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3D printed tissue and organ using additive manufacturing: An overview

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ABSTRACT

Background: Research papers on Additive Manufacturing (AM)/3D printing in tissue/organ printing are studied to understand its capability for tissue and organ printing with and new advancement in the medical field.

Aim of the research: To study and discuss the advantages and limitations of AM when used for printing of customised scaffold, tissue and organ, which are a challenge to the medical field.

Materials and methods: This literature-based study understands the creation of innovation in the medical field and its different areas to address upcoming challenges. Thus, relevant research papers from the Scopus database are identified and purposefully analysed.

Result: Studied the main components of additive manufacturing as required for tissue and organ printing and process used to create tissue/organ by using this technology. We have further identified different materials based requirements for tissue and organ printing and how this technology can fulfil this requirement to save the life of the patient. Finally, this paper identifies eight significant advancements of AM in the medical field with a brief description and limitations when additive manufacturing is used for tissue and organ printing.

Conclusion: In the current scenario, tissue engineering and cell therapy employ an innovative approach to reduce the mortality rate. However, the main challenge for this is customisation, which is somewhat taken up by AM technologies. This technology has already addressed different challenges in the medical field. For tissue and organ printing, this technique seems better as compared to 2D conventional cell technique. With the help of scanned data, 3D printing allows us to create intricate internal structures. Thus, it can be used to develop bone tissues, which are required for clinical applications towards the treatment of bone defects. It also plays an outstanding role in cardiac masses, heart disease, physiology, electrophysiology, tested for diagnosis and better treatment of valvular heart disease. Doctors and surgeon easily understand the aortic valve of the patient. It improves post-surgery, blood flow and helps proper selection of devices including stents. AM is to take up the challenge for the development of artificial bone with biomechanical properties as similar to bone. It uses the material in the form of powder, wire and ceramic. It has promising applications to print liver tissue and liver cell and fulfils the requirement of customisation in different fields.

1. Introduction

A large number of patients die due to the shortage of organs like kidney, heart, liver, etc., but these organs are highly customised, and here, Additive Manufacturing (AM) has extensive utility.^{1–3} In the medical field, AM technology is an innovative approach used for the production of tissues and human organs. It is applicable for highly complex native organs which can be transplanted in the human body in the operating room. New biomaterials are used to fabricate scaffolds, tissue and organs, and they show a better biocompatibility,^{4,5} but we need to research them thoroughly before making patient-specific

applications. In the medical field, AM is rapidly adopted due to its patient-specific implants, tissue, scaffolds and organs. This technology can print materials having excellent biodegradable and mechanical properties.⁶

Additive manufacturing becomes cheaper and efficient when used for specific applications and is the best method of creating a specific prototype. AM creates a product from computer-aided design (CAD) file, which is usually in standard triangulate language (STL) format. This format is imported in the printer to create an object, layer by layer. Here, the printing time depends on layer thickness and the size of the object. Complex shape object takes a long time for printing. Support

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Table 1
Components of AM for tissue and organ printing.

S No	Main Components	Description	References
1	Hardware	<ul style="list-style-type: none"> AM consists of hardware, and its hardware are a 3D printer, 4D printer, 5D printer and Scanner 3D printing technology is used as hardware to print any customised medical part There are different types of processes and technologies of 3D printing; each 3D printing technologies has its advantages and limitations The leading 3D printing technologies are used for the tissue, and organ printings are extrusion, inkjet and laser-assisted technology 	Derby, 2012 ²⁰ ; Bose et al., 2013 ²¹ ; Singh et al., 2017 ²² ; Maiullari et al., 2018 ²³
2	Software	<ul style="list-style-type: none"> 3D designing software provides an enhanced capability for the design and development of product There are different types of software available for the designing such as Solidworks, Mimics, Ansys, Fusion 360, Auto CAD, 3DS Max, Rhino, Inventor and Moment of Inspiration (Mol) 3D Software plays an essential role in the creation of design, modification, testing, analysis and reverse engineering 3D design software can precisely create any 3D surface model of any medical, industrial, dentistry, automobile and architecture product 	Gómez-Ciriza et al., 2015 ²⁴ ; Pati and Cho, 2017 ²⁵ ; Laschke and Menger, 2017 ²⁶ ; Haleem and Javaid, 2019 ²⁷
3	Bioink	<ul style="list-style-type: none"> Bioink having living cells are capable of recreating the desired shape The slurry of specific cells are loaded in the printing head which is moved through digital control to recreate the desired object Bioinks can be used in 3D printer technology to produce complex tissue model which have extracellular matrix environment Bioink can deposit filament while using the process of additive manufacturing These bioink exist hydrogel biomaterials and having natural polymers such as fibrin, gelatin, alginates, chitosan, and hyaluronic acids 	Stanton et al., 2015 ²⁸ ; Ligon et al., 2017 ²⁹ ; Onget al., 2017 ³⁰
4	Biomaterial	<ul style="list-style-type: none"> Extensive investment is made in medicine for the development of new biomaterial which encompasses elements of biological, medicine, tissue engineering, chemistry and material science Biomaterial having a biological system which easily interacts with the biological system Used in the medical field for treatment and replacement/repair of tissue of the body A biomaterial is used for heart valves, joint replacement, bone cement, medical implants, skin repair devices, stents, surgical mesh, vascular graft etc 	Butscher et al., 2013 ³¹ ; Usprech et al., 2017 ³² ; Jammalamada and Tappa, 2018 ³³

