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Review

Emerging polymeric materials in additive manufacturing for use in biomedical applications

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Abstract: Additive manufacturing is poised to enable the next biomedical revolution, where customized, patient-specific tools, therapies, pharmaceuticals, and even replacement organs are taking strides in the biomedical research and development space. Polymeric materials are capable of making inroads in a wide variety of biomedical applications, and in recent years a growing number are being used with additive manufacturing techniques. This review highlights some of the emerging classes of polymers used in additive manufacturing and examples of their use in biomedical applications, with a focus on the delineation of 'hard' polymers versus 'soft' polymers and the specific applications where they are utilized.

Keywords: additive manufacturing; polymers; biomedical applications

Abbreviations: AM: Additive manufacturing; 3DP: Three-dimensional printing; FDA: United States Food and Drug Administration; SLS: selective laser sintering; SLA: stereolithography; CLIP: Continuous Liquid Interface Production; FDM: fused deposition modeling; PEKK: polyetherketoneketone; PAEK: polyaryletherketone; PEEK: polyetheretherketone; PCL：polycaprolactone; PGA：poly(glycolic acid); PLA：polylactic acid; PDO：polydioxanone; PEG：polyethylene glycol; GelMA：gelatin methacrylol; MeHA：methacrylated hyaluronic acid; PDMS：polydimethylsiloxane; MRI：magnetic resonance imaging; CT：computed tomography; RGD：arginylglycylaspartic acid; PDMS：polydimethylsiloxane

1. Introduction

In recent years, the medical device community steadily adopted innovative uses of additive manufacturing (AM), also known as 3D printing (3DP), throughout the entire product lifecycle. Originally used only for rapid manufacture of visual aids or low-grade prototypes, advances in the quality and types of available materials and printing resolution have enabled medical device manufacturers opportunities to use AM as their final manufacturing methodology. In fact, as of December 4, 2017, the United States Food and Drug Administration (FDA) has cleared over 100 AM devices [1]. Some recent examples are listed in Table 1. Many of the approved devices address orthopedic specialties with joint replacements and bone grafts; however, devices for dentistry, general & plastic surgery, and neurology are also included.

The current devices capitalize on two key advantages offered by AM: the ability to fabricate complex porosities and patient-specific geometries. Being able to control the porosity of a material has significant implications for the improvement of implant osseointegration. For example, Stryker has commercialized a 3DP titanium alloy surface with defined porosity that enhances bone ingrowth (see an example product in Figure 1) [2,3]. Stryker describes this 'Tritanium' surface as consisting of 'random interconnected architecture with rugged, irregular pore sizes and shapes that are designed to mimic cancellous bone' [4]. This unique surface can only be manufactured by AM.

The FDA approved the first 3DP drug, Spritam, in 2015 [5]. Spritam is formulated using the ZipDose Technology, which is a proprietary platform that produces formulations that rapidly disintegrate within seconds with a sip of liquid. The method starts by depositing a powder blend in a single layer, which is then bound together with a binding fluid. The process is repeated several times to yield a highly porous structure which enables the rapid dissolution [6].

Figure 1. Stryker's Tritanium surface. Reproduced from [7].

Table 1. Examples of recently FDA-cleared class 2 devices that are manufactured with 3DP.

Company Name	Device Name	510(k) number	510k Review Panel	Clearance Date	Material
Additive Orthopaedics	Patient Specific 3D Printed Bone Segments	K180239	Orthopedic	5/16/2018	Medical Grade Titanium Alloy (Ti-6Al-4V)
Stryker	Intervertebral Fusion Device with Bone Graft	K1734776	Orthopedic	1/18/2018	Titanium Alloy (Ti-6Al-4V)
Clariance	Idys TLIF 3DTi Cages	K172465	Orthopedic	12/15/2017	Titanium Alloy (Ti-6Al-4V)
Medicrea International	IMPIX 3D Print Cages	K163595	Orthopedic	11/13/2017	Titanium Alloy (Ti-6Al-4V)
RTI Surgical	Fortilink Interbody Fusion with TETRAfuse 3D Technology	K172343	Orthopedic	10/23/2017	Radiolucent Polyetherketoneketone (PEKK)
Medtronic Sofamor Danek	ArTiC-L 3D Ti Spinal System with TiONIC Tech	K171689	Orthopedic	10/5/2017	Titanium
Medacta International	3DMetal Tibial Cones	K170149	Orthopedic	8/18/2017	Titanium Alloy
Materialise	TruMatch CMF Titanium 3D Printed Implant System	K170272	Dental	8/8/2017	Commercially Pure Titanium
HT Medical	NeoFuse Ti3D PLIF//TLIF/Cervical Interbody	K170318	Orthopedic	7/12/2017	Titanium Grade 23
Additive Orthopaedics	Bunion System	K163593	Orthopedic	6/20/2017	Medical Grade Titanium Alloy (Ti-6Al-4V)
MicroPort Orthopedics	BIOFOAM AM	K170288	Orthopedic	6/15/2017	Commercially Pure Titanium
RTI Surgical	Fortilink-C with TETRAfuse 3D Technology	K163673	Orthopedic	5/23/2017	Radiolucent Polyetherketoneketone (PEKK)
SI-Bone	iFuse Implant System - iFuse-3D implant	K162733	Orthopedic	3/10/2017	Medical Grade Titanium Alloy (Ti-6Al-4V)
Additive Orthopaedics	Hammertoe Correction System	K160264	Orthopedic	6/1/2016	Medical Grade Titanium Alloy (Ti-6Al-4V)
Renovis Surgical Technologies	Anterior Lumbar Interbody Fusion System	K142095	Orthopedic	10/15/2014	Titanium
Oxford Performance Materials	Osteofab Patient Specific Facial Device	K133809	General & Plastic Surgery	7/28/2014	Polyetherketoneketone (PEKK)
Renovis Surgical Technologies	Tesera Trabecular Technology (T3) Acetabular Shell System	K132312	Orthopedic	4/11/2014	Titanium Alloy (Ti-6Al-4V)
Stryker Orthopaedics	Triathlon Tritanium Metal-Backed Patella	K132624	Orthopedic	11/26/2013	Titanium
Tissue Regeneration Systems	TRS PCL Cranial Bone Void Filler	K123633	Neurology	8/16/2013	Polycaprolactone (PCL)

