

Poly(Glycerol-Sebacate) Elastomer: A Mini Review

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Abstract

Poly glycerol sebacate (PGS) is a synthetic polymer widely known in the field of tissue engineering and has achieved remarkable attention due to its desired properties such as having surface degradation and elastomeric behavior. Different synthesis methods based on pre-poly condensation step and crosslinking have been defined for PGS production till now. Thanks to its physico-chemical, mechanical, thermal and morphological properties; it has been proposed for numerous tissue engineering applications ranging from soft to hard tissue by researchers. Both *in-vitro* and *in-vivo* many research studies have been carried out not only upon PGS but also its composite forms. In addition, different production techniques and characterization methods have been pursued. Within the scope of this mini review article; the importance of PGS along with its discovery, production techniques, characterization and applications were described and explained.

Introduction

Regenerative medicine is an emerging field that uses different types of biomaterials consisting of polymers, ceramics, metals and their composites to restore or maintain the whole or partial tissues/organs. Some part of these materials mentioned above has potential to be used in clinical field owing to their superior properties, while another part needs further development. Both natural and synthetic polymeric materials are of enormous interest in the clinic due to their biocompatibility, mechanical properties, ECM like structures, degradation parallel to ECM formation etc.

Poly (glycerol-sebacate) (PGS) is a synthetic, biodegradable, thermo set and tough polymer first reported in 2002 by Wang et al. [1] and proposed for soft tissue engineering. It is emphasized in the first reported paper which introduces PGS to the scientific literature that it is cheap, bio-resorbable, bio degradable and has non-toxic degradation products [1]. Upon the discovery of PGS, many research studies in biomedical field had been launched by using this polymer including the development of polymer blends, composites, scaffold material for tissue engineering, adhesives, drug delivery system, sealants and coating materials [2]. PGS have mostly been proposed for soft tissue as a scaffold material. When the mechanical properties of soft tissues frequently studied in the context of tissue engineering are considered, Young Modulus values are observed between 0.1 and 11.1MPa [3]. As for the mechanical properties of PGS recorded in the previous studies, it seems to be extremely compatible with soft tissues regarding to its tunable mechanical properties via cross linking [2,4]. Despite being suitable for soft tissue, we have also found examples in the literature for hard tissue repair, often combined with osteo conductive materials

[5-7]. Moreover, the combination of this material with β -tricalcium phosphate ceramics was proposed for guided bone regeneration in our previous study [8].

The main purpose of drug delivery studies is to distribute the drugs to a local target and sustain the therapeutic effects of drugs within the therapeutic frame and reduced toxicity [9]. Many damaged organs and tissues in the body can be accepted as a target. Therefore, drug delivery has a wide range of application area from anticancer therapy and contraceptive methods, to infectious disease [10]. In the field of drug delivery, the local distribution of target drugs/molecules is in close relationship with the degradation profile and the rate of the matrix. Studies conducted on the degradation of PGS have found that PGS degrades via surface erosion and it is understood that surface degradation is due to the breakage of the ester bonds [11]. PGS has been proposed as a matrix for anticancer drug encapsulations by Sun et al. [12]. In another study, berberine and chlorhexidine were encapsulated into the PGS as an active ingredient for periodontal regeneration by Deng et al. [13].

Yet another application of PGS includes their usage as tissue adhesives. There has been an increasing demand in the clinic for tough biodegradable polymer adhesives that can cover the mechanical deformations while continuing to adhere to the tissue [14]. One of the possible reasons of demand can be disadvantages of conventional sutures and staples such as absence of elastic behavior and presence of toxicity or inflammatory effects. One of the other possible causes is that the elastic properties of conventional materials cannot adapt to every tissue [6]. Chen et al.

[15] developed a synthetic tissue sealant from (PGS) and poly lactic acid (PLA) copolymer as an alternative to fibrin or collagen based adhesives to eliminate their viral risks. Mahdavi et al. [16] has proposed a new generation tissue adhesives made of poly (glycerol-co-sebacate acrylate) to overcome the limitation of conventional materials due to adjustable elasticity through cross linking density.

Many biomaterial candidates have been combined with one another up to date to increase their mechanical or chemical properties or to cover their deficiencies. PGS is also one of these materials. PGS-fumarate and hydroxyapatite combination was proposed by Bodakhe et al. [17] to produce injectable, highly bioactive and biocompatible nano composites. The addition of hydroxyl apatite has been reported to increase ultimate strength of the structure. In another study, multi-walled carbon nanotube (MWCNT)/poly(glycerol-sebacate-citrate) (PGSC) elastomer composite was reported by Lui et al. [18]. The addition of carbon nanotubes was found to improve the strength and the modulus while degradation was reduced.

Production and Characterization of PGS as a Biomaterial

PGS is produced by combining glycerol and sebacic acid monomers with specific ratios. Hydroxyl groups of glycerol and carboxylic acids of sebacic acid undergo polycondensation reaction without any catalysts [19]. According to the first published article by Wang et al. [1] two step production protocols was needed to be followed: polycondensation and crosslinking. Equimolar mixtures of each starting monomers (1M of glycerol and sebacic acid) were reacted at 120 °C under argon atmosphere for 24 hours before the pressure was reduced from 1 Torr to 40m Torr. Consequently, the pre-polymer was exposed to 40m Torr vacuum at 120 °C for 48hours for cross linking to occur [1]. A group of scientist investigated the alternative synthesis methods of PGS by changing molar ratio, curing temperature and cross linking parameters [15,20]. Also in our previous study, we demonstrated a facile PGS production method via microwave-assisted pre-polymerization without using a gas, catalyst or vacuum [21].

