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Review

Bio-based polymers, supercritical fluids and tissue engineering

Aurelio Salerno*, Concepción Domingo Pascual

Institute of Materials Science of Barcelona (ICMAB-CSIC), Campus de la UAB s/n, Bellaterra 08193, Spain

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ABSTRACT

Tissue engineering and health care involve the diagnosis, treatment, and prevention of diseases with the ultimate goal to improve people's quality of life by developing advanced materials and therapeutic approaches based on scaffolds and drug delivery. Bio-based polymers are excellent candidate materials for these purposes as, for example, they provide biophysical and biochemical properties able to induce the correct biological response for both *in vitro* and *in vivo* applications. This review aims to provide the reader with an overview of the use of bio-based polymers, as well as their blends and composites, for tissue engineering and health care purposes. Special emphasis is given to supercritical fluid processing of bio-based polymers for drug delivery and scaffold fabrication, as they enable the preparation of biomedical systems and avoid the use of chemicals potentially harmful to cells and living tissues. The last part of this review highlights some significant *in vitro* and *in vivo* applications of bio-based polymeric scaffolds for the regeneration of specific tissues, namely bone, cartilage, blood vessel, nerve, skin and dermis.

Contents

1. Introduction

Many different biomaterials, both natural and synthetic, both biodegradable and permanent, have been investigated as scaffolds and drug delivery systems for health care and tissue engineering applications, including bioceramics, biocompatible pristine and composite polymers and hydrogels. Among them, the use of bio-based polymers (biopolymers) derived from renewable resources is emphasized. Depending on their nature and route of fabrication, these polymers can be classified into three main groups [1,2]: (i) naturally derived, such as proteins and polysaccharides; (ii) synthetic, obtained by the polymerization of bio-based monomers, mainly polylactic acid, polybutylene succinate and polyethylene; and (iii) microbially fermented, such as polyhydroxyalkanoates. The worldwide interest in biopolymers has increased progressively in the past years, as these materials can help to reduce the dependence on fossil fuels for plastics applications. Their use also has a positive environmental impact in terms of decreasing carbon dioxide emissions and reducing waste generation. Hence, many applications seek the use of biopolymers for their sustainability, eco-efficiency, industrial ecology, and renewable nature. In the last decades, these materials have also been used in tissue engineering (TE) and health care, as scaffolds and biopolymer supports for diagnosis and drug delivery [3–5]. As shown in Fig. 1 , a search of the ISI (Web of Science©) database using the words "biopolymer" and "tissue engineering" identified a total of more than 400

* Corresponding author. Tel.: +34 935801853.

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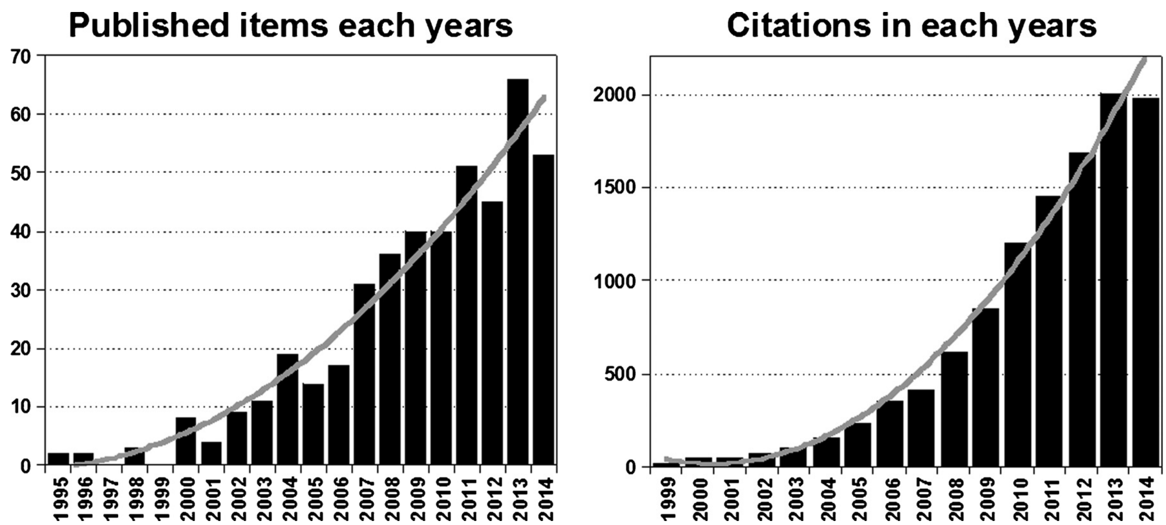

