REVIEW ARTICLE

Recent Updates on Metal-Polymer Nanocomposites in 3D Bioprinting for Tissue Engineering Applications

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Bableen Flora[a], Rohit Kumar[b], Ramisa Mahdieh[c], Kimiya Zarei[d], Shaghayegh Chehrazi[e], Simran Deep Kaur[f], Arushi Sharma[g], Priyanka Mohapatra[h], Akshita Sakshi[i], Anjuvan Singh[j], Kavindra Kumar Kesari[k], Piyush Kumar Gupta[l]

[a] Department of Biotechnology, School of Biosciences & Bioengineering, Lovely Professional University, Phagwara, Punjab 144411, India.

[b] Department of Life Sciences, Sharda School of Basic Sciences and Research, Sharda University, Greater Noida 201310, Uttar Pradesh, India.

[c] Isfahan University of Medical Sciences, Isfahan, Iran.

[d] Faculty of Pharmacy and Pharmaceutical Sciences, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

[e] Biology department, Islamic Azad University, Science and Research Branch, Tehran, Iran.

[f] School of Pharmaceutical Sciences, Shoolini University of Biotechnology and Management Sciences, Solan 173229, Himachal Pradesh, India.

[g] Department of Biotechnology, Panjab University, Sector 25, Chandigarh, Punjab, India.

[h] Department of Microbial Biotechnology, Panjab University, Sector 25, Chandigarh, Punjab, India.

[i] Department of Biproducts and Biosystems, School of Chemical Engineering, Aalto University, Espoo 00076, Finland.

[j] Department of Biotechnology, School of Biosciences & Bioengineering, Lovely Professional University, Phagwara, Punjab 144411, India.
Corresponding Author:
anjuvan.15950@lpu.co.in

[k] Department of Biproducts and Biosystems, School of Chemical Engineering, Aalto University, Espoo 00076, Finland.
Department of Applied Physics, School of Science, Aalto University, Espoo 00076, Finland.
Corresponding Author:
kavindra.kesari@aalto.fi

[l] Department of Life Sciences, Sharda School of Basic Sciences and Research, Sharda University, Greater Noida 201310, Uttar Pradesh, India.
Department of Biotechnology, Graphic Era Deemed to Be University, Dehradun 248002, Uttarakhand, India.
Faculty of Health and Life Sciences, INTI International University, Nilai 71800, Malaysia.
Corresponding Author:
dr.piyushkgupta@gmail.com

Abstract: Rapid tooling using additive manufacturing, or 3D printing, is an emerging manufacturing technology that has the potential to revolutionize the production of complex parts using only a computer and a design program. Lightweight structures with excellent dimensional precision and lower cost for customizable geometries are possible with these printed parts. In recent years, inherent constraints of polymers, metals, and ceramics have pushed researchers toward superior alternative composite materials to boost mechanical and other critical features; current 3D printing research follows this route from neat to composite materials. The characteristics, performance, and future uses of composite materials produced using additive manufacturing methods are discussed in this review. In addition, to discuss the state of the art in additive manufacturing, this article also fabricated many technologies, including robotics, machine learning, organ-on-a-chip, and 4D bioprinting..

Keywords: 3D bioprinting; Fabrication; Tissue engineering; Nanocomposite; Metal-Polymer; Organ-on-a-chip.

1. INTRODUCTION

Scientists and researchers continue to focus on tissue and organ damage as a significant concern. In tissue engineering and regenerative medicine, various biomaterials are used to model living tissue or organs, which may then be used as scaffolds or nano constructs to repair damaged tissue. Numerous biomaterials are used for the manufacturing of scaffolds. The key traits for selecting biomaterial include biocompatibility, bioactivity, and biodegradability. Various other structural, mechanical, and physicochemical features have been evaluated to mimic the target tissue or organ to be regenerated. Biomaterials have been briefly reviewed as metals, polymers, ceramics, composites, and hydrogels. Composites and hydrogel have been used for both hard and soft tissues, whereas ceramics showed brittleness and metals showed lower cell adhesion (Dolcimascolo *et al.*, 2019). Depending on how they are designed, biomaterials may exhibit an immunological response, even without immune stimulation. In addition, the impact of custom-made biomaterials on the adaptive immune system has been investigated. (Andorko & Jewell, 2017). Both conventional and advanced methods have been used to fabricate the composites. The traditional methods include solvent-casting, freeze drying, Salt leaching, Injection molding, extrusion-based, compression molding, film blowing, and electrospinning (Prasad & Kandasubramanian, 2019). These

fundamental approaches restrict their approach since they can't achieve the requisite size and functioning of a damaged tissue or organ model. 3D bioprinting overcomes these limits. Three-dimensional bioprinting, called "additive manufacturing" or fast prototyping, transformed the world by offering spatial orientation of the required scaffold (Comber *et al.*, 2019). Numerous techniques have been available for the processing of 3D printing, inclusive Selective Laser Sintering (SLS), Stereolithography, Vat-photopolymerization, Fused Deposition or 3D fiber deposition, Powder based fusion process, and Spheroid based method (Liu *et al.*, 2019; Moroni *et al.*, 2018a).

