3D printing in orthopedics and healthcare Applications – A Review

L. K. Tejhashwini
Department of Biotechnology
Sathyabama Institute of Science and Technology
Chennai, India
tejhashwinilk@gmail.com

Arun Karthick Selvam
Department of Biomedical Engineering
Sri Sivasubramaniya Nadar College of Engineering, Kalavakkam
Chennai, India
arunkarthicks@ssn.edu.in

K. Preetham Sai
Department of Biotechnology
Sathyabama Institute of Science and Technology
Chennai, India
Pree2605@gmail.com

S. Srimathi
Department of Biotechnology
Sathyabama Institute of Science and Technology
Chennai, India
srimathisrini.05@gmail.com

Shivangi Pandey
Department of Biomedical Engineering
Sri Sivasubramaniya Nadar College of Engineering, Kalavakkam
Shivangi1950@bme.ssn.edu.in

Devi Baskar
Department of Biotechnology
Sathyabama Institute of Science and Technology
Chennai, India
famidevi@gmail.com

*Haritha S
Department of Biotechnology
Sathyabama Institute of Science and Technology
Chennai, India
haritha2000rtn@gmail.com

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***Abstract*—This article reviews the immense potential of 3D printing using biomaterials in orthopedics and its innovative applications in other medical specialties. By analyzing current research and case studies, the review highlights the benefits of this innovation that has led to the development of solutions for complex anatomical challenges and improved patient outcomes by providing personalized implant design, and enhanced biocompatibility. Using advanced additive manufacturing techniques, surgeons can optimize surgical interventions, tailor treatment approaches, and set a new standard of care for patients with musculoskeletal and other special conditions. The combination of biomaterials and 3D printing technology has brought about some significant advancements in the fields of orthopedics and other medical specialties. It highlights key advancements, challenges, and future directions in these rapidly evolving fields.**

Keywords—3D printing, Orthopedics, Ocular prostheses, Biocompatibility, Surgical innovation, Personalized implants

I. INTRODUCTION

Biomaterials are bio-compatible materials that enhance the healing process of body parts by supporting the repair and regeneration of the body tissues of those parts damaged by both external and *in vivo* factors (cancer, etc). Sometimes they even replace the affected body parts as a whole by physically and functionally replacing them in the long term. In the last 50 years, three generations of materials have evolved and have been put to use individually or in combinations (using cross-links) through various techniques according to their subjective need in a field. They are classified into the first-generation, second-generation, and third-generation biomaterials. Currently, we are in the fourth generation of biomaterials.

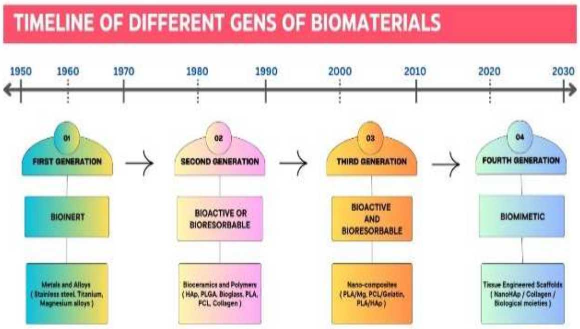

Fig 1. GENERATIONS OF BIOMATERIAL

The successive generation of biomaterials doesn't mean they are better than those belonging to the previous generation. For example, metallic stents (bio-inert material) are still used to replace knee fractures, cardiovascular defects, etc at present due to their easy availability. However, cons arose when they weren't able to interact with surrounding tissues, and adverse immune reactions were caused by them especially pure metals despite being strong and providing unmatched mechanical strength. Similarly, the second-generation biomaterials were bioactive, and porous and flexible structures (usually used in joints) but posed a challenge when it came to being applied during the case of critical repairs (ocular area) due to the lack of presence of biomolecules in them. Then came the third- generation of biomaterials with excellent bioactivity, which improved the functionality of parts promoted self-healing properties, and contained biomolecules. Complete replacements were healthily possible by these. One main ban was that it lacked anti-neoplastic drugs(taxanes). Now at present 4th fourth-generation biomaterials(bio-mimetic) have been developed and are put to use. These possess a high level of biocompatibility. They are developed to be multifunctional to tackle the combined anti-tumor and anti-infective effects. Smart biodevices are extensively preferred. They also have a targeted action for specific pathways and satisfy electrophysiology. Yet we aren't at the peak of biomaterial evolution. This present generation also possesses a few challenges. These still do not give us the controlled release of drug kinetics and also call for better fabrication techniques.