Table 2
Processes used to create tissue/organ using additive manufacturing.

S No	Process Steps	Description	References
1	CAD design	<ul style="list-style-type: none"> Create a 3D digital model of the scaffold, tissue and organ using different scanning technologies like CT, MRI, 3D scanner etc. 3D CAD data is exported to the desired printer in.STL format These scanning technologies easily capture exact data of the patient as per requirement 	Yoo et al., 2014 ³⁶ ; Ripley et al., 2016 ³⁷ ; Ackland et al., 2017 ³⁸
2	The input of specific Biomaterial	<ul style="list-style-type: none"> A specific biomaterial is used to fabricate a biocompatible medical part Bioactive drugs, protein and cells are used as inputs for 3D printing technology There are wide biomaterial variety is used, these include ceramics, metals, composites and polymers 	Schieker et al., 2006 ³⁹ ; Tappa and Jammalamadaka, 2018 ⁴⁰
3	3D printing of scaffold tissue/organ	<ul style="list-style-type: none"> After preparation of CAD data of the individual patient and specified biomaterial input, 3D physical scaffold tissue/organs are manufactured layer by layer Encouraging results while using AM applications in developing specific 3D scaffolds for tissue engineering, manufacturing of customised implants, drug delivery devices, prosthetics and regenerative medicine 3D printing technology can enhance its printability with the combination of polymers and ceramics 	Yang et al., 2008 ⁴¹ ; Do et al., 2015 ⁴² ; O'Brien et al., 2015 ⁴³ ; An et al., 2015 ⁴⁴ ; Qiu et al., 2018 ⁴⁵
4	Cell Seeding	<ul style="list-style-type: none"> 3D printing is an efficient method of supporting scaffolds with seeding cell These cell help to repair tissue and enhance the functions in the body This technology quickly helps to develop and fabricate self-assembled tissue by seeding cells 	Bertassoni et al., 2014 ⁴⁶ ; Csobonyeiova et al., 2015 ⁴⁷ ; Gao et al., 2017 ⁴⁸
5	Implementation of tissue/organ in the patient body	<ul style="list-style-type: none"> Medically required parts printed by this technology are implanted into the body of the patient Different types of tissue are made with particular cells; these include muscle tissue, Epithelial Tissue, Nervous Tissue etc. These make an excellent proactive cover of the body with attractive skin 	Li et al., 2014 ⁴⁹ ; Bishop et al., 2017 ⁵⁰ ; Kiraly and Khalifa, 2018 ⁵¹

material if used for certain conditions is removed after the completion of the object printing. AM produce specialized tools, detailed parts and related customised medical devices. This technology is cheaper to provide better business options.^{7–9}

Additive manufacturing is an innovative technology which

manufactures objects/parts layer by layer deposition of material. It employs different types of 3D printing technologies to fabricate tissues and organs using technologies like extrusion and inkjet. Fused deposits modelling (FDM) based 3D printer is used commonly which are lower in cost and has moderate flexibility. It uses plastic/other filaments

Table 3
Different requirements of materials for tissue and organ printing.