Bioprinters come in various forms and may be tailored to meet multiple requirements. A comparative analysis of different types of 3D printers has been envisaged. It has been accessed that laser-based 3D bioprinters were found to be the most expensive and require a lot of time for preparation but showed greater than 95 % of cellular viability. Compared to Extrusion-based 3D printers, versatility in gelation methods has been found with a medium cost of printing with a range of 40-80 % cell viability (Gao *et al.*, 2019). The details of various 3D bioprinting are as follows:

Inkjet 3D bioprinting

These bioprinters, also called drop-on-demand printers, give drops of bio-inks on the substrate on stimuli of thermal, piezoelectric, or electromagnetic forces. A layer-on-layer model was prepared through it. Inkjet bioprinting is reported to be well-known for its speed and accuracy. Materials including PVA, poly-DL-Lactide (PDLLA), citric acid, and water were used (Tappa & Jammalamadaka, 2018a).

Extrusion 3D bioprinting

Some of the commercial extrusion bioprinters are 3DDiscovery, BIO V1, BIO3D, 3DS Alpha and Omega, and INKREDIBLE. Extrusion-based bioprinters perform by mechanical or pneumatic stimulus, and a continuous structure is formed. Usually, polymers are printed through this method (Li *et al.*, 2016).

Laser-assisted 3D bioprinting

Due to its precision, quickness, and perfection, it has been hailed as the most effective service delivery. Nozzles are not required, and bio-ink is printed on a titanium or gold layer hanging underneath a ribbon. Using a laser pulse, a bubble of bio-ink is forced through a ribbon (Basara *et al.*, 2020).

3D bioprinting has different stages, which can be divided into many sequential steps:

Data acquisition through imaging

The organ or tissue of a patient is studied through various imaging techniques such as Computed tomography (CT-Scan), Magnetic resonance imaging (MRI), and X-ray (Gu *et al.*, 2019; Papaioannou *et al.*, 2019).

Biomaterial screening

Research has been conducted on various biomaterials, including metals, bioceramics, and polymers used in fabricating scaffolds. Live cells are selected and integrated into the bio-ink for 3D printing. The appropriate material is screened and selected for printing the functional model of organs and tissues to repair the damaged tissue (Parak *et al.*, 2019).

Computational design

Computational tools have been used, including computer-aided design and computer-aided manufacturing (CAD-CAM). This recreates the complex tissue or organ, and a .stl file was created, which was further simulated until an acceptable model was obtained (Moroni *et al.*, 2018b; Tappa & Jammalamadaka, 2018b).

Printing Parameters

Numerous bioprinters have been reported, including Extrusion, Inkjet, and Laser printers, and various parameters such as speed of printing, bio-ink type, patterns, type of sample, and orientation of printing required for bioprinting, calibration of printer should be done before reconstructing the target (Gu *et al.*, 2019).

Post-bioprinting

After printing and post-bioprinting testing, including maturation in the bioreactor, compatibility, and immunological testing according to the specified tissue or organ (Tappa & Jammalamadaka, 2018b).

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2. FABRICATION AND CHARACTERIZATION OF METAL-POLYMER NANOCOMPOSITES

Researchers and scientists combine many materials to develop stronger nanomaterials. Polymers' structural and functional variety makes them a ship-shaped material that may be utilized as a matrix and reinforced by fillers to form an indefectible product. Polymers-metal nanocomposites enhanced the material's mechanical, electrical, optical, and antibacterial characteristics studied through different techniques (Figure 1). The biodegradability and bioresorbability of polymers fueled the industrial need for bioimplant devices, such as epidural catheters (made from polyethylene, polytetrafluoroethylene), pacemakers, dental implants from PMMA, cochlear and nasal implants, synthetic blood vessels from polypropylene, titanium surgical implants using polydimethylsiloxane, orthopedic implants from poly hydroxy-alkenoates, and many others (Teo *et al.*, 2016). Incorporating metal and metal oxide into polymers demonstrated diversity in characteristics and uses. A starch-based nanocomposite along Tin oxide (Starch/SnO2) was generated using sol-gel and evaluated using XPS, XRD, BET, and FTIR analyses. SEM and TEM analyses demonstrate aggregation.

