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Review

A review: Fabrication of porous polyurethane scaffolds

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ABSTRACT

The aim of tissue engineering is the fabrication of three-dimensional scaffolds that can be used for the reconstruction and regeneration of damaged or deformed tissues and organs. A wide variety of techniques have been developed to create either fibrous or porous scaffolds from polymers, metals, composite materials and ceramics. However, the most promising materials are biodegradable polymers due to their comprehensive mechanical properties, ability to control the rate of degradation and similarities to natural tissue structures. Polyurethanes (PUs) are attractive candidates for scaffold fabrication, since they are biocompatible, and have excellent mechanical properties and mechanical flexibility. PU can be applied to various methods of porous scaffold fabrication, among which are solvent casting/particulate leaching, thermally induced phase separation, gas foaming, emulsion freeze-drying and melt moulding. Scaffold properties obtained by these techniques, including pore size, interconnectivity and total porosity, all depend on the thermal processing parameters, and the porogen agent and solvents used. In this review, various polyurethane systems for scaffolds are discussed, as well as methods of fabrication, including the latest developments, and their advantages and disadvantages.

Contents

1. Introduction

The main aim of tissue engineering is the fabrication of functional replacements for damaged tissues or organs. Scaffolds play a crucial role in tissue engineering, because they represent an alternative to the conventional implantation of organs and tissues. The main goal of scaffolds is to provide appropriate base for tissue growth and cell proliferation [1]. Biomaterials play a critical role in tissue engineering. For the preparation of scaffolds a great number of different natural or synthetic materials have been studied and proposed [2]. The most frequently employed polymers of natural origin in biomedical applications are polysaccharides (alginate, chitosan, starch, cellulose) and proteins (collagen, silk fibroin), due to their bioresorbability, low toxicity, and low manufacture and disposal costs [3,4]. Moreover, they offer a wide range of advantages for tissue engineering applications such as biological signalling, cell adhesion, cell responsive degradation and re-modelling [5]. However, the physical and mechanical properties of natural polymers do not always match to the properties of tissues, there is less control over the bioresorbability, the risk of immunorejection and disease transmission makes proper screening and purification necessary [6]. The most widely used synthetic polymers are polyesters, having FDA approval for various applications. Many are already clinically used as biomaterials for example poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(ε-caprolactone) and theirs copolymers [7,8]. However, they degrade via a random, bulk hydrolysis of ester bonds in the polymer chain, releasing acidic degradation products, which can cause a strong inflammatory response [9,10]. Other drawback of polyesters is their hydrophobicity, which can be unfavourable in tissue regeneration applications due to the poor wetting and lack of cellular attachment

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and interaction [11]. Next to polyesters applied in tissue engineering there are synthetic polymers called polyurethanes. They have unique segmented structure, due to which more diverse properties can be obtained using relevant raw materials and additives. PU can have a wide range of mechanical and physical properties, from thermoplastic to thermosetting, from stable to degradable materials, from hydrophobic to hydrophilic depending on the composition and synthesis procedure applied [12,13]. PUs exhibit moderate compatibility with blood, and are characterised by biocompatibility, bioresorbability and excellent mechanical properties, which can be adjusted to specific tissue [14,15].

In the beginning of their application in medicine PUs were used as artificial skin [16], vascular grafts [17], neural connections [18], bone grafts [19] and materials for the repair of articular cartilage [20]. The recent literature describes many polyurethane systems that are suitable for scaffolds (Table 1). PU as a material for scaffold fabrication must be bioresorbable, thus polyester-urethanes are mainly synthesised from PCL, PLA or PGA, whilst polyether-urethanes are from polyols such as poly(ethylene glycol) (PEG) or poly(propylene oxide) (POP). Aliphatic or cyclic diisocyanate (hexamethylene diisocyanate HDI, 4,4′-methylenebis(cyclohexyl isocyanate) HMDI, isophorone diisocyanate IPDI) is used instead of aromatic diisocyanate, for example MDI (4,4′-methylenebis(phenyl isocyanate)) and TDI (tolylene-2,4-diisocyanate), because they can degrade into carcinogenic and mutagenic aromatic amines [21]. One can find in the literature the use of 1,4-diisocyanatobutane (BDI) and lysine methyl ester diisocyanate (LDI), as they potentially degrade in the body to the biological diamine putrescine and to the amino acid lysine, respectively, a biogenic amines, which play an important role in cell growth and differentiation [22,23]. Degradation products from segmented poly(ester-urethane)urea elastomers comprising BDI, lysine ethyl ester and putrescine chain extenders, and poly(e-caprolactone) (PCL) diols demonstrated no toxic effects on human endothelial cells cultured in vitro [24]. However, the use of putrescine can be controversial, as some papers describe it as toxic substance [25].