Another class of devices that leverage the unique capabilities of AM are those that are printed on-demand in patient-specific geometries. Devices in this class include custom implants for cranial surgery, dentistry, and maxillofacial surgery, molds for making prosthetics, and surgical guides [8]. Patient-specific implants are designed from magnetic resonance imaging (MRI) or computed tomography (CT) scans of the patient's bone or joint, which enables better alignment and fit to the patient's unique anatomy [9]. Studies specifically assessing whether patient-specific instrumentation improves patient outcomes have demonstrated significant improvements in the selection of the optimal implant and reduction in misaligned implants [10]. Additionally, the ability to design customized implants will continue to have a strong impact on the reconstruction of traumatic injuries and in the treatment of other complex disease processes [11].

Of the FDA approved devices, the majority are made of titanium, but some are manufactured from polymers such as polyetherketoneketone (PEKK) and polycaprolactone (PCL). Due to the variability of polymer formulations, the approval process can be more involved for polymeric devices. Nonetheless, many biomedical applications require materials with properties that can only be met with polymers. Thus, to date, the impact of AM on the medical device industry has been in part hindered by the lack of materials which meet the demands of biocompatibility and appropriate structural and rheological properties. Significant effort has been expended to meet this need with polymeric materials and this review focuses on these recent developments.

Although a wide range of AM methods are available, developments in polymer printing are focused in three main approaches: 1) powder bed fusion processes such as Selective Laser Sintering (SLS), 2) deposition-on-demand processes which include extrusion-based technologies, such as Fused Deposition Modeling (FDM) and direct ink-write printing [12], and inkjet or drop-wise deposition methods, and 3) photopolymer-based printing methods, such as stereolithography (SLA) and Continuous Liquid Interface Production (CLIP). These, have proven to be successful in incorporating a variety of polymers as raw materials. AM methods and instrumentation are the subject of numerous reviews [13–15], and thus we will not elaborate further on this topic.

When considering AM material choices for biomedical applications, the requirements include appropriate mechanical properties, temperature stability and chemical resistance for sterilization, radiolucency, and biocompatibility and/or biodegradability. 'Hard' polymers, such as engineering thermoplastics and thermosets, are good choices for structural implants, rigid medical devices, and dental applications. 'Soft' polymers include hydrogels and elastomers. The former is of specific interest to the tissue engineering field and the latter in the development of surgical models and phantoms. First, we will discuss the traditional 'hard' polymers, which have already begun making inroads to the marketplace. Second, we will highlight the emerging applications related to 'soft' polymers.

2. Biomedical Applications of 'Hard' Polymers

While a variety of traditional thermoplastics and thermosets are commercially available for use in AM (e.g., nylon, ABS, epoxides) [16], a few key polymers have found use in the emerging biomedical space. Biodegradable polymers are of interest for implantable devices that initially require a structural element, but as the natural tissue grows to fill in the repair site, the structural element is no longer needed. Non-biodegradable polymers have use in applications where structural support in needed for

the lifetime of the implant. Table 2 lists some examples of hard polymers that are used in FDA approved devices and have been adapted for use in AM methods.