The composite's Hg2+ adsorption capability has also been examined. The effectiveness of eliminating harmful ions from an aqueous medium was 97%. In another study, cellulose was supplemented with bacterially reduced silver nanoparticles to develop a nanocomposite. SEM was used to examine nanoparticle dispersion in the matrix, while TEM revealed nano-spherical nanoparticles. Silver nanoparticles exhibit antibacterial activity despite reducing the composite's crystallinity and thermal stability (Muthulakshmi *et al.*, 2017). Enzyme immobilization uses polymer-metal nanocomposite. Subashini and colleagues produced glutaric acid, ethylene glycol, and acrylic acid (GEA) polymer through condensation and constructed with copper oxide to make a (GEA-CuO) nanocomposite. SEM and TEM exhibited 5-10nm nanocomposite morphology. Thermogravimetric measurement showed the nanocomposite's thermal stability (TGA). GEA-CuO nanocomposite resists S. aureus and E. coli. The cytotoxicity was also investigated on lung cancer cells (Subashini *et al.*, 2020).

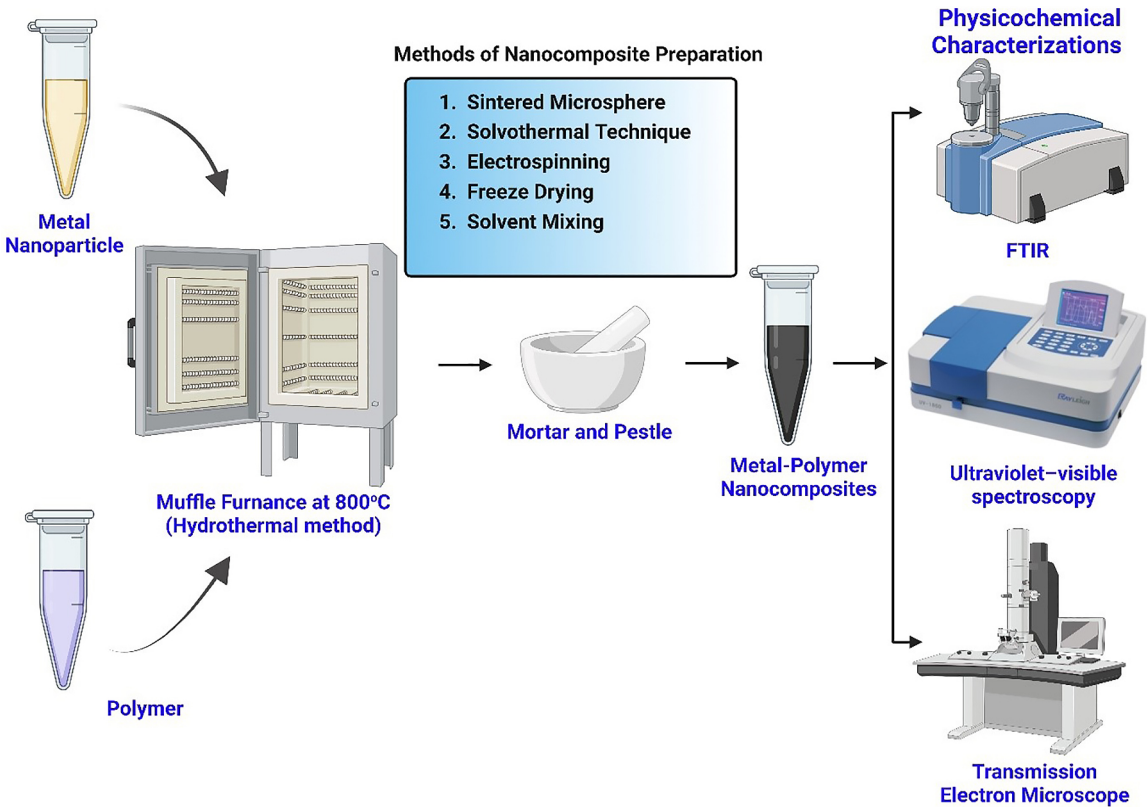

Figure 1. Several methodologies for metal-polymer nanocomposites fabrication and their characterization. via numerous physicochemical techniques.