S No	Requirement	Description	References
1	Biocompatibility	<ul style="list-style-type: none"> This is the performance of non-biological materials when implanted in the patient body having no biological tissue reaction It must have excellent biological properties and appropriate for clinical use The biocompatible material can perform appropriate response in the human body during a specific situation The biomaterial can perform the desired function of medical therapy and appropriate for cellular/tissue response 	Wang et al., 2007 ⁵³ ; Zhang et al., 2014 ⁵⁴ ; Luo et al., 2015 ⁵⁵ ; Zhang et al., 2016 ⁵⁶
2	Good & appropriate mechanical properties	<ul style="list-style-type: none"> Implants like a bone for a patient must have desired mechanical properties It assists a whole load of patient body and adjusts bone tissue It must be harmless which allows functioning as a natural substitute The material should possess mechanical stability for the reliability of the graft The material must be created under the consideration of Hardness, Fatigue, Fracture strength and toughness 	Wang et al., 2016 ⁵⁷ ; Mironov et al., 2017 ⁵⁸ ; Hangge et al., 2018 ⁵⁹
3	Porosity	<ul style="list-style-type: none"> 3D printed medical implants must have high porosity having cell attachment It should have an excellent degree of connectivity between the pores Porous materials show the ability to interact with biological molecules and ions throughout the bulk Porosity promotes tissue growth which employed for various part of the body like skin, cartilage, bone, vasculature etc Porosity allows specific interaction with target molecules of available surface area 	Seitz et al., 2005 ⁶⁰ ; Lee et al., 2008 ⁶¹ ; Zhou et al., 2008 ⁶²
4	Biological structure	<ul style="list-style-type: none"> It should have a biological structure which can survive tissue and other functions It varies from person to person as per the requirements The biological structure must deal with the molecular structure of biological macromolecules and cells It has to cater to the intricate and exquisite choreography of life 	Cohen et al., 2010 ⁶³ ; Bergmann et al., 2010 ⁶⁴ ; Kang et al., 2016 ⁶⁵

which are passed through a hot nozzle. This material is then deposited layer by layer on the print bed — these numbers of a required layer added to form a part. There are different types of materials used in FDM like thermoplastic, metal, wood, pastes, chocolates etc. In this process, the material is extruded through the nozzle, which is just passed its glass transition temperature. This technology uses two types of materials; one is modelling material which is used to create a finished object. Another is support material which supports the object during the printing of part. The main application of support material is to manufacture complicated design part without any defect precisely.^{10,11} These materials are in the plastic thread form, which fed through an extrusion nozzle. Nozzles are controlled through a computer in X, Y and Z coordinates and follow the printing path. It moves in built form vertically and horizontally as per the cross-section of an object. Once one layer is completed, the base is lowered as per layer thickness and makes room for the next layer. This process is repeated continuously until completing the object.^{12,13}

Another AM technology used for tissue and organ printing is inkjet technology. It uses a print head which contains different cell that allows producing multicellular organ/tissue and is used for the production of complex organ-regenerative scaffolds like liver tissue, aortic valves, cartilage and bone and is now getting popular.¹⁴

2. Research questions

AM can help produce complex tissue engineering scaffolds and organs as per patient-specific anatomical data. It is applicable for the preparation of tooling and devices moulds. This tissue printing is an innovative technique to fulfil the increasing demand for organ transplant.^{15–17} AM provides the right quality product with the input of good quality material. It is used to manufacture customised and complex end-use products without the requirement of any tooling. This study tries to address different research questions. It tries to identify the research status on “AM in tissue and organ printing” and “3D printing in tissue and organ printing” through a systematic study of the main components of AM for tissue and organ printing. Further, we need to identify

processes used to print organ and tissue using AM and also the different requirements of materials for tissue and organ printing. Thus, through this review based research, we need to identify innovative applications of AM in the medical field and undertake a study of different limitations of AM, when used for tissue and organ printing.

3. Research status

Research on additive manufacturing is continuously increasing in the area of tissue and organ printing. Here, we have identified research status on “Additive manufacturing in tissue and organ printing” and “3D printing in tissue and organ printing” from the Scopus database and discussed in the following sub-sections.

3.1. Research status on additive manufacturing in tissue printing

Taking data from Scopus by search keywords as “additive manufacturing” “tissue”, a total of 1174 research article published so far. The first article got published in 2004 and published only one research article in this year. After that, in 2006, two research articles were published. Again there was one year gap of publication in the research article. After that, there was continuously paper published in the year 2008. In year 2008 (2), 2009 (1), 2010 (15), 2011 (17), 2012 (28), 2013 (53), 2014 (80), 2015 (114), 2016 (176), 2017 (215), 2018 (239) articles was published. In this year, up to October 2019, 237 research articles are published so far.

Different sources and journal published research articles in this newly emerging area by the applications of additive manufacturing. Here, we show top five journals, and these include Biofabrication (47), Acta Biomaterialia (37), Journal of the Mechanical Behavior of Biomedical Materials (27), Materials Science and Engineering C (27) and Materials journal published 25 research articles.