2.1. Hard Biodegradable Polymer Materials

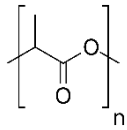
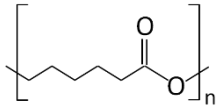
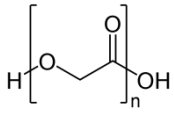
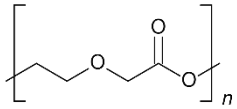
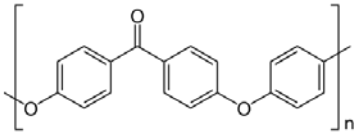
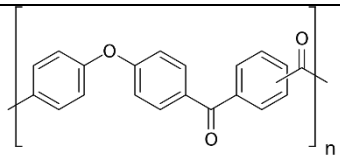
Many biodegradable polymers are polyesters that are degraded in the human body by hydrolysis of their ester linkages. Examples of such synthetic polymers that are used in biomedical devices and drug delivery platforms include polylactic acid (PLA), polycaprolactone (PCL), poly (glycolic acid) (PGA) and polydioxanone (PDO). Each of these polymers have different mechanical properties and degradation rates [17], which influence a product manufacturer's material selection process. The polymer properties can be further tuned by blending different polymers together.

PLA is arguably the most extensively used biodegradable polymer as it is derived from renewable resources, has good thermal processability, requires less energy to produce than petroleum-based polymers, and is biocompatible [18]. PLA's degradation products are neither toxic nor carcinogenic and do not interfere with tissue healing [19]. PLA has a relatively slow degradation rate with *in vivo* lifetimes normally in the range of 9–15 months [20], but can be up to 3 years [21], although degradation rate is a function of multiple factors, including degree of crystallinity, molecular weight, molecular weight distribution, morphology, water diffusion rate into the polymer, and stereoisomeric content. While PLA has many attractive qualities, it is also a very brittle material with less than 10% elongation at break, is relatively hydrophobic and lacks reactive side-chain groups limiting the ability to execute surface and bulk modifications.

PCL was first synthesized in the early 1930s, and is therefore one of the earliest polymers [22]. It is hydrophobic, semicrystalline, is easily processed at low temperatures, and is biocompatible. It degrades *in vivo* by both bulk and surface erosion mechanisms. PCL also has a relatively long lifetime *in vivo* with standard degradation times in the 9–12 month range [20], and has been widely used in long-term implants and controlled drug release applications [23]. To tune the degradation time and other properties, manufacturers can blend or copolymerize PCL with other polymers [24], for example as is done by Ethicon in their Monocryl resorbable sutures that is a co-polymer of glycolide and ε-caprolactone [25]. PGA is the simplest linear aliphatic polyester and was first patented in 1954 [26]. Due to its relatively high hydrolytic instability, PGA degrades *in vivo* by a bulk erosion mechanism with loss of mechanical properties in 1–2 months [20]. As previously mentioned, it is often combined with other polymers in biomedical applications [24].

PDO is a biodegradable polymer with repeating ether-ester units. Compared to the polyesters described above, PDO has been investigated less even though Ethicon introduced it to the marketplace in 1981 [27,28]. PDO has several unique properties, including shape memory. PDO is best known for its clinical use as a suture, but the shape memory property hinders knot tying. However, this feature is very useful in some applications to provide rebound and kink resistance, such as in vascular conduits [29] and as a structural component in a surgical meshes [30]. PDO is assumed to degrade via bulk erosion, and suture absorption rate is in the range of 180 to 210 days [31].

Table 2. Examples of AM-compatible hard polymeric materials used in FDA approved devices.

Polymer	Abbreviation	Type	Structure	Examples of use in FDA approved devices
Polylactic acid	PLA	Biodegradable polyester		SmartNail bone fixation nail (ConMed) [32]
Polycaprolactone	PCL	Biodegradable polyester		Monocryl sutures (Ethicon) [25]
Poly(glycolic acid)	PGA	Biodegradable polyester		Monocryl sutures (Ethicon) [25]
Polydioxanone	PDO	Biodegradable polyester		Ventrio Hernia Patch (BD Bard) [30]
Polyetheretherketone	PEEK	Thermoplastic		Rampart O Interbody Fusion (Spineology) [33]
Polyetherketoneketone	PEKK	Thermoplastic		Fortilink™-C Interbody Fusion (RTI Surgical) [34]

2.2. Hard Non-Biodegradable polymer materials

Of particular interest in the category of non-biodegradable polymers are the family of polyaryletherketones (PAEKs). Among the PAEK family, polyetheretherketone (PEEK) is without a doubt the most commercially successful polymer, introduced in a multitude of applications that directly benefit from its unique physical properties. PEEK is a semi-crystalline thermoplastic with a linear, highly aromatic molecular backbone including ether and ketone linkages [35–37]. PEEK exhibits unparalleled properties compared to most other plastic resins, displaying excellent mechanical properties over a wide range of environmental conditions. PEEK products offer a high elastic modulus and ultimate strength coupled with post-yield ductility, and excellent creep resistance. PEEK is used as an alternative to metals in a growing number of applications [35–37]. Moreover, PEEK's unique properties have allowed for the development of implantable grades that are fully recognized as biocompatible and bioinert. Compared to metals, PEEK exhibits lower density, lower thermal and electrical conductivity, greater corrosion resistance, and compatibility with X-rays and magnetic fields often used in diagnostic imaging [38–40]. PEEK resins exhibit excellent solvent resistance, thermal oxidative stability, and radiation resistance, and can be sterilized by steam, ethylene oxide, and gamma radiation.