S. No	Fabrication Method	Material used	Characterization	References
1	Fused Deposition Modeling	Carbonyl-Fe- PLA	FESEM, XRD, VSM, Dielectric Spectrophotometer	(Guan *et al.,* 2018)
2		PVDF-$BaTiO_3$-MWCNT	SEM, LCR	(Kim, Johnson, *et al.,* 2018)
3		PLA-Graphene	SEM, LCR, DMA, EMI	(Prashantha & Roger, 2017)
4		Li-Zn-$Fe_{2.36}O_4$/ PLA	XRD, FTIR, FESEM, EDS, UTM, TGA	(Y. Qian *et al.,* 2018)
5		PVA-CNT	FESEM, TGA, DSC, DMTA	(Rigotti *et al.,* 2018)
6		PVA-Graphene	SEM, TGA, DSC, XRD, DSA, UTM, FTIR, Raman Spectroscopy	(Yang *et al.,* 2020)
7		Carbon fiber-PLA	FESEM, DSC	(D. Lee & Wu, 2020)
8	Stereolithography (SLA)	PMMA-TiO_2	SEM, EDX, FTIR	(Totu et al., 2017)
9		PMMA-TiO_2	SEM-EDX, AFM, Micro-CT	(Cristache *et al.,* 2020)
10	Selective Laser Sintering	PA 12/PU-CNTs	TEM, FTIR, Micro-CT	(Yuan *et al.,* 2018)
11		Polyurethane / Graphene	SEM, TEM, TGA, DSC, Raman Spectroscopy	(Ronca *et al.,* 2019)
12		PA11/$BaTiO_3$/CNT	SEM, Raman Spectroscopy, XRD, DSC	(Qi *et al.,* 2018)
13	Liquid Deposition Modeling (LDM)	Polycaprolactone-Copper-Bioglass	Optical Microscopy, SEM, Micro-CT, TGA	(X. Wang *et al.,* 2019)
14	Sintered Microsphere Method	PLGA/ TiO_2	SEM, Contact angle analysis, Mechanical analysis, Density, and Porosity measurements	(Eslami *et al.,* 2018)
15	Electrospinning	PLGA/GNPs	FESEM, EDX, FTIR	(D. Lee *et al.,* 2018)
16		PCL-ZnO/CA PCL-CuO/ CACL-AgNPs/CA	XRD, FTIR, TEM, FESEM, Antibacterial assay	(Ahmed *et al.,* 2020)
17		PCL/nZnO	SEM, EDX, ATR-FTIR, XRD, TGA, Contact angle analysis	(Harikrishnan & Sivasamy, 2020)
18	Emulsion Solvent Diffusion Method	PLGA-AgNPs	FESEM, Antibacterial assay	(Takahashi *et al.,* 2017)
19	Spark Plasma Sintering	PLA/Graphene	XRD, FTIR, TGA, DSC, SEM	(Adesina *et al.,* 2020)
20	Injection Moulding	MWCNT/PLA	SEM, AFM, DSC, Polarized Light Microscopy, Electrical Conductivity	(Rivière *et al.,* 2017)
21	Freeze Drying	Chitosan-CMC- ZFHA	XRD, FESEM, Porosity analysis, Swelling behavior study, Antibacterial assay	(Saxena *et al.,* 2021)
22	Solvent Mixing	CMC/Cu-MOF@IB	FTIR, BET, XRD, UV-Visible Spectroscopy, SEM	(Javanbakht *et al.,* 2018)

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S. No	Fabrication Method	Material used	Characterization	References
23	Solvothermal Technique	CMC/ZnMOF/ GO-DOX	FTIR, EDX, XRD, BET, Zeta Potential, DLS, Solubility test, SEM, AFM	(Javanbakht *et al.,* 2019)
24	In-situ deposition and microwave irradiations	CMC/Cu NP, CMC/Fe NP, CMC/Ni NP	SEM, FTIR, XRD, TEM, Electrochemical studies, Corrosion analysis	(El-Lateef *et al.,* 2020)
25	Solvent casting	PbO/CMC/PVP	XRD, SEM, FTIR, Optical analysis, Dielectric traits	(El-Bana *et al.,* 2018)

Table 1. Various fabrication methods for metal-polymer nanocomposite and their characterization by different physicochemical techniques.