One of the requirements imposed on scaffolds is a suitable, porous structure with uniformly distributed interconnected pores. Materials should be characterised by great porosity (above 90%) and proper pore dimension (from ten to hundreds of μm) depending on the application. According to the literature, scaffolds for liver regeneration should have a pore diameter of 20 μm to allow the growth of hepatocytes, for skin, the proper pore diameter should be within a range from 20 to 150 μm, whilst, for bone, the best pore size is from 200 to 400 μm [26]. Moreover, pores must be interconnected to allow cell and tissue ingrowth. All of the above-mentioned properties depend either on the polymer used or the method of fabrication.

The fabrication of 3-dimensional porous structures is based on transforming polymers from the solid to liquid state, mostly by melting or dissolving. Generally, those techniques can be divided into two groups: conventional and advanced. Advanced techniques include, among others, electrospinning [27], 3D printing [28] and rapid prototyping [29], whilst conventional techniques include solvent casting/particle leaching (SCPL) [30,31], thermally-induced phase separation [32,33], gas foaming [34,35] and melt moulding [36,37]. In this paper, we present an overview of the conventional techniques used for fabricating polyurethane scaffolds.

2. Solvent casting/particle leaching (SC/PL)

Solvent casting combined with particle leaching involves leaching out solid particles from the polymer solution. To the polymer solution, which is usually prepared at a concentration from 5 to 20% [38] (Table 1, 1–3, 7–10), specified diameter particles are added. After solvent evaporation by air-drying, vacuum-drying or freeze-drying, salt particles remain embedded throughout the polymer matrix. After immersion in water, salt particles are leached out, leaving a porous structure (Fig. 1).

According to Zhu et al. [39], highly porous scaffolds with porosity up to 93% and average pore sizes of up to 500 μm can be obtained. The structure of the formed scaffold depends on many factors. The shape and size of pores are directly determined by the shape and dimensions of the leachable particles used (Table 1, 1–3). The pores take over the shape of the particles, and therefore, by selecting the size of the particles, it is possible to control the pore size. Salt particles are mainly used, but the use of sugar, ammonium chloride, sucrose, starch particles and gelatine, paraffin microspheres is also known [40,41]. According to Draghi et al. micropsheres are more effective than particles, because spherical pores improve fluid exchange and nutrient supply to cells. Moreover, the regular geometry obtained by microspheres leaching improved scaffolds mechanical performance. Another parameter which influences the structure is the amount of particles added. If the salt content is insufficient, the polymer solution will surround the particles and isolated pores will appear. On the other hand, if the amount of salt added is too high, a deficient structure with voids will be formed due to close geometric packing [42]. Another parameter which significantly affects the structure of the scaffold is the initial concentration of the polymer solution. The density of the polymer solution increases with increasing amounts of particles added; therefore, it is difficult to control the direct contact between the crystals and the polymer [43]. The effect of pore size on the mechanical properties of the scaffold should also be taken into account. According to Sin et al. [30]

Table 1
Techniques and systems used in scaffold fabrication.

Technique	No.	PU system	Solvent	PU concentration [%]	Porosity [%]	Pore size [μm]
SC/PL	1	Zytar® Z1A1 (termoplastic polyether-urethane) [30]	DMF/THF	15	>91	~250
	2	PCL/HMDI/EG [31]	1-Methylo-2-pirolidone	20	>70	100–400
	3	PCL/HMDI/isosorbide diol [38]	DMF		90	200 ± 16
TIPS	4	PHB-PCL/TMDI [32]	1,4-Dioxane	5		100–150
	5	PCL-PEG/BDI/Putrescyna [55]	DMSO	10	94	76–387
	6	PCL/BDI/BDO [55]	DMSO	10	>80	36–203
TIPS/PL	7	PCL/BDI/BDO [33]	1,4-Dioxane	17		150–300
	8	PCL/BDI/BDO [59]	DMSO	35	80	Different
	9	PCL/HDI/isosorbide diol [61]	DMF/THF	9,5	90	200 ± 45
	10	Poly(ethylene adipate) diol/IPDI/hexamethylene diamine [60]			87	50–400
Freeze-drying	11	PCL/BDI [86]	1,4-Dioxane/water		>80%	150–300
	12	PCL-PEG/IPDI/BDO/L-lysine [88]	Water	16		10–172
	13	PCL-PEBA-PLA/IPDI [89]	–	5	97%	
Melt moulding	14	Texin (termoplastic polyether-urethane) [73]	–	–	64	30–450
	15	PCL-PEG/HDI/benzoic acid [37]	–	–	88	153 ± 70
Gas foaming	16	PEG-PPG/TDI [77]	–	–	85	300–800
	17	POP/TDI [80]	–	–		95 ± 40
	18	PCL-PEG/HMDI [78]	–	–	>75	50–2000