

Electrospun Biopolymers: Hydrophobic Scaffolds with Favorable Biological Response

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Abstract

This article reviews electrospun biopolymer scaffolds, focusing on surface hydrophobicity, cell response, and applications in tissue engineering.

Editorial Note

A scaffold is defined as a 3D porous material that features characteristics such as biocompatibility, and biodegradability to serve as a temporary platform for tissue regeneration. While hydrophilicity was not initially mentioned as one of the requirements for scaffolding materials, the success of bio-derived hydrophilic natural polymers e.g. collagen, gelatin, won great acclaims for hydrophilic scaffolds [1]. However, more recent application of hydrophobic electrospun biopolymers in tissue engineering provides an opportunity to look at this matter from a different perspective and to identify the suitability of

hydrophobic scaffold materials as well.

For the last two decades, electrospun biopolymers have been an important class of scaffolding materials offering the advantages of electrospinning and biocompatibility of polyesters in one package. Electrospinning is a direct and versatile method that has the flexibility to be applied for fiber fabrication from various biopolymers [2]. It produces morphologies and dimensions similar to those of natural extracellular matrix (ECM) [3], an interwoven random fibrous structure of collagen and elastin with diameters ranging from tens to hundreds nanometers creating a matrix with considerable surface area for biomolecular interactions [4,5]. The morphological similarity of the electrospun scaffolds to natural ECMs facilitates cell seeding, adhesion, proliferation, and cell differentiation [4,6]. Two other common features of electrospun fibers is their high surface area to volume

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ratio and their porosity, which can lead to infiltration of cells into scaffolds resulting in stronger cell attachment [7]. The large surface area of the scaffolds is favorable for loading bioactive materials within the matrix [8] while the porous nature of the electrospun scaffolds facilitates food absorption and waste release by the cells [9].

Componental aspects of the scaffold materials are also of great significance. An ideal scaffold mimics the natural morphological and componental properties of an ECM [4]. Biopolymers are attractive materials for scaffolding applications, mainly due to their relatively low cost of synthesis, ease of degradation, and the ability to tailor their degradation rate through changes in the structure. This class of polymers degrade through hydrolysis of the ester bonds, producing non-toxic degradation products [10].

Polycaprolactone (PCL), polylactic acid (PLA), poly3-hydroxybutyrate (PHB), and its copolymer with hydroxvalerate (PHBV) are the most popular commercially available biopolymers that have been successfully electrospun and produced promising platforms for tissue engineering applications. All these materials are aliphatic linear polyesters produced from renewable resources. Their rheological and viscoelastic properties facilitate processing and fabrication of them into desired morphologies [3]. Electrospun scaffolds based on these biopolymers were successfully used for various types of cells including stem cells [11], osteoblasts [12], dermal fibroblasts [13], chondrocytes [14], keratocytes [15], vascular [16], and neural tissue [17]. Figure 1 shows laser microscope representation of the surface, water contact angle, and field emission scanning electron microscopy (FESEM) of PHB electrospun fibers seeded with keratocytes as an example for biopolymers. All these materials in the form of electrospun membranes exhibit hydrophobic behavior when analyzed by water contact angle (WCA) (Fig. 1.b, $\theta \sim 120^\circ$). This behavior is mainly due to the chemical structure of the biopolymers and the absence of hydrophilic functional groups as well as relative roughness of the electrospun surfaces, and the air trapped in the micropores of fibrous network [18]. Electrospun materials, due to their fibrous nature, typically possess rough surfaces. In surface topography

analysis, a rough surface has deviations and irregularities compared to a smooth surface [19]. While surface roughness, in a general sense, improves the cellular response to the substrate for higher availability of the surface area [20], hydrophobicity has mainly been considered as a less favorable attribute for the scaffolding materials [21]. Hydrophobic materials tend to exhibit poor wettability and cell attachment as well as uncontrolled biological interactions. Therefore, several methods have been considered to rectify these shortcomings and to introduce a more hydrophilic nature to the materials. These suggested modification techniques can be divided in four categories: plasma treatment, alkaline treatment, coating, and blending with other bioactive materials [3].

Despite being hydrophobic and contrary to the expectation, electrospun biopolymers have proven to be capable of promoting cell growth with desirable proliferation rates [15]. Volger et al. reported that hydrophilic surfaces with contact angle of $\theta < 65^\circ$ that do not lead to high level of cell attachment efficiency [22]. Similar reports suggested that fibroblast cells indicate maximum attachment at contact angles between 60° and 80° [23]. These results imply that a certain level of hydrophobicity can encourage and facilitate cell attachment and growth. This could be explained through protein adsorption and transient hydrogen bonding mechanisms. Attachment of the cells to the scaffold happens through a sequence of physico-chemical reactions in which protein adsorption plays a key role as mediator for cell adhesion. Adsorbed proteins to the scaffold provide the signal to the cells through adhesion receptors for which a series of cytoplasmic, transmembrane, and extracellular proteins are required [23]. It is well-known that moderate hydrophobic surfaces are capable of better absorption of proteins in comparison to the hydrophilic surfaces, which have more resisting forces at the surface [24-27]. The phenomenon could be due to unique physico-chemical properties of the water. As the main component in culture media, water has a unique self-association property. A water molecule has two hydrogen bond acceptors (unshared electron pairs of oxygen) and two hydrogen bond donors (protons) allowing the molecule to associate with maximum four