Another important member of the PAEK family is poly(etherketoneketone) (PEKK). Just like PEEK, PEKK is a semi-crystalline thermoplastic polymer with a linear, highly aromatic molecular

structure including ether and ketone linkages. PEKK's chemical structure and synthetic route offer unique abilities to produce polymers with a wide range of thermal properties, superior mechanical properties, chemical resistance and low flammability. PEKK polymers differ from the general class of PAEKs in that the incorporation of the second ketone group to the polymer backbone leads to two different isomeric forms, included as repeating units along the polymer chain. A 1,4 addition, through a para-phenylene radical (terephthalic, T) provides linearity and chain stiffness to the polymer. In contrast, a 1,3 addition, through a meta-phenylene radical (isophthalic, I) increases the degree of freedom of the chain, reducing linearity and affecting the overall rate of crystallization. The ratio of these isomeric units (T/I) is often used to control the physical and chemical properties of PEKK resins, favoring precise manipulation of key parameters, including among others very high melting points and glass transition temperatures, a wide range of crystallization rates and degrees of crystallinity [41,42]. These properties enable PEKK devices to be compatible with autoclave sterilization.

Unlike PEEK, in terms of crystal structure, PEKK resins are polymorphic and are able to crystallize in various crystalline unit cells, depending on the crystallization route. The crystal structure, polymorphism and morphology of PEKK has been reported in the literature [43–45]. Recent studies of the morphological changes observed in PEKK materials when subjected to specific heat treatments and processing conditions have provided useful information of particular interest for the introduction of PEKK resins in AM processes [41,42]. In addition, PEKK can be tuned such that it has mechanically similar properties to cortical bone and thus is attractive for bone replacement implants [46]. In some specific cases, these approaches have led to commercially successful grades introduced into biomedical applications, particularly for patient-specific implants [47,48].

Photocurable resins, which are thermosetting in nature, are another class of hard polymers employed in photopolymer-based printing methods such as SLA and CLIP, which have found particular use in dental applications (see Section 2.3.2). There are a number of commercial proprietary materials (e.g., polyurethane-based, cyanate ester-based, and acrylate-based) and printers used in this field [49–51].