In country-wise contribution, the United States has a maximum contribution of 22%, among all the countries. Whereas, China (8%), Germany (7%), United Kingdom (7%), Italy (6%), Australia (5%), Netherlands (4%) and other countries also contribute 41%.

Table 4
Different advancement of additive manufacturing in the medical field.

S. No	Advancements	Description	References
1	Human Organ	<ul style="list-style-type: none"> ● Researchers and scientist print kidney cell and sheets of cardiac tissue which works like an original ● 3D printed organs are used to provide similar functions as original ● Used for unique specific organs like main tissues of heart, nerves, blood vessels etc ● 3D printing used bioink to print tissue, human cells and livers to become more reality ● Helpful for regenerative medicine for 3D printed organ and tissue for transplant ● Easily create a biodegradable scaffold, and by using bioink in 3D printing, it creates an exact shape of organs with growing cell 	Murphy et al., 2014 ⁶⁹ ; Knowlton et al., 2016 ⁷⁰ ; Ji and Guvendiren, 2017 ⁷¹ ; Capel et al., 2019 ⁷²
2	Cells printing	<ul style="list-style-type: none"> ● In the human body, cells have excellent regenerative properties which can help to produce human tissues ● It can print tissue with cells which directly imparts in the patient body ● A scientist can print personalized 3D heart with human tissue and human cells ● 3D cell printing technology has excellent flexibility and potential to create advancement in the medical field 	Cai et al., 2005 ⁷³ ; Huh et al., 2011 ⁷⁴ ; Kolesky et al., 2014 ⁷⁵ ; Zhao et al., 2014 ⁷⁶ ; Jang et al., 2017 ⁷⁷
3	Printing of heart	<ul style="list-style-type: none"> ● This technology can easily create a heart and different valves as per patient shape and size ● It fabricates cardiac tissue like an original ● 3D printing can print heart and its customised parts with the help of bio-inks using fatty tissue ● A scientist can print 3D heart using human tissue, blood vessels, ventricles, cells and chambers 	Costello et al., 2015 ⁷⁸ ; Kolesky et al., 2016 ⁷⁹ ; Lau et al., 2018 ⁸⁰
4	Skin printing	<ul style="list-style-type: none"> ● This technology can be used for printing skin graft for the burn patient or skin cancer patient ● It can be somewhat successfully implemented into the patient body without any risk ● AM has the potential to print skin to save millions of lives ● This technology has promising applications for 3D printed human skin which creates a natural structure of the skin to get the protection of the external environment 	Lee et al., 2014 ⁸¹ ; Takahashi and Okano, 2015 ⁸²
5	Bone tissue engineering	<ul style="list-style-type: none"> ● Bone tissue engineering consists of three elements, i.e. bone scaffolds, cells and growth factors ● It can easily manufacture bone scaffolds which are essential for bone tissue engineering ● AM technology meets the requirements of bone defects and trauma of the patient ● It provides biological properties with the growth of surrounding tissue ● AM is useful for scaffolds fabrication that proves ideal for tissue bone engineering and with specific strength abilities ● In upcoming years, the ability of this technology is bound to increase due to its ability of custom bone tissue engineering for patient and clinical need 	Xiong et al., 2002 ⁸³ ; Leukers et al., 2005 ⁸⁴ ; Mota et al., 2016 ⁸⁵
6	Printing of smart material	<ul style="list-style-type: none"> ● Smart material has the capability of self-assembly and self-repairs to provide multi-functionality in the medical field ● AM is also useable to print smart materials, and this technology is the extension of 3D printing commonly known as 4D printing ● Smart materials provide shape-changing abilities over time and with the help of temperature and pressure ● Used to manufacture Smart stent, smart medical devices, implants etc. which can change shape as per the requirement of the patient 	Miao et al., 2017 ⁸⁶ ; Javaid and Haleem, 2018 ⁸⁷ ; Piedade, 2019 ⁸⁸ ; Bodaghi et al., 2019 ⁸⁹
7	Heart tissue	<ul style="list-style-type: none"> ● One of the main challenges of the heart tissue is to supply oxygen and nutrients for heart tissue ● This technology correctly creates heart tissue to increase outcome and proper function in the heart of the patient ● AM develops cardiac tissues to restore blood perfusion ● Heart tissue provides an option for a heart transplant for the cardiac patients 	Giannopoulos et al., 2016 ⁹⁰ ; Yoo et al., 2016 ⁹¹ ; Qasim et al., 2019 ⁹²
8	Vascular channels	<ul style="list-style-type: none"> ● AM is available to design and development of vascular channel and hollow tubes as per the required diameter ● This technology creates vascular channels with cells and biological matrices ● Used to construct larger perfusable channels to create innovation in the medical field ● It seems to be the best technology to fulfil challenges of complex vascularized tissue fabrications 	Will et al., 2008 ⁹³ ; Zhou et al., 2017 ⁹⁴ ; Datta et al., 2017 ⁹⁵ ; Javaid and Haleem, 2019 ⁹⁶

