for the printing the process. These CAD techniques can utilize computer automation system to assist and accelerate the design process

CLINICAL IMAGES can easily provide the all the details and information regarding the in-vivo tissue distribution of patients, and the anatomically realistic tissue geometries which can be determined via image processing. Clinical-image-based STLs therefore have the potential to become the starting point for on-demand tissue production in the future.

Apart from current research and drawbacks, BIO-CAM research not only provide a fast way to control and check design feasibility, but also provide a chance for better understand the physical and chemical principles which governing the printing, with the integration of BIO-CAD and BIO-CAM where BIO-CAM can ensure the quality of what is printed and BIO-CAD help in accelerating the speed of whole bioprinting program[6, 8,12]

3D BIOPRINTING APPLICATIONS

COSMETOLOGY: The role of bioprinting technology in tissue engineering and cosmetic science is as wide as ocean, currently it's mainly used in the transplantation of damage skin due to severe burn , accident and other skin injuries which is caused by chronic ulcers, cancer surgery, genetic and somatic diseases which require effective treatment to prevent mortality and mobidity, and many other different treatment of different skin diseases conditions and lesions and also includes cell therapy ,skin substitutes and wound healing treatment which is mainly based on biomaterial-based replacements and 3D system. [13]

SKIN GENERAL INTRODUCTION: The skin was the very first Tissue which have been successfully tissue engineered in vitro and has also successfully beneficial in clinical application.The skin is the largest complex organ of the human body and play a very vital role in the Temperature regulation, synthesis of vitamin D , evaporation control ,fluid balance and protection against environmental conditions and pathogens and also protects the body from the attack of foreign substances and also maintains the integrity of the body. The Skin consist of mainly three

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layer.The epidermis is made up of different cell types: keratinocytes, melanocytes, which is localized in the basal layer of the epidermis part and sometimes in the dermis . skin pigmentation is provided by the malenocyte cells which produce the melanin usually protect the skin from UV radiation, the amount of melanin production defines the color of skin . [14,15] Artificially skin transplantation or skin grafting for burn healing and wound or any accidentals severe wounds is one of the earliest challenges for in-vitro skin tissues engineering, skin grafing tools play a vital role which act as a bandage and help in restoring the normal barrier and regulatory functions, and in few cases like third degree burns which is referred to as a full thickness burn and completely destroy the outer layer of skin(epidermis) and also the entire layer beneath (the dermis). the different approaches of skin grafting in the therapeutic uses and the most of the illness, besides them there is an increasing demand for better authenticity of skin equivalents, in Topical drug delivery and development of formulation and patches, and also help in the understanding of permeability of drug and the inflammatory responses of drug agents which is highly valuable in-vitro models. Different in-vitro skin models act as a important tools for understanding and examine the skin disease and the fundamental skin biology and functioning. From the last decades, many groups of experts have made many efforts in the design of artificial human skin through 3D bioprinters. Industry and acedmia both are giving their best in the development and formation of novel approaches for making human skin and in-vitro skin models for research purposes. These 3D bioprinting of skin substitutes and help in overcome the drawbacks of earliest traditional skin treatment methods, as comparison of technology , duration and cost. it also help in minimizing the use of animals in products. The testing of drug and cosmetics is another area in which engineered skin are very much required , and needs, 3D bioprinting is a very promising technology with the help of which we can achieve reliable and rapid development and production of biomimetic cellular skin substitutes , which satisfied both industrial and clinical needs. [15,16,17,18]

IMPLICATIONS

- In the dermal drug development and drug screening.
- Testing of novel drug delivery system
- Transplantation of artificial human mimetic skin
- In the cosmetic testing and surgery

APPLICATION IN DIFFERENT FIELDS

Artificial tissues and different organs are printed by depositing the cells, biomaterials and molecules layer by layer. This bioprinting technology has the advantage of good resolution of the input cells, after applying this technology practically, successfully great efforts have been made in the development of bioprinting technologies for trying to print blood vessels, heart bone cartilage, skin, kidney, nerves and many other tissues. It also has a wide spectrum of application from the molecular level such as DNA and protein to organ level. Research and developments of medical science, regenerative medicines and materials science in future may allow the construct and repair of human body parts with the help of 3D bioprinting techniques and many new therapies for organ and tissue regeneration [17,18]

