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Polyurethanes as a Potential Medical--Grade Filament for Use in Fused Deposition Modeling 3D Printers – a Brief Review

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Abstract
The possibility of using 3D printing technology (3DP) in medical field is a kind of revolution in health care. This has contributed to a rapid growth in demand for 3D printers, whose systems and materials are adapted to strict medical requirements. In this paper, we report a brief review of polyurethanes as a potential medical-grade filament for use in Fused Deposition Modeling (FDM) 3D printer technology. The advantages of polyurethanes as medical materials and the basic operating principles of FDM printers are presented. The review of present solutions in the market and literature data confirms the large interest in 3D printing technologies for the production of advanced medical devices. In addition, it is shown that thermoplastic-elastomer polyurethanes may be an effective widespread class of material in the market as thermoplastic filament for FDM 3D printers.

Key words: *medical-grade polyurethanes, filaments, Fused Deposition Modeling (FDM), 3D printing.*

Introduction

Polyurethanes (PURs) have been used as biomedical devices since the 1960s [1], mosty as biostable polymers. Over the decades, PURs have been aligned and modified to meet strict medical requirements. As a result of this, nowadays PURs exhibit satisfactory biostability, biocompatibility and even biomimetic properties [2]. PURs belong to a special group of polymeric materials called thermoplastic elastomers and have unique mechanical properties while maintaining high processing versatility. The degree of usefulness of PURs in the medical field depends on the chemical composition and method used for their synthesis. Three major substrates are needed to synthesise PUR: macrodiol, diisoyanate and a chain extender. Macrodiols form soft segments of PURs, imparting elastic properties, while diisocyanates and low molecular weight chain extenders build hard segments which are responsible for extra mechanical resistance. Two main types of isocyanates used in the synthesis of medical-grade PUR can be identified, i.e. aromatic and aliphatic. Aromatic diizocyanates, such as 4,4′-methylenediphenyl diisocyanate (MDI) or toluene diisocyanates (TDI), are the most commonly used components of commercial medical-grade biostable PURs. These polymers possess great flexibility, toughness, tear resistance and structural stability, as well as being biocompatible; however, they should not be used as biodegradable implants. This is due to the possible release of toxic residues of degradation, consisting of carcinogenic aromatic amines [3]. Therefore, in the case of bioresorbable PUR products, aliphatic diisocyanates are more preferred by scientists [4-8]. The most commonly used macrodiols in the field of biomedical PURs are semi-crystalline polyesters like poly(caprolactone) diol PCL, poly(ethylene glycol) (PEG) or poly(tetramethylene glycol) (PTMG) [4]. The above-mentioned polymers possess good biocompatibility and are susceptible to degradation through hydrolysis; they also differ in strength properties. However, the semi-crystalline structure of the above polyesters is responsible for the less controlled degradation process than in the case of amorphous type macrodiols [9]. Moreover the hydrolytic and enzymatic degradation of PURs depends on the type of macrodiol and diisocyanate, wherein the degradation process is much more favorable for short-carbon chain macrodiols and aliphatic diisocyanates [10]. In turn, the reactivity level and degree of cross-linking of PURs depend on the type (diamine, diol) and functionality (bi-, tri-functional) of the chain extender, which directly affects thermal and mechanical properties of the PUR product [11]. Another criterion defining the final properties and application of medical-grade PUR is the processing method. PURs with a very low degree of cross-linking can be soluble in polar solvents (dimethylsulfoxide DMSO, tetrahydrofuran THF), which renders them suitable for use in electrospinning [12, 13] or emulsion freeze-drying modeling methods [14]. This can be further used to obtain porous tissue 3D structures (so called scaffolds). An additional advantage of PURs is their socalled thermoplastic-elastomer character. This feature combines the processability of thermoplastics and the great elastic properties of vulcanised rubber [15]. This allows to use polymer moulding techniques that are conventional for thermoplastics, such as extrusion, injection, blowing and compression moulding, which are based on the plasticising phenomenon. It should be noted that one of the 3D printing technologies that is based on the thermoplastic plasticisation effect is Fused Deposition Modeling (FDM) [16]. Moreover most of the medical materials currently used for FDM are conventional thermoplastics (polylactide PLA or polycaprolactone PCL) [17].

This brief review article shows the potential usefulness of thermoplastic-elastomer polyurethanes for obtaining new types of filaments, expanding thermoplastic medical-grade polymers currently used in Fused Deposition Modeling 3D printing technology. Moreover we present the latest scientific reports regarding the usefulness of the FDM printing process based on polyurethanes as a cost-effective tool in a wide range of medical areas.