In area wise contributions, the engineering field has a maximum contribution of 29%. The other field provides materials Science (24%), Biochemistry, Genetics and Molecular Biology (11%), Chemical Engineering (8%), Medicine (6%), Physics and Astronomy (5%), Computer Science (5%) and 7% contribution.

3.2. Research status on additive manufacturing in organ printing

Taking data from Scopus by using search keywords as “additive manufacturing” “Organ”, a total of 196 articles reported in this specific

area. In the year 2010, the first article on additive manufacturing in organ printing was published. In 2011 (3), 2012 (5), 2013 (6), 2014 (13), 2015 (22), 2016 (33), 2017 (34), 2018 (39) and in this year up to October 2019, total 39 research articles are published so far.

There are different sources and journal published research articles in this area. Here, we reported top-five journals, Biofabrication having maximum publications of 9. Materials (7), Annals of Biomedical Engineering (4), International Journal of Bioprinting (4) and Acta Biomaterialia journal published three research papers in this specific area. Other sources and journals were also having a good number of

Table 5
Limitations when additive manufacturing is used for tissue and organ printing.

S.No	Limitations	Description	References
1	Lack of diversity in biomaterials	<ul style="list-style-type: none"> The main limitation of this technology is the lack of diversity in biomaterials 3D printer having limited capabilities of speed and resolution depend upon individual cases Biomaterial must be biocompatible, printable, possess good degradation kinetics, appropriate mechanical properties, exhibits tissue bio-mimicry and safe degradation 	Guvendiren et al., 2016 ¹⁶ ; Przekora, 2019 ¹⁰⁰
2	The requirement of mechanical strength	<ul style="list-style-type: none"> It does not provide suitable mechanical strength to the printed part Highly challenging to manufacture the complex structure of bone which requires a complex combination of mechanical properties during the regeneration process 	Shao and Fu, 2013 ¹⁰¹ ; Tong et al., 2015 ¹⁰²
3	Human Trials	<ul style="list-style-type: none"> Extensive Human trials are necessary before the actual implementation of these tissue/organ in the patient body Sometimes it can be risky for the patient Different biomaterials are being developed and identified, but they have limited ability and functionality 	Turnbull et al., 2017 ¹⁰³ ; Ottensmeyer et al., 2018 ¹⁰⁴
4	Availability of limited biomaterials	<ul style="list-style-type: none"> Limited biocompatible materials available for each type of 3D printing technology There is a reasonable requirement for extensive research before commercial production of biomaterials for the medical field 	Tallawi et al., 2015 ¹⁰⁵ ; Javaid and Haleem, 2016 ¹⁰⁶
5	Appropriate selection of biomaterial	<ul style="list-style-type: none"> Proper selection of biomaterial must be required for appropriate printing of tissue and organ Biomaterials depend upon the condition of diseases; thus proper selection is required 	Hasan et al., 2016 ¹⁰⁷ ; Madrigal et al., 2017 ¹⁰⁸
6	Does not provide required cells	<ul style="list-style-type: none"> This technology cannot deliver the numbers of cells required for different tissue/organs It does not create the uniaxial nervous network/branched vascular in a construct 	Krishnan et al., 2014 ¹⁰⁹ ; Jiang et al., 2016 ¹¹⁰ ; Kant and Coulombe, 2018 ¹¹¹
7	Ethics	<ul style="list-style-type: none"> Need approval for the actual implementation of these 3D printed part for the patient Must require authorisation whether it will be feasible or not Safety of the patient must be required during implementation Regularity approval required from concerned health authorities 	Diomedea et al., 2018 ¹¹² ; Ebbing et al., 2018 ¹¹³
8	Limited polymers	<ul style="list-style-type: none"> It includes limited photocurable polymer resin and biodegradable polymer for printing In tissue engineering, there are uneven approaches in scaffolds cell seeding and face problem during incorporation of multiple cells 	Choi et al., 2017 ¹¹⁴ ; Liu et al., 2018 ¹¹⁵ ; González-Henríquez et al., 2019 ¹¹⁶
9	Damaging of cells	<ul style="list-style-type: none"> Shear force during rapid printing damages cells and create a dead core in the thickness 	Jackson et al., 2018 ¹¹⁷ ; Celikkin et al., 2019 ¹¹⁸
10	Standardisation	<ul style="list-style-type: none"> Sometimes, this creates a high risk for printed medical parts Evidence-based trials required for the best treatment and maintain standardisation which takes extra time No standards regarding safety and quality to the concerned patient 	Phan et al., 2016 ¹¹⁹ ; Lau and Sun, 2018 ¹²⁰ ; Javaid and Haleem, 2019 ¹²¹
11	Not readily accepted by the human body	<ul style="list-style-type: none"> Due to introducing of new biomaterials for tissue and organs, many times they do not have readable acceptability in the human body Requires very high level of research and development and the same is costly Extensive testing of new biomaterial testing is very much required, and it is quite costly 	Samorezov and Alsberg, 2015 ¹²² ; Bose et al., 2018 ¹²³ ; Javaid and Haleem, 2019 ¹²⁴
12	Requirements of tissue for long term usage	<ul style="list-style-type: none"> There are limited hydrogels (used to make soft contact) which are suitable for bioink These 3D printed tissue and organ do not survive for the long term in the patient body 	Song et al., 2018 ¹²⁵ ; Qasim et al., 2019 ⁹²
13	Understanding of the relation between the biomaterial properties and the printing outcomes	<ul style="list-style-type: none"> Relatively poor understanding of the relation between the biomaterial properties and the printing outcome Multilayered tissue engineering Scaffolds are new challenges Having limited computational power by which proper outcome does not achieve using biomaterials 	Butscher et al., 2013 ³¹ ; Gerstleat et al., 2014 ¹²⁶ ; Zadpoor, 2017 ¹²⁷