BONE AND CARTILAGE BIOPRINTING: Bone loss and cartilage injuries is slightly become increasingly prevalent now days and 3D bioprinting is becoming the novel therapeutic option that help in resolving the current treatment insufficiencies regarding bone and cartilage repair and provides satisfactory result and a long-term outcomes. Bone and cartilage tissue printing is the most mature field in utilizing bioprinting technology, the main thing is that the composition of hard tissues is not that complicated then other organs and is mainly composed of inorganic elements. The 3D bioprinting or bone engineering is widely used techniques, in which anatomic data is used and this data is generated from CT scans, Articular cartilage and menisci have the low tendency or low capacity for self repair and none of the available conventional treatment providing a satisfactory result, or a long-term outcomes. Further self- regenerating capabilities of bone tissue, and the mechanism may not be fully successfully or become insufficient, and required the need for surgical bone replacement, which is restrained by natural grafts accessiability. It’s a most rapidly developing and growing technology which is emerging as a most promising remedial therapy in orthopedics[17,19]

NEURONAL TISSUES PRINTING: 3D bioprinting of nervous tissues is one of the another application that has been explored by the researchers, large synthetic tissues will need to integrate with the host nervous system and the printing may be a means to generate mainly new nervous tissues or to enhance the innervation of tissues which are engineered constructs. This vast application is help in understanding the complicated nervous system and in nerve repair damage studies.[16]

BLOOD VESSEL AND HEART PRINTING: For the transportation of nutrition and metabolic waste, the fully functional blood vessels play an important role in the cardiovascular diseases and for the construction of artificial

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organs, mainly for the rich blood supply. Currently in the advances of developmental iconography and biology which have enabled significant progress in the printing vasculature in-vitro. Bioprinting assures the fabrication of network structures by using hydrogels or the different materials as bioink. For the printing of cardiac valves, tissue-engineered valve scaffolds mainly focused on the rebuilding of aortic valve. Many researchers have performed extensive studies of printing aortic valve structures with the hydrogels. Although the bioink materials are deficient in flexibility and elasticity, and their mechanical characteristics still do not meet any clinical needs yet. Although there is the need of improving resolution for printing small vessels and the increasing availability of bioink materials and the bioprinting [16,18]

SURGICAL SPECIALITIES: 3D bioprinting technology is one of the important tool help in the surgical specialties. it has a attracted significant attention in the different surgical specialties, especially within the head and neck surgical specialties; Maxillofacial, plastic surgery, and otorhinolaryngology, owning to its incredible ability to create complicated structures with high precision of many small parts and even organs. Different surgical planning can be improved by pre-operative simulation this will help surgeons in an accurate picture of complex anatomical structures, and parsing the physical models of 3D printing technology.This technology is also used in the orthopedic surgery, in the planning phase of revision and reconstructive operations, by developing personalized implants for the needed patients or specific instruments for bone tissue engineering. For the improved surgical results can be achieved with the three- dimensional printing technology. [18]Thus in the surgical planning phase for performing implants and prostates by representing a precise anatomical personalization, the technology can minimize the drawbacks of conventional methods in terms of visual discrepancy over the patient's body and insignificant anatomy.[20]

DRUG SCREENING:Bioprinting in drug design system is another promising application, as compared to manual methods, bioprinting can deposit cell uniformly on micro devices surface and these cell uniformity is very helpful for testing and screening the interaction between cells and drugs . bioprinting has also been used to seed cell layers uniformly on the each side of interface of micro devices for the formation of organ-on-a chip devices, it mimic the function of typical and complicated organs to analysis the interaction between drugs and their potential effects on tissues. Bioprinting play a vital role in oragn-on-a-chip technology by helping in giving a practical solution for the formation of uniformity and highly controllable tissue layers at a low cost. [20]