Fig. 1. Trend of (a) publications and (b) citations in biopolymers for TE applications (Thomson Reuters source, November 2014).

articles currently available on the subject, with approximately 90% of them published in the last decade, demonstrating the increasing interest of the biopolymers in this biomedical field. Indeed, biopolymers intrinsically exhibit important properties, such as antibacterial activity, biodegradability and biocompatibility [6]. Furthermore, naturally derived polymers have a chemical structure and composition similar to the macromolecules of the native extracellular matrix (ECM). As a direct consequence, the use of these materials in living systems would reduce the stimulation of chronic inflammation or immunological reactions and toxicity, often occurring when a man-made synthetic polymeric device is implanted into a host [3,7]. Additionally, biopolymers can be chemically modified to better meet the degradation rate and the mechanical and electrical properties required for each specific application [8–10].

A commonly used synthetic biopolymer is polylactic acid (PLA), a polyester that degrades when implanted *in vivo* to form lactic acid, a low molecular weight compound which can be easily removed from the body. Similar used materials are polyglycolic acid (PGA) and copolymers of the type poly(lactic-co-glycolic acid) (PLGA). Moreover, a significant body of research has focused recently on the utilization of bio-based hydrogels for various biomedical applications. Hydrogels are three-dimensional networks composed of hydrophilic polymers crosslinked either through covalent bonds or held together *via* physical intra and intermolecular attractions, which can absorb large amounts of water or biological fluids and swell readily without dissolving. Natural hydrogels, in particular different derivatives of the extracellular matrix, such as protein materials (collagen or fibrin) and polysaccharidic materials (chitosan or hyaluronic acid) have proved suitable in terms of cell compatibility. This review aims to provide the reader with an overview of the use of biopolymers, together with their blends and composites, in some important TE and health care applications. After this introduction, Section 2 describes three main classes of biomedical devices: particulate systems and two and three dimensional platforms, and their implementation for TE and health care purposes. Section 3 addresses the processing of biopolymers by means of supercritical fluids to design and fabricate micro- and nanostructured products. Section 4 highlights some important biomedical applications in use or suggested for the different classes of described biopolymers. Finally, in Section 5 some concluding remarks are presented.

2. Polymer-based platforms for TE and health care

The different aspects of TE, drug delivery and diagnosis are innovative and continuously expanding research fields, which hold the promise of improving the ability to fight specific diseases and to repair or regenerate biological tissues and organs by developing efficient therapeutic treatments. From the point of view of TE, the integration of therapeutic agents and molecular cues into a biomedical device is often necessary to stimulate the intrinsic capacities of cell or tissue for regeneration [11,12]. Hence, the use of one dimensional (1D) system involving micro- and nanoparticles is an important aspect of TE addressed in Section 2.1, either for drug delivery or for the development of biomaterials. Scientific advances in biomaterials, stem cells, growth and differentiation factors, and biomimetic environments have created unique opportunities to fabricate tissues in the laboratory from combinations of engineered extracellular matrices called scaffolds, cells, and biologically active molecules. The interaction of the surface of the scaffold with biological entities, such as cells and tissues, determines the feasibility of the used system and is treated in Section 2.2 about two-dimensional platforms (2D). For TE, cells are often seeded into an artificial porous structure or scaffold capable of supporting three-dimensional tissue formation. Important aspects determining the three dimensional (3D) growth of new tissue from porous scaffolds composed by bio-based polymers are described in Section 2.3.

2.1. 1D platform: micro- and nanoparticles for cell and drug delivery and diagnosis

In recent years, an increased interest by the industry and research community has been directed to the development of novel nano- and microcarriers for diagnosis and controlled drug delivery. Most of these systems have been obtained from naturally derived polymers because biopolymers have some exceptional characteristics in terms of biodegradability and non-antigenicity. Moreover, they can effectively protect entrapped substances against environmental degradation [13]. Concomitantly, the evolution of micro- and nanotechnology has enabled the production of particles of controlled sizes, shape and structure [14].

Fig. 2 presents a diagram of some important applications of polymeric micro- and nanoparticles of natural polymers. The small