publications in this emerging area.

In-country wise contribution on Additive manufacturing in organ printing, United States having maximum contribution of 28%, China (8%), Singapore (5%), Italy (5%), India (4%), United Kingdom (4%), Netherlands (4%) and other counties also contributes 42%.

In area wise contributions, “Engineering” field having a maximum contribution of 27%. Materials Science (18%), Biochemistry, Genetics and Molecular Biology (14%), Medicine (10%), Chemical Engineering (10%), Computer Science (5%), Physics and Astronomy (4%) and other field contribute 12%.

3.3. Research status on 3D printing in tissue

Numbers of research papers are published on 3D printing in tissue. By searching keyword as “3D printing” “tissue” from Scopus, total 2701 research articles are published so far up to October 2019. The first articles on this specific field by implementation this technology was published in 1998 and after a gap of four years, the second article was published in 2002, and this year two articles were published. In 2003 (1), 2004 (2), 2005 (7), 2006 (6), 2007 (8), 2008 (8), 2009 (12), 2010 (13), 2011 (14), 2012 (16), 2013 (44), 2014 (130), 2015 (231), 2016 (372), 2017 (507), 2018 (664), and in 2019 till last day of October 657 articles are published.

Different sources and journal published research articles in this field. Out these top five journals are Biofabrication (81), Acta Biomaterialia (59), Materials Science and Engineering C (52), Journal “ACS Applied Materials and Interfaces”, and “Chinese Journal of Tissue Engineering Research” both having 51 research publications.

In country-wise contribution, United States having maximum contribution of 27%, whereas China (17%), United Kingdom (6%), South Korea (6%), Germany (5%), Australia (4%), Singapore (3%) and other countries also have good contribution of 32% in this field.

In area wise contributions on 3D printing applications in tissue, “Engineering” field having a maximum contribution of 22%. Materials Science contributes 21%, Biochemistry, Genetics and Molecular Biology (13%), Medicine (12%), Chemical Engineering (8%), Physics and Astronomy (6%), Chemistry (5%) and other fields having 13% contributions.

3.4. Research status on 3D printing in organ

By the search of keywords as “3D printing” “organ” from Scopus, a total of 568 research articles are published so far up to October 2019. The first research articles on this specific field were published in 2006, and in this year, two articles were published. In 2007, no article was published. In 2008 (2), 2009 (2), 2010 (2), 2011 (3) and again, no research article was published in the year 2012. In the year 2013 (16), 2014 (27), 2015 (52), 2016 (107), 2017 (105), 2018 (134), and so far 116 research articles are published in this year in 2019.