BIOIMPLANTS PRINTING (scaffolds) For the printing of living tissues many several fields are there which are physiologically relevant cells and often used for Pharmaceutical research. In biomedicine field each component play a important role in finding a material that will satisfy the complete needs of complicated tissues, the task of creating biomedical devices must be heterogeneous in most of the time. The main advantage of 3D printing of t implants over the traditional machine technology is that 3D printing are much accurate, complexity and can achieve personalized real-time manufacturing and development of any complicated and sophisticated implants with high dimensional accuracy and short duration of production cycles, and this technology might be used for the formation and manufacturing of many scaffolds further which help in the printing of living tissues or whole organs. [19]

Modeling for biomedicine purposed, mainly for the bioprinting of living tissues and organs which needs to transmit and convert medicine and biological data in a accurate manner, these type of models must meet a number of special requirements which not only consider accuracy of data converting, but also many others which basically depend on the printers and model specifies all these considered software tools were subdivided on measure three groups :software tools for preprocessing , for processing and for post processing therefore the comparative analysis of these software tools was carried out and mainly based on the direction in the future development . different kind of bioprinting have their specific requirements for modeling software, currently the most popular software in the field of bioprinting for the generation of models is CAD Based software i;e Computer Aided Design which is considered as highly specialized tool in research and development. computer aided techniques, which is also known as BIO-CAM i;e bio-computer- aided- manufacturing **,** which play a vital role in during and after bio printing process. Bio-cam main aim is to predict the feasibility of fabrication process by simulating relevant and understable physical models on computer[17,18,19]

CURRENT AND FUTURE CHALLENGES: Bioprinting technologies has been made the great progress over the last decade, every research modality has its own drawbacks within various aspects, which includes its own limitations within various aspects, which contain scalability, availability of compatible bioinks, process resolution and biomimicry. There are Multiple challenges faced in the printing technology which has stunned the process and development of this technology from the several years.The specific challenges in 3D bioprinting technology include resolution printing speed, biocompatibility, and mainly scaling up, where high resolution specifically allows for the construction of intricate single cell structures such as capillary networks, the biocompatibility of 3D printing has been limited in cell viability and basic functions and the various effects on gene and protein level have yet to be determined, additionally the scaling up of bioprinted is still remains a challenge for researchers.[21]

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MATERIAL SELECTION: Selection of the material is one of the major challenges in this novel promising technology where multiple types of materials is used in the 3D bioprinting and this material is broadly divided into two main groups which are based on the source of the production, namely natural polymers like collagen, chitosan, hyaluronic and synthetic polymers such as polylactic acid (PLA), polyglycolic acid (PGA), poly(lactic-co-glycolic-acid).Natural polymers have the good biocompatibility properties but usually in the performance very poorer at mechanical properties, which makes it achieve the required formability as a single printed materials. By contrast, synthetic biopolymers mainly have the good formability with poor biocompatibility. Now researchers are usually focusing in the building blending system between the different materials since the single material always not satisfied the needs of manufacturing, which has both natural and synthetic materials constituents, in that way combining the advantages of both materials and overcoming the drawbacks to achieve the demand material properties. Meanwhile another popular method is to control the crosslinking parameters, such as the crosslinking reactions between hydrogels to improve the forming property which makes it possible to achieve the good biocompatibility and the suitable formability[21]

CHALLENGES IN SELECTION OF CELL SOURCE: Cell source selection is one the very important step in the translation , cells is used in bioprinting to create the simple tissue structures such as heart valves which could feasibly be derived from the animals or humans, animal sources are likely to enable the greater mass production of tissues or for the surgical uses but consist of the allogenic materials which have the high risk of disease called XENOTRANSMISSION. Meanwhile the human sources offers the great biological compatibility and the opportunity for the personalization, but theis uses is likely to be approached with high regulation, production time and the very high costs.Many of the donor related to the ethical concerns could be bypassed by the used of multiple autologous cell sources. And the another thing is that currently there is a decline ratio of the successful clinical trials and the limited human sources. [20]

BIOLOGICAL INK (BIOINK) SELECTION: Thematerials which are selected for the bioink production must have the property of biocompatibility before the material is considered for use in the humans. The immunogenicity and the toxicity of the bioinks are the two main parameters which will be necessitate further investigation which are prior to the human trials. Multiple materials are derived from the natural or non-human sources such as alginate from seaweed and the gelatin from the procine materials. The foreign behavior of these components have the high risk of infection, inflammation and the immunogenicity. Furthermore, different hydrogels materials is used as a bioinks which are required to be crosslinked post-printing which help in maintaining their 3D shape[20,21]