Musculoskeletal disorders can range from fractures and sports injuries to degenerative conditions like arthritis and spinal disorders caused due to trauma, disease, congenital abnormalities, or degenerative conditions. In addition, bone diseases alone account for 50% of chronic diseases in people over the age of 50. Together they bring great harm to the health and impact one's quality of life. It is imperative to address the significant demands that exist today in the field of orthopaedics which calls for constant advancements. In orthopedics, 3D printing enables the creation of implants customized to match a patient's specific needs with precise geometries and mechanical properties. This promotes osseointegration, thereby reducing the risk of complications related to the implant.

Despite the remarkable progress achieved in the field of biomaterials and 3D printing, significant challenges persist. Optimization of material properties, scalability of manufacturing processes, and translation of laboratory findings into clinical practice are among the key hurdles that must be overcome to fully realize the potential of these technologies. Additionally, regulatory considerations, ethical concerns, and cost-effectiveness remain important factors to consider in the widespread adoption of biomaterials and 3D printing in healthcare.

In this comprehensive review, we explore the evolution of biomaterials and 3D printing in medicine, highlighting their applications across various medical specialities and discussing current challenges and future directions. By examining recent advancements in material science, manufacturing techniques, and biomedical engineering, we aim to provide insights into the transformative potential of biomaterials and 3D printing in shaping the future of healthcare. Through interdisciplinary collaboration, innovative research, and strategic investment, we envision a future where biomaterials and 3D printing technologies play pivotal roles in delivering personalized, precise, and effective medical interventions, ultimately improving patient outcomes and enhancing quality of life.

II. ROLE of 3D PRINTED MATERIALS IN ORTHOPEDICS

The development of biomaterials has advanced as the number of surgical treatments in the orthopedic field has expanded. Biomaterials have osteobiologic properties, including osteogenic properties, osteo-conduction and osteo-induction. In Orthopedics, biomaterials are utilized in the creation of implants. These implant devices correct posture and movement(orthosis) or substitute a part of the body (prosthesis) while maintaining functionality [1]. Due to their ability to promote effective bone healing and improve patient outcomes osteobiologic and metallic biomaterials are being preferred more. Moreover with immediate consideration of the mechanical properties the suitable biomaterial is chosen according to the need for either a temporary or permanent replacement of the body part [4]. In the early stage, the most important characteristic for an orthopedic device to have was biological inertness, which resonates with being not affected by the biological environment. Some of our body fluids are highly corrosive and some are sensitive and can create harmful reactions and cause adverse effects like inflammation, etc. yet, bio-inertness does not help in bone healing. But for decades now biomaterials have continuously evolved. The recent advances including rapid prototyping using newly incorporated computer-aided design (CAD), computer-aided engineering (CAE), and computer-aided manufacturing (CAM) tools along with certain/suitable biomaterials in the orthopedic industry, particularly the manufacturing process of ortho-prosthetic aids are mind-blowing. On top of that these orthotic and prosthetic devices are manufactured efficiently in terms of cost, quality time, and quality, highly customizable and accurate in terms of matching the patient's anatomy, which elevates their self and social integrity making them feel more confident in themselves.

The manufacturing process is a carefully drawn out process where the subject's morphology is taken followed by individual manufacture through adjustments done to the prototype. However, the key revolution took place during the application of rapid prototyping technologies (RPT). Techniques such as Fused Deposition Modeling (FDM), Selective Laser Sintering (SLS), Laminated Object Manufacturing (LOM), and 3D printing (3DP) are some major examples of the available methods in the manufacturing industry [3].

In the 1970s the demand for attractive orthotic devices boomed. Due to this, new techniques like plastic coating (applying a tinted rubber-based plastic film) were developed. In the early 1980s, the rise of additive manufacturing technologies (AMT), popularly known as 3D printing technologies came into play. In the following years, other AMTs were introduced, such as Fused Deposition Modeling (FDM), laminated object manufacturing (LOM), Selective Laser Sintering (SLS), 3D printing, and variable rapid prototyping (Polyjet Technology) [2,4].