Practical use of 3D printing technologies in the health-care industry

Medicine increasingly uses advanced technologies provided by materials engineering technology the mechatronics

industry. One of those that is becoming more and more common in the healthcare industry is 3D printing (3DP). The greatest benefits of 3DP technologies in medicine are possibilities to combine the freedom of shape and geometry production with radiographic methods such as computerised tomography (CT) scans, magnetic resonance imaging (MRI) and x-rays. This allows to convert the received DICOM's (*Digital Imaging and Communications in Medicine*) files to the STL format, which is supported by 3D printers, and then produce customised and personalised medical 3D structures [18]. The practical use of 3DP in medical fields is no longer unreachable for scientists. Innovative approaches which use computer-aided design (CAD) data and AM technologies are already successfully used to fabricate customised implants [19-21], tissue engineering structures [22-24], anatomical models for surgical planning [25-27] and drug delivery systems [28-31]. Moreover companies such as Organovo, K2M and Stryker already supply ready-made medical products obtained using 3DP technologies ***Table 1***. As can be seen, manufacturers use a number of different 3DP technologies for various medical products.

Table 1. *Examples of companies providing medical products obtained with the use of 3D printing.*

Company	3DP technology	Product
Organovo	Bioprinting	Functional human tissues, organs
K2M	Selective laser sintering (SLS) (Lamellar 3D Titanium Technology ®)	Titanium spinal implants
Apercia Pharmaceuticals	Powder bed and inkjet 3DP (PBIH) (ZipDose® Technology)	Highly porous pills
Regenovo	Bioprinting / 3DP	Tissue scaffolds, anatomical models, drug discovery models, metabolic syndrome models
Cognionics	Fused deposition modeling FDM	Dry EEG electrodes
L'Oreal – Organovo (*in progress)	Bioprinting	Human skin tissue
Fasotec	MultiJet printing (MJP)	Surgical training systems (artificial organs, anatomical models)
Stryker	Direct metal laser sintering (DMLS)	Permanent implants

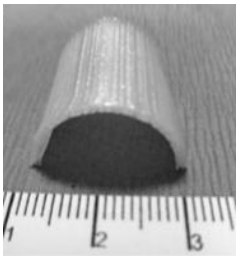
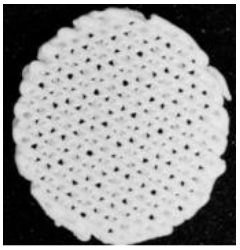
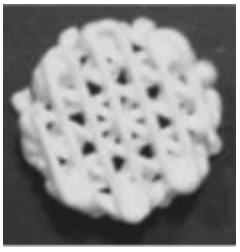
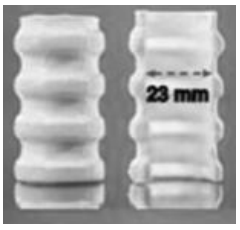
Selective laser sintering (SLS) together with direct metal laser sintering (DMLS) belong to the so called powder bed fusion (PBF) 3DP processes. Both methods use a high-power laser to melt and fuse material in the form of a powder together [18]. The powder is placed in a specially constructed bed and sintered layer by layer. Unlike SLS, the DMLS technique uses only metal powders. SLS can utilise metallic, ceramic and polymer powders. As an example, Bertol et. al. [32] used DMSL with titanium alloy powder (Ti-6Al-4V) to fabricate a customised preoperative implant based on a patient's CT scans. In turn, Hao et. al. [33] prepared bioactive structures for tissue engineering purposes using SLS with composite powder of hydroxyapatite-polyethylene (HA-HDPE). 3DP technology that is noted for the highest resolutions, accuracy and precision is MultiJet printing (MJP). MJP is based on the inject printing process, which uses photocurable plastic resins and casting wax materials. Each layer of material is precisely dispensed by the printing nozzles and hardened with a UV lamp [18]. Medical-grade photocurable resins may include biodegradable caprolactone and trimethylene carbonate (CL/TMC) [34] or poly(propylene fumarate) (PPF) [35] for tissue engineering application. Bioprinting is a completely different technology based on the deposition of biomaterials (bioinks) on a special substrate [36]. This technology is intended for the production of ready-made living tissues and organs [37]. However, bioprinting is still being developed and improved and is available only in large specialist corporations. Nevertheless these technologies are not without drawbacks. These include a limited number of materials (especially those of the medical-grade) or the need for post-processing treatments. In addition, all of the apparatus is mentioned extremely expensive and may be beyond the reach of a private customer.