CHALLENGES IN THE NUTRIENT SUPPLY: Currently a major problem in the construction of in vitro large size organs lies in the inability to achieve effective microvasculature , thus it is difficult to supply the nutrition to the cells in the interior section of the constructed organs. One current method is to constructed the some channels inside the bio-fabricated organs and perfuse nutrients to simulate vasculature; then endothelial cells, smooth muscle cells or fibroblast cells are mainly injected to form vascular structures. Although there is still a long way to achieve the real vascularized structure some of the researchers also found that printing the large vessels in certain areas, which will induce the micro vasculatures to generate asides though which can't meet the construction of all the organs. but the building of a micro vascular network is still remains a big challenge in the bioprinting field .[21]

REGULATORY CHALLENGES: Regulation of these materials and products and their sources is the another challenge. The high approach of personalization in the construction of shape and the genetic material renders bioprinted tissue a custom made device. Challenge with regenerative medicine and the tissue engineered technologies and their components and the classifications and the main ultimate regulations in all the facets of the design, production, handling [22]

ETHICAL CHALLENGES: The design and rules and regulations of the clinical trials will also be proved challenging, it might be unethical to trial the tissue engineered organ transplantation on the healthy volunteers, and the use of patient specific cell populations, that means the patient has themselves could need to act as their own control, and introducing the high degree of the hetrogenicity when attempting to assess treatment efficacy. Other challenges in the designing of the clinical trials which include the facts that patients can't be able to withdraw the post implantation, and the conscent for the trial inclusion is the challenging where the extent of complications was uncertain.[21,22]

CURRENT LIMITATIONS: Various developing bioprinting technologies have been rapidly growing developed and utilized for many applications in clinical and life sciences, which ranges from constructing organ and tissues for implantation to studying cellular mechanisms, these printing technologies have shown results for safely deliver cells, biological molecules and biomaterials to target location in a uniform and precise manner. [26]

Through the studies of researchers the thing is analyze that bioprinting of simple tissue structures is possible but meanwhile the constructing a more complex and composite tissue structures such as complicated solid organs is still remaining a challenge however printing a fully functioning organs seems to be far fetched at the current time, these

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printing technologies provide a enormous potential and a great promise to become an very essential tool in the field of medicine in the future, for the further development and harness these technologies for clinical and industrial use, while many of the technological challenges have to be addressed[21,23]

CELL AND MATERIAL LIMITATION: Material selection always remain a major concern and a drawback for bioprinting technique. Many others biomimetic materials often lack the mechanical strength to be the part of sole material in printed tissues, which required support from stronger but less bioactive inks, the wide range of material properties could be a solution to this problem and further may be able to achieve through the development and creation of new composite mixtures to enhance the crosslinking or many others desirable parameters should be concerned while during the parameters selection of the base bioinks. POLY(ethylene glycol) PEG, grabed all the attention due to its tunable mechanics and shows the suitable parameters for the composite bioinks, multiple incorporating materials also remains a challenge for the suitable parameters for the base bio inks. For the most of the printers, the materials which has to be printed are prepared in bulk before the printing process begins and switching the materials include changing to secondary pre-loaded reservoirs which help in separating the syringe or bioink cartridage. [23,24]

FUTURE PROSPECTS

3D bioprinting may be considered as a nano-fabrication technique as a important tool for artificial organ generation, because of its advantage on the micrometer scale, and highly controllable dispensing of living cells. Different types of 3D printing technologies are utilized for the applications that range from studies of cellular behavior for the investigation of tissue toxicological and pharmacodynamics mechanisms. As printing technology develops, additional biomimetic, tissue engineered organs will be created and decreases in the reestablishment time and cost should also be addressed before bioprinting of organs could be applied in the clinic uses. [24]

CONCLUSION

This review paper provides a general overview of the most emerging 3D bioprinting technology in the multiple fields, it is the novel promising technology which combines additional manufacturing with the biomanufacturing which will further help in mechanism, material, biology and the medicines. It gave a method to deal with the complexities of the tissue engineering and the regenerative medicines. In the cosmetic science it brings a novel revolution from the cosmetic surgery to developing the bio-mimetic tissues, cell or organs. This technology has the diverse advantages and applications which have already been demonstrated on a global scale. However, despite the novel developments and the multiple challenges or breakthroughs from the many research, bioprinting technology is still is in the state of infancy and there is a needs to overcome the different challenges and the limitations.