A. *Fused Deposition Modelling (FDM)*

This process involves extruding semi-molten material (Polycarbonate (PC) or Acrylonitrile butadiene styrene (ABS), known for their thermoplastic characteristics are commonly used materials in FDM.) through a moving extrusion head, creating layers in the X and Y axes to build a 3D model. Two extrusion nozzles compose the movable extrusion head- one to deposit the build material and the other that contains the support material. The process involves constructing layers by extruding the perimeter first and then filling the delimited zone. The main advantage of FDM technology is that it utilizes low-cost materials but the manufacture time is relatively high. Since then, several applications have shown up for FDM in the biomedical field for upper and lower limb orthoses, hand prostheses, facial prostheses, and drug delivery systems. The recent advancements in the FDM technology involve continuous development in the FDM materials, improvement in the speed and precision of the FDM printers, advancements in FDM that enable the use of simultaneous use of multiple materials during the printing process, innovations in support structures that reduces material waste and enhance the overall quality and the integration with other technologies like artificial intelligence and machine learning [4].

B. Selective Laser Sintering (SLS):

The first SLS system was introduced by the DTM Corporation (Desktop Manufacturing) in the 90s. This SLS method uses CO_2 lasers to fuse powdered polymers and builds an object layer by layer. PA (polyamide)12, ABS (acrylonitrile butadiene styrene) and PC (polycarbonate) are the most commonly used thermoplastics. With high accuracies and low discrepancies, SLS has been successfully applied in manufacturing Ankle Foot Orthoses (AFO). It is also proven effective in creating splints for the upper extremities that show good results in manufacturing quality and improved design for comfort. SLS is promising in producing comfortable and functional rehabilitation devices despite limited clinical validations. The recent advancements in the SLS technology focus on refining the surface finish of SLS-printed parts and the integration with Industry 4.0 that incorporates smart technologies such as IoT sensors [4].

C. Powder Bed and Inkjet Head 3D Printing:

3DP refers to three-dimensional printing in which the product is made of powder layers that stick together using an adhesive. In this process, firstly a powder layer is spread onto the build platform followed by the deposition of liquid binder through an inkjet printhead. This forms a patterned layer by lowering the platform and repeating the process. The 3DP process is somewhat similar to SLS. In 3DP, a printing head places liquid adhesive in the material whereas, in SLS a CO2 laser is used to fuse the layers. The accuracy of this process is lower than SLS but is comparatively cost-effective and quick which makes its role predominant in the prototyping industry. Similar to SLS, it uses thermoplastics like ABS as it has the required properties to be used in orthotic and prosthetic applications. It was investigated whether this technology was suitable to produce functional prostheses, it was proven that, despite the manufacturing levels being limited, patients felt relatively more comfortable with prostheses made with 3DP machines than the traditional handmade ones but the resistance was not studied in that work and therefore the durability of the product was unknown. The 3DP technology was used for patient-specific maxillofacial implants that reported a reduction in operation times. The versatility and precision of 3DP make it particularly interesting for its application in regenerative medicine and tissue engineering [4].

III. APPLICATIONS IN OTHER MEDICAL SPECIALITIES

One of the notable uses of fused deposition modelling (FDM) is to create synthetic trabecular bone models using PLA/HA composite materials. PLA, a degradable polymer, is combined with hydroxyapatite (HA) to mimic the mechanical properties and biodegradability of real bone. While FDM allows for customized structures, incorporating HA reduces printing accuracy but enhances mechanical properties [5].

A study delves into the viability of utilizing 3D printing technology to fabricate patient-specific incisor teeth using biopolymers, specifically polylactic acid (PLA) and polyamide 11 (PA11). By conducting comprehensive mechanical tests, including tensile, compression, wear, and creep evaluations under conditions simulating real incisor teeth, the study compares the performance of these two biopolymers. Remarkably, the results demonstrate that PLA showcases superior mechanical properties compared to PA11. This investigation underscores the potential of 3D printing in dentistry, particularly in crafting implants using biocompatible materials, therefore paving the way for more personalized and effective dental treatments [6].