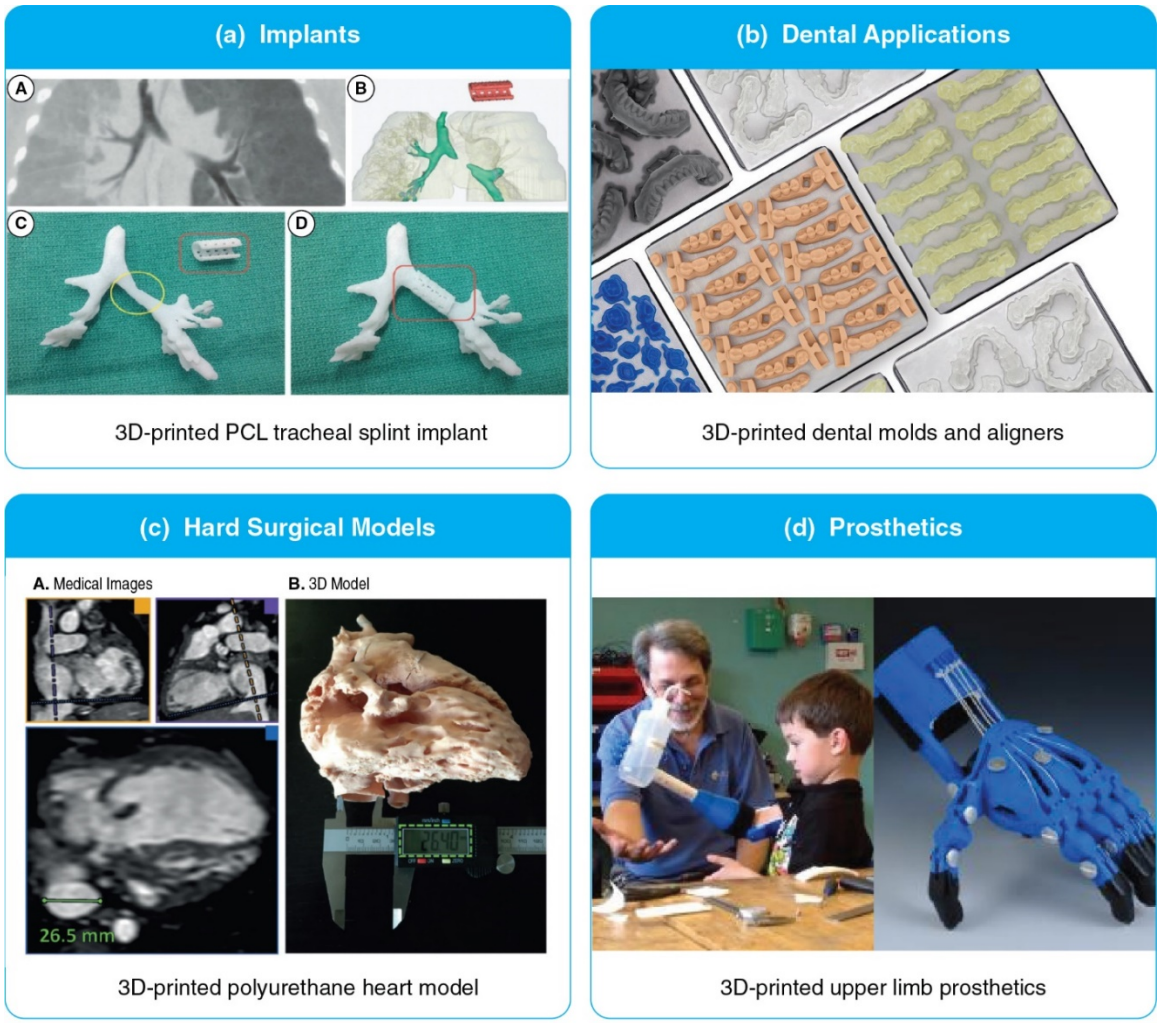


Figure 2. Examples of the use of AM with hard polymeric materials for biomedical applications. a) Implants [52], b) Dental Applications [53], c) Hard Surgical Models [54], d) Prosthetics [55].

2.3. Hard polymer examples of biomedical AM applications

2.3.1. Implants

Biomedical implants, which can be permanent or transient solutions for repair or replacement of biological tissues, are one of the most commonly investigated applications for AM in the biomedical space. Here, tissue engineering scaffolds can be fabricated with open network structures that enable structural function as well as integration with host tissue, and is most commonly employed for mesenchymal tissue (e.g., bone and cartilage) [56]. FDM-based processes have utilized PCL materials to fabricate bone and cartilage tissue scaffolds [57,58], and there is continued research in scaffolds comprised of natural biological materials as will be discussed below. 3D powder binding with PLA and

PLGA has been used to fabricate scaffolds for tissue engineering and drug delivery [59]. For the case of PEEK, high temperature laser sintering studies focused on the effect of build orientation have been recently reported with a focus on the introduction of PEEK to cranial implants and the healthcare sector in general [60,61]. Importantly, patient-specific imaging data can be utilized to resolve the specific geometry needed for the implant, which can be imported into the 3D printing software to create the exact morphology necessary for the implant [62]. In an exciting example of the impact that polymer-based AM can have on biomedical implants, researchers recently successfully printed a tracheal split for at least four children suffering from tracheobronchomalacia since 2013 (Figure 2a) [52,63]. There are a number of technical and regulatory considerations to ensure that 3D-printed implants have a path to commercial adoption [64]. While PDO is poised to be used in AM with resins available [65], no published examples of 3DP biomedical devices were found.

2.3.2. Dental

The dental market has been one of the earliest adopters of AM technology in the biomedical industry (Figure 3). Silicone and wax based materials are currently used to 3D print molds for various dental elements, and in some cases acrylates and other materials are used for the direct printing of teeth or jaw implants, prosthetics, and other applications including modeling and drilling guides for facial surgeries and dental instruments [66]. In orthodontics, dental alignment services currently produce millions of custom aligners per year using SLA-based technologies (Figure 2b). A variety of commercial printers and materials are available for use in the dental industry [49–51] with continued development of advanced polymeric and composite resins.

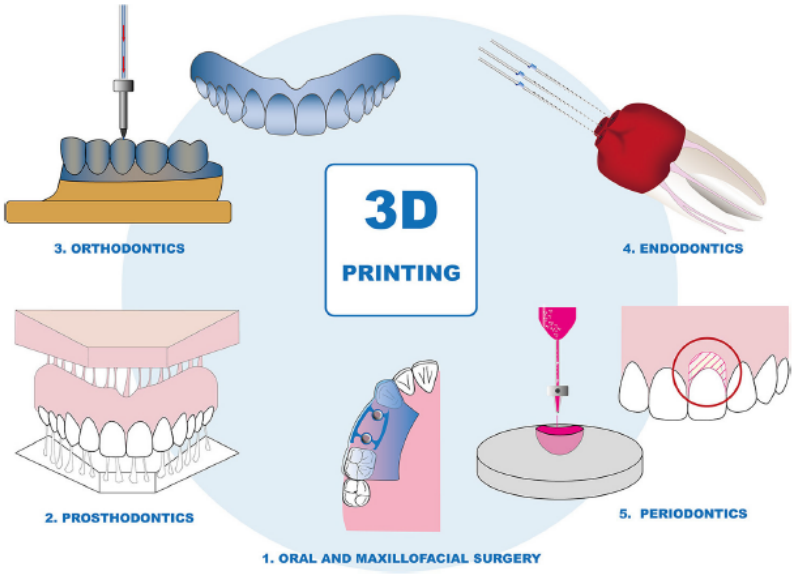


Figure 3. Examples of the possible applications for AM in dentistry, reproduced with permission from [67].