REFRENCES

1. Williams D F, 2008, On the mechanisms of biocompatibility. Biomaterials, vol.29(20): 2941–2953. http://dx.doi.org/10.1016/j.biomaterials.2008.04.023.
2. Gao B, Yang Q, Zhao X, et al., 2016, 4D bioprinting for biomedical applications, Trends in Biotechnology. http://dx.doi.org/10.1016/j.tibtech.2016.03.004
3. S. Kannan, The 3D bioprinting revolution, Harv. Sci. Rev. (May 1, 2014). http://harvardsciencereview.com/2014/05/01/the-3d-bioprinting-revolution/.
4. Loo Y, Lakshmanan A, Ni M, et al., 2015, Peptide bioink: self-assembling nanofibrous scaffolds for three-dimensional organotypic cultures. Nano Letters, vol.15(10): 6919–6925. http://dx.doi.org/10.1021/acs.nanolett.5b02859
5. Talbot E, Berson A, Brown P, et al., 2012, Evaporation of picoliter droplets on surfaces with a range of wettabilities and thermal conductivities. Physical Review E, vol.85(6): 061604. http://dx.doi.org/10.1103/PhysRevE.85.061604
6. Karp J M, Yeh J, Eng G, et al., 2007, Controlling size, shape and homogeneity of embryoid bodies using poly (ethylene glycol) microwells. Lab on a Chip, vol.7(6): 786–794. http://dx.doi.org/10.1039/b705085m
7. Ahn S, Lee H, Bonassar L J, et al., 2012, Cells (MC3T3- E1)-laden alginate scaffolds fabricated by a modified solid-freeform fabrication process supplemented with an aerosol spraying. Biomacromolecules, vol.13(9): 2997–3003.http://dx.doi.org/10.1021/bm3011352
8. Gaole D, Wenfeng W, Yuliang Z, et al., 2016, Controllable 3D alginate hydrogel patterning via visible- light induced electrodeposition. Biofabrication, vol.8(2): 025004. http://dx.doi.org/10.1088/1758-5090/8/2/025004
9. LeRoux M A, Guilak F and Setton L A, 1999,Compressive and shear properties of alginate gel: effects of sodium ions and alginate concentration. Journal of Biomedical Materials Research, vol.47(1): 46–53.http://dx.doi.org/10.1002/(SICI)1097-4636(199910)47:1%3C46::AID-JBM6%3E3.0.CO;2-N