Another case study exemplifies the utilization of Fused Deposition Modelling (FDM) technology in the creation of a breast implant pattern. With dimensions measuring 170 mm × 120 mm × 80 mm, the implant's design and fabrication process were guided by principles of Design for Additive Manufacturing (DfAM). This involved meticulous selection of biomaterials and attention to FDM-specific design parameters, such as geometry optimization and optimal build orientation. The implementation of these strategies ensured the successful production of the breast implant pattern.

This technique of fused deposition modelling (FDM) has found itself useful in developing drug-loaded cardiovascular prostheses, targeting the prevention of infections associated with vascular grafts according to a study. By utilizing FDM technology, medicated vascular grafts are fabricated using thermoplastic polyurethane (TPU) combined with rifampicin (RIF) as a model drug. The incorporation of RIF into TPU filaments is achieved through hot melt extrusion (HME), enabling controlled drug release for up to 80 days and exhibiting antimicrobial properties against Staphylococcus aureus. Additionally, the methodology is extended to include dipyridamole (DIP) as another model drug. This innovative approach demonstrates the potential of FDM in producing personalized vascular grafts with tailored drug delivery capabilities, offering a promising solution to enhance the efficacy and safety of cardiovascular implants [7].

3D printing is applied in bone repair and regeneration in the craniofacial region of humans and animals. Human studies involved 81 patients with craniofacial bone defects, primarily treated with titanium or hydroxyl-apatite scaffolds. Animal studies utilized various biomaterials and cells, offering insights through histological and biochemical findings. It underscores the promising results of 3D printing for craniofacial bone repair, emphasizing the need for further well-designed clinical trials to validate its efficacy. Emerging as a transformative technology, 3D printing holds significant potential for tissue engineering in treating craniofacial bone defects, offering personalized solutions with customized scaffolds and biomaterials [8].

3D printing, combined with the sublimation technique, has been applied to manufacture eyeball prostheses. Data acquisition about the patient's anatomy, medical imaging (both 2D and 3D), and segmentation using CT scanning of craniomaxillofacial structures were done. The virtual model alone was not enough, so with the help of advanced tools (Autodesk Meshmixer) were utilized to produce 3D physical models. This helped medical specialists and scientists together to develop the prototype of the customised oculopalpebral prosthesis. Eye colour, eyebrows, and other anatomical and physical details were matched. Surgical glue was used to fix the prosthesis prototype without any inconvenience to the patient. FDM 3D

(PLA) was utilized to match and create the facial features of the patient at relatively low manufacturing costs [9].

Research also explored the use of Selective Laser Sintering (SLS) technology in fabricating oral tablets containing isoniazid, an antitubercular drug, with the incorporation of carbonyl iron as a multifunctional ingredient. Carbonyl iron serves as both a magnetic and heat-conductive component, offering advantages in the manufacturing process. Through SLS 3D printing, tablets with optimized quality attributes are produced by adjusting printing parameters such as laser scanning speed, hatching space, and surface/chamber temperature. The study demonstrated that tablets containing carbonyl iron require lower laser energy input for sintering while exhibiting enhanced drug release under a magnetic field. These findings suggested that magnetic nanoparticles hold promise as conductive materials for facilitating the SLS 3D printing of pharmaceutical dosage forms [10].

A synthetic osteo-regenerative biomaterial called hyper-elastic "bone" (HB) to mend current deficiencies in osteoregenerative products was introduced. HB comprises 90% hydroxyapatite and 10% polycaprolactone or poly (lactic-co-glycolic acid) and can be rapidly printed using 3D printing at high speed (up to 275 cm3/hour) at room temperature. The resulting 3D-printed HB exhibits elastic mechanical properties, and high absorbency, and supports cell viability, proliferation, and osteogenic differentiation of bone marrow–derived human mesenchymal stem cells in vitro. *In vivo*, evaluations in mouse, rat, and non-human primate models demonstrate HB's biocompatibility, vascularization, integration with surrounding tissues, and rapid ossification without the need for additional biological factors. This study highlights the potential of HB as a versatile and effective solution for osteo-regenerative applications [11].