2.3.3. Hard surgical models

AM can also supplement the medical design product development process by aiding in low cost device verification by replacing testing in animal and/or cadaver models, for example in the case of surgical tools [68], with 3D printed anatomical models. Besides the obvious limitations of cost, biosafety, availability and ease of use concerns with testing on cadavers, the conventional models do not usually have the specific pathologies that the medical device is meant to address. Thus, AM anatomical models are increasingly being used [69,70]. Moreover, expected anatomical variations, e.g., small, medium, and large or straight and tortuous lumens can easily be printed. These models, particularly patient-specific models, are also being applied to surgical preparation for complex anatomies. Numerous examples have been published demonstrating improved outcomes of patients when physicians have been trained on 3D-printed models from patient CT-scans vs. preparation by studying the images alone [54,71–75]. These models may incorporate a variety of commodity-grade AM polymeric materials as they do not require biocompatibility or biodegradability (Figure 2c). Some polymers such as polyurethane can produce either hard polymeric structures or soft polymeric structures based on the specific chemistry and degree of cross-linking, and as such can be considered in either category depending upon the formulation.

2.3.4. Prosthetics

The trend in prosthetic arms and hands has moved towards systems that include additional degrees of actuation. AM has been applied to address various hardware design challenges, patient-specific customization, and facile repairs [76]. Additionally, efforts are being made to increase accessibility of prosthetic designs in low-resource settings for the ~40 million amputees by providing guidelines for non-assembly based designs [77]. As AM moves into the consumer space, open-source designs for customizable prosthetics are being collected in centralized repositories [55]. Many different types of polymeric materials and printing techniques have been utilized for this application (Figure 2d).

3. Biomedical applications of soft polymers

Unlike many of the hard materials utilized in AM of biomedical applications, which build upon commercial success of traditional AM methods and materials, the use of soft materials such as hydrogels in this space is a nascent development requiring further research and development before commercial adoption. This is partly due to some of the unique applications such as drug delivery and tissue engineering, which require more complex performance and regulatory considerations.

3.1. Soft polymer materials

Soft polymers used in biomedical AM applications can be categorized as natural, synthetic, or hybrid materials. Natural soft polymers are those commonly associated with the extracellular matrix such as collagen, hyaluronic acid, fibrin/fibrinogen, and mixtures thereof [78]. Such natural polymers are highly favored due to their inherent biocompatibility and bioactivity, but often suffer from limitations in processability and cost. A subset of natural polymers used in biomedical AM are not

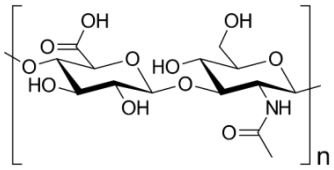
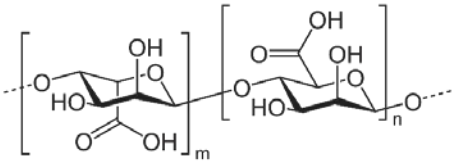
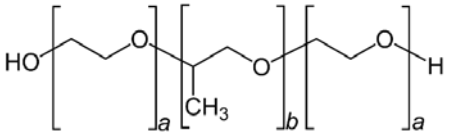
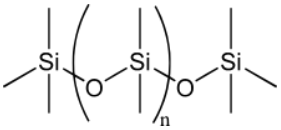
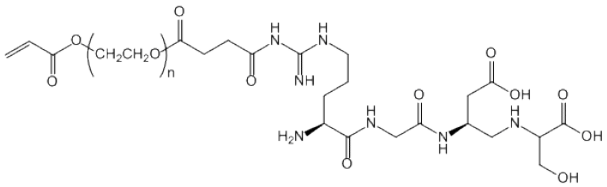
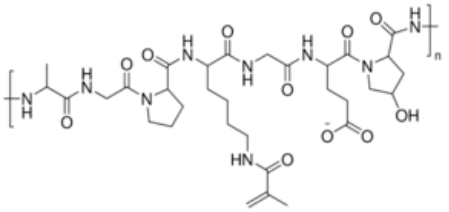
native to humans, which include cellulose, silk, alginate, chitosan, and agarose, as well as gelatin, which is a denatured form of collagen [78]. Researchers often employ blends or composites of these materials to capitalize on the enhancements in mechanical performance and biofunctionality when combined [79]. Almost all polymers in this category are biodegradable and thus are intended to serve as transient implants or delivery vehicles.