Different sources and journals published articles on 3D printing applications in organ printing. In top five journals, “Biofabrication” journal publishes 12 research articles, Advanced Healthcare Materials having publications of 10 articles, Progress in Biomedical optics and imaging proceedings of SPIE and Scientific Reports have an equal number of publications of 8 research articles, Artificial Organs published seven articles. Various other journals also have a significant contribution to publication in this specific field.

In country-wise contribution, United States has a maximum contribution of 24%, whereas China (15%), South Korea (8%), Germany (5%), United Kingdom (5%), Japan (4%), Singapore (4%) and other countries also have 35% contribution.

In area wise contribution Engineering field having maximum contribution of 22% and material science (16%), Medicine (15%), Biochemistry, Genetics and Molecular Biology (11%), Chemical Engineering (8%), Physics and Astronomy (5%), Computer Science (5%) and other field having 16% contribution.

Therefore, from Scopus data, it has been identified that the applications of this technology emerge in this specific field of medical. Further, in this section, we analysed that there are a large number of papers being published in the area of tissue and organ. This technology assists and provides direction to researchers.

4. Main components of additive manufacturing for tissue and organ printing

Additive manufacturing can undertake quick scaling and has excellent flexibility of the material. It uses almost all types of material depending upon the requirements and the available technologies. It can also scale design as per cost to size ratio. The process of tissue and organ printing start with biomaterials which meet different needs like bioactivity, biodegradability, shape, size, porosity etc. 3D printing has revolutionized the healthcare for the manufacturing of patient-specific complex implants and prosthetic. Biomaterials support the survival of a cell for the required function in the patient body.^{18,19} These biomaterials have cell adhesion capability using three strategies physical modification, chemical modification, and surface coatings having better interaction. Table 1 provides a list of critical components of additive manufacturing useable for tissue and organ printing.

Scientist and researcher are developing and commercialising AM

technology to produce a realistic structure. As, it seems a useful tool for tissue engineering to help create a structure with required shape, strength, volume, that easily resemble natural tissue. It prints different materials, and during the printing process, it keeps cells alive. It can maintain the mechanical properties of the medical part by using innovative materials. This technology is used for the replacement of infarcted cardiac tissues and regeneration of progenitor cells. It efficiently produces artificial organs, tissue and implants to fulfil the requirement.

5. Processes used to create tissue/organ using additive manufacturing

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) is a useful technique to design and develop patient-specific parts. 3D printing can fabricate required functional organ and tissue with biomaterials and multiple cells.^{34,35} These biomaterials have excellent biological, chemical and mechanical properties. There are different materials which have bone-like properties and are used in 3D printing. These materials include silica, graphene, zirconium oxide, and bio glass. Processes used to create tissue/organ using AM are discussed in Table 2.

3D data play an essential role in the design and development of customised 3D implants obtained from MRI and CT. This technique easily captures the organ, bone and tissue to make further development without any harmful effect. Medical image captured by these scanning technologies is saved further in Digital Imaging and Communication in Medicine (DICOM) format. This file is converted into a 3D CAD file and exported in STL format in 3D printing technologies. Finally, the printed model is implemented in the body of the patient to fulfil the desired requirement.⁵²

6. Different requirements of materials for tissue and organ printing

Biomaterials support cell function and proliferation while introducing cell in the scaffolds. AM is an innovative technique for scaffold fabrication for tissue. This technology has various advantages over conventional method such as multi-material printing, complex geometries manufacturing in lesser time and cost. A few researchers and scientists have created tissue with multiple cells. Table 3 provides different requirements for materials to be employed for tissue and organ printing.

Researchers have used this technology for congenital heart problems and diagnosis of heart diseases. Biomaterials model printed by this technology is precisely used to compare surgical finding with an actual demonstration. It increases the confidence level of the surgeon, which is not possible with different medical scanning technique. Further, this technology is used as advance medical education and learning about the cause and impact of various diseases. Surgeon and patient can now better understand the surgical treatment and diseases.⁶⁶

7. Different advancement of additive manufacturing in the medical field

The personalized reconstructed of tissue engineering scaffold is done using data from medical CT/MRI scan. There are different materials used for the precise development of a scaffold, tissue, organs, and other medical parts. AM bio-printing is used to rebuild the damaged organ of the various region of the body. This technology can print muscle, organ, cartilage, bone and skin tissue.^{67,68} AM significantly contributes to advancement in tissue engineering with the help of innovative biomaterials. Table 4 discusses different advancement of additive manufacturing in the medical field.