Notes:
VSM – Vibrating sample magnetometer
PVDF – Poly(vinylidene) fluoride
MWCNT – Multiwalled carbon nanotubes
PLA – Poly (lactic acid)
EMI – Electromagnetic induction
DMA – Dynamic mechanical analysis
UTM – Universal testing machine
TGA – Thermogravimetric analysis
DSC – Differential Scanning calorimetry
DMTA – Dynamic mechanical thermal analysis
PVA – Polyvinyl alcohol
DSA – Drop shape analysis system
AFM – Atomic Force Microscopy
PA – Polyamide, GNPs – Gold nanoparticles
AgNPs – Silver nanoparticles
CA – Cellulose acetate
TEM – Transmission electron microscope
FESEM – Field emission scanning electron microscope
ZFHA – Zinc-Iron doped hydroxyapatite
CMC – Carboxymethyl cellulose
DOX – Doxorubicin
ZnMOF – Zinc based metal-organic framework

3. METAL-POLYMER NANOCOMPOSITE IN 3D PRINTING

Various advanced methods have been implemented to form 3D-printed scaffolds using metal-polymer nanocomposites with distinctive features for several tissue engineering applications (Figure 2). These nanomaterials were found to be promising for reinforcing the cells' growth. A Kagome structured composite scaffold using a 3D printing material-extrusion system has been reported incorporating zinc ions with variable thicknesses of 10, 100, and 200 nm on polycaprolactone and nano-hydroxyapatite scaffold. It has been revealed that scaffolding PCL/nano HA with 100 nm thick Zinc oxide showed enhanced cell proliferation and antibacterial behavior (Cho *et al.*, 2020).

Further, a nanocomposite of Polyvinylidene fluoride (PVDF) reinforced with homogeneous dispersion of BaTiO3 has been fabricated through fused deposition modeling (FDM), showing higher piezoelectric properties (Kim, Fernando, *et al.*, 2018). In another study, using the melt extrusion method, a polylactic acid polymer (PLA) reinforced with silver nanoparticles in different concentrations along PEG and PVP was made in the filament. The antimicrobial activity of S. aureus and E. coli and their mechanical strength have been scrutinized (Vidakis *et al.*, 2020). An ameliorated antibacterial activity against E. coli and S. aureus has been examined in 3D-printed PLA braced with silver nanowires showing a 100 % death rate in 2 h (Bayraktar *et al.*, 2019). Nevertheless, the 3D-printed PLA reinforced with ZnO has been evaluated for mechanical, thermal, and morphological properties. On the mechanical analysis of the FDM fabricated PLA/ZnO nanocomposite, a maximum young's Modulus of 233.68 MPa has been obtained (Singh *et al.*, 2020). Seyedsalehi and coworkers successfully fabricated a PCL-reinforced reduced graphene oxide scaffold through the extrusion-based 3D printer, elevated the mechanical strength by 185 %, and also found it compatible after being assessed on human adipose stem cells (Seyedsalehi *et al.*, 2020).

Polylactic acid (PLA) mixed with graphite nanoplatelets and L-Arginine increased tensile strength by 43.6% and degradation rate at 60 °C, increasing the current degradation temperature. 3D-printed gold nanoparticle-filled PCL nanocomposite enhances mechanical characteristics (Wang *et al.*, 2020).

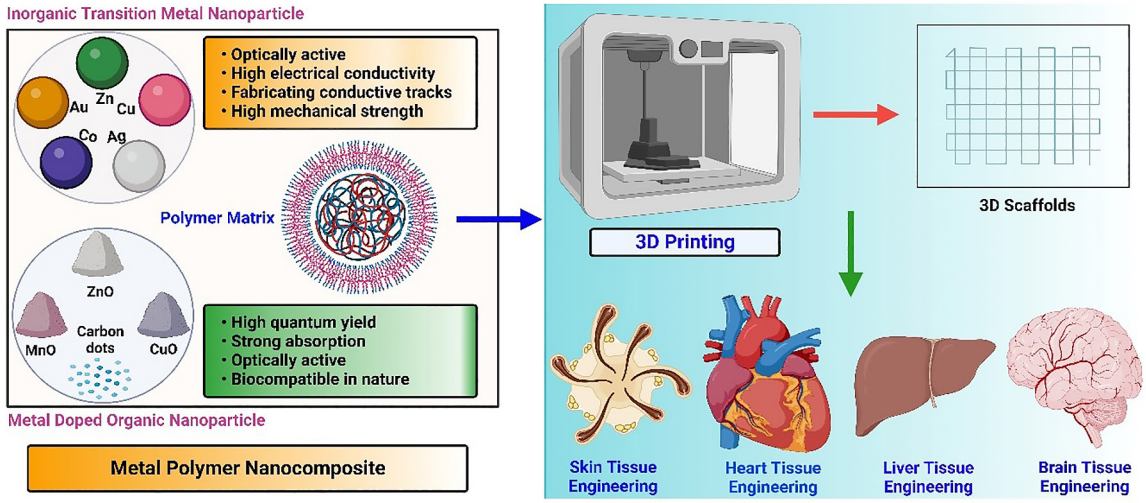

Figure 2. Various metal or metal oxides reinforced with different polymer matrices as nanocomposite in 3D printing for fabrication scaffolds in tissue engineering.