PGS, as a biomaterial, needs to be characterized to identify its possible application areas. For this purpose, physicochemical, mechanical and thermal properties of PGS together with its degradation and biocompatibility were investigated in detail [2]. PGS can be defined as transparent, almost odorless and colorless polyester. Wang et al. [1] characterized the chemical structure of PGS by FTIR analyses. The peaks differ in the spectra with respect to its crosslinking density, curing temperature and curing time [22]. According to the Nuclear Magnetic Resonance (NMR) spectroscopy analyses, the hydroxyl groups were bonded covalently to the carbon backbone, which provides hydrophilicity. Hydrogenbonding interactions between the hydroxyl groups, on the other hand, represents elasticity [1]. The hydrophilicity of the structure can be tunable by changing the crosslink parameters. As the curing time was increased, hydrophilicity was reduced due to the removal of hydroxyl groups from the structure [23].

The average Young modulus of PGS was calculated between 0.02 and 1.2MPa and ultimate tensile strength was found greater than 0.5MPa [4,20,24]. The mechanical properties can be adjusted by changing the curing temperature, curing time and molar ratio of the monomers [25]. Thermal properties of PGS can be studied by Differential Scanning Calorimetry (DSC) analysis. Thermal properties of PGS depend on the transition temperature (T_g) of the amorphous phase and melting temperature (T_m) of the crystalline phase as it is a partially semi-crystalline polymer. As stated in the literature, PGS exhibits a T_g at -37 °C with broad melting transition at temperature ranging from -20 °C to 40 °C according to the DSC diagram [26].

Crystallinity and morphology of PGS can be revealed by X-Ray Diffraction (XRD) analysis. PGS shows a broaden peak in the spectra. The main diffraction peak is centered at 19.8 °C due to the doped sebacate in the structure. It was observed that the intensity of the diffraction peak decreased as the amount of sebacic acid in the structure increased. On the other hand once the curing time and temperature was increased, the crystallinity of PGS decreased [22,27]. The degradation mechanism of PGS can be defined as the surface degradation due to the cleavage of the ester bonds in the structures [11]. Wang et al. [1] noted on the first article on PGS that *in-vitro* and *in-vivo* degradation of PGS differs. *In-vitro* degradation of PGS was measured as 17.6% weight loss while it was completely absorbed *in-vivo* in a study that lasted 60 days. The degradation kinetics can be affected by production parameters such as curing time and temperature. For instance, if crosslink density increases in proportion with curing time or heat, the degradation kinetics decreases [1,4].

Biocompatibility of PGS is one of its superior properties originated from its components: glycerol and sebacic acid approved by FDA [28]. Nevertheless, its biocompatibility was investigated by many researchers [29-31]. Although there is still no study emphasizing the toxicity of PGS, Chen et al. [32] reported that the local acidic environments encountered due to the hydrolysis of the ester groups releasing carboxylic acid [32]. Therefore, a number of surface functionalization methods have been suggested to enhance the cell migration, adhesion, differentiation and proliferation such as surface coating with a biomolecule, grafting of hydrophilic groups or enzyme treatment [33,34,50].

Biomedical Applications of PGS

As summarized above, PGS has numerous advantages compared to other existing synthetic bio-degradable polymeric materials. Its elastic and biocompatible nature has attracted great attention of the researches who work in biomedical field. In the light of increasing demand on biomedical materials, researchers have been investigating the PGS in many different areas listed on Table 1.

Conclusion

PGS has a pivotal role in biomedical arena regarding to its elasticity, biocompatibility and biodegradability. Research studies are ongoing to develop PGS based material both alone and in

combination with other materials in different forms and sizes. In addition to the technical specifications, providing a cheap, practical production method that does not require a lot of equipment will lead researchers to develop new biomaterials in the future.

Table 1: Biomedical application of PGS.

Material	Application	Reference
PGS	Cardiac Tissue Engineering	[4,35,36]
PGS/Bioactive Glass	Bone Tissue Engineering	[5]
PGS	Bone Tissue Engineering	[7]
PGS/ β -TCP	Bone Tissue Engineering	[8,37]
PGS	Drug Delivery	[12,13]
PGS/PLA	Surgical Sealants/Tissue Adhesives	[15]
PGS/Acrylate	Surgical Sealants/Tissue Adhesives	[16]
PGS/Fumarate/HA	Bone Tissue Engineering	[17]
PGS	Cartilage Tissue Engineering	[20]
PGS	Shape Memory	[26]
PGS	Nerve Tissue Engineering	[31]
PGS	Soft Tissue Engineering	[38,39]
PGS/PCL	Cardiac Tissue Engineering	[40]
PGS/PBS-DLA	Cardiac Tissue Engineering	[41]
PGS/ ϵ -PCL	Cornea Tissue Engineering	[42]
PGS	Retina Tissue Engineering	[43]
PGS/HA	Bone Tissue Engineering	[44]
PGS/PMMA-Gelatin	Nerve Tissue Engineering	[45]
PGS/Curcumin	Drug Delivery	[46]
PGS	Coating Material	[47]
Acr-PGS	3D Printing	[48]
PGS/Urethane/Cellulose	Shape Memory	[49]

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