One of the major organs for transplant for a patient is liver and kidney, which are being experimented using AM technology. Polymers

also are used in AM technologies for a few types of tissues, which are helpful in transplantation.^{97–99} One of the significant challenges in tissue engineering is the research & development on different types of tissue, and another is the fabrication of complex tissue which can adequately be taken up by this technology.

8. Limitation of additive manufacturing for tissue and organ printing

There are different limitations of additive manufacturing for the printing of tissue/organ. Due to low mechanical strength and properties of available biomaterials, it does not print appropriate tissue and organs which can directly implement in the human body. Table 5 shows, different limitations of additive manufacturing for tissue and organ printing.

Additive manufacturing does not provide the capability to deliver the required numbers of cells required for different tissue. It includes limited photocurable polymer resin and biodegradable polymer for printing during incorporation of multiple cells. These limitations will be developed by new biomaterials and AM technology to make advancement in the medical field. There is a requirement of effect health,¹²⁸ so this technology is implemented in the medical field to address required problem.^{129–131}

9. Discussion

Additive manufacturing rapidly embraced in medical field, as it provides freedom of design and material for printing of tissue, organs and cells. It fabricates hydrogel structure by incorporation of cells. This is an innovative technology which can convert a digital design into physical objects. There is vast research going on tissue engineering for the replacement of tissue and organ. Biomaterial fabricated scaffold plays a vital role during the replacement of human tissue and organ. These biomaterials are used in skin, bone, cartilage, vessel, tendons, bladder, tissue, nerves and liver. There are different polymers like chondroitin sulphate, collagen and chitosan used for biomedical applications. Bone is one of the parts widely used in daily life. During any trauma or disease, bone can quickly regenerate by using AM technology. It enhances bone regeneration defect and bone tissue engineering. Currently, bioactive inorganic materials and composites of polymers are developing to increase the mechanical stability of scaffold and tissue interaction.

Biocompatible materials are necessary to create a scaffold, which helps cells to perform routine functions. Additive manufacturing helps in biocompatible printing materials as per the required shape and size. Implants printed by these materials have much better efficiency and lesser reaction after implantation in the patient body. A customised, cost-effective scaffold for bone tissue engineering is possible with AM. Further with this advancement, a wide variety of bimetallic, bioceramics, biopolymers, and biocomposites materials are now available for meeting challenges, and these materials are more suitable for cell adhesion and growth for tissue and organs. This technology is suitable for tissue engineering of complex structure to meet the personalized medical requirement. It can incorporate cells, proteins to form excellent biological properties. This technology quickly constructs scaffolds by which living cells are grown. The regeneration of damaged tissue is done quickly and repairs the body without any problem/side effect.

10. Future scope

In future, AM will enhance its potential for personalized tissue engineering. It will bring significant advancement in diagnostics and therapeutics. AM meets the future demand of tissue, organs and vascular structure as per patient demand. It shows great interest in the design and development of an artificial heart with the help of biomaterials. In upcoming years, the medical profession will explore this

technology to print microchannels, which can be used to maximize the amount of oxygen and nutrients from neighbouring tissues. AM may change the way of the manufacturing of tissue, organs and other devices if used as per the patient's requirements. With proper research & development, it is to provide confidence to doctors, surgeon, researcher and medical practitioner in this essential area to save humanity. In future, there is a possibility to use this technology to seed neuronal cells, which will be helpful to repair spinal cord and brain injury.

11. Conclusion

Additive manufacturing is used to print biomaterial and provides efficient technologies to combine cell and improve their growth factor. By 3D printing, biomaterial can be added layer by layer and to form tissue-like structure. This can easily print tissue, cell and organ, which help to regenerate joints and ligaments. Liquefied material which provides oxygen and nutrients for alive is mixed with the cells. This mixing of cells, nutrients and matrix is known as bioink. It is placed in the head of the 3D printer, and layers are deposited as per the data of patient captured by CT and MRI. It is a biological construct of cells and constructs of artificial organs like kidney, liver and other working blood vessels. After printing, it is necessary to create the growth of tissues and the ability to survive transplants. This technology is now being used as an innovative approach of autonomous self-assembly, biomimicry, and to fabricate mini-tissue building blocks. Researchers are focus to develop living organs having excellent biological and mechanical properties using 3D printing. The main goal of this technology is to create a structure like natural, which can be survived in the human body. It quickly creates a cellular part of the organs having self-assembly approaches.

Declaration of competing interest

None.

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