Synthetic soft polymers for use in biomedical AM include polyethylene glycol (PEG), acrylate-based hydrogels, elastomers, and hydrogels with unique thermal properties such as the poloxamer Pluronic F127 [80]. Such materials have finer control in chemistry, structure, and physical properties such as rheological flow, but often lack biocompatibility and degradation pathways. Elastomers (e.g., polyurethanes and silicones) are most commonly used as tissue phantoms or surgical models due to their mechanical and tactile resemblance to native tissue (See Section 3.2.3), but are less commonly considered for implantables due to their lack of biodegradability. Synthetic hydrogels may find use in 3D-printed contact lenses [81] or pharmaceutical delivery applications (See Section 3.2.2). Pluronic F127 (a poly(ethylene oxide)–poly(propylene oxide) copolymer) has found unique use as a templating material for bioprinting, where the polymer can be applied in specific patterns and encapsulated with another material of choice [82–84]. Upon exposure to refrigeration temperature, the micellar structure of the Pluronic F127 disassembles, liquefying the gel. With application of a light suction, the Pluronic F127 can be removed to reveal open structures, most notably serving as vascularization paths for the printed scaffold or tissue construct or as templates for other tubular tissue structures such as renal proximal tubules [82–84].

Hybrid soft polymers, or those which contain both natural and synthetic moieties, find themselves at the intersection of synthetic and natural polymer attributes. Natural polymers like gelatin and hyaluronic acid suffer from processing and stability challenges in their native form [85] and thus rheological properties must be tuned to enable extrusion-based printing. Gelatin is a thermally reversible gel, which returns to the liquid state at body temperature, making it difficult to maintain 3D-printed conformation at physiological conditions [86] in its natural state. Hyaluronic acid is a linear polymer, which forms a loose physical entanglement that provides minimal structural integrity in solution [87]. A common strategy to improve the structural integrity of such materials involves the reaction of free amine groups with methacrylic anhydride to produce methacrylated compounds (i.e., gelatin methacrylol or GelMA, methacrylated hyaluronic acid or MeHA) [88,89]. The methacrylation enables the hydrogels to be covalently crosslinked via free radicals to form stable network gels, which retain their native enzymatic degradation capabilities, but have greater control over rheological and mechanical properties. Both GelMA and MeHA have found use in biomedical AM applications [84,90,91].

Another form of hybrid soft polymers for medical AM applications involves the conjugation of bioactive moieties to synthetic polymer backbones. The most notable example of this type is the conjugation of arginylglycylaspartic acid (RGD) peptide to synthetic polymer backbones such as PEG or acrylated-PEGs, although a variety of bioactive additives have been considered [92]. Here, the peptide enables the synthetic polymer to adhere to the cell membrane, thus promoting cellular adhesion and proliferation on the surface of printed scaffolds and structures. This technique allows for the fine control over molecular weight, network structure, and rheology with synthetic hydrogel backbones while integrating cellular response.

Table 3. Examples of chemical structures for certain AM-compatible natural, synthetic, and hybrid soft polymers used in biomedical applications.

Class of Soft Polymer	Example polymers	Example structure
Natural polymer	hyaluronic acid	
	alginate	
	Pluronic F127	
Synthetic polymer	silicone	
	acrylate-PEG-RGD	
Hybrid soft polymers	GelMA	

3.2. Soft polymer examples of biomedical AM applications and outlook

3.2.1. Tissue engineering and bioprinting

One of the applications that would have the most disruptive impact on the biomedical field is in AM-driven tissue engineering and bioprinting, where cell-laden or cell-free scaffolds and tissue constructs could enable functional implants and devices for disease modeling, and tissue/organ repair and replacement [93]. While this field has yet to penetrate the commercial biomedical market, the research and development in this space in the last few decades has expanded substantially. The most common methods employed in bioprinting are extrusion-based printing (e.g., direct-write), photopolymer-based printing such as SLA, electrohydrodynamic printing or droplet-based printing methods such as inkjet printing [94–96]. A variety of polymeric materials, including natural, synthetic, and natural-synthetic hybrids have been utilized in each of these methods, with specific materials highlighted above. In each case, if live cell printing is being conducted, careful attention to processing parameters that may affect cell viability and function must be considered, such as light and temperature exposure and shear stresses [97].

One notable advancement in AM-based tissue engineering and bioprinting is the incorporation of vascularization. The tissue engineering field has suffered for decades with the inability to incorporate functional vasculature, which prevent tissue constructs from reaching substantial thicknesses necessary for use as implants or viable tissue models. By the use of sacrificial templates or direct printing of hollow tubes, researchers have enabled the patterning of vascular structures, which can reveal open vascular networks capable of lining with native vascular cells such as endothelial cells [84,98]. This advancement has enabled tissue constructs to be printed upwards of a centimeter in thickness with actively perfusable vasculature, enabling viability greater than one month (Figure 4a) [83].