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

10. Song S J, Choi J, Park Y D, et al., 2011, Sodium alginate hydrogel-based bioprinting using a novel multinozzle bioprinting system. Artificial Organs, vol.35(11): 1132– 1136. http://dx.doi.org/10.1111/j.1525-1594.2011.01377.x
11. Jia J, Richards D J, Pollard S, et al., 2014, Engineering alginate as bioink for bioprinting. Acta Biomaterialia, vol.10(10): 4323–4331.http://dx.doi.org/10.1016/j.actbio.2014.06.034
12. Lee J B, Wang X, Faley S, et al., 2016, Development of 3D microvascular networks within gelatin hydrogels using thermoresponsive sacrificial microfibers. Advanced Healthcare Materials, vol.5(7): 781–785.http://dx.doi.org/10.1002/adhm.201500792.
13. Bocquier A A, Potts J R, Pickford A R, et al., 1999, Solution structure of a pair of modules from the gelatin-binding domain of fibronectin. Structure, vol.7(12): 1451–S1453. http://dx.doi.org/10.1016/S0969-2126(00)88336-7
14. Sawatjui N, Damrongrungruang T, Leeanansaksiri W, et al., 2015, Silk fibroin/gelatin–chondroitin sulfate–hyaluronic acid effectively enhances in vitro chondrogenesis of bone marrow mesenchymal stem cells. Materials Science and Engineering: C, vol.52: 90–96. http://dx.doi.org/10.1016/j.msec.2015.03.043Billiet T, Gevaert E, De Schryver T, et al., 2014, The 3D printing of gelatin methacrylamide cell-laden tissue-engineered constructs with high cell viability. Biomaterials, vol.35(1): 49–62.http://dx.doi.org/10.1016/j.biomaterials.2013.09.078.
15. Schuurman W, Levett P A, Pot M W, et al., 2013, Gelatin-methacrylamide hydrogels as potential biomaterials for fabrication of tissue-engineered cartilage constructs.Macromolecular Bioscience, vol.13(5): 551–561.
16. Pescosolido L, Schuurman W, Malda J, et al., 2011, Hyaluronic acid and dextran-based semi-IPN hydrogels as biomaterials for bioprinting. Biomacromolecules, vol.12(5): 1831–1838.http://dx.doi.org/10.1021/bm200178w.
17. Skardal A, Zhang J, McCoard L, et al., 2010, Photocrosslinkable hyaluronan-gelatin hydrogels for two-step bioprinting. Tissue Engineering Part A, vol.16(8): 2675–2685. http://dx.doi.org/10.1089/ten.tea.2009.0798.
18. Zhao Y, Li Y, Mao S, et al., 2015, The influence of printing parameters on cell survival rate and printability in microextrusion-based 3D cell printing technology.Biofabrication, vol.7(4): 045002.http://dx.doi.org/10.1088/1758-5090/7/4/045002
19. Ghosh S, Parker S T and Wang X, 2008, Direct-write assembly of microperiodic silk fibroin scaffolds for tissue engineering applications. Advanced Functional Materials, vol.18(13): 1883–1889.http://dx.doi.org/10.1002/adfm.200800040.
20. Das S, Pati F, Choi Y J, et al., 2015, Bioprintable, cell-laden silk fibroin–gelatin hydrogel supporting multilineage differentiation of stem cells for fabrication of three-dimensional tissue constructs. Acta Biomaterialia, vol.11: 233–246.http://dx.doi.org/10.1016/j.actbio.2014.09.023
21. Dr. Aarushi Kataria, Dr. Naveen Nandal and Dr. Ritika Malik, Shahnaz Husain -A Successful Indian Woman Entrepreneur, International Journal of Disaster Recovery and Business ContinuityVol.11, No. 2, (2020), pp. 88–93
22. Lutolf MP and Hubbell J A, 2005, Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. Nature Biotechnology, vol.23(1): 47–55.http://dx.doi.org/10.1038/nbt1055
23. Pirlo R K, Wu P, Liu J, et al., 2012, PLGA/hydrogel biopapers as a stackable substrate for printing HUVEC networks via BioLP™. Biotechnology and Bioengineering, vol.109(1): 262–273.http://dx.doi.org/10.1002/bit.23295
24. Cui X, Breitenkamp K, Finn M G, et al., 2012, Direct human cartilage repair using three-dimensional bioprinting technology. Tissue Engineering Part A, vol.18(11–12): 1304–1312. http://dx.doi.org/10.1089/ten.tea.2011.0543
25. Holländer J, Genina N, Jukarainen H, et al., 2016, Three-dimensional printed PCL-based implantable prototypes of medical devices for controlled drug delivery.Journal of Pharmaceutical Sciences..http://dx.doi.org/10.1016/j.xphs.2015.12.012
26. Loo Y and Hauser C A, 2015, Bioprinting synthetic self-assembling peptide hydrogels for biomedical applications. Biomedical Materials, vol.11(1): 014103. http://dx.doi.org/10.1088/1748-6041/11/1/014103
27. Hauser C A E, Deng R, Mishra A, et al., 2011, Natural trito hexapeptides self-assemble in water to amyloid β-type fiber aggregates by unexpected α-helical intermediate structures. Proceedings of the National Academy of Sciences, vol.108(4): 1361–1366. http://dx.doi.org/10.1073/pnas.1014796108