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Correlating synthesis parameters with physicochemical properties of poly(glycerol sebacate)

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ABSTRACT

Poly(glycerol sebacate), PGS, is an elastomeric biodegradable polyester increasingly proposed in a variety of biomedical applications. It is prepared by polycondensation of sebacic acid and glycerol in a first stage in which a prepolymer is obtained, followed by a curing to conveniently crosslink it. In this work, synthesis parameters such as the curing temperature and time, and the molar ratio between reactants, were systematically varied to correlate them with the physicochemical properties of the resulting polymer networks. The efficiency of each manufacturing process was quantified through the relative mass effectively crosslinked and insoluble in tetrahydrofuran. Infrared spectra gave an estimation of the ratio of non-condensed polar terminal groups. These results were correlated with swelling results, which in turn provided the means to calculate the chains density through Flory-Rehner equilibrium swelling equation for lightly crosslinked polymers. The role of the synthesis parameters on the physical state of the resulting polymers, as well as their proneness to hydrolyze, were followed. The results obtained highlight the relevance of rinsing them following synthesis, to remove non-crosslinked chains that easily diffuse to the surrounding medium. Curing under mild conditions equimolar mixtures of sebacic acid and glycerol proved to lead to poorly crosslinked swellable networks, which hydrolyze easily in bulk mode. Alternative molar ratios yield sticky and difficult to handle materials at higher polyol fractions in the reactive mixture, whilst an excess of acid terminal groups leads to a faster mass loss by hydrolysis in aqueous media together with surface salts deposition, concomitant with a lesser cell viability in *in vitro* culture. PGS synthesized from an equimolar ratio between reactants and cured at 130 °C or higher, for 48 h or longer, show suitable features for their use in tissue engineering applications where hydrophobic surface-degradable rubbers are required, without significant differences among them.

1. Introduction

Functional, partial or total failure of tissues and organs is one of the most serious health concerns and economically costly. Traditional strategies involving the use of artificial prostheses and mechanical devices have improved and saved the lives of millions of patients, but entail a number of inconveniencies, such as long-term mechanical failure following implantation

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that can trigger an immune response in the host, damaging healthy tissues around the implant. Surgical reconstruction of tissues and organs is feasible in occasions, but pose the risk of surgical and postoperative complications and the development of malignant tumors in the affected areas [1].

Aiming to solve these issues, progress has been made in the tissue engineering field leading to the development of new polymeric biomaterials. Within this group, the most widely evolving in recent decades have been the synthetic biodegradable polymers, for their easier manufacture monitoring in a vast variety of porous structures and more precise tailoring of the degradation process against those of natural origin [2–4]. Furthermore, they are highly versatile in terms of controlling their physicochemical properties and the ease of adaptation to the desired application. Indeed, the mechanical properties and degradation rate of the implant are determined not only by its chemical composition but, to some extent, by the conditions of synthesis of the polymer [5].

Among the many bioresorbable synthetic polymers, poly(glycerol sebacate), PGS, is a tough, flexible and biodegradable elastomer with excellent biocompatibility and physical characteristics similar to biological soft tissues and has subsequently emerged for soft tissue engineering applications [6,7] and as drug carrier [8]. Its synthesis procedure was first reported by Wang et al. in 2002 [9] and later enhanced by Gao et al. [10]. PGS is able to stay and recover from deformation in dynamic environments and furthermore displays shape memory, *i.e.* it is able to return after a phase of deformation to its original state thanks to the action of an external stimulus [11]. Another interesting feature is that, unlike other polymers, PGS is degraded mainly by surface erosion, due to its hydrophobic nature, undergoing a linear mass loss over time. This allows the polymer to largely retain its structural integrity and mechanical properties [12], and allows it to be used for controlled drug release throughout its degradation process.

The versatility of PGS synthesis, coupled with its excellent characteristics of biocompatibility and elasticity, make it a polymer of great interest in tissue engineering applications. One of the most important performance areas is the cardiovascular system, where it has been proposed for myocardial regeneration and reconstruction of blood vessels [13] or cardiac valves, where it is used together with other polymers such as collagen [14,15]. Similarly, PGS has also been developed for its use in cartilage tissue engineering, mainly for degenerative arthritis [16], or as regenerative solution to musculoskeletal problems, and the reconstruction of nerve pathways [17].

PGS is obtained by polycondensation of glycerol and sebacic acid [11]. Sebacic acid is a natural intermediary metabolite of ω fatty acid oxidation and long chain glycerol is one of the major components of lipids, both being US Food and Drug Administration approved monomers. The synthesis process comprises two stages: a first prepolymerization phase, resulting in a viscous prepolymer by formation of linear chains between reacting monomers, and a second curing step in which the chains intertwine to form the polymer network. The reaction for the formation of PGS is an esterification between a dicarboxylic acid, sebacic acid, and an alcohol, glycerol. The hydroxyl groups of the polyol act as initiators of the reaction. Thus, initially, a primary hydroxyl group of glycerol attacks a carboxyl group to form a monoester with a free carboxyl group and water as byproduct [18]. This monoester reacts next with another primary group of glycerol to form another monoester, and so on with all available functional groups.

The prepolymerization is usually carried out at a temperature of about 120–130 °C for 24 h whilst maintaining an inert atmosphere, usually nitrogen, though a microwave-assisted process that can be carried out in minutes with no need of purge gas has been reported [19]. The latter induces an intensive glycerol evaporation leading to stiffer PGS networks. The synthesis conditions of the curing stage may vary (120 °C/48 h in [9] or 130 °C/1 to 12 days in [12]), resulting in polymers with different mechanical properties and biodegradability [20] to fit with different applications. At this stage, the inert atmosphere is no longer required for crosslinking to occur. However, no rinsing or conditioning process following synthesis has been conducted anywhere, other than vacuum-drying before characterization or sterilization by UV radiation and soaking in growth medium before cultures [9]. Thus, the presence of unreacted monomers and especially non-crosslinked chains has not been yet considered in previous discussions.

The enormous interest that involves the use of this polymer in the tissue engineering field raises thus the question of the relationship between the physicochemical and biological characteristics and the mechanical behavior of PGS with its synthesis conditions, and which would be the optimal preparation protocol according to the targeted application. Herein, the purpose is thus to highlight the relevance of such rinsings following synthesis, and correlate the properties of the networks obtained with their structural parameters after removing the effect of non-crosslinked species. To do this, synthesis parameters such as the curing temperature and time, and the molar ratio between reactants, have been herein systematically varied and the polymeric networks obtained have been characterized after their thorough rinsing to eliminate any unreacted monomers and non-crosslinked chains.

2. Materials and methods

2.1. Preparation of PGS films

The synthesis of poly(glycerol sebacate) was carried out in two stages: an initial prepolymerization to allow the polycondensation of the reactants, glycerol (VWR International) and sebacic acid (Sigma-Aldrich) yielding ester bonds and thus branched chains, followed by a curing, when crosslinks eventually result in a three-dimensional network.