Plasma-treated PCL/Au nanocomposite showed outstanding biocompatibility and minimal cytokine production of TNF-α and IL-8 (Joseph *et al.*, 2021). 3D-printed PLA filament was functionalized with COS, zinc, Halloysite, and silver nanoparticles to form PLA/COS-ZnHNT-Ag. The nanocomposite's antibacterial properties were examined using disc diffusion and biofilm tests (Humayun *et al.*, 2020). To improve the nanocomposite's mechanical properties employing metal or metal oxides, a PVDF nanocomposite with 1% and 2% ZnO nanoparticles was reported. ZnO reduces mechanical strength relative to clean PVDF polymer but improves heat capacity from 25.16 J/g in PVDF to 33.07 J/g in 2% ZnO/PVDF composite (Kumar *et al.*, 2020). In recent research, in varying concentrations, Poly hydroxybutyrate-co-hydroxy valerate (PHBV) was braced with zirconia oxide along water content (ZrO2.nH2O). The nanocomposite above was investigated for thermal and morphological examination, and 7.5% ZrO2 on PHBV demonstrated increased microhardness in Vickers' test (de Carvalho *et al.*, 2021).

Several biopolymers have been intricated for 3D printing to expand tissue engineering, and metals added fuel for a suitable scaffold or nanocomposite. The manufacturing technique and printing settings impact thermal and mechanical composite behavior. The filler employed also impacts the composite's properties (Wasti & Adhikari, 2020).

4. APPLICATIONS OF 3D PRINTED METAL-POLYMER NANOCOMPOSITES IN TISSUE ENGINEERING

The world is being revolutionized by 3D printing and tissue engineering. In recent decades, efforts have been undertaken to manufacture biomimetic tissue or organs via additive manufacturing (Zhang & Wang, 2019). Faramarzi and colleagues developed a bio-ink employing PRP to attenuate host immune response. Alginate/CaCl2/PRP bio-ink was tested for mechanical, rheological, and degradation kinetics. PRP exhibited tissue regeneration when planted onto Mesenchymal stem cells (MSCs) and Endothelial cells (EC)(Faramarzi *et al.*, 2018). Researchers were intrigued by 3D bioprinting using growth factors or cells. Biomimetic tissue has been reconstructed using biocompatible and biodegradable biomaterials. The metal-polymeric nanocomposite's polymeric matrix has been reinforced with metal or metal oxide fillers. Metals strengthen polymers, improving their bone tissue engineering capabilities. Further research revealed that organs like the liver and heart have further opportunities for 3D printing to be used in tissue engineering (Figure 3) (Xie *et al.*, 2020).

Several biopolymers have been implemented to widen the approach to tissue engineering. Natural polymers include Fibrin, collagen, gelatin, alginate, Matrigel, and chitosan, whereas synthetic polymers mainly contribute to cardiac tissue engineering, including PLLA, PGA, PLGA, PCL and PEG (Mohammadi Nasr *et al.*, 2020).

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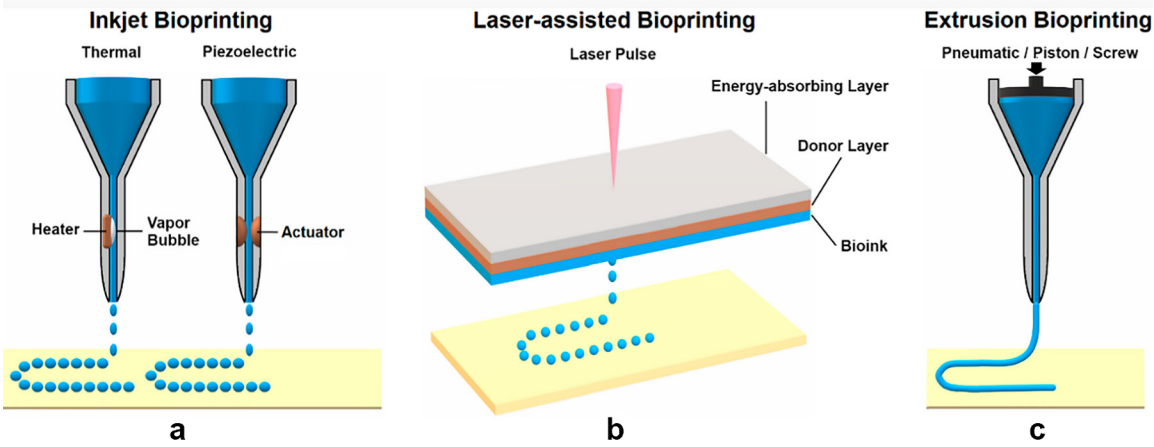