3.2.2. Drug delivery

Drug delivery applications are seeing a growing interest in the biomedical AM community [99]. The first FDA-approved 3D-printed drug, Spritam, was approved in 2015 for treatment of epilepsy [100]. The powder-bed based printing method (ZipDose Technology [6]) enabled a rapidly disintegrating tablet to be produced, marketed for patients with difficulty swallowing tablets [101]. While bioresorbable materials such as PLA and PCL have been employed, hydrophilic, water-soluble polymers such as PEG and cellulose have also been investigated as drug-delivery platforms via AM [102]. Printed stimuli-responsive hydrogels have garnered interest for drug-delivery systems due to their ability to release pharmaceutical agents in response to a specific environmental trigger (Figure 4b) [103–105]. These AM drug-delivery strategies enable unique geometries as well as graded and layered structures with control over composition and release kinetics that may enable ‘personalized’ medicine.[106]

3.2.3. Tissue phantoms and soft surgical models

Tissue phantoms and surgical models are currently attainable applications for soft (and in some cases hard) polymers as they are intended to be models that do not intend to be implanted or therapeutic in nature. Instead, tissue phantoms enable validation of disease modeling and assistance with diagnosis

and treatment plans for injuries and disease states. They may mimic tissue properties in tactile or visual representations, or mimic ultrasound or CT imaging representations [107]. Such materials must have the aforementioned characteristics of native tissue with precise control over geometry. Elastomers (e.g., polyurethane elastomers and polydimethylsiloxane (PDMS)) are commonly employed for this application, where AM can enable fine control over spatial resolution [107–109]. Multimaterial or gradient printing can be employed to enable printed structures with localized regions of relatively stiff or soft materials for mimicking the tactile properties of a given tissue, and can also vary the color and translucency for visual inspection by medical professionals (Figure 4c) [110].

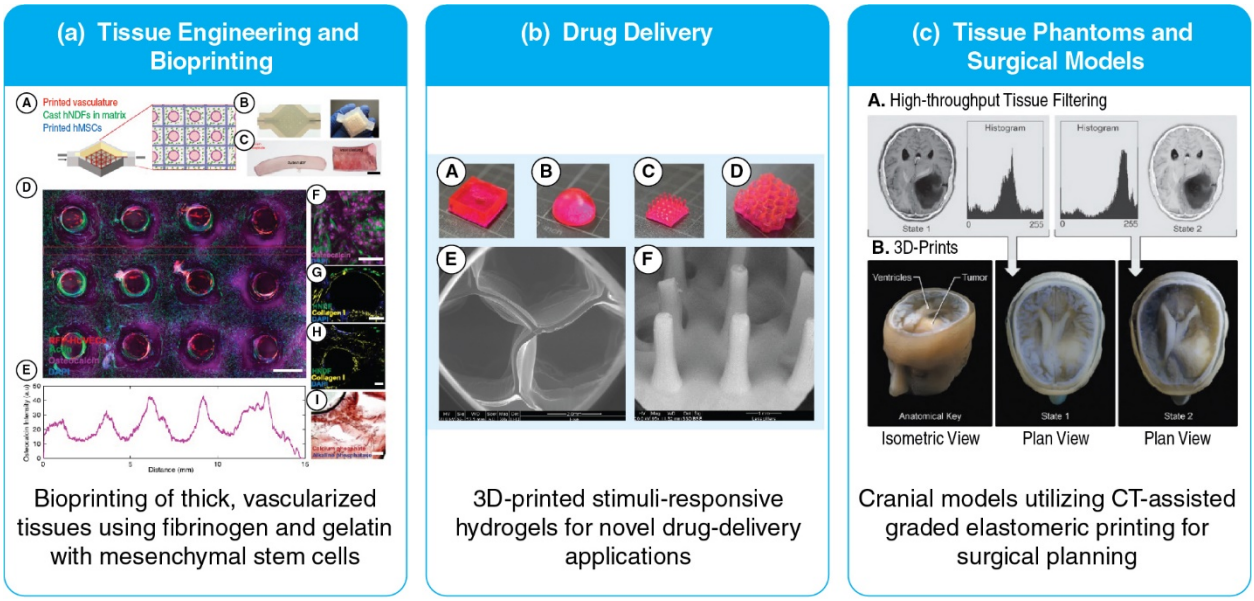


Figure 4. Examples of the use of AM with soft polymeric materials for biomedical applications: a) Tissue engineering and bioprinting [83], b) Drug delivery [103], c) Tissue phantoms and surgical models [110].

4. Conclusions

Biomedical applications will continue to benefit from the additive manufacturing of polymeric materials. Hard polymers, which have seen early adoption by the medical community, will continue to be utilized due to their emerging success in FDA-approved implantable devices and their market penetration in the dental community. Research in soft polymers for biomedical AM applications is accelerating, and with continued development, clinical breakthroughs are anticipated particularly in the area of tissue engineering, bioprinting, and personalized medicine. Both types of polymers contribute to the successful implementation of realistic surgical models or phantoms due to AM's unmatched ability to produce complex models with fine geometrical features, and in some cases, tunable mechanical properties. Nascent breakthroughs in additive manufacturing include holographic printing [111] and 4D printing (i.e., printed stimuli-responsive structures capable of changing over time) [112]. The former may enable exceedingly fast printing speeds for the fabrication of large biomedical devices and implants,

while the latter produces responsive shape-changing geometries that may impact drug delivery or 'smart' implantables. There remains a need for continued development and characterization of polymeric materials suitable for AM methods for use in these biomedical applications, and with time, many believe that a 3D printer will become a standard outfit in the clinic to assist medical professionals in every aspect of their care and treatment.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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