Fused Deposition Modeling as an effective tool in the medical field

Fused Deposition Modeling (FDM) is becoming a very promising 3DP technology for the use in medicine applications [38]. FDM is one of the most inexpensive 3D printing technologies on terms of service, cost of purchase and operation of printers [39]. This method consists in the layered deposition of plasticised polymeric material in the form of a filament on a movable platform. For this purpose, FDM uses a miniature temperature-controlled extruder [40]. 3D objects can be formed from both computer models and DICOM files. In comparison with other 3DP technologies, FDM offers the possibility to use more than one type of material during the printing process (dual extruder FDM printers). The starting material is dosed in the form of so-called filament, which is a thin wire of predetermined diameter. Filament can be obtained via different techniques, among which is melt extrusion [41-43]. The filament diameter required for FDM 3D printers should be constant and equal to 1.75, 2.85 or 3.0 mm, depending on the type of printer extruder. It should be noted that in the literature there are more and more studies on new medical filaments for FDM 3DP. As an example, Hutmacher et al. described fabrication via FDM 3DP of bioresorbable polycaprolactone-based tissue scaffold [24] as well as cornstarch/gelatin/dextran – based tissue scaffolds [44]. On the other hand, Wu et al. [45] obtained biocompatible composite filament consisting of polylactide and chitosan, which revealed improved antibacterial properties. Whereas Corcione et. al. [46] fabricated polylactic acid-nanohydroxyapatite composites as a filament for use in bone regeneration.

According to our knowledge, the companies Poly-Med (USA) and Taulman3D (USA) are probably the only suppliers of certified medical-grade filaments for FDM 3DP. Poly-med provides a series of filaments, such as Lactoprene® 100M (based on PLA), Caproprene® 100M (based on PCL), Max-Prene® 955 (based on PGLA) and Dioxaprene® 100M (based on PDO). These materials possess good biocompatibility and are bioresorbable [47-50]. A study conducted confirmed the potential use of the materials mentioned in hard and soft tissue engineering applications from a physico-chemical point of view [51]. While Taulman 3D offers guidel!ne® – FDA proved PETG (glycol-modified polyethylene terephthalate) based filament. Nevertheless all of the above filaments do not provide desired flexibility, toughness and durability while maintaining the biomedical properties required (in particular, the ability of controlled biodegradation, of which PURs are capable [52-54])

Table 2. *Summary of current literature on PUR scaffolds fabricated by 3D printing technology.* ***Note:*** *PLA – polylactide, PEBA – polyethylene-butylene-adipate diol, IPDI – isophorone diisocyanate, DMPA – dimethylolpropionic acid, EDA – ethylenediamine, HA – hyaluronic acid, PEO – polyethylene oxide, PCL – polycaprolactane, MDI – diphenylmethane diisocyanate, BDO – butanediol.*

Material	Description	3DP technique	Product/application	Biological test	Image	Ref.
Tecoflex ® (PUR)	Medical grade – aliphatic polyether--based PUR	custom-made 3D printing system based on a metal printing syringe and nozzle (200μm), printing with a PUR solution of (40% in chloroform).	tracheal scaffold/ patch-type prosthesis	*in vivo/implanted into the tracheal defect of rabbits*		Fig. 1d. from Jung et al. [63]
Water dispersion of PUR	Poliols – PLA, PEBA, Diisoyanate – IPDI, Chain extenders – DMPA/EDA + HA as viscosity enhancer	low-temperature fused deposition manufacturing (LFDM)	scaffolds for cartilage regeneration	*in vitro/human MSCs, in vivo/ implanted into the chondral defects of rabbit knees*		Fig. 1c. from Hung et al. [64]
Water dispersion of PUR	Poliols – PLA/PEBA, Diisoyanate – IPDI, Chain extenders – DMPA/EDA + PEO as viscosity enhancer	low-temperature fused deposition manufacturing (LFDM)	scaffolds for cartilage regeneration	*in vitro/rat chondrocyte cell line*		Fig. 3a. from Hung et al. [65]
PUR/PLA/GO	Nanocomposite – enhanced with GO graphene oxide, PUR – Pearlthane® (PCL-based)	FDM	tissue engineering scaffolds	*in vitro/NIH3T3 cells*		Fig. 1f. from Chen et al. [66]
PUR	Poliols – polyether/ PCL), Diisocyanate – MDI, Chain extender – BDO	FDM	tracheal tissue/ cartilaginous rings	*in vitro/HDF, BEC cells*		Fig. 3a. from Tsai et al. [67]

Polyurethanes as promising materials for Fused Deposition Modeling technology

There are many possibilities of PUR modification and customisation by selecting synthesis substrates or choosing an appropriate forming method. Currently PURs are used as long-term implants (artificial heart valves [55], catheters [56] the suitability of poly(ethylene oxide), wound dressing [57], artificial skin [58], bone graft substitutes [59], components of drug delivery systems [60] and porous scaffolds for regeneration of damaged tissues [61]. Hence there is great interest in these polymer materials in the world of science and the medical industry. However, in the era of new technologies, PURs might find other application , for example as a medical-grade flexible material for use in 3D printing technology.