Figure 3. Common bioprinting techniques: (a) Inkjet bioprinting uses an electric heater or piezoelectric actuator to create a pressure pulse that propels the bioink droplet onto the substrates. (b) Laser-assisted bioprinting has a pulsed laser source and a ribbon structure (energy-absorbing layer, donor layer, and bioink layer). The laser pulse energizes the ribbon, generating a vapor bubble to propel bioink droplets onto the receiving substrate. (c) Extrusion bioprinting utilizes a pneumatic, piston, or screw-based pressure to extrude the bioink through a micro-nozzle as a continuous filament (Xie *et al.*, 2020).

S. NO.	Composite	Polymer Used	Reinforcing Material	Applications	References
1	PMMA-TiO_2	Poly (methyl methacrylate) PMMA	TiO_2	Dental Prosthesis	(Totu *et al.*, 2017)
2	Collagen/ β-TCP /SrO	Collagen	β-TCP-Sr	Bone tissue engineering	(Goodarzi *et al.*, 2019)
3	PCL/MH	Polycaprolactone (PCL)	Magnesium hydroxide (MH)	Bone tissue engineering	(Abdal-hay *et al.*, 2020)
4	PLGA/ TiO_2	Poly lactic-co-glycolic acid (PLGA)	TiO_2	Bone tissue engineering	(Rasoulianboroujeni *et al.*, 2019)
5	TPU/ELS/ MNPs and TPU/ELS/ SWCNT	Polyurethane	Magnetite NP- SWCNT	Artificial gastrointestinal Lumen	(Karbasian *et al.*, 2021)
6	LZFO/PLA	Poly-L-lactic acid (PLLA)	Zn doped Silica	Bone tissue engineering	(G. Qian *et al.*, 2021)
7	PLGA/ Cu(I)@ZIF-8	Polylactic-co-glycolic acid (PLGA)	Cu(I)-ZIF-8	Infected bone regeneration	(Zou *et al.*, 2020)
8	GNR-GelMA	Gelatin methacryloyl (GelMA)	Gold nanorod (GNR)	Cardiac tissue engineering	(Zhu *et al.*, 2017)
9	PCL-PPSu	Polycaprolactone, Poly propylene succinate	Silver	Skin tissue engineering	(Afghah *et al.*, 2020)
10	Ti3C2T*x* MXene hydrogel	Polyethylene Glycol (PEG)	Titanium carbide Mxene Ti3C2Tx	Cardiac tissue engineering	(Basara *et al.*, 2020)

S. NO.	Composite	Polymer Used	Reinforcing Material	Applications	References
11	PCL/rGO	Polycaprolactone (PCL)	Reduced Graphene oxide	Neural tissue engineering	(Vijayavenkataraman *et al.,* 2019)
12	PCL/ MWCNTs	Polycaprolactone (PCL)	Multiwalled Carbon nanotubes (MWCNT)	Bone tissue engineering	(e Silva *et al.,* 2021)
13	P(VDF-TrFE)/ TNW	Poly (vinylidene fluoride-trifluoroethylene) (P(VDF_TrFE))	TiO_2	Bone tissue engineering	(Augustine *et al.,* 2019)
14	SF-PCL-CNF-UCM	Silk fibroin-PCL	Carbon nanofiber	Nerve tissue engineering	(Pillai *et al.,* 2020)

Table 2. Applications of 3D printed metal-polymer nanocomposites in tissue engineering.

Notes:

TPU – Thermoplastic Polyurethane
ELS – Elastin
MNPs – Magnetite nanoparticles
SWCNT – Single-walled carbon nanotube
LZFO – $Li_{0.44}Zn_{0.2}Fe_{2.36}O_4$
PCL – Polycaprolactone
PPSu – Poly (Propylene) Succinate
Ti3C2T*x* – Titanium carbide
rGO – Reduced graphene oxide
MWCNTs – Multiwalled Carbon nanotubes
(P(VDF-TrFE)) – poly(vinylidene fluoride-trifluoroethylene)
TNW – Titanium Nanowires
SF – Silk Fibroin
CNF – carbon nanofiber
UCM – Unique combination of biomolecule supplemented medium

5. FUTURE DIRECTIONS

Additive manufacturing (AM) made biomaterial production possible. Researchers expedite the bioprinting process by utilizing other techniques to produce biomimetic tissue or organs and functioning organs. Neoteric technologies have been used for decades to create 3D organs that resemble the biological environment. Organ-on-a-chip, Robotics, Machine Learning, Deep Learning, and Big Data have altered the world. When combined, these blue-blooded technologies provide exceptional outcomes. 4D bioprinting adds stimulus responsiveness and cells to the build. Bioactuators, biosensors, and robots are also explored (Ashammakhi *et al.*, 2018).