3D printing of controlled release of high-dose pharmaceutical dosage form was done using Selective Laser Sintering. The dosage form contained a test model substance, crystalline paracetamol, and a small amount of dye was also added. After analyzing the pore space, drug release, and dissolution modelling, the printlet was characterized. It revealed that many degrees of freedom were available for tuning into its functional properties, particularly the dissolution performance. Two degrees of freedom were found to be substantial: macrostructure shaping in terms of active surface: volume ratio and microstructure shaping in terms of pore space structure, which aids modification. This approach is advantageous in terms of controlling the dissolution performance of the pharmaceutical dosage [12].

IV. DISCUSSION

In recent years, there has been a significant surge in research and development focused on leveraging biomaterials to revolutionize the treatment of various chronic diseases. From immunomodulation to injectable biomaterials and supramolecular biomaterials, scientists are exploring innovative approaches to address complex health conditions such as type 1 diabetes, bone defects, cancer, and heart attacks. Let's delve into these advancements and their potential implications: (13)

A. Immunomodulation:

One of the most promising areas of research involves the use of immunomodulating biomaterials to fine-tune the immune response, particularly in autoimmune diseases like type 1 diabetes. Recent studies have showcased remarkable progress, with researchers successfully reversing type 1 diabetes in mice using injectable synthetic biomaterials. This breakthrough offers hope for developing effective treatments that could potentially halt or even reverse the progression of autoimmune disorders in humans. However, translating these findings from preclinical models to clinical applications remains a crucial challenge that requires further investigation [13]. Interestingly, Orthopedic biomaterial-associated infections, driven by Staphylococcus aureus biofilms, posed clinical challenges. Using a defective rat bone model, one study observed the immune response to infections like those continuous decrease in T cells and a simultaneous increase in immunosuppressive myeloid-derived suppressor cells (MDSCs). The results show us the complex host-pathogen interaction in orthopedic infections and potential diagnostic and therapeutic areas.

B. Injectable Biomaterials:

The emergence of injectable biomaterials represents a paradigm shift in drug delivery, enabling precise targeting of therapeutic agents while bypassing immune system barriers. Both synthetic and naturally derived injectable biomaterials are being explored across diverse medical domains, including orthopedics, oncology, and cardiology. By delivering therapeutics directly to the site of action, these biomaterials hold immense potential for enhancing treatment outcomes and minimizing adverse effects. However, optimizing the biocompatibility, stability, and controlled release kinetics of injectable biomaterials poses significant technical hurdles that necessitate ongoing research and development efforts. (3) Among injectable biomaterials, injectable hydrogels have made it to the top of the list due to their design flexibility that promotes bone repair. However, hydrogels alone cannot induce molecular signals to induce self-healing. Therefore, a group of researchers recently incorporated the addition of inorganic nanoparticles with the injectable hydrogel. That was proven to increase the osteoconductive properties of bone. Out of the inorganic materials that can be used these researchers used MBGNs (mesoporous bioactive glass nanoparticles) to modify the hydrogel. Further to reckon with they have come up with an injectable, dual-crosslinked hydrogel by self-crosslinking periodate-oxidized dextran (oxDex) and phenylboronic acid-grafted gelatin (PBA-Gel) [14].

C. Supramolecular Biomaterials:

These smart biomaterials offer unprecedented versatility, allowing for dynamic adjustments in response to specific biological signals. By mimicking natural biological processes, such as cell signaling pathways, supramolecular biomaterials hold promise for tailored interventions in injury repair and disease management. Nonetheless, harnessing the full potential of these biomaterials requires interdisciplinary collaboration between materials scientists, bioengineers, and medical researchers to overcome challenges related to stability, reproducibility, and scalability [13].

Supramolecular hydrogels have recently proved to be an amazing biomimetic material. The features of hydrogels are well suited for cell culture, release of drugs with control, tissue adhesion, and molecular sensing. They are used as artificial gel substitutes. (e.g., vitreous humour and synovial fluids), and these properties cannot be achieved by permanently cross-linked covalent hydrogels. As a consequence, supramolecular hydrogels have widely gained popularity in these years, especially in biomedical applications [15].