PLA and PCL biopolymers seem to be the most common and known filaments for medical application. They belong to the group of thermoplastic polymers. There are not many alternatives that would provide excellent elastic properties and tailored-made possibility for a controlled degradation rate. Polyurethanes (PUR) seem to have great potential in this field, as they are highly biocompatible and hemocompatible materials with a wide range of properties which can be tailored to requirements [62]. PURs may also combine great elasticity with thermoplastic characteristics, necessary in the FDM process. In addition, the huge vari-

ety of synthesis substrates allows to customise PUR to a specified application. This can distinguish PURs from other medical-grade filaments available on the market. The recently published literature reports presented in ***Table 2*** may confirm these considerations.

It should be pointed out that in the literature there are only a few available reports related to PUR filaments for 3DP application. Jung et al. [63] developed a novel 3D printed PUR tracheal scaffold with micro-scale architecture to provide host tissue infiltration with adequate biomechanical properties which withstand the physiological tracheal condition. The mechanical properties of the scaffolds were: an ultimate tensile strength of approx. ~3.2 MPa and Young's modulus of about 2.8 MPa. The elongation at break reached a value of 725%. Examination *in vivo* was conducted by implementation of the scaffolds in the anterior tracheal defect of rabbits. After 8 weeks of implementation, a ciliated respiratory epithelium with ciliary beating were observed at the lumen of the implanted tracheal scaffolds, which is a very positive and promising result. Hung et al. [64], developed a water-based 3D printing method with the use of the water dispersion of elastic and biodegradable PUR. Printed PUR scaffolds showed mechanical properties (compressive strength ~1.6 MPa, tanδ ~0.2) close to those of native cartilage. According to the results reported, chondrocytes were seeded efficiently on PUR scaffolds, and proliferated and secreted the extracellular matrix. The system developed was then modified. Water-based 3D printed scaffolds exhibited controlled bioactivity by adding the growth factor TGFβ3 and small molecule drug Y27632 into printing ink dispersion of hyaluronan [65]. The authors dedicated these systems to customised cartilage tissue engineering. Chen et al. [66] prepared PUR/PLA/GO nanocomposite structures via FDM 3DP technology. Nanocomposite was obtained by a solvent-based mixing process and extruded into thin wire (filament) for FDM printing. The incorporation of GO into the polymer blend enhanced the mechanical properties and thermal stability of the nanocomposite. It was proven that the scaffolds produced exhibit good biocompatibility with NIH3T3 cells. The procedure used allowed to fabricate a nontoxic and highly elastic nanocomposite PUR scaffold containing graphene oxide (GO), with increased cytocompatibility. The research team lead by Tsai [67] also demonstrated the possibility of using FDM in the processing of PURs. They produced a series of tubular structures of different size and shape for use as a trachea scaffold. They also demonstrated the biomimicry of a ligament structure with distinct collagen bundles at the microscopic level, which may confirm the possibility of using the structures obtained as tissue substitutes. Details related to PUR 3D printing of the research described are presented in ***Table 2***.

What is worth pointing out here is that Xiao et al. [41] is probably the only author who has described the procedure of medical-grade PUR filament fabrication. For this purpose, they used commercially available Tecoflex® LM-95A, produced by Lubrizol. The filament obtained was successfully tested using an FDM 3D printer. Hence it can be concluded that studies on PUR filaments in the field of medicine are at the early stage of development.

Summary

In summary, according to the literature overview, the most commonly used synthetic polymers for FDM 3D printing of medical devices are thermoplastic poly ε-caprolactone (PCL) and polylactide (PLA). These polymers exhibit several advantages as medical filaments for 3DP; however, there is a shortage of available filaments with a texture, flexibility and tactile sensation similar to tissues or organs. These are particularly important aspects in the case of printing products from the group of surgical training systems, which should reproduce not only the shape but also the tactile properties. This is particularly important for a surgeon or medical student [68]. On the other hand, properly designed polyurethanes can be a new group of materials competing with PCL and PLA tissue engineering constructs, providing increased viscoelasticity or counter-balanced degradation and resorption rate [10]. Moreover, according to our knowledge, currently there are no certified medical-grade bioresorbable PUR filaments for FDM 3D printing available on the market. There are a limited number of researches reporting new PUR filaments for use in medical applications (***Table 2***). Moreover most of them require additional adaptation and modification of 3D printers to their needs [69, 70]. Thus studies on new medical-grade PURs may be the right direction of future researches on novel filaments for FDM 3DP. The development of new elastic materials for low-budget FDM printers may contribute to the popularisation of this technology in everyday use in the medical industry and scientific centers. Additionally the increasing number of successful scientific works on the optimisation of FDM printers as well as on their resolution and accuracy [63, 64, 71] allow us to suppose that this technology can become one of the most powerful and accessible tools of future medicine.

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