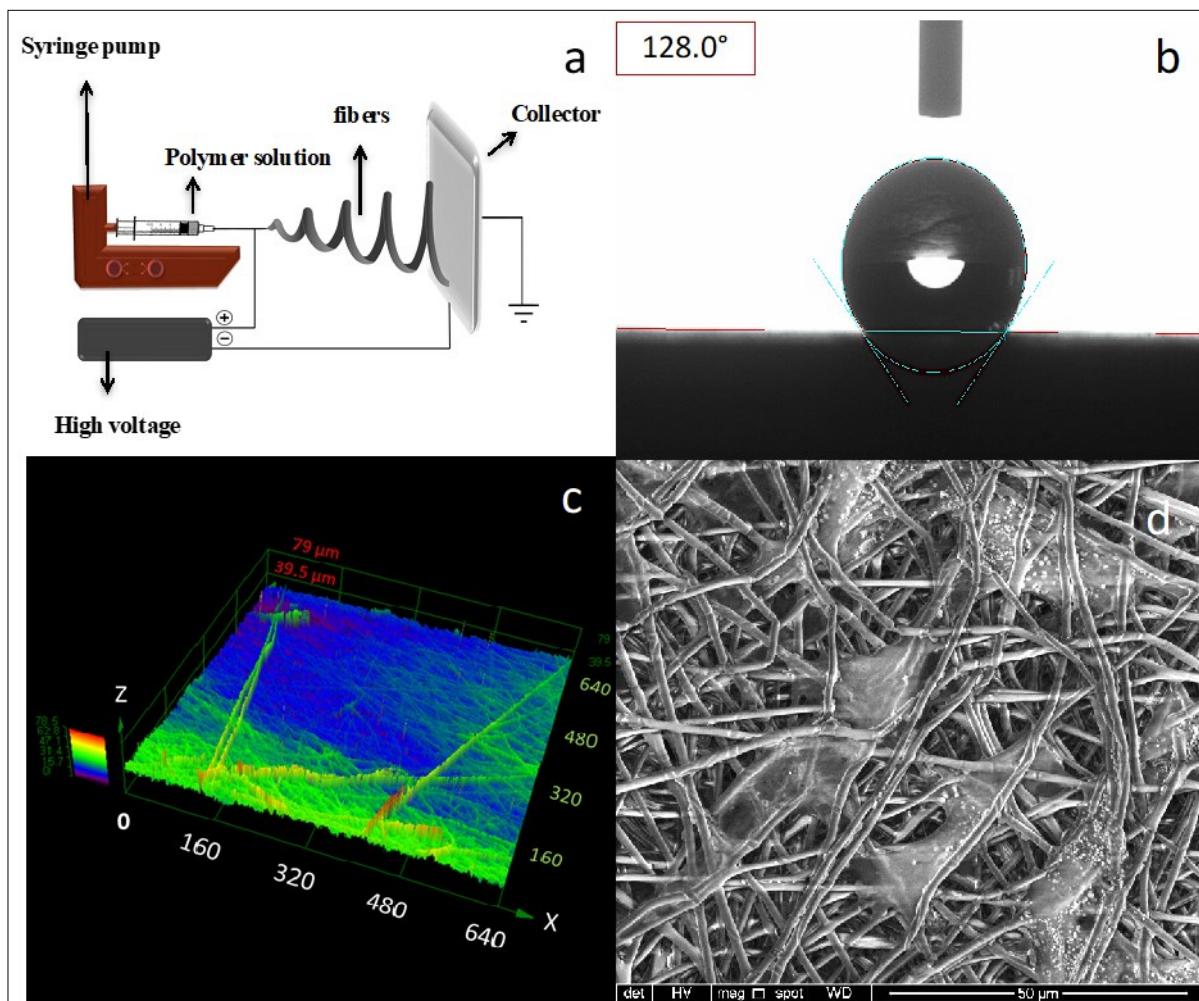


Fig. 1. Electrospinning setup for fabrication of randomly deposited fibers (a); Water-in-air contact angle for untreated electrospun PHB fibers (b, $\theta = 128^\circ$); 3D confocal laser microscopic image of PHB with average roughness of $S_a = 11.02 \mu\text{m}$ (c); and Electrospun PHB fibers seeded with rabbit keratocytes showing a successful cell attachment (d).

neighboring molecules. Since these associations are relatively weak and almost equivalent to the energy level transferred from one molecule to another neighboring molecule, the hydrogen bonds possess a transient nature. The presence of Lewis acid/base sites on hydrophilic surfaces suppresses self-association of water molecules as they enter a competition through hydrogen bonding resulting in presence of repulsive forces at the interface while surfaces with $\theta \geq 65^\circ$ can establish a wider range of attractive forces [22].

Although the natural hydrophobicity of the electrospun biopolymers is higher than the reported optimum numbers for scaffolding materials, it has been proven that relative hydrophobicity can offer rather more favorable platforms for such applications. As mentioned earlier, several surface modification methods are also available for treatment of super-hydrophobic biopolymer candidates to reduce the hydrophobicity [3]. Furthermore, WCA $\approx 120^\circ$ applies to unprocessed electrospun biopolymer. The general practice of scaffold preparation for cell culturing involves various wet processing steps including sterilization with ethanol, washing with phosphate buffered saline (PBS), and soaking in culturing medium [28]. These wet processing steps can cause a significant reduction in WCA, providing promising cell-scaffold interactions even on the unmodified electrospun biopolymers.

While not discrediting the previous understanding in regard to hydrophilic polymeric scaffolds, this short note suggests that surfaces with moderate hydrophilicity could be optimal platforms for tissue engineering applications. In conclusion, electrospun biopolymers should be considered within the unique family of scaffolding materials that offers desirable features for tissue engineering with addressable shortcomings.

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