TABLE 1: RECENT MODIFICATIONS IN APPLIED BIOMATERIALS AT PRESENT

S.NO:	***FEW EXAMPLES***		
	BIOMATERIALS	***RECENT MODIFICATION***	***APPLICATION***
1.	Hyrogels	Albumins's negatively charged surface can bind to a lot of bodily substances such as vitamins, drugs, etc. Albumin-hydrogel formed by gelations induced by heat, Ph, cross-linkings.[16]	These albumin hydrogels are used in specific drug delivery, 3D cell culture, tumour treatment , and tissue engineering. [16]
2.	Dental implants	Dental implants are coated with many nanocoats. E.g.: Zirconia / PEEK coated dental implants. [17]	PEEK- Fabrication of implant, temporary and healing abutments; and healing caps. ZIRCONIA - Less damage, especially in patients susceptible to periodontal disease. [17]
3.	Collagen	Modifying acid - soluble collagen using excessive succinic anhydride in alkaline condition to protect all its active amino groups. Telopeptides of this modified collagen are removed using pepsin to give SPSC (Succinylated Pepsin-Soluble Collagen). It forms a biconjugate (SPSC - PNIPAAm) [18]	Biotherapeutics, cosmetics, applied in In-situ gelling cell delivery scaffold and Kaolin Flocculant. [18]
4.	Implants made of silicon and rubber	Agarose is grafted upon Silicon - Rubber surface to prevent / inhibit the growth of bacterial biofilms on them. [19]	Finds various application in specific tissue engineering, drug delivery, wound dressing, etc, due to its hydrophilicity and anti-biofilm capacity. (Prevents infection issues and its non - toxic) [19]

In conclusion, the ongoing advancements in immunomodulation, injectable biomaterials, and supramolecular biomaterials along with developments to tackle orthopedic biomaterial-associated infections represent groundbreaking strides toward personalized and precision medicine. By harnessing the unique properties of biomaterials, researchers aim to develop innovative therapies capable of addressing the complex challenges associated with chronic diseases.

V. CONCLUSION

In conclusion, the field of biomaterials and 3D printing in orthopedics and beyond has undergone a remarkable evolution, from the early stages of bio-inert materials to the current era of bio-mimetic and smart biomaterials. The advent of 3D printing technologies has revolutionized the landscape of orthopedic treatments, offering customized implants with precise geometries and mechanical properties that promote osseointegration and reduce the risk of complications. Moreover, advancements in biomaterials have led to the development of osteobiologic materials with osteogenic properties, fostering bone healing and improving patient outcomes. The application of biomaterials and 3D printing extends beyond orthopedics, encompassing various medical specialties such as dentistry, cardiovascular medicine, and tissue engineering. These technologies enable the fabrication of patient-specific implants, drug-loaded prostheses, and synthetic biomaterials tailored to address specific clinical needs. From synthetic trabecular bone models to personalized incisor teeth and breast implant patterns, 3D printing offers unparalleled flexibility and precision in manufacturing medical devices and pharmaceutical dosage forms. Furthermore, recent innovations in immunomodulating biomaterials, injectable hydrogels, and supramolecular biomaterials hold promise for revolutionizing the treatment of chronic diseases, including autoimmune disorders and orthopedic biomaterial-associated infections. By fine-tuning the immune response, delivering therapeutics directly to target sites, and sensing and responding to physiological cues, these smart biomaterials offer tailored interventions with enhanced efficacy and minimized adverse effects. However, despite the significant progress achieved thus far, challenges remain in optimizing the biocompatibility, stability, and controlled release kinetics of biomaterials and 3D-printed constructs. Moreover, translating these advancements from preclinical models to clinical applications requires interdisciplinary collaboration, regulatory oversight, and continued investment in research and clinical translation. In summary, the ongoing advancements in biomaterials and 3D printing technologies hold immense potential for revolutionizing patient care across various medical specialties. By harnessing the unique properties of biomaterials and leveraging cutting-edge manufacturing techniques, researchers aim to develop innovative therapies capable of addressing the complex challenges associated with chronic diseases and improving the quality of life for patients worldwide. As we look toward the future, further exploration and refinement of these technologies are essential to unlock their full potential. Continued research efforts, interdisciplinary collaboration, and investment in infrastructure and regulatory frameworks will be crucial in overcoming existing challenges and translating scientific discoveries into tangible clinical benefits. With concerted efforts from researchers, clinicians, industry partners, and regulatory agencies, the field of biomaterials and 3D printing holds the promise of transforming healthcare and advancing personalized medicine for the betterment of society as a whole.

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