Organ on a chip (OOAC) allowed for accurate research of organ-tissue interactions with the extracellular matrix. Antibiotic testing became efficient using organ-on-a-chip technology and produced useful medical output. An organ on a chip manages concentration gradients, tissue-organ interactions, shape, mechanical behavior, and cell patterning (Bhatia & Ingber, 2014; Galie *et al.*, 2014; Hassan *et al.*, 2020; L. Wang *et al.*, 2013). Combining stem cell technology with organs on a chip allowed a detailed analysis of the more productive technique. Embryonic stem cells were most promising for organ-on-a-chip development(Wnorowski *et al.*, 2019). 3D bioprinting and organ on a chip have been created to imitate the functions and shape of an indigenous organ. 3D printing may satisfy structural needs and solve other functionality concerns in conjunction with organs on a chip (Wnorowski *et al.*, 2019).

The desirable properties, both electrical and mechanical, can be easily achieved through 3D printed organ-on-a-chip technology, both with microfluidics and without microfluidics that can be witnessed through Lung-on-a–chip (Shrestha *et al.*, 2019), Liver-on-a-chip (Lee & Jun 2019), Nervous system (Johnson *et al.*, 2016), Kidney-on-a-chip (Homan *et al.*, 2016), Gut-on-a-chip (Beaurivage *et al.*, 2020), Brain-on-chip (Haring & Johnson, 2020). Nowadays, 3D printing has been taken over by the newest technologies. Machine learning is the up-and-coming approach to augment 3D printing. Machine learning is the technology that involves the learning of the machine through the prior existing model to recapitulate the biomimetic structure. Smart manufacturing by Machine learning not only improves the printing efficacy but also lowers the production cost. In addition, optimization of the experiments

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can be achieved through machine learning that specifically limits the use of material resources and hence the cost and augmented product quality (Aoyagi *et al.*, 2019; Menon *et al.*, 2019). Dimensional mastery can be easily using unsupervised learning methods (Khanzadeh *et al.*, 2018), deep learning (Francis & Bian, 2019), and cloud data (Samie Tootooni *et al.*, 2017).

Nevertheless, the defects in the manufacturing can also be amended through Image processing (Caggiano *et al.*, 2019) and through controlling the porosity parameters (Zhang & Wang, 2019). The composite designing can be simulated through machine learning (Grierson *et al.*, 2021). Moreover, machine learning can predict surface roughness in the extrusion-based manufacturing process (Li *et al.*, 2019). Baumann and coworkers recently scrutinized the pros of using machine learning in additive manufacturing (Baumann *et al.*, n.d.). Digital bioprinting was the remarkable result of machine learning using big data to develop vital databases that boost the designing of digital twins of human organs has been precisely discussed by An and a coworker (An *et al.*, 2021). Researchers are moving the needle forward in 3D bioprinting through robotics. Recently in a study, robotics facilitated in-situ 3D bioprinting of tissue for cartilage regeneration has been done using the hyaluronic acid methacrylate and acrylate terminated 4-armed polyethylene glycol with a minimal printing error, biomimetic properties scrutinized (Ma *et al.*, 2020). In another approach, for larger bone defects, robotics-assisted in situ 3D bioprinting also has been reported with a swine model (Li *et al.*, 2021). Lipkas and coworkers briefly explain the Remote center of motion (RCM) model for 3D printing, mainly for extrusion-based systems promising for bone and cartilage regeneration (Lipskas *et al.*, 2019).

6. CONCLUSION

The regime of 3D bioprinting has revolutionized the world with the development of functional and desirable biomimetic constructs resulting in many applications, including tissue engineering and drug discovery. The advanced technologies mastered manufacturing through emerging technologies such as robotics, machine learning, and 4D bioprinting. Adding functionality to the desired construct along the cell seeding has only been possible through 3D printing. The different types of printers, the process of bioprinting, and the need for patient-specific bio-inks have been impeding the approach. Metals showing versatility in grooming various mechanical, physio-chemical, thermal, and electrical properties of the nanocomposite have also been noticed. The fabrication modes through conventional and advanced methods for metal-polymer nanocomposites and their validation through different methods have been tabulated in this review. The tissue engineering field has been fueled by the additive manufacturing technique that can also be witnessed through its applications in bone, nerve, and skin tissue engineering.

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Conflicts of interest

All authors have no competing interests to declare relevant to this article's content.

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